Original Investigation | LESS IS MORE

Intensive Treatment and Severe Hypoglycemia Among Adults With Type 2 Diabetes

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IMPORTANCE Intensive glucose-lowering treatment among patients with non–insulin-requiring type 2 diabetes may increase the risk of hypoglycemia.

OBJECTIVES To estimate the prevalence of intensive treatment and the association between intensive treatment, clinical complexity, and incidence of severe hypoglycemia among adults with type 2 diabetes who are not using insulin.

DESIGN, SETTING, AND PARTICIPANTS Retrospective analysis of administrative, pharmacy, and laboratory data from the OptumLabs Data Warehouse from January 1, 2001, through December 31, 2013. The study included nonpregnant adults 18 years or older with type 2 diabetes who achieved and maintained a hemoglobin A_{1c} (HbA_{1c}) level less than 7.0% without use of insulin and had no episodes of severe hypoglycemia or hyperglycemia in the prior 12 months.

MAIN OUTCOMES AND MEASURES Risk-adjusted probability of intensive treatment and incident severe hypoglycemia, stratified by patient clinical complexity. Intensive treatment was defined as use of more glucose-lowering medications than recommended by practice guidelines at specific index HbA_{1c} levels. Severe hypoglycemia was ascertained by ambulatory, emergency department, and hospital claims for hypoglycemia during the 2 years after the index HbA_{1c} test. Patients were categorized as having high vs low clinical complexity if they were 75 years or older, had dementia or end-stage renal disease, or had 3 or more serious chronic conditions.

RESULTS Of 31 542 eligible patients (median age, 58 years; interquartile range, 51-65 years; 15 483 women [49.1%]; 18 188 white [57.7%]), 3910 (12.4%) had clinical complexity. The risk-adjusted probability of intensive treatment was 25.7% (95% CI, 25.1%-26.2%) in patients with low clinical complexity and 20.8% (95% CI, 19.4%-22.2%) in patients with high clinical complexity. In patients with low clinical complexity, the risk-adjusted probability of severe hypoglycemia during the subsequent 2 years was 1.02% (95% CI, 0.87%-1.17%) with standard treatment and 1.30% (95% CI, 0.98%-1.62%) with intensive treatment (absolute difference, 0.28%; 95% CI, −0.10% to 0.66%). In patients with high clinical complexity, intensive treatment significantly increased the risk-adjusted probability of severe hypoglycemia from 1.74% (95% CI, 1.28%-2.20%) with standard treatment to 3.04% (95% CI, 1.91%-4.18%) with intensive treatment (absolute difference, 1.30%; 95% CI, 0.10%-2.50%).

CONCLUSIONS AND RELEVANCE More than 20% of patients with type 2 diabetes received intensive treatment that may be unnecessary. Among patients with high clinical complexity, intensive treatment nearly doubles the risk of severe hypoglycemia.

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Clinical guidelines recommend targeting a hemoglobin A_{1c} (HbA_{1c}) level less than 7.0% for most nonpregnant adults with type 2 diabetes. Although tight glycemic control may have benefits for some patients with type 2 diabetes, achieving an HbA_{1c} level of less than 7.0% in others may result in higher burden of treatment, higher cost, more adverse drug reactions, and increased risk of hypoglycemia.[1-4] In particular, patients with complex health problems, limited life expectancy, and advanced age are unlikely to benefit from tight glycemic control and are more likely to be harmed by it compared with younger, healthier patients.[5-12] Accordingly, the American Geriatrics Society (AGS) Choosing Wisely initiative advises against use of medications other than metformin to achieve an HbA_{1c} level of less than 7.5% in most older adults with diabetes because of the risk of hypoglycemia and other harms, including mortality.[13] Instead, the AGS recommends targeting an HbA_{1c} level of 7.0% to 7.5% in healthy older adults with a long life expectancy, 7.5% to 8.0% in adults with moderate comorbidity and a life expectancy of less than 10 years, and 8.0% to 9.0% in patients with multiple comorbidities and a shorter life expectancy.[13] These recommendations are consistent with, although not explicitly stated by, other clinical guidelines that promote individualized evidence-based diabetes care.[14-21] However, despite these recommendations, intensive control remains prevalent among older, sicker patients with diabetes.[22,23]

Prior studies[22,23] have not assessed the prevalence or effect of intensive treatment among younger patients or those using medications other than insulin or sulfonylureas. Moreover, relatively little is known about treatment practices and outcomes among patients once they achieve recommended tight glycemic targets. A recent study[24] from the US Veterans Health Administration revealed that treatment is rarely deintensified among patients with very low (<6.0%) and moderately low (6.0%-6.4%) HbA_{1c} levels. In addition to the lack of deintensification, patients with controlled diabetes (HbA_{1c} level <7.0%) are also at risk for treatment intensification and potentially unnecessary polypharmacy. High rates of redundant HbA_{1c} testing were previously found among low-risk patients with stable, controlled, non–insulin-requiring type 2 diabetes.[25] Such overtesting was associated with treatment intensification, although overall treatment intensity could not be ascertained. Moreover, that study[25] focused specifically on low-risk patients rather than patients with clinical complexity. The goals of this study were therefore to quantify the prevalence of intensive treatment specifically among patients with clinically complex controlled type 2 diabetes and to estimate the association between intensive treatment, clinical complexity, and incidence of severe hypoglycemia.

Key Points

Question What is the association between and frequency of intensive glucose-lowering treatment and severe hypoglycemia among adults with type 2 diabetes mellitus?

Findings In this cohort study of 31 542 US adults with type 2 diabetes, of whom 12% had clinically complexity because of serious comorbidities and/or age of 75 years or older, 731 patients (18.7%) with high clinical complexity and 7317 patients (26.5%) with low clinical complexity received intensive glucose-lowering treatment. Intensive treatment of patients with high clinical complexity significantly increased the adjusted incidence of severe hypoglycemia from 1.7% to 3%.

Meaning Clinically complex and elderly patients with type 2 diabetes are frequently treated intensively, thereby increasing their risk of severe hypoglycemia.

Methods

Data Source

We conducted a retrospective analysis of data from the OptumLabs Data Warehouse (OLDW), a deidentified administrative claims database of more than 100 million individuals enrolled in private and Medicare Advantage plans across the United States (eMethods 1 in the Supplement).[26,27] There was no patient involvement in this study. Study data were accessed using techniques adherent to the Health Insurance Portability and Accountability Act of 1996, and because this study involved analysis of preexisting, deidentified data, the Mayo Clinic Institutional Review Board deemed it exempt from institutional review board approval.

Study Population

We identified adults (≥18 years old) with stable, controlled type 2 diabetes from January 1, 2001, through December 31, 2011, who had 2 consecutive HbA_{1c} tests that revealed levels less than 7.0% within a 24-month period (**Figure 1** and eMethods 1 and eFigure 1 in the Supplement). Date of cohort entry was defined by the second (index) HbA_{1c} test. As shown in Figure 1 and detailed in eMethods 2 in the Supplement, we first identified 5 297 670 patients within the OLDW who met the Healthcare Effectiveness Data and Information Set criteria[28] for diabetes between 2001 and 2011. Patients with no HbA_{1c} results or HbA_{1c} levels of 7.0% and higher were excluded, leaving 619 231 individuals. Most patients were excluded on the basis of absent HbA_{1c} because the OLDW includes laboratory results for a convenience sample based on data-sharing agreements between OptumLabs and commercial laboratories. To restrict the study population to patients with stable glycemic control, only 329 973 individuals with another HbA_{1c} level less than 7.0% preceding the index HbA_{1c} within 24 months were included.

We excluded 12 108 patients with severe hypoglycemia or hyperglycemia during the 12 months preceding the index HbA_{1c} because they are at increased risk for recurrent hypoglycemia and likely not subject to usual care; 52 016 patients with type 1, gestational, nonclinical, and secondary diabetes because these conditions may have different treatment goals and natural histories; 10 134 patients with any insulin prescription during 120 days preceding the index date because insulin is a known risk factor for hypoglycemia and claims data do not allow for ascertainment of insulin dose and treatment intensity change; 214 033 patients with lack of continuous enrollment for 24 months; 8999 patients younger than 18 years;

and 1141 patients with incomplete demographic or enrollment information.

Patients entered the cohort once, the first time they became eligible, and were followed for 24 months (up to 2013). They were stratified on the basis of index HbA_{1c} measurements into 3 categories based on guideline recommendations for diabetes diagnosis and management: 5.6% or less, 5.7% to 6.4%, and 6.5% to 6.9%.[14-20] Patients were censored on a severe hyperglycemic event because that may precipitate changes in therapy and confound analyses.

Clinical Complexity

High vs low clinical complexity was defined based on the framework developed by the American Diabetes Association and the AGS[21] as a composite measure of age of 75 years or older or high comorbidity burden defined by the presence of end-stage renal disease, dementia, or 3 or more serious chronic conditions (eMethods 3 in the Supplement).

Independent Variables

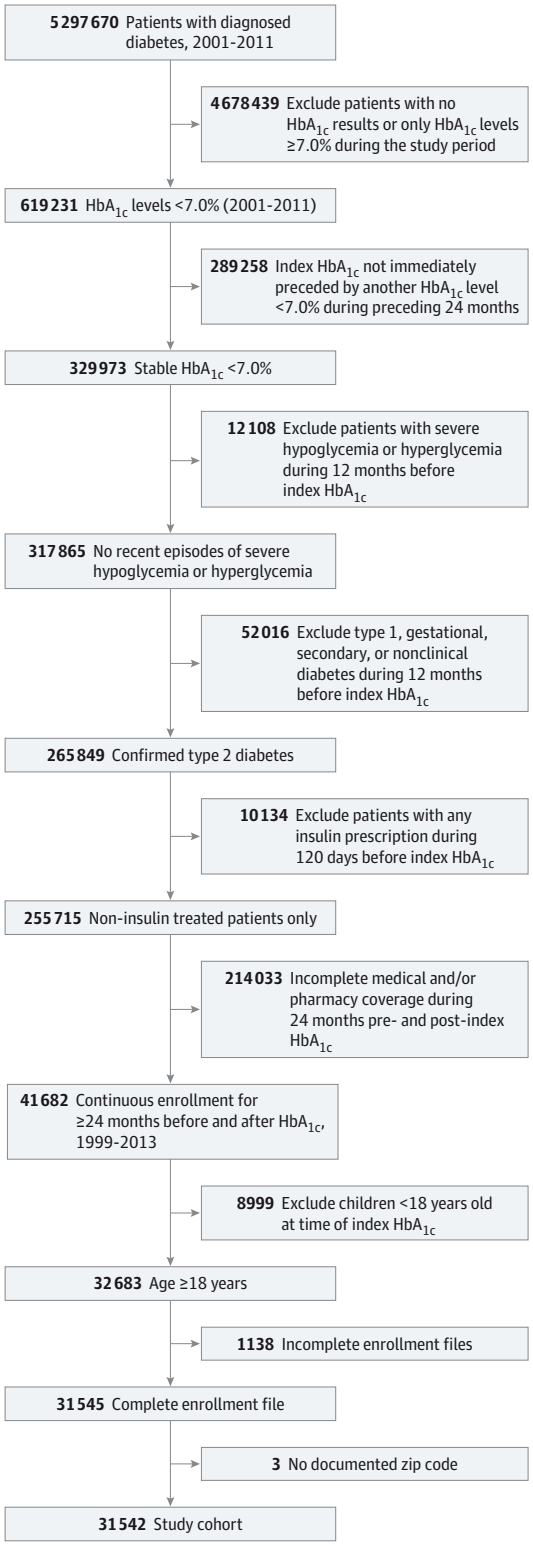
Date of index HbA_{1c} test (2001-2011) was recorded to account for secular trends in glycemic targets, treatment practices, and glucose-lowering medications and presented in 2-year increments except in 2011. Demographic variables included age, sex, race/ethnicity, and US Census region at the time of index HbA_{1c} test. Specialties of health care professionals seen were measured for the 12-month period after the index HbA_{1c} test because patients receiving specialty care may have different disease severity, comorbidity burden, health care use, and prescribed treatments than patients cared for by generalists. Endocrinologists, cardiologists, and nephrologists were chosen because they were the most commonly seen diabetes-related specialists in this population. Patients seen by multiple specialists were counted toward each specialty.

Treatment Intensity

Baseline treatment regimens were identified from pharmacy claims within 120 days preceding the index HbA_{1c} test date. Diabetes medications were grouped into 9 classes (eTable 1 in the Supplement); combination tablets were considered as belonging to both classes. Treatment changes were ascertained by comparing pharmacy claims 120 days after vs before the index HbA_{1c} test date, which accounts for a health care professional's review of HbA_{1c} test results (30 days) and an additional 90 days for the preceding prescription to be completed until time for next medication fill.

Intensive treatment was defined based on the index HbA_{1c} test and either treatment regimen at the time that HbA_{1c} test was performed or treatment change after that HbA_{1c} test result (eFigure 1 in the Supplement). For patients with an index HbA_{1c} level of 5.6% or less, intensive treatment was defined as use of any medications on the index date or treatment initiation within 120 days of index date because this HbA_{1c} level is below the threshold for treatment as recommended by clinical guidelines.[14-20] For patients with an index HbA_{1c} level of 5.7% to 6.4%, intensive treatment was defined as use of 2 or more drugs at the time of the index test (because the HbA_{1c} level was also <7.0% before that test) or treatment intensification by addition of 1 or more new drugs or insulin after the index date (because

Figure 1. Study Cohort Creation



HbA_{1c} indicates hemoglobin A_{1c}.

these patients' diabetes was already controlled per the guidelines).[14-20] For patients with an index HbA_{1c} level of 6.5% to 6.9%, intensive treatment was defined as the addition of 2 or more drugs or insulin after the index HbA_{1c} test date (no baseline treatment criterion). The last definition is a conservative criterion that underestimates intensive treatment as defined by most professional societies that recommend targeting an HbA_{1c} level of 7.0% rather than 6.5% and may view any treatment escalation at this point to be intensive treatment.[15-20] None of the guidelines recommend the addition of 2 drugs for HbA_{1c} levels of 6.5% to 6.9%.[14-20]

Treatment deintensification was defined by removing 1 or more drugs within 120 days after the index HbA_{1c} test date. Treatment regimens that did not meet the criteria for intensive treatment were classified as standard treatment.

Severe Hypoglycemia

First episode of severe hypoglycemia during the 24 months after the index HbA_{1c} test was identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), codes 251.x and 250.8 (Ginde algorithm)[29] and 962.3 in the principal position of any (ambulatory, emergency department, or hospital) evaluation and management encounter.

Sensitivity Analyses

To separate the incidence of hypoglycemia caused by sulfonylurea agents vs otherwise intensive treatment, we conducted a sensitivity analysis for the risk of hypoglycemia (observed and risk adjusted) after excluding 7601 patients receiving sulfonylurea or glinide drugs after the index HbA_{1c} test date (eMethods 4 in the Supplement). Furthermore, because metformin may be used to treat prediabetes and other conditions, we conducted a second sensitivity analysis that excluded 5030 patients classified as receiving intensive treatment solely on the basis of metformin (eMethods 5 in the Supplement).

Statistical Analysis

Data are presented as frequencies and means for all variables. Univariate between-group comparisons were performed using χ^2 tests for categorical and binary variables and Kruskal-Wallis tests for continuous variables.

Multivariable logistic regression separately examined the risk-adjusted probabilities of intensive treatment and severe hypoglycemia. Adjustment variables were set to the sample means[30] of sex, race (white, nonwhite, unknown), household income, US region, index HbA_{1c} test date, and health care professional specialty.

Risk-adjusted probabilities and 95% CIs for intensive treatment were calculated for patients with low and high clinical complexity, adjusting for the aforementioned variables. The association between intensive treatment and severe hypoglycemia was examined in a second logistic regression model in which the main predictor was a 4-level measure of patient complexity and treatment intensity: (1) low complexity with standard treatment, (2) low complexity with intensive treatment, (3) high complexity with standard treatment, and (4) high complexity with intensive treatment. Adjustment variables were set to the sample means of index HbA_{1c} level, medications used after testing, and the aforementioned variables. Analyses were conducted using SAS statistical software, version 9.3 (SAS Institute Inc), and STATA software, version 13.1 (StataCorp).

Results

Study Cohort

Baseline characteristics of the 31 542 patients included in the study stratified by clinical complexity are given in **Table 1**. Overall, the median age was 58.0 years, 15 483 (49.1%) were female, and 18 188 (57.7%) were white. The index HbA_{1c} level was 5.6% or less in 3283 patients (10.4%), 5.7% to 6.4% in 18 014 patients (57.1%), and 6.5% to 6.9% in 10 245 patients (32.5%). At the time that the index HbA_{1c} level was measured, 10 370 (32.9%) were not taking any glucose-lowering medications, 11 883 (37.7%) received 1 drug, 6710 (21.3%) received 2 drugs, and 2579 (8.2%) received 3 or more drugs. High clinical complexity was present in 3910 patients (12.4%) because of age of 75 years or older (n = 3048 [9.7%]), high burden of illness (n = 470 [1.5%]), or both (n = 392 [1.2%]). Patients with high clinical complexity were significantly more likely to be treated with lifestyle management or only 1 diabetes medication, and had higher index HbA_{1c} levels, compared with patients with low clinical complexity who had greater prevalence of polypharmacy and lower index HbA_{1c} levels (Table 1).

Prevalence of Intensive Treatment

In total, 8048 patients (25.5%) were treated intensively, including 7317 patients (26.5%) with low clinical complexity and 731 patients (18.7%) with high clinical complexity (**Table 2**). Most patients met the criteria for intensive treatment based on their baseline treatment regimen (6033 patients [21.8%] with low clinical complexity and 620 patients [15.9%] with high clinical complexity); a smaller proportion had their treatment intensified despite low index HbA_{1c} level (1592 patients [5.8%] with low clinical complexity and 139 patients [3.6%] with high clinical complexity). Importantly, 5053 intensively treated patients (76.0%) did not have their treatment deescalated after the low HbA_{1c} test result was obtained, with 4571 patients (75.8%) with low clinical complexity and 482 patients (77.7%) with high clinical complexity continuing with their baseline intensive regimen.

The risk-adjusted probability of intensive treatment was 25.7% (95% CI, 25.1-26.2) for patients with low clinical complexity and 20.8% (95% CI, 19.4%-22.2%) for patients with high clinical complexity (absolute difference, 4.9%; 95% CI, 3.4%-6.4%; $P < .001$). This probability includes the higher risk-adjusted probability of intensive baseline regimen among patients with low vs high clinical complexity (21.0% [95% CI, 20.5%-21.5%] vs 17.3% [95% CI, 16.0%-18.6%]), as well as undergoing treatment intensification despite low index HbA_{1c} levels (5.3% [95% CI, 5.1%-5.6%] vs 4.0% [95% CI, 3.3%-4.7%]) (Table 2).

Table 1. Characteristics of the Study Cohort at the Time of the Index Hemoglobin A_{1c} Test[a]

Characteristic	Complexity		*P* Value
	Low	High	
Patients	27 632 (87.6)	3910 (12.4)	...
Age, median (IQR), y	56.0 (49.0-62.0)	79.0 (76.0-82.0)	...
Age, y			
18-44	3549 (12.8)	12 (0.3)	<.001
45-54	8067 (29.2)	62 (1.6)	
55-64	11 589 (41.9)	191 (4.9)	
65-74	4427 (16.0)	205 (5.2)	
≥75	0	3440 (88.0)	
Female	13 348 (48.3)	2135 (54.6)	<.001
Race			
Nonwhite	9095 (32.9)	1386 (35.4)	<.001
White	15 895 (57.5)	2293 (58.6)	
Unknown	2642 (9.6)	231 (5.9)	
Household income, $			
<40 000	4540 (16.4)	1463 (37.4)	<.001
40 000-49 999	3128 (11.3)	517 (13.2)	
50 000-59 999	2948 (10.7)	421 (10.8)	
60 000-74 999	3829 (13.9)	482 (12.3)	
75 000-99 999	4904 (17.7)	424 (10.8)	
≥100 000	6037 (21.8)	324 (8.3)	
Unknown	2246 (8.1)	279 (7.1)	
Region			
South	15 809 (57.2)	1671 (42.7)	<.001
Midwest	3075 (11.1)	600 (15.3)	
Northeast	6449 (23.3)	1505 (38.5)	
West	2299 (8.3)	134 (3.4)	
HbA_{1c} level, %			
≤5.6	2954 (10.7)	329 (8.4)	<.001
5.7-6.4	15 791 (57.1)	2223 (56.9)	
6.5-6.9	8887 (32.2)	1358 (34.7)	
Comorbidities			
Myocardial infarction	360 (1.3)	230 (5.9)	<.001
Congestive heart failure	836 (3.0)	669 (17.1)	<.001
Stroke/TIA	1322 (4.8)	831 (21.3)	<.001
Dementia	0	361 (9.2)	<.001
Renal disease[b]	814 (2.9)	581 (14.9)	<.001
ESRD	0	65 (1.7)	<.001
Cancer	1512 (5.5)	579 (14.8)	<.001
Pulmonary disease	3042 (11.0)	829 (21.2)	<.001
Peripheral vascular disease	1412 (5.1)	819 (20.9)	<.001
Liver disease	1380 (5.0)	171 (4.4)	.09
Baseline treatment			
None	8922 (32.3)	1448 (37.0)	<.001
1 Drug	10 309 (37.3)	1574 (40.3)	
2 Drugs	6016 (21.8)	694 (17.7)	
≥3 Drugs	2385 (8.6)	194 (5.0)	

(continued)

Patients with high clinical complexity were significantly less likely to be treated intensively than patients with low clinical complexity (odds ratio [OR], 0.76; 95% CI, 0.69-0.83) (eFigure 2 in the Supplement). Women (OR, 0.84; 95% CI, 0.80-0.89) and nonwhite patients (OR, 0.91; 95% CI, 0.86-0.96) were also less likely to be treated intensively compared with men and white patients. Patients cared for by endocrinologists were more likely to be intensively treated (OR, 1.66; 95% CI, 1.53-1.79). Although the

Table 1. Characteristics of the Study Cohort at the Time of the Index Hemoglobin A_{1c} Test[a] (continued)

Characteristic	Complexity		P Value
	Low	High	
Baseline drug class			
Metformin	14 424 (52.2)	1486 (38.0)	<.001
Sulfonylureas	6147 (22.2)	1269 (32.5)	<.001
Thiazolidinediones	5711 (20.7)	453 (11.6)	<.001
DPP-4 inhibitors	2013 (7.3)	245 (6.3)	.02
GLP-1 analogues	770 (2.8)	21 (0.5)	<.001
Glinides	304 (1.1)	59 (1.5)	.02
α-Glucosidase inhibitors	69 (0.2)	14 (0.4)	.22
Amylin analogues	8 (0.0)	0	.29

Abbreviations: ellipses, data not applicable; DDP-4, dipeptidyl peptidase 4; ESRD, end-stage renal disease; GLP-1, glucagon-like peptide *1;* IQR, interquartile range.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Renal disease does not include ESRD.

Table 2. Observed Prevalence and Risk-Adjusted Probability of Intensive Treatment Stratified by Clinical Complexity

Intensive Treatment	Complexity		Difference Between Low and High Complexity Patients, % (95% CI)[a]
	Low (n = 27 632)	High (n = 3910)	
Observed, No. (%)			
Composite	7317 (26.5)	731 (18.7)	7.8 (6.5-9.1)
Intensive baseline regimen	6033 (21.8)	620 (15.9)	6.0 (4.7-7.2)
Intensification with low HbA_{1c} level	1592 (5.8)	139 (3.6)	2.2 (1.6-2.8)
Adjusted Probability, % (95% CI)[b]			
Composite	25.7 (25.1-26.2)	20.8 (19.4-22.2)	4.9 (3.4-6.4)
Intensive baseline regimen	21.0 (20.5-21.5)	17.3 (16.0-18.6)	3.7 (2.3-5.1)
Intensification with low HbA_{1c} level	5.3 (5.1-5.6)	4.0 (3.3-4.7)	1.4 (0.6-2.1)

Abbreviation: HbA_{1c}, hemoglobin A_{1c}.

[a] $P < .001$ for all.

[b] Probability of overtreatment was adjusted for patient sex, race, household income, region, date of index HbA_{1c} test, and health care professional specialty.

likelihood of intensive treatment was stable between 2001 and 2008, it decreased significantly after 2009 (OR, 0.71 [95% CI, 0.60-0.84] for 2009-2010, and OR, 0.64 [95% CI, 0.54-0.77] for 2011 compared with 2001-2002).

Intensive Treatment and Severe Hypoglycemia

The overall unadjusted 2-year incidence of severe hypoglycemia was 1.4%, of which 326 cases (73.1%) were documented during ambulatory encounters, 82 (18.4%) resulted in emergency department visits, and 38 (8.5%) required hospital admission. Severe hypoglycemia was significantly more frequent among patients with high vs low complexity (112 [2.9%] vs 334 [1.2%]; $P < .001$). Among patients with low clinical complexity, the risk-adjusted probability of severe hypoglycemia did not increase with intensive treatment (1.02% [95% CI, 0.87-1.17] with standard treatment and 1.30% [95% CI, 0.98-1.62] with intensive treatment) (**Figure 2**). In contrast, among patients with high clinical complexity, the risk-adjusted probability of severe hypoglycemia increased significantly with intensive treatment from 1.74% (95% CI, 1.28%-2.20%) with standard treatment to 3.04% (95% CI, 1.91%-4.18%) with intensive treatment (absolute difference, 1.30%; 95% CI, 0.10%-2.50%).

The ORs of severe hypoglycemia were 1.72 (95% CI, 1.29-2.31) for high complexity with standard treatment vs low complexity with standard treatment groups, 3.05 (95% CI, 1.99-4.67) for high complexity with intensive treatment vs low complexity with standard treatment groups, and 1.77 (95% CI, 1.12-2.80) for high complexity with intensive treatment vs high complexity with standard treatment groups (**Figure 3**). Sulfonylurea and glinide therapy significantly raised the risk of severe hypoglycemia (OR, 2.19; 95% CI, 1.77-2.71). Patients treated by endocrinologists had significantly higher risk of hypoglycemia (OR, 1.65; 95% CI, 1.25-2.20), even after adjustment for the HbA_{1c} level and medications used.

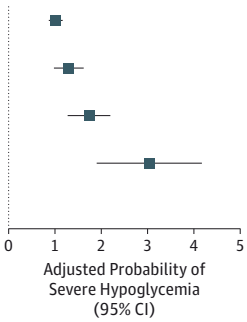
To determine whether our findings were driven by use of sulfonylureas, we performed sensitivity analyses excluding individuals using insulin secretagogues after the index HbA_{1c} test date. All results remained consistent, although not always statistically significant given the smaller sample size (eResults 1, eTable 2, and eTable 3 in the Supplement). None of the study results were altered by excluding patients who were classified as intensively treated on the basis of metformin use or start only (eResults 2, eTable 4, and eTable 5 in the Supplement).

Discussion

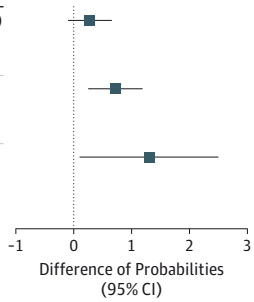
In this large national cohort of adults with controlled type 2 diabetes, more than a quarter of patients received intensive glucose-lowering therapy, including nearly 20% of patients with clinical complexity whose advanced age and comorbidities placed them at risk for treatment-related adverse events without substantial long-term benefit.[12] Indeed, we found that even with standard glucose-lowering treatment, patients with high clinical complexity had almost double the rate of severe

Figure 2. Risk-Adjusted Probability of Hypoglycemia as a Function of Patient Clinical Complexity and Treatment Intensity

Source	Adjusted Probability of Severe Hypoglycemia (95% CI)
Low complexity with standard treatment	1.02 (0.87 to 1.17)
Low complexity with intensive treatment	1.30 (0.98 to 1.62)
High complexity with standard treatment	1.74 (1.28 to 2.20)
High complexity with intensive treatment	3.04 (1.91 to 4.18)



Source	Difference of Probabilities (95% CI)
vs low complexity with standard treatment $P = .15$	0.28 (-0.10 to 0.66)
vs low complexity with standard treatment $P < .01$	0.72 (0.25 to 1.19)
vs high complexity with standard treatment $P = .03$	1.30 (0.10 to 2.50)



High clinical complexity was defined as a composite measure of age of 75 years or older or high comorbidity burden defined by presence of end-stage renal disease, dementia, or 3 or more chronic conditions (myocardial infarction, congestive heart failure, pulmonary disease, non–end-stage chronic renal disease, or cancer). Intensive treatment was defined as a composite measure of intensive baseline regimen (use of greater number of medications than recommended for a given index hemoglobin A_{1c} [HbA_{1c}] level) and treatment intensification despite a low index HbA_{1c} result. Risk-adjusted probabilities are adjusted for patient sex, race, household income, residency region, index HbA_{1c} year, and specialty of treating health care professional. Error bars indicate 95% CIs.

hypoglycemia compared with patients with low clinical complexity, and their risk of severe hypoglycemia was further nearly doubled by intensive treatment. Intensive treatment did not, however, significantly increase hypoglycemia risk among patients with low clinical complexity.

Recent guidelines, issued between 2010 and 2015, recommend initiation or escalation of pharmacotherapy for diabetes when the HbA_{1c} level exceeds recommended targets (6.5% or 7.0%) in patients with low risk for hypoglycemia, low comorbidity burden, and life expectancy consistent with anticipated benefits of glycemic control.[14-20] However, 1731 patients (5.5%) in our study, including 139 patients (3.6%) with high clinical complexity, began treatment or had their treatment intensified despite HbA_{1c} levels much lower than these thresholds. Treatment deintensification is also an important aspect of individualized diabetes management, and clinical inertia encompasses not only failure to intensify therapy in response to elevated HbA_{1c} levels[31] but also failure to deescalate therapy in response to low HbA_{1c} levels, particularly if treated with multiple glucose-lowering medications. In our study, 5053 patients (76.0%) receiving intensive treatment did not have their treatment deescalated, including 482 intensively treated patients (77.7%) with high clinical complexity. These data are similar to rates reported by Sussman and colleagues[24] in the US Veterans Health Administration. Such failure to deescalate therapy in patients with very low HbA_{1c} levels increases the risk of hypoglycemia, has no proven clinical benefit, exposes patients to potential adverse effects, and increases burden of treatment.[32]

Our study identified several factors associated with intensive treatment and hypoglycemia. Women and nonwhite patients were less likely to be treated intensively, which may reflect underlying disparities in diabetes care.[33,34] Patients treated by endocrinologists and nephrologists were more likely to be treated intensively, consistent with prior studies[35,36] and possibly attributable to greater emphasis on lowering HbA_{1c} levels to reduce complications or a focus on treating diabetes without placing it in the context of multiple potentially competing diseases. Patients under endocrinology and nephrology care were also more likely to experience severe hypoglycemia even after treatment intensity and medical complexity were accounted for, warranting further investigation.

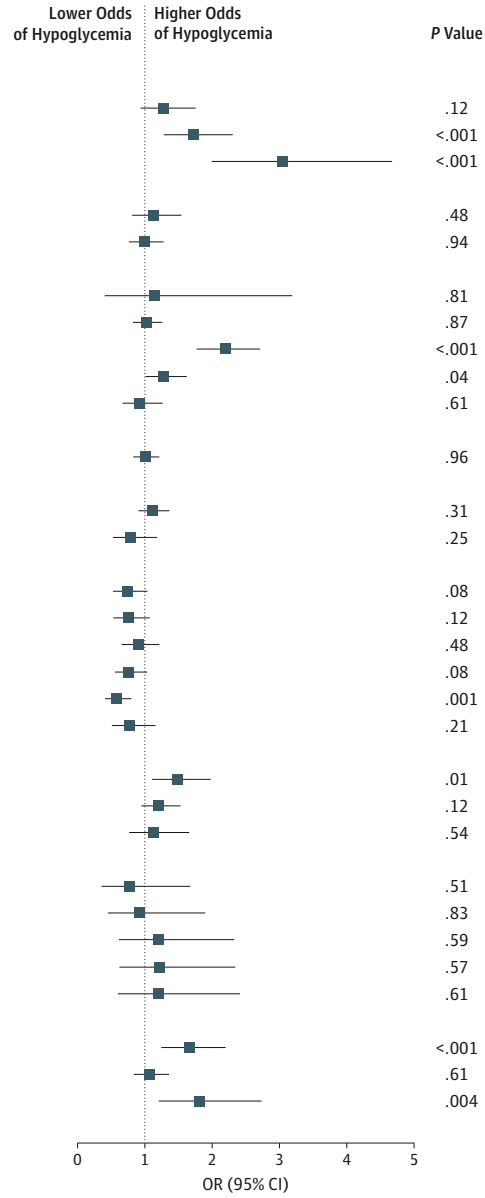
Furthermore, we examined the often concurrent effects of sulfonylurea use and intensive treatment on hypoglycemia. We were concerned to find significantly more sulfonylurea and glinide use among patients with high clinical complexity (6294 low complexity patients [22.8%] and 1307 high complexity patients [33.4%] were treated with either sulfonylurea or glinide after the index HbA_{1c} test), despite the AGS strongly advising against sulfonylurea use by elderly individuals.[37] As expected, sulfonylureas increased hypoglycemia risk irrespective of treatment intensity. However, we also found that patients with high clinical complexity had significantly higher rates of severe hypoglycemia even without sulfonylurea use, and intensive treatment that does not include sulfonylureas may further elevate hypoglycemia risk.

The rates of intensive treatment decreased during the study, particularly after 2009. This finding may be attributable to increasing uncertainty about long-term benefits of tight glycemic control[4,38,39] and awareness of hypoglycemia risk posed by targeting HbA_{1c} levels less than 6.5% to 7.0%.[2,3] However, the association between intensive treatment and hypoglycemia remained unchanged over time, despite more prevalent use of novel glucose-lowering agents with lesser risk of hypoglycemia.[36,40,41] Intensive treatment with any glucose-lowering drugs, even those not typically associated with hypoglycemia, should therefore be prescribed with caution, particularly to patients with high clinical complexity.

Our study has several important limitations, including stringent inclusion criteria that restricted the population to

Figure 3. Risk Factors for Incident Severe Hypoglycemia During the 2 Years After the Index Hemoglobin A_{1c} (HbA_{1c}) Test

Source	OR (95% CI)	P Value
Clinical complexity and treatment (vs low with standard)		
Low with intensive	1.28 (0.94-1.75)	.12
High with standard	1.72 (1.29-2.31)	<.001
High with intensive	3.05 (1.99-4.67)	<.001
Baseline HbA_{1c} (vs ≤5.6%)		
5.7% - 6.4%	1.12 (0.81-1.54)	.48
6.5% - 7.0%	0.99 (0.77-1.28)	.94
Medications (after testing)		
Insulin	1.13 (0.40-3.19)	.81
Metformin	1.02 (0.82-1.26)	.87
Sulfonylurea or glinide	2.19 (1.77-2.71)	<.001
Thiazolidenedione	1.28 (1.01-1.62)	.04
Incretins	0.92 (0.67-1.27)	.61
Sex (vs male)		
Female	1.00 (0.83-1.22)	.96
Race (vs white)		
Nonwhite	1.11 (0.91-1.36)	.31
Unknown	0.79 (0.52-1.18)	.25
Household income (vs <$40 000)		
$40 000 - $49 999	0.74 (0.53-1.04)	.08
$50 000 - $59 999	0.76 (0.53-1.07)	.12
$60 000 - $74 999	0.90 (0.66-1.22)	.48
$75 000 - $99 999	0.76 (0.56-1.03)	.08
≥$100 000	0.57 (0.41-0.80)	.001
Unknown	0.77 (0.51-1.16)	.21
US region (vs south)		
Midwest	1.48 (1.11-1.98)	.01
Northeast	1.21 (0.95-1.53)	.12
West	1.13 (0.77-1.66)	.54
Year (vs 2001-2002)		
2003-2004	0.77 (0.35-1.68)	.51
2005-2006	0.92 (0.45-1.90)	.83
2007-2008	1.20 (0.62-2.33)	.59
2009-2010	1.21 (0.62-2.35)	.57
2011	1.20 (0.60-2.41)	.61
Clinician specialty		
Endocrinology	1.65 (1.25-2.20)	<.001
Cardiology	1.07 (0.83-1.36)	.61
Nephrology	1.82 (1.21-2.73)	.004



High clinical complexity was defined as a composite measure of age of 75 years or older or high comorbidity burden defined by the presence of end-stage renal disease, dementia, or 3 or more chronic conditions (myocardial infarction, congestive heart failure, pulmonary disease, non–end-stage chronic renal disease, or cancer). Intensive treatment was defined as a composite measure of intensive baseline regimen (use of greater number of medications than recommended for a given index HbA_{1c} level) and treatment intensification despite a low index HbA_{1c} result. Error bars indicate 95% CIs.

patients with type 2 diabetes who achieved and maintained glycemic control without use of insulin. Patients receiving insulin therapy at baseline were excluded because insulin may precipitate hypoglycemia for reasons beyond intensive treatment (eg, missed meals, illness, physical activity) and insulin dose changes cannot be reliably captured by pharmacy claim data. Because the study cohort was derived from a data set of privately insured and Medicare Advantage beneficiaries, the unadjusted rates of intensive treatment and severe hypoglycemia may not be directly generalizable to the broader US or international population. The association between intensive treatment and severe hypoglycemia, however, is likely comparable once pertinent covariates are accounted for. Another limitation stems from the fact that we considered treatment change that occurred within 120 days of the HbA_{1c} test but measured rates of severe hypoglycemia during 2 years of follow-up, which may miss patients who received standard treatment at the time of cohort entry but were intensified later, causing hypoglycemia. Conversely, patients who were intensively treated at baseline and had treatment deintensified later may have avoided hypoglycemia, thereby decreasing the measured association between intensive treatment and severe hypoglycemia. Individuals who may have died during follow-up were excluded because of lack of continuous enrollment. Finally, not all hypoglycemic events culminate in a clinical encounter, which would underestimate the incidence of severe hypoglycemia, particularly among younger and healthier

patients, because frail and elderly patients and those without readily available support are more likely to require medical attention for severe hypoglycemia.

Conclusions

Intensive glucose-lowering therapy is common, including among older adults and those with high a burden of comorbidity. Although young and relatively healthy patients may tolerate intensive treatment, it nearly doubles the risk of severe hypoglycemia among elderly patients and patients with clinical complexity, yet it has uncertain short- and long-term benefits in this population. Individualized assessment of clinical complexity, in addition to careful consideration of likely risks and benefits of intensive glucose-lowering therapy, is therefore an important part of patient-centered diabetes management.

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Acquisition, analysis, or interpretation of data: All authors.
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Invited Commentary

LESS IS MORE

Deintensification of Routine Medical Services
The Next Frontier for Improving Care Quality

Eve A. Kerr, MD, MPH; Timothy P. Hofer, MD, MS

The study by McCoy and colleagues[1] in this issue of *JAMA Internal Medicine* adds to an increasing body of research[2-4] that older patients with type 2 diabetes mellitus often receive unnecessarily intensive treatment. The authors found that nearly 20% of patients with clinical complexity (75 years or older or with multiple comorbidities) with a hemoglobin A_{1c} (HbA_{1c}) level less than 7.0% are receiving intensive oral treatment regimens (they excluded patients taking insulin at baseline). Furthermore, patients with clinical complexity had a higher likelihood of severe hypoglycemia, even if their treatments did not meet the definition of high intensity. The results were consistent regardless of medications used, although one-third of patients with clinical complexity were treated with sulfonylureas, despite guidelines advising against their use. Moreover, more than three-quarters of intensively treated patients did not have their treatments deintensified after testing revealed a low HbA_{1c} level. This finding is consistent with research by Sussman et al,[5] who found that once intensive treatments are started, even older patients with very tight control (eg, HbA_{1c} level <6.0%) rarely have medications deintensified.

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There is an increasing consensus that overtreatment and overtesting expose some patients to services they may not need or prefer or that may harm them. This consensus first achieved national prominence with the Choosing Wisely campaign, and in fact, the American Geriatric Society has a Choosing Wisely recommendation on avoiding intensive medication treatment for diabetes in most older adults.[6] The preponderance of recommendations for decreasing overuse focus on avoiding one-time diagnostic procedures or treatment at the beginning of a discrete episode of care, such as not treating with antibiotics for acute sinusitis. However, a substantial amount of health care involves the long-term use of medical interventions for chronic and ongoing conditions, such as diabetes. Little guidance exists on when physicians and patients should begin the process for deintensifying medical services—stopping or scaling back the intensity or frequency of medical interventions that are currently part of a patient's ongoing management.