



National Rates of Initiation and Intensification of Antidiabetic Therapy Among Patients With Commercial Insurance

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OBJECTIVE

Prompt initiation and intensification of antidiabetic therapy can delay or prevent complications from diabetes. We sought to understand the rates of and factors associated with the initiation and intensification of antidiabetic therapy among commercially insured patients in the U.S.

RESEARCH DESIGN AND METHODS

Using 2008–2015 commercial claims linked with laboratory and pharmacy data, we created an initiation cohort with no prior antidiabetic drug use and an HbA_{1c} ≥8% (64 mmol/mol) and an intensification cohort of patients with an HbA_{1c} ≥8% (64 mmol/mol) who were on a stable dose of one noninsulin diabetes drug. Using multivariable logistic regression, we determined the rates of and factors associated with initiation and intensification. In addition, we determined the percent of variation in treatment patterns explained by measurable patient factors.

RESULTS

In the initiation cohort ($n = 9,799$), 63% of patients received an antidiabetic drug within 6 months of the elevated HbA_{1c} test. In the intensification cohort ($n = 10,941$), 82% had their existing antidiabetic therapy intensified within 6 months of the elevated HbA_{1c} test. Higher HbA_{1c} levels, lower generic drug copayments, and more frequent office visits were associated with higher rates of both initiation and intensification. Better patient adherence prior to the elevated HbA_{1c} level, existing therapy with a second-generation antidiabetic drug, and lower doses of existing therapy were also associated with intensification. Patient factors explained 7.96% of the variation in initiation and 7.35% of the variation in intensification.

CONCLUSIONS

Approximately two-thirds of patients were newly initiated on antidiabetic therapy, and four-fifths of those already receiving antidiabetic therapy had it intensified within 6 months of an elevated HbA_{1c} in a commercially insured population. Patient factors explain 7–8% of the variation in diabetes treatment patterns.

Slightly more than 30 million individuals in the U.S., ~10% of the population, have diabetes (1). Each year, over 1.5 million new cases are diagnosed (2). Diabetes accounts for \$245 billion in health care costs annually, ~\$70 billion of which is due to lost productivity (2,3). A key aspect of effective diabetes management depends on the appropriate use of pharmacologic therapies to delay and prevent future microvascular

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and macrovascular complications. Despite robust evidence that improved glycemic control decreases diabetes complication rates (4–8), only one-third of patients with diabetes achieve optimal glycemic control (9). Suboptimal glycemic control is driven, at least in part, by delays in the initiation and intensification of antidiabetic therapy, a concept termed “clinical inertia” (10). Clinical inertia is estimated to contribute to at least 200,000 adverse diabetes-related events per year (11), but despite increased awareness, improved testing methods, and new antidiabetic drugs, clinical inertia remains common and a significant driver of variation in practice patterns (11–13).

Clinical inertia is due to a combination of patient, provider, and health care system factors (8,9,11,12). Despite guidelines about when to initiate and when to intensify therapy (14), the clinical treatment of diabetes remains highly nuanced, and current guidelines recommend shared decision making between patients and providers (14,15). When deciding if and how to initiate or intensify therapy, providers must consider many issues including patient factors such as adherence and attitude, medical factors such as comorbidities and potential side effects (16–19), and social/economic factors such as medication access and cost (20,21). These myriad factors create practice variation. At present, there is no contemporary assessment of antidiabetic therapy initiation and intensification rates and their trends in recent years, nor has there been an analysis focused on the drivers of such practice variation among a nationally representative, commercially insured population of patients with diabetes in the U.S.

Using data from a national, commercial insurer in the U.S., our goal was to describe the current rates of initiation and intensification of antidiabetic therapy within 3 and 6 months after an elevated HbA_{1c} $\geq 8\%$ (64 mmol/mol) and which patient factors are associated with higher rates of initiation or intensification.

RESEARCH DESIGN AND METHODS

Data Source

We used 2008–2015 medical, laboratory, and pharmacy data from a large, nationally representative, commercial insurer with beneficiaries in all 50 states. We analyzed medical claims from ~14.5 million individuals annually, 26% of whom have linked laboratory data and 47% of

whom have linked pharmacy data. The availability of linked laboratory and pharmaceutical data is determined by the insurer based on where and how beneficiaries receive laboratory work and fill prescriptions. Approximately 25% of all patients in the commercial claims database had linked medical, laboratory, and pharmacy data available, and there were no systematic differences between those with and without laboratory and pharmacy data based on measured covariates (Supplementary Table 1).

Cohorts

Eligible patients were identified after an HbA_{1c} level $\geq 8\%$ (64 mmol/mol) (date of test is the index date). We then required 6 months of pharmacy coverage before and after the index date. Patients with <1 year of continuous enrollment, aged <18 or ≥ 65 years, and with type 1 diabetes, identified using ICD-9 codes were excluded.

Among eligible beneficiaries with linked laboratory and pharmacy data, two cohorts were created. The initiation cohort was composed of patients with an HbA_{1c} level $\geq 8\%$ (64 mmol/mol), no use of any antidiabetic drugs for ≥ 6 months prior to index date, ≥ 6 months of pharmacy coverage after the index date, and no HbA_{1c} levels $<8\%$ (64 mmol/mol) for at least 90 days after the index date (Supplementary Fig. 1). Between 2008 and 2015, there were 9,799 eligible beneficiaries included in the initiation cohort.

The intensification cohort was composed of beneficiaries with an HbA_{1c} level $\geq 8\%$ (64 mmol/mol), ≥ 2 fills for one noninsulin antidiabetic drug without any dose changes for ≥ 6 months prior to index date, ≥ 6 months of pharmacy coverage after the index date, and no HbA_{1c} levels $<8\%$ (64 mmol/mol) for at least 90 days after the index date (Supplementary Fig. 2). Between 2008 and 2015, there were 10,941 eligible beneficiaries included in the intensification cohort.

Initiation and Intensification Definitions

For patients in each of the two cohorts, we determined the proportion initiated or intensified on antidiabetic therapy within 6 months of an elevated HbA_{1c} level $\geq 8\%$ (64 mmol/mol). Initiation was defined as ≥ 1 fill for any antidiabetic drug. Intensification was defined as any

of the following: 1) a dose increase in existing therapy, 2) the addition of ≥ 1 antidiabetic drugs to existing therapy, 3) the addition of insulin to existing therapy, and 4) a drug switch to another antidiabetic drug or insulin (with cessation of the initial therapy). Drug use was determined using National Drug Codes from the linked pharmacy data.

Patient Characteristics

Age and sex were available in the enrollment file. Using U.S. census data, percent white/black/Hispanic or Latino, percent below the poverty line, and percent college educated were assigned to each patient using the average for the zip code in which they resided (22). Population density for a zip code was determined using Rural Urban Commuting Area codes (23). Geographic region was determined using beneficiary zip code and classified into regions (West/Midwest/South/Northeast). Other comorbidities and the DxCG risk score, an overall assessment of medical complexity, were determined using the DxCG Intelligence tool (Verscend, Waltham, MA) (24). The index HbA_{1c} level was included from the laboratory file. Drug copayments were assigned to beneficiaries using the average generic and brand name copayment for a beneficiary's insurance plan. For employers with <10 beneficiaries, copayments were averaged by the state in which the employer and the majority of beneficiaries resided. For employers with >10 members, copayments were averaged by the beneficiaries' insurance plan and their respective employer. Office visits within 6 months after the index date were determined using current procedural terminology codes for office visits (99201–99215, 99241–99245, G0402, G0438, and G0438) in which the physician had a specialty code for family practice (08), internal medicine (11), geriatric medicine (38), general practice (01), or endocrinology (46). The percentage of patients in each cohort without a follow-up visit and whether or not they were initiated or intensified are included in Supplementary Table 2.

For the intensification cohort, initial drug type was determined using National Drug Codes and classified as first-generation, second-generation, or combination drug. Because patients with more advanced disease or longer disease duration are often managed differently in clinical practice, patients on insulin therapy were excluded to control, as much

as possible, for disease severity. First-generation diabetes drugs included metformin, sulfonylureas, thiazolidinediones, α -glucosidase inhibitors, and meglitinides. Second-generation diabetes drugs included amylin analogs, glucagon-like peptide 1 (GLP-1) agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium–glucose cotransporter 2 (SGLT2) inhibitors. Combination drugs included single therapies with two active drugs and were grouped with second-generation drugs if either of the two active antidiabetic drugs was a second-generation drug. The top quartile of dosing was determined for each antidiabetic drug using dosing information from the pharmacy file. Adherence was determined by taking the ratio of medication days dispensed (from the pharmacy file) to medication days possible (the 6 months prior to the index date). These ratios were then divided into adherence quartiles (25).

Statistical Analysis

Baseline beneficiary characteristics and rates of initiation and intensification are described using percentages and group means. Patient characteristics thought to potentially be associated with the initiation and intensification of antidiabetic therapy were identified using a priori, clinical knowledge. The association of these patient factors with the initiation and intensification of therapy was determined using multivariable logistic regression. The amount of variation in initiation and intensification explained by patient factors was determined using the Cox and Snell generalized coefficient of determination (adjusted R^2) of the multivariable logistic regression models. The statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

The rate of initiation within 6 months after an elevated $\text{HbA}_{1c} \geq 8\%$ (64 mmol/mol) was 63%, and most initiation (84%) occurred within the first 3 months after the index date (Table 1). The rate of initiation increased from 49% in 2008 to 69% in 2015 ($P < 0.01$). The intensification rate within 6 months of an elevated $\text{HbA}_{1c} \geq 8\%$ (64 mmol/mol) was 82%, and most intensification (89%) also occurred within the first 3 months. The rate of intensification increased from 76% in 2008 to 86% in 2015 ($P < 0.01$).

Baseline characteristics for the initiation and intensification cohorts, stratified based on whether therapy was initiated/intensified or not, are presented in Table 2. The rates of initiation and intensification did not vary based on age, sex, race, socioeconomic status, population density, geographic region, or comorbidities. However, the average generic drug copayment was lower among those initiated (\$9.66 vs. \$10.23; $P < 0.001$) and among those intensified (\$9.37 vs. \$9.85; $P < 0.001$) compared with those who were not. There was no significant difference in the branded drug copayment between those initiated/intensified and those who were not. Those initiated and intensified had a higher average number of office visits in the 6 months after the index date and a higher index HbA_{1c} compared with those who were not. Among those in the highest adherence quartile, 87% were intensified, compared with only 75% in the lowest adherence quartile. Among those in the top quartile for medication dose/amount, 81% were intensified. Eighty percent of those already on a first-generation antidiabetic drug and 90% of those already on a second-generation antidiabetic drug had therapy

intensified within 6 months after an index $\text{HbA}_{1c} > 8\%$.

In the multivariable analysis, each percentage increase in index HbA_{1c} was associated with higher odds of being initiated on antidiabetic therapy within 6 months (odds ratio [OR] 1.15 [95% CI 1.12, 1.18]; $P < 0.01$) (Table 3). The distributions of index HbA_{1c} levels for both cohorts are included in Supplementary Fig. 3. In addition, for every dollar increase in the generic drug copayment, there were lower odds of being initiated within 6 months (OR 0.96 [95% CI 0.95, 0.98]; $P < 0.01$). Each additional office visit was also associated with greater odds of initiation (OR 1.15 [95% CI 1.12, 1.17]; $P < 0.01$). Hyperlipidemia was the only comorbidity associated with higher odds of initiation (OR 1.21 [95% CI 1.34, 1.25]; $P < 0.01$). Overall, patient characteristics explained 7.96% of the variation in antidiabetic therapy initiation.

Multivariable analysis of patient characteristics associated with intensification revealed similar findings compared with the analysis of therapy initiation (Table 4). Again, for every percentage increase in HbA_{1c} , there were higher odds of intensification of antidiabetic therapy (OR 1.10 [95% CI 1.06, 1.14]; $P < 0.01$), and for every dollar increase in the generic drug copayment, there were lower odds of therapy being intensified within 6 months (OR 0.97 [95% CI 0.95, 0.98]; $P < 0.01$). Each additional office visit was again associated with greater odds of intensification (OR 1.10 [95% CI 1.08, 1.13]; $P < 0.01$). Compared with those in the highest quartile for adherence, those in the lowest adherence quartile had the lowest odds of intensification (OR 0.45 [95% CI 0.38, 0.53]; $P < 0.01$). In contrast, compared with those on the lowest doses of existing therapy, those on the higher doses of existing therapy had the lower odds of intensification (OR 0.58 [95% CI 0.49, 0.67]; $P < 0.01$). Finally, as compared with existing therapy with a first-generation drug, existing therapy with a second-generation drug was associated with almost double the odds of intensification (OR 1.91 [95% CI 1.62, 2.26]; $P < 0.01$). Patient characteristics explained 7.35% of the variation in antidiabetic therapy intensification.

CONCLUSIONS

Initiation and intensification of antidiabetic therapy are important for optimal

Table 1—Rates of initiation and intensification of pharmacologic therapy

	2008	2015	Total 2008–2015
Initiation of therapy			
<i>N</i> (on no drugs, with $\text{HbA}_{1c} \geq 8\%$ [64 mmol/mol])	254	1,705	9,799
Initiation within 6 months of index date, <i>n</i> (%) [*]	125 (49)	1,176 (69)	6,140 (63)
Within 3 months	105 (84)	1,027 (87)	5,131 (84)
Between 4 and 6 months	20 (16)	149 (13)	1,009 (16)
Intensification of therapy			
<i>N</i> (on one noninsulin drug, with $\text{HbA}_{1c} \geq 8\%$ [64 mmol/mol])	190	2,780	10,941
Intensification within 6 months of index date, <i>n</i> (%) [*]	145 (76)	2,377 (86)	8,972 (82)
Within 3 months	127 (88)	2,192 (92)	8,026 (89)
Between 4 and 6 months	18 (12)	185 (8)	946 (11)

^{*}Index date is date of HbA_{1c} level $\geq 8\%$ (64 mmol/mol).

Table 2—Baseline characteristics of beneficiaries who had antidiabetic therapy initiated or intensified vs. not within 6 months after HbA_{1c} ≥8% (64 mmol/mol), 2008–2015

	Initiation cohort		Intensification cohort	
	Initiated	Not initiated	Intensified	Not intensified
<i>N</i> (total)	6,140	3,659	8,972	1,969
Age-group (years)				
18–30	171 (63)	99 (37)	78 (75)	26 (25)
31–40	826 (66)	418 (34)	610 (76)	189 (24)
41–50	1,969 (64)	1,111 (36)	2,303 (81)	544 (19)
51–60	2,461 (62)	1,501 (38)	4,277 (83)	871 (17)
61–65	713 (57)	530 (43)	1,704 (83)	339 (17)
Sex				
Male	3,626 (63)	2,146 (37)	5,301 (82)	1,125 (18)
Female	2,514 (62)	1,513 (38)	3,671 (81)	844 (19)
Race, %*				
White	64	62	65	63
Black	18	20	17	19
Hispanic/Latino	21	21	20	20
SES*				
Percent below poverty	15	15	14	15
Percent college educated	28	27	28	28
Population density				
Urban	5,591 (62)	3,373 (38)	8,170 (82)	1,779 (18)
Rural	5,591 (62)	261 (34)	725 (81)	175 (19)
Unknown	40 (62)	25 (38)	77 (84)	15 (16)
Geographic region				
Midwest	504 (63)	298 (37)	855 (83)	180 (17)
Northeast	1,362 (55)	1,115 (45)	2,002 (81)	469 (19)
South	3,049 (65)	1,676 (35)	4,296 (82)	937 (18)
West	1,221 (68)	565 (32)	1,813 (83)	381 (17)
Unknown	4 (44)	5 (56)	6 (75)	2 (25)
Comorbidities				
HTN	3,459 (64)	1,948 (36)	5,924 (83)	1,209 (17)
HL	3,675 (65)	1,963 (35)	6,087 (84)	1,202 (16)
CKD	180 (64)	103 (36)	475 (87)	68 (13)
COPD	161 (66)	82 (34)	257 (86)	42 (14)
HF	158 (60)	107 (40)	303 (82)	65 (18)
IHD/CAD	467 (62)	291 (38)	936 (85)	162 (15)
Average generic drug copay, \$†	9.66	10.23	9.37	9.85
Average branded drug copay, \$†	49.73	49.95	48.68	49.11
No. of office visits within 6 months after index date‡	2.91	2.04	2.84	2.17
Average index date HbA _{1c} level, %	10.42	9.98	9.61	9.56
DxCG risk score§	2.23	2.00	2.47	2.18
Adherence quartile				
First	NA	NA	2,349 (87)	360 (13)
Second	NA	NA	2,337 (85)	403 (15)
Third	NA	NA	2,254 (81)	520 (19)
Fourth	NA	NA	2,032 (75)	686 (25)
Top quartile of dosing for initial antidiabetic drug	NA	NA	7,082 (81)	1,704 (19)
Initial antidiabetic drug				
First generation	NA	NA	7,178 (80)	1,760 (20)
Second generation	NA	NA	1,794 (90)	209 (10)

Data are *n* (%) unless otherwise indicated. CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; HL, hyperlipidemia; HTN, hypertension; IHD, ischemic heart disease; NA, not applicable; SES, socioeconomic status. *Race and SES are calculated using the beneficiary's zip code and census averages for the beneficiary's zip code. †Average copay for drugs in each member's health plan. ‡Number of office visits within 6 months after index date of elevated HbA_{1c} level. §DxCG risk score is an overall measure of medical complexity. ||Initial drug is the first diabetes drug a patient is prescribed—the one noninsulin diabetes drug they are already taking on the index date. First-generation antidiabetic drugs include metformin, sulfonylureas, thiazolidinediones, α -glucosidase inhibitors, and meglitinides. Second-generation antidiabetic drugs include amylin analogs, GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors.

Table 3—Characteristics associated with initiation within 6 months after HbA_{1c} ≥8% (64 mmol/mol)

Characteristic	OR	95% CI	P value
Age	0.99	0.99, 1.00	<0.01
Sex (male vs. female)	1.06	0.96, 1.16	0.28
Race/ethnicity			
White	1.00	1.00, 1.01	0.68
Black	1.00	0.99, 1.00	0.47
Hispanic	1.00	0.99, 1.00	0.21
Socioeconomics			
Percent below poverty	1.00	0.99, 1.00	0.19
Percent college educated	1.00	1.00, 1.00	0.72
Population density (urban vs. rural)	0.97	0.79, 1.19	0.76
Geography			
Northeast vs. West	0.53	0.45, 0.62	<0.01
Midwest vs. West	0.69	0.56, 0.86	<0.01
South vs. West	0.77	0.65, 0.90	<0.01
Comorbidities			
Hypertension	1.01	0.91, 1.12	0.85
Hyperlipidemia	1.21	1.09, 1.34	<0.01
Chronic kidney disease	0.89	0.66, 1.21	0.46
COPD	0.96	0.69, 1.31	0.78
Heart failure	0.79	0.57, 1.08	0.14
IHD/CAD	0.92	0.76, 1.12	0.41
Overall risk score*	0.99	0.98, 1.01	0.39
Index HbA _{1c} level	1.15	1.12, 1.18	<0.01
Average generic drug copay†	0.96	0.95, 0.98	<0.01
Average branded drug copay†	1.00	1.00, 1.00	0.07
Office visits‡	1.15	1.12, 1.17	<0.01

Adjusted R²: 7.96%. CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease. *DxCg risk score (generated using proprietary DxCg algorithm of risk factors and comorbidities). †Average copay for drugs in each member's health insurance plan. ‡Number of office visits within 6 months after index date of elevated HbA_{1c} test.

management of diabetes. Though we observe rates improving over time, the rate of antidiabetic therapy initiation within 6 months of an HbA_{1c} ≥8% (64 mmol/mol) was only 63%, and the rate of intensification was 82%. Patient factors associated with higher rates of both initiation and intensification include higher index HbA_{1c} levels, lower generic drug copayments, and more frequent office visits. Better adherence, lower doses of existing therapy, and existing therapy with a second-generation drug were also associated with higher rates of intensification. Overall, however, patient factors explained <8% of the variation observed.

Prior studies of antidiabetic therapy initiation from the U.K. have relied on diagnostic codes (i.e., medical claims) to define the appropriate timing of antidiabetic therapy initiation or intensification (26). However, this study was able to define its initiation and intensification cohorts using linked laboratory results and an HbA_{1c} threshold of ≥8% (64 mmol/mol), and thus these results may be more clinically relevant. Older

work from 1996 to 1998 in the U.S., using data from the American Medical Group Association on ~5,000 patients, found that 54% of patients with an elevated HbA_{1c} ≥8% (64 mmol/mol) did not have their therapy intensified within 90 days (27). Thus, our study suggests improvements in intensification rates in the U.S. since then.

In this study, we found modest associations between lower generic drug copays and higher rates of both initiation and intensification. Although prior studies have demonstrated an association between lower drug copayments and better adherence to chronic medications (28–30), much of this work has not been specific to diabetes. The limited prior work specific to diabetes, however, has also found that higher copayments decrease adherence to oral antidiabetic therapy over time (31). Our study confirms these prior studies and extends the knowledge in this field by highlighting the impact on both initiation and intensification rates with higher generic drug copayments, even among commercially

insured patients with diabetes. This may have important implications for commercial payers and ongoing efforts to use value-based insurance design in copayments for chronic illness.

We found a strong association between adherence and intensification, a finding that confirms the work of Grant et al. (25) and extends it to a nationally representative population. The underlying mechanism for this association is unclear. However, one hypothesis is that if physicians are unsure what a patient is actually taking, escalation may not be appropriate. Moreover, before further uptitrating therapy, providers may appropriately choose to focus on increasing adherence to existing therapy. In addition, we also found a strong novel association between existing second-generation drug monotherapy and higher rates of therapy intensification. The explanation for this is also unclear, but because specialists are more apt to prescribe second-generation drugs, this observation may point to the importance of provider characteristics in determining practice variation. We also noted another strong novel association between higher doses of existing therapy (for any drug) and lower rates of intensification. This finding may suggest a reluctance on the part of providers to aggressively increase therapy for those receiving high drug doses or may simply reflect the higher clinical inertia that surrounds the addition of a new drug.

Patient factors considered in this study explained only 7–8% of the variation observed in initiation and intensification. Based on this finding, we hypothesize that much of the variation in treatment escalation may be driven by other, unmeasured patient, physician, and/or practice characteristics. There has been some prior work examining the provider and practice/system characteristics associated with antidiabetic treatment patterns. For example, prior work has found that diabetes-focused nurses and clinics may decrease clinical inertia (32), but other physician, practice, and health system factors have not been well studied. Additional examination of these potential drivers of practice variation could enable the optimization of quality improvement programs and the improvement of existing quality metrics for diabetes care.

Importantly, these findings are unique to a population of patients in the U.S. with commercial insurance and may not

Table 4—Characteristics associated with intensification within 6 months after HbA_{1c} ≥8% (64 mmol/mol)

Characteristic	OR	95% CI	P value
Age	1.01	1.00, 1.02	0.01
Sex (male vs. female)	1.10	0.99, 1.23	0.09
Race/ethnicity			
White	1.00	0.99, 1.00	0.41
Black	1.00	0.99, 1.00	0.49
Hispanic	1.00	1.00, 1.01	0.20
Socioeconomics			
Percent below poverty	0.99	0.98, 1.00	0.05
Percent college educated	1.00	0.99, 1.00	0.26
Population density (urban vs. rural)	1.10	0.88, 1.38	0.39
Geography			
Northeast vs. West	1.02	0.80, 1.30	0.90
Midwest vs. West	0.80	0.67, 0.96	0.02
South vs. West	0.93	0.77, 1.11	0.41
Comorbidities			
Hypertension	1.00	0.88, 1.13	0.94
Hyperlipidemia	1.18	1.04, 1.34	0.01
Chronic kidney disease	1.22	0.90, 1.64	0.20
COPD	1.17	0.80, 1.71	0.41
Heart failure	0.78	0.57, 1.09	0.14
IHD/CAD	1.05	0.85, 1.29	0.65
Overall risk score*	0.99	0.98, 1.01	0.26
Index HbA _{1c} level	1.10	1.06, 1.14	<0.01
Average generic drug copay†	0.97	0.95, 0.98	<0.01
Average branded drug copay†	1.00	1.00, 1.01	0.05
Office visits‡	1.10	1.08, 1.13	<0.01
PDC quartile (fourth vs. first)§	0.45	0.38, 0.53	<0.01
PDC quartile (third vs. first)	0.67	0.57, 0.79	<0.01
PDC quartile (second vs. first)	0.87	0.74, 1.03	0.10
Existing therapy (second vs. first generation)	1.91	1.62, 2.26	<0.01
Top quartile of dosing for existing therapy	0.58	0.49, 0.67	<0.01

Adjusted R^2 : 7.35%. CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; PDC, percent days covered. *DxCG risk score (generated using proprietary DxCG algorithm of risk factors and comorbidities). †Average copay for drugs in each member's health insurance plan. ‡Number of office visits within 6 months after index date of elevated HbA_{1c} level. §PDC is a measure of adherence. The first quartile is the highest (best) adherence group, and the fourth quartile is the lowest (worst) adherence group. ||Existing therapy is the first diabetes drug a patient is prescribed—the one noninsulin antidiabetic drug they are already taking on the index date. First-generation diabetes drugs include metformin, sulfonylureas, thiazolidinediones, α -glucosidase inhibitors, and meglitinides. Second-generation diabetes drugs include amylin analogs, GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors. Combination drugs include therapies with two active antidiabetic drugs and are considered second-generation drugs if either of the two active antidiabetic drugs is a second-generation drug.

generalize to patients with other forms of insurance. In addition, although this study uses data from a very large, national insurer, it may not generalize to other insurers. Although this study combines medical claims, laboratory, and pharmacy data, as in all studies of this nature we lack the granular information of medical records and thus the ability to measure other patient factors such as expectations, preferences, and health literacy or provider factors such as medications prescribed but never filled. In addition, because of the fragmented nature of commercial claims, we are not able to

determine the duration of patients' elevated HbA_{1c} levels, review previously trialed therapies, or reliably exclude pregnant patients. Although the treatment strategy and glycemic targets in pregnancy are different from those of nonpregnant adults, we estimate that this population is small and would be unlikely to have a meaningful impact on the outcomes of the study. To control for disease duration and/or severity, we limited the intensification analysis to individuals on only one noninsulin antidiabetic drug. Finally, we did not allow time for lifestyle changes after an elevated

HbA_{1c} owing to the uncertainty that surrounds for how long this should be allowed to continue before the initiation of medications (33). The 2018 American Diabetes Association Standards of Care now recommend initiation of therapy for anyone with a diagnosis of type 2 diabetes and an HbA_{1c} >7% (53 mmol/mol), absent contraindications. Thus, our purposefully high HbA_{1c} of \geq 8% (64 mmol/mol), if anything, renders our estimates conservative.

In conclusion, the average rate of initiation of antidiabetic therapy within 6 months after an HbA_{1c} \geq 8% (64 mmol/mol) among commercially insured Americans is only 63% but has risen over the past 8 years. The rate of intensification within 6 months after an HbA_{1c} \geq 8% (64 mmol/mol) is 82% and has also risen (though less) over the past 8 years. Higher index HbA_{1c} levels, lower generic prescription drug copayments, and more frequent office visits are associated with higher rates of antidiabetic therapy initiation and intensification. Patient adherence and existing therapy choice and dosing also appear to impact the rate of intensification among those already on one antidiabetic therapy. Taken together, however, the patient factors considered in this study, derived from linking medical, laboratory, and pharmacy data from a large, commercial insurer, explain only 7.96% of the variation in initiation and 7.35% of the variation in intensification. Additional work to examine whether other patient, physician, or practice factors explain more of the variation in antidiabetic treatment patterns should be considered to optimize quality improvement efforts, refine existing quality metrics, and improve care of patients with diabetes.

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assisted with revision of the introduction and conclusions and provided diabetes and endocrinology expertise to the study team. M.E.C. assisted with study design, reviewed and edited the manuscript, and contributed to the conclusions section. M.E.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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