Title

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DIABETES AND AGING

Trends in Drug Utilization, Glycemic Control, and Rates of Severe Hypoglycemia, 2006–2013

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OBJECTIVE

To examine temporal trends in utilization of glucose-lowering medications, glycemic control, and rate of severe hypoglycemia among patients with type 2 diabetes (T2DM).

RESEARCH DESIGN AND METHODS

Using claims data from 1.66 million privately insured and Medicare Advantage patients with T2DM from 2006 to 2013, we estimated the annual *1*) age- and sex-standardized proportion of patients who filled each class of agents; *2*) age-, sex-, race-, and region-standardized proportion with hemoglobin A_{1c} (HbA_{1c}) <6%, 6 to <7%, 7 to <8%, 8 to <9%, ≥9%; and *3*) age- and sex-standardized rate of severe hypoglycemia among those using medications. Proportions were calculated overall and stratified by age-group (18–44, 45–64, 65–74, and ≥75 years) and number of chronic comorbidities (zero, one, and two or more).

RESULTS

From 2006 to 2013, use increased for metformin (from 47.6 to 53.5%), dipeptidyl peptidase 4 inhibitors (0.5 to 14.9%), and insulin (17.1 to 23.0%) but declined for sulfonylureas (38.8 to 30.8%) and thiazolidinediones (28.5 to 5.6%; all $P < 0.001$). The proportion of patients with HbA_{1c} <7% declined (from 56.4 to 54.2%; $P < 0.001$) and with HbA_{1c} ≥9% increased (9.9 to 12.2%; $P < 0.001$). Glycemic control varied by age and was poor among 23.3% of the youngest and 6.3% of the oldest patients in 2013. The overall rate of severe hypoglycemia remained the same (1.3 per 100 person-years; $P = 0.72$), declined modestly among the oldest patients (from 2.9 to 2.3; $P < 0.001$), and remained high among those with two or more comorbidities (3.2 to 3.5; $P = 0.36$).

CONCLUSIONS

During the recent 8-year period, the use of glucose-lowering drugs has changed dramatically among patients with T2DM. Overall glycemic control has not improved and remains poor among nearly a quarter of the youngest patients. The overall rate of severe hypoglycemia remains largely unchanged.

Glycemic management of type 2 diabetes (T2DM) has changed considerably over the past decade (1,2). Clinicians and patients can now choose from 12 different classes of glucose-lowering medications to manage hyperglycemia. Unlike insulin or sulfonylurea drugs, most of the newer agents have not been implicated as a cause of hypoglycemia, which can be a serious complication of glucose-lowering therapy, particularly in the elderly (3). However, utilization of these newer agents has significantly contributed to increasing costs of diabetes management (4,5).

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In addition to changes in drug therapies to reduce glucose levels, the recommended target glucose levels have changed as well. In 2009, based on new evidence from randomized clinical trials (6–8), the American Diabetes Association (ADA) clinical practice guidelines specifically recommended individualization of glycemic targets according to age and multimorbidity (9). In 2012, the ADA and the American Geriatrics Society developed a consensus statement that recognized that older adults with life-limiting comorbidities are less likely to benefit from tight glycemic control (i.e., reaching a hemoglobin A_{1c} [HbA_{1c}] <7%) and are more vulnerable to hypoglycemia compared with younger, healthier patients (10). Therefore, less stringent glycemic targets (i.e., HbA_{1c} <8 or <9%) may be appropriate in older patients, particularly in those with multiple chronic conditions and established vascular complications (11).

Given these changes in management approaches, it is important to examine the temporal trends in glucose-lowering medication use, as well as resultant glycemic control and rates of severe hypoglycemia. These trends provide information about care patterns in response to changes in treatment options and treatment targets and can identify gaps in diabetes care and areas for potential improvement.

A number of studies have separately examined some of these trends (2,12–16). Data from physician audits have shown that patients with diabetes are being prescribed an increasing number of glucose-lowering medications in ambulatory care settings (1,2). Separate analysis of data from the National Health and Nutrition Examination Survey (NHANES) suggested that glycemic control has improved, and just over half of patients achieved an HbA_{1c} <7% in 2007–2010 (13). Several other studies indicated that treatment-related hypoglycemia continues to pose a significant health threat, particularly for older adults and for those with multiple chronic conditions (12,14,15,17,18).

However, studies looking at medication prescribing patterns were conducted at different times and in different patient populations compared with the studies looking at glycemic control, precluding potential inferences about any association between medication use, glycemic control, and hypoglycemia. Moreover, they did not examine how these trends differ across age and comorbidity subgroups.

Accordingly, we examined trends in utilization of drug treatment for diabetes, as well as concurrent trends in glycemic control and rates of hypoglycemia among privately insured and Medicare Advantage patients with T2DM from geographically diverse regions across the U.S. using OptumLabs Data Warehouse (OLDW). We examined these trends in the overall population and in subgroups of younger and older patients and among patients with a varying number of other serious chronic conditions.

RESEARCH DESIGN AND METHODS
Data Source
We conducted a retrospective analysis of medical and pharmacy administrative claims from a large database, OLDW, which includes privately insured and Medicare Advantage enrollees throughout the U.S. (19). The database contains data on more than 100 million enrollees from geographically diverse regions across the U.S., with the greatest representation from the South and Midwest (20). We included commercial health plans in OLDW that provided full coverage for inpatient, outpatient, and pharmacy services. Medical claims from inpatient and outpatient visits include ICD-9-CM (ICD-9, clinical modification) diagnosis codes, ICD-9 procedure codes, Current Procedural Terminology, version 4 procedure codes, Healthcare Common Procedure Coding System procedure codes, site of service codes, and provider specialty codes. Pharmacy claims include information on medications dispensed and size and dates of prescriptions. Study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996. Because this study involved an analysis of preexisting, de-identified data, it was exempt from institutional review board approval.

Study Population
All adults (age ≥18 years) with at least 1 year of continuous enrollment between 2006 and 2013 were included if they met criteria for T2DM during at least 1 year of the study period. The definition of diabetes was based on Health Plan Employer Data and Information Set criteria: two face-to-face encounters with a diagnosis of diabetes (ICD-9 codes 250.x, 357.2, 362.0, and 366.41 [21] in any position on the claim [22–24]) on different dates of service in an outpatient setting or nonacute inpatient setting, or one face-to-face encounter in an acute inpatient or emergency department (ED) setting, or use of insulin or oral antihyperglycemic agents (except metformin monotherapy) based on pharmacy data. We examined claims for diabetes ICD-9 codes over a 2-year period, which included the year of interest and the preceding year. Once patients met criteria for diabetes in 1 year, they were considered to have the diagnosis in subsequent years. We excluded adults with a diagnosis of gestational diabetes (ICD-9 code 648.0) and those with codes for T1DM (250.x1 and 250.x3). If patients had codes for both T1DM and T2DM, we excluded patients who had no claims for oral glucose-lowering medications.

Main Outcomes
In each year, we determined the proportion of the study population with one or more pharmacy fills for the different classes of glucose-lowering agents. Combination agents were counted as two different agents filled on the same date. Because patients could fill more than one class of agent during each year, the proportion of patients in each year could exceed 100%. Because patterns of medication fills may change over time, we also calculated the mean number of days covered for each oral glucose-lowering class of medications in each year based on the date of fill and days' supply. In each year, we determined glycemic control category (HbA_{1c} <6, 6 to <7, 7 to <8, 8 to <9, or ≥9%) based on the last HbA_{1c} obtained during that calendar year. Data for HbA_{1c} were available for a subset of patients based on specific lab vendor. In each year, we also determined rates of severe hypoglycemia requiring ED visit or hospital admission or observation stay based on validated principal discharge diagnosis ICD-9 codes (25) among people who filled at least one glucose-lowering agent. These values were reported as events per 100 person-years at risk. Person-years at risk were calculated based on days the patient was alive, enrolled in the health plan, and not hospitalized. A separate analysis was performed among people who filled insulin or insulin secretagogues, other glucose-lowering medications, and no diabetes agents.

Independent Variables
Independent variables included baseline age (18–44, 45–64, 65–74, and ≥75 years), sex, race (white, black, Hispanic, Asian, or unknown), region (Midwest,

Northeast, South, and West), and the number of serious chronic conditions (zero, one, and two or more). The serious chronic conditions were based on ICD-9 codes and included chronic kidney disease, chronic lung disease, heart failure, myocardial infarction or coronary artery disease, dementia, depression, atrial fibrillation, and stroke (see Supplementary Table 1 for definitions). Household income was based on data from AmeriLINK (obtained through KnowledgeBase Marketing) and linked to claims data.

Statistical Analyses

We summarized the characteristics of the cohort by year. For drug utilization, glycemic control, and rates of severe hypoglycemia, we calculated age- and sex-standardized rates for each year using 2013 as the reference year. Because HbA_{1c} was available only for a subset of the total sample, which varied nonrandomly by year, we estimated the annual proportions of patients in each glycemic control category using multinomial logistic regression with HbA_{1c} category as the outcome and age, sex, race, and region as independent variables. We used this model to estimate the HbA_{1c} category distribution for each year. We used logistic regression to assess annual trends in the use of each diabetes medication class and assess trends in each glycemic control category from 2006 to 2013. The trend in the number of hypoglycemia events was assessed using linear regression.

Sensitivity Analyses

Some patients were captured in multiple years of data, raising concern that increasing disease severity over time could contribute to secular trends. We performed sensitivity analyses that included only 1 year of data per patient, selected at random from all available years for that patient (2006–2013). Analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC) and Stata 14.1 (Stata Corp, College Station, TX).

RESULTS

There were 1,657,610 unique patients with T2DM who met the inclusion criteria between 2006 and 2013. Among the study cohort, 33.7% were included in 1 year only, 25.1% were included in 2 years only, and 41.2% were included in 3 or more years.

From 2006 to 2013, as the OLDW expanded, and as diabetes prevalence

increased, the number of patients with T2DM who contributed data nearly doubled, from ~385,000 in 2006 to ~700,000 in 2013 (Table 1). Most notably, the annual proportion of patients aged 65–74 years and 75 years or older increased over this 8-year period as OLDW captured an increasing number of Medicare Advantage enrollees. The burden of comorbidities and the proportion of patients with two or more serious chronic conditions also increased during the observation period.

Drug Utilization

Standardized utilization trends are shown in Fig. 1 and Supplementary Table 2. From 2006 to 2013, use increased for metformin (from 47.6 to 53.5%), dipeptidyl peptidase 4 (DPP-4) inhibitors (0.5 to 14.9%), glucagon-like peptide 1 agonists (3.3 to 5.0%), and insulin (17.1 to 23.0%) but declined for sulfonylureas (38.8 to 30.8%) and thiazolidinediones (28.5 to 5.6%; all $P < 0.001$). The increased utilization of insulin was primarily driven by adoption of basal insulin analogs (10.9 to 19.3%; $P < 0.001$) and rapid-acting insulin analogs (6.7 to 11.6%; $P < 0.001$). The use of human insulin products actually declined (11.6 to 5.6%; $P < 0.001$). The proportion of patients with a diagnosis of diabetes who did not fill any glucose-lowering medications declined slightly (25.7 to 24.1%; $P < 0.001$). When considering treatment complexity, the use of oral monotherapy increased slightly (from 24.3 to 26.4%) and the use of multiple (two or more) oral agents declined (from 33.0 to 26.5%), whereas the use of insulin alone and in combination with oral agents increased (from 6.0 to 8.5% and from 11.1 to 14.6%, respectively; all P values <0.001).

The mean number of days covered for each class of oral glucose-lowering medications per year increased over the study period (Supplementary Table 3), even for drug classes with reduced rates of utilization.

Drug utilization varied by age, but overall trends were qualitatively similar (Supplementary Table 4). The use of metformin was most prevalent among the youngest age-group (18–44 years). Among the oldest patients, metformin surpassed sulfonylureas as the most prevalent diabetes drug class after 2010. DPP-4 inhibitor use increased among all age subgroups, with the highest rates of use among middle-age patients (45–64 years) in 2013. Use of any insulin increased across all

age subgroups, most steeply among middle-age and older patients.

Drug utilization also varied by comorbidity burden (Supplementary Table 5). Among patients with two or more serious comorbidities, metformin, insulin, and sulfonylureas were all used to a similar extent, with a slight increase in metformin and insulin use and slight decline in sulfonylureas by 2013.

Glycemic Control

Laboratory testing for HbA_{1c} was available on a subset of the total sample (25.6%). There were regional differences among patients with and without HbA_{1c} available (Supplementary Table 6).

Standardized rates of glycemic control are shown in Fig. 2. From 2006 to 2013, there were increasing trends in the proportion of patients with $HbA_{1c} \geq 9\%$ and HbA_{1c} 8 to $<9\%$ (from 9.9 to 12.2% and 9.9 to 10.6%, respectively; $P < 0.001$). The trend in the proportion of patients with HbA_{1c} 7 to $<8\%$ was not significant (from 23.8 to 23.0%; $P = 0.31$). In contrast, there were decreasing trends in the proportion with HbA_{1c} 6 to $<7\%$ (41.1 to 43.1%) and $HbA_{1c} <6\%$ (15.3 to 13.1%; both $P < 0.001$). Of note, the overall slight decreasing trend for HbA_{1c} 6 to $<7\%$ occurred despite a slightly higher proportion of patients in this glycemic category in 2013. Finally, the overall proportion of patients with $HbA_{1c} <7\%$ declined over this 8-year period: 56.4% in 2006 and 54.2% in 2013, $P < 0.001$.

Glycemic control varied by age (Supplementary Fig. 1) and number of serious comorbidities (Supplementary Fig. 2). Poor glycemic control ($HbA_{1c} \geq 9\%$) was most common among the youngest patients but increased slightly over time across all age subgroups (among the youngest: 21.1 to 23.3%, $P = 0.001$; and among the oldest: 5.3 to 6.3%, $P < 0.001$). Similarly, poor glycemic control was most common among patients without comorbidities but increased slightly across all comorbidity subgroups (no comorbidities: 14.0 to 14.8%, one comorbidity: 12.0 to 12.5%, and two or more comorbidities: 10.6 to 11.8%; all $P < 0.001$).

Severe Hypoglycemia

The age- and sex-standardized rate of severe hypoglycemia among people who filled at least one prescription for diabetes medications was 1.3 events per 100 person-years in both years 2006 and 2013 (P value for trend over time 0.72)

Table 1—Characteristics of privately insured patients with T2DM included in the study, 2006–2013

	2006	2007	2008	2009	2010	2011	2012	2013
Total, n	384,964	447,634	469,528	538,239	593,422	642,817	682,310	700,117
Age (years)								
18–44	15.0	14.1	13.4	11.7	10.1	9.3	8.5	8.0
45–64	58.7	56.3	54.9	50.3	45.8	44.0	41.6	41.1
65–74	14.8	16.5	17.7	21.3	25.0	26.7	28.7	29.1
≥75	11.5	13.1	14.0	16.7	19.0	20.0	21.2	21.7
Sex								
Female	47.3	48.2	48.3	48.8	49.2	49.3	49.2	49.0
Male	52.7	51.8	51.7	51.2	50.8	50.7	50.8	51.0
Race								
White	63.3	64.6	66.2	66.4	67.5	67.3	67.1	64.1
Black	9.6	10.5	11.2	13.1	13.6	14.0	14.1	15.9
Hispanic	10.4	10.9	11.0	10.7	9.8	9.8	9.7	10.8
Asian	4.2	4.5	4.7	4.5	4.3	4.3	4.3	4.5
Unknown	12.5	9.5	6.9	5.4	4.8	4.7	4.8	4.8
Region								
Midwest	25.0	22.6	22.3	23.0	23.6	24.2	24.8	25.5
Northeast	19.1	19.5	20.0	18.8	17.9	19.7	20.5	20.3
South	40.1	42.3	43.0	44.4	45.7	44.7	43.5	43.0
West	14.9	14.2	13.1	12.6	12.0	10.8	10.6	10.6
Unknown	0.9	1.4	1.7	1.3	0.7	0.6	0.6	0.6
Household income ($)								
<40K	14.5	18.5	22.5	26.1	28.5	28.6	28.7	28.4
40–49K	5.2	6.3	7.6	8.5	8.8	9.0	9.1	9.3
50–59K	5.0	5.9	7.2	7.9	8.1	8.2	8.3	8.4
60–74K	6.7	7.8	9.5	10.2	10.2	10.4	10.5	10.6
75–99K	8.9	10.5	12.6	13.2	12.9	13.1	13.0	13.1
≥100K	17.2	19.7	23.3	23.6	22.3	22.2	22.0	21.8
Unknown	42.5	31.3	17.3	10.4	9.2	8.4	8.5	8.4
Comorbidities								
CAD/MI	18.7	19.1	19.7	21.1	21.8	21.9	22.0	21.9
CHF	8.3	8.7	8.8	9.7	10.2	10.4	10.6	10.7
Lung disease	13.8	14.5	15.3	16.4	17.0	17.2	17.7	18.0
CKD	6.1	6.9	7.9	9.8	11.1	11.9	12.8	13.9
Depression	6.1	6.3	6.5	7.2	7.5	7.7	8.1	8.4
Dementia	2.4	2.8	3.0	3.4	3.6	3.8	4.3	4.5
Stroke	2.9	3.1	3.2	3.5	3.6	3.6	3.8	3.9
Atrial fibrillation	4.5	5.0	5.3	6.1	6.9	7.3	7.7	8.0
Number of chronic conditions								
0	61.9	60.6	59.0	55.8	54.0	53.1	52.1	51.3
1	23.2	23.5	24.4	25.3	25.8	26.0	26.1	26.2
≥2	14.9	15.9	16.6	18.9	20.2	20.9	21.8	22.5

Data are presented as % unless otherwise indicated. CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; MI, myocardial infarction.

(Fig. 3A). The proportion of severe hypoglycemia that led to hospital admission declined from 19.2 to 18.2% over this time period. Rates of severe hypoglycemia among patients using insulin or insulin secretagogues or other glucose-lowering agents and among those who filled no medications are shown in Fig. 3B.

Rates of severe hypoglycemia were highest among the oldest patients and those with multiple comorbidities compared with younger, healthier adults (Supplementary Figs. 3 and 4). Rates of severe hypoglycemia increased slightly among the youngest (from 0.8 to 0.9 events per 100 person-years; $P = 0.025$) and middle-age (0.6 to 0.9 events per 100 person-years; $P < 0.001$) patients and decreased among the older (1.4 to 1.3 events per 100 person-years; $P < 0.001$) and oldest (2.9 to 2.3 events per 100 person-years; $P < 0.001$) patients over the study period. Rates of severe hypoglycemia were also highest among patients with two or more comorbidities compared with those with one or no comorbidities and did not significantly change over time (3.2 to 3.5 events per 100 person-years; $P = 0.36$).

Sensitivity Analyses

Analyses that included only 1 year of data per patient showed qualitatively similar results for trends in glycemic control (Supplementary Table 7). However, in analyses of severe hypoglycemia, the standardized rate decreased from 1.5 to 1.2 events per 100 person-years with a trend P value of <0.01 (Supplementary Fig. 5).

CONCLUSIONS

The landscape of glucose-lowering medications available for T2DM has changed
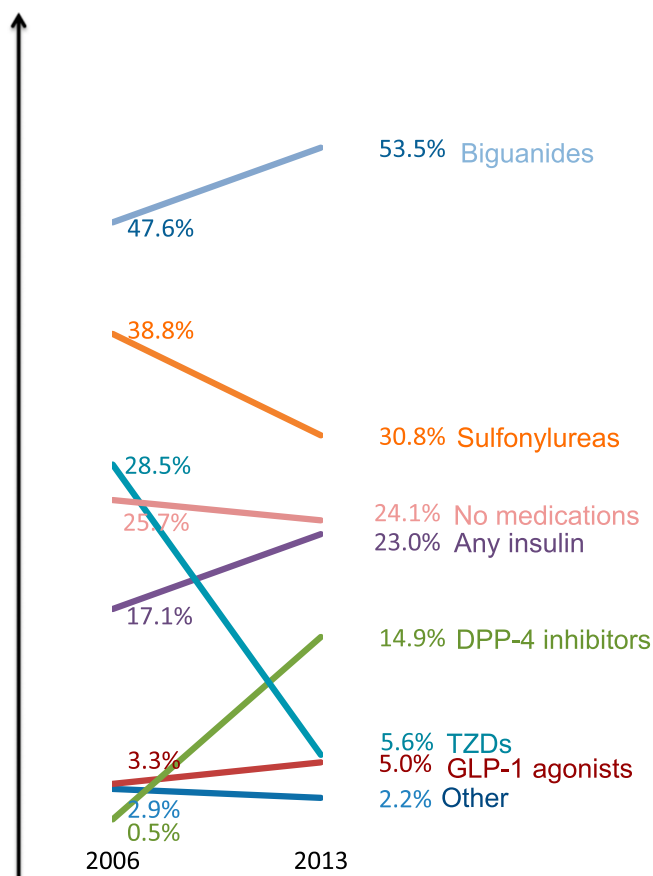
Figure 1—Age- and sex-standardized proportion of patients with T2DM who filled each class of glucose-lowering agents, 2006 and 2013 (see Supplementary Table 2 for annual data). Since patients may fill more than one class in each year, percentages do not add up to 100%. Other medications were comprised of meglitinides, α-glucosidase inhibitors, SGLT-2 inhibitors, and amylin analogs. Patients with no fills for glucose-lowering medications were included in the "No medications" group.

dramatically over the past two decades. From 2006 to 2013, utilization of newer glucose-lowering agents, such as DPP-4 inhibitors and newer insulin analogs and their formulations, increased considerably among privately insured patients with T2DM. The use of older classes of medications, such as sulfonylureas and thiazolidinediones, declined. During this time, glycemic control of T2DM did not improve in the overall population and remained poor among nearly a quarter of the youngest patients. Rates of severe hypoglycemia remained largely unchanged, with the oldest patients and those with multiple comorbidities at highest risk. These findings raise questions about the value of the observed shifts in drug utilization toward newer and costlier medications.

Our findings are consistent with a prior study of drug prescribing in U.S. ambulatory practice conducted from 1997 to 2012 (2).

In that study, similar increases in DPP-4 inhibitor and insulin analog prescribing were observed; these changes were accompanied by a 61% increase in drug expenditures (2). Our study extends these findings to drug utilization and demonstrates that these increases occurred in all age and comorbidity subgroups.

In contrast, metformin use increased only modestly between 2006 and 2013 and remained relatively low among older patients and those with two or more comorbidities. Although metformin is recommended as first-line therapy (26), it may be underutilized as the initial agent for the treatment of T2DM (27). Its use may be additionally limited by coexisting contraindications, such as chronic kidney disease (28). Recently, the U.S. Food and Drug Administration (FDA) issued a labeling change, congruent with recommendations from the ADA (26), which permits cautious use of metformin in those with

mild to moderate kidney disease (29). As a result, it is possible that use of metformin in these patients may increase further.

We found no overall improvements in glycemic control among patients with T2DM; in fact, the proportion of patients with poor glycemic control increased. A prior study based on NHANES data showed an overall 8% increase in the proportion of patients with HbA_{1c} <7% from 1999–2002 to 2007–2010 (13). However, the increase occurred early on in the study, with no significant change in this proportion from 2003–2006 to 2007–2010. It is possible that enthusiasm for intensive glycemic control may have been dampened by the findings of increased mortality with this strategy in one trial published in 2008 (8) and the lack of cardiovascular benefit reported in two others (6,7). In addition, the expected glucose-lowering efficacy associated with some newer agents, such as the DPP-4 inhibitors, may be relatively modest (30). In our study, the mean number of days covered for each class of glucose-lowering medications increased over the study period, thereby reducing the likelihood that the overall trend in poor glycemic control was due to declining adherence.

Since the balance of benefits and harms of glycemic control differs by age and comorbidity burden, we examined glycemic control trends in relevant subgroups. In our study, less than half of the youngest patients (48.0%) but >60% of the oldest patients (61.6%) achieved an HbA_{1c} <7% by 2013. In contrast, nearly a quarter of the youngest patients (23.3%) but only a small minority of the oldest patients (6.3%) had poor glycemic control at the end of the study period. The youngest adults in NHANES were also least likely to achieve recommended HbA_{1c} targets (13). Limited access to care and lack of insurance coverage for medications are known to contribute to suboptimal glycemic control and may partly explain poor control among the youngest NHANES participants (31). However, our study included adults with full medical and pharmacy benefits coverage, so lack of access to care is unlikely to explain our findings. Young age at diabetes onset has been associated with worse glycemic control (32) and more aggressive disease (33,34). Younger adults also use health care less often. However, the youngest adults are generally expected to derive
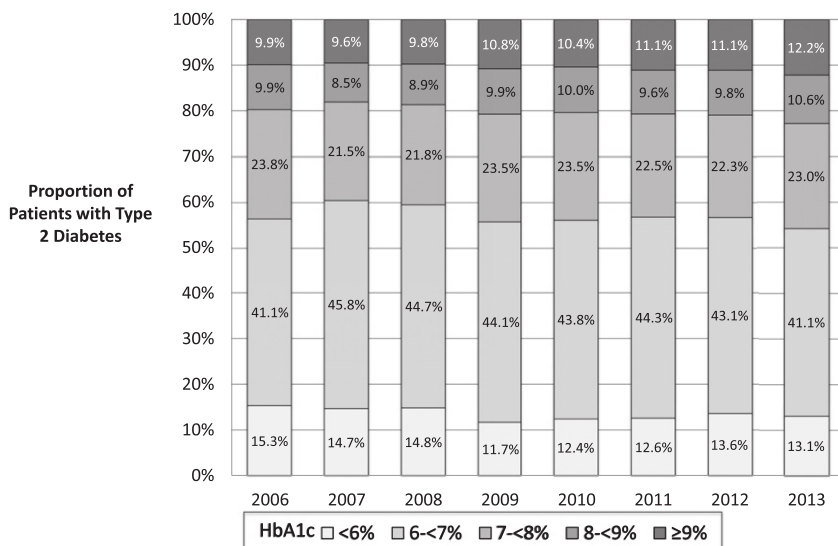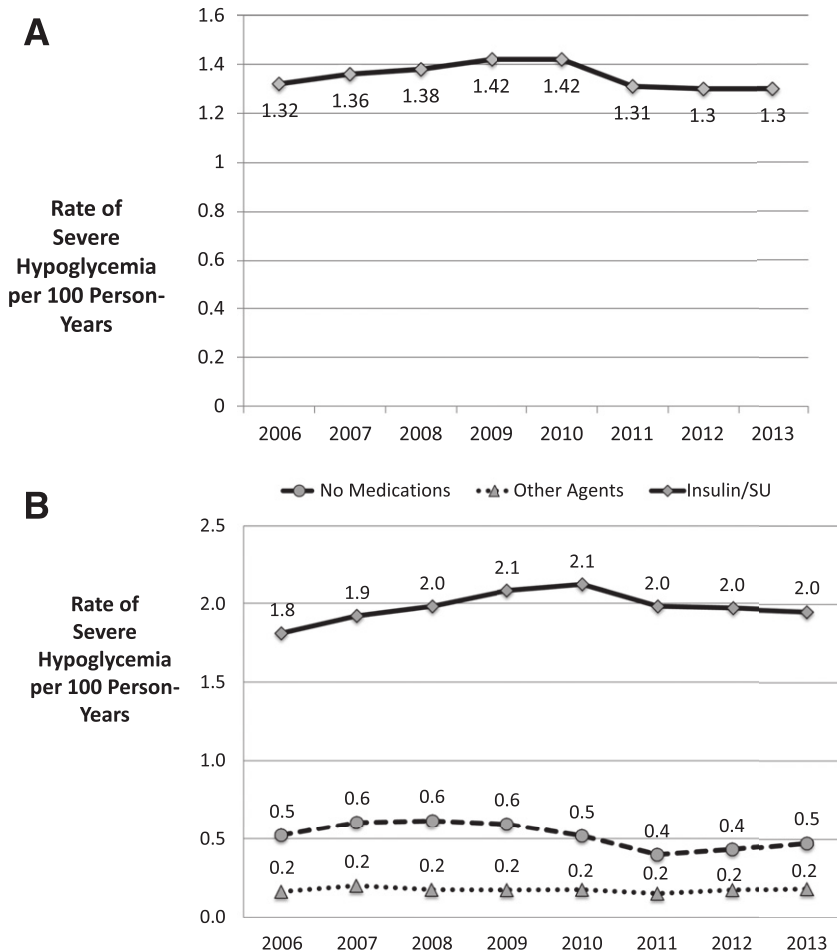
Figure 2—Glycemic control among patients with T2DM, 2006–2013. Estimates were standardized by age, sex, race, and region to the 2013 cohort of people included in the study.

Figure 3—Age- and sex-standardized rate of severe hypoglycemia resulting in hospital admission, observation stay, or emergency department visit per 100 person-years, 2006–2013. A: Patients with T2DM who filled at least one glucose-lowering agent. B: Patients with T2DM who filled insulin or insulin secretagogues (diamonds), other glucose-lowering agents (triangles), and no glucose-lowering agents (circles). SU, sulfonylurea.

the most benefit from glycemic control in the long-term (35). In contrast, many older adults are less likely to benefit and are more likely to be harmed by overly aggressive glycemic control, especially those with multiple competing health problems (10,36). At the population level, the quality of glycemic control in our study appears to be misaligned given the likelihood of benefits and harms expected from intensive glycemic control.

Greater utilization of newer, more expensive drugs that do not typically cause hypoglycemia might be expected to result in lower rates of severe hypoglycemia over time. In addition, recent guidelines have specifically called for more relaxed glycemic targets and less intensive treatment among patients at risk for hypoglycemia (37). However, we found that the rate of hypoglycemic events leading to either ED visit or hospitalization did not improve over time. We did find an overall increase in insulin use (predominantly insulin analogs), which could have contributed to these trends, although we also found a decline in the use of sulfonylureas.

Consistent with prior studies, rates of severe hypoglycemia were highest among oldest adults and those with multiple comorbidities (18,38,39). These differences likely reflect greater vulnerability to hypoglycemia among these patients, greater prevalence of comorbidities that increase the risk of events (such as renal failure and dementia), as well as differences in drug utilization among these age and comorbidity subgroups, as discussed above. Despite the well-known adverse impacts of hypoglycemia on health-related quality of life and on multiple health outcomes (40–42), severe hypoglycemia continues to pose a threat to the oldest adults and those with multiple comorbidities.

Our results should be interpreted cautiously, in light of several limitations. Our analyses were based on medical and pharmacy claims data, supplemented by laboratory data. Our large sample of privately insured patients with T2DM may not be representative of all privately insured patients in the U.S. Lower rates of adoption of newer, costlier medications might be expected in an uninsured population. Moreover, our database (OLDW) included an increasing number of adults over time, requiring us to standardize data by age, race, sex, and region. This may incompletely capture changes in

the types of patients included in the study. Our analyses of glycemic control relied on HbA$_{1c}$ obtained during routine care in a subset of the total sample; it is possible that differences in HbA$_{1c}$ testing may have occurred over time. In addition, some patients were captured in multiple years of data, raising concern that increasing disease severity over time contributed to secular trends. Our sensitivity analyses showed qualitatively similar trends but with a reduction in overall hypoglycemia over time; however, these analyses included the greatest representation of patients who became eligible to enter the cohort during the last year, and thus with the shortest duration of diabetes. Our analyses of severe hypoglycemia captured only those events that led to hospital or emergency department use, but did not capture events treated outside of those settings. Finally, our study design precludes causal inference regarding the relationships between the trends in drug utilization, glycemic control, and hypoglycemia. Therefore, our discussion with respect to causality remains speculative.

Costs of diabetes care have dramatically increased (2,4,43). Between 1987 and 2011, per person medical spending attributable to diabetes doubled (4). More than half of the increase was due to prescription drug spending (4). Despite these spending increases and greater utilization of newly developed medications, we showed no concurrent improvements in overall glycemic control or the rates of severe hypoglycemia in our study. Although the use of newer and more expensive agents may have other important benefits (44), further studies are needed to define the value and cost-effectiveness of current treatment options.

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