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Severe Hypoglycemia Attributable to Intensive Glucose-Lowering Therapy Among US Adults With Diabetes: Population-Based Modeling Study, 2011-2014

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Abstract

Objective: To estimate the contemporary prevalence of intensive glucose-lowering therapy among US adults with diabetes and model the number of hypoglycemia-related emergency department (ED) visits and hospitalizations that are attributable to such intensive treatment.

Patients and Methods: US adults with diabetes and glycated hemoglobin (HbA_{1c}) levels less than 7.0% who were included in the National Health and Nutrition Examination Survey (NHANES) between 2011 and 2014. Participants were categorized as clinically complex if 75 years or older or with 2 or more activities of daily living limitations, end-stage renal disease, or 3 or more chronic conditions. Intensive treatment was defined as any glucose-lowering medications with HbA_{1c} levels of 5.6% or less or 2 or more with HbA_{1c} levels of 5.7% to 6.4%. First, we quantified the proportion of clinically complex and intensively treated individuals in the NHANES population. Then, we modeled the attributable hypoglycemia-related ED visits/hospitalizations over a 2-year period based on published data for event risk.

Results: Almost half (48.8% [10,719,057 of 21,980,034]) of US adults with diabetes (representing 10.7 million US adults) had HbA_{1c} levels less than 7.0%. Among them, 32.3% (3,466,713 of 10,719,057) were clinically complex, and 21.6% (2,309,556 of 10,719,057) were intensively treated, with no difference by clinical complexity. Over a 2-year period, we estimated 31,511 hospitalizations and 30,954 ED visits for hypoglycemia in this population; of these, 4774 (95% CI, 954-9714) hospitalizations and 4804 (95% CI, 862-9851) ED visits were attributable to intensive treatment.

Conclusion: Intensive glucose-lowering therapy, particularly among vulnerable clinically complex adults, is strongly discouraged because it may lead to hypoglycemia. However, intensive treatment was equally prevalent among US adults, irrespective of clinical complexity. Over a 2-year period, an estimated 9578 hospitalizations and ED visits for hypoglycemia could be attributed to intensive diabetes treatment, particularly among clinically complex patients. Patients at risk for hypoglycemia may benefit from treatment deintensification to reduce hypoglycemia risk and treatment burden.

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Control of hyperglycemia as a way of reducing acute and chronic diabetes symptoms and complications is the cornerstone of diabetes management. Long-term glycemic control is associated with reduced risk for microvascular and, particularly among patients with type 1 diabetes, macrovascular complications and death.[1-6] As a result, most clinical practice guidelines recommend striving for glycated hemoglobin (HbA_{1c}) levels less than 6.5% to 7.0% in most nonpregnant adults with diabetes, as long as this can be achieved without hypoglycemia, polypharmacy, and undue burden of treatment and the patient is likely to meaningfully benefit from such glycemic control.[7-9] Though the ideal HbA_{1c} treatment target for patients with diabetes is still debated, higher HbA_{1c} levels are consistently recommended for patients with multiple or

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advanced comorbid conditions[7-10] because they are at increased risk for hypoglycemia, treatment burden, and adverse drug reactions. Moreover, patients with limited life expectancy are less likely to derive long-term benefit from intensive glycemic control, which can take up to a decade to be realized.[3] Despite these recommendations, several studies have demonstrated that very intensive treatment and potential overtreatment remain common, including among the elderly, those with dementia or chronic kidney disease (CKD), and the clinically complex.[11-13]

Prior population-level studies of potential overtreatment focused on older patients with complex or very complex health status who were treated with insulin or sulfonylurea drugs but did not assess for overtreatment more broadly or explore the association between overtreatment and hypoglycemia.[11-13] These studies, examining treatment patterns in the general US population[12] and the US Department of Veterans Affairs[11,13] up to 2010, found that up to 50% of relatively healthy patients and up to 60% of patients with poor health status may be overtreated. These studies defined potential overtreatment as attaining HbA_{1c} levels less than 7.0% using insulin and/or sulfonylurea drugs, without considering polypharmacy at low or very low HbA_{1c} levels as a potential indicator of overtreatment or the potentially appropriate use of sulfonylurea/insulin in clinical contexts in which no alternatives may be available.

Another study, conducted among commercially insured and Medicare Advantage beneficiaries with non−insulin-requiring type 2 diabetes who achieved HbA_{1c} levels less than 7.0%, estimated the prevalence of potential overtreatment between 2001 and 2013 to be 26.5% [7317 of 27,632] of patients with low clinically complexity and 18.7% [731 of 3910] of patients with high clinical complexity).[14] This study defined potential overtreatment as the use of more glucose-lowering medications of any class than recommended or clinically necessary to achieve low HbA_{1c} levels. Using this definition, overtreatment increased the risk for severe hypoglycemia among clinically complex patients by 77%.[14] However, this study quantified potential overtreatment in a subset of US adults (those with commercial and Medicare Advantage health insurance) and included information up to 2013. As such, there are no contemporary data about the full extent of intensive treatment (and potential overtreatment) and its effect on the rates of severe hypoglycemia among US adults with diabetes.

Patients at risk for hypoglycemia may benefit from timely evaluation, screening for hypoglycemia, and proactive treatment deintensification. Although the Centers for Disease Control and Prevention provide general estimates of hypoglycemia-related emergency department (ED) visits and hospitalizations among US adults with diabetes,[15] how many of these events are due to an immediately modifiable factor such as intensive treatment is unknown. The objective of our study was therefore 2-fold. First, we quantify the rates of intensive treatment among US adults using population-level data from 2011 to 2014 provided by the National Health and Nutrition Examination Survey (NHANES). Next, we model the estimated population-level burden of ED visits and hospitalizations for severe hypoglycemia among patients with HbA_{1c} levels less than 7.0% and calculate the estimated proportion of events directly attributable to intensive treatment by applying event rates observed in comparable patient populations.[14]

PATIENTS AND METHODS

Study Design

To estimate the total number of hypoglycemia-related ED visits and hospitalizations in the United States and quantify the number of events attributable to intensive treatment, we applied published hypoglycemia-related ED/hospitalization event rate data[14] to the general US population included in NHANES 2011 to 2012 and 2013 to 2014. The NHANES program is composed of household interviews, physical examinations, and diagnostic/laboratory studies designed to provide a

comprehensive cross-sectional representation of the health and nutritional status of adults and children in the United States. NHANES does not include longitudinal health information or data regarding diabetes-related outcomes, including hypoglycemia; this information therefore had to be obtained from the published literature. NHANES uses stratified multistage probability-cluster techniques to ensure that sample populations are representative of US noninstitutionalized civilians, thereby complementing studies conducted in narrow patient populations.

This study used deidentified data and was therefore exempt from review by the Mayo Clinic Institutional Review Board.

Study Population

We included all adults (aged ≥18 years) who reported a diagnosis of diabetes from a health professional and had a measured HbA_{1c} level less than 7.0%. Blood samples were collected in mobile examination centers and measurement of HbA_{1c} was performed using the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8. Interview responses were used to ascertain patient age, sex, and race/ethnicity.

We also used interview responses to identify chronic conditions. Functional limitations were assessed based on a series of questions designed to measure functional status. Impairment in activities of daily living (ADLs) was deemed present if a participant reported some or much difficulty with an ADL (dressing, feeding, walking from room to room, and/or getting in or out of bed) or was unable to perform the ADL entirely.

Respondents were categorized as clinically complex if they met at least 1 of the following criteria: (1) 75 years or older, (2) end-stage renal disease or 1 or more dialysis session during the preceding 12 months, (3) limitation in 2 or more ADLs, and (4) self-report of 3 or more chronic conditions from among coronary heart disease, congestive heart failure, stroke, chronic lung disease, kidney disease, and cancer other than nonmelanoma skin cancer, with first date of cancer diagnosis within 5 years. This classification of clinical complexity is based on prior studies of diabetes intensive treatment or overtreatment and is consistent with American Diabetes Association[10] and American Geriatric Society (AGS) guidance.[16] It parallels the definitions used previously by McCoy et al[14] in a study using administrative claims data (from which estimates of severe hypoglycemia were derived, as described later) and by Lipska et al[12] in a study of glycemic overtreatment using NHANES data. Importantly, because NHANES does not include information about dementia (which was used to define clinical complexity in the McCoy et al[14] study) and the American Diabetes Association and AGS both specify advanced functional limitations as warranting more relaxed glycemic treatment targets,[10,16] we relied on self-report of ADL limitations in lieu of a dementia diagnosis, as previously published.[12]

Defining Intensive Therapy

Based on guideline-supported thresholds for initiating and intensifying pharmacotherapy[7-9] and consistent with McCoy et al,[14] intensive treatment was defined as the use of any glucose-lowering medications with HbA_{1c} levels of 5.6% or less, or 2 or more medications with HbA_{1c} levels between 5.7% and 6.4%. All other patients were considered non—intensively treated. Medication use is ascertained in NHANES through participant self-report. Combination medications were counted toward both medication classes, and insulin was considered as either short/rapid acting or intermediate/long acting. Patients using both short/rapid- and intermediate/long-acting insulins were categorized as using 2 (or more, if used in combination with noninsulin agents) medications.

Primary Outcome

The population-level estimates of rates of ED visits and hospitalizations for hypoglycemia were modeled by applying hypoglycemia rate estimates for clinically complex and non—clinically complex adults receiving intensive and nonintensive glucose-lowering treatment from the observational study by

McCoy et al[14] to participants meeting these definitions within the NHANES sample (Figure). Whereas published data in the McCoy et al[14] study provided 2-year incidence (first event) rates of a composite hypoglycemia measure (ED visits, hospitalizations, and ambulatory face-to-face encounters), we used that study data set to de novo identify all (not just first) ED visits and hospitalizations during the 2-year time frame (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). Ambulatory visits for hypoglycemia were not included in the primary outcome.

We calculated the number of ED visits and hospitalizations that may be attributed to intensive treatment as the difference between the total number of observed hypoglycemic events among intensively treated patients minus the number of events expected if nonintensive treatment event rates (Supplemental Table 1) were applied to the intensively treated cohort.

Sensitivity Analyses

The study by McCoy et al[14] excluded patients with a recent episode of severe hypoglycemia and those receiving insulin therapy because the objective of that study was to establish the relationship between overtreatment and incident hypoglycemia with minimal confounding by known hypoglycemia risk factors. Insulin-treated patients were included in this study to estimate the total population burden of hypoglycemia among all potentially overtreated patients. Nonetheless, recognizing that the true hypoglycemia event rate is likely to be much higher among insulin-treated patients[17-19] (and hence the general diabetes population that includes both insulin-treated and non—insulin-treated adults) than would be modeled in the primary

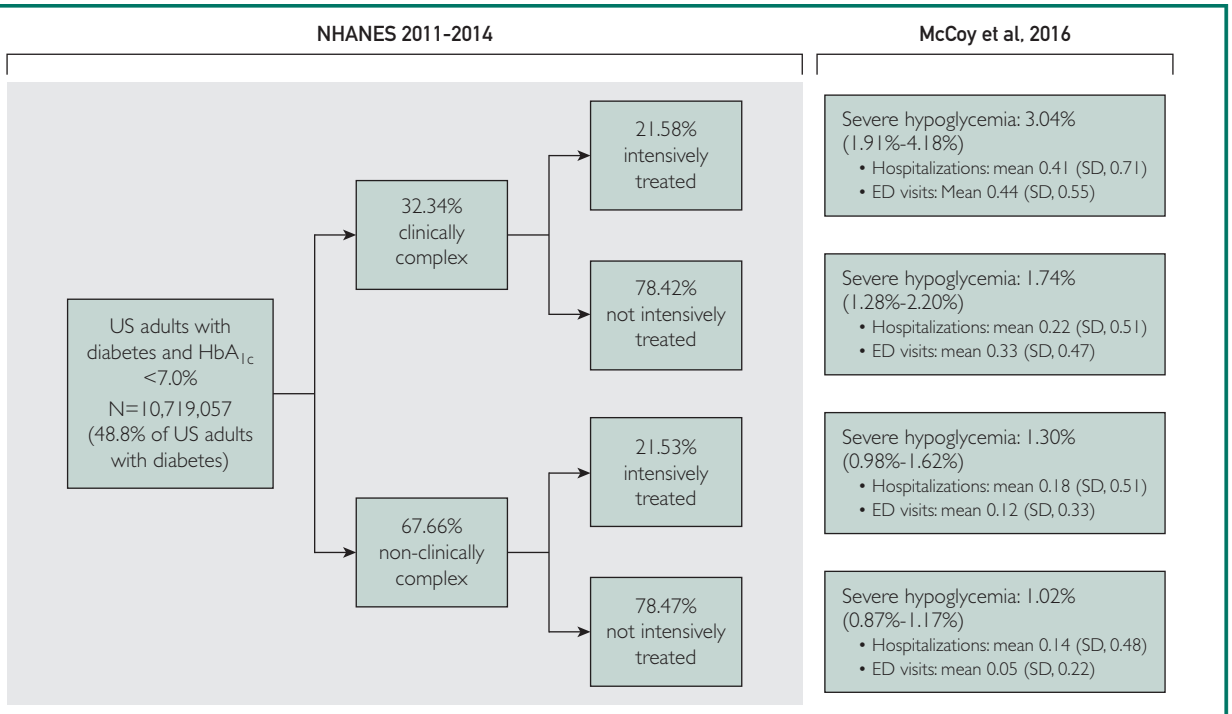

FIGURE. Study design. Population-level estimates of rates of emergency department (ED) visits and hospitalizations for hypoglycemia were estimated by applying hypoglycemia rate estimates for clinically complex and non—clinically complex adults receiving intensive and nonintensive glucose-lowering treatment from the observational study by McCoy et al[14] to participants meeting these definitions within the National Health and Nutrition Examination Survey (NHANES) sample. The shaded boxes provide data from the NHANES population-level estimate, while non-shaded boxed on the right reflect previously published data from McCoy et al on percent of patients with any hospitalization(s) or any ED visit(s) for severe hypoglycemia during a 2-year study period and the mean (SD) number of events.

analysis, we performed a sensitivity analysis that restricted the study population to NHANES participants not treated with insulin and report those findings in the Supplemental Material. Respondents with a history of hypoglycemia were not excluded (even though they were excluded in the study by McCoy et al[14]) because these data are not available in NHANES. This further underestimates the hypoglycemia event rate because prior hypoglycemia is one of the strongest risk factors for future hypoglycemia.[18-24]

Statistical Analyses

We calculated the weighted proportions of NHANES participants who were clinically-complex and/or intensively treated. Analyses incorporated a complex survey design using NHANES-recommended methods to produce nationally representative estimates. All data show annualized estimates of the number of US adults with the outcome of interest based on the mean of values across the 4 study years. Univariate between-group comparisons were conducted using Rao-Scott χ^2 tests for categorical variables and log-linear Wald χ^2 tests for continuous variables, with mean ± SDs values presented when applicable. Analyses were performed using SAS, version 9.4 (SAS Institute Inc).

National estimates of hypoglycemia-related ED visits and hospitalizations among intensively treated patients were derived using a decision analytic model developed in Microsoft Excel. To assess uncertainty when estimating attributable events, a probabilistic sensitivity analysis (PSA) was performed for hospitalizations and ED visits directly attributable to intensive treatment. The PSA was performed by simultaneously drawing from appropriate distribution functions for each model parameter according to their mean values and standard errors. This process of drawing parameters and running the model was repeated 1000 times and results are presented graphically. In the PSA, NHANES estimates (population size, proportion of high complexity, and proportion treated intensively), probability of a severe hypoglycemic event, and number of hypoglycemia-related ED visits and hospitalizations were included. Results are presented as the resampling derived 95% CI (eg, the 2.5 and 97.5 percentiles).

RESULTS

Between 2011 and 2014, we identified 662 nonpregnant adults with diagnosed diabetes and HbA_{1c} levels less than 7.0%, representing an estimated 10.7 million individuals (48.8% of the total US adult diabetic population). Mean patient age was 61.2 years; 2,153,814 of 10,719,057 (20.1%) were 75 years or older (Table 1). Overall, 21.5% of participants (representing 2,309,556 of 10,719,057 US adults) were treated intensively and 8,409,501 of 10,719,057 (78.5%) were treated nonintensively. Nearly one-third (32.3%; 3,466,713 of 10,719,057) of the study population were clinically complex. Non-Hispanic whites comprised 64.3% (6,888,284 of 10,719,057) of the population, and 26.8% (2,867,012 of 10,696,283 who had responded to the education question) had less than a high school education.

Prevalence of Intensive Glucose-Lowering Therapy

The prevalence of intensive treatment was 21.6% (748,111 of 3,466,713) among clinically complex patients and 21.5% (1,561,445 of 7,252,344) among non−clinically complex patients. Table 1 compares intensively and non−intensively treated patients. Intensively treated patients were more likely to use insulin (20.4% [471,195 of 2,309,556] vs 10.5% [879,597 of 8,409,501]) and take 2 or more glucose-lowering medications. There was no statistically significant difference in comorbidity burden between intensively treated and non−intensively treated patients. However, the point estimates for nearly all conditions were higher among intensively treated patients except for cancer and CKD. There was also no difference in patient age, race/ethnicity, diabetes duration, or educational attainment between intensively treated and non−intensively treated patients. Intensively treated patients were significantly less likely to be uninsured or have private health insurance but much more likely to have public health insurance (P=.04).

TABLE 1. Characteristics of US Adults With Controlled Diabetes, 2011 to 2014[a,b]

	Total % (N[c])	Intensive treatment % (N[c])	Nonintensive treatment % (N[c])	*P*
No. of patients	10,719,057	2,309,556	8,409,501	
Clinically complex	32.34 (3,466,713)	32.39 (748,111)	32.33 (2,718,602)	.99
Age (y), mean ± SD	61.24±0.56	61.27±1.11	61.23±0.56	.30
Age category (y)				
18-44	11.61 (1,244,165)	8.55 (197,564)	12.45 (1,046,600)	
45-64	44.23 (4,740,936)	48.07 (1,110,114)	43.18 (3,630,822)	
65-74	24.07 (2,580,142)	28.92 (667,862)	22.74 (1,912,280)	
≥75	20.09 (2,153,814)	14.46 (334,016)	21.64 (1,819,798)	
Female	52.69 (5,647,870)	42.06 (971,461)	55.61 (3,733,092)	.05
Race/ethnicity				.57
Hispanic	12.26 (1,313,667)	9.38 (216,521)	13.05 (1,097,146)	
Non-Hispanic white	64.26 (6,888,284)	67.78 (1,565,440)	63.30 (5,322,844)	
Non-Hispanic black	15.03 (1,611,179)	15.77 (364,153)	14.83 (1,247,026)	
Non-Hispanic Asian	5.21 (558,978)	5.02 (115,830)	5.27 (443,148)	
Other/multiracial	3.24 (346,950)	2.06 (47,613)	3.56 (299,336)	
Education[g]				.22
<High school	26.80 (2,867,012)	24.48 (561,588)	27.44 (2,305,424)	
High school/General Education Development	23.38 (2,501,062)	15.91 (365,001)	25.42 (2,136,062)	
Some college	31.72 (3,392,522)	35.71 (819,192)	30.63 (2,573,330)	
College degree	18.10 (1,935,686)	23.90 (548,235)	16.51 (1,387,451)	
Hemoglobin A_{1c} range				—
≤5.6%	14.17 (1,519,233)	32.71 (755,493)	9.08 (763,740)	
5.7%-6.4%	52.55 (5,632,568)	67.29 (1,554,063)	48.50 (4,078,504)	
6.5%-6.9%	33.28 (3,567,257)	—	42.42 (1,983,921)	
Insulin use[d]	12.60 (1,350,792)	20.40 (471,195)	10.46 (879,597)	.01
Noninsulin medication use[e]				<.001
0 drug	24.95 (2,674,428)	8.18 (188,947)	37.30 (3,137,084)	
1 drug	44.67 (4,788,016)	33.56 (775,178)	49.27 (4,143,611)	
2 drugs	20.61 (2,209,155)	44.39 (1,025,238)	10.71 (900,948)	
3 drugs	8.25 (884,512)	10.98 (253,673)	2.71 (227,858)	
4 drugs	1.52 (162,946)	2.88 (66,521)	0.00 (0)	
Primary insurance				.04
None	9.67 (1,036,736)	7.46 (172,270)	10.28 (864,465)	
Medicare	37.57 (4,027,552)	35.16 (811,937)	38.24 (3,215,615)	
Medicaid	7.02 (752,676)	6.12 (141,230)	7.27 (611,445)	
Dual-eligible	5.90 (632,466)	8.02 (183,319)	5.32 (447,148)	
Private	30.64 (3,284,501)	25.82 (596,374)	31.97 (2,688,127)	
Other public[f]	9.19 (985,126)	17.42 (402,426)	6.93 (582,701)	
Comorbid conditions[g]				
≥2 activity of daily living limitations[c]	12.74 (1,365,383)	14.93 (344,896)	12.13 (1,020,487)	.62
End-stage renal disease or dialysis	2.12 (227,766)	3.01 (69,597)	1.88 (158,169)	.62
Chronic kidney disease (non–end stage)	7.26 (761,159)	4.15 (92,896)	8.11 (668,263)	.06
Heart failure	10.46 (1,116,906)	11.17 (257,382)	10.26 (859,524)	.82
Coronary heart disease	15.64 (1,669,618)	15.99 (367,296)	15.55 (1,302,321)	.92
Stroke	9.36 (1,002,388)	12.39 (286,099)	8.53 (716,290)	.21
Lung disease	18.73 (1,995,211)	25.96 (594,929)	16.74 (1,400,282)	.06
Cancer in past 5 y	5.29 (528,140)	3.65 (75,607)	5.72 (452,533)	.42
Diabetes duration (y)				.81
<5	39.42 (4,225,486)	37.63 (869,088)	39.91 (3,356,397)	

Continued on next page

TABLE 1. Continued

	Total % (N[c])	Intensive treatment % (N[c])	Nonintensive treatment % (N[c])	*P*
Diabetes duration (y), continued				
5-10	22.69 (2,432,379)	20.25 (467,666)	23.36 (1,964,713)	
≥10	37.89 (4,061,192)	42.12 (972,801)	36.73 (3,088,391)	

[a]Percentages are calculated down each column (ie, with the denominator set to the total, intensively treated, and non–intensively treated patient populations). All percentages were calculated taking into account complex survey design. Estimated numbers of US adults corresponding to each percentage are shown in parentheses, except when otherwise specified. Raw numbers for the NHANES participants are omitted because they do not directly correspond to the percentages due to weighting.

[b]National Health and Nutrition Examination Survey design is not a simple random sample but uses complex multistage techniques to select participants representative of the noninstitutionalized US civilian population. Oversampling of particular subgroups is done to account for differences in response rates and improve the statistical precision of underrepresented populations. Appropriate survey weights are then applied to obtain nationally representative population estimates from this sample.

[c]Activities of daily living include dressing/bathing, eating, walking, toileting, and hygiene.

[d]Insulin use, alone or in combination with noninsulin drugs. Each type of insulin (eg, rapid acting or long acting) was considered separately.

[e]Number of noninsulin glucose-lowering medications used by the patient, with or without concurrent insulin use.

[f]Other public health insurance types included State Children's Health Insurance Program, military health care, Indian Health Service, state-sponsored health plan, or other government insurance as reported in the National Health and Nutrition Examination Survey. Patients with Medicare and any other insurance type except for Medicaid were considered as being covered by Medicare only.

[g]Due to missing information as NHANES respondents refused to answer or did not know, denominators may be smaller than those reported as the number of patients in each column. Percentages reported are based on the denominator associated with the reported count.

Estimate of Severe Hypoglycemia-Related Events

Over a 2-year period, we predicted 31,511 hospitalizations and 30,954 ED visits to occur for severe hypoglycemia among US adults with diabetes and HbA_{1c} levels less than 7.0%. Most of these events would be experienced by clinically complex patients (Table 2). Of these, an estimated 4,774 hospitalizations (95% CI, 945-9,714) and 4,804 ED visits (95% CI, 862-9,851) could be directly attributed to intensive glucose-lowering therapy.

Sensitivity Analyses

There were 573 participants within NHANES who had HbA_{1c} levels less than 7.0% and were not treated with insulin, corresponding to 87.4% of the base population, or approximately 9.4 million people (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org). They were generally similar to the broader study population. When compared with the general population of US adults with HbA_{1c} levels less than 7.0%, the subset not treated with insulin was slightly younger (60.8 vs 61.2 years), mostly due to having a higher proportion of patients aged 45 to 64 years. Patients who were intensively treated without the use of insulin were also more likely to have HbA_{1c} levels of 5.6% or less (by definition, they were treated with another glucose-lowering medication at that low HbA_{1c} level). The prevalence of nearly all chronic conditions was lower in the non–insulin-treated cohort, with the exception of cancer, which was equally prevalent in both.

In the non–insulin-treated cohort, we estimated a total of 50,337 severe hypoglycemic events with 25,712 hospitalizations (51.1%) and 24,625 ED visits (48.9%) over a 2-year period. Most of these events would also occur among the clinically complex (Supplemental Table 3, available online at http://www.mayoclinicproceedings.org). Of these, an estimated 3428 (95% CI, 878-6701) hospitalizations and 3409 (95% CI, 768-7022) ED visits could be directly attributed to intensive treatment.

DISCUSSION

More than 10.7 million, or nearly half of, US adults with diabetes had HbA_{1c} levels less than 7.0% between 2011 and 2014, and 2.3 million of these patients were treated much more intensively than recommended by current evidence-based guidelines.[7-9] Such intensive treatment is not harmless. It promotes polypharmacy, with 13.9% (320,194 of 2,309,556) of intensively treated patients

TABLE 2. Severe Hypoglycemia-Related Events Within 2 Years[a]

	Nonintensive treatment	Intensive treatment	Total	Events attributable to intensive treatment
Hospitalizations				
Low complexity	8127	3654	11,781	787 (95% CI, 0-1812)
High complexity	10,406	9324	19,730	3987 (95% CI, 374-8925)
US total	18,533	12,978	31,511	4774 (95% CI, 945-9714)
Emergency department visits				
Low complexity	2902	2436	5338	525 (95% CI, 0-1241)
High complexity	15,610	10,006	25,616	4279 (95% CI, 431-9286)
US total	18,512	12,442	30,954	4804 (95% CI, 862-9851)

[a]The number of severe hypoglycemia hospitalizations and emergency department visits was estimated by applying rates from McCoy et al[14] 2016 to nonpregnant National Health and Nutrition Examination Survey participants with diabetes who met analogous inclusion criteria (≥18 years and glycated hemoglobin <7.0%). Events attributable to intensive treatment were calculated by applying event rates expected with nonintensive treatment to patients receiving intensive therapy. The 95% CIs were estimated using probabilistic sensitivity analysis.

taking 3 or more noninsulin medications, sometimes in addition to insulin, thereby increasing treatment burden, risk for adverse drug reactions, and costs of diabetes care. In addition, we estimated that such intensive glucose-lowering therapy contributed to at least 4774 hospitalizations and 4804 ED visits for severe hypoglycemia over 2 years, primarily among clinically complex patients. Such hypoglycemia can in turn lead to death,[25-29] cardiovascular disease,[28-30] cognitive decline,[31] disability,[32] impaired quality of life,[33] and high costs of care.[32]

There is little evidence that treating to very low HbA_{1c} levels improves patient outcomes, especially in the context of multimorbidity and advanced age.[34] Despite explicit guidance to avoid intensive treatment in clinically complex and elderly patients,[7-10] this did not translate into clinical practice because the prevalence of intensive treatment was nearly identical irrespective of patient clinical complexity. More relaxed glycemic targets are also recommended for patients with long-standing diabetes, and we found no difference in treatment intensity by diabetes duration.

These findings are consistent with historical data demonstrating a high prevalence of potential overtreatment in a variety of settings in the United States,[11-14] and lack of improvement in recent years despite growing recognition of the harms of overtreatment is concerning. The most recent population-level assessment of intensive glycemic control in the United States before our study focused on the use of insulin and sulfonylurea drugs to achieve HbA_{1c} levels less than 7.0% among patients 65 years or older between 2001 and 2010.[12] By this definition, 55% of older adults with diabetes were potentially overtreated, with a greater prevalence of overtreatment among patients with worsening health status. Similarly, there was no variation in potential overtreatment by clinical complexity or life expectancy in studies conducted among Veterans Affairs patients, in which 50% of patients 75 years or older or with dementia or CKD were treated with insulin or sulfonylurea to achieve HbA_{1c} levels less than 7.0%,[11] or in the privately insured population, in which the prevalence of potential overtreatment (defined by the use of more glucose-lowering medications than recommended at low HbA_{1c} levels) among the clinically complex was 18.7% (731 of 3910).[14]

The prevalence of intensive treatment in our study was lower than that in the mentioned population-based studies[11-13] due to the inclusion of adults of all ages and use of a more stringent definition of intensive treatment, which was predicated on both HbA_{1c} level and the number of medications used to achieve it. We chose the latter definition because use of insulin and sulfonylurea drugs to achieve HbA_{1c} levels less than 7.0% does not necessarily translate to overtreatment. These medications can be used safely and may be the only treatment options available for the management of diabetes in specific

clinical contexts. In contrast, use of glucose-lowering medications to achieve HbA_{1c} levels of 5.6% or lower, or the use of 2 or more medications to achieve HbA_{1c} levels of 5.7% to 6.4%, is not consistent with clinical practice guidelines and is more likely to denote excessive glucose-lowering therapy. When compared with the earlier study of potential overtreatment among commercially insured and Medicare Advantage beneficiaries between 2001 and 2013, the current prevalence of intensive treatment among US adults was higher among high-complexity patients but lower among low-complexity patients. Specifically, our study found that 21.6% (corresponding to 748,111 of 3,466,713 US adults) of high-complexity adults were treated intensively compared with 18.7% (731 of 3910) of privately insured complex patients.[14] Conversely, intensive treatment rates were 21.5% (1,561,445 of 7,252,344) among low-complexity US adults in this study vs 26.5% (7317 of 27,632) among corresponding low-complexity privately insured beneficiaries.[14] These differences likely reflect our study's inclusion of patients with public or no health insurance, as well as temporal changes in diabetes management. For example, individuals without health insurance were much less likely to be intensively treated and also less likely to be clinically complex (eg, older patients, patients with end-stage renal disease, and patients with multiple comorbid conditions are more likely to be insured). These individuals were included in this study but excluded from the earlier work.

There are no population-level data for the rates of ED visits and hospitalizations for hypoglycemia among adults with HbA_{1c} levels less than 7.0%, which based on HbA_{1c} parameters alone is considered to reflect well controlled diabetes. Although our study could not directly quantify all ED visits and hospitalizations for hypoglycemia across the United States, these estimates are the best available data about the number of events attributable to intensive treatment and thus potentially avoidable with guideline-concordant care.

Our sensitivity analysis, which restricted the study cohort to patients not treated with insulin to fully mimic the source data for hypoglycemic event rate estimates, suggested that a substantial number of ED visits and hospitalizations for severe hypoglycemia occurred among insulin-treated clinically complex patients. This reinforces the importance of considering treatment deintensification, including simplification of insulin regimens, among clinically complex patients to reduce their risk for hypoglycemia.

Although there is no standard and universally accepted definition of clinical complexity, the approach used in our study was grounded in the framework proposed by the AGS.[16] It is broader than earlier studies of potential overtreatment, which primarily focused on patients with CKD or dementia,[11,13] but is similar to the approach taken by Lipska et al.[12] Nonetheless, because the same definitions of clinical complexity and intensive treatment were applied to the NHANES population as were used in the source data, the specifics of these definitions do not affect the study results. Specifically, because all events among all patients were counted in the source data and all comparable patients were identified among NHANES respondents, changing the definition of clinical complexity and/or treatment intensity would not alter the total number of observed events. It would merely shift the distribution of events among the 4 subsets of patients, keeping the estimated total number of events in the overall population unchanged. However, the reliance on self-report of comorbid conditions is a limitation because different conditions and ADL limitations are prone to under- and overreporting.

A major limitation of our study is its reliance on hypoglycemia-related hospitalization and ED visit event rates ascertained in a different study population.[14] Source data were obtained from the OptumLabs Data Warehouse, which includes deidentified claims data for privately insured and Medicare Advantage enrollees in a large private US health plan.[35,36] People included in the OptumLabs Data Warehouse represent a diverse mix of ages, ethnicities, and geographic regions across the United States, but nonetheless are not fully representative of the US population. Furthermore, because rates of hypoglycemia-related

ED visits and hospitalizations from a different study cohort were applied to population-level estimates for the distributions of treatment intensities and clinical complexity among US adults, results presented here are an estimate of the number of hospitalizations and ED visits for hypoglycemia rather than the true count of events. The CIs around these estimates are wide, reflecting the relatively low rate of hypoglycemia-related ED visits and hospitalizations in this otherwise low-risk population. This is most noticeable in Table 2, in which the 95% CIs include a lower bound of zero hospitalizations and ED visits due to the low number of those classified as having severe hypoglycemia among those non–clinically complex receiving intensive treatment. Still, this is the only available population-level estimate of the number of hypoglycemia-related events directly attributable to intensive treatment and therefore potentially avoidable.

Importantly, our findings underestimate the true scope of hypoglycemia in the United States because rates of hypoglycemia were extrapolated from lower risk patients: not using insulin, without prior hypoglycemia, and commercially insured.[14] True numbers are likely to be much higher. These estimates also reflect the most severe episodes that required ED care or hospitalization and not the much higher true burden of hypoglycemia in the management of diabetes. Most hypoglycemic events do not come to medical attention but are treated by the patient or caregivers or by medical personnel outside the ED or hospital setting.[37-39] Furthermore, most hypoglycemic events occur in patients with elevated HbA_{1c} levels and are not captured in our study. However, the objective of this study was to estimate the number of events directly attributable to intensive treatment and thus potentially avoidable with preemptive identification, treatment de-escalation or simplification, and closer monitoring.[40,41]

CONCLUSION

High-quality diabetes care is predicated on balancing the benefits and harms of glucose-lowering therapy, including avoiding very intensive treatment, particularly among the elderly, the clinically complex, and those with a long duration of diabetes. Hypoglycemia is the most common serious adverse effect of glucose-lowering therapy, but its rates can be reduced with patient-centered evidence-based care. In this study, we found that intensive treatment with glucose-lowering therapy remains common in the United States. There is also no apparent individualization of therapy based on patient clinical complexity, life expectancy, or the likelihood of benefit from targeting low HbA_{1c} levels. Such uniformity of intensive glycemic control and treatment are estimated to have contributed to an excess of over 9500 potentially preventable ED visits and hospitalizations for severe hypoglycemia in the span of 2 years.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ADL** = activities of daily living; **AGS** = American Geriatric Society; **CKD** = chronic kidney disease; **ED** = emergency department; **HbA_{1c}** = glycated hemoglobin; **NHANES** = National Health and Nutrition Examination Survey; **PSA** = probabilistic sensitivity analysis

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