HHS Public Access

Author manuscript

Stroke. Author manuscript; available in PMC 2020 February 01.

Published in final edited form as:

Stroke. 2019 February ; 50(2): 291–297. doi:10.1161/STROKEAHA.118.023682.

Inverse association between high-density lipoprotein cholesterol and stroke risk among patients with type 2 diabetes

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Abstract

Background and Purpose—Very few studies have assessed the association of high-density lipoprotein (HDL) cholesterol with stroke risk among patients with type 2 diabetes. We aimed to investigate the association of HDL cholesterol with total and type-specific stroke risk in patients with type 2 diabetes.

Methods—We performed a retrospective cohort study of 27,113 African Americans and 40,431 whites with type 2 diabetes. Cox proportional hazards regression models were used to estimate the association of different levels of HDL cholesterol with stroke risk.

Results—During a mean follow-up period of 3.0 years, 8,496 patients developed stroke (8,048 ischemic and 448 hemorrhagic). Multivariable-adjusted hazard ratios across levels of HDL at baseline (<30 [reference group], 30–39.9, 40–49.9, 50–59.9, 60–69.9, 70–79.9, and ≥80 mg/dL) were 1.00, 0.86, 0.77, 0.71, 0.71, 0.77, and 0.69 (P_{trend} <0.001) for total stroke, 1.00, 0.89, 0.82, 0.75, 0.78, 0.76, and 0.75 (P_{trend} <0.001) for ischemic stroke, and 1.00, 0.89, 0.69, 0.66, 0.47, and 0.94 (P_{trend} =0.021) for hemorrhagic stroke, respectively. When we used an updated mean value of HDL cholesterol, the inverse association of HDL cholesterol with stroke risk did not change. This

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Contributions: YS and GH wrote the manuscript and researched data. LS, EN, PTK, EPH, ANB, and SN reviewed and edited the manuscript. GH is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Disclosures: The authors have no conflict of interest to disclose.

inverse association was consistent among patients of different ages, races, sexes, body mass index, HbA1c levels, never and past or current smokers, and patients with and without using glucose-lowering, cholesterol-lowering, or antihypertensive agents.

Conclusions—The present study found consistent inverse associations between HDL cholesterol and the risk of total, ischemic and hemorrhagic stroke among patients with type 2 diabetes.

Keywords

high-density lipoprotein cholesterol; ischemic stroke; hemorrhagic stroke; type 2 diabetes

Low level of high-density lipoprotein (HDL) cholesterol is a well-established risk factor for cardiovascular diseases (CVD).[1] A recent meta-analysis of individual data from 61 prospective studies found a strong inverse association of HDL cholesterol with CVD mortality.[1] However, the association between HDL cholesterol and risk of total and type-specific stroke is less clear. Both a meta-analysis and a Japanese study among the general population found a positive association between HDL cholesterol and intracerebral hemorrhage,[2, 3] while other studies reported an inverse association between HDL cholesterol and the risk of total stroke.[4, 5]

Diabetes and lipoprotein abnormalities are two important public health problems in the US.[6] Over 50% of people aged ≥18 years who have diabetes are also affected by lipoprotein abnormalities.[7] Low levels of HDL cholesterol as one of major contributors for lipoprotein abnormalities have been found to be associated with an increased risk of CVD among patients with type 2 diabetes.[8–10] However, very few studies have assessed whether low levels of HDL cholesterol were also associated with an increased risk of stroke among patients with type 2 diabetes. The aim of the present study was to evaluate the role of HDL cholesterol on the risks of total and type-specific stroke events in patients with type 2 diabetes.

Materials and Methods

Study participants

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data on patients with type 2 diabetes in the Louisiana Experiment Assessing Diabetes outcomes (LEAD) cohort study were obtained through the Research Action for Health Network (REACHnet). The dataset included electronic health record data for the study cohort between January 1, 2013 and October 10, 2017. For the present study, data from three REACHnet partner health systems were included in the final pooled analysis. A unique global identifier was used to link records across the three partners to avoid duplication of individual patients in the pooled dataset. Totally 18,706 patients were identified as duplicates across the three partner health systems.

The definition of type 2 diabetes in the present study was formulated according to the SUPREME-DM definitions as follows[11]: a) 1 or more of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes and Tenth Revision,

Clinical Modification (ICD-10-CM) codes for type 2 diabetes associated with in-patient encounters; b) 2 or more ICD codes associated with out-patient encounters on different days within 2 years; c) combination of 2 or more of the following associated with out-patient encounters on different days within 2 years: 1) ICD codes; 2) fasting glucose level ≥ 126 mg/dl; 3) 2-hour glucose level ≥ 200 mg/dl; 4) random glucose ≥ 200 mg/dl; 5) HbA1c ≥ 6.5%; and 6) prescription for an antidiabetic medications. A total of 107,562 patients between the ages of 30 and 94 years were identified. After the exclusion of patients with incomplete data, the present study included 67,544 patients with diabetes (40,431 whites and 27,113 African Americans). Compared with patients with diabetes excluded in the present study, the patients included in the present study were similar in age (66.5±12.1 versus 66.3±12.5 years of age), included more African Americans (40.1% versus 36.2%), and included slightly fewer men in percentage (47.5% versus 49.1%). The study and analysis plan were approved by the Pennington Biomedical Research Center, Tulane University, and Ochsner Health System Institutional Review Boards. We used an electronic dataset compiled from medical records but not containing personally identifiable information except date of birth; thus, we did not obtain written informed consent from patients in the observational study cohort.

Baseline measurements

The National Patient-Centered Clinical Research Network (PCORnet) common data model is a specification that defines a standard organization and representation of data for the PCORnet distributed research network.[12] Patients' data extracted from this common data model for the present study included date of birth, age of diabetes diagnosis, race/ethnicity, sex, date of examination, weight, height, body mass index (BMI), blood pressure, tobacco use, diagnosis of various diseases and date of diagnosis, laboratory test date, total cholesterol, triglycerides, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, glycosylated hemoglobin (HbA1c), estimated glomerular filtration rate (eGFR), and medication history such as antihypertensive drugs, glucose-lowering drugs and lipid-lowering drugs. These data elements were collected starting from date of the diabetes diagnosis (baseline). Using smoking status reported at each clinical visit, we classified the patients into 3 groups: current smokers, ever smokers, and never smokers. The eGFR was estimated using the Modification of Diet in Renal Disease (MDRD).[13]

Follow-up

We created the follow-up database in electronic form by using the number assigned to every patient who visited the health system as a unique patient identifier. The updated mean value of HDL cholesterol was calculated for each participant from baseline to each year of follow-up. For example, after 1 year, the updated mean was the average of the baseline and 1-year values, and after 3 years it was the average of baseline, 1-, 2-, and 3-year values. In case of an event occurring during follow-up, the period for estimating the updated mean value was from baseline to the year before the event occurred. The average number of HDL cholesterol measurements during the follow-up period was 3.95. Stroke (ischemic or hemorrhagic) was identified as the outcome in the present analysis. The ICD-9-CM and ICD-10-CM codes were used to identify hemorrhagic stroke (ICD-9-CM codes 430–432 and ICD-10-CM codes I60 –I62), ischemic stroke (ICD-9-CM codes 433–436; ICD-10-CM codes I63-I66), and any

stroke (ICD-9-CM codes 430–436; ICD-10-CM codes I60-I66) events. The distributions of all ICD-9 and ICD-10 codes were as the following: 430 (0.4%), 431 (1.0%), 432 (1.2%), 433 (26.9%), 434 (19.3%), 435 (7.6%), 436 (1.0%), 437 (7.9%), I60 (0.5%), I61 (0.8%), I62 (1.2%), I63 (14.8%), I65 (17.2%) and I66 (0.2%). These diagnoses were recorded in the course of routine patient care by the patients' treating clinicians. The duration of follow-up for each cohort member (person-years) was tabulated from the date of the first documented diabetes diagnosis to the date of diagnosis of the outcome, death of inpatients or October 31, 2017.

Statistical analyses

Cox proportional hazards regression was used to estimate hazard ratios (HRs) for incident stroke according to levels of HDL cholesterol. HDL cholesterol was evaluated in the following 2 ways: (1) as categories (<30, 30–39.9, 40–49.9, 50–59.9, 60–69.9, 70–79.9, and ≥80 mg/dL); and (2) as a continuous variable. HDL cholesterol levels were included in the models as dummy variables, and the significance of the trend across categories of HDL cholesterol was tested in the same models by giving an ordinal numeric value for each dummy variable. The proportional hazards assumption in the Cox model was assessed with graphical methods and with models including time-by-covariate interactions.[14] In general, all proportionality assumptions were appropriate. All analyses were first carried out adjusting for age and race (Model 1), and further for smoking, BMI, systolic blood pressure, HbA1c, LDL cholesterol, triglycerides, eGFR (Model 2), and finally use of antihypertensive drugs, use of glucose-lowering medications, and use of lipid-lowering medications (Model 3). Statistical significance was considered to be $P < 0.05$. All statistical analyses were performed by using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, N.Y., USA).

Results

Characteristics of the study population are presented in Supplemental Table I. During a mean follow-up period of 3.0 years from initial diabetes diagnosis, 8,496 people developed an incident stroke event (8,048 ischemic and 448 hemorrhagic).

Multivariable-adjusted (Model 3) hazard ratios for total stroke across different levels of HDL cholesterol at baseline (<30 [reference group], 30–39.9, 40–49.9, 50–59.9, 60–69.9, 70–79.9, and ≥80 mg/dL) tended to decrease both in men (P_{trend} =0.013) and in women (P_{trend} <0.001), as well as in men and women combined (P_{trend} <0.001) (Table 1). When HDL cholesterol was examined as a continuous variable, the multivariable-adjusted (Model 3) hazard ratios of total stroke for 15 mg/dL increase of HDL cholesterol at baseline were 0.90 (95% confidence interval [CI, 0.86–0.94]) in men, 0.89 (95% CI, 0.85–0.92) in women, and 0.89 (95% CI, 0.86–0.91) for men and women combined. When we used a mean value of HDL cholesterol, we found the same inverse association between HDL cholesterol and the risk of total stroke (Table 1).

In the analysis of subtypes of stroke (Table 2), we separated the outcomes into hemorrhagic stroke and ischemic stroke. Multivariable-adjusted hazard ratios across levels of HDL cholesterol by categories at baseline (<30, 30–39.9, 40–49.9, 50–59.9, 60–69.9, 70–79.9,

and 80 mg/dL) also tended to decrease both for ischemic stroke (P_{trend} <0.001) and for hemorrhagic stroke (P_{trend} =0.021) in men and women combined. When HDL cholesterol was examined as a continuous variable, the multivariable-adjusted (Model 3) hazard ratios for 15 mg/dL increase of HDL cholesterol at baseline were 0.89 (95% CI, 0.86–0.92) for ischemic stroke, and 0.83 (95% CI, 0.73–0.95) for hemorrhagic stroke. When we used an updated mean value of HDL cholesterol, we found the same inverse association between HDL cholesterol and the risks of ischemic and hemorrhagic stroke (Table 2).

In the subgroup analyses, the significant inverse association of HDL cholesterol at baseline with the risk of total stroke was confirmed among patients with different ages, races, BMI, HbA1c levels, never and current or past smoking, using and not using cholesterol-lowering agents, antihypertensive drugs, glucose-lowering agents, and oral hypoglycemic agents or insulin (Table 3). There were no significant interactions of age, race, BMI, HbA1c level, smoking status, the use of cholesterol-lowering agents, antihypertensive drugs, glucose-lowering agents and HDL cholesterol with the risk of total stroke (all P for interaction >0.25).

We further conducted subgroup analysis of HDL cholesterol with the risk of subarachnoid hemorrhage and intracerebral hemorrhage respectively (Supplemental Table II); however, the trends were not statistically significant, likely due to the reduction in the sample sizes associated with the further stratification of the sample.

Discussion

In this large cohort study, we found that serum HDL cholesterol levels were inversely associated with the risks of total stroke as well as the hemorrhagic and ischemic stroke among patients with type 2 diabetes.

A lower level of HDL cholesterol is observed in patients with diabetes along with various metabolic disorders[15] and is also regarded as one of the components of metabolic syndrome.[16] HDL cholesterol has long been studied and considered as a potential protective factor against CVD.[17] Although LDL cholesterol can be efficiently reduced by the use of statins, there is still not a specific drug targeting HDL cholesterol on the market. Therefore, the association between HDL cholesterol and CVD or atherosclerosis is gathering more and more attention. It was previously and generally accepted that HDL cholesterol was inversely associated with the risks of CVD including stroke among the general population. The Multi-Ethnic Study of Atherosclerosis showed that although higher HDL cholesterol was associated with a lower risk of stroke in the general population, the association between HDL cholesterol and stroke risk was significant only in Blacks but not in other races.[5] Another Japanese cohort found that small to medium-sized HDL cholesterol, not large HDL cholesterol was inversely associated with total stroke risk.[4]

It has been noted that more than 50% of patients with diabetes have low HDL cholesterol.[7] Several studies have indicated an inverse association between HDL cholesterol and the risk of CVD among patients with type 2 diabetes.[8–10] However, only one Japanese study has found an inverse association of HDL cholesterol with total stroke risk among patients with

type 2 diabetes in the last 10 years.[18] The present study also found an inverse association between serum HDL cholesterol levels and the risk of total stroke among patients with type 2 diabetes. In addition, we extended this inverse association among both African Americans and whites, men and women, non-obese and obese patients, never and ever or current smokers, and patients using or not using glucose-lowering, cholesterol-lowering, or antihypertensive agents.

Few studies have assessed the association between HDL cholesterol levels and the risk of hemorrhagic stroke among the general population, and results remained controversial. A meta-analysis in 2013 showed that HDL cholesterol seemed to be positively associated with the risk of intracerebral hemorrhage.[2] However, another study using medical records found that HDL cholesterol values were significantly and inversely associated with aneurysmal subarachnoid hemorrhage.[19] One Finnish study did not find any associations between HDL cholesterol and the risk of hemorrhagic stroke.[20] The lack of a clear association between HDL cholesterol and the risk of hemorrhagic stroke in the general population may be due to low incident cases of hemorrhagic stroke. The present study found an inverse association between HDL cholesterol and hemorrhagic stroke risk among patients with type 2 diabetes, however, there was no further decrease in hemorrhagic stroke risk in the group with very high levels of HDL cholesterol. Another large cohort study from Denmark has also confirmed a U-shaped association between HDL cholesterol and major CVD risk.[21] This is mainly because of the genetic variants in patients with extremely high HDL cholesterol levels.[22] These genetic variants may cause high incidence of the disease and share the genetic background of an extremely high HDL cholesterol phenotype. Further studies among patients with extremely high levels of HDL cholesterol are needed.

Although results regarding hemorrhagic stroke are quite controversial, reports of an association between HDL cholesterol and ischemic stroke risk are consistent in the general population. A Finnish study indicated an inverse association between HDL cholesterol and ischemic stroke.[20] Another study analyzing 185 genome-wide lipids-associated single nucleotide polymorphisms found that a 1-SD genetically elevated HDL cholesterol was associated with a decreased risk of small artery occlusion stroke.[23]

Several underlying mechanisms of an increased stroke risk associated with low levels of HDL cholesterol may be proposed. HDL cholesterol has been found as a protective factor against atherosclerosis in animal studies.[17] It can reverse the cholesterol transport by exchanging its cholesteryl esters with triglycerides in very low density lipoprotein or chylomicrons, causing a rapid clearance of the cholesteryl esters.[24] In addition, the functionality of HDL cholesterol seems to be as important as its levels in preventing atherosclerosis.[25] Increasing the levels as well as improving the functionality of HDL cholesterol may be a potential target in the pharmaceutical development.

The major strength of this study was the large sample size with rich clinical data, the latest data collected from patients with diabetes, and a high proportion of African American participants. We reported the adjusted hazard ratios for stroke among patients with type 2 diabetes, which provide important information for understanding the dose-response association of HDL cholesterol with stroke risk. The data we used derived from

administrative databases, avoiding the problem of differential recall bias. Data in this study were extracted from three partners of REACHnet, which minimizes the influence of low accessibility of health care.

There are several limitations in our study. First, health system records were subject to misclassification. We were unable to evaluate the socioeconomic status of the study cohort due to lack of education level and family income information in the REACHnet EHR data infrastructure. Second, the stroke diagnoses in our study were based on physician diagnosis. However, most American and European cohort studies, such as the Kaiser Permanente Medical Care Program,[26] the Atherosclerosis Risk in Communities Study,[27] and the Framingham Study[28] have used the same method to diagnose stroke. The agreement with the diagnosis of stroke in these cohort studies is 75–90%.[27–29] Third, Our analyses adjusted for some confounding factors, however, unmeasured factors such as family history of diabetes, other related chronic diseases, dietary factors and physical activity status cannot be excluded. Finally, the information of HDL cholesterol subclasses was not complete in the dataset, so only HDL cholesterol levels were selected as the exposure.

Summary

In conclusion, the present study reported an inverse association between HDL cholesterol and the risks of total, ischemic and hemorrhagic stroke among patients with type 2 diabetes. This association is important to keep in mind when studying HDL cholesterol level and other cardiovascular risk factors in the patients with type 2 diabetes and when planning a strategy to prevent stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

The LEAD Study would like to acknowledge the contributions of our partners. The success of this study depended on their ongoing support and expertise. These partners include Ochsner Health System and the Ochsner Patient Research Advisory Board; Tulane Medical Center; Louisiana State University (LSU); Research Action for Health Network (REACHnet, a PCORnet CDRN) and their multi-stakeholder Diabetes Advisory Groups; Pennington Biomedical Research Center; Blue Cross and Blue Shield of Louisiana; Peoples Health; and our patient and community partners Patricia Dominick, Catherine Glover, and Peggy Malone.

Sources of Funding: This work was supported by a Patient-Centered Outcomes Research (PCORI) cooperative agreement (NEN-1508–32257) as part of Natural Experiments for Translation in Diabetes 2.0 (NEXT-D2). All statements in this manuscript, including findings and conclusions, are solely those of the authors and do not necessarily represent the views of PCORI, its Board of Governors, or Methodology Committee. Drs. Hu and Katzmarzyk were partly supported by a grant from the National Institute of General Medical Sciences (U54GM104940) of the National Institutes of Health.

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Table 1.

Hazard ratios of total stroke by different levels of high-density lipoprotein cholesterol at baseline and during follow-up among patients with type 2 diabetes

	High-density lipoprotein cholesterol (mg/dL)							P for trend
	<30	30–39.9	40–49.9	50–59.9	60–69.9	70–79.9	≥80	
Baseline value								
Men	5,870	13,317	8,457	3,007	916	287	219	
Cases	851	1,649	975	332	109	32	25	
Person-years	15,952	38,707	24,519	8,367	2,558	725	551	
Model 1	1.00	0.79 (0.73-0.86)	0.72 (0.65-0.79)	0.69 (0.61-0.78)	0.72 (0.59-0.88)	0.83 (0.58-1.18)	0.85 (0.57-1.27)	<0.001
Model 2	1.00	0.86 (0.79-0.94)	0.81 (0.73-0.89)	0.74 (0.65-0.85)	0.74 (0.60-0.91)	0.86 (0.60-1.23)	0.82 (0.55-1.22)	<0.001
Model 3	1.00	0.89 (0.82-0.97)	0.85 (0.77-0.93)	0.80 (0.70-0.91)	0.83 (0.67-1.02)	0.89 (0.62-1.27)	0.93 (0.62-1.39)	0.013
Women	2,207	8,729	11,991	7,323	3,296	1,206	719	
Cases	362	1237	1475	832	385	155	77	
Person-years	5,435	25,109	35,386	21,497	9,578	3,341	1,973	
Model 1	1.00	0.77 (0.68-0.87)	0.62 (0.55-0.69)	0.55 (0.49-0.62)	0.55 (0.48-0.63)	0.61 (0.50-0.74)	0.55 (0.43-0.70)	<0.001
Model 2	1.00	0.87 (0.77-0.98)	0.74 (0.66-0.83)	0.67 (0.59-0.76)	0.66 (0.56-0.76)	0.70 (0.57-0.85)	0.57 (0.44-0.74)	<0.001
Model 3	1.00	0.86 (0.77-0.97)	0.75 (0.67-0.85)	0.70 (0.61-0.79)	0.72 (0.62-0.83)	0.76 (0.62-0.92)	0.63 (0.49-0.81)	<0.001
Men and women combined	8,077	22,046	20,448	10,330	4,212	1,493	938	
Cases	1213	2886	2450	1164	494	187	102	
Person-years	21,387	63,816	59,905	29,864	12,136	4,066	2,524	
Model 1	1.00	0.80 (0.74-0.85)	0.68 (0.64-0.73)	0.61 (0.57-0.67)	0.61 (0.55-0.68)	0.68 (0.58-0.79)	0.63 (0.51-0.77)	<0.001
Model 2	1.00	0.89 (0.83-0.96)	0.81 (0.75-0.87)	0.74 (0.68-0.80)	0.73 (0.66-0.82)	0.79 (0.67-0.93)	0.70 (0.57-0.86)	<0.001
Model 3	1.00	0.86 (0.80-0.92)	0.77 (0.72-0.83)	0.71 (0.65-0.77)	0.71 (0.64-0.80)	0.77 (0.66-0.91)	0.69 (0.56-0.85)	<0.001
Updated mean value								
Men	3,098	10,711	7,312	2,401	684	187	96	
Cases	507	1449	924	303	94	25	11	
Person-years	9,047	33,424	22,877	7,411	2,090	560	310	
Model 1	1.00	0.76 (0.69-0.84)	0.69 (0.62-0.77)	0.66 (0.57-0.76)	0.72 (0.58-0.90)	0.74 (0.50-1.11)	0.56 (0.31-1.01)	<0.001
Model 2	1.00	0.84 (0.75-0.93)	0.78 (0.69-0.87)	0.73 (0.63-0.85)	0.75 (0.59-0.94)	0.72 (0.48-1.08)	0.56 (0.31-1.02)	<0.001
Model 3	1.00	0.89 (0.80-0.99)	0.86 (0.76-0.96)	0.83 (0.71-0.97)	0.86 (0.68-1.08)	0.91 (0.60-1.36)	0.72 (0.39-1.31)	0.205

	High-density lipoprotein cholesterol (mg/dL)							P for trend
	<30	**30–39.9**	**40–49.9**	**50–59.9**	**60–69.9**	**70–79.9**	**≥80**	
Women	862	6,044	9,955	6,455	2,715	876	500	
Cases	175	999	1,318	811	350	130	53	
Person-years	2,288	18,106	31,471	20,438	8,563	2,663	1,534	
Model 1	1.00	0.72 (0.61-0.84)	0.53 (0.45-0.62)	0.47 (0.40-0.55)	0.47 (0.39-0.56)	0.56 (0.44-0.70)	0.41 (0.30-0.55)	<0.001
Model 2	1.00	0.82 (0.69-0.96)	0.64 (0.54-0.75)	0.59 (0.49-0.70)	0.56 (0.46-0.68)	0.65 (0.51-0.82)	0.44 (0.32-0.60)	<0.001
Model 3	1.00	0.89 (0.75-1.05)	0.70 (0.60-0.83)	0.66 (0.55-0.78)	0.66 (0.55-0.80)	0.78 (0.62-0.99)	0.54 (0.40-0.74)	<0.001
Men and women combined	3,960	16,755	17,267	8,856	3,399	1,063	596	
Cases	682	2448	2242	1114	444	155	64	
Person-years	11,335	51,530	54,348	27,849	10,653	3,223	1,844	
Model 1	1.00	0.77 (0.71-0.84)	0.64 (0.59-0.70)	0.58 (0.52-0.63)	0.57 (0.51-0.65)	0.66 (0.55-0.79)	0.48 (0.37-0.62)	<0.001
Model 2	1.00	0.86 (0.78-0.93)	0.75 (0.68-0.82)	0.69 (0.63-0.77)	0.68 (0.60-0.77)	0.77 (0.64-0.92)	0.54 (0.42-0.70)	<0.001
Model 3	1.00	0.84 (0.77-0.92)	0.73 (0.66-0.80)	0.68 (0.61-0.75)	0.67 (0.59-0.76)	0.77 (0.65-0.93)	0.55 (0.42-0.71)	<0.001

Data are hazard ratios (95% confidence intervals) unless otherwise indicated. Model 1 adjusted for age and race. Model 2 adjusted for age, race, body mass index, systolic blood pressure, HbA1c, low-density lipoprotein cholesterol, triglycerides, estimated GFR, and smoking. Models 3 adjusted for age, race, body mass index, systolic blood pressure, HbA1c, low-density lipoprotein cholesterol, triglycerides, estimated GFR, smoking, use of antihypertensive drugs, use of diabetes medications, and use of lipid-lowering agents.

Table 2.

Hazard ratios of subtypes of stroke by different levels of high-density lipoprotein cholesterol at baseline and during follow-up among patients with type 2 diabetes

	High-density lipoprotein cholesterol (mg/dL)							P for trend
	<30	30-39.9	40-49.9	50-59.9	60-69.9	70-79.9	≥80*	
Hemorrhagic								
Baseline value								
Cases	73	160	117	58	30	22	-	
Person-years	19,929	60,140	56,623	28,320	11454	6209	-	
Model 1	1.00	0.74 (0.56-0.98)	0.56 (0.42-0.76)	0.54 (0.38-0.77)	0.40 (0.24-0.68)	0.92 (0.56-1.50)	-	<0.001
Model 2	1.00	0.84 (0.63-1.12)	0.65 (0.48-0.90)	0.61 (0.42-0.90)	0.45 (0.26-0.78)	0.93 (0.55-1.57)	-	0.009
Model 3	1.00	0.89 (0.67-1.18)	0.69 (0.51-0.95)	0.66 (0.45-0.96)	0.47 (0.27-0.80)	0.94 (0.56-1.59)	-	0.021
Updated mean value								
Cases	38	123	87	47	18	11	-	
Person-years	10,453	48,204	51,142	26,328	10042	4752	-	
Model 1	1.00	0.71 (0.49-1.02)	0.47 (0.32-0.69)	0.47 (0.30-0.74)	0.76 (0.46-1.26)	0.60 (0.30-1.19)	-	<0.001
Model 2	1.00	0.81 (0.56-1.18)	0.55 (0.36-0.83)	0.55 (0.34-0.88)	0.87 (0.51-1.49)	0.64 (0.31-1.49)	-	0.012
Model 3	1.00	0.85 (0.58-1.23)	0.58 (0.38-0.88)	0.58 (0.36-0.93)	0.89 (0.52-1.53)	0.63 (0.31-1.31)	-	0.024
Ischemic								
Baseline value								
Cases	1,140	2,726	2,333	1,106	476	166	101	
Person-years	21,279	63,542	59,708	29,763	12,102	4,024	2,523	
Model 1	1.00	0.81 (0.75-0.86)	0.70 (0.65-0.75)	0.64 (0.59-0.69)	0.65 (0.58-0.72)	0.66 (0.56-0.78)	0.69 (0.56-0.85)	<0.001
Model 2	1.00	0.88 (0.82-0.94)	0.79 (0.73-0.85)	0.71 (0.65-0.78)	0.70 (0.63-0.79)	0.69 (0.59-0.82)	0.67 (0.54-0.82)	<0.001
Model 3	1.00	0.89 (0.83-0.96)	0.82 (0.76-0.89)	0.75 (0.69-0.83)	0.78 (0.70-0.88)	0.76 (0.64-0.90)	0.75 (0.61-0.92)	<0.001
Updated mean value								
Cases	644	2,325	2,155	1,067	414	145	63	
Person-years	11,269	51,300	54,188	27,764	10,595	3,205	1,840	
Model 1	1.00	0.78 (0.72-0.86)	0.66 (0.61-0.72)	0.60 (0.55-0.67)	0.59 (0.52-0.67)	0.69 (0.57-0.82)	0.53 (0.41-0.69)	<0.001
Model 2	1.00	0.85 (0.77-0.93)	0.73 (0.66-0.80)	0.66 (0.60-0.74)	0.62 (0.54-0.71)	0.69 (0.57-0.84)	0.50 (0.39-0.66)	<0.001
Model 3	1.00	0.91 (0.83-0.99)	0.81 (0.73-0.89)	0.75 (0.67-0.83)	0.73 (0.64-0.84)	0.84 (0.70-1.02)	0.63 (0.48-0.82)	<0.001

Data are hazard ratios (95% confidence intervals) unless otherwise indicated. Model 1 adjusted for age, race and sex. Model 2 adjusted for age, race, sex, body mass index, systolic blood pressure, HbA1c, low-density lipoprotein cholesterol, triglycerides, estimated GFR, and smoking. Models 3 adjusted for age, race, sex, body mass index, systolic blood pressure, HbA1c, low-density lipoprotein cholesterol, triglycerides, estimated GFR, smoking, use of antihypertensive drugs, use of diabetes medications, and use of lipid-lowering agents.

* Since no hemorrhagic event occurred in this subgroup, we combined this group with HDL cholesterol 70–79.9 mg/dL group.

Table 3.

Hazard ratios of stroke by different levels of high-density lipoprotein cholesterol at baseline among subpopulation of patients with type 2 diabetes

	High-density lipoprotein cholesterol (mg/dL)							P for trend
	<30	**30-39.9**	**40-49.9**	**50-59.9**	**60-69.9**	**70-79.9**	**≥80**	
Age								
<60 years	1.00	0.84 (0.71-1.01)	0.68 (0.56-0.83)	0.66 (0.52-0.84)	0.74 (0.54-1.01)	0.44 (0.25-0.78)	0.48 (0.27-0.88)	<0.001
≥60 years	1.00	0.88 (0.81-0.94)	0.80 (0.74-0.87)	0.72 (0.65-0.79)	0.71 (0.63-0.80)	0.81 (0.69-0.96)	0.70 (0.56-0.88)	<0.001
Race								
African American	1.00	0.87 (0.77-0.99)	0.84 (0.74-0.95)	0.77 (0.67-0.89)	0.82 (0.69-0.97)	0.83 (0.66-1.04)	0.72 (0.55-0.95)	0.026
White	1.00	0.90 (0.82-0.97)	0.79 (0.72-0.87)	0.73 (0.65-0.81)	0.70 (0.60-0.82)	0.76 (0.60-0.96)	0.67 (0.48-0.94)	<0.001
Body mass index								
<30 kg/m^2	1.00	0.83 (0.74-0.93)	0.79 (0.70-0.89)	0.72 (0.63-0.82)	0.71 (0.60-0.84)	0.80 (0.64-1.00)	0.74 (0.57-0.96)	<0.001
≥30 kg/m^2	1.00	0.93 (0.85-1.01)	0.82 (0.74-0.90)	0.76 (0.68-0.86)	0.82 (0.70-0.96)	0.82 (0.64-1.04)	0.64 (0.44-0.94)	<0.001
HbA1c								
<7%	1.00	0.81 (0.73-0.90)	0.75 (0.67-0.83)	0.69 (0.61-0.78)	0.73 (0.62-0.85)	0.79 (0.64-0.98)	0.70 (0.53-0.91)	<0.001
≥7%	1.00	0.96 (0.87-1.05)	0.87 (0.78-0.96)	0.80 (0.71-0.90)	0.77 (0.65-0.91)	0.75 (0.58-0.97)	0.66 (0.47-0.92)	<0.001
Smoking status								
Never smoking	1.00	0.84 (0.77-0.91)	0.75 (0.69-0.82)	0.69 (0.62-0.76)	0.69 (0.60-0.78)	0.68 (0.56-0.83)	0.53 (0.40-0.71)	<0.001
Current and past smoking	1.00	0.88 (0.78-1.01)	0.79 (0.68-0.91)	0.68 (0.57-0.81)	0.70 (0.56-0.87)	0.95 (0.71-1.28)	0.95 (0.69-1.31)	<0.001
Anti-diabetic medications								
No use	1.00	0.74 (0.64-0.85)	0.72 (0.62-0.83)	0.66 (0.56-0.78)	0.61 (0.50-0.75)	0.61 (0.45-0.82)	0.62 (0.44-0.88)	<0.001
Oral agents	1.00	0.90 (0.79-1.04)	0.78 (0.67-0.90)	0.72 (0.61-0.85)	0.84 (0.69-1.04)	0.95 (0.72-1.26)	0.56 (0.36-0.90)	<0.001
Insulin	1.00	1.02 (0.93-1.12)	0.94 (0.84-1.05)	0.85 (0.75-0.98)	0.81 (0.68-0.97)	0.81 (0.61-1.06)	0.79 (0.58-1.09)	0.009
Lipid-lowering medications								
No use	1.00	0.86 (0.76-0.97)	0.79 (0.69-0.90)	0.67 (0.57-0.79)	0.72 (0.59-0.88)	0.68 (0.51-0.91)	0.75 (0.55-1.02)	<0.001
Use	1.00	0.91 (0.84-0.99)	0.83 (0.76-0.91)	0.78 (0.70-0.87)	0.79 (0.69-0.91)	0.87 (0.72-1.06)	0.67 (0.51-0.90)	<0.001
Anti-hypertensive medications								
No use	1.00	0.79 (0.65-0.96)	0.77 (0.63-0.95)	0.69 (0.54-0.88)	0.69 (0.51-0.94)	0.70 (0.46-1.08)	0.84 (0.52-1.33)	0.095
Use	1.00	0.90 (0.84-0.97)	0.82 (0.75-0.88)	0.75 (0.69-0.83)	0.77 (0.68-0.87)	0.82 (0.69-0.97)	0.67 (0.53-0.85)	<0.001

Data are hazard ratios (95% confidence intervals) unless otherwise indicated. Adjusted for age, race, sex, body mass index, systolic blood pressure, HbA1c, low-density lipoprotein cholesterol, triglycerides, estimated GFR, smoking, use of antihypertensive drugs, use of diabetes medications, and use of lipid-lowering agents, other than the variables for stratification.

Stroke. Author manuscript; available in PMC 2020 February 01.

All P for interaction >0.25.