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# Sex Differences in the Risk of Stroke and HbA1c among Diabetic Patients

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## Abstract

**Aims/hypothesis—**Sex differences in macrovascular disease, especially in stroke are observed across studies of epidemiology. We studied a large sample of patients with type 2 diabetes to better understand the relationship between glycemic control and stroke risk.

**Methods—**We prospectively investigated the sex-specific association between different levels of $HbA_{1c}$ and incident stroke risk among 10,876 male and 19,278 female patients with type 2 diabetes.

**Results—**During a mean follow up of 6.7 years, 2,949 incident cases of stroke were identified. The multivariable-adjusted hazard ratios (HRs) of stroke associated with different levels of $HbA_{1c}$ at baseline (<6.0%, 6.0–6.9% [reference group], 7.0–7.9%, 8.0–8.9%, 9.0–9.9%, and ≥10.0%,) were 0.96 (95% confidence interval [CI] 0.80, 1.14), 1.00, 1.04 (0.85, 1.28), 1.11 (0.89, 1.39), 1.10 (0.86, 1.41), and 1.22 (0.92, 1.35) (P trend =0.66) for men, and 1.03 (0.90, 1.18), 1.00, 1.09 (0.94, 1.26), 1.19 (1.00, 1.42), 1.32 (1.09, 1.59), and 1.42 (1.23, 1.65) (P trend <0.001) for women, respectively. The graded association of $HbA_{1c}$ during follow-up with stroke risk was observed among women (P trend=0.066). When stratified by race, with glucose-lowering agents or not, this graded association of $HbA_{1c}$ with stroke was still present among women. When stratified by age, the adjusted HRs were significantly higher in women older than 55 years compared to younger women.

**Conclusions/interpretation—**The current study suggests a graded association between $HbA_{1c}$ and the risk of stroke among women with type 2 diabetes. Poor control of blood sugar has a stronger effect in diabetic women older than 55 years.

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**Contribution statement**

WZ designed the study, acquired the data, performed statistical analysis, interpreted the data, drafted the article, and approved the final version to be published. GH designed the study, acquired the data, reviewed and critically revised the article, and approved the final version to be published. PTK received tables of analysis output, suggested some reanalyses, and helped interpret these analyses in the writing of the results and discussion, reviewed and critically revised the article, and approved the final version to be published. All other authors acquired the data, reviewed and critically revised the article, and approved the final version to be published. GH was responsible for the integrity of the work as a whole.

**Duality of interest**

The authors have no relevant financial interest in this article.

### Keywords

Clinical diabetes; Epidemiology; Macrovascular disease

## Introduction

Stroke is a leading cause of disability, cognitive impairment, and death in the United States and accounts for 1.7% of national health expenditures [1]. In the United States, nearly 32,000 more women than men died of stroke in 2000 and this number is predicted to be 68,000 in 2050 [2]. Sex differences in stroke are observed across epidemiologic studies, pathophysiology, treatments, and outcomes. These sex differences have profound implications for effective prevention and treatment of stroke. Increased knowledge of stroke risk factors in the population may lead to improved prevention of stroke. Epidemiological studies have reported that type 2 diabetes is an independent risk factor for stroke [3–7], but how much its effect varies by sex is uncertain. Some studies showed that type 2 diabetes may have a stronger effect on stroke risk in women [3, 4, 8–10], but one study showed a greater effect in men [11]. Because randomized clinical trials (RCTs) and meta-analyses failed to show the benefit of intensive glucose control on rates of stroke [12], and with the under-representation of females in RCTs [13], more observational data are needed to assess if there is a sex-specific association between $HbA_{1c}$ and the risk of stroke. The aim of the present study is to examine whether the associations of $HbA_{1c}$ at baseline and during follow-up with the risk of incident stroke are different between men and women with type 2 diabetes in the Louisiana State University Hospital-Based Longitudinal Study (LSUHLS).

## Methods

### Study Population

LSU Health Care Services Division (LSU HCSD) operates seven public hospitals and affiliated clinics in Louisiana, which provide quality medical care regardless of the patient's income or insurance coverage [14–22]. Since 1997, administrative, anthropometric, laboratory, clinical diagnosis, and medication data are available in electronic form. The LSUHLS was established in 2010 by using these data [14]. Using the ICD-9 (code 250), we established a cohort of diabetic patients who used LSU HCSD hospitals from 01.01. 1999 to 12.31. 2009. All diabetic patients in the LSU HCSD hospitals were diagnosed by using the American Diabetes Association criteria: a fasting plasma glucose ≥ 7.0mmol/l or 2-hour glucose ≥ 11.1mmol/l after a 75-g 2-hour oral glucose tolerance test (OGTT) or a patient with classic symptoms plus a random plasma glucose level ≥11.1mmol/l [23]. In the present study, we only included patients who had newly diagnosed diabetes. Before diabetes diagnosis, these patients have used the LSU HSCD system for a mean of 5.0 years (range 2–11 years). We have done a validated study for the diabetes diagnosis in LSU HCSD hospitals [14], and 20,919 patients of a sample of 21,566 hospital discharge diagnoses based on ICD codes also had physician-confirmed diabetes using the ADA diabetes criteria (the agreement was 97%)[23].

After excluding subjects with a history of stroke or coronary heart disease (CHD) at baseline and patients with incomplete data on any of the required variables for analysis, the sample included 30,154 patients with type 2 diabetes (10,876 male and 19,278 female). Both the Pennington Biomedical Research Center and LSU Health Sciences Center Institutional Review Boards, LSU System, approved this study and analysis plan. Informed consent was not obtained from participants involved in our study because we used pseudo-anonymised data compiled from electronic medical records.

## Baseline and follow-up measurements

The patients' characteristics, including demographic (age of diabetes diagnosis, gender, race/ethnicity, family income, smoking status, types of health insurance), risk factors (body weight, height, body mass index [BMI], blood pressure, $HbA_{1c}$, total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, triglycerides, estimated glomerular filtration rate [eGFR]), and medication (cholesterol lowing drug, antihypertensive drug, and antidiabetic drug) information within a half year after the diabetes diagnosis (baseline) and during follow-up after the diabetes diagnosis (follow-up) were extracted from the electronic medical records. The calculation of updated mean values of $HbA_{1c}$, LDL cholesterol, BMI, blood pressure and eGFR were performed as previously described [24, 25]. The average number of $HbA_{1c}$ measurements during the follow-up period was 7.7.

## Prospective follow-up

We obtained follow-up information of clinical diagnosis (date of diagnosis, diagnosis code, priority assigned to diagnosis, and ICD-9) from the LSUHLS inpatient and outpatient database by using the unique number assigned to every patient who visits the LSUHCSD hospitals each time. The ICD-9 codes were used to identify stroke (ICD-9 codes 430–436) from the LSU HCSD database for a routine clinical care visit. The stroke events occurred before or at the diabetes diagnosis were identified from the LSU HCSD database retrospectively and were excluded from the analyses. Each cohort member was followed to May 31, 2012, for stroke diagnosis, the date of the last visit if the subject stopped the use of LSUHCSD hospitals, or death (other than inpatients stroke death), which ever occurred first [15, 21].

## Statistical analyses

The Cox proportional hazards models were used to estimate the association between $HbA_{1c}$ and the risk of stroke. $HbA_{1c}$ was evaluated in the following 2 ways: (1) as 6 categories ($HbA_{1c}$<6.0% [42 mmol/mol], 6.0–6.9% [42–52 mmol/mol] [reference group], 7.0–7.9% [53–63 mmol/mol], 8.0–8.9% [64–74 mmol/mol], 9.0–9.9% [75–85 mmol/mol], and ≥10.0% [86 mmol/mol]), and (2) as a continuous variable. The significance of the trend over different categories of $HbA_{1c}$ was tested in models with the median of each category as a continuous variable. All analyses were adjusted for age and race, and further for smoking, income, type of insurance, BMI, systolic blood pressure, LDL cholesterol, eGFR, use of antihypertensive drugs, use of diabetes medications, and use of cholesterol-lowering agents (Multivariable model). We adjusted for updated means of BMI, LDL cholesterol, systolic blood pressure and eGFR instead of these variables at baseline when we analyzed the

association between updated means of $HbA_{1c}$ and stroke risk. Because there was a significant interaction of gender and $HbA_{1c}$ on stroke risk, men and women were analyzed separately. To avoid the potential bias due to occult diseases at baseline, additional analyses were carried out excluding the subjects who were diagnosed with stroke during the first two years of follow-up. Statistical significance was considered to be $P<0.05$. All statistical analyses were performed with PASW for Windows, version 20.0 (IBM SPSS Inc, Chicago, IL).

## Results

General characteristics of the study population are presented by sex in Table 1. During a mean follow-up period of 6.7 years, 2949 subjects (1093 male and 1856 female) developed incident stroke (2848 ischemic, 115 hemorrhagic). The overall incidence of strokes among men (16.0/1000 person-years) is higher than women (13.9/1000 person-years). There was a significantly positive association of baseline $HbA_{1c}$ with stroke risk among females but not among males (Table 2). After further adjustment for other confounding factors (smoking, income, type of insurance, BMI, $HbA_{1c}$, LDL cholesterol, eGFR, use of antihypertensive drugs, use of diabetes medications, and use of cholesterol-lowering agents), this positive association remained significant among females (P trend<0.001). Each one percentage increase in baseline $HbA_{1c}$ was associated with a 5% (95% confidence interval [CI] 1.02, 1.07) increased risk of stroke in females and a 1% (95% CI 0.99, 1.04) increased risk of stroke in males. The risk of stroke associated with $HbA_{1c}$ was higher in females than in male patients with diabetes ($\chi 2=7.85$, df =1, P for interaction=0.005).

The interactions between age and HbA1c, and between use of glucose-lowering agents and HbA1c with stroke risk were significant (P<0.005 and P<0.001). This graded positive association of $HbA_{1c}$ with stroke risk was confirmed among patients with diabetes whether they used glucose-lowering agents or not (all P trend<0.05) (Table 3). When stratified by race, the positive association of baseline $HbA_{1c}$ with stroke risk was present among both African American and white patients with type 2 diabetes (all P trend <0.01) (Table 3). When stratified by age, each one percentage increase in baseline HbA1c was associated with a 2% (95% confidence interval [CI] 1.00, 1.05) increased risk of stroke in females aged <55 years and a 5% (95% CI 0.99, 1.04) increased risk of stroke in females aged ≥55 years. Compared with women with baseline $HbA_{1c}$ at 6.0–6.9% (42–52 mmol/mol), an increased risk of stroke was found among women with baseline $HbA_{1c}$ ≥10% (86 mmol/mol), who were ≥55 years [1.41 (1.11, 1.80)] and <55 years [1.24 (1.02, 1.50)] (Table 4).

When we did an additional analysis by using an updated mean of $HbA_{1c}$ during follow-up, each one percentage increase in follow-up HbA1c was associated with a 3% (95% CI 1.00, 1.06) increased risk of stroke in females and a 3% (95% CI 0.99, 1.07) increased risk of stroke in males. When $HbA_{1c}$ was evaluated as categories, we found almost the same graded positive associations between $HbA_{1c}$ and stroke risk among females with type 2 diabetes. There was a marked attenuation in the association of HbA1c and stroke risk in female after adjusting for confounders (P trend >0.05) (Tables 2–4).

We also compared absolute sex risk of incident stroke by different $HbA_{1c}$ levels (Table 5). The absolute sex differential for incident stroke appeared only among diabetic patients with $HbA_{1c}$ <7.0% (53 mmol/mol) at baseline and <8.0% (64 mmol/mol) during follow-up, and decreased or disappeared among diabetic patients with $HbA_{1c}$ >7.0 % at baseline and >8.0% during follow-up.

After excluding the subjects who were diagnosed with stroke during the first two years of follow-up (n =866), the multivariable-adjusted HRs of stroke associated with different levels of $HbA_{1c}$ did not change (data not shown).

When we performed another analysis by different types of stroke, the result of ischemic stroke is similar to the total stroke. For hemorrhagic stroke, a significantly increased risk of stroke [1.72 (1.03, 2.87)] was observed among diabetic patients with $HbA_{1c}$ <6.0% (42 mmol/mol) during follow-up (data not shown).

## Discussion

Our study found a graded positive association between $HbA_{1c}$ and the risk of stroke among female patients with type 2 diabetes and this graded positive association was more significant in women ≥55 years than in women <55 years of age. In addition, we found that this graded association was present in different race groups and among patients with diabetes who were using glucose-lowering agents and those who were not.

Epidemiological studies have previously identified differences in stroke occurrence between women and men. Worldwide, stroke is more common among men, but women are more severely ill [26]. These sex differences have profound implications for effective prevention and treatment of stroke. Increased knowledge of stroke risk factors in the population may lead to improved prevention of stroke. Epidemiological studies have reported that type 2 diabetes is an independent risk factor for stroke (2–4). Some studies showed that diabetes may have a stronger effect on stroke risk in women than in men [3, 4, 8–10]. However, a sub-data analysis of the DECODE study showed diabetes increased stroke risk more in men than in women [11]. Thus there is considerable uncertainty, and the magnitude of the risk has not been described in sufficient detail from observational studies. On the other hand, RCTs and even meta-analyses of RCTs failed to show the benefit of intensive glucose control on rates of stroke [12], and the under-representation of females in RCTs [13] limited the power of RCTs to interpret why these sex differences exist. In the present study with a mean follow up of 6.7 years, 2,949 incident cases (1093 male and 1856 female) of stroke were identified among 30,154 patients (10,876 male and 19,278 female) with type 2 diabetes. The overall incidence of stroke among men was higher than among women. We found a graded positive association by various $HbA_{1c}$ intervals of clinical relevance or by using $HbA_{1c}$ as a continuous variable at baseline and during follow-up with stroke risk among females but not males. The interaction between race and HbA1c on stroke risk was not significant. In a previous paper we described a graded positive association between HbA1c and CHD in both male and female members of this cohort [22]. In addition, we found that this graded positive association was present in African American and white female patients and in patients with and without glucose-lowering agent treatment. There is

some inconsistency between the findings of baseline and follow-up $HbA_{1c}$, which may suggest that relying on baseline HbA1c levels only may lead to biased results.

Several mechanisms could explain why diabetes has a greater adverse effect in women than in men. In the general population, higher numbers of strokes occurring among women than men is at least partly attributed to the longer life expectancy of women [27]. Some studies have suggested that the sex difference in cardiovascular risk might mainly come from differences in the levels of cardiovascular risk factors, for example, women with diabetes have significantly higher levels of blood pressure and lipids than men with diabetes [28]. Others suggested that the greater risk associated with diabetes seen in women may reflect a treatment bias that favors men. Several recent studies found that men with diabetes or cardiovascular disease are more likely to receive aspirin, statins, or antihypertensive drugs than women [29]. In our study, after adjusting for systolic blood pressure, LDL cholesterol and medication treatment, this graded association remained significant among females with type 2 diabetes. When stratified by age, the adjusted HRs were more significantly increased in women ≥55 years than in women <55 years. This might suggest that poor blood glucose control is more harmful in elderly women than in younger ones. The possible explanation may point to the role for estrogen. After onset of menopause when estrogen levels decline, the incidence of cerebrovascular disease in women increases. Pre-clinical studies have indicated that estrogen is neuroprotective and reduces stroke infarct volume [30], but clinical trials failed to show the benefit [31–33]. There is a need for more research to clarify this association. In a geriatric population with considerable comorbidities, the competing risk of death is especially high. We described a graded positive association between HbA1c and CHD in both male and female members in a previous paper [22]. There is the possibility that men with higher $HbA_{1c}$ values die of CHD rather than having a stroke.

There are several strengths and limitations in our study. The LSUHLS diabetic cohort is a hospital-based cohort with a large sample size of white and African American patients with type 2 diabetes. The follow-up time is long, and has allowed for the accumulation of 2949 incident cases of stroke during follow-up. The confounding influence from health care access and socioeconomic status may be minimized in our study samples between white and African American patients. Since a large proportion of our population are minorities and uninsured with low socioeconomic status, the generalizability of the findings to a middle or high socioeconomic status population may be limited. However, LSUHCSD hospitals are public hospitals and cover over 1.6 million patients, most of whom are low income persons living in Louisiana. Thus, the results of the current study will have wide applicability for the nearly 50 million Americans who meet poverty rate in 2012. Second, stroke diagnoses in our study were based on LSUHCSD hospital discharge registers and have not been confirmed by specialists. However, most of American and European cohort studies, such as the Kaiser Permanente Medical Care Program [34, 35], the Atherosclerosis Risk in Communities (ARIC) Study [36], the Framingham Study [37], the National FINRISK Survey [38], have used the same method to diagnose stroke. The agreement of the diagnoses of stroke by using hospital discharge registers in these cohort studies is 75%–90% [35, 39]. Third, only inpatient fatal strokes are included in the outcome. We do not have access of the causes of outpatient death. Fourth, we cannot completely exclude the effects of residual confounding

due to the measurement error in the assessment of confounding factors or some unmeasured factors.

Our study demonstrates a graded association between $HbA_{1c}$ and the risk of stroke among females with type 2 diabetes even though the overall incidence of stroke among men was higher than among women. This graded positive association was more significant in women ≥55 years than in women <55 years. This is important to keep in mind when studying blood sugar and other CVD risk factors in the diabetic population and when planning a strategy to prevent CVD, especially in the female with type 2 diabetes.

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## Abbreviations

| | |
|---|---|
| **ARIC** | Atherosclerosis Risk in Communities |
| **BMI** | body mass index |
| **CI** | confidence interval |
| **eGFR** | estimated glomerular filtration rate |
| **HDL** | high-density lipoprotein |
| **HRs** | hazard ratios |
| **LDL** | low-density lipoprotein |
| **LSU** | Louisiana State University |
| **LSU HCSD** | Louisiana State University Health Care Services Division |
| **LSUHLS** | Louisiana State University Hospital-Based Longitudinal Study |
| **OGTT** | Oral glucose tolerance test |
| **RCTs** | randomized clinical trials |

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## Table 1

Baseline characteristics of male and female patients with diabetes

| | Male | Female | P value |
|---|---|---|---|
| No. of participants | 10,876 | 19,278 | |
| African American, N (%) | 6,106 (56.1) | 11,403 (59.3) | <0.001 |
| Age, mean (SD), yr | 50.90 (10.1) | 51.48 (10.1) | <0.001 |
| Income, mean (SD), $/family | 20,989 (31,594) | 20,617 (27,409) | <0.001 |
| Body mass index, mean (SD) | 32.4 (8.0) | 35.5 (8.7) | <0.001 |
| Baseline blood pressure, mean (SD), mm Hg | | | |
| Systolic | 143 (23) | 145 (24) | <0.001 |
| Diastolic | 82 (14) | 79 (13) | <0.001 |
| $HbA_{1c}$, mean, % (mmol/mol) | 8.1 (65) | 7.6 (60) | <0.001 |
| HbA1c during follow-up, mean, % (mmol/mol) | 7.8 (62) | 7.5 (58) | <0.001 |
| LDL cholesterol, mean (SD), mmol/l | 2.80 (1.06) | 3.00 (1.04) | <0.001 |
| Glomerular filtration rate (ml/min/1.73 $m^2$), N (%) | | | <0.001 |
| ≥90 | 5,501 (50.7) | 9,031 (46.9) | |
| 60–89 | 4,096 (37.7) | 7,717 (40.1) | |
| 30–59 | 1,054 (9.7) | 2,238 (11.6) | |
| 15–29 | 135 (1.2) | 184 (1.0) | |
| <15 | 72 (0.7) | 74 (0.4) | |
| Current smoker, N (%) | 4,629 (42.6) | 5,746 (29.8) | <0.001 |
| Type of insurance, N (%) | | | <0.001 |
| Free | 7,918 (72.8) | 15,793 (81.9) | |
| Self-pay | 832 (7.7) | 817 (3.7) | |
| Medicaid | 524 (4.8) | 1,016 (5.3) | |
| Medicare | 1,297 (11.9) | 1,385 (7.2) | |
| Commercial | 305 (2.8) | 366 (1.9) | |
| Uses of medications, N % | | | |
| Lipid-lowering medication | 6,470 (59.5) | 12,530 (65.0) | <0.001 |
| Antihypertensive medication | 8,782 (80.3) | 16,340 (84.8) | <0.001 |
| Glucose-lowering medication | 8,218 (75.6) | 14,466 (75.0) | <0.001 |
| Metformin | 5,871 (54.0) | 11,237 (58.3) | <0.001 |
| Sulfonylurea | 4,099 (37.7) | 6,955 (36.1) | <0.001 |
| Insulin | 4,168 (38.3) | 6,770 (35.1) | <0.001 |

Values represent mean or percentage. Body mass index was calculated as the weight in kilograms divided by the square of the height in meters. SD of $HbA_{1c}$ is 2.7% and 2.3% for baseline and 2.0% and 1.8% for follow up, respectively.

**Table 2**

Hazard ratio of stroke according to different levels of $HbA_{1c}$ at baseline and during follow-up among male and female patients with diabetes

| | $HbA_{1c}$ (%) (mmol/mol) | | | | | | P for trend | Each 1% increase (continuous variable) |
|---|---|---|---|---|---|---|---|---|
| | <6.0 (42) | 6.0–6.9 (42–52) | 7.0–7.9 (53–63) | 8.0–8.9 (64–74) | 9.0–9.9 (75–85) | ≥10.0 (86) | | |
| **Baseline** | | | | | | | | |
| *Male* | 2,615 | 2,042 | 1,220 | 854 | 751 | 2,301 | | |
| No. of cases | 276 | 255 | 153 | 113 | 85 | 211 | | |
| Person-years | 16,583 | 14,732 | 8,960 | 6,538 | 5,606 | 15,945 | | |
| Age adjusted HR (95% CI) | 0.99 (0.83, 1.17) | 1.00 | 1.07 (0.87, 1.30) | 1.16 (0.93, 1.45) | 1.12 (0.88, 1.44) | 1.12 (0.92, 1.35) | 0.60 | 1.01 (0.99, 1.04) |
| Multivariable adjusted HR (95% CI) | 0.96 (0.80, 1.14) | 1.00 | 1.04 (0.85, 1.28) | 1.11 (0.89, 1.39) | 1.10 (0.86, 1.41) | 1.12 (0.92, 1.35) | 0.66 | 1.01 (0.99, 1.04) |
| *Female* | 5,101 | 4,578 | 2,389 | 1,561 | 1,100 | 2,693 | | |
| No. of cases | 456 | 464 | 289 | 186 | 138 | 323 | | |
| Person-years | 34,320 | 34,659 | 20,011 | 13,299 | 9,298 | 22,057 | | |
| Age adjusted HR (95% CI) | 1.00 (0.87, 1.13) | 1.00 | 1.13 (0.98, 1.31) | 1.23 (1.04, 1.46) | 1.36 (1.12, 1.65) | 1.49 (1.29, 1.73) | <0.001 | 1.06 (1.04, 1.08) |
| Multivariable adjusted HR (95% CI) | 1.03 (0.90, 1.18) | 1.00 | 1.09 (0.94, 1.26) | 1.19 (1.00, 1.42) | 1.32 (1.09, 1.59) | 1.42 (1.23, 1.65) | <0.001 | 1.05 (1.02, 1.07) |
| **Follow-up** | | | | | | | | |
| *Male* | 2,103 | 2,213 | 1,782 | 1,286 | 947 | 1,452 | | |
| No. of cases | 206 | 262 | 240 | 160 | 111 | 114 | | |
| Person-years | 12,019 | 15,314 | 13,679 | 9,939 | 7,351 | 10,065 | | |
| Age adjusted HR (95% CI) | 1.05 (0.88, 1.26) | 1.00 | 1.12 (0.94, 1.33) | 1.20 (0.98, 1.46) | 1.23 (0.98, 1.54) | 1.08 (0.86, 1.36) | 0.41 | 1.02 (0.98, 1.05) |
| Multivariable adjusted HR (95% CI) | 1.01 (0.83, 1.23) | 1.00 | 1.09 (0.91, 1.30) | 1.18 (0.96, 1.44) | 1.30 (1.03, 1.63) | 1.14 (0.90, 1.44) | 0.28 | 1.03 (0.99, 1.07) |
| *Female* | 4,090 | 4,865 | 3,240 | 2,000 | 1,365 | 1,862 | | |
| No. of cases | 373 | 502 | 378 | 246 | 177 | 180 | | |
| Person-years | 25,791 | 35,763 | 27,105 | 17,220 | 12,239 | 15,526 | | |
| Age adjusted HR (95% CI) | 1.06 (0.93, 1.21) | 1.00 | 1.11 (0.97, 1.27) | 1.30 (1.12, 1.52) | 1.41 (1.19, 1.68) | 1.33 (1.11, 1.59) | <0.001 | 1.06 (1.03, 1.09) |
| Multivariable adjusted HR (95% CI) | 1.12 (0.97, 1.30) | 1.00 | 1.08 (0.95, 1.24) | 1.21 (1.03, 1.42) | 1.27 (1.06, 1.52) | 1.19 (0.99, 1.43) | 0.066 | 1.03 (1.00, 1.06) |

Abbreviations: HR, hazard ratio; CI, confidence interval.

Adjusted age, race, type of insurance, income, smoking, body mass index, low-density lipoprotein cholesterol, systolic blood pressure, glomerular filtration rate at baseline (in the baseline analyses) and during follow-up (in the follow-up analyses), use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agents.

**Table 3**

Hazard ratio of stroke according to different levels of $HbA_{1c}$ at baseline and during follow-up among various subpopulations

| | $HbA_{1c}$ (%) (mmol/mol) | | | | | | P for trend |
|---|---|---|---|---|---|---|---|
| | <6.0 (42) | 6.0–6.9 (42–52) | 7.0–7.9 (53–63) | 8.0–8.9 (64–74) | 9.0–9.9 (75–85) | ≥10.0 (86) | |
| **Baseline** | | | | | | | |
| *Male* | | | | | | | |
| African American | 0.99 (0.77, 1.28) | 1.00 | 1.06 (0.80, 1.40) | 0.92 (0.66, 1.28) | 1.13 (0.81, 1.57) | 1.16 (0.90, 1.48) | 0.72 |
| White | 0.91 (0.71, 1.17) | 1.00 | 1.03 (0.77, 1.37) | 1.35 (0.99, 1.83) | 1.09 (0.75, 1.59) | 1.07 (0.78, 1.46) | 0.29 |
| *Female* | | | | | | | |
| African American | 1.01 (0.83, 1.22) | 1.00 | 1.03 (0.85, 1.26) | 1.04 (0.83, 1.32) | 1.24 (0.96, 1.61) | 1.39 (1.15, 1.67) | 0.007 |
| White | 1.05 (0.86, 1.27) | 1.00 | 1.14 (0.91, 1.42) | 1.38 (1.07, 1.78) | 1.39 (1.04, 1.87) | 1.36 (1.06, 1.75) | 0.033 |
| **Follow-up** | | | | | | | |
| *Male* | | | | | | | |
| African American | 1.20 (0.91, 1.58) | 1.00 | 0.99 (0.77, 1.28) | 1.13 (0.85, 1.49) | 1.22 (0.89, 1.68) | 1.17 (0.87, 1.58) | 0.56 |
| White | 0.84 (0.63, 1.12) | 1.00 | 1.22 (0.95, 1.56) | 1.29 (0.96, 1.74) | 1.42 (1.02, 1.98) | 1.06 (0.71, 1.60) | 0.049 |
| *Female* | | | | | | | |
| African American | 1.16 (0.95, 1.42) | 1.00 | 0.97 (0.80, 1.17) | 1.06 (0.86, 1.31) | 1.15 (0.91, 1.44) | 1.06 (0.85, 1.33) | 0.53 |
| White | 1.09 (0.88, 1.34) | 1.00 | 1.24 (1.01, 1.51) | 1.45 (1.14, 1.84) | 1.42 (1.06, 1.90) | 1.33 (0.96, 1.85) | 0.03 |
| **Baseline** | | | | | | | |
| *Male* | | | | | | | |
| Not using glucose-lowering agents | 0.98 (0.74, 1.29) | 1.00 | 0.92 (0.63, 1.33) | 0.87 (0.56, 1.37) | 0.92 (0.53, 1.58) | 1.06 (0.74, 1.53) | 0.97 |
| Using glucose-lowering agents | 0.93 (0.74, 1.17) | 1.00 | 1.09 (0.86, 1.39) | 1.20 (0.93, 1.56) | 1.16 (0.87, 1.54) | 1.15 (0.91, 1.44) | 0.39 |
| *Female* | | | | | | | |
| Not using glucose-lowering agents | 0.99 (0.79, 1.23) | 1.00 | 1.16 (0.88, 1.53) | 1.08 (0.77, 1.53) | 1.70 (1.17, 2.47) | 1.74 (1.32, 2.31) | <0.001 |
| Using glucose-lowering agents | 1.07 (0.90, 1.27) | 1.00 | 1.06 (0.89, 1.27) | 1.23 (1.01, 1.51) | 1.23 (0.98, 1.54) | 1.35 (1.13, 1.60) | 0.018 |
| **Follow-up** | | | | | | | |
| *Male* | | | | | | | |
| Not using glucose-lowering agents | 0.92 (0.69, 1.23) | 1.00 | 1.10 (0.79, 1.54) | 0.92 (0.61, 1.40) | 1.11 (0.68, 1.80) | 1.17(0.77, 1.79) | 0.85 |
| Using glucose-lowering agents | 1.10 (0.84, 1.45) | 1.00 | 1.10 (0.89, 1.36) | 1.29 (1.02, 1.63) | 1.38 (1.06, 1.80) | 1.15 (0.87, 1.53) | 0.18 |
| *Female* | | | | | | | |
| Not using glucose-lowering agents | 1.14 (0.92, 1.41) | 1.00 | 1.10 (0.84, 1.45) | 1.48 (1.09, 2.00) | 1.16 (0.80, 1.69) | 1.34 (0.94, 1.92) | 0.19 |

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| | $HbA_{1c}$ (%) (mmol/mol) | | | | | | P for trend |
|---|---|---|---|---|---|---|---|
| | **<6.0 (42)** | **6.0–6.9 (42–52)** | **7.0–7.9 (53–63)** | **8.0–8.9 (64–74)** | **9.0–9.9 (75–85)** | **≥10.0 (86)** | |
| Using glucose-lowering agents | 1.12 (0.91, 1.36) | 1.00 | 1.07 (0.91, 1.25) | 1.12 (0.93, 1.35) | 1.29 (1.05, 1.58) | 1.13 (0.91, 1.40) | 0.26 |

Adjusted for age, gender, race, type of insurance, income, smoking, body mass index, low-density lipoprotein cholesterol, systolic blood pressure, glomerular filtration rate at baseline (in the baseline analyses) and during follow-up (in the follow-up analyses),use of antihypertensive drugs, glucose-lowering agents, and cholesterollowering agents, other than the variable for stratification.

**Table 4**

Hazard ratio of stroke according to different levels of $HbA_{1C}$ at baseline and during follow-up among male and female patients with different age

| | $HbA_{1c}$ (%) (mmol/mol) | | | | | | P for trend |
|---|---|---|---|---|---|---|---|
| | <6.0 (42) | 6.0–6.9 (42–52) | 7.0–7.9 (53–63) | 8.0–8.9 (64–74) | 9.0–9.9 (75–85) | ≥10.0 (86) | |
| **Baseline** | | | | | | | |
| *Male* | | | | | | | |
| <55yrs | 0.85 (0.65, 1.12) | 1.00 | 0.78 (0.57, 1.12) | 0.89 (0.65, 1.22) | 1.11 (0.82, 1.51) | 0.89 (0.69, 1.14) | 0.35 |
| ≥55yrs | 1.04 (0.83, 1.32) | 1.00 | 1.25 (0.96, 1.62) | 1.28 (0.93, 1.77) | 0.78 (0.49, 1.24) | 1.20 (0.88, 1.63) | 0.72 |
| *Female* | | | | | | | |
| <55yrs | 1.02 (0.82, 1.25) | 1.00 | 1.02 (0.82, 1.27) | 1.11 (0.87, 1.40) | 1.20 (0.93, 1.55) | 1.24 (1.02, 1.50) | 0.23 |
| ≥55yrs | 1.04 (0.87, 1.24) | 1.00 | 1.12 (0.91, 1.36) | 1.20 (0.93, 1.54) | 1.32 (0.98, 1.78) | 1.41 (1.11, 1.80) | 0.057 |
| **Follow-up** | | | | | | | |
| *Male* | | | | | | | |
| <55yrs | 1.01 (0.77, 1.32) | 1.00 | 0.99 (0.75, 1.32) | 1.11 (0.82, 1.50) | 0.94 (0.71, 1.26) | 1.00 (1.00, 1.00) | 0.91 |
| ≥55yrs | 1.05 (0.82, 1.35) | 1.00 | 1.13 (0.89, 1.43) | 1.27 (0.94, 1.71) | 1.30 (0.89, 1.88) | 0.98 (0.62, 1.56) | 0.56 |
| *Female* | | | | | | | |
| <55yrs | 0.98 (0.77, 1.24) | 1.00 | 0.98 (0.81, 1.20) | 1.00 (0.81, 1.24) | 1.15 (0.92, 1.43) | 0.90 (0.72, 1.12) | 0.53 |
| ≥55yrs | 1.20 (1.00, 1.44) | 1.00 | 1.13 (0.94, 1.36) | 1.36 (1.07, 1.71) | 1.09 (0.78, 1.51) | 1.37 (0.96, 1.97) | 0.09 |

Abbreviations: HR, hazard ratio; CI, confidence interval.

Adjusted age, race, type of insurance, income, smoking, body mass index, low-density lipoprotein cholesterol, systolic blood pressure, glomerular filtration rate at baseline (in the baseline analyses) and during follow-up (in the follow-up analyses), use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agents, other than the variable for stratification.

**Table 5**

Hazard ratio (95% confidence interval) of stroke according to different levels of HbA1c with reference to the same female group

| | $HbA_{1c}$ (%) (mmol/mol) | | | | | |
|---|---|---|---|---|---|---|
| | **<6.0 (42)** | **6.0–6.9 (42–52)** | **7.0–7.9 (53–63)** | **8.0–8.9 (64–74)** | **9.0–9.9 (75–85)** | **≥10.0 (86)** |
| **Baseline** | | | | | | |
| *Age adjustment HR (95% CI)* | | | | | | |
| Male | 1.24 (1.07, 1.44)* | 1.27 (1.09, 1.48)* | 1.35 (1.12, 1.62) | 1.48 (1.20, 1.81) | 1.42 (1.13, 1.79) | 1.42 (1.20, 1.68) |
| Female | 1.00 (0.88, 1.14) | 1.00 | 1.13 (0.98, 1.31) | 1.23 (1.04, 1.46) | 1.36 (1.12, 1.65) | 1.49 (1.29, 1.72) |
| *Multivariable adjustment HR (95% CI)* | | | | | | |
| Male | 1.26 (1.08, 1.47) | 1.28 (1.10, 1.49)* | 1.35 (1.12, 1.62) | 1.43 (1.16, 1.76) | 1.42 (1.12, 1.79) | 1.46 (1.23, 1.72) |
| Female | 1.03 (0.90, 1.18) | 1.00 | 1.10 (0.95, 1.27) | 1.21 (1.02, 1.44) | 1.35 (1.11, 1.63) | 1.48 (1.28, 1.72) |
| **Follow-up** | | | | | | |
| *Age adjustment HR (95% CI)* | | | | | | |
| Male | 1.26 (1.07, 1.49)* | 1.22 (1.05, 1.42)* | 1.37 (1.18, 1.60)* | 1.47 (1.23, 1.75) | 1.50 (1.22, 1.85) | 1.33 (1.08, 1.64) |
| Female | 1.06 (0.93, 1.21) | 1.00 | 1.11 (0.97, 1.27) | 1.30 (1.12, 1.52) | 1.41 (1.19, 1.68) | 1.32 (1.11, 1.58) |
| *Multivariable adjustment HR (95% CI)* | | | | | | |
| Male | 1.24 (1.05, 1.47) | 1.18 (1.02, 1.37) | 1.29 (1.10, 1.51) | 1.35 (1.13, 1.62) | 1.49 (1.21, 1.84)* | 1.29 (1.04, 1.59) |
| Female | 1.11 (0.96, 1.27) | 1.00 | 1.10 (0.96, 1.26) | 1.24 (1.06, 1.45) | 1.32 (1.11, 1.57) | 1.24 (1.04, 1.49) |

Adjusted for age, race, type of insurance, income, smoking, body mass index, low-density lipoprotein cholesterol, systolic blood pressure, glomerular filtration rate at baseline (in the baseline analyses) and during follow-up (in the follow-up analyses),use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agents, other than the variable for stratification.

*Significant difference between genders in the same $HbA_{1c}$ group.