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Paradox of glycemic management: multimorbidity, glycemic control, and high-risk medication use among adults with diabetes

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ABSTRACT

Introduction Glycemic targets and glucose-lowering regimens should be individualized based on multiple factors, including the presence of comorbidities. We examined contemporary patterns of glycemic control and use of medications known to cause hypoglycemia among adults with diabetes across age and multimorbidity.

Research design and methods We retrospectively examined glycosylated hemoglobin (HbA_{1c}) levels and rates of insulin/sulfonylurea use as a function of age and multimorbidity using administrative claims and laboratory data for adults with type 2 diabetes included in OptumLabs Data Warehouse, 1 January 2014 to 31 December 2016. Comorbidity burden was assessed by counts of any of 16 comorbidities specified by guidelines as warranting relaxation of HbA_{1c} targets, classified as being diabetes concordant (diabetes complications or risk factors), discordant (unrelated to diabetes), or advanced (life limiting).

Results Among 194 157 patients with type 2 diabetes included in the study, 45.2% had only concordant comorbidities, 30.6% concordant and discordant, 2.7% only discordant, and 13.0% had ≥1 advanced comorbidity. Mean HbA_{1c} was 7.7% among 18–44 year-olds versus 6.9% among ≥75 year-olds, and was higher among patients with comorbidities: 7.3% with concordant only, 7.1% with discordant only, 7.1% with concordant and discordant, and 7.0% with advanced comorbidities compared with 7.4% among patients without comorbidities. The odds of insulin use decreased with age (OR 0.51 (95% CI 0.48 to 0.54) for age ≥75 vs 18–44 years) but increased with accumulation of concordant (OR 5.50 (95% CI 5.22 to 5.79) for ≥3 vs none), discordant (OR 1.72 (95% CI 1.60 to 1.86) for ≥3 vs none), and advanced (OR 1.45 (95% CI 1.25 to 1.68) for ≥2 vs none) comorbidities. Conversely, sulfonylurea use increased with age (OR 1.36 (95% CI 1.29 to 1.44) for age ≥75 vs 18–44 years) but decreased with accumulation of concordant (OR 0.76 (95% CI 0.73 to 0.79) for ≥3 vs none), discordant (OR 0.70 (95% CI 0.64 to 0.76) for ≥3 vs none), but not advanced (OR 0.86 (95% CI 0.74 to 1.01) for ≥2 vs none) comorbidities.

Conclusions The proportion of patients achieving low HbA_{1c} levels was highest among older and multimorbid patients. Older patients and patients with higher comorbidity burden were more likely to be treated with insulin to achieve these HbA_{1c} levels despite potential for hypoglycemia and uncertain long-term benefit.

Significance of this study

What is already known about this subject?

- Glycemic targets and glucose-lowering regimens should be individualized based on multiple factors, including the presence of comorbidities. Earlier studies revealed high prevalence of intensive glycemic control (ie, low HbA_{1c} levels) and insulin or sulfonylurea use among older patients and patients with chronic kidney disease or dementia, but there are no contemporary data about glycemic control and insulin or sulfonylurea use among patients with these and other diabetes-concordant, diabetes-discordant, and advanced comorbidities.

What are the new findings?

- Multimorbidity is common among adults with type 2 diabetes: 45.2% had only diabetes-concordant comorbidities, 30.6% had both concordant and discordant, 2.7% had only discordant, and 13.0% had advanced comorbidities.
- The proportion of patients achieving low HbA_{1c} levels, and the odds of doing so using insulin, increased with older age and with accumulation of diabetes-concordant and, to a lesser degree, discordant and advanced comorbidities.
- Younger patients and patients with few comorbidities were least likely to achieve low glycemic levels or to be treated with insulin at higher HbA_{1c} levels.

How might these results change the focus of research or clinical practice?

- Our study suggests ample opportunity for insulin deintensification among older patients and patients with advanced and/or multiple comorbidities, which may lower their risk of hypoglycemia. Conversely, younger and healthier patients may benefit from treatment intensification and addressing of barriers to optimal diabetes control.

INTRODUCTION

Person-centered diabetes care is predicated on aligning glycemic targets and therapeutic regimens with the patient's clinical situation and preferences for care. This includes the patient's comorbidities and clinical

complexity, life expectancy, and burden of treatment (eg, number, administration complexity, and side effect profiles of glucose-lowering medications required to achieve the desired glycemic targets). Ideally, patients with multiple and/or advanced comorbidities would be treated less intensively, with glycemic targets that prioritize avoidance of symptomatic hypoglycemia and hyperglycemia, while patients with a lesser comorbidity burden and longer life expectancy would be treated more intensively.[1–5] However, earlier studies exposed high rates of potential overtreatment among older adults and those who have serious comorbidities.[6–13] At the same time, glycemic control among younger adults with diabetes is often worse than among older adults.[14 15] Whether this risk/treatment paradox continues to persist in the USA, and how it is affected by age and the type and extent of multimorbidity is unknown.

The American Diabetes Association (ADA), American Geriatrics Society (AGS), and the US Department of Veterans Affairs/Department of Defense (VA/DoD) have identified several health conditions that warrant relaxation of glycemic targets due to their association with heightened hypoglycemia risk, diminished life expectancy, functional impairment, or frailty.[1–3 16 17] These and other guidelines, including the National Institute for Health and Care Excellence (NICE), also advise cautious use of insulin and sulfonylurea drugs by older and clinically complex patients, as these can lead to hypoglycemia.[2–4 16–18] Optimal alignment of treatment and risks/benefits therefore dictates that intensive glucose-lowering therapy be delivered to people most likely to benefit and least likely to be harmed by it. On the other hand, a more conservative therapeutic approach is appropriate for patients likely to be harmed and/or unlikely to derive meaningful benefit from intensive control, that is, those who are older and clinically complex.

However, different comorbidities have varying effects on diabetes management strategies, on patients' abilities to successfully manage their condition,[19] and their association with hypoglycemia.[20] For example, comorbidities can be classified on the basis of their concordance with diabetes, clinical dominance, and presence of symptoms.[19] Understanding comorbidity types is important for contextualizing diabetes management and identifying opportunities for more patient-centered, evidence-based care. Of the guideline-specified comorbidities, many are diabetes concordant as they share common pathogenesis, therapeutic goals, or treatment strategies with diabetes; for example, retinopathy, neuropathy, heart failure, myocardial infarction, stroke, chronic kidney disease (CKD), and hypertension. These conditions are comanaged with diabetes and their presence may amplify the desired intensity of diabetes control, though the risk of having these conditions is also increased by uncontrolled diabetes. Conversely, discordant conditions such as chronic obstructive pulmonary disease (COPD), liver disease, falls, incontinence, arthritis, and depression may compete with, rather than augment, diabetes for management focus and prioritization. Finally, advanced or clinically dominant conditions such as end-stage renal disease (ESRD), dementia, and cancer may take precedence over all other disease management, thereby deprioritizing glycemic control.

In the context of increasing prevalence of multimorbidity, growing awareness about the potential harms of overtreatment, and recent availability of glucose-lowering medications that do not cause hypoglycemia, we examined the contemporary landscape of diabetes management across a wide spectrum of morbidity. We focus specifically on the use of insulin and sulfonylurea because of their associated risk for hypoglycemia.[20 21] Our goal was to examine treatment regimens overall and among patients who achieved low HbA_{1c} levels as a function of patient age and comorbidity, examining the impact of having diabetes-concordant, discordant, and advanced health conditions.

METHODS

Study design

We analyzed deidentified administrative claims data with linked laboratory results from OptumLabs Data Warehouse (OLDW) between 1 January 2014 and 31 December 2016. OLDW includes deidentified medical and pharmacy claims, laboratory results, and enrollment records data for commercial and Medicare Advantage enrollees. The database contains longitudinal health information on enrollees and patients, representing a diverse mixture of ages, ethnicities, and geographic regions across the USA.[22 23] Because this study involved statistically deidentified data, it was exempt from Mayo Clinic Institutional Review Board review.

Study population

We identified adults (aged ≥18 years) with type 2 diabetes, an available HbA_{1c} result between 1 January 2015 and 31 December 2015 and ≥12 months of medical and pharmacy claims data before and after that index HbA_{1c} date. If multiple HbA_{1c} results were available in 2015, the latest was used as the index date.

The diagnosis of diabetes was established using Healthcare Effectiveness Data and Information Set criteria applied to 2013–2014 claims.[24] Patients with plurality of Evaluation & Management (E&M) diagnosis codes reflecting type 1 diabetes and with claims for bolus insulin, or those with an equal number of E&M codes reflecting type 1 as type 2 diabetes *and* bolus insulin claims *and* no sulfonylurea claims, were considered to have type 1 diabetes and therefore excluded.[20 25 26] Patients with only gestational diabetes (International Classification of Diseases Ninth Revision (ICD-9) 648.8x, ICD-10 O024.4xx) were not included.

Explanatory variables

Glycemic management was ascertained by (1) age group: 18–44, 45–64, 65–74, ≥75 years; (2) each of the 16 guideline-specified comorbidities; (3) Charlson

Comorbidity Index, categorized as 0–1, 2, 3, ≥4; and (4) type of diabetes-specific comorbidity profile: none, concordant conditions only (1, 2, ≥3 total), discordant conditions only (1, 2, ≥3 total), both concordant and discordant conditions (1, 2, ≥3 total), and advanced±concordant/discordant conditions (1, 2, ≥3 total).

The Charlson index weighs comorbid conditions by the strength of their association with 1-year mortality[27 28]; it has been previously validated for use in diabetes.[29] Additionally, specific comorbidities were ascertained from among the 16 health conditions specified by the ADA,[1 17] AGS,[16] and/or VA/DoD[2 3] guidelines using claims from 12 months preceding the index HbA_{1c} date (online supplementary table S1). These were categorized as *diabetes concordant* (CKD stages 3–4, heart failure, myocardial infarction, hypertension, cerebrovascular disease, proliferative retinopathy, and peripheral neuropathy), *discordant* (liver disease/cirrhosis, depression, COPD, urinary incontinence, falls, arthritis), or *advanced* (dementia, ESRD, cancer (excluding non-melanoma skin cancer)) based on the framework delineated by Piette and Kerr.[19] Comorbidities were counted within each category and presented as the number of concordant only, discordant only, both concordant and discordant, and advanced±any additional concordant or discordant conditions.

Outcome

Glycemic management was examined as the proportion of people treated with sulfonylurea (without insulin) or insulin (with or without sulfonylurea), each with or without other glucose-lowering medications, at each HbA_{1c} level for the different age and comorbidity subsets. HbA_{1c} levels were categorized as ≤5.6%, 5.7%–6.4%, 6.5%–6.9%, 7.0%–7.9%, 8.0%–8.9%, 9.0%–9.9%, and ≥10.0%. Diabetes medications were identified from ambulatory pharmacy fills during 100 days preceding the index HbA_{1c}, classified as insulin (basal only, bolus±basal), sulfonylurea, or other (metformin, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose transport protein 2 (SGLT2) inhibitors, α-glucosidase inhibitors, thiazolidinediones, meglitinides, and amylin analogs).

Independent variables

Patient age, sex, annual household income, and race/ethnicity were identified from OLDW enrollment files.

Statistical analysis

We calculated overall frequencies (percentages) and means (SD) for all patient characteristics, including age, sex, race/ethnicity, annual household income, comorbidities, index HbA_{1c}, and the different glucose-lowering regimens using χ^2 and t-tests, as appropriate. HbA_{1c} level categories and use of sulfonylurea and insulin were assessed by age group, each comorbidity, and each comorbidity profile. The main analysis considered comorbidity burden as the total number of concordant, discordant, and advanced comorbidities present. Secondary analyses modeled multimorbidity as a function of (1) the Charlson Comorbidity Index or (2) the presence of concordant only, discordant only, both concordant and discordant, and any advanced comorbidities as compared with none. Variables associated with insulin and sulfonylurea use (age, sex, race/ethnicity, annual household income level, HbA_{1c} level, comorbidity groupings) were examined using logistic regression analysis with results reported as ORs and 95% CIs. All statistical analyses were performed using SAS software V.9.4 (SAS Institute).

RESULTS

Study population

The study population was comprised of 194157 adults with type 2 diabetes; mean age 66.2 years (SD 11.7), mean HbA_{1c} 7.2% (SD 1.5), 50.9% female, and 58.5% white (table 1). The vast majority (91.5%) had at least one comorbidity in addition to diabetes, with mean 2.1 (SD 1.5) comorbidities overall. Mean Charlson Comorbidity Index was 3.0 (SD 2.3) and 33.5% had Charlson index ≥4. The most common diabetes-concordant comorbidities were hypertension (84.3%), neuropathy (23.6%), cerebrovascular disease (11.9%), and CKD (11.4%). The most common diabetes-discordant comorbidities were arthritis (21.6%), COPD (13.5%), and depression (10.5%). Advanced comorbidities were less prevalent: 9.5% had cancer, 2.7% had dementia, and 1.4% had ESRD.

Overall, 80.2% had at least one fill for a glucose-lowering medication in the 100 days preceding the index HbA_{1c}; expanding the medication capture period to 12 months did not identify any new pharmacologically treated patients (data not shown). As shown in table 2, 31.9% were treated with medications other than insulin/sulfonylurea, 25.3% with sulfonylurea (no insulin), 9.8% with basal insulin (5.0% without concurrent sulfonylurea and 4.8% with), and 13.1% were treated with bolus±basal insulin (9.5% without concurrent sulfonylurea and 3.6% with). Mean HbA_{1c} achieved was lowest among patients without fills for glucose-lowering medications (6.5%; SD 1.0) and those using non-insulin/sulfonylurea drugs (6.7%; SD 1.0), and was highest among patients treated with bolus±basal insulin, particularly in combination with sulfonylurea (8.5%; SD 1.8).

Comorbidities and glycemic control

HbA_{1c} levels were inversely associated with age, with highest mean HbA_{1c} among those 18–44 years old (7.7%; SD 2.0) and the lowest among those ≥75 years old (6.9%; SD 1.2) (table 2). The plurality of patients had only diabetes-concordant comorbidities (45.2%), while 30.6% had both concordant and discordant comorbidities, 2.7% had only discordant comorbidities, and 13.0% had at least one advanced comorbid condition. Mean HbA_{1c} was highest among patients with no comorbidities (7.4%; SD 1.7), slightly lower among those with only concordant comorbidities (7.3%; SD 1.5), and much lower among those with discordant only (7.1%; SD 1.5), discordant and concordant

Table 1 Study population

	Total (n=194 157)
Age (years), mean (SD)	66.2 (11.7)
Gender, n (%)	
Female	98 882 (50.9)
Male	95 275 (49.1)
Race/ethnicity, n (%)	
White	113 645 (58.5)
Black	31 859 (16.4)
Hispanic	28 985 (14.9)
Asian	11 300 (5.8)
Other/unknown	8368 (4.3)
Household income, n (%)	
<$40 000	59 181 (30.5)
$40 000–$49 999	18 884 (9.7)
$50 000–$59 999	16 828 (8.7)
$60 000–$74 999	20 601 (10.6)
$75 000–$99 999	25 455 (13.1)
≥$100 000	40 098 (20.7)
Unknown	13 110 (6.8)
Charlson index, mean (SD)	3.0 (2.3)
Comorbidity count,* mean (SD)	2.1 (1.5)
Comorbidities, n (%)	
Dementia	5184 (2.7)
End-stage renal disease	2783 (1.4)
Chronic kidney disease (stages 3–4)	22 115 (11.4)
Myocardial infarction	7353 (3.8)
Heart failure	18 436 (9.5)
Cerebrovascular disease	23 175 (11.9)
Chronic obstructive pulmonary disease	26 165 (13.5)
Cancer	18 438 (9.5)
Cirrhosis	1764 (0.9)
Retinopathy	3880 (2.0)
Neuropathy	45 910 (23.6)
Hypertension	163 653 (84.3)
Arthritis	42 010 (21.6)
Urinary incontinence	7073 (3.6)
Depression	20 295 (10.5)
Falls	6352 (3.3)
HbA_{1c}, mean (SD)	7.2 (1.5)
HbA_{1c} range, n (%)	
≤5.6%	9960 (5.1)
5.7%–6.4%	57 246 (29.5)
6.5%–6.9%	39 624 (20.4)
7.0%–7.9%	46 014 (23.7)
8.0%–8.9%	20 054 (10.3)
9.0%–9.9%	9663 (5.0)
≥10.0%	11 596 (6.0)

Patient characteristics ascertained at the time of the index glycosylated hemoglobin (HbA_{1c}) date.
*Comorbidity count was ascertained from among the 16 chronic health conditions specified by clinical practice guidelines as warranting pursuit of more relaxed treatment targets.

(7.1%; SD 1.4), and advanced (7.0; SD 1.3) comorbidities. Moreover, among patients with only discordant comorbidities, mean HbA_{1c} declined as the number of comorbidities increased from 7.1% (SD 1.6) with 1 to 6.6% (SD 1.2) with ≥3.

Comorbidities, HbA_{1c}, and high-risk medication use

We then examined the proportions of patients within each age and comorbidity category who were treated with either sulfonylurea or insulin as they achieved their respective HbA_{1c} levels, and found opposing trends for the two medication classes. The crude proportion treated with sulfonylurea increased with patient age at low HbA_{1c} levels (<8%), but decreased with age at high HbA_{1c} levels (≥9%) (figure 1A). Indeed, 18.1% of patients ≥75 years old whose HbA_{1c} was ≤5.6% were treated with a sulfonylurea, compared with 10.5% of those 18–44 years old. In contrast, among patients with HbA1c ≥10%, 21.6% of those ≥75 years old were treated with a sulfonylurea compared with 28.2% of those 18–44 years old. We saw similar patterns with increasing Charlson index (figure 1B) and increasing numbers of concordant only (figure 1C), concordant and discordant (figure 1E), and advanced (figure 1F) comorbidities.

After adjusting for sex, race/ethnicity, income, and HbA_{1c} level, the odds of sulfonylurea use increased with age and decreased with greater multimorbidity, irrespective of the type of comorbidities present (table 3). Patients ≥75 years old had 36% higher odds of sulfonylurea use than patients 18–44 years old. Compared with patients with no concordant conditions, odds of sulfonylurea use were 0.76 (95% CI 0.73 to 0.79) in the presence of ≥3 concordant comorbidities, and 0.70 (95% CI 0.64 to 0.76) in the presence of ≥3 discordant comorbidities, compared with none. Patients who had an advanced comorbidity had a 10% lower odds of sulfonylurea use than those without.

In contrast, prevalence of insulin use within each HbA_{1c} stratum increased as the number of comorbidities increased, also irrespective of how multimorbidity was ascertained (figure 2). For example, 4.4% of patients with HbA_{1c} ≤5.6% and none of the examined comorbidities were treated with insulin, compared with 12.8% of patients with ≥3 concordant comorbidities, 10.3% of patients with both concordant and discordant

Table 2 Glycemic control as a function of age, multimorbidity, and glucose-lowering treatment regimen

	Number (%) of patients (Population n=194 157)	HbA_{1c} (%) Mean (SD)
Glucose-lowering treatment regimen		
Sulfonylurea (no insulin)	49 200 (25.3)	7.41 (1.39)
Basal insulin (no sulfonylurea)	9782 (5.0)	7.89 (1.74)
Basal insulin+sulfonylurea	9311 (4.8)	8.38 (1.72)
Bolus±basal insulin (no sulfonylurea)	18 470 (9.5)	8.24 (1.77)
Bolus±basal insulin+sulfonylurea	7013 (3.6)	8.54 (1.82)
Other meds only	61 917 (31.9)	6.74 (1.04)
No fills	38 464 (19.8)	6.50 (1.02)
Age (years)		
18–44	9638 (5.0)	7.71 (2.01)
45–64	63 055 (32.5)	7.49 (1.71)
65–74	74 418 (38.3)	7.08 (1.30)
≥75	47 046 (24.2)	6.92 (1.15)
Type and degree of multimorbidity		
No comorbidities	16 562 (8.5)	7.41 (1.72)
Charlson Comorbidity Index		
0–1	69 427 (35.8)	7.23 (1.53)
2	25 565 (13.2)	7.10 (1.43)
3	34 051 (17.5)	7.26 (1.49)
≥4	65 114 (33.5)	7.19 (1.43)
Concordant comorbidities* only	87 699 (45.2)	7.30 (1.49)
1	56 693 (64.6)	7.27 (1.49)
2	22 293 (25.4)	7.31 (1.50)
≥3	8713 (9.9)	7.40 (1.50)
Discordant comorbidities† only	5202 (2.7)	7.06 (1.53)
1	4319 (83.0)	7.10 (1.56)
2	786 (15.1)	6.86 (1.37)
≥3	97 (1.9)	6.62 (1.16)
Concordant and discordant comorbidities	59 384 (30.6)	7.12 (1.42)
2	22 674 (38.2)	7.07 (1.37)
≥3	36 710 (61.8)	7.15 (1.45)
Advanced‡±concordant/discordant comorbidities	25 310 (13.0)	7.00 (1.32)
1	971 (3.8)	7.09 (1.48)
2	5794 (22.9)	6.98 (1.27)
≥3	18 545 (73.3)	7.00 (1.33)

The mean (SD) glycosylated hemoglobin (HbA_{1c}) levels achieved by the study population as a function of age, comorbidity profile, and glucose-lowering treatment regimen.
*Concordant comorbidities included stage 3–4 chronic kidney disease, heart failure, myocardial infarction, hypertension, cerebrovascular disease, proliferative retinopathy, and peripheral neuropathy.
†Discordant comorbidities included cirrhosis, depression, chronic obstructive pulmonary disease, urinary incontinence, falls, and arthritis.
‡Advanced comorbidities included dementia, end-stage kidney disease, and cancer.

comorbidities, and 12.0% of patients with ≥3 comorbidities at least one of which was advanced. Among patients with HbA_{1c} ≥10%, 36.7% of those without comorbidities were treated with insulin, compared with 76.6% of patients with ≥3 concordant comorbidities, 77.5% of patients with both concordant and discordant comorbidities, and 71.3% of patients with ≥3 comorbidities at least one of which was advanced. Insulin use trends by age were mixed, with higher proportions of older patients treated with insulin at high HbA_{1c} levels (≥8%), but lower proportions treated with insulin at low HbA_{1c} levels (<7%).

In multivariable analysis (table 3), odds of insulin use decreased significantly with older age and increased with greater multimorbidity: OR 5.50 (95% CI 5.22 to 5.79) for ≥3 concordant comorbidities compared with none; OR 1.72 (95% CI 1.60 to 1.86) for ≥3 discordant comorbidities compared with none; and OR 1.45 (95% CI 1.25 to 1.68) for ≥2 advanced comorbidities compared with none.

We saw similar trends in a secondary analysis where multimorbidity was modeled using the Charlson index (online supplementary table S2). Moreover, in the secondary analysis examining rates of sulfonylurea and insulin use as a function of broader comorbidity phenotypes (ie, whether the patient had only concordant, only discordant, both, or advanced comorbidities; online supplementary table S3), we found that the odds of sulfonylurea use were lowest among patients with advanced (OR 0.78; 95% CI 0.74 to 0.82) or both concordant and discordant (OR 0.81; 95% CI 0.78 to 0.85) comorbidities compared with none. There was no difference between patients with concordant comorbidities only and those with none. In contrast, insulin use was significantly more likely among patients with any category of multimorbidity: 3.3-fold more likely among patients with advanced, 2.9-fold more likely with both concordant and discordant, 2.0-fold more likely with concordant alone, and 1.3-fold more likely with only discordant.

DISCUSSION

Clinical practice guidelines advise against pursuit of low glycemic targets, and caution with use of insulin and sulfonylureas, among patients with complex and very complex health status,[1 3–5 16–18] as doing so exposes patients to risk of hypoglycemia without yielding meaningful improvements in health outcomes.[30–34] Yet, in a contemporary cohort of 194 157 US adults with type 2 diabetes, we found that older patients and patients with multiple and/or advanced comorbidities frequently achieved very low HbA_{1c} levels using insulin and, to a lesser degree, sulfonylureas. Indeed, patients *least* likely to benefit from intensive glycemic control and *most* likely to experience hypoglycemia with insulin therapy (ie, older and multimorbid adults) were *most* likely to achieve low HbA_{1c} levels and to be treated with insulin to achieve them. In contrast, patients who are likely to

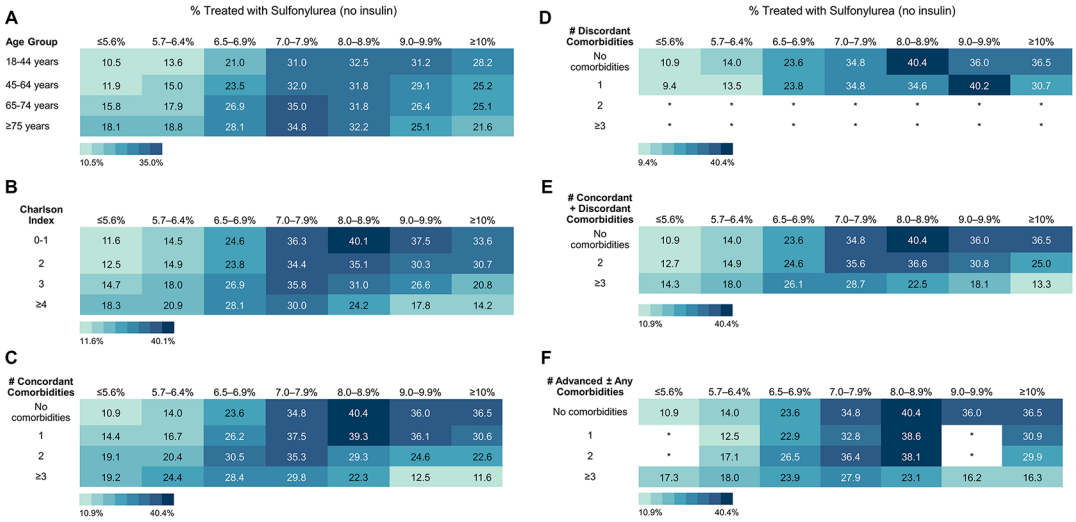

Figure 1 Glycemic control and sulfonylurea use in the context of advanced age and multimorbidity. Shown are the proportions of patients within each hemoglobin A1c (HbA_{1c}) category treated with sulfonylurea (no insulin) as a function of (A) age, (B) Charlson index, (C) number of concordant comorbidities among patients with only concordant comorbidities, (D) number of discordant comorbidities among patients with only discordant comorbidities, (E) number of concordant and/or discordant comorbidities among patients with both, and (F) total number of comorbidities among patients with at least one advanced illness, with or without concurrent concordant and/or discordant conditions.

benefit from, and less likely to be harmed by, intensive control (ie, younger and healthier adults) more often had high HbA_{1c} levels and were less frequently treated with insulin despite suboptimal glycemic control. The impact of cumulative multimorbidity on insulin use was strongest with diabetes-concordant comorbidities (eg, CKD, cardiovascular disease, retinopathy, and so on), but was still apparent with advanced comorbidities (eg, dementia, ESRD, cancer) and discordant comorbidities (eg, cirrhosis, COPD, depression, and so on), suggesting that the perception of shared treatment goals and potential for disease comanagement may prompt more intensive glucose-lowering strategies that rely on insulin.

The AGS,[16] ADA,[1 17] and VA/DoD[3] clinical practice guidelines have identified a number of comorbid health conditions that contribute to clinical complexity, predispose patients to undesired effects of intensive glucose-lowering therapy (including increased risk of hypoglycemia), make it difficult to manage diabetes, and/or signal underlying frailty or diminished life expectancy. Yet, in our patient population, mean HbA_{1c} levels were lower among patients with comorbidities compared with patients without, especially if the comorbidities were unrelated to diabetes or were advanced: 7.4% with no comorbidities, 7.3% with only concordant comorbidities, 7.1% with only discordant comorbidities (decreasing further as the number of discordant comorbidities increased), and 7.0% with advanced comorbidities. Higher HbA_{1c} levels observed among patients with concordant comorbidities may reflect guideline-recommended relaxation of glycemic targets in these patients, greater difficulty managing diabetes in the setting of existing complications, or longer diabetes duration. This association may also reflect greater risk of having diabetes complications in the setting of poor glycemic control. Low HbA_{1c} levels among patients with discordant and advanced comorbidities are concerning, and suggest an opportunity to de-escalate therapy in the presence of multimorbidity. Importantly, these HbA_{1c} levels reflect HbA_{1c} levels *achieved* by the patient, not necessarily HbA_{1c} levels *pursued* by the clinician. Examination of whether clinicians subsequently deintensified or intensified therapy in response to potentially excessive or inadequate treatment, respectively, was beyond the scope of this study.

The odds of insulin use were increased fivefold, independent of HbA_{1c} level, among patients with ≥3 concordant comorbidities compared with patients with none. Patients with concordant comorbidities were also 24% less likely to be treated with a sulfonylurea, suggesting that clinicians may preferentially rely on insulin in this population. This may reflect longer diabetes duration and greater insulin deficiency. Moreover, some diabetes-concordant conditions, most notably CKD, may necessitate use of insulin or sulfonylureas when other medications are inadequate or contraindicated. However, this does not justify the observed attainment of very low HbA_{1c} levels using these drugs. Indeed, nearly 13% of patients who have an advanced comorbidity and achieved HbA_{1c} ≤5.6% or 5.7%–6.4% were treated with insulin, and nearly 18% were treated with a sulfonylurea. We saw similar, high rates of insulin and sulfonylurea use at low HbA_{1c} levels among patients with concordant-only, discordant, and both concordant and discordant comorbidities, though there were relatively few patients in our cohort (2.7%) who had only discordant comorbidities. For patients with concordant comorbidities, attainment of low HbA_{1c} may reflect the clinician's and/or patient's desire to slow the progression of existing diabetes complications and/or prevent the onset of others. In addition,

Table 3 Factors associated with insulin and sulfonylurea use among US adults with diabetes

	Sulfonylurea (no insulin)		Insulin (±sulfonylurea)	
	OR (95% CI)	P value	OR (95% CI)	P value
Age groups				
18–44 years	Ref		Ref	
45–64 years	1.09 (1.03 to 1.14)	0.002	0.94 (0.89 to 0.99)	0.03
65–74 years	1.27 (1.20 to 1.34)	<0.001	0.72 (0.68 to 0.77)	<0.001
≥75 years	1.36 (1.29 to 1.44)	<0.001	0.51 (0.48 to 0.54)	<0.001
Gender				
Male	Ref		Ref	
Female	0.80 (0.78 to 0.82)	<0.001	1.10 (1.07 to 1.13)	<0.001
Race				
White	Ref		Ref	
Black	1.01 (0.98 to 1.04)	0.70	1.00 (0.97 to 1.04)	0.89
Hispanic	1.18 (1.15 to 1.22)	<0.001	0.86 (0.83 to 0.89)	<0.001
Asian	1.23 (1.17 to 1.28)	<0.001	0.59 (0.55 to 0.62)	<0.001
Unknown	0.95 (0.90 to 1.00)	0.06	0.76 (0.72 to 0.82)	<0.001
Household income				
<$40 000	Ref		Ref	
$40 000–$49 999	1.00 (0.96 to 1.04)	0.91	0.88 (0.84 to 0.92)	<0.001
$50 000–$59 999	0.97 (0.94 to 1.01)	0.19	0.88 (0.84 to 0.92)	<0.001
$60 000–$74 999	0.93 (0.89 to 0.96)	<0.001	0.89 (0.85 to 0.93)	<0.001
$75 000–$99 999	0.93 (0.90 to 0.97)	<0.001	0.84 (0.80 to 0.87)	<0.001
≥$100 000	0.85 (0.82 to 0.88)	<0.001	0.83 (0.80 to 0.86)	<0.001
Unknown	0.90 (0.85 to 0.94)	<0.001	0.97 (0.92 to 1.02)	0.20
HbA_{1c} range				
≤5.6%	0.52 (0.49 to 0.56)	<0.001	0.43 (0.39 to 0.46)	<0.001
5.7%–6.4%	0.60 (0.58 to 0.61)	<0.001	0.48 (0.46 to 0.50)	<0.001
6.5%–6.9%	Ref		Ref	
7.0%–7.9%	1.46 (1.42 to 1.51)	<0.001	2.41 (2.32 to 2.50)	<0.001
8.0%–8.9%	1.37 (1.32 to 1.42)	<0.001	5.21 (5.00 to 5.43)	<0.001
9.0%–9.9%	1.13 (1.08 to 1.19)	<0.001	7.82 (7.43 to 8.23)	<0.001
≥10.0%	0.99 (0.94 to 1.04)	0.73	9.43 (8.97 to 9.90)	<0.001
Type and degree of multimorbidity				
Concordant comorbidities				
0	Ref		Ref	
1	1.02 (0.99 to 1.06)	0.24	1.45 (1.39 to 1.51)	<0.001
2	0.96 (0.92 to 1.00)	0.03	2.79 (2.66 to 2.93)	<0.001
≥3	0.76 (0.73 to 0.79)	<0.001	5.50 (5.22 to 5.79)	<0.001
Discordant comorbidities				
0	Ref		Ref	
1	0.89 (0.87 to 0.91)	<0.001	1.17 (1.14 to 1.20)	<0.001
2	0.76 (0.72 to 0.79)	<0.001	1.37 (1.31 to 1.43)	<0.001
≥3	0.70 (0.64 to 0.76)	<0.001	1.72 (1.60 to 1.86)	<0.001
Advanced comorbidities				
0	Ref		Ref	
1	0.90 (0.87 to 0.93)	<0.001	1.24 (1.20 to 1.29)	<0.001
≥2	0.86 (0.74 to 1.01)	0.06	1.45 (1.25 to 1.68)	<0.001

Two multivariable logistic regression analyses examined the odds of (1) sulfonylurea without insulin and (2) insulin with or without sulfonylurea use controlling for patient age, sex, race/ethnicity, annual household income, glycosylated hemoglobin (HbA_{1c}) level, and type of comorbidity profile. In each model, comorbidity burden was reflected by the number of comorbidities within each comorbidity category (ie, diabetes concordant, discordant, and advanced).

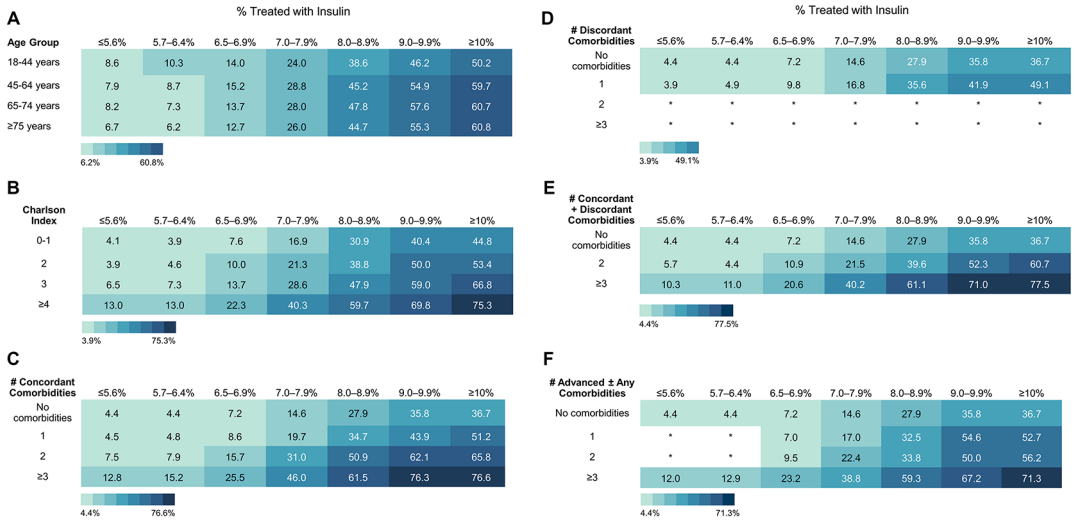

Figure 2 Glycemic control and insulin use in the context of advanced age and multimorbidity. Shown are the proportions of patients within each hemoglobin A1c (HbA_{1c}) category treated with insulin (with or without sulfonylurea) as a function of (A) age, (B) Charlson index, (C) number of concordant comorbidities among patients with only concordant comorbidities, (D) number of discordant comorbidities among patients with only discordant comorbidities, (E) number of concordant and/or discordant comorbidities among patients with both, and (F) total number of comorbidities among patients with at least one advanced illness, with or without concurrent concordant and/or discordant conditions.

patients with diabetes-concordant comorbidities may be more likely to see their healthcare providers for diabetes management, resulting in greater focus on diabetes and higher intensity of treatment. Yet, such encounters also present an opportunity to re-evaluate current care, engage in shared decision-making, and deintensify therapy if the current level of glycemic control is not aligned with evidence or goals of care.

We also examined glycemic management among younger and healthier adults in the context of emerging concerns about increased rates of diabetes-related complications and hyperglycemic emergencies in the younger age groups.[15 35 36] Our findings confirmed the presence of a risk/treatment paradox, with overall worse glycemic control and low rates of insulin therapy despite elevated HbA_{1c} levels among younger patients and patients with few comorbidities. Just 46.3% of patients 18–44 years old achieved HbA_{1c} ≤6.9%, compared with 62.5% of patients 75 years and older. Conversely, 23.1% of patients 18–44 years old had HbA_{1c} ≥9.0%, compared with just 5.6% of people ≥75 years old. ADA guidelines recommend insulin therapy when HbA_{1c} levels exceed 10%.[18] Yet, even with HbA_{1c} ≥10%, only half of patients 18–44 years old were treated with insulin, compared with 61% of those ≥65 years old. Analogously, only 37% of patients without any of the examined comorbidities and HbA_{1c} ≥10% were treated with insulin, compared with more than 70% of patients with multiple comorbidities. While diabetes management is complex at any age, some of the challenges that young people face may be unique and need to be considered. For instance, younger people with commercial and employer-sponsored insurance are more likely to have high deductible health plans, limited coverage, and/or higher out-of-pocket costs than older adults with Medicare Advantage plans. Younger people may have less contact with healthcare providers and fewer opportunities to intensity treatment. They also have to balance the needs of their diabetes with other responsibilities, such as education, employment, and family. While we considered cumulative clinical complexity in our analyses, we could not capture the intangible work of living with diabetes and the overall burden of disease that people with diabetes face.[37]

AGS, as part of the American Board of Internal Medicine Choosing Wisely initiative, advised against using medications other than metformin to achieve HbA_{1c} <7.5% in most older adults.[38] Similarly, NICE used a higher HbA_{1c} threshold to recommend starting medications associated with heightened hypoglycemia risk.[4] In contemporary clinical practice, however, older patients were frequently treated with sulfonylureas and insulin at low HbA_{1c} levels. Sulfonylureas were used by 18%, 19%, and 28% of patients ≥75 years old whose HbA_{1c} levels were ≤5.6%, 5.7%–6.4%, and 6.5%–6.9%, respectively. Similarly, insulin was used by 7%, 6%, and 13%, respectively. Overall, increasing age was independently associated with greater odds of sulfonylurea use and decreasing odds of insulin use, suggesting that clinicians may be more hesitant to treat older adults with insulin but not with sulfonylureas. Finally, the proportions of older and clinically complex patients treated with insulin/sulfonylurea to achieve low HbA_{1c} targets were comparable to earlier studies,[7–9 12] despite the increasing availability of medications posing a lower risk of hypoglycemia (DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors) and with additional cardiovascular and renal benefits (GLP-1 receptor agonists, SGLT2 inhibitors)[18] than insulin and sulfonylurea. This is consistent with recent findings that older patients and patients with CKD, heart failure, and cardiovascular disease are all less likely to be prescribed

SGLT2 inhibitors than younger and healthier people, despite their benefit in these contexts.[39] Our study therefore reinforces the age and comorbidity-driven risk/treatment paradox in glucose-lowering therapy.

Our work builds on prior studies of glycemic overtreatment, which heretofore focused primarily on select comorbidities (most often, CKD or dementia)[6 9 10] or older adults,[7–12] by expanding analysis to wide ranges of age and multimorbidity. This is important, as treatment regimens and goals need to consider the patient's overall health status, clinical complexity, and disease burden, not a few select comorbidities or chronological age. Similarly, a study by McAlister and colleagues found a similar risk/treatment paradox in glucose and blood pressure management among patients with diabetes (not restricted to type 2) in UK primary care practices between 2003 and 2015 as a function of frailty.[13] However, our findings also need to be considered in the context of the study's limitations. Some health conditions are not reliably captured in claims data, including dementia, incontinence, and falls. Claims also cannot capture disease severity, frailty, symptom burden, or life expectancy. Cases resulting in billed visits and thereby identified in claims are likely to be more severe or sufficiently bothersome to seek medical care, making individualized diabetes management especially important in this context. The prevalence of these conditions is likely much higher than suggested by our study. HbA_{1c} levels may not reliably reflect average glycemia, particularly in patients with anemia of chronic disease, uremia, or cirrhosis.[40] Medication capture may also not be complete, and some patients without fills may be treated with medications obtained through low-cost generic drug programs (these would be metformin, sulfonylurea, and human insulin)[41] or those obtained as samples. However, because our objective was to identify potentially inappropriate use of sulfonylurea/insulin drugs, missing medication data is likely to underestimate the prevalence of potential overtreatment.

The study population was comprised of commercially insured and Medicare Advantage beneficiaries with prescription drug coverage, and both glycemic control and glucose-lowering treatment regimens likely differ among patients with no or public health coverage who may be more likely to use lower cost medications such as human insulin and sulfonylurea. Similarly, the study cohort is older than the general US population, with 62.5% of patients aged 65 years and older. As such, the prevalence of comorbidities and multimorbidity may be higher in our study than in the general population. Finally, claims data cannot inform us about the patients' individualized treatment targets, goals and preferences for care, day-to-day blood glucose levels, and conversations that took place between patients and their clinicians all of which can impact treatment decisions.

Nevertheless, our study suggests ample opportunity for treatment deintensification among older patients and patients with advanced and/or multiple comorbidities, which may lower their risk of hypoglycemia. At the same time, younger and healthier adults would benefit from continued focus on improving access to diabetes care and better control of hyperglycemia. Population health management efforts and policy solutions, implemented through performance measurement,[42 43] can support individualized diabetes care and align it with scientific evidence and clinical practice guidelines.[17] Most importantly, clinicians should continue to engage their patients in shared and informed decision-making, weighing the risks and benefits of glucose-lowering treatment regimens in the specific context of each patient, carefully considering the patient's comorbidity burden, age, and goals and preferences for care.

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Contributors RGM designed the study, interpreted the data, and wrote the manuscript. KJL contributed to the discussion and reviewed/edited the manuscript. HKVH analyzed the data and reviewed/edited the manuscript. NDS supervised the study design and data interpretation, contributed to the discussion, and reviewed/edited the manuscript.

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