Glucose Control, Sulfonylureas, and Insulin Treatment in Elderly People With Type 2 Diabetes and Risk of Severe Hypoglycemia and Death: An Observational Study

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OBJECTIVE

To estimate the relative and absolute risk of severe hypoglycemia and mortality associated with glucose control, sulfonylureas, and insulin treatment in elderly people with type 2 diabetes.

RESEARCH DESIGN AND METHODS

We identified elderly subjects (≥70 years old) with type 2 diabetes between 2000 and 2017 in the U.K. Clinical Practice Research Datalink primary care database with linkage to hospitalization and death data. Subjects with three consecutive HbA_{1c} values <7% (53 mmol/mol) while on insulin and/or sulfonylureas within 60 days prior to the third HbA_{1c} value (exposed) were matched with subjects not exposed. Hazard ratios (HRs) and absolute risks were estimated for hospitalizations for severe hypoglycemia and cardiovascular and noncardiovascular-related mortality.

RESULTS

Among 22,857 included subjects (6,288 [27.5%] exposed, of whom 5,659 [90.0%] were on a sulfonylurea), 10,878 (47.6%) deaths and 1,392 (6.1%) severe hypoglycemic episodes occurred during the follow-up. In comparison with nonexposed subjects, the adjusted HR in exposed subjects was 2.52 (95% CI 2.23, 2.84) for severe hypoglycemia, 0.98 (0.91, 1.06) for cardiovascular mortality, and 1.05 (0.99, 1.11) for noncardiovascular mortality. In a 70-, 75-, 80-, and 85-year-old subject, the 10-year risk of severe hypoglycemia was 7.7%, 8.1%, 8.6%, and 8.4% higher than in nonexposed subjects, while differences for noncardiovascular mortality ranged from 1.2% (95% CI −0.1, 2.5) in a 70-year-old to 1.6% (−0.2, 3.4) in an 85-year-old subject. Sulfonylurea and insulin use were more relevant predictors of severe hypoglycemia and death than were glucose levels.

CONCLUSIONS

Elderly subjects with type 2 diabetes and low HbA_{1c} on sulfonylurea or insulin treatment experienced a substantially higher risk of hospitalization for severe hypoglycemia but had no clear evidence of increased risks of mortality.

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Glucose control in people with type 2 diabetes plays an important role in reducing the risk of cardiovascular disease (CVD) (1). While there is robust epidemiological evidence of a progressive association between glucose levels and risk of long-term vascular complications (2), intensive glucose control aiming at normal glucose levels has not been consistently associated with a reduced risk of cardiovascular events or mortality in randomized controlled trials (RCTs) of subjects with type 2 diabetes (3–5). Conversely, intensive glucose control could increase the short- and long-term risk of hypoglycemia-related complications (6). Combined with the emerging observational evidence showing a higher mortality in patients experiencing severe hypoglycemic episodes (7,8), the results of these RCTs raised a greater awareness of the risk associated with excessive glucose control and contributed to the development of the clinical concept of "diabetes overtreatment," whereby intense glucose control may result in more harm than benefit, particularly in elderly patients (9).

A definition of "overtreatment" based on combination of glucose (HbA_{1c}), treatment (medications associated with a higher risk of hypoglycemia), and demographic (age, given the higher risk of hypoglycemia and hypoglycemia-associated complications in elderly patients) criteria has been adopted in many observational studies (10), particularly those using electronic health records (11,12), although other definitions have been reported in the literature (13). In particular, HbA_{1c} <7% (53 mmol/mol) in subjects >65 years old who are at risk for hypoglycemia while on insulin and/or a sulfonylurea has been suggested as criteria for identification of patients at risk for potential overtreatment (11,14). To date, the available epidemiological studies have mainly described the incidence and risk factors of overtreatment (10–13,15,16); to what extent overtreatment is associated with the relative and absolute risk of severe hypoglycemia and cause-specific mortality remains, however, largely unknown. At the same time, there is limited evidence on the comparative relevance of the defining elements of overtreatment to long-term outcomes, which may contribute to the heterogeneous definitions.

To help clarify the evidence, we used U.K. primary care data to investigate the presence and the magnitude of the association of potential overtreatment, and of its defining elements age, HbA_{1c}, and glucose-lowering agents, with the relative and absolute risk of hospitalization for severe hypoglycemia and CVD- and non-CVD-related mortality in elderly people with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Data Source

In conducting and reporting this study, we followed the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines (17). We used the Clinical Practice Research Datalink (CPRD) to identify a cohort of elderly subjects with type 2 diabetes in the U.K. CPRD is a primary care database of anonymized electronic health records from general practices, with ~7% of the U.K. population, of which it is broadly representative in terms of age and sex; CPRD has been validated and extensively used for epidemiological research during the last 30 years (18,19). CPRD routinely collects data on demographics, laboratory tests, diagnoses, referrals, prescriptions, and health-related behaviors (18). We used Hospital Episode Statistics (HES) Admitted Patient Care to define the medical history of included subjects and the Office for National Statistics (ONS) death registration to obtain date and cause of death. The patient-level linkage is carried out by a trusted third party with an eight-stage stepwise deterministic methodology (20). This study has been approved by the Independent Scientific Advisory Committee (protocol no. 18_156R2). The code lists used in the study are available from https://github.com/supingling/overtreatment.

Population

We included all elderly subjects (≥70 years old) with diagnosis code(s) of type 2 diabetes between 1 January 2000 and 31 December 2017 and randomly assigned a day and month of birth to each subject, as they are not available in CPRD due to the anonymization process. All subjects were considered at risk for being exposed to overtreatment since the 70th birthday, if diagnosed with type 2 diabetes before 70 years of age, or since the date of diagnosis, if it occurred after age 70 years. Subjects also had to be registered within an up-to-standard practice for a minimum of 1 year before the diagnosis of type 2 diabetes; those without linkage to HES or ONS death registration were not eligible for this study.

Exposure

In line with the available evidence from previous epidemiological studies with use of electronic health records and the clinical recommendations about the definition of "overtreatment" (11–14), we defined the exposure based on the glycemic control and the concurrent use of glucose-lowering agents associated with a higher risk of hypoglycemia. The exposed group included subjects with three consecutive values of HbA_{1c} <7% (53 mmol/mol) while on insulin and/or a sulfonylurea within 60 days prior to the third HbA_{1c} measurement date; index date was identified as the first occurrence of these criteria. Up to three nonexposed subjects were matched to those exposed by year of birth ± 1 year, year of type 2 diabetes diagnosis, sex, number of HbA_{1c} measurements since being at risk for overtreatment until index date, and the length of the time frame from being at risk for overtreatment to index date ± 6 months. The nonexposed group included all subjects with type 2 diabetes aged ≥70 years between 1 January 2000 and 31 December 2017 who did not meet the criteria for the exposure. We further excluded subjects with history of severe hypoglycemia before index date in both the exposed and nonexposed group.

Outcomes

Outcomes included hospitalization for severe hypoglycemia and CVD- and non-CVD-related death. Severe hypoglycemia was defined as an admission to the hospital with reporting of the ICD-10 code of E16.0, E16.1, or E16.2 in HES Admitted Patient Care; date and the underlying cause of death, defined with ICD-10 codes, were ascertained via linkage to ONS death registration. For severe hypoglycemia, subjects were followed up until the first event, death, or 31 December 2017 (HES linkage date)—whichever occurred first. For mortality, they were followed up until death or 14 February 2018 (ONS linkage date).

Covariates

Sociodemographic factors included age at index date, sex, ethnicity (White or non-White and obtained from HES and CPRD), diabetes duration, and deprivation (Townsend score in 2001: quintile 1, most affluent; quintile 5, most deprived). BMI; alcohol consumption (no drinker, ex-drinker, yes but unknown units, yes

with ≤14 units/week, yes with >14 units/week); smoking status (not smoker, ex-smoker, current smoker); HbA_{1c}; blood pressure; total, HDL, and LDL cholesterol; and estimated glomerular filtration rate (eGFR) (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) were identified in CPRD with use of the closest value to the index date. Glucose-lowering medications, ACE inhibitors, angiotensin II receptor blockers, and statins were identified through prescriptions in CPRD within 60 days prior to the index date. Heart failure, stroke, myocardial infarction, cancer, peripheral arterial disease, chronic kidney disease, nontraumatic lower-limb amputation, dementia, anemia, and depression were assessed by the presence of at least one diagnosis (or procedure) code in CPRD or HES before the index date.

Statistical Analysis

We report the characteristics of included subjects stratified by exposure status as median and interquartile range for continuous and number and percentage for categorical variables. We used the Royston-Parmar-Lambert parametric survival model, with time into the study (i.e., from index date) as time scale (21); the index date of the nonexposed subjects was the same calendar date of the matched exposed subjects. The advantage of this model over the Cox regression is the possibility of investigating relative (hazard ratio [HR]) as well as absolute effects. Accounting for competing risk, we used standardized cause-specific cumulative incidence functions to quantify the 5-year and 10-year absolute risk in severe hypoglycemia, CVD- and non-CVD-related death in exposed and nonexposed subjects, and their difference (22,23). To allow the effect of the exposure to change across age, we tested a nonlinear interaction between a restricted cubic spline transformation of age and the exposure. We further adjusted for sociodemographic and lifestyle factors, laboratory tests, medications, and previous medical conditions. To account for missing data, we performed multiple imputation and combined estimates using Rubin's rules across 10 imputed data sets (24); we also conducted a complete-case analysis. To assess the robustness of our results, and investigate the comparative role of glucose control and therapies on the risk of the three outcomes, we performed several supplemental analyses (details reported in the Supplementary Material).

All analyses were conducted with Stata/IC 16.0, and estimates are reported with 95% CI.

Data and Resource Availability

Data access is through permission from CPRD only; please send any enquiries to enquiries@cprd.com.

RESULTS

Cohort Characteristics

The details of the cohort definition are shown in Supplementary Fig. 1. Overall, of 69,993 people with type 2 diabetes aged ≥70 years and with linkage to HES and ONS, 6,974 were defined as exposed. After matching, 686 exposed and 46,450 nonexposed subjects were excluded due to no matching or history of severe hypoglycemia, leaving 6,288 (27.5%) and 16,569 subjects, respectively, for the analysis.

The pattern of missing data is reported in Supplementary Table 1. The characteristics of included subjects at index date, stratified by exposure, are shown in Table 1. Compared with nonexposed, exposed subjects had lower HbA_{1c} (6.4% [46 mmol/L] for exposed and 6.8% [51 mmol/L] for nonexposed), eGFR, diastolic blood pressure, and cholesterol, and they were also more likely to be nondrinkers and on thiazolidinedione, ACE inhibitors, angiotensin II receptor blockers, and statins. Among the exposed subjects, 90.0% were on a sulfonylurea compared with 75.2% among the nonexposed; corresponding proportions for insulin were 9.2% and 19.7%. Marginal differences were observed for preexisting comorbidities, ranging from 0.8% for depression (21.5% in the exposed and 22.3% in the nonexposed) to 3.0% for anemia (15.9% and 12.9%, respectively). All other sociodemographic and clinical characteristics were balanced between the two groups.

Hospitalization for Severe Hypoglycemia

During 121,457 person-years of follow-up (median 4.9 years), 1,392 (6.1%) subjects were admitted to hospital for severe hypoglycemia; hospitalization rates were 17.5 (95% CI 16.1, 18.9) and 9.2 (8.6, 9.8) per 1,000 person-years in exposed and nonexposed subjects, respectively. With adjustment only for age, the rate of hospitalization for severe hypoglycemia was higher in the exposed compared with nonexposed group (HR 1.90 [95% CI 1.71, 2.11]). Upon further adjustment for other potential confounders, the HR increased to 2.52 (2.23, 2.84) (Table 2).

Figure 1 shows the absolute risk of severe hypoglycemia in exposed and nonexposed subjects. Regardless of age, the risk of severe hypoglycemia was always higher in the exposed than in the nonexposed subjects: in a 70-year-old subject, the risk progressively increased up to 6.0% at 5 years and 13.6% at 10 years; corresponding estimates in a 75-, 80-, and 85-year-old subject were 6.8% and 14.4%, 7.9% and 15.2%, and 8.5% and 14.8%, respectively. In contrast, in a 70-year-old nonexposed subject, the risk similarly increased over time but to a smaller extent, resulting in 2.5% at 5 years and 5.9% at 10 years; corresponding estimates in a 75-, 80-, and 85-year-old subject were 2.9% and 6.2%, 3.3% and 6.6%, and 3.6% and 6.4%, respectively. These estimates translated in a 10-year absolute risk difference, in comparison of exposed with nonexposed, of 7.7% (95% CI 6.0, 9.4) for a 70-year-old subject, 8.1% (6.7, 9.6) for a 75-year-old subject, 8.6% (7.2, 10.0) for an 80-year-old subject, and 8.4% (6.9, 9.8) for an 85-year-old subject, respectively (Figs. 1 and 2).

Cardiovascular and Noncardiovascular-Related Mortality

During 125,409 person-years of follow-up (median 5.2 years), 3,670 (16.1%) CVD-related and 7,208 (31.5%) non-CVD-related deaths occurred. The crude CVD-related mortality rates were 29.7 (95% CI 28.0, 31.6) and 29.1 (28.0, 30.2) per 1,000 person-years in exposed and nonexposed subjects, respectively; corresponding estimates for non-CVD-related death were 59.6 (57.1, 62.2) and 56.7 (55.1, 58.2). In multivariable models, the adjusted HR was 1.05 (95% CI 0.99, 1.11) for non-CVD-related and 0.98 (0.91, 1.06) for CVD-related death comparing exposed with nonexposed subjects (Table 2).

Figure 1 presents the absolute risk of CVD- and non-CVD-related death over 10 years in exposed and nonexposed subjects. In a 75-year-old nonexposed subject, the risk of CVD- and non-CVD-related death was 8.9% and 16.7% at 5 years and 17.0% and 36.3% at 10 years, respectively; in an 85-year-old subject, corresponding estimates were 16.1% and 28.9% at 5 years and 25.9% and 51.5% at 10 years. In contrast, in a

Table 1—Characteristics of subjects at index date by exposure

	Nonexposed (n = 16,569)	Exposed (n = 6,288)	P
Age, years	76.6 (73.1–81.3)	76.8 (73.1–81.5)	0.370
≤75	6,531 (39.4)	2,449 (38.9)	0.230
75–80	4,901 (29.6)	1,820 (28.9)	
80–85	3,276 (19.8)	1,255 (20.0)	
>85	1,861 (11.2)	764 (12.2)	
Age at type 2 diabetes diagnosis, years	72.4 (68.3–77.1)	72.3 (68.1–77.3)	0.720
Sex			0.940
Male	8,881 (53.6)	3,374 (53.7)	
Female	7,688 (46.4)	2,914 (46.3)	
Ethnicity			0.470
White	14,878 (93.5)	5,678 (93.2)	
Non-White	1,034 (6.5)	412 (6.8)	
Townsend score quintiles			0.033
1, most affluent	3,597 (21.7)	1,304 (20.8)	
2	4,017 (24.3)	1,525 (24.3)	
3	3,587 (21.7)	1,294 (20.6)	
4	3,380 (20.4)	1,377 (21.9)	
5, most deprived	1,975 (11.9)	784 (12.5)	
Diabetes duration, years	4.1 (2.2–6.9)	4.2 (2.2–7.1)	0.026
HbA_{1c} measurements from being at risk for overtreatment	5 (3–9)	5 (3–9)	<0.001
Time from being at risk for overtreatment, years	2.7 (1.7–4.7)	2.7 (1.6–4.9)	0.820
HbA_{1c}			
%	6.8 (6.3–7.5)	6.4 (6.0–6.7)	<0.001
mmol/mol	51 (45–59)	46 (42–50)	
BMI, kg/m^2	28.3 (25.3–31.8)	28.2 (25.1–32.0)	0.190
eGFR, mL/min/1.73 m^2	62 (50–76)	58 (44–73)	<0.001
Blood pressure, mmHg			
Diastolic	74 (68–80)	72 (67–80)	<0.001
Systolic	137 (128–144)	137 (127–145)	0.690
Cholesterol, mmol/L			
Total	4.1 (3.6–4.8)	3.9 (3.4–4.6)	<0.001
HDL	1.3 (1.0–1.5)	1.2 (1.0–1.5)	<0.001
LDL	2.1 (1.6–2.7)	2.0 (1.6–2.6)	<0.001
Smoking status			0.590
Current smoker	1,314 (7.9)	488 (7.8)	
Ex-smoker	7,325 (44.3)	2,829 (45.0)	
Nonsmoker	7,897 (47.8)	2,963 (47.2)	
Alcohol consumption			0.001
Nondrinker	4,084 (25.3)	1,675 (27.4)	
Ex-drinker	892 (5.5)	370 (6.0)	
Drinker, <14 units/week	5,402 (33.4)	2,016 (33.0)	
Drinker, >14 units/week	1,106 (6.8)	367 (6.0)	
Drinker, unknown units	4,689 (29.0)	1,688 (27.6)	
Glucose-lowering medications			<0.001
None	7,483 (45.2)	0 (0.0)	
1	6,344 (38.3)	2,992 (47.6)	
2	2,265 (13.7)	2,922 (46.5)	
3	453 (2.7)	361 (5.7)	
4	23 (0.1)	13 (0.2)	
5	1 (0.0)	0 (0.0)	
Glinide	42 (0.3)	12 (0.2)	0.380
Metformin	7,288 (44.0)	2,917 (46.4)	0.001
DPP-4i	506 (3.1)	204 (3.2)	0.460
GLP-1RA	60 (0.4)	21 (0.3)	0.750
SGLT-2i	23 (0.1)	5 (0.1)	0.250
Thiazolidinedione	694 (4.2)	402 (6.4)	<0.001
Mixed oral medication	158 (1.0)	62 (1.0)	0.820
Other diabetes medications	26 (0.2)	7 (0.1)	0.420
Use of a sulfonylurea and insulin*			<0.001
Sulfonylurea and insulin	172 (5.1)	53 (0.8)	

Continued on p. 919

Table 1—Continued

	Nonexposed (n = 16,569)	Exposed (n = 6,288)	P
Sulfonylurea only	2,526 (75.2)	5,659 (90.0)	
Insulin only	663 (19.7)	576 (9.2)	
Type of insulin*			
Basal	398 (2.4)	217 (3.5)	<0.001
Intermediate	431 (2.6)	399 (6.3)	<0.001
Prandial	148 (0.9)	77 (1.2)	0.023
Combination	139 (0.8)	64 (1.0)	0.200
Cardiovascular medications			
ACE inhibitor	6,710 (40.5)	2,910 (46.3)	<0.001
ARB	2,633 (15.9)	1,226 (19.5)	<0.001
Statin	10,617 (64.1)	4,422 (70.3)	<0.001
Number of morbidities†			<0.001
0	6,367 (38.4)	2,262 (36.0)	
1	5,599 (33.8)	2,073 (33.0)	
2	2,873 (17.3)	1,159 (18.4)	
3	1,142 (6.9)	501 (8.0)	
4	424 (2.6)	213 (3.4)	
5	131 (0.8)	62 (1.0)	
6	23 (0.1)	16 (0.3)	
7	9 (0.1)	2 (0.0)	
8	1 (0.0)	0 (0.0)	
Myocardial infarction	2,007 (12.1)	832 (13.2)	0.022
Cancer	3,189 (19.2)	1,244 (19.8)	0.360
Heart failure	1,765 (10.7)	774 (12.3)	<0.001
Peripheral arterial disease	906 (5.5)	377 (6.0)	0.120
Stroke	2,433 (14.7)	1,002 (15.9)	0.018
Dementia	553 (3.3)	208 (3.3)	0.910
Depression	3,688 (22.3)	1,350 (21.5)	0.200
Nontraumatic lower-limb amputation	139 (0.8)	80 (1.3)	0.003
Chronic kidney disease	514 (3.1)	300 (4.8)	<0.001
Anemia	2,137 (12.9)	999 (15.9)	<0.001

Data are shown as median (interquartile range) for continuous variables and n (%) for categorical variables; P values obtained with Wilcoxon rank sum test for continuous and Pearson χ^2 test for categorical variables. eGFR calculated using the CKD-EPI equation. ARB, angiotensin II receptor blocker. *Could be combined with other drugs. †Maximum number of conditions: 10.

75-year-old exposed subject, the risk of CVD- and non-CVD-related death was 8.7% and 17.4% at 5 years and 16.6% and 37.7% at 10 years; in an 85-year-old subject, corresponding estimates were 15.7% and 30.1% at 5 years and 25.1% and 53.1% at 10 years. These estimates led to marginal absolute risk differences across ages and over time (Figs. 1 and 2). The 10-year risk of non-CVD-related mortality, in comparison of subjects exposed with those nonexposed, ranged from a minimum increase of 1.2% (95% CI −0.1, 2.5) in a 70-year-old subject to a maximum increase of 1.6% (−0.2, 3.4) in an 85-year-old subject (Fig. 2). Differences in CVD-related death were smaller: for the same comparison at the same follow-up time, differences ranged from a minimum decrease of 0.3% to a maximum decrease of 0.8%.

Table 2—HRs for hospitalization for severe hypoglycemia and cause-specific mortality

			HR (95% CI)	
Outcome	Person-years	Events/subjects, n	Age adjusted	Multivariable adjusted
Hospitalization for severe hypoglycemia	121,457	1,392/22,857	1.90 (1.71, 2.11)	2.52 (2.23, 2.84)
Cardiovascular mortality	125,409	3,670/22,857	1.02 (0.95, 1.10)	0.98 (0.91, 1.06)
Noncardiovascular mortality	125,409	7,208/22,857	1.05 (1.00, 1.10)	1.05 (0.99, 1.11)

HRs comparing exposed vs. nonexposed to overtreatment. Multivariable models adjusted for age (restricted cubic spline with four knots); number of HbA_{1c} measurements from being at risk for overtreatment to index date; length of time frame from being at risk for overtreatment to index date; sex; ethnicity (White, non-White); deprivation (quintiles); diabetes duration; BMI; blood pressure (diastolic and systolic); alcohol (no drinking, ex-drinker, yes but unknown units, yes with ≤14 units/week, yes with >14 units/week), smoking (no smoker, ex-smoker, current smoker); HbA_{1c}; total, HDL, and LDL cholesterol; eGFR (CKD-EPI equation); glucose-lowering medication (glinide, metformin, DPP-4i, GLP-1RA, SGLT-2i, thiazolidinedione, mixed oral glucose-lowering medications, and other glucose-lowering medications); ACE inhibitor; angiotensin II receptor blocker; statin; and medical history of heart failure, stroke, myocardial infarction, cancer, peripheral arterial disease, chronic kidney disease, nontraumatic lower-limb amputation, depression, dementia, and anemia.

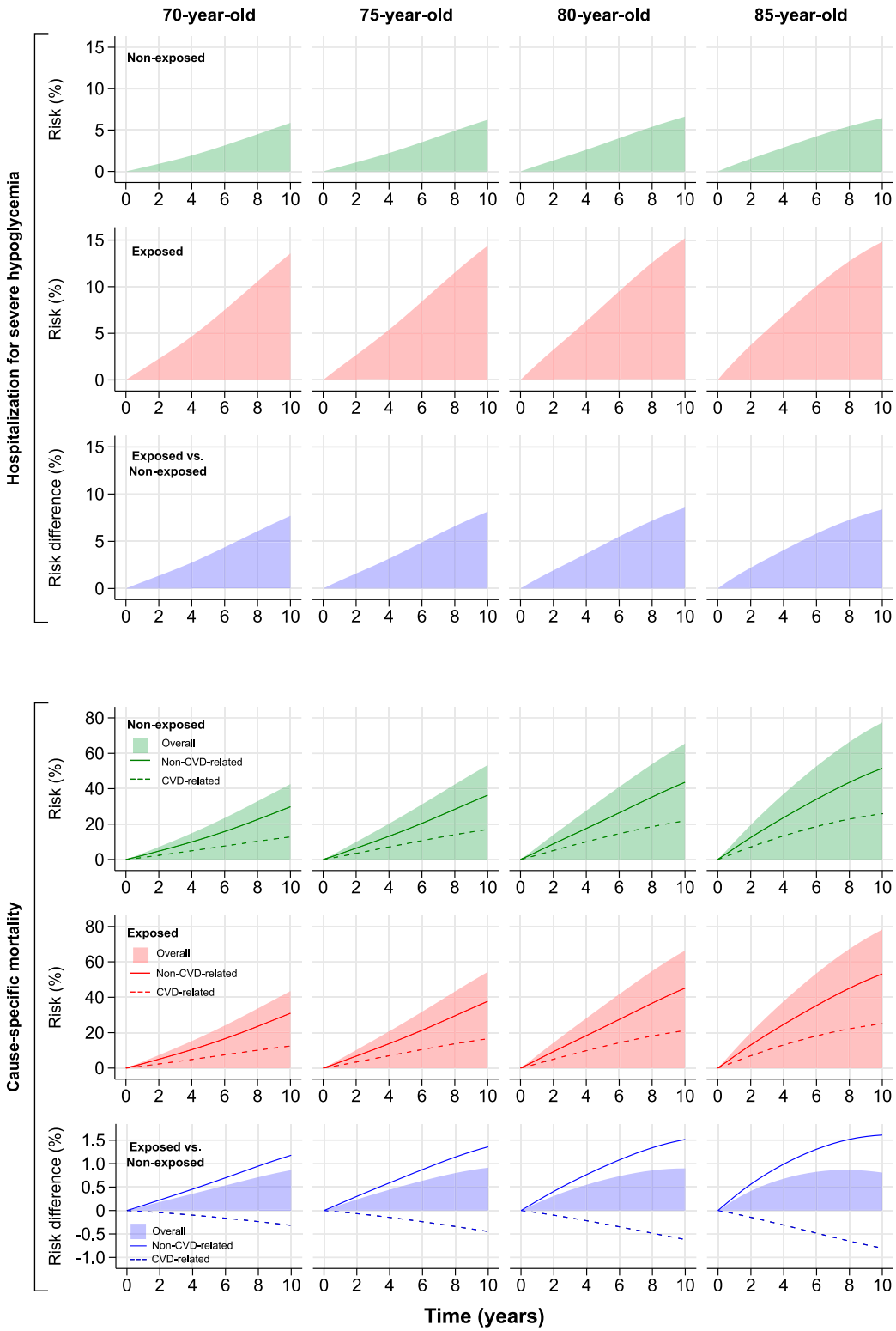

Figure 1—Absolute risk and risk difference of hospitalization for severe hypoglycemia and mortality. Absolute risks in hospitalization for severe hypoglycemia (top three panels) and CVD- and non-CVD-related mortality (bottom three panels) over 10 years of follow-up at different ages in subjects exposed (overtreatment [red]) and nonexposed (green); the difference (exposed vs. nonexposed) is shown in blue. Estimates were multivariable adjusted and accounted for all-cause deaths as competing risk for severe hypoglycemia and for non-CVD-related deaths for CVD-related mortality. In the bottom three panels, solid lines represent the risk of non-CVD-related death, dash lines indicate the risk of CVD-related death, and the area indicates the overall risk of death (non-CVD-related plus CVD-related death). Please note the different *y*-axis scale.

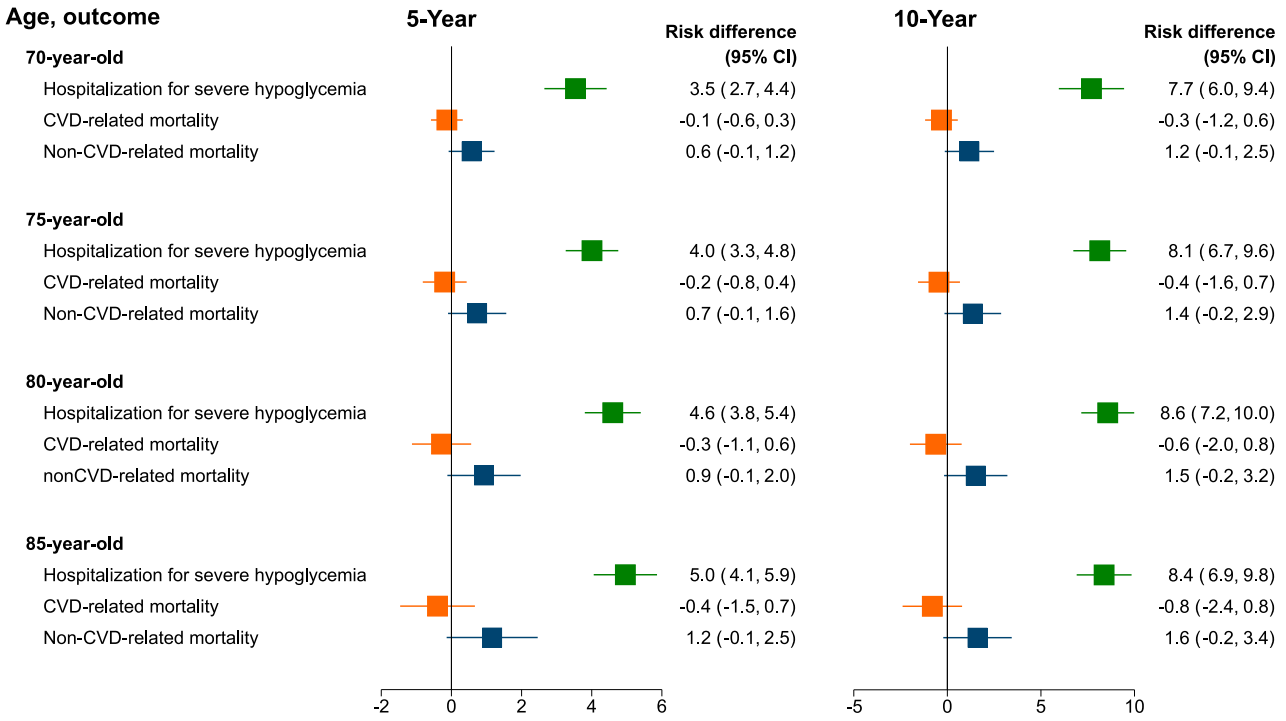

Figure 2—Five-year and 10-year risk difference in hospitalization for severe hypoglycemia and mortality. Five-year and 10-year differences (exposed vs. nonexposed to overtreatment) in hospitalization for severe hypoglycemia (green), CVD-related mortality (orange), and non-CVD-related mortality (blue) across ages are estimated in the multivariable-adjusted model with multiple imputation.

Supplemental Analyses

Results of the complete-case analysis, shown in Supplementary Figs. 2 and 3, were consistent with those of the main analysis.

Supplemental analyses investigating the risk of hypoglycemia and cause-specific death for alternative definitions of the exposure are detailed in Supplementary Material. With definition of overtreatment as three consecutive values of HbA_{1c} <7% (53 mmol/mol) and insulin only or a sulfonylurea only (there were only 53 exposed subjects to both medications) (Table 1), the estimates for three outcomes were virtually identical to those of the main analysis for the group of subjects on a sulfonylurea only. In the group of subjects on insulin only, however, the HRs for hospitalization for severe hypoglycemia (3.91 [95% CI 2.74, 5.59]) and CVD-related mortality (1.31 [1.01, 1.70]) were higher compared with those obtained in the main analysis (Supplementary Fig. 2); these differences in the HRs were mirrored in the absolute risk estimates (Supplementary Figs. 4 and 5). Using three consecutive HbA_{1c} values <6.5% (48 mmol/mol) while subjects were on insulin and/or a sulfonylurea within 60 days prior to the index date did not result in different relative (Supplementary Fig. 2) or absolute (Supplementary Figs. 6 and 7) risks compared with the 7% (53 mmol/mol) threshold. Conversely, in subjects on insulin and/or a sulfonylurea within 60 days prior to the index date, people with three consecutive HbA_{1c} <7% (53 mmol/mol) had a lower risk of hospitalization for severe hypoglycemia (HR 0.71 [0.58, 0.87]), CVD-related mortality (0.81 [0.68, 0.96]), and non-CVD-related mortality (0.76 [0.68, 0.85]) compared with those without (Supplementary Fig. 2). Lastly, with the definition limited only to the HbA_{1c} criterion (i.e., subjects with three HbA_{1c} values <7% [53 mmol/mol] regardless of medications at baseline), compared with no treatment the use of insulin and/or a sulfonylurea was associated with a higher risk of admission for severe hypoglycemia (HR 5.20 [4.44, 6.08]) and of CVD-related (1.15 [1.06, 1.25]) and non-CVD-related (1.27 [1.19, 1.34]) mortality, while no associations were found with the newer medications sodium–glucose cotransporter protein 2 inhibitor (SGLT-2i), dipeptidyl peptidase 4 inhibitor (DPP-4i), or glucagon-like peptide 1 receptor agonist [GLP-1RA]) for all three outcomes (Supplementary Fig. 2).

Stratified analyses by calendar time (to account for changes in clinical recommendations on the management of diabetes), age at diagnosis of type 2 diabetes, diabetes duration, renal function, or prevalent CVD; exclusion of subjects with previous comorbidities (to reduce the risk of reverse causation); or use of alternative statistical methods (robust SEs or inverse probability of treatment weighting) yielded results consistent with those obtained in the main analysis (Supplementary Figs. 2, 8, and 9). There was no evidence of severe hypoglycemia as a mediating factor between the exposure and CVD- or non-CVD-related mortality (Supplementary Table 2).

CONCLUSIONS

In this retrospective population-based study, we used data of primary care subjects with type 2 diabetes aged ≥70 years and low HbA_{1c} while on insulin and/or a sulfonylurea to estimate the relative and absolute risk of hospitalization for severe hypoglycemia and of CVD- and non-CVD-related mortality. These subjects, who have been considered as exposed to a potential overtreatment (11,14), had a 2.5-fold increased hazard of severe hypoglycemia, translating into a 7–9% higher absolute risk at 10 years, compared with those not exposed. However, there was no clear evidence of increased risks of mortality associated with the combination of low HbA_{1c} and insulin and/or a sulfonylurea. It is important to note, however,

that in our cohort 90% of the exposed subjects were on a sulfonylurea; therefore, our findings should be interpreted in relation to this characteristic of the exposed cohort. In our comprehensive analyses using alternative definitions of overtreatment, we also investigated the different prognostic relevance of glucose levels and glucose-lowering medications: when overtreatment is considered in view of the long-term risk of severe hypoglycemia and death, sulfonylurea and insulin treatments are more relevant predictors than glucose levels.

Driven by the results of large-scale RCTs showing a neutral or increased risk of death in subjects with type 2 diabetes randomized to intensive compared with standard glucose control (3–5,25), there has been an emerging interest in the potential harms associated with glucose overtreatment, particularly among older, frail, multimorbid patients (26). This is also reflected in the changes in clinical recommendations on diabetes management, which currently suggest relaxed HbA_{1c} goals in older patients with type 2 diabetes and other coexisting comorbidities (27). Notwithstanding, in recent years a high prevalence of diabetes overtreatment, with varied definitions, has been reported in different countries (10,12,15,16,28). While a HbA_{1c} <7% (53 mmol/mol) is widely accepted as a threshold of potential overtreatment among older adults (14,28), most studies also considered the high risk for hypoglycemia as one of the key criteria, including insulin and/or sulfonylurea use (10,11,13,15,16), three or more oral glucose-lowering medications (13,16), and/or coexisting comorbidities (12,16). In our study, to define potential overtreatment we initially considered subjects with type 2 diabetes aged ≥70 years and included the HbA_{1c} criterion (three consecutive values of HbA_{1c} <7% [53 mmol/mol]) alongside the medication criterion (concurrent use of glucose-lowering agents associated with a higher risk of hypoglycemia: insulin and/or a sulfonylurea): in this cohort, these criteria resulted in 90% of exposed participants being on a sulfonylurea. However, in view of the different definitions reported in the literature and a lack, to date, of a consensus, we also investigated associations using other possible definitions; these analyses allowed us to assess the combined and disjointed impact of the two criteria on the risk of severe hypoglycemia and mortality. We conducted extensive adjustment for other glucose-lowering medications, preexisting comorbidities, and other potential confounders and estimated both relative and absolute risks, as a "statistically significant" increase in the relative risk may translate into a modest absolute risk difference; the combined information of these two metrics gives more insights into the individual and public health relevance of HbA_{1c} levels, glucose-lowering treatments, and age (a component of any definition of overtreatment).

There is a growing consensus on the increased risk of hypoglycemia and its associated complications in elderly patients with type 2 diabetes under intensive glycemic control, possibly related to their slower counterregulatory response to hypoglycemia (27). A previous meta-analysis of five RCTs has shown that intensive glycemic control was associated with an approximately twofold increased risk of severe hypoglycemia (25); this estimate is in line with our findings. Of note, we included subjects aged ≥70 years with a median diabetes duration of 4 years and an HbA_{1c} <7% (53 mmol/mol) in the exposed group; in contrast, in these RCTs the mean/median age and diabetes duration were 52–66 years and 8–11 years, respectively, while the HbA_{1c} targets in the intensive treatment arms were <6.5% (48 mmol/mol) or <6.0% (42 mmol/mol) (25). However, our analysis with the 6.5% (48 mmol/mol) threshold showed results virtually identical to those of the main analysis, with a possible slightly higher risk of severe hypoglycemia in subjects with a longer diabetes duration. Moreover, a post hoc analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in older (≥65 years) participants indicated that the proportion of subjects reporting a severe hypoglycemia was three times higher in the intensive compared with standard therapy arm (29), consistent with our relative hazard estimate. Although the relative risk of severe hypoglycemia in our study was similar to the effect size reported in the ACCORD trial and the meta-analysis of intensive glycemic control, the absolute rates of severe hypoglycemia in our real-world study were lower compared with those reported in these trials, except in comparison with the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial. In our study, rates of hospitalization for severe hypoglycemia were 17.5 and 9.2 per 1,000 person-years among exposed and nonexposed subjects, respectively; rates in the intensive and standard arms were 7 and 4 per 1,000 person-years in ADVANCE (hypoglycemia requiring assistance from a third party) (5), 30 and 10 in the Veterans Affairs Diabetes Trial (VADT) (hypoglycemia resulting in complete loss of consciousness) (4), and 44.5 and 13.6 in the ACCORD subgroup of older participants (hypoglycemia requiring medical assistance) (29,30).

Meta-analyses of RCTs have concluded that intensive glucose reduction may reduce CVD events compared with standard therapy, while intensive glucose reduction does not result in a reduction of all-cause or CVD-related mortality (31,32). In ACCORD, in particular, a 22% higher mortality rate was observed in subjects randomized to intensive compared with standard glycemic control (3), while we found no clear evidence of increased risks of mortality. In contrast with the uncertainty around intensive glucose control and cause-specific mortality, there is more robust and consistent evidence of a substantial excess risk of death (particularly non-CVD-related death) in subjects with a previous severe episode of hypoglycemia (33). A pathway whereby overtreatment leads to an increased risk of severe hypoglycemia that, in turn, would increase the risk of death has been postulated (34). Although it was not the primary aim of our study, we did not find evidence of a mediating role of severe hypoglycemia in the association between overtreatment and mortality. The significantly greater risk of severe hypoglycemia compared with that of death in exposed subjects in our study would rather imply a different prognostic relevance of the factors considered in our models for these two outcomes; at the same time, our findings would suggest that other factors might be more relevant for the risk of death in patients who experienced a severe hypoglycemic episode.

Our extensive supplemental analyses suggested that treatment with insulin or a sulfonylurea, rather than the low HbA_{1c} levels alone, is the key prognostic factor for hospitalization for severe hypoglycemia and mortality. In subjects with three consecutive HbA_{1c} values <7% (53 mmol/mol), use of insulin and/or a sulfonylurea was associated with a higher risk of severe hypoglycemia and mortality than use of any other glucose-lowering

medications. Furthermore, among all subjects on insulin and/or a sulfonylurea at baseline, those with three consecutive HbA_{1c} values <7% (53 mmol/mol) had a lower risk of all outcomes. Interestingly, these two observations very closely mirror an observational study in subjects with type 2 diabetes aged >75 years, where HbA_{1c} levels between 6.5 and 6.9% (48–52 mmol/mol) alone were not associated with a higher risk of death; contrariwise, in consideration jointly with insulin or sulfonylurea therapy, the risk of death was more than doubled (35). Moreover, in people with low HbA_{1c} levels, for SGLT-2i, DPP-4i, or GLP-1RA—which did not increase the risk of hypoglycemia in RCTs—there was no evidence of an association with hospitalization for severe hypoglycemia or cause-specific mortality compared with no treatment. Overall, our results contribute to the current evidence and debate over HbA_{1c}, glucose-lowering medications, and age as distinct yet complementary prognostic factors in the risk of severe hypoglycemia and mortality and give insights into the definition of "diabetes overtreatment" from both an epidemiological and clinical perspective.

To our knowledge, this is the first study investigating the relative and absolute magnitude of the association between potential diabetes overtreatment and severe hypoglycemia hospitalization as well as cause-specific mortality. Our findings have important clinical implications. Currently, no clinical parameters are available to suggest when well-controlled glucose levels are indicative of an overtreatment and a possible "deintensification" of glucose treatments should be considered (36): in this respect, the findings of heterogeneous prognostic roles of HbA_{1c} and sulfonylurea and insulin therapy may help clarify the evidence. Although during the study period new glucose-lowering agents have been made available and changes in the recommendations about glucose-lowering strategies occurred (particularly following the results of ACCORD), we observed similar associations for all three outcomes over time, translating in very similar absolute risk estimates in hospitalization for severe hypoglycemia and small differences in cause-specific mortality. Some limitations of this study should also be considered. Our analyses are based on a large U.K. electronic health record database: the generalizability of these findings should therefore be considered within the context of the health care systems where data have been collected and the potential misclassification bias in clinical coding, which cannot be completely ruled out, as data were not collected for research purposes. Moreover, information collected in these databases is not as granular as that available in cohort studies or RCTs, where data are prospectively collected in line with a specific research plan. As such, we did not include other factors, i.e., neuropathies or the hemoglobin glycation index (the difference between the observed and the fasting plasma glucose–predicted HbA_{1c}), which may act as confounders, mediators, or effect modifiers. In ACCORD and previous cohort studies, the risk of severe hypoglycemia and death has indeed been associated with the presence of neuropathy (peripheral and autonomic) and the hemoglobin glycation index (30,37–39). We used consecutive HbA_{1c} measures to define overtreatment, which may lead to misclassification bias. However, in addition to age, sex, and type 2 diabetes diagnosis year, we also matched by the number of HbA_{1c} measurements and the duration between being at risk for overtreatment and index date to minimize such bias. To account for confounding by indication, we have adjusted models for several potential confounders and assessed the robustness of our results using the inverse probability of treatment weighting; nevertheless, residual confounding may still be present and causality cannot be definitively established given the observational nature of the study.

In conclusion, a potential overtreatment of hyperglycemia, defined by consistently low HbA_{1c} measures and concurrent use of insulin and/or a sulfonylurea, is common in elderly patients with type 2 diabetes and associated with a substantially higher risk of hospitalization for severe hypoglycemia, while there is no clear of evidence of increased risks of mortality. Given the much greater number of exposed participants on a sulfonylurea than insulin in our cohort, the results should be interpreted in this context, and other investigations with larger samples are needed to disentangle the potential distinct effects of these two medications. In view of the increasing prevalence of multimorbid, older patients with type 2 diabetes (40), and the prognostic role of insulin and sulfonylureas, further research is warranted to explore the net clinical benefit of deintensification by replacement of these treatments with other glucose-lowering medications in these patients.

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