Atherosclerosis 358 (2022) 34–40

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Risk of stroke in genetically verified familial hypercholesterolemia: A prospective matched cohort study

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ARTICLE INFO

Keywords:
FH
Stroke
Hypercholesterolemia
Registry
Statins
Anti-thrombotic medication

ABSTRACT

Background and aims: Individuals with familial hypercholesterolemia (FH), causing severely elevated LDL-C, are expected to have a higher risk of ischemic stroke. The risk of hemorrhagic stroke and impact of statin use are, however, not known. We aimed to investigate the risk of incident total, ischemic and hemorrhagic stroke in individuals with FH compared to controls, and to explore the association between cumulative statin use and risk of total stroke in FH.

Methods: This prospective cohort study consists of 4186 individuals with genetically verified FH and 82 180 age and sex matched controls followed from 2008 to 2018 for incident stroke. Daily defined doses (DDD) described cumulative statin exposure: 0–5000 DDD ("low"), 5000–10,000 DDD ("intermediate"), and >10 000 DDD ("high"). Results were presented as hazard ratio (95% CI) derived from Cox proportional hazards models.

Results: Individuals with FH did not have a higher risk of total stroke (1.16 (0.95–1.43) nor ischemic stroke (1.11 (0.88–1.38). Excess risk of hemorrhagic stroke was observed (1.63 (1.07, 2.48) but attenuated after adjusting for antithrombotic medication (1.25 (0.81, 1.93). Among individuals with FH, there was no association between statin use and total stroke for intermediate *vs.* low DDD [0.69 (0.32, 1.48)] or for high *vs.* low DDD [0.83 (0.41, 1.67)].

Conclusions: No significant excess risk of incident total and ischemic stroke in FH, and no difference in total stroke risk among the FH population with low, intermediate, and high statin exposure were observed. The observed relationship between FH and hemorrhagic stroke was no longer significant after adjusting for use of anti-thrombotic medication.

1. Introduction

Risk factors for stroke include high age, hypertension, severe small vessel disease and smoking [1]. Randomized controlled trials have demonstrated a clear relationship between therapeutic LDL-C lowering and ischemic stroke risk [2,3]. The association of high LDL-C with other stroke subtypes is however uncertain [4]. Several studies, including one recent cohort study found that high LDL-C predicted coronary heart disease (CHD) but not stroke [5,6]. In familial hypercholesterolemia (FH) untreated LDL-C levels are about 2-fold increased compared to the general population [7]. Even though a genetic FH diagnosis does not seem to be associated with higher risk of total stroke [8–10], data on the risk of ischemic stroke and particularly hemorrhagic stroke, are less clear [9–11]. A recent systematic review and meta-analysis of studies including adults with FH showed that a clinical diagnosis of FH was associated with higher risk of ischemic stroke, whereas genetically

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https://doi.org/10.1016/j.atherosclerosis.2022.08.015
Received 23 June 2022; Received in revised form 14 August 2022; Accepted 24 August 2022
Available online 28 August 2022

confirmed FH did not confer higher risk of total or ischemic stroke [12]. These findings warrant further studies on risk of stroke in genetically verified FH [10,11,13].

We have previously reported that individuals with genetically verified FH do not have increased risk of total or ischemic stroke [10]. However, when these findings were published, no matched control group was included, and there were only 46 events (26 ischemic strokes) of cerebrovascular disease. Furthermore, our previous publication did not adjust for comorbidities and did not include data on statin use [10]. Indeed, statin use has been shown to protect against ischemic stroke [14–16], possibly by mechanisms that go beyond LDL-C-lowering such as prevention of brain and nerve tissue degeneration [17]. However, there is limited documentation on the effects of different levels of statin exposure on stroke risk in individuals with FH. Given the high statin exposure in individuals with FH, the present study may provide additional insight into level of statin exposure and stroke risk. Finally, the risk of hemorrhagic stroke, which is not generally associated with atherosclerosis [12,16,18], remains to be studied separately in individuals with FH [19] and take into account the use of anti-thrombotic medication known to increase the risk of hemorrhagic stroke [20].

Expanding on previous findings, the aim of this study was thus to investigate the risk of incident total, ischemic and hemorrhagic stroke in individuals with genetically verified FH compared to age and sex matched controls. A secondary aim was to examine the relationship between cumulative statin exposure and risk of total stroke among individuals with FH.

2. Patients and methods

2.1. Study population

We performed a prospective matched cohort study in 5691 individuals with genetically verified FH and 112 680 age and sex-matched controls. Genetic testing for FH in Norway, funded by the Norwegian healthcare system, is performed by the Unit for Cardiac and Cardiovascular Genetics (UCCG), Oslo University Hospital [21]. The UCCG database includes all individuals from Norway with a genetically verified FH diagnosis; 93.5% with mutation in the LDLR gene [21]. Inclusion date in the UCCG corresponds to date of diagnosis from January 1st, 1992, and onwards.

The FH population in this study was obtained from the UCCG database and comprises individuals diagnosed between January 1992 and May 2014 as previously described [22]. The control population was randomly selected from the Population Registry of Norway and matched by age (at FH diagnosis) and sex to the FH population (ratio 1:20). We excluded individuals who were hospitalized with stroke or deceased before study start [date of inclusion to the registry, age 20, or start of patient registry data (January 1, 2008), whichever occurred last]. The final cohort consisted of 4186 individuals with FH and 82 180 controls who were followed from study start until December 31, 2018, at the latest. Each matched control was followed from the same date as the individual with FH in the matched set.

2.2. Registry linkages

2.2.1. Incident stroke

Data on incident strokes were obtained from several health registries in Norway and linked to the study population by using a unique personal identification number that is available for all residents in Norway.

The Norwegian Patient registry (NPR) contain data on hospitalizations, outpatient visits and visits at contracted specialist care for the entire population of Norway from 2008 and onwards. The Cause of Death registry (CDR) contains information on date of death and underlying, intermediate and immediate causes of death from 1951 and onwards. The Norwegian Prescription database (NorPD) contains information about all drug prescriptions dispensed from Norwegian pharmacies since 2004, including type and strength of medications prescribed, daily defined doses (DDD) and dates of dispensing. Total stroke and subtypes of stroke were defined using International Classification of Diseases (ICD) version 10 (ICD-10) codes: Total stroke [ICD10: I6I, I63 (excluding I63.6) and I64], ischemic stroke [including unspecified stroke, ICD10: I63 (not 163.6) and I64], and hemorrhagic stroke (ICD10: I61).

An incident case of total stroke and subgroups of stroke were defined as a hospitalization with stroke as main or secondary discharge diagnosis, or stroke as the underlying cause of death without prior stroke events during 2008–18.

2.2.2. Sensitivity analysis

Since the NPR lack hospitalization data before 2008, we were not able to exclude individuals with stroke before 2008. In addition, lack of data before 2008 gives limited possibility to search for comorbidities prior to start of follow-up. To investigate the impact of prior comorbidities, we replicated our main analyses in another data linkage containing hospitalizations or deaths from total stroke and subtypes of stroke from 1994 to 2007 from the CDR and the Cardiovascular Disease in Norway Project (CVDNOR) at the University of Bergen, and the NPR during 2008–2017. The period 1994–2000 was used as wash-out for previous events [23] and risk of incident total stroke and subgroups of stroke were analyzed for the period 2001–17 (see Supplementary Tables S1 and S2). Since this data linkage did not include data on drug prescriptions, it was not used as the main data source.

2.2.3. Covariates

The available covariates reported during 2008–2018 included previous CHD (ICD10: I20-25), hypertension (ICD10: I10-15), and atrial fibrillation (ICD-10: I48). These were defined based on main and secondary diagnoses from hospitalizations registered in the NPR before study start. Following the Anatomical Therapeutic Chemical (ATC) classification system, data on use of statins (C10A) and antithrombotic agents (B01A) from the NorPD during 2004–18 were obtained. The definition of a statin user was two or more dispensed prescriptions registered the same year as start of follow-up. Some anti-thrombotic medications are used in a limited time following a CHD event. Therefore, we choose to define a user of anti-thrombotic medication as having more than one dispensed prescription the same year as start of follow-up. Since statin type and strength can vary over time both within and between individuals, we used the international standard measurement unit DDD to describe continuously statin use [24]. A DDD is defined as the assumed average maintenance dose per day for a drug used on its main indication in adults. Since both 30 mg simvastatin and 20 mg atorvastatin are equivalent to 1 DDD of statins, the use of DDDs as a measure of cumulative dose during 2004–2018, takes statin potency into account [25].

2.3. Statistical methods

Participant characteristics are reported as mean (standard deviation [SD]) for continuous variables and n (%) for categorical variables. Cumulative incidences were visualized with age as the time scale and death from other causes than stroke treated as competing events. Cox proportional hazards analyses were performed to obtain hazard ratios (HR) and corresponding 95% confidence intervals (CI) for the associations between a FH diagnosis and stroke incidence during 2008–18. The association between FH and total stroke, ischemic stroke, ischemic + unspecified stroke and hemorrhagic stroke were assessed using two models. *Model 1* was adjusted for the matching variables (age and sex) and *model 2* was additionally adjusted for strong predictors of stroke including previous CHD, hypertension, and atrial fibrillation.

In models where hemorrhagic stroke was the outcome, a *model 2a* was created additionally that included anti-thrombotic medications. For consistency, *model 2a* were also reported for all stroke outcomes in

Table 1
Study populations of individuals with familial hypercholesterolemia (FH) and age and sex matched controls.

	FH	Control
N	4186	82 180
Age at inclusion (FH diagnosis), mean (SD)	45.9 (14.8)	45.5 (14.6)
Age at first total stroke event, mean (SD)	68 (13.1)	68 (12.3)
Females, n (%)	2219 (53)	43 660 (53.1)
Males, n (%)	1967 (47)	38 520 (46.9)
Total stroke events, n (%)	100 (2.39)	1610 (1.96)
Ischemic strokes, n (%)	74 (1.77)	1244 (1.51)
Ischemic + unspecified strokes, n (%)	79 (1.89)	1338 (1.63)
Hemorrhagic strokes, n (%)	24 (0.573)	271 (0.33)
Use of antithrombotic medications, n (%)[a]	1063 (25.4)	5907 (7.19)
Previously coronary heart disease, n (%)[b]	223 (5.33)	1851 (2.25)
Atrial fibrillation, n (%)	72 (1.72)	882 (1.07)
Hypertension, n (%)	27 (0.645)	269 (0.327)
Statin use at start of follow-up, n (%)	2996 (71.6)	6684 (8.13)

Total stroke defined as ICD10: I6I, I63 (excluding 163.6) and I64, ischemic + unspecified stroke, ICD10: I63 (not 163.6) and I64 and hemorrhagic stroke (ICD10:I61). Statins; 2 or more prescriptions of ATC code C10A. Antithrombotic agents; > 1 prescription of ATC code B01A the same year as start of follow-up.
[a] Most frequent used: ATC code B01AC: 25.5% in FH (n = 1067) and 6.7% (n = 5492) in controls.
[b] No information on non-fatal CVD events before 2008.

Supplementary Table S3.

Models stratified by age group (0–39, 40–69, 70 years) and sex were similarly adjusted with the exception of the stratification variable. The assumption of proportional hazards was checked by calculating and visualizing Schoenfeld residuals for all models.

2.3.1. Secondary analysis

To account for competing risk of death from other causes, a separate sub-distribution hazard model was created adjusting for *model 2* covariates [26]. Furthermore, an intercurrent, non-fatal CHD event would likely impact the treatment regime of both FH individuals and controls. The potential effect of CHD treatment on stroke risk was tested in two steps. First, the risk of total stroke was analyzed in two groups, split according to the presence or absence of non-fatal CHD events that occurred before a stroke. Secondly, we adjusted for CHD using a time-dependent modeling approach, which was split by follow-up time before and after an intercurrent CHD event.

2.3.2. Cumulative statin exposure

DDDs were used to assess cumulative statin exposure in individuals with FH during 2004–2018. We divided the cumulative statin exposure into three intervals; 0–5000 DDD (defined as "low" DDD), 5000–10000 DDD ("intermediate DDD"), and >10 000 DDD ("high" DDD). Cumulative DDD was treated as a time-varying exposure variable in Cox models with age as the time-scale and adjustment for sex. Individual follow-up time was split at the date when individuals switched category for cumulative DDD (1–5000 DDD, 5000–1000 DDD and >10 000 DDD). HRs were further adjusted for *model 2* covariates.

2.3.3. Sensitivity analyses

The sensitivity analyses performed on the data material from 2001 to 2018 generally built on the same models as for the 2008–2018 with the exception of adjustments for anti-thrombotic medications and statin exposure, as these data were not available.

All statistical analyses were conducted using Stata version 16 and R versions 4.1.0 (Foundation for Statistical Computing, Vienna, Austria). In R the following libraries were used for data handling and analysis: haven, tidyverse, survival, survminer, casebase, modelr, broom, comprsk, stataXml, ezfun and kableExtra.

2.4. Ethics

This study was approved by The Regional Committee of Medical and Health Research Ethics for South-Eastern Norway (reference 2011/1343 REK Sør-Øst B), and by the Norwegian Data Protection Officer at Oslo University Hospital. The implementation of the study complies with the Declaration of Helsinki. Consent was required to be included in the FH study cohort, whereas no consent was needed to be included in the control cohort. No additional consent was needed to be included in the present study (but individuals in the FH cohort had the opportunity to withdraw from the study until May 1, 2014).

3. Results

3.1. Study population

The FH and control populations were similar in terms of age at inclusion, age at first stroke and sex and age distribution (Table 1 and Supplementary Table S4). As expected, at start of follow-up there was a higher proportion of individuals with previous CHD in the FH population (5.3 versus 2.3%) and more statin users (71.6 versus 8.2%). There was also a higher proportion of anti-thrombotic medication users in FH (25.4 versus 7.2%) (Table 1), of which platelet aggregation inhibitors were most frequently used in both populations (Supplementary Table S5). The rates of hypertension and atrial fibrillation appeared similar between the FH population and controls (Table 1).

3.2. Incident stroke and stroke subtypes during 2008–2018

There were 100 events of total stroke in the FH population and 1610 in controls (41 270 person-years of follow-up in FH and 813 134 person-years in controls) (Table 1 and Supplementary Table S6). Cumulative incidence curves for the FH and control populations are presented in Fig. 1. There was no significant association between FH and incidence of total stroke [HR: 1.16 (0.95, 1.43)] in *model 1*, which remained similar in *model 2* [HR: 1.14 (0.93, 1.40)], and also after considering competing risk from deaths. The risk estimates were also similar when the analysis was stratified according to intercurrent non-fatal CHD event during follow-up time [intercurrent CHD, HR: 1.08 (0.77, 1.52); no intercurrent CHD, HR: 1.14, (0.92–1.41)], and when adjusting for intercurrent CHD as a time-varying covariate [HR: 1.15 (0.94, 1.41)].

The risk estimates in *model 1* were similar in men [HR: 1.08 (0.81, 1.4)] and women [HR: 1.28 (0.96, 1.71)] (Fig. 2), and between age groups (Supplementary Table S7).

There was no association between FH and risk of ischemic stroke (HR: 1.11 (0.88, 1.41) in the total population in *model 1*, and the risk estimates were minimally affected by additional adjustment in *model 2*. The results were similar separated by men and women (Fig. 2). Additional adjustment for anti-thrombotic medication lowered the point estimate for the HR for ischemic stroke to 0.86 (0.68, 1.10)

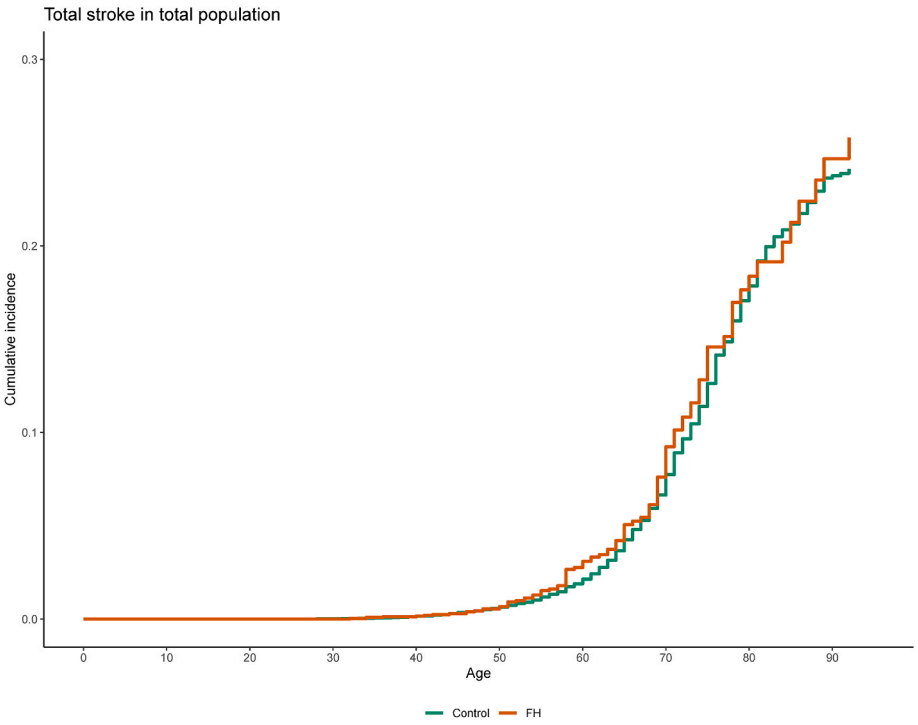

Fig. 1. Cumulative incidence of total stroke in the FH and control population with age as the time-scale.

(Supplementary Table S3).

We observed a higher risk of hemorrhagic stroke among individuals with FH compared to controls [HR: 1.63 (1.07, 2.48)] in *model 1*. In *model 2*, the HR for the total population was minimally reduced [HR: 1.58 (1.02, 2.41)]. Of the 24 hemorrhagic stroke events in the FH population, 70.8% (n = 17) used anti-thrombotic medication, compared to 32.5% % (n = 88) in the control population. After additional adjustment for antithrombotic medication, the point estimate for the HR for hemorrhagic stroke was strongly attenuated [HR 1.25 (0.81, 1.93)] (Fig. 2).

3.3. Sensitivity analysis of data from 2001 to 2017

In sensitivity analyses during 2001–2017 with a prior wash-out period (1994–2000) for previous events, the risk estimates were similar to the results from 2008 to 18: We observed no excess risk of total stroke in FH [HR: 1.12 (0.91–1.37)] nor ischemic stroke [HR: 1.03 (0.82, 1.31)]. The associations for total stroke and ischemic stroke were attenuated in *model 2*. Similar to the 2008–2018 data, we observed higher risk of hemorrhagic stroke for the total population [HR: 1.58 (1.05, 2.38)] during 2001–2017 that was attenuated in *model 2* [HR: 1.40 (0.92, 2.15)] (Supplementary Table S2).

3.3.1. Cumulative statin use

Among the FH population, 18 187 person-years were reported for high DDD, 9601 for intermediate DDD and 13 482 for low DDD. In *model 1*, there was no association between statin use and risk of total stroke for intermediate *vs.* low DDD [HR: 0.69 (0.32, 1.48)] or for high *vs.* low DDD [HR 0.83 (0.41, 1.67)] in the FH population. The results remained similar in *model 2* (Table 2).

4. Discussion

In this prospective matched cohort study during 2008–18 using real world data, we found no excess risk of total stroke nor ischemic stroke in individuals with genetically verified FH.

We observed a higher risk of hemorrhagic stroke that was strongly attenuated when adjusting for use of anti-thrombotic medications. There was no association between levels of cumulative statin exposure and risk of total stroke in individuals with FH.

4.1. Total stroke and ischemic stroke

Our findings of no significant higher risk of total stroke during 2008–2018 in individuals with genetically verified FH, support and extend the results from our previous publication during 2001–2009 [10]. Neither previous, nor intercurrent CHD during follow-up, altered the risk estimates. The HRs for total stroke risk between individuals with FH and controls were also similar between sexes and across age groups. Since the results from our main analysis (2008–2018) were similar to the results reported in the sensitivity analysis with data from the period 2001–17, it appears that lack of data on stroke, cardiovascular disease and comorbidities before 2008 did not impact the main results.

In accordance with our findings, no increased risk of total stroke was found in an observational study of 2752 individuals with genetically determined FH and 993 unaffected relatives [8]. In another study based on data from England and Wales, there was no increase in the standardized mortality ratio for stroke in definite/probable FH compared to the general population [9].

Like for total stroke, there was no significantly higher risk of ischemic stroke in the total FH population, nor in men and women separately. Previous observational studies have shown positive associations between LDL-C concentrations and risk of ischemic stroke [6,7]. Both the Copenhagen General Population Study [11] and a recent meta-analysis found no association between genetic FH and ischemic stroke [12]. However, for the latter study, having an LDL-C >4.9 mmol/L (190 mg/dL) resulted in significantly increased risk in the same sample (OR: 1.42 [95% CI: 1.06–1.89]) [12].

A large meta-analysis showed that clinical FH [e.g. diagnosing based on Dutch Lipid Clinic Network Score, Simon Broome criteria, among others [12,27]] was associated with increased risk of ischemic stroke, whereas genetically confirmed FH was not [12], pointing to the underlying cause of hypercholesterolemia as important for risk and as a possible contributing factor to the conflicting results. Furthermore, the pattern and magnitude of association of lipoproteins with ischemic

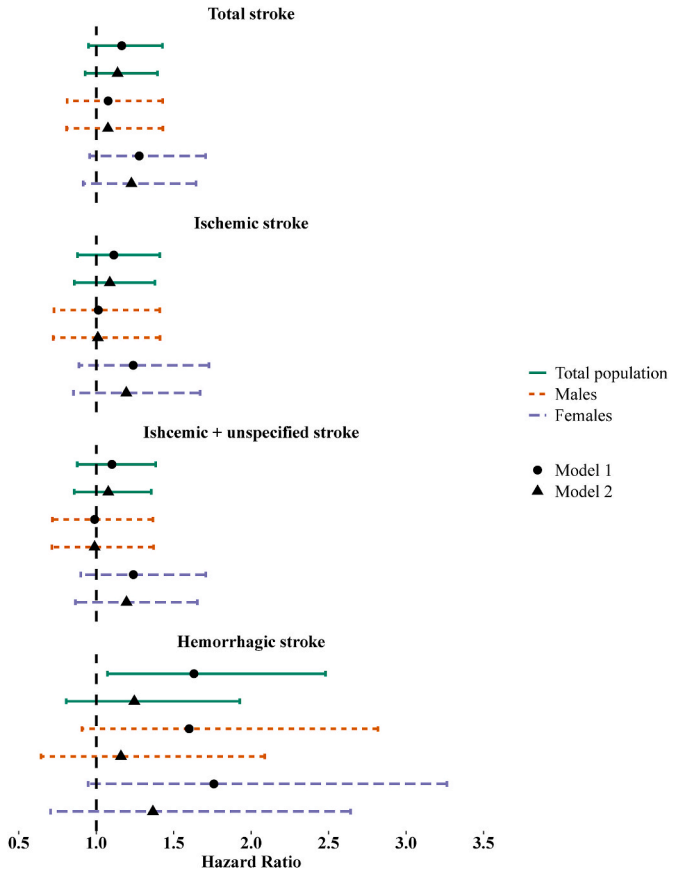

Fig. 2. Risk of total stroke and subtypes of stroke between individuals with FH and matched controls, according to sex.
Total stroke defined as ICD10: I6I, I63 (excluding 163.6) and I64. Hazard ratios (HR) with 95% confidence intervals (CI) derived from Cox proportional hazards models. Model 1 = adjusted for matching variables (sex and age in total population). Model 2 = adjusted for matching variables + previous coronary heart disease, hypertension, and atrial fibrillation, and for hemorrhagic stroke also anti-thrombotic medication (Model 2a).

stroke risk can vary by stroke etiology [28]. The largest subgroup of ischemic strokes in this population was ICD10-code 63.9 unspecified ischemic stroke, accounting for 44% and 42% of all ischemic strokes in FH and controls respectively (Supplementary Table 8). Detailed information on ischemic stroke etiology according to TOAST criteria [29] was however not available. Anti-thrombotic medication may protect against ischemic stroke [30]. In the present study, after adjusting for anti-thrombotic medication, the HR for ischemic stroke was reduced to 0.86 (0.68, 1.10). The confidence intervals for ischemic stroke risk were however wide, particular for women [HR: 1.24 (0.89, 1.73) in *model 1*], and we cannot therefore rule out that larger study population and longer follow-up times could have altered the results.

4.2. Hemorrhagic stroke

In our previous publication of stroke risk in FH [10], we did not study risk of hemorrhagic stroke as a separate endpoint since hemorrhagic stroke is not thought to be associated with atherosclerosis [12,16,18,28]. In our primary age and sex adjusted analysis, we found 63% higher risk of hemorrhagic stroke in individuals with genetically verified FH compared to matched controls, a finding that was confirmed in the sensitivity analysis using data from the period 2001–2017 (58% higher risk). However, the confidence intervals were wide, and the results should be interpreted with caution. The relationship between LDL-C and hemorrhagic stroke risk is also controversial and non-conclusive [14,28,31,32]. When adjusting for use of anti-thrombotic medication in our cohorts, the risk estimate for hemorrhagic stroke was considerably lowered and the relationship was no longer significant. From the early area of preventive cardiology, antithrombotic medication such as aspirin was widely used in primary prevention [33]. The 2021 ESC Guidelines [34] on CVD prevention does not however recommend aspirin in any primary prevention patients, except for diabetes mellitus patients at high- or very high risk where it *may be* considered (Class IIb). We cannot generalize on the rationale for use of anti-thrombotic medication in the present study, but the study highlights the risk of hemorrhagic stroke associated with use of anti-thrombotic medication.

4.3. Cumulative statin use

Studying statin use in apparently healthy controls is likely subject to confounding by indication. Therefore, the impact of cumulative statin use on risk of total stroke was only studied in individuals with FH who, according to guidelines [4], should use statins. Furthermore, it has been suggested that statin adherence can modify the relationship between a FH diagnosis and stroke [35]. Large clinical trials have shown that statin use results in lower stroke risk [14–16], and some even suggest a dose-response relationship between statin use and higher risk of stroke [36]. We therefore studied if treatment with statins was associated with risk of stroke in FH, but did not find an association between levels of cumulative statin exposure, taking statin potency to account [25], and risk of total stroke in this study. The results were adjusted for age at FH diagnoses (which usually corresponds to age at start of treatment). Hence, age at start of statin use had no influence on the risk of total stroke.

We cannot rule out confounding of any lifestyle factors. Since 72% of the current FH population use statins, it is also possible that statin use could have masked a significant relationship between FH and risk of ischemic stroke. However, in the same FH Norwegian population, a severely increased risk of myocardial infarction [37], aortic stenosis, aortic aneurism [38] and peripheral artery disease [39] were observed, leaving stroke as the so far only "exception that proves the rule" of high risk of cardiovascular diseases in FH.

A recent study from the Danish stroke registry reported that the relative risk of intracerebral hemorrhage was reduced by 26% in the statins [40]. Our data suggests a role of anti-thrombotic medication for hemorrhagic stroke in FH, but we had too few cases to study any

Table 2
Cumulative statin exposure and risk of total stroke in individuals with FH during 2004–2018.

Statin doses	Person years by dose of follow-up	Comparison	HR (95% CI) (model 1)	HR (95% CI) (model 2)
0-5000 DDD	13,482	5000-10,000 DDD *vs.* 0-5000 DDD	0.69 (0.32, 1.48)	0.67 (0.31, 1.41)
5000-10000 DDD	9601	>10,000 DDD *vs.* 0–5000 DDD	0.83 (0.411, 1.67)	0.77 (0.38, 1.59)
>10 000 DDD	18,187			

DDD = defined daily dose of statins (ATC code C10A). Total stroke defined as ICD10: I6I, I63 (excluding 163.6) and I64. Hazard ratios (HR) with 95% confidence intervals (CI) derived from Cox proportional hazards models. Model 1 = adjusted for matching variables (sex and age in total population). Model 2 = adjusted for matching variables + previous coronary heart disease, hypertension, and atrial fibrillation.

association between use of statins and risk of stroke subtypes.

4.4. Strengths and limitations

A major strength of this study is the long-term follow-up (10 year in main analyses and 16 years in sensitivity analysis) for incident stroke, yielding more stroke cases than previously reported in genetically verified FH. Furthermore, the mandatory inclusion in Norwegian health registries ensures complete registration of stroke cases and prescription data from start of the registries (2008 for NPR and 2004 for NorPD). Although we cannot rule out selection bias, we included the total sample of individuals with FH diagnosed between January 1992 and May 2014. Norway is in a unique position with the second largest FH database, extensive testing for FH and easy access to healthcare and treatment [21], which could impact the representativeness of these results outside the Norwegian FH population. Our results are strengthened by the inclusion and adjustment for several stroke risk factors such as previous CHD, hypertension and atrial fibrillation, and use of anti-thrombotic medication. Statin exposure was measured using DDDs that change over time to reflect changes in prescription types and strength over time in real world data. However, a general limitation using registry data for medication use is that prescribed medications do not reflect recommended prescribed dose, nor adherence [24]. Classification of ischemic strokes according to the TOAST criteria [29] would have yielded important information on stroke etiology. However, since data in this study is solely based on ICD10-codes reported in the registry, and no data from patient records, it was not possible to group cases according to etiology. The most important limitation of this study is that we do not have information on possible strong predictors of stroke, such as lipid values, blood pressure levels, smoking habits, body weight, inactivity, diet and alcohol consumption.

In summary, we observed, in a large Norwegian cohort of individuals with genetically verified FH and age and sex matched controls followed from 2008 to 18, a positive association with risk of hemorrhagic stroke. The risk was however attenuated, and the relationship no longer significant, after adjusting for anti-thrombotic medication, which was more frequent used among the FH population. The results for total and ischemic stroke support no excess risk in the FH population. However, the confidence limits were wide, and the results should be interpreted with caution. Levels of cumulative statin exposure were not associated with total stroke risk among individuals with FH.

Financial support

Helse Sør-Øst RHF (Norway), award number 2018095.

CRediT authorship contribution statement

Karianne Svendsen: Conceptualization, Methodology, Project administration, Writing – original draft, Reviewed, edited and approved the final manuscript. **Thomas Olsen:** Formal analysis, Visualization, Reviewed, edited and approved the final manuscript. **Kathrine J. Vinknes:** Formal analysis, Reviewed, edited and approved the final manuscript. **Liv J. Mundal:** Conceptualization, Methodology, Project administration, Reviewed, edited and approved the final manuscript. **Kirsten B. Holven:** Conceptualization, Reviewed, edited and approved the final manuscript. **Martin P. Bogsrud:** Conceptualization, Reviewed, edited and approved the final manuscript. **Trond P. Leren:** Conceptualization, Reviewed, edited and approved the final manuscript. **Jannicke Igland:** Conceptualization, Methodology, Project administration, Data curation, Formal analysis, Reviewed, edited and approved the final manuscript. **Kjetil Retterstøl:** Conceptualization, Methodology, Project administration, Supervision, Funding acquisition, Reviewed, edited and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Sensitivity analyses were conducted using data from the CVDNOR project and hence we thank Grethe S. Tell for making these data available for this project. Further, the authors also thank Tomislav Dimoski at The Norwegian Institute of Public Health, Norway, for his contribution by developing the software necessary for obtaining data from Norwegian hospitals 1994–2009 (the CVDNOR database), conducting the data collection and quality assurance of data in this project. Data is obtained from several Norwegian health registries. However, the registries have no role in the interpretation and presentation of data.

One author (Jannicke Igland) had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2022.08.015.

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