Incidences of Severe Hypoglycemia and Diabetic Ketoacidosis and Prevalence of Microvascular Complications Stratified by Age and Glycemic Control in U.S. Adult Patients With Type 1 Diabetes: A Real-World Study

Jeremy H. Pettus,[1] Fang Liz Zhou,[2] Leah Shepherd,[3] Ronald Preblick,[2] Phillip R. Hunt,[4] Sachin Paranjape,[2] Kellee M. Miller,[5] and Steven V. Edelman[6]

Diabetes Care 2019;42:2220–2227 | https://doi.org/10.2337/dc19-0830

OBJECTIVE

To assess the burden of disease for adults with type 1 diabetes in a U.S. electronic health record database by evaluating acute and microvascular complications stratified by age and glycemic control.

RESEARCH DESIGN AND METHODS

This is a retrospective observational study of adults with type 1 diabetes (1 July 2014–30 June 2016) classified using a validated algorithm, with disease duration ≥24 months and, during a 12-month baseline period, not pregnant and having one or more insulin prescriptions and one or more HbA_{1c} measurements. Demographic characteristics, acute complications (severe hypoglycemia [SH], diabetic ketoacidosis [DKA]), and microvascular complications (neuropathy, nephropathy, retinopathy) were stratified by age (18–25, 26–49, 50–64, ≥65 years) and glycemic control (HbA_{1c} <7%, 7% to <9%, ≥9%).

RESULTS

Of 31,430 patients, ∼20% had HbA_{1c} <7%. Older patients had lower HbA_{1c} values than younger patients ($P < 0.001$). Patients with poor glycemic control had the highest annual incidence of SH (4.2%, 4.0%, and 8.3%) and DKA (1.3%, 2.8%, and 15.8%) for HbA_{1c} <7%, 7% to <9%, and ≥9% cohorts, respectively (both $P < 0.001$), and a higher prevalence of neuropathy and nephropathy (both $P < 0.001$).

CONCLUSIONS

For adults with type 1 diabetes, glycemic control appears worse than previously estimated. Rates of all complications increased with increasing HbA_{1c}. Compared with HbA_{1c} <7%, HbA_{1c} ≥9% was associated with twofold and 12-fold higher incidences of SH and DKA, respectively. Younger adults had more pronounced higher risks of SH and DKA associated with poor glycemic control than older adults.

[1]University of California San Diego, San Diego, CA
[2]Sanofi, Bridgewater, NJ
[3]Evidera, London, U.K.
[4]Evidera, Waltham, MA
[5]Jaeb Center for Health Research, Tampa, FL
[6]Veterans Affairs Medical Center, University of California San Diego, San Diego, CA

Corresponding author: Fang Liz Zhou, liz.zhou@sanofi.com

Received 25 April 2019 and accepted 27 August 2019

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-0830/-/DC1.

Poor glycemic control in patients with type 1 diabetes has been associated with severe hypoglycemia (SH) and diabetic ketoacidosis (DKA), complications that can have burdensome acute effects on patients, and with chronic complications that may become debilitating (1). Because reduction of HbA_{1c} is associated with a reduced risk of microvascular and macrovascular complications (2), the American Diabetes Association (ADA) recommends a target HbA_{1c} of $<$7% ($<$53 mmol/mol) for most nonpregnant adults with type 1 diabetes (3). However, large observational studies of patients with type 1 diabetes indicate that, for many, HbA_{1c} targets are not reached. For example, a recent analysis of data from the T1D Exchange clinic registry, which included 22,697 participants with type 1 diabetes from 82 U.S. pediatric and adult endocrinology practices, showed that HbA_{1c} goals set by the ADA are achieved by only 21% of adults and 17% of children (4). Further, compared with adult patients with excellent glycemic control (HbA_{1c} $<$6.5% [$<$48 mmol/mol]), patients with poor control (HbA_{1c} $>$8.5% [$>$69 mmol/mol]) had different clinical and socioeconomic characteristics and had a lower rate of insulin pump use, more frequently missed insulin doses, and less frequently performed self-monitoring of blood glucose (5). While there is a growing body of literature describing HbA_{1c} goal attainment and cardiovascular disease in patients with type 2 diabetes, few large-scale real-world studies have been conducted in the type 1 diabetes population.

For identification of and reporting of the status of adults with type 1 diabetes in the broader real-world clinical setting, Optum Humedica electronic health record (EHR) data were used in the Adult Type 1 Diabetes Patient Characteristics, Disease Burden, and Clinical Outcome in U.S. EHR Database (T1PCO) study. One T1PCO analysis (6) examined, in detail, the characteristics of adult patients with type 1 diabetes during a 12-month baseline period and assessed the incidences of SH and DKA and the prevalence of microvascular complications. Glycemic control was suboptimal (HbA_{1c} $\geq$7%) in 80% of the adult patients with type 1 diabetes in the T1PCO study, and only 59% had an endocrinologist at baseline (compared with 100% in the T1D Exchange registry). The analysis showed that patients with suboptimal control were more likely to experience SH, DKA, or neuropathy and to incur more frequent inpatient and emergency department visits than were patients with good glycemic control. Moreover, patients with suboptimal glycemic control were more likely to experience various comorbidities, including hypertension, hyperlipidemia, and depression, than were patients with good glycemic control.

In the present analysis, baseline data from the T1PCO study were examined to explore relations between glycemic control, age, and diabetes complications by evaluation of the incidences of acute complications and the prevalence of microvascular complications in the context of age-group (18–25, 26–49, 50–64, and $\geq$65 years) and baseline glycemic control (HbA_{1c} $<$7% [$<$53 mmol/mol], 7% to $<$9% [53 to $<$75 mmol/mol], and $\geq$9% [$\geq$75 mmol/mol]).

RESEARCH DESIGN AND METHODS

Data Source

The study was conducted using data from the Optum Humedica EHR database (7), which has been used to measure clinical outcomes in type 1 diabetes by the Institute for Clinical Research and Health Policy Studies at Tufts Medical Center and others (8). Data on ~80 million patients were available from records made between 1 July 2007 and 30 June 2017, by $>$140,000 physicians at $>$700 hospitals and 7,000 clinics in all census regions of the U.S., and included EHR data from $>$80 integrated delivery systems (7). All patient records were deidentified.

Study Population

Patients who had a type 1 diabetes diagnosis, as specified below, between 1 July 2014 and 30 June 2016, were included in the study. The index date was defined as the date of the first occurrence of a "type 1 diabetes" or "unspecified diabetes" code within the identification period, and the baseline period began 12 months before the index date. Patients were followed for up to 12 months, until the first occurrence of the end of activity in the EHR (last encounter), death, or 12 months after the index date.

Inclusion criteria were age $\geq$18 years, type 1 diabetes as defined by the Klompas algorithm (9) (Supplementary Table 1), type 1 diabetes duration $\geq$24 months in the EHR database, having one or more insulin prescriptions during the baseline period, and having one or more HbA_{1c} measurements during the baseline period. Exclusion criteria were type 2 diabetes, having no sex recorded, and/or being pregnant during the baseline period.

Patient Characteristics and Outcomes

All measurements were made during the baseline period. Patient characteristics ascertained include age, race, BMI, systolic blood pressure (SBP), and estimated glomerular filtration rate (eGFR). BMI and SBP values used were those recorded closest to the index date, whereas the eGFR used was the average of all eGFRs recorded during the baseline period. For HbA_{1c}, the measurement used was made closest to the index date.

History of Clinical Outcomes

Acute complications included SH, of which an event was defined either as an ICD-9 or an ICD-10 diagnosis code for hypoglycemia reported upon inpatient admission or at an emergency room (ER) visit as the primary or discharge diagnosis or as a laboratory test result of plasma glucose $<$70 mg/dL ($<$3.9 mmol/L) and inpatient admission or an ER visit on the same date, and DKA was defined as the presence of an ICD-9 or ICD-10 diagnosis code at any point in the inpatient setting. Microvascular complications, which included neuropathy, nephropathy, and retinopathy, were defined using diagnosis codes (see Supplementary Table 2 for details, including diagnosis codes).

Statistical Analyses

The proportion of patients having HbA_{1c} $<$7% was reported overall and stratified by a number of key metrics (age-group, race, BMI, SBP, and eGFR). Locally weighted scatterplot smoothing (LOESS) curves with CI bands were produced to compare mean baseline HbA_{1c} estimates by age in the T1PCO study with those in the T1D Exchange clinic registry (10).

The incidences of SH and DKA and prevalence of microvascular complications were determined during the baseline period at each baseline HbA_{1c} range ($<$7%, 7% to $<$9%, $\geq$9%), overall and stratified by age (18–25, 26–49, 50–64, $\geq$65 years). Relative rates (RRs)

and CIs were calculated for highest and lowest HbA_{1c} groups (≥9% vs. <7%) within age-groups. *F* tests were conducted to test for effects of interaction between age and glycemic control on SH and DKA incidences. Also determined were the incidences of SH and DKA within narrower baseline HbA_{1c} categories (≤6% to >13% at 0.5% intervals).

RESULTS

Patient Selection

In total, 430,335 patients were identified with a type 1 or unspecified diabetes diagnosis during the identification period and selected for potential inclusion in the study. Of those, 31,430 were identified as having type 1 diabetes by the Klompas algorithm, met the inclusion criteria, and had none of the exclusion criteria (9). Selection and sample attrition are reported in Supplementary Fig. 1.

Of the final sample of patients, 16%, 40%, 29%, and 15% were aged 18–25, 26–49, 50–64, and ≥65 years, respectively; 7% were African American and 88% were Caucasian. The majority of patients (58%) had commercial insurance, 16% had Medicare, 8% had Medicaid, and 19% were uninsured. Among patients with known BMI, 33% were categorized as having normal weight (BMI <25 kg/m^2), 35% were overweight (BMI 25 to <30 kg/m^2), and 33% were obese or severely obese (BMI ≥30 kg/m^2). Detailed demographic information is reported in Supplementary Table 3. Most patients were in the East North Central U.S. census division (35%), 26% in the South Atlantic/West South Central division, and 17% in the West North Central division. Geographic information is reported in Supplementary Table 3.

Baseline Goal Attainment by Demographic Characteristics

Figure 1 shows the proportions of patients with HbA_{1c} <7% by different baseline characteristics. Of the 31,430 patients in the study, only 20% had an HbA_{1c} <7%. The percentage of patients with HbA_{1c} <7% increased substantially with age-group, from 12% of patients aged 18–25 years to 29% of patients aged ≥65 years. Mean HbA_{1c} of the study population was 8.3% and decreased monotonically with age: mean HbA_{1c} was highest (9.4%) in patients aged 18 years and lowest (7.6%) in those aged 80 years. To compare our results with those of the T1D Exchange clinic registry, we calculated a LOESS curve for HbA_{1c} by age and overlaid the result on a similar curve produced by Miller et al. (10) in Fig. 2. Notably, patients in the T1PCO study had a higher mean HbA_{1c} at each age. For example, mean HbA_{1c} values for patients in the T1PCO study versus those in the study by Miller et al. were, respectively, 9.4% vs. 8.8% at age 20 years, 8.3% vs. 7.6% at age 40 years, and 7.8% vs. 7.5% at age 65 years.

A smaller proportion of African American than Caucasian patients had HbA_{1c} <7% (15% vs. 21%), and a smaller proportion of obese than normal-weight patients had HbA_{1c} <7% (18% vs. 21%) (Fig. 1). The percentage of patients with HbA_{1c} <7% and commercial insurance was approximately the same as the percentage with HbA_{1c} <7% in the total population (20%), whereas a higher percentage (26%) had HbA_{1c} <7% and Medicare and a smaller percentage (12%) had HbA_{1c} <7% and Medicaid.

Incidences of SH and DKA Per Year by Age and Glycemic Control

Figures 3 and 4 show the results of incidences of SH and DKA, respectively, stratified by HbA_{1c} category (with a 0.5 incremental interval [Figs. 3*A* and 4*A*]) and by age-group/glycemic control (Figs. 3*B* and 4*B*) during the 12-month baseline period. The incidence of SH (per year, during the 12-month baseline period) in patients with HbA_{1c} ≤6% or >6% to 6.5% (6.9% and 4.0%, respectively) was higher than that in patients with HbA_{1c} >6.5% to 7% (3.3%) (Fig. 3*A*). For patients with HbA_{1c} >7%, the incidence of SH (per year) increased to 13.5% in those with HbA_{1c} >13%. The impact of poor glycemic control on SH incidence was more pronounced among younger patients, as the RRs of SH by poor versus good glycemic control (HbA_{1c} ≥9% vs. <7%) were higher for the youngest patients (RR 3.7) than for older patients (RR 2.2 for patients aged 26 to 49 years, 1.5 for patients aged 50 to 64 years, and 1.6 for patients aged ≥65 years, all $P < 0.05$; *P* for interaction <0.001) (Fig. 3*B*).

The incidence of DKA (per year) increased with worsening control from 1.0% in patients with HbA_{1c} ≤6.0 to 34.0% in patients with HbA_{1c} >13% (Fig. 4*A*). Above an HbA_{1c} of ~9.5%, incidence of DKA appears to increase dramatically. As for SH, the impact of poor glycemic control on DKA incidence was more pronounced among younger patients, as the RRs of DKA by poor versus good glycemic control (HbA_{1c} ≥9% vs. <7%) were higher for the youngest patients (RR 12.7) than for older patients (RR 11.9 for patients aged 26 to 49 years, 6.2 for patients aged 50 to 64 years, and 6.1 for those aged ≥65 years, all $P < 0.01$; *P* for interaction <0.001) (Fig. 4*B*).

Prevalence of Microvascular Complications by Age and Glycemic Control

Patients with HbA_{1c} ≥9% vs. <7% had a greater prevalence of neuropathy overall (13% vs. 9%; $P < 0.001$) and in each age-group ($P < 0.05$ for RRs in all age-groups) (Supplementary Fig. 2*A*). Patients with HbA_{1c} ≥9% vs. <7% also had a greater prevalence of nephropathy overall (11% vs. 9%; $P < 0.001$) and in each age-group ($P < 0.05$ for RRs in all age-groups) (Supplementary Fig. 2*B*). The prevalence of retinopathy was similar across HbA_{1c} groups in patients aged 18–25 years ($P > 0.20$) and increased monotonically with HbA_{1c} in patients aged 26–49 years or 50–64 years (all $P < 0.05$). In the ≥65 years age-group, only patients with HbA_{1c} 7% to <9% had a significantly higher prevalence of retinopathy than those with HbA_{1c} <7% ($P = 0.01$).

CONCLUSIONS

To our knowledge, the T1PCO study is the largest study to date to evaluate the burden of illness for U.S. adults with type 1 diabetes using EHR data from real-world clinical practice. The current study showed that optimal glycemic control is not achieved in the vast majority of adults with type 1 diabetes. Those with suboptimal glycemic control have a significant burden of illness, both acute and chronic. Younger adults with suboptimal glycemic control appear to be at greater risk of acute and chronic diabetes-related complications than older adults with comparable glycemic control.

Notably, the T1PCO study cohort may be more representative than other cohorts of "real-world" adult patients with type 1 diabetes: only 59% of patients in this cohort were seen by an endocrinologist in 1 year, whereas 100% of patients in the T1D Exchange clinic registry were managed by specialists (4). Involvement in a prospective study such as the T1D Exchange clinic registry may come with

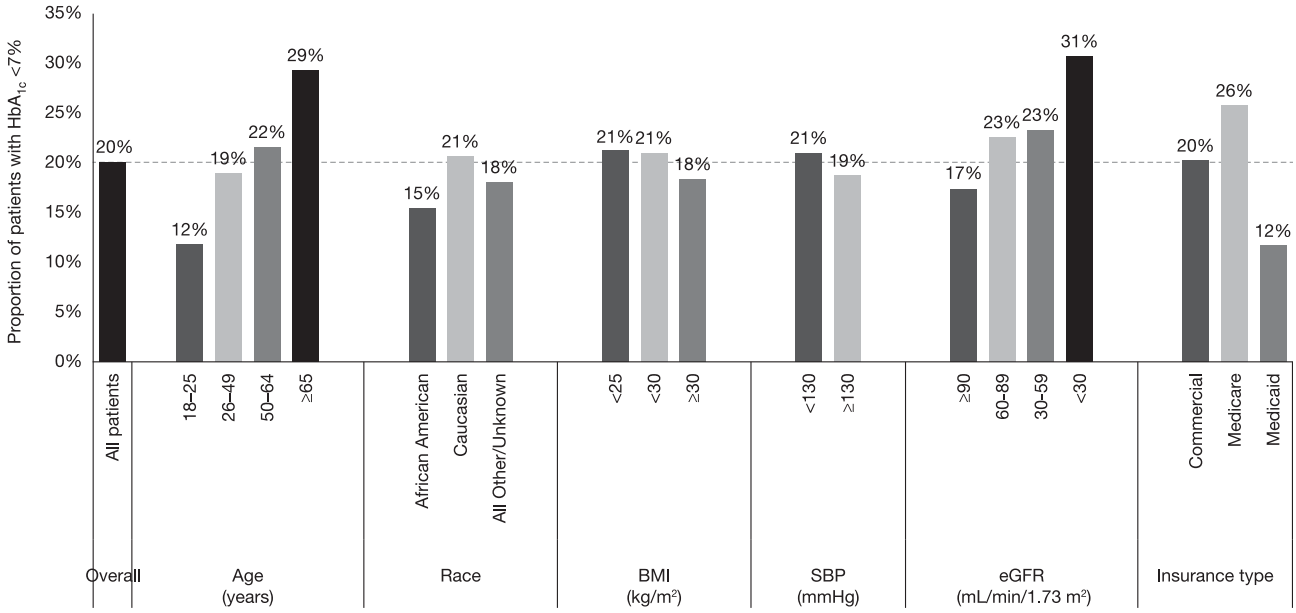

Figure 1—Proportion of adults with type 1 diabetes and HbA_{1c} <7%, stratified by baseline characteristics. Overall, $n = 31,430$. Age-groups: 18–25 years, $n = 4,913$; 26–49 years, $n = 12,724$; 50–64 years, $n = 9,040$; ≥65 years, $n = 4,753$. Race: African American, $n = 2,214$; Caucasian, $n = 27,697$; all other or unknown, $n = 1,519$. BMI: <25 kg/m^2, $n = 10,036$; <30 kg/m^2, $n = 10,624$; ≥30 kg/m^2, $n = 9,984$; no measurement, $n = 786$. SBP: <130 mmHg, $n = 20,235$; ≥130 mmHg, $n = 10,580$; unknown, $n = 615$. eGFR: ≥90 mL/min/1.73 m^2, $n = 14,398$; 60–89 mL/min/1.73 m^2, $n = 8,468$; 30–59 mL/min/1.73 m^2, $n = 3,225$; <30 mL/min/1.73 m^2, $n = 997$; no measurement, $n = 4,342$. Insurance type: commercial, $n = 18,056$; Medicare, $n = 4,940$; Medicaid, $n = 2,387$; other, uninsured, or unknown, $n = 6,047$. HbA_{1c} goal attainment was calculated as the percentage of the overall n for each category.

greater frequency of care and benefits, similar to those typically seen in clinical trials. Our population is, in contrast, more representative in age of the general adult population with type 1 diabetes in the U.S., and our findings may better represent the current standard of care for adults with type 1 diabetes. In our study, 100% of the reported subjects were adults and 15% were aged ≥65 years. In contrast, in the T1D Exchange clinic registry, roughly 40% of patients were adults, of whom only 3% were aged >65 years (11). Finally, our cohort included subjects from all over the U.S.—as opposed to those living within driving distance of the institutions involved in the T1D Exchange registry.

Baseline Goal Attainment by Demographic Characteristics

Suboptimal glycemic control (HbA_{1c} ≥7%) was more common in younger patients (discussed further below), patients identifying as African American, obese patients, and patients using Medicaid. Although previous research on socioeconomic disparities in HbA_{1c} goal achievement has primarily focused on youth, findings from the T1D Exchange clinic registry corroborate the current findings that suboptimal glycemic control is more common in adults identifying as African American or using noncommercial insurance (5). Because previous research indicates that diabetes interventions targeting African Americans may improve quality of care and that socioeconomic status is an independent risk factor for type 1 diabetes complications, the disparities observed here are particularly notable (12,13).

Normal weight and overweight patients (BMI <30 kg/m^2) were more likely than obese patients (BMI ≥30 kg/m^2) to have an HbA_{1c} <7%. Although the percentage of patients who were obese (33%) was larger than in the T1D Exchange registry (26%) (5), the finding that BMI correlates with HbA_{1c} goal corroborates findings from the T1D Exchange registry, which showed that patients in the "excellent" glycemic control group (HbA_{1c} <6.5%) were substantially more likely to be normal weight or underweight (BMI <25 kg/m^2) than to be obese (BMI ≥30 kg/m^2) (48% vs. 16%, respectively) (5). However, T1D Exchange clinic registry data on patients with "fair or poor" glycemic control (HbA_{1c} ≥8.5%) did not show any meaningful difference in the proportions of patients in each BMI group. Because the current study and the T1D Exchange study used the same HbA_{1c} thresholds for all patients, regardless of personal HbA_{1c} targets, further research is necessary to describe the association between glycemic control and BMI in type 1 diabetes.

Baseline Glycemic Control by Age

Younger patients (aged 18–25 years) had the highest HbA_{1c} level on average; as age increased, HbA_{1c} level decreased. Consequently, the percentage of patients having HbA_{1c} <7% increased with age. These results suggest that stratifying patients by age, as done in this study, is indeed appropriate and informative because comparisons made strictly on the basis of HbA_{1c} control may be confounded by age.

Corroborating the current study findings, the T1D Exchange data show a similar trend of increasing HbA_{1c} goal attainment with age (10). In particular, HbA_{1c} was highest in 19-year-old patients and declined with age to ≤7.5% in ≥65-year-old patients. This difference is similar to that observed in the current study: 9.4% among 20-year-old patients and 7.8% among 65-year-old patients (mean difference 1.6%). However, mean HbA_{1c} estimates in the T1D Exchange study are lower than our estimates across all age-groups, and the gap

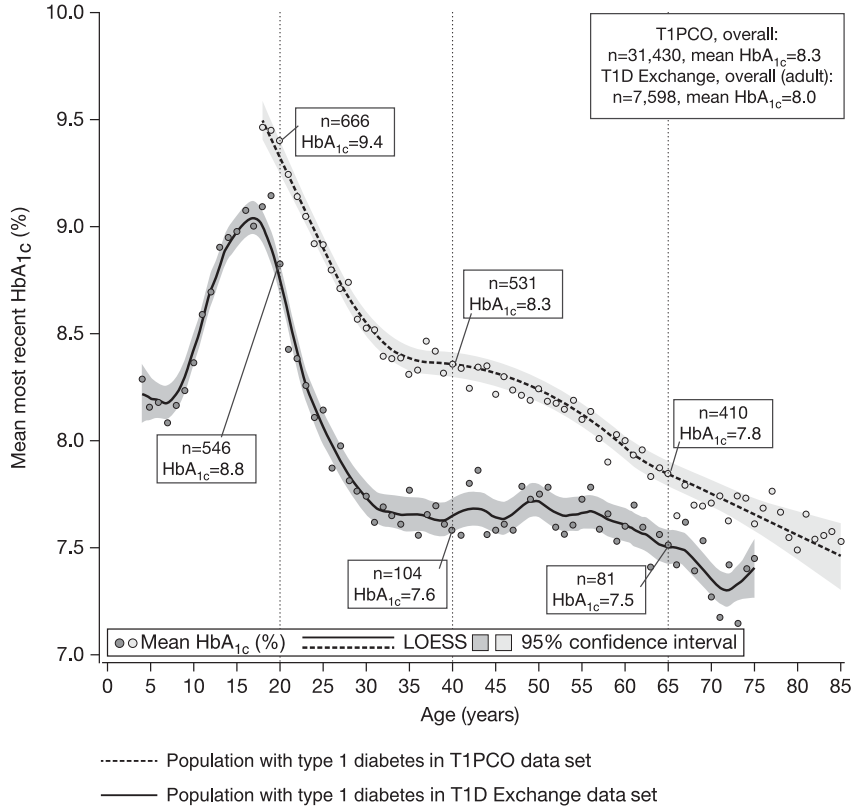

Figure 2—Mean HbA_{1c} stratified by age: a comparison of T1D Exchange and T1PCO data. For the T1D Exchange data set, the average HbA_{1c} for each year of age was plotted using the most recent value available for each of the 16,057 participants with a recent update. Participants <4 years old were grouped at age 4, and participants >75 years old were grouped at age 75. For the T1PCO data set, the average HbA_{1c} for each year of age was plotted using the most recent value available from a random sample of 16,000 participants. Participants >85 years old were grouped at age 85. The lines were estimated using LOESS, a nonparametric method for estimating the regression equation that fits a smoothing parameter. Circles represent the mean HbA_{1c} for each year of age. The gray shaded area represents the 95% CI around the smoothed LOESS line.

seems larger in the 26–50 years age-group. This discrepancy may be due to differences in the patient populations of the two studies. Indeed, although the present analysis sampled a broader "real-world" adult population with type 1 diabetes, the T1D Exchange study included patients who may have received overall better care and support for their disease. Regardless of age, however, a substantial proportion of patients did not have optimal glycemic control in either study.

SH and DKA at Baseline by Age and Glycemic Control

Although poor glycemic control was common across groups, it was associated with a higher incidence of SH, an association that, to our knowledge, has not been reported in a large-scale study of type 1 diabetes. In particular, although we found a higher incidence of SH in patients with HbA_{1c} <6.5% than in patients with HbA_{1c} >6.5% to 7%, patients with higher HbA_{1c} levels had an even greater incidence of SH than patients with HbA_{1c} <6.5%. Though perhaps contrary to the conventional belief that hypoglycemia events occur, in general, as a result of strict glycemic control, our conjecture is that poor glycemic control may lead to greater variability in glucose levels and, therefore, a greater number of hypoglycemia events. The prospect of experiencing hypoglycemia events may also deter some patients from striving to achieve optimal HbA_{1c} control. Further investigation is therefore warranted.

Liu et al. (14) found that, during a 5-year period, 9% of patients with type 1 diabetes were admitted to the ER and 4% were hospitalized for SH. During a substantially shorter period (1 year), we found that 5% of patients had an SH event (ER and inpatient events were pooled). Therefore, hypoglycemia rates may have been underestimated in our study. In contrast to these findings, the T1D Exchange study found no association between glycemic control and SH (5). It should be noted, however, that the current study only included SH events that were associated with ER visits or hospitalizations. In contrast, the T1D Exchange study included episodes without ER visits or hospitalizations. This may have contributed to differences in incidence estimates between the two studies. In particular, this may have led to underreporting of SH in the current study.

We found that increasingly poor glycemic control is associated with a larger increase in DKA incidence in young patients than in older patients. Overall, and within age-groups, the incidence of DKA increased with increasing HbA_{1c}, with HbA_{1c} 9.5% being a threshold above which DKA incidence increased markedly. These findings underscore the importance of patient-physician discussions about optimization of insulin therapy, including whether to add therapeutic agents. Indeed, we found that patients with high HbA_{1c} levels have a profoundly high risk of DKA, such that one in three patients with HbA_{1c} ≥13% had a DKA episode per year.

Similar to our results, those reported from the T1D Exchange study showed that DKA is more common in patients with suboptimal glycemic control than in those with optimal glycemic control (4). Indeed, although one or more DKA events occurred in 0.7% of patients per year with HbA_{1c} <8% in the T1D Exchange study and in 1% of patients per year with HbA_{1c} <7% in our study, the incidence of DKA increases with HbA_{1c}, and one or more DKA events occurred per year in 7% of patients with HbA_{1c} ≥9% in the T1D Exchange study and in 16% of patients per year with HbA_{1c} ≥9% in our study.

Notably, T1D Exchange data show that DKA events are more likely in younger patients than in older patients and peak at an incidence of 4% per year in the 13–17 and 18–25 years age-groups (compared with ≤2% per year in the other age-groups). With this taken with our findings that younger patients with poor glycemic control are particularly adversely affected by DKA, we highlight

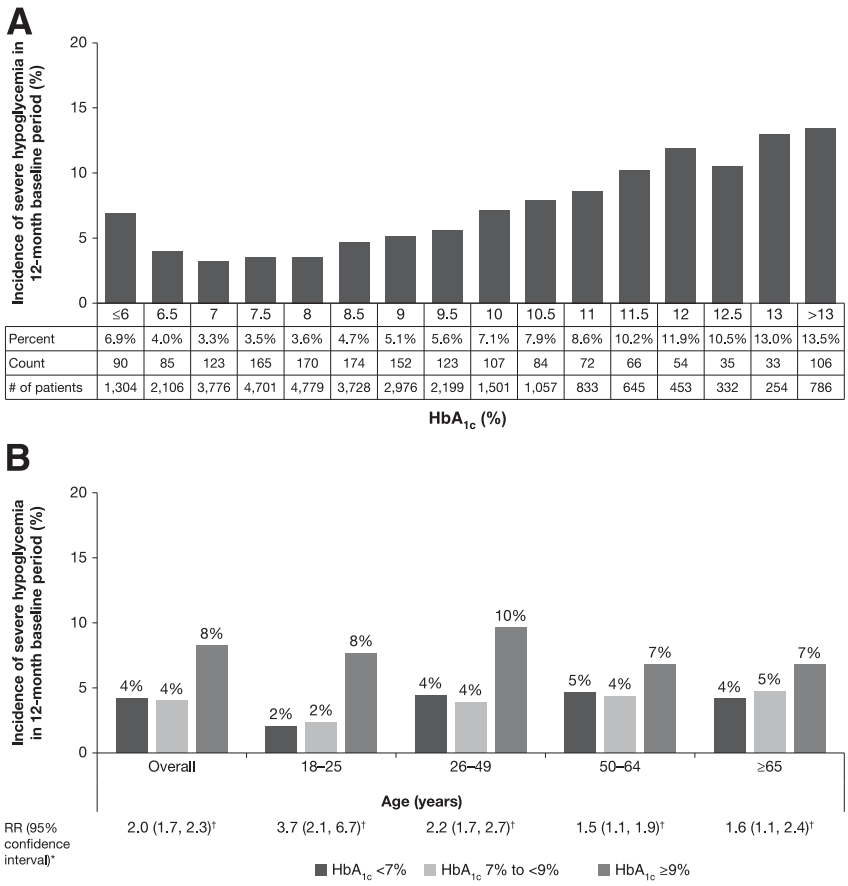

Figure 3—SH during the 12-month baseline period. *A*: Stratified by HbA_{1c} category. Total number of patients: 31,430. The incremental interval between each HbA_{1c} category was 0.5; each category had an open lower bound and a closed upper bound, e.g., category of HbA_{1c} 6.5% included patients with HbA_{1c} >6% and patients with HbA_{1c} ≤6.5%. *B*: Stratified by age-group and glycemic control. The values beneath each set of bars show the RRs of SH among those with HbA_{1c} ≥9% vs. <7% within each age category. Overall, in the HbA_{1c} <7%, 7% to <9%, and ≥9% groups, respectively, n = 6,331, 16,539, and 8,560. Age-group 18–25 years, n = 570, 2,072, and 2,262; 26–59 years, n = 2,406, 6,604, and 3,714; 60–64 years, n = 1,952, 5,153, and 1,935; ≥65 years, n = 1,394, 2,710, and 649. *RR for HbA_{1c} ≥9% vs. <7%. †$P < 0.05$.

the need to better understand the role of age in type 1 diabetes interventions.

Microvascular Complications by Age and Glycemic Control

We found that patients with HbA_{1c} ≥9% have higher prevalence (and RRs) of neuropathy and prevalence of nephropathy than patients with HbA_{1c} <7%, overall and within each age-group. Generally, our results corroborate findings from the Diabetes Control and Complications Trial, in which suboptimal glycemic control was associated with increased risks of neuropathy and nephropathy (15). The association between poor glycemic control and prevalence of retinopathy was not consistent overall or within age-groups in our study. We used EHR data to detect specific microvascular complications and classified a patient as having had a complication only if diagnostic codes had been recorded for that patient during the baseline period (12 months). This duration may not have been adequate to allow detection of the true prevalence of retinopathy in the study population. Indeed, the T1D Exchange study, which used medical chart reviews to determine whether patients had ever been treated for retinopathy, showed a clear association between poor glycemic control and prevalence of retinopathy (11).

Potential Ways to Improve HbA_{1c} Control

On average, HbA_{1c} in the current study stratified by age was 0.3–0.5% higher than that in the T1D Exchange study; however, in terms of achievement of HbA_{1c} 7%, the percentage was similar (20% in the T1PCO study and 23% in adults from the T1D Exchange study) (11). Reasons for poor HbA_{1c} control are likely multifactorial and include issues with access to specialist care, insurance coverage, limited use of technology and newer insulins, problems with adherence and persistence with medical regimens, and psychological issues such as depression. In the current study, 40% of patients did not have an endocrinologist encounter during the 12-month baseline period, implying that diabetes management was often provided by primary care physicians. It would, therefore, be beneficial to provide further training and support to primary care physicians for the management of patients with type 1 diabetes. With optimized insulin treatment and the introduction of continuous glucose monitoring and insulin pumps (4), we could see improved management and clinical outcomes (including glucose variability) in the adult population with type 1 diabetes.

Limitations

Coding algorithms were used to identify the study population. Although a validated algorithm was used to identify a diagnosis of type 1 diabetes (9), misclassification may have occurred, and a study to validate the data source's coding was not conducted. Hypoglycemia (any or severe) is typically underreported in claims and EHRs, and the true incidence of hypoglycemia, especially in the population with type 1 diabetes, could be much higher than that captured using ICD codes or plasma glucose values. Furthermore, hypoglycemia was defined using both ICD codes and laboratory tests, and hypoglycemia events identified by laboratory tests may be secondary to treatment rather than primary hypoglycemia events. While there may be racial differences in the relationship between serum glucose and HbA_{1c} (16), race was not controlled in the statistical models. Further, while HbA_{1c} should potentially be interpreted differently for individuals with substantially impaired renal function, differences in renal function were not adjusted for in the statistical models. Although EHR data have great depth, they provide information only about care that was given by providers that contribute to the database. Medication use is particularly difficult to assess from EHR data because only prescription orders from the provider are available. Use of ICD codes to

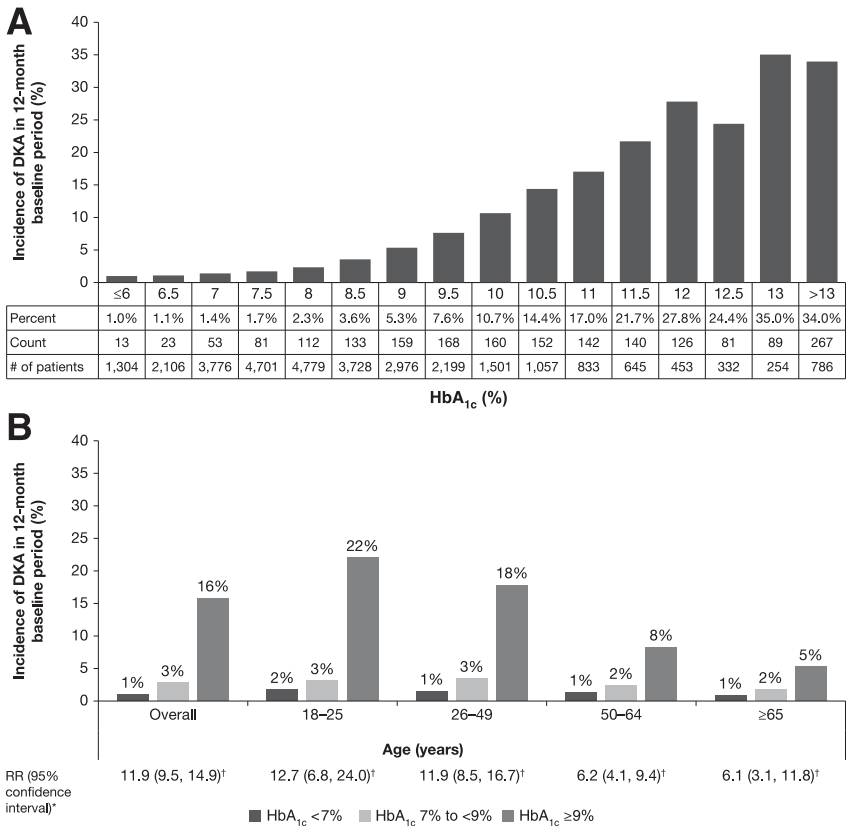

Figure 4—DKA during the 12-month baseline period. *A*: Stratified by HbA_{1c} category. Total number of patients: 31,430. The incremental interval between each HbA_{1c} category was 0.5; each category had an open lower bound and a closed upper bound, e.g., category of HbA_{1c} 6.5% included patients with HbA_{1c} >6% and patients with HbA_{1c} ≤6.5%. *B*: Stratified by age category and glycemic control. The values beneath each set of bars show the RRs of DKA among those with HbA_{1c} ≥9% vs. <7% within each age category. Overall, in the HbA_{1c} <7%, 7% to <9%, and ≥9% groups, respectively, $n = 6,331$, 16,539, and 8,560. Age-group 18–25 years, $n = 570$, 2,072, and 2,262; 26–59 years, $n = 2,406$, 6,604, and 3,714; 60–64 years, $n = 1,952$, 5,153, and 1,935; ≥65 years, $n = 1,394$, 2,710, and 649. *RR for HbA_{1c} ≥9% vs. <7%. †$P < 0.05$.

identify microvascular complications may lead to underestimation of the prevalence of this complication, particularly retinopathy, in the adult population with type 1 diabetes because many ophthalmology practices do not integrate their EHRs into the larger integrated delivery system. While ICD codes allowed for robust measurement of whether complication events occurred or medical care was given for particular conditions, the severity of the events or conditions was not measured. Insulin pump use and continuous glucose monitoring data are also not robustly captured in the EHR and are therefore not reported; we intend to explore the use of these modalities in subsequent analyses.

The LOESS curves (see RESEARCH DESIGN AND METHODS) comparing T1D Exchange data with our data were created using a random sample of only 16,000 patients in the T1PCO study because of computation limits of the algorithm. We did not have estimates for the duration of diabetes and instead used age as a proxy. The ADA-recommended HbA_{1c} cutoff value of 7.0% was used to classify control and suboptimal control and applied to all patients regardless of individual goals. Estimates are based on univariable analyses and not adjusted for potential confounding factors. This study is observational, which means that although associations can be identified and described, causality cannot be established.

In conclusion, this real-world study of 31,430 patients with type 1 diabetes represents the largest study to date to describe the adult population with type 1 diabetes. Our findings from this population may paint a more "real-world" picture of the management of type 1 diabetes in adult patients. Nearly 40% of patients had not seen an endocrinologist during the baseline period, exemplifying the need to educate primary care physicians, who may be the point of care for these patients. Suboptimal control was associated with patients identifying as African American, patients having higher BMI or higher eGFR, and patients with Medicaid insurance. Individuals with HbA_{1c} ≥9% had a twofold risk of SH and a 12-fold greater incidence of DKA than those with HbA_{1c} <7%. These data suggest that in adults with type 1 diabetes, glycemic control is worse than previously estimated and rates of both acute and chronic complications increase with increasing HbA_{1c}.

Acknowledgments. The authors received writing/editorial support from Yunyu Huang, of Excerpta Medica, funded by Sanofi.

Duality of Interest. This study was funded by Sanofi. The sponsor was involved in the study design, study funding and execution, data collection and analysis, and support for authors (including authors affiliated with the sponsor) in the preparation of the manuscript. J.H.P. is a consultant for Diasome, Insulet, Lexicon, Lilly, Mannkind, Novo Nordisk, Sanofi, and Senseonics. F.L.Z., R.P., and S.P. are employees and stockholders of Sanofi. L.S. and P.R.H. were employees of Evidera at the time the study was conducted, under contract with Sanofi. S.V.E. is a medical advisor for AstraZeneca, BrightSight, InPen, Lexicon, Lilly USA LLC, MannKind, Merck, Novo Nordisk, and Sanofi; a speaker for AstraZeneca, Lilly USA LLC, MannKind, Merck, and Sanofi; and an advisory board member for Senseonics and Team Type 1. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. J.H.P., F.L.Z., L.S., R.P., P.R.H., S.P., K.M.M., and S.V.E. contributed to data interpretation and the drafting, critical review, and revision of the manuscript. F.L.Z. designed the study. L.S. and P.R.H. acquired and analyzed data. F.L.Z. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this analysis were presented in abstract form at the 12th International Conference on Advanced Technologies & Treatments for Diabetes, Berlin, Germany, 20–23 February 2019.

References

1. Dhaliwal R, Weinstock RS. Management of type 1 diabetes in older adults. Diabetes Spectr 2014;27:9–20

2. Fowler MJ. Microvascular and macrovascular complications of diabetes. Clin Diabetes 2008;26:77–82

3. Chamberlain JJ, Rhinehart AS, Shaefer CF Jr., Neuman A. Diagnosis and management of diabetes: synopsis of the 2016 American Diabetes

Association Standards of Medical Care in Diabetes. Ann Intern Med 2016;164:542–552
4. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016–2018. Diabetes Technol Ther 2019;21:66–72
5. Simmons JH, Chen V, Miller KM, et al.; T1D Exchange Clinic Network. Differences in the management of type 1 diabetes among adults under excellent control compared with those under poor control in the T1D Exchange Clinic Registry. Diabetes Care 2013;36:3573–3577
6. Zhou FL, Shepherd L, Mercaldi K, Preblick R, Hunt P, Pettus J. Glycemic control and risk factors for adults with type 1 diabetes (T1D): clinical characteristics for glycemic controlled vs suboptimal controlled patients from T1PCO study. J Manag Care Spec Pharm 2018;24:S41
7. Wallace PJ, Shah ND, Dennen T, Bleicher PA, Crown WH. Optum Labs: building a novel node in the learning health care system [published correction appears in Health Aff (Millwood) 2014;33:1703]. Health Aff (Millwood) 2014;33:1187–1194
8. Zhong Y, Lin PJ, Cohen JT, Winn AN, Neumann PJ. Cost-utility analyses in diabetes: a systematic review and implications from real-world evidence. Value Health 2015;18:308–314
9. Klompas M, Eggleston E, McVetta J, Lazarus R, Li L, Platt R. Automated detection and classification of type 1 versus type 2 diabetes using electronic health record data. Diabetes Care 2013;36:914–921
10. Miller KM, Foster NC, Beck RW, et al.; T1D Exchange Clinic Network. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. Diabetes Care 2015;38:971–978
11. Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, DuBose SN, Hall CA; T1D Exchange Clinic Network. The T1D Exchange clinic registry. J Clin Endocrinol Metab 2012;97:4383–4389
12. Ricci-Cabello I, Ruiz-Pérez I, Nevot-Cordero A, Rodríguez-Barranco M, Sordo L, Gonçalves DC. Health care interventions to improve the quality of diabetes care in African Americans: a systematic review and meta-analysis. Diabetes Care 2013;36:760–768
13. Secrest AM, Costacou T, Gutelius B, Miller RG, Songer TJ, Orchard TJ. Associations between socioeconomic status and major complications in type 1 diabetes: the Pittsburgh epidemiology of diabetes complication (EDC) Study. Ann Epidemiol 2011;21:374–381
14. Liu J, Wang R, Ganz ML, Paprocki Y, Schneider D, Weatherall J. The burden of severe hypoglycemia in type 1 diabetes. Curr Med Res Opin 2018;34:171–177
15. Nathan DM; DCCT/EDIC Research Group. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 years: overview. Diabetes Care 2014;37:9–16
16. Bergenstal RM, Gal RL, Connor CG, et al.; T1D Exchange Racial Differences Study Group. Racial differences in the relationship of glucose concentrations and hemoglobin A1c levels. Ann Intern Med 2017;167:95–102