Cardiovascular Outcomes in Patients With Both Diabetes and Phenotypic Familial Hypercholesterolemia: A Nationwide Register-Based Cohort Study

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OBJECTIVE

Patients with diabetes or familial hypercholesterolemia (FH) have an increased incidence of cardiovascular diseases compared with the population, but whether this risk is exacerbated in patients with combined traits is unknown.

RESEARCH DESIGN AND METHODS

In this Swedish nationwide, register-based cohort study, patients with diabetes were included between 2002 and 2020. Adjusted Cox proportional hazards models were used to assess the risk of cardiovascular events in patients with or without phenotypic FH (≥6 points for phenotypic FH according to Dutch Lipid Clinic Network criteria) compared with general population control subjects without diabetes as reference.

RESULTS

A total of 45,585 patients with type 1 diabetes (227,923 control subjects) and 655,250 patients with type 2 diabetes (655,250 control subjects) were followed for a median of 14.1 and 7.9 years, respectively. Of those, 153 and 7,197, respectively, had phenotypic FH. Compared with control subjects, patients with diabetes and phenotypic FH had higher risk of cardiovascular mortality (type 1: hazard ratio 21.3 [95% CI 14.6–31.0]; type 2: 2.40 [2.19–2.63]) and of a cardiovascular event (type 1: 15.1 [11.1–20.5]; type 2: 2.73 [2.58–2.89]). Further, patients with diabetes and phenotypic FH had higher LDL-cholesterol levels during observation ($P < 0.05$) and increased risk of all major cardiovascular outcomes ($P < 0.0001$) than patients with diabetes but without FH. The proportion receiving lipid-lowering treatment was higher in patients with phenotypic FH ($P < 0.0001$).

CONCLUSIONS

Patients with both diabetes and phenotypic FH are more at risk for adverse cardiovascular outcomes and have higher LDL-cholesterol levels despite receiving intensified lipid-lowering therapy.

Patients with type 1 and type 2 diabetes are at more risk of mortality and cardiovascular morbidity than the general population (1). The age of onset of diabetes (2), glycemic control, and the successful management of cardiovascular risk factors are important determinants of cardiovascular outcomes in these populations (3,4).

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Familial hypercholesterolemia (FH) is an autosomal-dominant dyslipidemia that also induces the development of premature atherosclerotic cardiovascular disease (ASCVD) (5). In its heterozygous form, FH has a prevalence of 1 in 311–313 in the general population (6,7) and is characterized by elevated LDL cholesterol from birth. Data from the cause-of-death registry in Norway has shown that, at the time of death, 93% of patients with FH had established ASCVD and, on average, were only 44 years old when they suffered their first cardiovascular event (8). Additionally, the world's largest register for FH, the Familial Hypercholesterolemia Studies Collaboration, demonstrates that patients with FH are predominantly affected by coronary disease (9). Despite its severe impact on cardiovascular health, the proportion of patients diagnosed with FH remains low in most countries (5,10).

Whether cardiovascular risk is exacerbated in patients with diabetes and FH is studied scarcely. Indeed, data detailing the consequences for mortality and cardiovascular morbidity in populations with the combined traits of these disorders are limited to small studies, mostly focused on patients with type 2 diabetes (11–17). Considering this, the aim of this large, nationwide, register-based cohort study was to assess the risk of mortality and cardiovascular outcomes in patients with diabetes and phenotypic FH compared with that in patients with diabetes alone and matched control subjects from the general population.

RESEARCH AND DESIGN METHODS

Study Design and Population

This nationwide, register-based cohort study used the Swedish National Diabetes Register (NDR), which covers ∼90% of all Swedish residents ≥18 years of age with type 1 or type 2 diabetes. All patients listed in the NDR between 1 January 2002 and 31 December 2020 with a registered LDL-cholesterol value were included in the study and followed until death or the end of the study period (31 December 2020). Baseline was defined as the time point when the first measurement of LDL cholesterol was registered that corresponded to entry into NDR in 63.4% of the cases with type 1 diabetes and 68.8% of the cases with type 2 diabetes; within 2 years, >85% of all cases in both diabetes cohorts had an LDL-cholesterol measurement recorded. Each patient with diabetes was matched (according to age, sex, and county of residence) at the date of entry into the NDR with randomly selected control subjects from the Swedish population without diabetes (1:5 for type 1 diabetes and 1:1 for type 2 diabetes), meaning that a 50-year-old man with diabetes included in 2005 would be matched to a control subject without diabetes aged 50 years in 2005. The population register, from which the control subjects were matched, does not contain data on anthropometrics, blood pressure, or lipid levels. Matching was executed with replacement, meaning that one individual could be selected as a control for multiple cases, both within and between the cohorts with diabetes, but each cohort was analyzed separately. No individual with a prevalent diabetes diagnosis (type 1 or type 2) at the time of inclusion could be selected as a control subject, but individuals were not excluded as control subjects if diabetes developed during the study period. Diabetes type was defined according to epidemiologic criteria (see Supplementary Materials and Methods for details), as previously described (2,4). All patients consented for their data to be reported in the registry. However, according to Swedish law, individual consent was not required for those data to be included in this study. The Regional Ethical Review Board in Gothenburg, Sweden, approved the study.

Sources of Data and Outcomes

Baseline characteristics (age, sex, smoking status, blood pressure, complications of diabetes, and laboratory values) were sourced from the NDR. Laboratory analyses were performed at local hospitals according to standardized methods. Each patient's data were linked to the mandatory Swedish National Board of Health and Welfare registries, which include the Swedish National Inpatient Register (information regarding all visits to hospitals and specialized outpatient clinics) and the Swedish Cause of Death Register, both logging data according to the ICD-9 and ICD-10 codes and surgical intervention codes. The Swedish Prescribed Drug Register, which details all dispensed prescription drugs according to the Anatomical Therapeutic Chemical classification system, was also linked. The validity of the diagnoses in the Swedish Inpatient Registry is considered high (18). Statistics Sweden provided socioeconomic data, including annual income, place of birth, marital status, and education.

Outcomes of interest in the Inpatient Register and the Cause of Death Register were: all-cause mortality, cardiovascular mortality, acute myocardial infarction, ischemic stroke, revascularization or limb amputation for peripheral artery disease, coronary revascularization by percutaneous coronary intervention or coronary artery bypass graft surgery, and hospitalization for heart failure. An ASCVD event was a composite outcome defined as one of the following: acute myocardial infarction, ischemic stroke, and/or revascularization or lower-limb amputation due to peripheral artery disease. The complete list of ICD codes and surgical intervention codes used to define each outcome is shown in Supplementary Tables 4 and 5. Lipid-lowering therapies (LLT) were evaluated in the Prescribed Drug Register between 2006 and 2020. Three drug classes were the focus: statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors. High-intensity statin therapy was defined as ≥40 mg atorvastatin or ≥20 mg rosuvastatin daily.

Identification of Phenotypic FH

Phenotypic FH was identified using a truncated version of the Dutch Lipid Clinic Network (DLCN) criteria (19), with scoring based on the first recorded LDL-cholesterol value (i.e., the baseline value) in the NDR and the presence of premature cardiovascular disease according to type, age, and sex. If LLT were used when this baseline value was registered, the LDL-cholesterol value was corrected to correspond to an untreated level before scoring was conducted. Information regarding family history, signs of clinical hypercholesterolemia, or the occurrence of pathogenic mutations was not available in the registries and, therefore, not included in the criteria. Scoring according to the DLCN criteria, use of ICD codes for defining the presence of premature cardiovascular disease, and the calculation of untreated LDL-cholesterol levels are all described in the Supplementary Materials and Methods and Supplementary Tables 1–3. Individuals with ≥6 points were considered to have phenotypic FH, whereas those with ≤5 points were not.

Statistics

Categorical variables were summarized as frequencies and percentages. Numerical variables were summarized as the mean (SD) or median (interquartile range [IQR]), depending on the distribution of data. Cox regression was used to study the risk of mortality and cardiovascular outcomes (hazard ratio [HR] with 95% CI). The cohorts with type 1 and type 2 diabetes were analyzed separately to compare outcomes between the groups with and without phenotypic FH, using the matched control subjects as a group (n = 227,923 for type 1 diabetes and n = 655,250 for type 2 diabetes) as a reference (see Supplementary Materials and Methods for details). This approach was chosen because it generated a larger control group and thus gave more statistical power to the analysis. The proportional hazards assumption was checked by Schoenfeld residuals. All models were adjusted for age, sex, and socioeconomic factors. The proportion of missing data was low: 3.2% for the cohort with type 1 diabetes and 1.9% for the cohort with type 2 diabetes, accounted for using listwise deletion. Crude incidence rates were estimated with exact 95% CI based on the Poisson distribution. Annual mean LDL-cholesterol levels (Supplementary Materials and Methods, Supplementary Tables 8 and 9) with 95% CI were estimated using a linear mixed model with interaction terms of FH status and calendar year. The proportions of individuals using an LLT were summarized with 95% Wald CI. All statistical analyses were performed separately in the two cohorts with diabetes using R Statistical Software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 45,585 patients with type 1 diabetes and 655,250 patients with type 2 diabetes were included with a median follow-up time of 14.1 years (IQR 8.1–18.6) and 7.9 years (IQR 3.7–11.6), respectively. Within each cohort, 153 individuals with type 1 diabetes (0.33%) and 7,197 patients with type 2 diabetes (1.10%) had phenotypic FH.

Baseline characteristics for each respective cohort with diabetes, stratified by the presence of phenotypic FH, are presented in Table 1 alongside the characteristics of the matched control subjects. The cohort with type 1 diabetes had a mean age of 33.9 years and consisted of 44.9% women. Patients with type 1 diabetes and phenotypic FH were, at the time of inclusion, older (46.5 vs. 33.9 years), had an increased prevalence of cardiovascular disease (45.1 vs. 5.9%), and had higher LDL cholesterol levels (5.48 vs. 2.65 mmol/L), despite wider use of LLT (87.6 vs. 16.1%) than that cohort without phenotypic FH. A contributing factor to the observed age difference between the phenotypic FH and the group without FH was a later registration of the first LDL cholesterol, which defines the baseline of the study. After 2 years in the NDR, a cumulative percentage of 78.4% of phenotypic FH patients had their first LDL recorded compared with 86.4% of patients without FH.

The cohort with type 2 diabetes consisted of 42.4% women and was more balanced in terms of age (mean 62.2 vs. 64.3 years) between those with and those without phenotypic FH. Otherwise, there was a similar pattern of more prevalent cardiovascular disease (39.4 vs. 21.3%), higher LDL-cholesterol levels (5.22 vs. 2.88 mmol/L), and higher use of LLT (89.4 vs. 46.5%) in the phenotypic FH group compared with without FH, as observed in the cohort with type 1 diabetes. However, the difference in the prevalence of cardiovascular disease between patients with and without phenotypic FH was larger in the cohort with type 1 diabetes.

Patients with type 1 diabetes, regardless of whether they had phenotypic FH or not ($P < 0.0001$ for all comparisons), had a higher risk for all-cause mortality (phenotypic FH: HR 8.50 [95% CI 6.46–11.19]; without FH: HR 2.35 [95% CI 26.3–2.43]), for cardiovascular mortality (phenotypic FH: HR 21.29 [95% CI 14.63–30.97]; without FH: HR 4.15 [95% CI 3.89–4.42]), and for an ASCVD event (phenotypic FH: HR 15.06 [95% CI 11.10–20.45]; without FH: HR 3.68 [95% CI 3.54–3.83]) than the matched control subjects. The extent of risk for ASCVD events, acute myocardial infarction, ischemic stroke, coronary revascularization, and hospitalization for heart failure were on a comparable level within each of these cohorts (phenotypic FH and without FH) with type 1 diabetes (Fig. 1*A*). However, compared with the matched control subjects, the risk of lower-limb amputation or revascularization due to peripheral artery disease was further elevated in those with (HR 61.06 [95% CI 37.22–100.18]) and those without phenotypic FH (HR 14.15 [95% CI 12.65–15.82]).

Patients with type 2 diabetes, with or without phenotypic FH, also had a higher risk for all-cause mortality (phenotypic FH: HR 1.58 [95% CI 1.49–1.67]; without FH: HR 1.21 [95% CI 1.20–1.22]), for cardiovascular mortality (phenotypic FH: HR 2.40 [95% CI 2.19–2.63]; without FH: HR 1.41 [95% CI 1.39–1.43]), and for an ASCVD event (phenotypic FH: HR 2.73 [95% CI 2.58–2.89]; without FH: HR 1.46 [95% CI 1.45–1.48]) than the matched controls ($P < 0.0,001$ for all comparisons) (Fig. 1*B*). Similar to the cohort with type 1 diabetes, patients with type 2 diabetes, with (HR 4.90 [95% CI 4.23–5.68]) or without phenotypic FH (HR 2.45 [95% CI 2.37–2.53]), were at greatest risk of revascularization or lower-limb amputation due to peripheral artery disease out of any other cardiovascular outcome.

In direct comparisons between patients with or without phenotypic FH (Table 2), the risk for all cardiovascular outcomes was higher in those with phenotypic FH, in both the cohort with type 1 diabetes (cardiovascular mortality: HR 4.71 [95% CI 3.40–6.53]; an ASCVD event: HR 3.80 [95% CI 2.94–4.91]) and the cohort with type 2 diabetes (cardiovascular mortality: HR 1.67 [95% CI 1.53–1.83]; an ASCVD event: HR 1.82 [95% CI 1.72–1.93]). Data on the number of cardiovascular events in each group are presented in Supplementary Table 7.

The annual estimated mean plasma LDL-cholesterol levels for patients with or without phenotypic FH are detailed in Fig. 2. Patients with phenotypic FH consistently had higher LDL-cholesterol levels over the study period than those without FH, in both the cohort with type 1 diabetes and the cohort with type 2 diabetes (Supplementary Tables 8 and 9). In patients with type 1 diabetes, the estimated mean difference in LDL cholesterol between those with and those without phenotypic FH decreased from 3.40 mmol/L (95% CI 3.10–3.71) in 2002 to 0.42 mmol/L (95% CI 0.22–0.63) in 2020. Similarly, the estimated mean difference in LDL cholesterol levels also decreased in patients with type 2 diabetes throughout the same period, from 3.74 mmol/L (95% CI 3.60–3.87) to 0.73 mmol/L (95% CI 0.70–0.76).

Table 1—Baseline characteristics of patients with diabetes and matched control subjects

	Control subjects	Type 1 diabetes without FH	Type 1 diabetes with phenotypic FH	Control subjects	Type 2 diabetes without FH	Type 2 diabetes with phenotypic FH
Total numbers	227,923	45,432	153	655,250	648,053	7,197
Characteristics						
Sex, women	102,369 (45.0)	20,361 (44.9)	65 (42.5)	277,537 (42.4)	273,744 (42.3)	3,520 (49.0)
Age, years	31.2 (13.8)	33.9 (14.9)	46.5 (13.1)	63.3 (12.2)	64.3 (12.3)	62.2 (10.3)
Age at diabetes diagnosis, years		15.1 (7.7)	16.0 (8.4)		60.0 (12.5)	59.4 (10.9)
Smokers		5,794 (13.8)	31 (22.8)		86,348 (15.8)	1,264 (21.3)
BMI, kg/m^2		25.3 (4.4)	28.1 (6.2)		30.2 (5.6)	30.5 (5.3)
Systolic blood pressure, mmHg		124.9 (16.0)	138.6 (19.7)		137.4 (17.2)	138.1 (17.9)
Diastolic blood pressure, mmHg		73.0 (9.1)	77.7 (11.5)		78.8 (10.0)	80.5 (10.7)
Socioeconomic factors						
Education						
Elementary school	76,787 (34.9)	13,329 (30.1)	37 (24.7)	201,830 (31.3)	237,605 (37.5)	2,244 (31.8)
Upper secondary school	95,685 (43.5)	20,777 (46.9)	89 (59.3)	269,983 (41.8)	273,639 (43.2)	3,419 (48.4)
College	47,582 (21.6)	10,216 (23.0)	24 (16.0)	173,617 (26.9)	121,691 (19.2)	1,403 (19.9)
Marital status						
Married	54,767 (24.1)	11,612 (25.6)	55 (35.9)	362,404 (55.3)	349,150 (54.0)	3,570 (49.7)
Divorced	13,339 (5.9)	3,055 (6.7)	27 (17.6)	113,579 (17.3)	113,531 (17.5)	1,657 (23.1)
Single	157,629 (69.2)	30,194 (66.6)	68 (44.4)	113,780 (17.4)	111,841 (17.3)	1,347 (18.7)
Widowed	1,955 (0.9)	453 (1.0)	3 (2.0)	65,220 (10.0)	72,622 (11.2)	612 (8.5)
Place of birth						
Sweden	193,503 (85.0)	41,402 (91.4)	134 (87.6)	561,087 (85.7)	508,800 (78.6)	5,429 (75.6)
Europe	15,925 (7.0)	2,000 (4.4)	8 (5.2)	64,936 (9.9)	78,693 (12.2)	1,108 (15.4)
Rest of the world	18,245 (8.0)	1,910 (4.2)	11 (7.2)	28,931 (4.4)	59,609 (9.2)	648 (9.0)
Mean income*	1,172 (1,663)	1,359 (1,731)	1,491 (976)	2,297 (7,172)	1,995 (5,635)	2,038 (1,684)
Laboratory parameters						
Triglycerides, mmol/L		1.15 (0.83)	2.19 (1.47)		1.87 (1.15)	2.54 (1.62)
Cholesterol, mmol/L		4.68 (0.97)	7.75 (1.44)		4.95 (1.11)	7.44 (1.36)
HDL cholesterol, mmol/L		1.54 (0.46)	1.41 (0.43)		1.26 (0.39)	1.25 (0.33)
LDL cholesterol, mmol/L		2.64 (0.82)	5.48 (1.18)		2.88 (0.97)	5.22 (1.11)
HbA_{1c}, mmol/mol		64.9 (16.3)	75.7 (18.5)		54.0 (15.6)	57.4 (19.3)
Creatinine, mmol/L		79.8 (46.8)	99.4 (55.8)		79.2 (29.6)	76.8 (31.5)
Estimated GFR, mL/min/1.73 m^2		86.3 (29.1)	86.2 (29.2)		76.8 (24.0)	76.1 (24.6)
Medical history						
Any ASCVD†	1,669 (0.7)	2,688 (5.9)	69 (45.1)	73,404 (11.2)	138,015 (21.3)	2,834 (39.4)
Coronary artery disease	1,883 (0.8)	2,158 (4.7)	54 (35.3)	59,484 (9.1)	113,680 (17.5)	2,410 (33.5)
Myocardial infarction	884 (0.4)	1,044 (2.3)	28 (18.3)	28,324 (4.3)	58,467 (9.0)	1,443 (20.1)
Ischemic stroke	747 (0.3)	706 (1.6)	19 (12.4)	25,942 (4.0)	40,586 (6.3)	701 (9.7)
Peripheral artery disease	257 (0.1)	1,064 (2.3)	27 (17.6)	7,916 (1.2)	16,034 (2.5)	338 (4.7)
Heart failure	531 (0.2)	694 (1.5)	12 (7.8)	21,276 (3.2)	43,392 (6.7)	567 (7.9)
Medication						
LLT	1,282 (1.2)	7,166 (16.1)	134 (87.6)	88,862 (17.1)	300,111 (46.5)	6,435 (89.4)
Antihypertensive treatment	688 (0.6)	832 (4.0)	7 (10.9)	11,481 (7.5)	20,249 (16.6)	90 (19.1)

Data are *n* (%) or mean (SD). GFR, glomerular filtration rate. *Income in 100 Swedish krona (SEK)/year; 100 SEK is equivalent to U.S. $11.65. †ASCVD includes coronary artery disease, ischemic stroke, and peripheral artery disease. Each patient with diabetes (1:5 for type 1 and 1:1 for type 2) was matched with control subjects according to age, sex, and county of residence. Matching was performed at the time of the patient's entry into the NDR.

The proportions of LLT dispensed on an annual basis, from 2006 to 2020, to patients with and patients without phenotypic FH are presented in Fig. 3. The proportion of patients using any combination of LLT was higher in those with phenotypic FH, in both types of diabetes ($P < 0.0001$ for all comparisons) (Supplementary Tables 11 and 12). In 2020, 83% (95% CI 75–91) of patients with type 1 diabetes and phenotypic FH were using any LLT, compared with 39% (95% CI 38–39) of that cohort without FH. The proportions of patients in the cohort with type 2 diabetes, with or without phenotypic FH, using any LLT were 85% (95% CI 84–86) and 66% (95% CI 66–66), respectively.

More intense treatment strategies were used by patients with phenotypic FH, with a wider use of high-intensity statin therapy and two or more classes of an LLT. In 2020, 57% (95% CI 46–67) of patients with type 1 diabetes and phenotypic FH were using a high-intensity statin therapy, while 24% (95% CI 15–33) were using two or more LLT compared with 14% (95% CI 13–14) and 3% (95% CI 3–3), respectively, in those without FH. In the cohort with type 2 diabetes, the proportions of patients with phenotypic FH using a high-intensity statin therapy and/or two or more LLT were 50% (95% CI

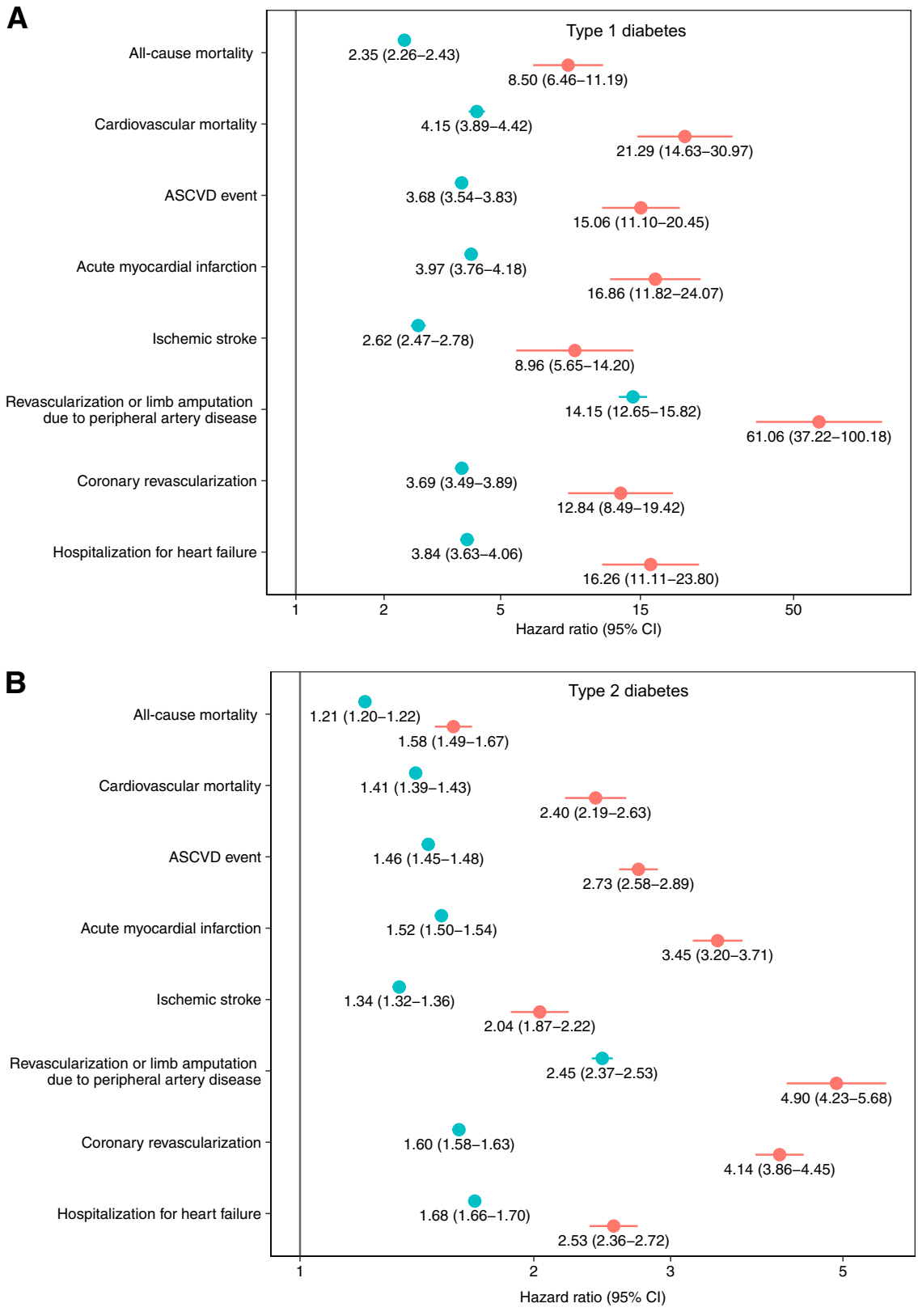

Figure 1—HRs for mortality and cardiovascular outcomes for patients with diabetes. Patients with type 1 diabetes (*A*) and type 2 diabetes (*B*), with or without phenotypic FH, were compared with matched control subjects without diabetes from the Swedish population. The median follow-up time was 14.1 years for patients with type 1 and 7.9 years for patients with type 2 diabetes. Analyses were based on Cox regression and adjusted for age, sex, and socioeconomic factors. An ASCVD event was defined as acute myocardial infarction, ischemic stroke, or revascularization or limb amputation due to peripheral artery disease. Blue circles, without FH; red circles, phenotypic FH.

Table 2—HRs for mortality and cardiovascular outcomes for patients with phenotypic FH

	Type 1 diabetes without FH (reference)	Type 1 diabetes with FH, HR (95% CI)	*P* value	Type 2 diabetes without FH (reference)	Type 2 diabetes with FH, HR (95% CI)	*P* value
All-cause mortality	1	3.53 (2.77–4.51)	<0.0001	1	1.29 (1.22–1.37)	<0.0001
Cardiovascular mortality	1	4.71 (3.40–6.53)	<0.0001	1	1.67 (1.53–1.83)	<0.0001
ASCVD event	1	3.80 (2.94–4.91)	<0.0001	1	1.82 (1.72–1.93)	<0.0001
Acute myocardial infarction	1	4.10 (2.98–5.63)	<0.0001	1	2.22 (2.06–2.38)	<0.0001
Ischemic stroke	1	3.21 (2.10–4.89)	<0.0001	1	1.48 (1.36–1.61)	<0.0001
Revascularization or limb amputation due to peripheral artery disease	1	4.25 (2.69–6.69)	<0.0001	1	1.99 (1.72–2.30)	<0.0001
Coronary revascularization	1	3.46 (2.41–4.97)	<0.0001	1	2.51 (2.34–2.69)	<0.0001
Hospitalization for heart failure	1	3.86 (2.76–5.39)	<0.0001	1	3.86 (2.76–5.39)	<0.0001

Analyses were based on Cox regression and adjusted for age, sex, and socioeconomic factors.

49–52) and 16% (95% CI 15–17), respectively, while the proportions in patients without FH were 21% (95% CI 21–21) and 3% (95% CI 3–3), respectively.

When identifying phenotypic FH in each cohort, an imputed correction factor was used (before DLCN scoring) to calculate the untreated LDL-cholesterol levels in 9.7% of cases in the cohort with type 1 diabetes and in 11.8% of cases in the cohort with type 2 diabetes. A sensitivity analysis was performed to verify that the imputed data did not affect the outcomes of the analysis; no major differences were observed (Supplementary Table 8). A sensitivity analysis was also made to verify that the age difference observed between control subjects and the phenotypic FH group with type 1 diabetes did not influence the outcome analysis. The HRs for fatalities and cardiovascular outcomes displayed a comparable pattern (Supplementary Table 12).

CONCLUSIONS

Diabetes and the hereditary dyslipidemia, FH, are diseases that induce and compound the development of ASCVD. Using data from one of largest and most comprehensive diabetes registries globally, this study demonstrates that patients with both diabetes and phenotypic FH are substantially more at risk for mortality and cardiovascular morbidity than patients with diabetes alone and matched control subjects from the general population. These results also highlight that the additional cardiovascular risk conferred by FH is clinically relevant in the vulnerable populations of patients with diabetes who are already under active risk-factor management.

The prevalence of phenotypic FH observed in this study's nationwide cohort of patients with type 1 diabetes (0.33%) was similar to the prevalence in the general population (0.32%) (6,7). However, the prevalence in the cohort with type 2 diabetes was three times higher than expected (1.10%), suggesting that the register-based method used in this study to identify FH might have wrongly diagnosed a proportion of those patients as having phenotypic FH. However, it should be acknowledged that the key characteristics of FH, elevated LDL cholesterol (5–5.5 mmol/L) and the presence of ASCVD (~40%), were similar at baseline between the two cohorts with diabetes (type 1 and type 2) and phenotypic FH. The fundamental differences in the pathophysiology of type 1 and type 2 diabetes, in terms of the age of onset, insulin resistance, and glycemic control, limit the capacity to make nonconfounded comparisons between each population. Diagnostic score algorithms cannot completely discriminate between monogenic caused disease and phenotypic FH, but both groups have substantial risk for ASCVD (20).

Cardiovascular disease is a leading cause of death for patients with type 1 and type 2 diabetes (2,21). Similarly, the lifetime risk to develop ASCVD in an individual with FH may be >90%, at least if primary preventive LLT is not initiated (8). In this study, the risk of cardiovascular mortality was almost fivefold times greater in patients with type 1 diabetes and phenotypic FH when compared with the risk in those with diabetes alone. In that same comparison, the risk of an ASCVD event was increased fourfold in patients with type 1 diabetes and FH. In patients with type 2 diabetes and phenotypic FH, the risk of cardiovascular mortality and an ASCVD event were 1.7-fold and 1.8-fold, respectively. Observations from smaller cross-sectional studies (11,12,14,16) have shown 1.5–6-fold increases in the risk of suffering from a cardiovascular event in individuals with FH and metabolic syndrome or diabetes compared with those with FH alone; ultimately, emphasizing the detrimental impact of having both traits. Data from the Familial Hypercholesterolemia Studies Collaboration (9) demonstrate that coronary artery disease (17.4%) was the most prevalent form of cardiovascular disease in patients with FH at enrollment into the registry, followed by peripheral artery disease (5.2%) and stroke (2.1%). In comparison, the current study in patients with diabetes and phenotypic FH also reports that coronary artery disease was the most prevalent preexisting cardiovascular condition at baseline, but by almost twofold.

It is estimated that 50% of patients with diabetes have underlying peripheral artery disease, but it often remains undiagnosed and without the classical preceding symptoms until presentation, when there can be severe tissue loss or limb amputation (22). Patients with genetically confirmed FH have recently been shown in a prospective register-based study to have a threefold increased risk of peripheral artery disease compared with the general population (23). In the

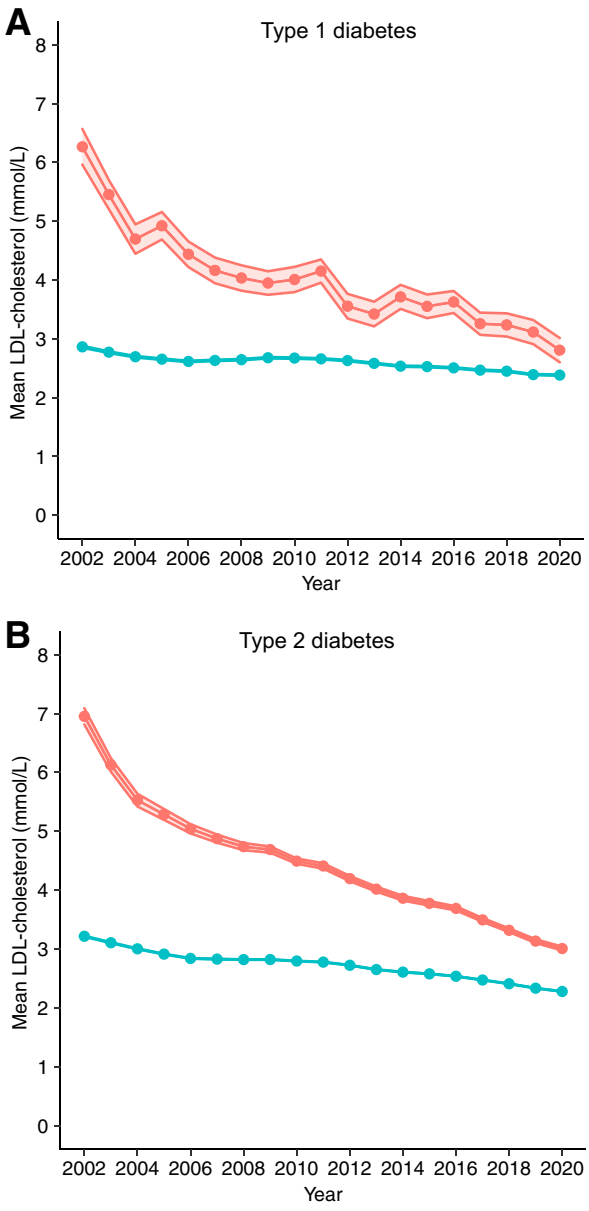

Figure 2—LDL-cholesterol levels in patients with type 1 (*A*) or type 2 (*B*) diabetes. The annual estimated mean LDL-cholesterol levels and the corresponding 95% CIs are presented for each cohort with diabetes, stratified by the presence of FH. Blue circles, without FH; red circles, phenotypic FH.

current study, patients with type 1 or type 2 diabetes who did not have phenotypic FH had a severely elevated risk of a peripheral artery disease event compared with matched control subjects. This risk was exacerbated in patients with a diabetes and phenotypic FH regardless of diabetes type. The exceptionally elevated risk of a peripheral artery disease event in patients with type 1 diabetes, beyond that observed in patients with type 2 diabetes, could be partly explained by an increased incidence at baseline. Additionally, patients with type 1 diabetes have longer diabetes duration and, typically, poorer glycemic control than patients with type 2 diabetes, factors that only increase the risk of aggravated peripheral artery disease (24).

The detrimental cardiovascular effects of diabetes and FH can be mitigated by global risk factor management and LLT in primary prevention, respectively (3,25,26). Given that LDL cholesterol is a pivotal and modifiable risk factor in patients with FH (27), the elevated LDL-cholesterol levels observed in patients with phenotypic FH, beyond that of the goal stated in lipid management guidelines (28), highlights the need to intensify LLT in order to improve cardiovascular outcomes. It is encouraging that the use of high-intensity statins increased fourfold during the study period in patients with phenotypic FH in both cohorts of diabetes, possibly reflecting new evidence and updates to clinical practice guidelines (28,29). However, lowering LDL cholesterol to <1.8 mmol/L in patients with FH remains daunting. Data from the Familial Hypercholesterolemia Studies Collaboration indicate that monotherapy is not enough to achieve that goal, but the use of two or even three classes of LLT in combination increases the probability significantly (9).

There are several limitations to this study. Phenotypic FH was identified in the study cohort using a truncated version of the DLCN criteria, not accounting for family history of cardiovascular disease or clinical signs of FH. However, the omittance of any parameter of the DLCN criteria will only yield a more conservative score that underestimates the proportion of individuals with phenotypic FH. The gold standard for diagnosing FH is genetic testing, but the most common methods used worldwide are still scoring-based algorithms such as the DLCN criteria, the Simon Broome Register criteria and the MEDPED (Make Early Diagnosis to Prevent Early Death) criteria (30). Truncated DLCN criteria have been used in registry-based research before in the general population (31) and in cohorts with coronary disease (32) and by extraction from electronic medical records (33). The DLCN criteria was also used for the diagnosis of FH in the world's largest FH registry, the Familial Hypercholesterolemia Studies Collaboration, with 75% of individuals diagnosed with probable (6–8 points) or definite FH (>8 points) (9).

In cases in which only a treated LDL-cholesterol value was available for DLCN scoring, it was corrected by calculating an untreated LDL-cholesterol value according to the dispensed LLT. Indeed, this increases imprecision when identifying phenotypic FH due to variations in each patient's response to the LLT. The difference in the prevalence of phenotypic FH between the two cohorts with type 2 diabetes remains unexplained, and a lack of data for genetically confirmed FH diagnoses limits the possibility to validate the register-based method used to identify phenotypic FH in this

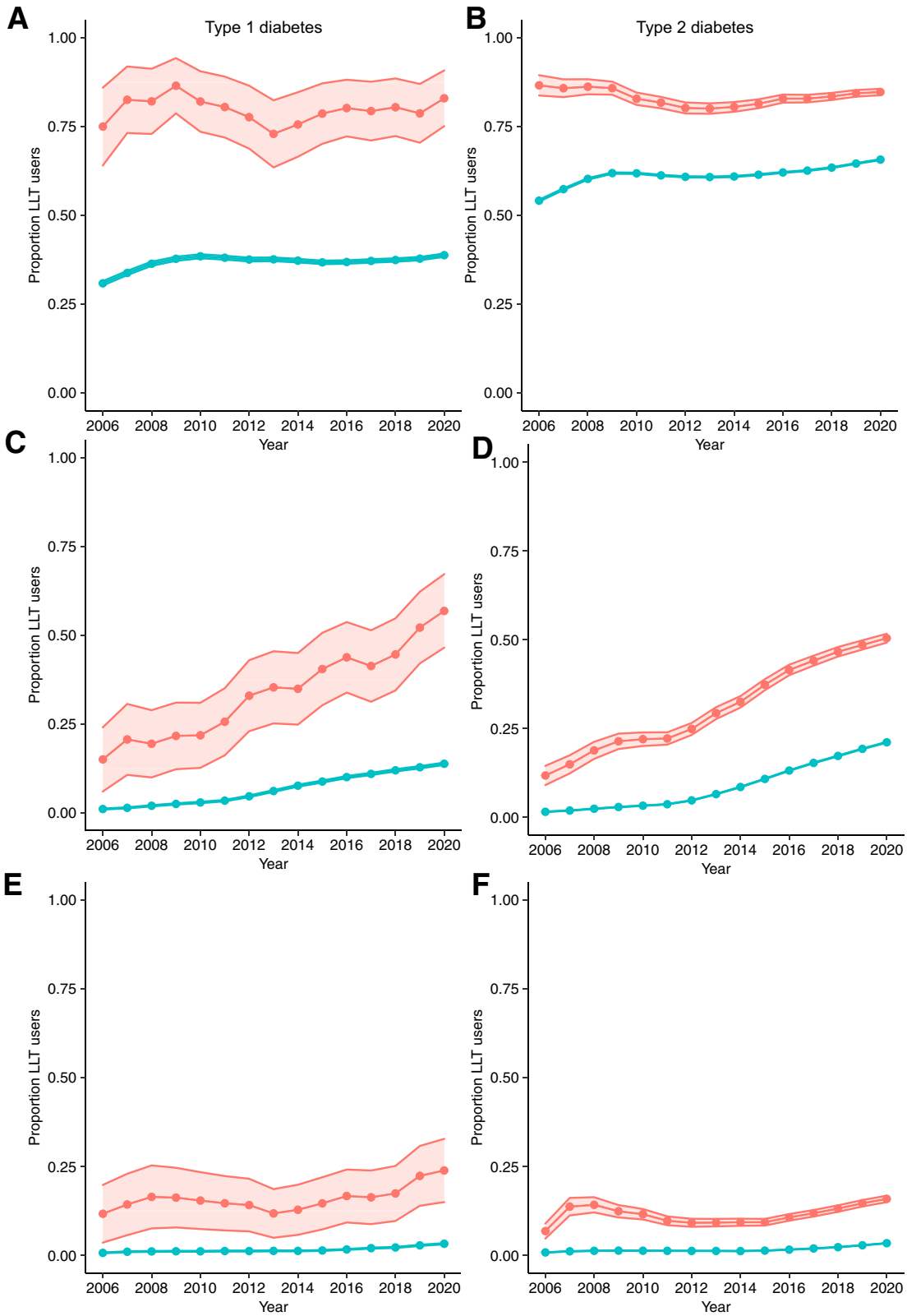

Figure 3—Proportion of patients with type 1 (*A*, *C*, and *E*) or type 2 diabetes (*B*, *D*, and *F*) using LLT. Each cohort is stratified by the presence of FH. Drug classes of interest included statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors. High-intensity statin therapy is defined as ≥40 mg atorvastatin or ≥20 mg rosuvastatin daily. Blue circles, without FH; red circles, phenotypic FH.

study. However, analyses were conducted on a large study population covering most of the patients with diabetes in Sweden, strengthening the findings of this study. The age difference observed between the group with phenotypic FH and without FH and type 1 diabetes is also a limitation because it cannot be entirely explained. A future diabetes

study with genetically confirmed FH cases would help to better understand the differences in patient characteristics between FH and non-FH groups, which is restricted with the current study design. In conclusion, the combination of diabetes and FH confer a substantial increase in the incidence of adverse cardiovascular outcomes in both types of diabetes, despite background risk factor management routinely performed in patients with diabetes. Ultimately, this highlights the need for intensified LLT, in primary or secondary prevention, to meet LDL-cholesterol goals and improve cardiovascular prognosis.

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