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Treated glycosylated hemoglobin levels in individuals with diabetes mellitus vary little by health status

A retrospective cohort study

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Abstract

As choosing wisely has raised the issue of whether some individuals with type 2 diabetes may be overtreated, we examined the intensity of glycemic control across health status strata defined by comorbidities or frailty.

This is a retrospective cohort study of commercially insured patients from 50 US states (Clinformatics Data Mart). We evaluated treated HbA1c levels in adults with new diabetes diagnosed between January 2004 and December 2009 who had HbA1C measured after at least 1 year of follow-up.

Of 191,590 individuals with diabetes, 78.5% were otherwise healthy, 10.6% had complex health status (3 or more chronic conditions), and 10.9% were very complex (Johns Hopkins Adjusted Clinical Groups frailty marker or end-stage chronic disease). The proportion of patients who were tightly controlled (HbA1C <7%) was similar in otherwise healthy patients (66.1%) and in complex patients (65.8%, $P=0.37$), and although it was lower (60.9%, $P<0.0001$) in very complex patients, the magnitude of the difference was small. A substantial proportion of complex/very complex patients were taking sulfonylurea or insulin despite being at an increased risk for adverse effects from these agents and having tightly controlled HbA1C: 40.6% had HbA1C <7% and 24% had HbA1C <6.5%. Among patients with HbA1C <7%, use of insulin or sulfonylureas was associated with an increased risk for all-cause hospitalization [aHR 1.54, 95% confidence interval (95% CI) 1.45–1.64] and for emergency room visits (aHR 1.44, 95% CI 1.35–1.53) over the subsequent median 6 months follow-up.

Diabetic control was similar regardless of comorbidity burden and frailty status. Despite being at a higher risk for adverse effects, nearly half of complex and very complex patients were still receiving insulin or sulfonylureas despite having treated HbA1C levels <7%, and these patients did exhibit higher risk of all-cause hospitalizations or emergency visits subsequently.

Abbreviations: ACG = adjusted clinical groups, ADA = American Diabetes Association, AGS = American Geriatrics Association, aHR = adjusted hazard ratio, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, ED = emergency department, EDWG = European Diabetes Working Group, eGFR = estimated Glomerular Filtration Rate, HbA1C = Glycosylated hemoglobin, HF = heart failure, ICD-9 = International Classification of Disease-9th Revision, IQR = Interquartile Range, NHANES = National Health And Nutrition Examination Survey, TIA = transient ischemic attack, VA = Veterans Affairs.

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1. Introduction

Although intensive glucose control [glycosylated hemoglobin (HbA1c) <7%] produces microvascular and mortality benefits in younger patients with type 1 diabetes mellitus (DM),[1,2] the benefits of intensive control in patients with type 2 DM are less certain with conflicting trial results and pooled data suggesting no impact on all-cause mortality and indeterminate results for micro or macrovascular events.[3–5] Moreover, observational studies suggest that comorbidities increase the risks and lessen the benefits of pursuing intensive glycemic control in patients with Type 2 DM, especially older patients.[6–10] Thus, current guidelines from the American Diabetes Association,[11] the American Geriatrics Society,[12] the Canadian Diabetes Association,[13] and the European Diabetes Working Group[14] recommend individualization of treatment intensity based on each patient's burden of comorbidities, frailty status, and life expectancy. However, a recent analysis of NHANES data suggested that most older individuals with diabetes may be overtreated in that nearly two-third had HbA1c <7% with no differences between healthy individuals and those with extensive comorbidities and/or foreshortened life expectancy.[15]

The guidelines recommend HbA1c goals of less than 7.0% in healthy individuals (<7.5% in healthy patients older than 65 years), less than 8.0% in those who are "complex" (defined as having 3 or more chronic conditions), and less than 8.5% for patients who are very complex (defined as having at least 1 end-stage chronic illness or impairments in 2 or more activities of daily living).[11–14] The purpose of this study is to examine blood glucose control in a large cohort of insured patients with incident diabetes and explore whether control varies by health status to confirm or refute the findings from the NHANES analysis done in less than 1300 patients.[15]

2. Methods

As previously described,[16] we conducted a population-based retrospective cohort study using a large US claims and integrated laboratory database that included employed, commercially insured patients and their dependents from all 50 States (Clinformatics Data Mart Database; OptumInsight, Eden Prairie, MN). Clinformatics Drug Mart is a research affiliate of United Healthcare, 1 of the largest health care companies in the United States, with over 13 million lives included per annum and 340,000 affiliated physicians among all 50 states. Clinformatics collects complete health service utilization data, including US medical, pharmacy, and laboratory results. All patients are in standard commercial or managed care plans. Clinformatics places a significant emphasis on the quality of the data and uses a series of internal data evaluation and reconciliation steps to ensure the completeness, validity, and consistency of the data. Indeed, Clinformatics (formerly i3) is one of the few data sources approved by the FDA's Mini-Sentinel Program to perform active surveillance of the safety of marketed medical products, including drugs and biologics because of the internal strength and representativeness of the US population. Patient-level data are collected directly from each clinical encounter (inpatient and outpatient) and the database includes de-identified longitudinal patient clinical data, all laboratory tests and results, and pharmacy claims data (de-identified prescribing physician, drug dispensed based on National Drug Codes, quantity and date dispensed, drug strength, days supply, cost of service). The database contains over 13 million annual lives and data are updated every 90 days.

All patients in our cohort were followed prospectively until death, termination of medical insurance, or December 31, 2010, providing a maximum follow-up of 6 years. All data were de-identified and accessed with protocols compliant with the Health Insurance Portability and Accountability Act. The study was approved by the ethics review board of the University of Alberta, Edmonton, Alberta, Canada, and the New England Ethics Institutional Review Board, Massachusetts.

2.1. Cohort selection

We identified all patients aged 20 years or older with at least 1 hospitalization or 2 physician claims within 2 years for ICD-9 250.x (DM) using physician claims, hospital discharge abstracts, and/or ambulatory care visits, or a first claim for an oral antihyperglycemic drug or insulin, between January 1, 2004, and December 31, 2009. These were all incident cases, as none had a history of diabetes visits or diabetes drug therapy in the previous 2 years. This definition of incident diabetes has been widely utilized and validated, and has a specificity of 92% to 97% for correctly identifying patients with diabetes.[17,18] In order to be eligible for this study, patients in the cohort had to have had at least 1 HbA1C measurement after the diagnosis of diabetes and had to have at least 1 year of coverage before the last HbA1C (to ensure that we had sufficient data to accurately classify patients' health status at the time of the index HbA1C measurement as described below).

2.2. Definition of health status

For each patient, we calculated the Johns Hopkins Adjusted Clinical Groups (ACG) Case-Mix System score (a single comorbidity score weighted by the 32 Adjusted Diagnostic Groups that performs equally or better than the Charlson and Elixhauser comorbidity scores) using all visits up to and including the date that the HbA1C we used to define their DM control was drawn (see below).[19] In addition, the Johns Hopkins ACG System includes a frailty marker for any patients with notations of malnutrition, abnormal weight loss, difficulty walking, fecal/urinary incontinence, morbid obesity, dementia, falls, or decubitus ulcer.

To mirror the NHANES study[15] and the recommendations from the ADA and AGS,[11,12] we defined complex health status if a patient had 3 or more chronic conditions: arthritis, heart failure but without hospitalization as most responsible diagnosis in the past year, chronic obstructive pulmonary disease (COPD) without hospitalization as most responsible diagnosis in the past year, chronic kidney disease but not requiring dialysis, coronary heart disease (prior MI or angina), stroke, urinary incontinence, cancer, depression, or hypertension.

We defined very complex health status if a patient had the frailty marker derived by the Johns Hopkins ACG system (which corresponds to the variable "impairments in activities of daily living"[20] suggested by the ADA and AGS) or if they had end-stage renal disease requiring dialysis, heart failure with a most responsible heart failure hospitalization in the past year, COPD with a most responsible COPD hospitalization in the past year, metastatic cancer, or severe cognitive impairment.

Finally, mirroring a recent publication from the Veterans Health Administration,[21] we examined HbA1C control among patients being treated with sulfonylureas and/or insulin who had comorbidities, which made them high-risk for hypoglycemia

(such as advanced age, chronic kidney disease, dementia, or advanced diabetes complications).

2.3. Definition of diabetic control

We used the last recorded HbA1C for each patient. Thus, health status, medications, and covariates were all drawn from the database up to, and including, the date of that HbA1C measurement.

2.4. Covariates

The specific variables included were age; sex; socioeconomic status [type of medical insurance (Health Maintenance Organization insurance agreements, preferred provider plans, exclusive provider plans, point of service plans, etc) and median household income based on Census region and according to the 2010 US census]; clinical laboratory data [HbA1c, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, estimated glomerular filtration rate (eGFR) (according to the modified diet in renal disease calculation: ≥90; 89.9–60; 59.9–30; <30), albuminuria]; and glucose-lowering medications. For all covariates, we used values closest to the index HbA1C measurement date (up to and including the index date) and for medications we used all prescriptions in the 90 days before and including the index date. To further control for comorbidities, we used the Johns Hopkins ACG System score. In addition, we included the Expanded Diagnosis Cluster for Diabetes embedded within the Johns Hopkins Adjusted Clinical Groups Case-Mix System, which includes validated algorithms for 16 diabetes complications (ranging from ketoacidosis to renal/retinal manifestations) to further control for diabetes-specific complications.

2.5. Other outcomes

In those patients with index HbA1C <7%, we examined the frequency of all-cause hospitalizations or emergency department (ED) visits and hospitalizations/ED visits for major cardiovascular events (acute coronary syndrome, stroke/transient ischemic attack, heart failure) after the index HbA1C measurement as secondary outcomes. We conducted multivariable Cox proportional hazards regression to examine which factors predicted hospitalizations or ED visits.

2.6. Statistical analysis

Patient characteristics were reported as means and standard deviations for continuous variables and proportions for categorical variables. Analysis of variance (ANOVA) and Chi-squared tests were used to compare characteristics between health status tiers. Diabetic control was determined by calculating the proportion of patients having HbA1C within specified cut-points (i.e., <7%; 7.0–7.9%, 8.0–8.9%, and >9%) and compared among the health status groups using Chi-squared tests. For the secondary outcomes (hospitalizations and ED visits), multivariable Cox proportional hazards models were used to calculate adjusted hazard ratios, including covariates for health status, age, sex, type of insurance, ADG comorbidity score, lab measurements, time between incident diagnosis of diabetes and HbA1c measurement, and diabetes medications. Only lab values contained any missing values, and in such cases, the missing indicator approach was used so that no patients were excluded from the analysis. In addition to our primary analyses involving all incident diabetes patients over age 20, we restricted our analyses to only those patients 65 years and older (at the time of HbA1c measurement) in a sensitivity analysis. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

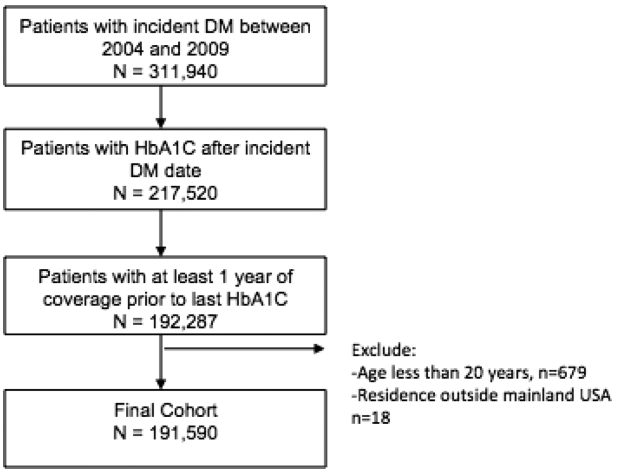

Figure 1. Derivation of study cohort.

3. Results

Of 311,940 individuals with incident diabetes during the study period, 191,590 had a HbA1C drawn after diabetes diagnosis and had at least 1 year of coverage before that HbA1C being drawn and thus formed our study cohort (Fig. 1). The median time until the HbA1C measurement (used to define diabetic control) after the diagnosis of diabetes was 744 days [interquartile range (IQR) 436–1191].

Most patients (78.5%) in the study cohort were relatively healthy, but 10.6% met the definition for complex and 10.9% for very complex health status. Not surprisingly, the frequency of comorbidities, diabetes complications, lower eGFR, prior hospitalizations or ED visits, number of outpatient visits in prior year, and number of physicians seen in prior year were all greater in the complex and very complex patients, although it is noteworthy that even in the relatively healthy subgroup, 30.7% had a diabetes complication recorded by the time the HbA1C we used to define diabetic control was measured (Table 1). Interestingly, although use of metformin and thiazolidinediones was similar across patient subgroups, insulin and sulfonylurea use was greater in complex and very complex patients (Table 1). Patterns were identical when we restricted the analysis to patients 65 years or older (data available upon request).

Diabetic control was identical in patients who were relatively healthy compared with those with complex health status (mean HbA1C 6.9% in both groups) but was marginally less intensive in patients with very complex health status (mean 7.1%, $P<0.0001$). The proportion of patients who were tightly controlled (HbA1C <7%) was similar in relatively healthy patients (66.1%) and in complex patients (65.8%, $P=0.37$), and although it was lower (60.9%, $P<0.0001$) in very complex patients, the magnitude of the difference was small (Fig. 2). In fact, on-treatment HbA1C was <6.5% not only in 49.4% of relatively healthy patients but also in 48.8% of those meeting the definition

Table 1

Patient socio-demographics, health care utilization, lab results, and prescription drug use up until the time of the index HbA1C measurement, stratified according to patient health status.

Characteristics	Overall (N = 191,590)	Relatively healthy (N = 150,420)	Complex (N = 20,245)	Very complex (N = 20,925)	*P*
Age, mean (SD)	54.0 (9.9)	53.2 (9.9)	59.4 (8.1)	54.2 (10.1)	<0.0001
Female, n (%)	89,151 (46.5)	69,317 (46.1)	8691 (42.9)	11143 (53.3)	<0.0001
Income, mean (SD)	49,314.8 (6906.1)	49,390.2 (6947.8)	48,721.7 (6521.4)	49,346.3 (6939.9)	<0.0001
Insurance type					<0.0001
Point of service	114,795 (59.9)	91,108 (60.6)	11,614 (57.4)	12,073 (57.7)	
Exclusive provider	33,826 (17.7)	26,275 (17.5)	3597 (17.8)	3954 (18.9)	
Health maintenance	27,296 (14.2)	20,901 (13.9)	3257 (16.1)	3138 (15.0)	
Preferred provider	14,644 (7.6)	11,416 (7.6)	1604 (7.9)	1624 (7.8)	
Independent	940 (0.5)	675 (0.4)	153 (0.8)	112 (0.5)	
Other	89 (0.0)	45 (0.0)	20 (0.1)	24 (0.1)	
Adjusted diagnostic groups comorbidity score (median, IQR)	15 (5–22)	11 (4–19)	25 (19–32)	21 (13–29)	<0.0001
History of diabetes complications*	74,530 (38.9)	46,152 (30.7)	16,367 (80.8)	12,011 (57.4)	<0.0001
Criteria for very complex group (any 1)					
Frailty	18,551 (9.7)	0 (0.0)	0 (0.0)	18551 (88.7)	<0.0001
CKD requiring dialysis	359 (0.2)	0 (0.0)	0 (0.0)	359 (1.7)	<0.0001
Heart failure with MRDx hospitalization in the past year	566 (0.3)	0 (0.0)	0 (0.0)	566 (2.7)	<0.0001
COPD with MRDx hospitalization in the past year	333 (0.2)	0 (0.0)	0 (0.0)	333 (1.6)	<0.0001
Metastatic cancer	744 (0.4)	0 (0.0)	0 (0.0)	744 (3.6)	<0.0001
Severe cognitive impairment	1594 (0.8)	0 (0.0)	0 (0.0)	1594 (7.6)	<0.0001
Criteria for Complex Group (at least 3)					
Arthritis	1978 (1.0)	827 (0.5)	804 (4.0)	347 (1.7)	<0.0001
Heart failure without hospitalization as MRDx in the past year	8357 (4.4)	1123 (0.7)	4992 (24.7)	2242 (10.7)	<0.0001
COPD without MRDx hospitalization in the past year	10,370 (5.4)	3092 (2.1)	5206 (25.7)	2072 (9.9)	<0.0001
CKD not requiring dialysis	8243 (4.3)	2845 (1.9)	3566 (17.6)	1832 (8.8)	<0.0001
Coronary heart disease (prior MI or angina)	40,287 (21.0)	18,121 (12.0)	15,631 (77.2)	6535 (31.2)	<0.0001
Stroke	18,574 (9.7)	5807 (3.9)	9258 (45.7)	3509 (16.8)	<0.0001
Urinary incontinence	2354 (1.2)	907 (0.6)	903 (4.5)	544 (2.6)	<0.0001
Nonmetastatic cancer	7047 (3.7)	3055 (2.0)	2892 (14.3)	1100 (5.3)	<0.0001
Depression	17,471 (9.1)	8443 (5.6)	5465 (27.0)	3563 (17.0)	<0.0001
Hypertension	151,780 (79.2)	112,498 (74.8)	20,051 (99.0)	19,231 (91.9)	<0.0001
At least one inpatient hospitalization in prior year, n (%)	16,449 (8.6)	7347 (4.9)	4163 (20.6)	4939 (23.6)	<0.0001
At least one ED visit in prior year, n (%)	19,083 (10.0)	12,134 (8.1)	3347 (16.5)	3602 (17.2)	<0.0001
Estimated glomerular filtration rate category, mL/min					<0.0001
<30	1578 (0.8)	503 (0.3)	550 (2.7)	525 (2.5)	
30 to <60	19,685 (10.4)	12548 (8.4)	4176 (20.7)	2961 (14.2)	
≥60	168,317 (88.8)	135,587 (91.2)	15,411 (76.5)	17,319 (83.2)	
Mean (SD) HbA1C value	6.9 (1.5)	6.9 (1.5)	6.9 (1.4)	7.1 (1.7)	<0.0001
Mean (SD) hemoglobin, mg/dL	14.0 (1.5)	14.1 (1.5)	13.8 (1.6)	13.5 (1.6)	<0.0001
Drug use in the 90d preceding the index HbA1C measurement (not mutually exclusive)					
Insulin	21,325 (11.1)	14,640 (9.7)	3010 (14.9)	3675 (17.6)	<0.0001
Sulfonylurea	35,806 (18.7)	27,328 (18.2)	4124 (20.4)	4354 (20.8)	<0.0001
Metformin	73,350 (38.3)	58,132 (38.6)	6877 (34.0)	8341 (39.9)	<0.0001
Thiazolidinedione	27,742 (14.5)	21,818 (14.5)	2749 (13.6)	3175 (15.2)	<0.0001
Dipeptidyl peptidase 4 inhibitor	12,013 (6.3)	8898 (5.9)	1502 (7.4)	1613 (7.7)	<0.0001
Other antidiabetic agent	6688 (3.5)	4793 (3.2)	767 (3.8)	1128 (5.4)	<0.0001
Health care utilization in the year before index HbA1C measurement					
Number of unique physicians, mean (SD)	2.0 (2.0)	1.7 (1.3)	3.5 (2.9)	3.3 (3.4)	<0.0001
Number of physician visits, mean (SD)	5.3 (6.6)	4.2 (3.7)	9.4 (9.2)	9.5 (13.2)	<0.0001
Number of primary care visits, mean (SD)	3.5 (3.5)	3.0 (2.6)	4.8 (4.4)	5.3 (6.0)	<0.0001
Number of specialist care visits, mean (SD)	1.8 (4.6)	1.1 (2.4)	4.6 (6.9)	4.3 (9.2)	<0.0001

Patient characteristics are reported as means and standard deviations for continuous variables and proportions for categorical variables.

Complex health status defined by presence of 3 or more of arthritis, heart failure but without hospitalization as most responsible diagnosis in the past year, lung disease (COPD), chronic kidney disease but not requiring dialysis, coronary heart disease (prior MI or angina), stroke, urinary incontinence, cancer, depression, hypertension, or falls.

Very complex health status defined by presence of frailty marker or at least one of end-stage renal disease requiring dialysis, heart failure with a most responsible heart failure hospitalization in the past year, oxygen-dependent lung disease, metastatic cancer, or severe cognitive impairment.

* Derived from the Expanded Diagnosis Cluster for Diabetes embedded within the Johns Hopkins Adjusted Clinical Groups Case-Mix System, which includes validated algorithms for 16 diabetes complications (ranging from ketoacidosis to renal/retinal manifestations).

for complex health status and in 44.8% of the very complex status patients.

Of the complex/very complex patients who were using sulfonylurea or insulin despite being at an increased risk for adverse effects from these agents (Table 2), a substantial proportion had very tightly controlled HbA1C. For example, 40.6% of patients aged 75 years or older, or with dementia, or with chronic kidney disease were still taking sulfonylurea or

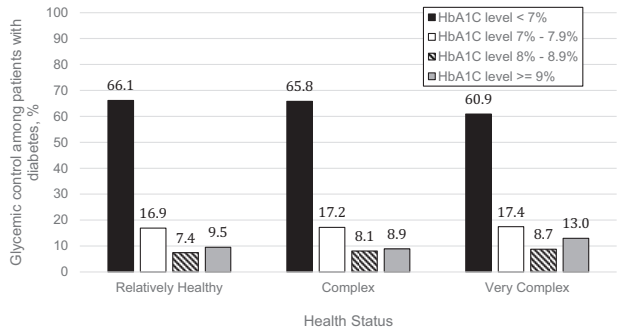

Figure 2. Achieved glycemic control among adults with diabetes mellitus across 3 health status categories.

insulin even though their HbA1C was <7% (and 24% were still taking those agents despite having HbA1C <6.5%).

As expected, higher proportions of patients with complex or very complex health status had all-cause hospitalizations or ED visits (Table 3) over a median follow-up of 6 months after the index on-treatment HbA1C measurement. Rates were highest in patients with poor glycemic control and lowest in those with on-treatment HbA1C within guideline-defined optimal ranges (Table 3). Among those patients with on-treatment HbA1C <7%, use of insulin or sulfonylureas was associated with an increased risk for both outcomes (Table 4) even after adjusting for other prognostic factors.

4. Discussion

4.1. Overall findings

Classifying individual health status on the basis of comorbidity burden and presence/absence of frailty, we found that diabetic control was similar for relatively healthy patients, complex patients, and very complex patients, with nearly two-thirds of all 3 groups having HbA1C <7% and nearly one half having HbA1C < 6.5%. Complex and very complex patients were more likely to be treated with insulin or sulfonylureas, and nearly 40% of those at a high risk for hypoglycemia from these agents were still receiving them despite the fact their HbA1C was <7% (and nearly one quarter had HbA1C <6.5%). All-cause hospitalizations or ED visits were more likely in patients with HbA1C <7% being treated with insulin/sulfonylureas even after adjusting for other covariates.

4.2. Comparison with other studies

Recent reports from an elderly subgroup of NHANES participants[15] and the Veterans Health Administration[21] (mean age 66 years, but 48% were younger than 65) have suggested substantial rates of potential overtreatment of diabetic individuals, especially those who are elderly or have multiple comorbidities. Indeed, overtreatment of diabetes in the elderly is one of the conditions highlighted by the Choosing Wisely Campaign.[22] Another recent report from 31,545 patients with well controlled type 2 diabetes not being treated with insulin in the Optum Labs

Table 2

Evaluation of rates of possible overtreatment in high-risk patients being treated with sulfonylurea or insulin.

			Number (percentage) of patients with			
High risk factors	**Number of patients**	**Percentage of total cohort***	**HbA1C < 6.0%**	**HbA1C < 6.5%**	**HbA1C < 7.0%**	**Median HbA1C (IQR)**
75 yrs or older, or CKD, or dementia	5684	10.7	527 (9.3)	1372 (24.1)	2310 (40.6)	7.3 (6.5–8.4)
Above and advanced diabetes complications	7412	13.9	609 (8.2)	1601 (21.6)	2757 (37.2)	7.4 (6.6–8.6)
Above and diminished life expectancy	10,675	20.0	907 (8.5)	2373 (22.2)	4058 (38.0)	7.3 (6.5–8.5)
Above and major neurologic disorders	12,030	22.6	1005 (8.4)	2636 (21.9)	4516 (37.5)	7.4 (6.6–8.6)
Above and cardiovascular disease	23,283	43.7	1783 (7.7)	4818 (20.7)	8563 (36.8)	7.4 (6.6–8.6)
Above and depression	23,733	44.6	1814 (7.6)	4886 (20.6)	8690 (36.6)	7.4 (6.6–8.6)
Above and alcohol/substance abuse	23,973	45.0	1842 (7.7)	4944 (20.6)	8776 (36.6)	7.4 (6.6–8.6)

*Total cohort includes only those being treated with sulfonylurea or insulin (N = 53,258).

Table 3

Hospitalization and emergency department visits after index HbA1C measurement, median follow-up 6 months.

		Relatively healthy patients			Complex patients				Very complex patients			
Outcome	**Full cohort (N = 191,590)**	**HbA1C <7% (N = 99,478)**	**HbA1C >7% (N = 50,942)**	***P***	**HbA1C <7% (N = 13,325)**	**HbA1c 7% to <8% (N = 3483)**	**HbA1C ≥8% (N = 3437)**	***P***	**HbA1C <7% (N = 12,735)**	**HbA1c 7% to <8.5% (N = 4694)**	**HbA1C ≥8.5% (N = 3496)**	***P***
Hospitalization												
All cause	13,308 (6.9)	5041 (5.1)	3151 (6.2)	<0.0001	1611 (12.1)	444 (12.7)	548 (15.9)	<0.0001	1509 (11.8)	495 (10.5)	509 (14.6)	<0.0001
Major cardiovascular event	1914 (1.0)	557 (0.6)	434 (0.9)	<0.0001	263 (2.0)	87 (2.5)	151 (4.4)	<0.0001	236 (1.9)	93 (2.0)	93 (2.7)	0.0107
ED visit												
All cause	14,902 (7.8)	6195 (6.2)	4189 (8.2)	<0.0001	1361 (10.2)	373 (10.7)	466 (13.6)	<0.0001	1319 (10.4)	493 (10.5)	506 (14.5)	<0.0001
Major cardiovascular event	363 (0.2)	136 (0.1)	75 (0.1)	0.6062	46 (0.3)	15 (0.4)	27 (0.8)	0.0022	38 (0.3)	12 (0.3)	14 (0.4)	0.4874

Major cardiovascular event includes acute coronary syndrome, stroke/transient ischemic attack, HF = heart failure.

Table 4

Results of multivariable time to event Cox models for patients with HbA1C < 7% (n = 125,538).

	All-cause hospitalization		All-cause ED visit	
Parameter	**aHR (95% CI)**	***P***	**aHR (95% CI)**	***P***
Health status				
Relatively healthy	1 (Ref)		1 (Ref)	
Complex	1.57 (1.47–1.67)	<0.0001	1.35 (1.27–1.45)	<0.0001
Very complex	1.90 (1.78–2.02)	<0.0001	1.42 (1.33–1.52)	<0.0001
Age	1.02 (1.01–1.02)	<0.0001	0.99 (0.99–1.00)	<0.0001
Female	0.94 (0.90–0.99)	0.02	1.28 (1.22–1.35)	<0.0001
Insurance type				
Point of service	1 (Ref)		1 (Ref)	
Exclusive Provider	1.03 (0.97–1.09)	0.37	1.15 (1.09–1.22)	<0.0001
Health maintenance	1.05 (0.99–1.13)	0.12	1.31 (1.23–1.39)	<0.0001
Preferred provider	1.02 (0.94–1.11)	0.64	1.13 (1.05–1.23)	0.002
Independent	1.02 (0.86–1.20)	0.85	1.02 (0.85–1.23)	0.80
Other	0.72 (0.40–1.31)	0.28	0.48 (0.20–1.16)	0.10
Johns Hopkins Adjusted Clinical Groups Comorbidity Score	1.03 (1.03–1.03)	<0.0001	1.03 (1.02–1.03)	<0.0001
HbA1C	1.01 (0.96–1.06)	0.68	1.16 (1.11–1.22)	<0.0001
GFR	0.997 (0.996–998)	<0.0001	0.999 (0.998–1.000)	0.03
Hemoglobin	0.88 (0.86–0.89)	<0.0001	0.95 (0.93–0.96)	<0.0001
Diabetes complications	1.18 (1.12–1.25)	<0.0001	1.13 (1.07–1.19)	<0.0001
Diabetes medications – any exposure in the 90d prior to event				
None	1 (Ref)		1 (Ref)	
Insulin/Sulfonylureas	1.54 (1.45–1.64)	<0.0001	1.44 (1.35–1.53)	<0.0001
Other	1.13 (1.07–1.19)	<0.0001	1.30 (1.24–1.37)	<0.0001

Variables adjusted for all others listed in this table and time between diabetes diagnosis and time of index HbA1C measurement.

Data Warehouse documented that over 60% had their HbA1C measured more frequently than recommended in guidelines and that excessive testing was associated with treatment intensification despite these patients already being well controlled—raising the spectre of overtreatment.[23] Others have pointed to the imbalance in pay-for-performance measures for diabetes, which have focused on detecting undertreatment of diabetes and have ignored the issue of potential overtreatment.[24–26] Although diabetes performance measures frequently exclude patients older than 75 years, we speculate that Continuing Medical Education events emphasizing the tight control of blood glucose in young patients with Type 1 diabetes may have encouraged a culture of intensification in the management of diabetes at the expense of the concept of individualization based on the health status of each individual patient. Moreover, pay-for-performance programs often provide monetary incentives for meeting treatment targets and we are not aware of any such programs that currently reward de-implementation of therapy or treating some patients to less stringent targets.[27]

Although intensive control in type 2 diabetes does not necessarily mean "overtreatment," the substantial proportion of complex/very complex patients who were still utilizing sulfonylureas or insulin despite having HbA1C <7% (and even <6%) is concerning, particularly as this has been proposed as a potential marker for overtreatment in type 2 diabetes.[28] Insulin is already one of the most common causes of adverse drug reactions and ED visits.[29–31] Both insulin and sulfonylureas can also cause weight gain, which may be problematic in patients with existing comorbidities or frailty. There is also substantial debate over the cardiovascular safety of these drugs, with several studies suggesting harm compared with other glucose-lowering therapies,[32] and increasing recognition of the potential hazards from polypharmacy in patients with type 2 diabetes.[33]

4.3. Strengths and limitations

Despite several strengths of our study, including the availability of detailed clinical data and the relatively large population-based sample size of patients with incident diagnoses of diabetes, there are several potential limitations to our work. First, to the extent that the clinical records may have undercaptured comorbidities (particularly likely for conditions such as dementia or frailty), we may have underestimated the proportion of individuals with complex health status and thus the true proportion who are potentially overtreated may be even higher. Second, although we acknowledge that some comorbidities have more profound effects on life expectancy or functional status than others, we used the ADA and AGS framework to define complex/very complex health status to replicate the work done with NHANES data.[15] Third, as the ADA only advocated individualization of treatment targets in 2012, the intensity of treatment may have declined since then, although the AGS guidelines endorsed individualization of treatment targets for almost a decade earlier, including during the years we had access to data for. Fourth, this dataset only included commercially insured patients and thus the results may not be generalizable to other patient populations, but our patient characteristics are similar to those from another US national administrative claims database[23] and our findings are similar to an earlier report from the VA system.[21] Fifth, as with any study using laboratory data, HbA1C measurements demonstrate measurement variability and measurement error can be up to ±0.5%.[34] Sixth, we did not evaluate patient adherence rates and thus cannot definitively say that lower HbA1C levels in patients taking insulin or sulfonylureas were due to those agents. Seventh, the association between use of insulin and higher all-cause hospitalizations and ED visits may be due to residual bias, as other hypoglycemic medications are relatively contraindicated in patients with some comorbidities such as advanced kidney disease or heart failure. Finally, it should be

acknowledged that there may have been clinical reasons why a particular patient might appropriately be treated to an intensive HbA1C goal even if they had conditions that placed them in the complex or very complex health status groups and that intensive control does not mean overtreatment in all cases.

5. Conclusion and implications

Nearly two-thirds of all diabetic individuals in this cohort of commercially insured patients had treated HbA1C <7%, and the intensity of glycemic control was similar regardless of the number and severity of comorbidities and/or markers of frailty—this raises the spectre of potential overtreatment. Although they were at a higher risk for adverse effects, complex and very complex patients were more likely to be treated with insulin or sulfonylureas, and nearly half were still receiving these agents despite having treated HbA1C levels <7% (and nearly one quarter had HbA1C <6.5%)—meeting another proposed indicator for potential overtreatment. In the era of Choosing Wisely, the issue of potential overtreatment needs to be considered in future diabetes quality improvement initiatives.

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