Association of Diabetes and Glycated Hemoglobin With the Risk of Intracerebral Hemorrhage: A Population-Based Cohort Study

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OBJECTIVE

To examine the association of diabetes and glycated hemoglobin (HbA_{1c}) with the risk of intracerebral hemorrhage (ICH) in a large population-based cohort.

RESEARCH DESIGN AND METHODS

The computerized database of the largest health care provider in Israel was used to identify adult members aged 40 years or older and alive at 1 January 2010 (297,486 with diabetes and 1,167,585 without diabetes). The cohort was followed until 31 December 2017 for incidence of ICH. Multivariable Cox proportional hazards regression models, adjusted for baseline disease risk score, were applied to estimate the hazard ratio (HR) of ICH.

RESULTS

Overall 4,170 ICH cases occurred during 10,730,915 person-years of follow-up. Diabetes was independently associated with increased ICH risk, with hazard ratio (HR) 1.36 (95% CI 1.27–1.45), and increased with longer diabetes duration: 1.23 (1.12–1.35) and 1.44 (1.34–1.56) for diabetes duration ≤5 years and >5 years, respectively. The increased ICH risk associated with diabetes was more pronounced in patients ≤60 years old ($P_{interaction}$ <0.001). Among patients with diabetes, HbA_{1c} had a nonlinear J-shaped relationship with ICH (P for nonlinearity = 0.0186). Compared to the fourth HbA_{1c} decile, 6.5–6.7% (48–50 mmol/mol), the HR for ICH was 1.27 (1.01–1.59) and 2.19 (1.75–2.73) in the lowest HbA_{1c} decile, ≤6.0% (≤42 mmol/mol), and highest HbA_{1c} decile, >9.3% (>78 mmol/mol), respectively.

CONCLUSIONS

Diabetes is associated with increased risk of ICH that is directly associated with diabetes duration. ICH and HbA_{1c} appear to have a J-shaped relationship, suggesting that both poor control as well as extreme intensive diabetes control might be associated with increased risk.

Spontaneous intracerebral hemorrhage (ICH) is a devastating condition accounting for 10–15% of all stroke cases. It is associated with a dismal prognosis, as only 38% of affected patients survive the first year (1).

Type 2 diabetes affects more than 415 million adults worldwide and is a well-known contributor to cardiovascular morbidity, cognitive decline, and all-cause mortality (2). Although diabetes is an independent risk factor for ischemic stroke (3), as yet there

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is no conclusive evidence for the association between diabetes and ICH, as previous studies showed conflicting results (4–8).

In addition, low and high fasting blood glucose concentrations were associated with higher risk of incident ICH in populations with diabetes and populations without diabetes (8,9). No previous studies however have looked at the association of glycated hemoglobin (HbA_{1c}), a much more accurate measure of glycemic control than glucose levels (10), and ICH risk. We sought to determine *1*) the association of diabetes and ICH and *2*) the relationship between HbA_{1c} levels and ICH in a large nationwide population-based cohort.

RESEARCH DESIGN AND METHODS

Source of Data

This study is based on data from the computerized database of Clalit Health Services (CHS), which provides inclusive health care for more than half of the Israeli population. Health care coverage in Israel is mandatory according to the National Health Insurance Law (1995) and is provided by four groups akin to not-for-profit HMOs. All members of the different HMOs have a similar health insurance plan and similar access to health services. The electronic medical record database of CHS includes data from multiple sources: records of primary care physicians, community specialty clinics, hospitalizations, laboratories, and pharmacies. A registry of chronic disease diagnoses is compiled from these data sources. Diagnoses are captured in the registry by diagnosis-specific algorithms, using ICD-9 code reading, text reading, laboratory test results, and disease-specific drug usage. A record is kept of the data sources and dates used to establish the diagnosis, with the earliest recorded date, from any source, considered to be the defining date of diagnosis. A number of high-quality, population-based studies have been conducted based on the data retrieved from the CHS database (11,12).

Selection of Study Population

The study cohort consisted of all CHS adult members aged 40 years or older and alive at 1 January 2010 (n = 1,496,094). Individuals with $<$2 years of continuous membership in the CHS prior to cohort entry date were excluded (n = 15,379). Of the remaining 1,480,715 individuals, 313,130 patients had a preexisting diagnosis of diabetes and 1,167,585 individuals were without diabetes. Patients with diabetes had to have at least one test result for HbA_{1c} in the 2 years before cohort entry (n = 297,486). Cohort participants (n = 1,465,071) were followed-up until reaching the study outcome (ICH), death, loss to follow-up, or end of follow-up at 31 December 2017—whichever came first.

Study Variables

The outcome of interest was ICH, defined as primary discharge diagnosis with ICH (ICD-9 code 431). A systematic review of studies that evaluated the accuracy of using administrative data for identifying ICH showed that the positive predictive value ranged from 79 to 97% for the inpatient ICD-9 code 431 (13). We conducted a validation study to evaluate the accuracy of using inpatient ICD-9 code 431 to identify ICH in the CHS database. We reviewed the medical files of 1,614 cases of ICH that were detected in 297,486 patients with diabetes; unfortunately 110 files could not be reached, and of the remaining 1,504 files there was a convincing evidence for secondary ICH in 78 cases and spontaneous ICH in 1,222 cases (805 deep and 355 lobar, and in 62 patients location could not be determined), yielding a positive predictive value 86.4%, in line with the systemic review (13).

The diagnosis of diabetes was retrieved from the CHS chronic disease registry that relies on different sources, including clinical diagnosis of diabetes (ICD-9 code 250), HbA_{1c} $\geq$6.5% [$>$48 mmol/mol], and diabetes-specific drug usage (ATC code A10). Data on medication use are considered to be complete because of the very low copayment required in the CHS making it unlikely that prescription medications are purchased in non-CHS pharmacies. It should be noted that diabetes has been used along with five other areas of health care to assess the quality of community health care in Israel; hence, health care providers, including CHS, have invested efforts to achieve accurate diagnosis of diabetes (14).

HbA_{1c} test results performed, in patients with diabetes, during the 2 years prior to cohort entry were retrieved from the CHS laboratory database. The most recent HbA_{1c} test performed during this period was used to assess the association between HbA_{1c} and ICH in the main analysis, and the median HbA_{1c} of all tests performed in this period was used in separate sensitivity analyses. HbA_{1c} was studied as a continuous variable and for descriptive purpose was also classified into deciles based on its distribution among patients with diabetes.

In addition, for each patient the following baseline data were retrieved from the computerized database of the CHS: demographic and other descriptive variables, health habits, socioeconomic status (SES) defined based on the SES score of the clinic neighborhood as defined by the Israel Central Bureau of Statistics, LDL cholesterol (LDL), HDL cholesterol (HDL), presence of selected chronic medical conditions and ICH risk factors, medication use of selected drug categories, and medical services utilization as shown in Table 1. SES, LDL, and HDL had missing values (0.47%, 16.3%, and 15.1%, respectively); hence, these variables were used as categorical variables that include a category of missing values.

Statistical Methods

Statistical analyses were performed using IBM SPSS Statistics 22.0 (IBM, New York, NY), and SAS, version 9.4, software. For all analyses, $P < 0.05$ for the two-tailed tests was considered statistically significant. The association between diabetes and ICH was evaluated using Cox proportional hazards regression models to estimate the crude and the adjusted hazard ratio (HR). Further, patients with diabetes were classified according to their HbA_{1c} distribution into deciles, with the group without diabetes serving as the reference category. In the analysis limited to patients with diabetes, HbA_{1c} was first modeled as a continuous variable. Nonlinearity of the relationship of HbA_{1c} with ICH was tested using a likelihood ratio test comparing two Cox regression models: one including only linear effect and the second including also quadratic and cubic terms. For graphical presentation, a smoothed plot of adjusted HR (relative to an HbA_{1c} reference value of 6.5% [48 mmol/mol]) was estimated along with point-wise 95% CI. For this purpose, HbA_{1c} was flexibly modeled in a Cox regression

Table 1—Baseline characteristics of the study population

	Cohort without diabetes	Cohort with diabetes
n	1,167,585	297,486
Age (years)	58.5 ± 13.2	66.4 ± 11.9
Sex		
Male	529,290 (45.3)	142,899 (48.0)
Female	638,295 (54.7)	154,587 (52.0)
Ethnicity		
Jewish	1,001,860 (85.8)	243,386 (81.8)
Arab	165,725 (14.2)	54,100 (18.2)
District		
A	107,553 (9.2)	27,530 (9.3)
B	116,468 (10.0)	31,373 (10.5)
C	128,347 (11.0)	32,241 (11.2)
D	132,152 (11.3)	33,167 (11.1)
E	215,838 (18.5)	54,200 (18.2)
F	132,548 (11.4)	3,511 (10.9)
G	161,533 (13.8)	40,027 (13.5)
H	173,146 (14.8)	45,437 (15.3)
SES		
Low	418,133 (36.0)	124,733 (42.1)
Middle	478,101 (41.2)	118,313 (39.9)
High	265,563 (22.9)	53,353 (18.0)
Comorbidities and risk factors (%)		
Smoking	420,800 (36.0)	113,445 (38.1)
Alcohol consumption	9,155 (0.8)	2,453 (0.8)
Obesity	179,141 (15.3)	121,404 (40.8)
Previous ICH	1,418 (0.12)	886 (0.3)
Previous stroke/TIA	54,122 (4.6)	38,850 (13.1)
Hypertension	363,171 (31.1)	208,451 (70.1)
Atrial fibrillation	39,763 (3.4)	23,156 (7.8)
Congestive heart failure	22,186 (1.9)	23,724 (8.0)
Vascular disease	89,176 (7.6)	61,295 (20.6)
Chronic kidney disease	40,088 (3.4)	57,834 (19.4)
Chronic obstructive lung disease	46,874 (4.0)	24,225 (8.1)
Chronic liver disease	6,965 (0.6)	5,276 (1.8)
Medication use (%)		
Antiaggregants	206,869 (17.7)	163,008 (54.8)
Anticoagulants	23,001 (2.0)	14,021 (4.7)
ACE inhibitors and ARBs	215,728 (18.5)	184,155 (61.9)
β-Blockers	182,221 (15.6)	114,021 (38.3)
Calcium channel blockers	129,544 (11.1)	87,504 (29.4)
Digoxin	3,757 (0.3)	3,404 (1.1)
Diuretics	109,518 (9.4)	74,283 (25.0)
Antiarrhythmics	14,119 (1.2)	7.033 (2.4)
Statins	333,787 (28.6)	206,126 (69.3)
Cholesterol level		
Total cholesterol	192 ± 37	174 ± 39
LDL cholesterol	115 ± 31	96 ± 31
HDL cholesterol	51 ± 13	46 ± 12
Number of medical services used in previous year		
Primary physician visits	12.2 ± 10.7	20.5 ± 12.7
Cardiologist visits	0.18 ± 0.77	0.39 ± 1.11
Inpatient visits	0.22 ± 0.93	0.55 ± 1.75
Emergency visits	0.20 ± 0.63	0.29 ± 0.740

Data are means ± SD or *n* (%) unless otherwise indicated. ARB, angiotensin receptor blocker.

using restricted cubic spline function with five knots corresponding to ~5%, 25%, 50%, 75%, and 95% percentiles of HbA_{1c} among patients with diabetes (15). In addition, because of the nonlinear relationship with ICH, HbA_{1c} was also modeled as a categorical variable (deciles), with the fourth decile 6.5–6.7% (48–50 mmol/mol) used as the reference category.

Because of the large number of potential confounders, we performed adjustment for a disease risk score (DRS), a summary measure of disease probability. The DRS was estimated using a Cox proportional hazards regression model for ICH outcome that included most clinically relevant ICH risk factors and other clinical covariates likely to be correlated with ICH (Table 1). In comparison with conventional multivariate analyses, adjustment for the single variable DRS increases the efficiency of the analyses (16,17). It has been shown than the DRS and propensity score methods had comparable performance and that DRS has an advantage when multiple comparison groups are studied (16,17).

In addition, we performed the following sensitivity analyses: *1*) for assessment of the association between diabetes and ICH, instead of adjustment for DRS we adjusted for propensity score (probability of having diabetes) that was calculated using a logistic regression model that included all variables in Table 1; *2*) we repeated the analysis by adjusting for the most clinically relevant variables (i.e., standard multivariable regression); *3*) because in patients without diabetes ICH may be mediated by newly diagnosed diabetes occurring after study entry, we performed two sensitivity analyses, firstly by censoring at the time of diabetes diagnosis and secondly by excluding individuals with diabetes detected during follow-up; *4*) instead of using the most recent HbA_{1c} test result for assessing the association with ICH, we repeated all analyses using the median HbA_{1c} of all tests performed in the 2 years prior to study entry; *5*) we examined whether the association between diabetes and ICH was modified by age, sex, and hypertension. Finally, we performed an additional sensitivity analysis to assess the relationship between HbA_{1c} and ICH type (deep vs. lobar). This analysis was restricted to patients with diabetes (*n* = 297,486), in whom the diagnosis of ICH was validated and classified into lobar and deep ICH by reviewing patients' files, as described above. The multiple imputation procedure (SAS MI procedure) was performed to account for missing type of ICH. Five imputation data sets were created, where all model variables were included in the imputation process.

Table 2—Descriptive statistics, incidence density rate, and crude HRs for the association between diabetes, HbA_{1c}, and ICH

	No. of patients	No. of events	Follow-up duration (person-years)	Incidence rate (per 100,000 person-years)	Crude HR (95% CI)
No diabetes	1,167,585	2,556	8,684,976	29.4	Reference
Diabetes	297,486	1,614	2,045,939	78.9	2.69 (2.53–2.87)
Diabetes duration*					
≤5 years	129,192	554	932,180	59.4	2.02 (1.85–2.20)
>5 years	168,294	1,060	1,113,758	95.2	3.26 (3.03–3.50)
HbA_{1c} deciles*					
≤6.0% (≤42 mmol/mol)	37,563	201	246,740	81.5	2.79 (2.41–3.22)
6.0–6.3% (42–45 mmol/mol)	32,555	157	225,209	69.7	2.38 (2.02–2.80)
6.3–6.5% (45–48 mmol/mol)	30,121	134	210,952	63.5	2.17 (1.82–2.58)
6.5–6.7% (48–50 mmol/mol)	29,955	124	209,700	59.1	2.02 (1.68–2.41)
6.7–6.9% (50–52 mmol/mol)	25,366	131	177,440	73.8	2.52 (2.11–3.0)
6.9–7.2% (52–55 mmol/mol)	29,364	143	203,631	70.2	3.40 (2.02–2.84)
7.2–7.6% (55–60 mmol/mol)	28,709	152	197,943	76.8	2.62 (2.23–3.09)
7.6–8.1% (60–65 mmol/mol)	24,373	156	167,440	93.2	3.18 (2.71–3.74)
8.1–9.3% (65–78 mmol/mol)	31,399	201	213,880	94.0	3.21 (2.78–3.71)
>9.3% (>78 mmol/mol)	28,081	215	193,003	111.4	3.80 (3.31–4.37)

*No diabetes is the reference.

RESULTS

A total of 1,465,071 patients (297,486 with diabetes and 1,167,585 without diabetes) with mean (SD) age 60.1 (13.4) years were included in the study, of whom 792,882 (54.1%) were female. Table 1 shows the distribution of baseline demographic and clinical characteristics among the study population with and without diabetes. Patients with diabetes were older with lower SES and generally were more likely to have comorbidities and to use medication and health services. Previous history of ICH was detected in 0.30% of patients with diabetes compared with 0.12% in patients without diabetes ($P < 0.001$). Anticoagulant use was more frequent (4.7%) among patients with diabetes compared with (2.0%) in patients without diabetes ($P < 0.001$).

Overall 4,170 patients had incident ICH during a mean (SD) follow-up of 7.3 (1.8) years and 10,730,915 person-years, reflecting an ICH crude incidence rate of 38.8 per 100,000 person-years. The univariate and multivariate association of each variable, included in Table 1, with ICH is shown in Supplementary Table 1. The strongest risk factors for ICH were prior ICH, prior stroke/transient ischemic attack (TIA), use of anticoagulation, hypertension, alcohol abuse, male sex, Arab ethnicity, chronic liver disease, and older age. Of note, statin use was associated with decreased risk of ICH (Supplementary Table 1), in line with our previous report (11) looking at statin users only.

Diabetes and ICH

The crude incidence rate of ICH was 78.9 per 100,000 person-years among patients with diabetes and 29.4 per 100,000 person-years among patients without diabetes (crude HR 2.69 [95% CI 2.53–2.87]) (Table 2). Diabetes remained significantly associated with ICH after adjustment for DRS (1.36 [1.27–1.45]). The results were unchanged after exclusion of new cases of diabetes and after censoring at the time of new diabetes diagnosis occurring during follow-up: DRS-adjusted HR 1.37 (95% CI 1.28–1.46) and 1.38 (1.29–1.47), respectively. Similar results were reached with adjustment for propensity score, 1.47 (1.36–1.59), and for the clinically relevant risk factors, 1.51 (1.40–1.62) (Table 3). Predefined subgroup analyses had shown statistically significant interactions with age ($P_{interaction}$ <0.001) and hypertension ($P_{interaction}$ <0.001) but not with sex: ICH risk associated with diabetes was more pronounced in patients ≤60 years old and in nonhypertensive patients, although the CI overlapped in hypertensive and nonhypertensive patients (Supplementary Fig. 1).

The risk of ICH was directly associated with diabetes duration. Compared with the group without diabetes, the DRS-adjusted HR was 1.23 (95% CI 1.12–1.35) and 1.44 (1.34–1.56) for diabetes duration ≤5 years and >5 years, respectively. The corresponding HRs with adjustment for propensity score were 1.27 (1.15–1.41) and 1.65 (1.50–1.80), respectively (Table 3).

The risk of ICH associated with diabetes was clearly related to HbA_{1c} in a J-shaped manner. The HRs associated with each HbA_{1c} decile in comparison with the group without diabetes are shown in Table 2. The lowest risk was observed in the fourth HbA_{1c} decile, 6.5–6.7% (48–50 mmol/mol), and was comparable with the risk in the group without diabetes, with DRS-adjusted HR 0.98 (95% CI 0.82–1.18).

HbA_{1c} and ICH Among Patients With Diabetes

HbA_{1c} was significantly associated with ICH among patients with diabetes: adjusted HR 1.14 (95% CI 1.10–1.17) for each 1% increase in HbA_{1c} (Table 4). However, HbA_{1c} appears to have a nonlinear J-shaped relationship with ICH ($P_{nonlinearity}$ = 0.0186), with the lowest risk observed at HbA_{1c} of 6.5% (48 mmol/mol). A smoothed plot of adjusted HRs (relative to HbA_{1c} reference level of 6.5% [48 mmol/mol]) is presented in Supplementary Fig. 2.

To avoid assuming linearity, we studied HbA_{1c} as a categorical variable according to deciles of the distribution, with the fourth decile, 6.5–6.7% (48–50 mmol/mol), serving as the reference group. Compared with the reference group, the HR for ICH was 1.27 (95% CI 1.01–1.59) and 2.19 (1.75–2.73) in the lowest HbA_{1c} decile, ≤6.0% (<42 mmol/mol), and highest HbA_{1c} decile, >9.30% (>78 mmol/mol), respectively (Table 4). The effect of HbA_{1c} was modified by age ($P_{interaction}$ = 0.025). No statistically

Table 3—Adjusted HRs (95% CI) for the association between diabetes, HbA_{1c}, and ICH

	Adjusted for age and sex	Adjusted for clinically relevant risk factors†	Adjusted for propensity score‡	Adjusted for DRS§
No diabetes	Reference	Reference	Reference	Reference
Diabetes	1.84 (1.73–1.96)	1.51 (1.40–1.62)	1.47 (1.36–1.59)	1.36 (1.27–1.45)
Diabetes duration*				
≤5 years	1.53 (1.40–1.68)	1.33 (1.21–1.46)	1.27 (1.15–1.41)	1.23 (1.12–1.35)
>5 years	2.06 (1.91–2.21)	1.64 (1.51–1.78)	1.65 (1.50–1.80)	1.44 (1.34–1.56)
HbA_{1c} deciles*				
≤6.0% (≤42 mmol/mol)	1.79 (1.55–2.07)	1.41 (1.22–1.64)	1.63 (1.40–1.89)	1.26 (1.09–1.46)
6.0–6.3% (42–45 mmol/mol)	1.49 (1.27–1.76)	1.27 (1.08–1.50)	1.37 (1.16–1.62)	1.16 (0.98–1.36)
6.3–6.5% (45–48 mmol/mol)	1.35 (1.40–1.61)	1.18 (0.99–1.41)	1.26 (1.05–1.51)	1.09 (0.91–1.29)
6.5–6.7% (48–50 mmol/mol)	1.26 (1.05–1.51)	1.08 (0.90–1.30)	1.16 (0.96–1.39)	0.98 (0.82–1.18)
6.7–6.9% (50–52 mmol/mol)	1.59 (1.33–1.90)	1.38 (1.16–1.65)	1.40 (1.16–1.67)	1.25 (1.05–1.49)
6.9–7.2% (52–55 mmol/mol)	1.54 (1.30–1.82)	1.30 (1.10–1.55)	1.28 (1.08–1.53)	1.17 (0.99–1.39)
7.2–7.6% (55–60 mmol/mol)	1.73 (1.47–2.04)	1.46 (1.23–1.73)	1.37 (1.16–1.63)	1.29 (1.10–1.52)
7.6–8.1% (60–65 mmol/mol)	2.26 (1.92–2.65)	1.86 (1.57–2.19)	1.63 (1.38–1.93)	1.62 (1.38–1.90)
8.1–9.3% (65–78 mmol/mol)	2.52 (2.19–2.91)	1.98 (1.71–2.30)	1.62 (1.39–1.88)	1.69 (1.46–1.95)
>9.3% (>78 mmol/mol)	3.78 (3.29–4.35)	2.90 (2.51–3.36)	2.05 (1.77–2.37	2.46 (2.14–2.82)

†Adjusted for age, sex, ethnicity, SES, alcohol consumption, smoking, obesity, previous ICH, previous stroke/TIA, atrial fibrillation, congestive heart failure, vascular disease, hypertension, chronic kidney disease, chronic liver disease, LDL cholesterol, HDL cholesterol, and use of antiaggregants, anticoagulants, and statins. ‡The propensity score (probability of having diabetes) was calculated using a logistic regression model that included all variables in Table 1. §DRS, a summary measure of ICH probability, was calculated using a Cox proportional hazards regression model that included all variables in Table 1. *No diabetes is the reference.

significant interactions were observed with sex, hypertension, or diabetes duration (Supplementary Table 2). We reached similar results when, instead of using the most recent HbA_{1c} result, we used the median HbA_{1c}, of all tests performed in the 2 years prior to study entry, to assess the association with ICH.

The magnitude of the association between HbA_{1c} and ICH type was more pronounced for deep ICH than for lobar ICH. For each 1% increase in HbA_{1c}, adjusted HR was 1.17 (95% CI 1.13–1.22) for deep ICH and 1.09 (1.02–1.17) for lobar ICH ($P_{interaction}$ = 0.066).

CONCLUSIONS

To the best of our knowledge, this is the largest nationwide study to date looking at the association between diabetes and ICH encompassing HbA_{1c} levels. We found that diabetes and diabetes duration are associated with increased risk for ICH, also after adjustment for potential confounders, and that low, as well as high, HbA_{1c} levels are associated with ICH risk.

It is puzzling that despite the fact that diabetes promotes overall cardiovascular morbidity, as yet no consensus has emerged concerning the role of diabetes in the occurrence of ICH, as results across studies showed inconsistent associations. Some studies found no significant relationship between diabetes and ICH (18,19), while others found significant positive association (5,20). Another Mendelian randomization study showed no significant association of diabetes with ICH risk (21). Surprisingly, other studies found that that ICH occurs significantly less in patients with diabetes (22,23). For explaining the latter, authors speculated that diabetes-induced thickening of basement membrane and the proliferation of the endothelium render the cerebral

Table 4—Adjusted HRs (95% CI) for the association between HbA_{1c} and ICH among patients with diabetes

	Adjusted for age and sex	Adjusted for clinically relevant risk factors†	Adjusted for DRS§
HbA_{1c} continuous variable*	1.17 (1.13–1.20)	1.15 (1.12–1.19)	1.14 (1.10–1.17)
HbA_{1c} deciles (D)			
D1: ≤6.0% (≤42 mmol/mol)	1.41 (1.13–1.76)	1.31 (1.05–1.64)	1.27 (1.01–1.59)
D2: 6.0–6.3% (42–45 mmol/mol)	1.19 (0.94–1.50)	1.17 (0.93–1.49)	1.17 (0.92–1.48)
D3: 6.3–6.5% (45–48 mmol/mol)	1.07 (0.74–1.37)	1.09 (0.85–1.39)	1.10 (0.86–1.40)
D4: 6.5–6.7% (48–50 mmol/mol)	**1.0 (reference)**	**1.0 (reference)**	**1.0 (reference)**
D5: 6.7–6.9% (50–52 mmol/mol)	1.25 (0.98–1.60)	1.27 (1.0–1.63)	1.27 (0.99–1.62)
D6: 6.9–7.2% (52–55 mmol/mol)	1.21 (0.95–1.54)	1.20 (0.94–1.52)	1.18 (0.93–1.51)
D7: 7.2–7.6% (55–60 mmol/mol)	1.35 (1.06–1.71)	1.33 (1.05–1.69)	1.30 (1.02–1.64)
D8: 7.6–8.1% (60–65 mmol/mol)	1.71 (1.35–2.17)	1.66 (1.31–2.12)	1.60 (1.26–2.03)
D9: 8.1–9.3% (65–78 mmol/mol)	1.86 (1.48–2.33)	1.73 (1.38–2.17)	1.63 (1.30–2.03)
D10: >9.3% (>78 mmol/mol)	2.59 (2.07–3.23)	2.38 (1.90–2.99)	2.19 (1.75–2.73)

The reference categories appear in boldface type. †Adjusted for age, sex, ethnicity, SES, alcohol consumption, smoking, obesity, previous ICH, previous stroke/TIA, atrial fibrillation, congestive heart failure, vascular disease, hypertension, chronic kidney disease, chronic liver disease, LDL cholesterol, HDL cholesterol, and use of antiaggregants, anticoagulants, and statins. §DRS, a summary measure of ICH probability, was calculated using a Cox proportional hazards regression model that included all variables in Table 1. *HR for each 1% increase in HbA_{1c}.

vessels less prone to rupture. Another explanation was that in diabetes aggregation, coagulation and plasminogen activator inhibitor levels are increased, while fibrinolytic activity is decreased (23).

A meta-analysis including 102 prospective studies with 698,782 cases showed that diabetes is a risk factor with relative risk of 1.56 for ICH (5). Of note, most of the individual studies included in this meta-analysis focused on coronary heart disease and major stroke subtypes, encompassing only a small number of ICH cases for each, and information for duration of diabetes was lacking; therefore, generalization of association was hard.

A more recent systemic meta-analysis (4), conducted in view of the inconsistencies among previous individual studies and systemic reviews, found association between diabetes and ICH occurrence in 19 case-control studies, whereas association was not identified in three population-based cohort studies (4).

The other main finding in our study is the J-shaped relationship between HbA_{1c} and ICH risk, with the lowest risk observed at HbA_{1c} of 6.5% (48 mmol/mol). The risk of ICH among patients with HbA_{1c} of 6.5–6.7% (48–50 mmol/mol) was comparable with the risk in patients without diabetes, suggesting that albeit having diabetes, patients with good, but not extreme, diabetes control do not appear to have excess risk of ICH compared with patients without diabetes. Previous studies showed similar relations between fasting blood glucose and ICH (8,9), reinforcing the validity of our results. None, however, have looked at the association between HbA_{1c}, reflecting glycemic control much more reliably, and ICH.

Indeed, previous studies have demonstrated J-shape or U-shape relationships between fasting glucose levels and cardiovascular diseases, all-cause mortality (24), and ICH (8). It has been suggested that hypoglycemia as well as rapid changes in plasma glucose may lead to elevation of counterregulatory hormones such as epinephrine or neuroepinephrine, promoting vasoconstrictions and hemodynamic alternations that may end in ICH (25). Another suggested explanation is that low glucose levels may reflect disease burden or frailty (8).

To date, the exact mechanisms underlying the association between diabetes, HbA_{1c}, and ICH remain unknown. Hopefully, in the future more will be learned about the pathogenesis of this potential association.

A notable strength of this study is being a population-based study with a large number of ICH cases (n = 4,170) encompassing both recent HbA_{1c} result and median HbA_{1c}. As opposed to some previous studies, we also included duration of diabetes in our analysis. Controlling for DRS as a single variable increases the efficiency of the analysis compared with conventional multivariate analyses. Yet, this study has some limitations; firstly, despite the multivariate model adjustment that accounted for a large number of potential confounders, some residual confounding might still exist owing to unmeasured variables. Hence, because our retrospective cohort study is observational in nature, this study could not prove a cause-effect relationship; such evidence should rely on randomized controlled clinical studies. Secondly, we rely solely on an administrative computerized database that was not specifically designed for the current study. In addition, we had no information about prevalence of type 1 or 2 diabetes. We also looked at ICH location only among a subgroup of patients with diabetes (n = 1,614). Furthermore, HbA_{1c} results were available only in patients with diabetes; hence, we cannot argue for a relationship between HbA_{1c} and ICH in patients without diabetes. However, HbA_{1c} in patients with diabetes, which are by definition $<$6.5% (48 mmol/mol), is not expected to be associated with increased risk of ICH. This seems to be unlikely because HbA_{1c} $<$6.5% (48 mmol/mol) in diabetes may be a marker of hypoglycemia that probably mediates increased risk for ICH, whereas in patients without diabetes, lower HbA_{1c} is not a marker of hypoglycemia. In addition, we have no data on cerebral amyloid angiopathy status among study participants.

In summary, our study suggests that diabetes is associated with increased risk of ICH that is directly associated with diabetes duration. ICH and HbA_{1c} appear to have a J-shaped relationship, suggesting that both poor control as well as extreme intensive diabetes control might be associated with increased risk. These findings and their clinical implications need to be assessed with future randomized clinical trials.

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