Association Between Use of Lipid-Lowering Therapy and Cardiovascular Diseases and Death in Individuals With Type 1 Diabetes

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Christel Hero,[1] Araz Rawshani,[1] Ann-Marie Svensson,[2] Stefan Franzén,[2] Björn Eliasson,[1] Katarina Eeg-Olofsson,[1] and Soffia Gudbjörnsdottir[1,2]

OBJECTIVE

To evaluate the effect of lipid-lowering therapy (LLT) in primary prevention on cardiovascular disease (CVD) and death in type 1 diabetes.

RESEARCH DESIGN AND METHODS

We used the Swedish National Diabetes Register to perform a propensity score–based study. Propensity scores for treatment with LLT were calculated from 32 baseline clinical and socioeconomic variables. The propensity score was used to estimate the effect of LLT in the overall cohort (by stratification). We estimated risk of acute myocardial infarction, stroke, coronary heart disease, and cardiovascular and all-cause mortality in individuals with and without LLT using Cox regression. A total of 24,230 individuals included in 2006–2008 with type 1 diabetes without a history of CVD were followed until 31 December 2012; 18,843 were untreated and 5,387 treated with LLT (97% statins). The mean follow-up was 6.0 years.

RESULTS

The propensity score allowed balancing of all 32 covariates, with no differences between treated and untreated after accounting for propensity score. Hazard ratios (HRs) for treated versus untreated were as follows: cardiovascular death 0.60 (95% CI 0.50–0.72), all-cause death 0.56 (0.48–0.64), fatal/nonfatal stroke 0.56 (0.46–0.70), fatal/nonfatal acute myocardial infarction 0.78 (0.66–0.92), fatal/nonfatal coronary heart disease 0.85 (0.74–0.97), and fatal/nonfatal CVD 0.77 (0.69–0.87).

CONCLUSIONS

This observational study shows that LLT is associated with 22–44% reduction in the risk of CVD and cardiovascular death among individuals with type 1 diabetes without history of CVD and underlines the importance of primary prevention with LLT to reduce cardiovascular risk in type 1 diabetes.

People with type 1 diabetes have a documented shorter life expectancy than the general population without diabetes (1). Cardiovascular disease (CVD) is the main cause of the excess morbidity and mortality, and despite advances in management and therapy, individuals with type 1 diabetes have a markedly elevated risk of cardiovascular events and death compared with the general population (2).

Lipid-lowering treatment with hydroxymethylglutaryl-CoA reductase inhibitors (statins) prevents major cardiovascular events and death in a broad spectrum of patients (3,4). The Cholesterol Treatment Trialists' Collaborators (CTT) meta-analysis

[1]Institute of Medicine, University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden
[2]Swedish National Diabetes Register, Västra Götalandsregionen, Gothenburg, Sweden

Corresponding author: Christel Hero, christel.hero@vgregion.se.

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of statins in 18,686 subjects with diabetes (type 1 and 2) demonstrated 21% reduction in major cardiovascular events for each 1.0 mmol/L (38.7 mg/dL) reduction in LDL cholesterol (5). The efficacy and safety of statins have shaped guidelines to advocate liberal prescribing and low thresholds for instituting therapy. The 2013 American College of Cardiology/American Heart Association cholesterol guidelines recommend moderate statin therapy for primary prevention of atherosclerotic CVD in individuals with type 1 diabetes aged 40–75 years with LDL cholesterol 70–189 mg/dL. They recommended use of an estimated 10-year risk score for atherosclerotic CVD $\geq$7.5% to help in the decision to consider high-intensity statin therapy (6).

National Institute for Health and Care Excellence guidelines on lipid modification in primary prevention of CVD, updated July 2014, suggest statin treatment be considered in all adults with type 1 diabetes and offered to all who are older than 40 years or who have had diabetes for $>$10 years (7).

The recommendations for patients with type 1 diabetes are principally based on subgroup analyses and extrapolations of the effects demonstrated in other populations. The CTT study was a meta-analysis including 1,466 patients with type 1 diabetes; mean age was 55 years, and 56% had a history of stroke, myocardial infarction, or peripheral artery disease. This is not representative for the patient population with type 1 diabetes that could be eligible for primary prevention with statins (5). Furthermore, the trial data are now up to 20 years old and diabetes management has changed considerably since. No study has thus far examined the effect of lipid-lowering medication in primary prevention in type 1 diabetes.

We hypothesized that primary prevention with lipid-lowering therapy (LLT) can reduce the incidence of cardiovascular morbidity and mortality in individuals with type 1 diabetes. The aim of the study was to examine this in a nationwide longitudinal cohort study of patients with no history of CVD.

RESEARCH DESIGN AND METHODS

Study Design and Setting

The Swedish National Diabetes Register (NDR) was initiated in 1996 as a tool for local quality assurance and as a feedback tool in diabetes care. Roughly 95% of all individuals age 18 years and older with type 1 diabetes in Sweden are included. Data are provided by nurses and physicians trained in register procedures and obtained at visits in outpatient clinics of hospitals nationwide. The study was approved by the regional ethics review board at the University of Gothenburg, Gothenburg, Sweden. All patients give informed consent before inclusion in the NDR.

Study Cohort

We identified 27,133 individuals with type 1 diabetes who had at least one listing in the NDR between 1 January 2006, and 31 December 2008. Type 1 diabetes was defined on the basis of epidemiologic data: treatment with insulin alone and a diagnosis at the age of 30 years or younger. We excluded 2,186 individuals with a history of CVD and another 717 individuals owing to missing data regarding use of statins on the index observation. The remaining 24,230 individuals were included. In the overall cohort, there were 18,843 untreated and 5,387 treated with lipid-lowering medication. We also included a one-to-one matched cohort with 4,025 untreated and 4,025 treated with lipid-lowering medication. A flowchart of the study design is presented in Supplementary Fig. 1.

Examinations at Baseline

Index date for each patient was the date at inclusion, at which time use of lipid-lowering medication and all other baseline characteristics were assessed. Earlier studies from the NDR have shown that $>$97% of the patients given lipid-lowering medication are treated with statins (8). Thirty-two baseline variables were used to estimate the propensity score. Age, sex, duration of diabetes, and age at onset of diabetes were assessed. Data on income in Swedish kronor (latest annual income, not adjusted for inflation), highest educational level, country of birth, and marital status were retrieved from the Longitudinal Integration Database for Health Insurance and Labor Market Studies, which is an official database administered by Statistics Sweden. Education was stratified into lower ($\leq$9 years), intermediate (10–12 years), and higher (college/university). Immigrant status was defined as Swedish native or immigrant, depending on country of birth. Marital categories were single (defined as never married and not cohabiting), married/cohabiting, divorced, or widowed.

Glycemic control was measured as HbA_{1c}. Analyses were quality assured nationwide by regular calibration with the high-performance liquid chromatography Mono-S method and then converted to millimoles per mole (International Federation of Clinical Chemistry) (9). Triglycerides and LDL, HDL, and total cholesterol were measured in millimoles per liter. LDL cholesterol values were calculated using Friedewald formula: LDL cholesterol = total cholesterol – HDL cholesterol – (0.45 $\times$ triglycerides), if triglycerides $<$4.0 mmol/L (10). Microalbuminuria was defined as two positive tests out of three samples taken within a year, with albumin-to-creatinine ratio 3–30 mg/mmol or urinary albumin 20–200 μg/min or 20–300 mg/L, and macroalbuminuria was defined as albumin-to-creatinine ratio $>$30 mg/mmol or urinary albumin $>$200 μg/min or $>$300 mg/L. Glomerular filtration rate (eGFR) was estimated with the MDRD equation (11). Systolic and diastolic blood pressure (BP) were calculated as the means of two supine readings (Korotkoff 1–5) with a cuff of appropriate size and after at least 5 min of rest. Anthropometric measures assessed were waist circumference (cm), weight (kg), and height (m). BMI was calculated as weight in kilograms divided by the square of height in meters. Method of insulin delivery was defined as either multiple daily injections or use of continuous subcutaneous insulin infusion. Use of lipid-lowering medications, antihypertension medications, and aspirin was dichotomized. Smoking was coded as present if the patient was a current smoker. Physical activity was graded from 1 to 5; never (level 1), less than 1 time per week (level 2), 1–2 times per week (level 3), regular 3–5 times per week (level 4), or daily (level 5), where "time" denotes periods of at least 30 min.

Comorbidities and events were collected before baseline examination and during follow-up by linking data from the NDR to the Swedish Inpatient Registry (IPR) and the Causes of Death Registry. The IPR was initiated in the 1960s and has nationwide coverage since 1987. It includes mandatory information on all principal and secondary hospital discharge diagnoses. The ICD system is used to classify diagnoses in the IPR.

Sensitivity and specificity for diagnoses of acute myocardial infarction (AMI), coronary heart disease (CHD), hospitalization for heart failure, atrial fibrillation, and stroke have been validated (12,13). The following comorbidities were assessed: heart failure (ICD-10 code I50, ICD-9 code 428), atrial fibrillation (ICD-10 code I48, ICD-9 code 427D), any cancer (ICD-10 codes C00–C97, ICD-9 codes 140–208), liver disease (ICD-10 codes K70–74), and mental disorders (ICD-10 codes F20–29 and F30–39); for renal dialysis and transplantation, the following codes were used: V42A, V45B, V56A, and V56 W (ICD-9) and Z94.0, Z49, and Z99.2 (ICD-10). Stage 5 chronic kidney disease was defined as the need for renal dialysis or renal transplantation or as an eGFR of $<$15 mL/min. Previous amputations were assessed via the NDR and the IPR.

Follow-up and End Points

Nonfatal CHD was defined as nonfatal myocardial infarction (ICD-10 code I21), unstable angina (ICD-10 code I20.0), percutaneous coronary intervention, and/or coronary artery bypass grafting. Fatal CHD was defined as ICD-10 codes I20–I25. Stroke was defined as nonfatal or fatal cerebral infarction, intracerebral hemorrhage, or unspecified stroke (ICD-10 codes I61–I64). CVD was defined as the composite of CHD or stroke—whichever came first. Cardiovascular mortality was defined as I00–I99. All individuals were followed from the baseline examination until a first incident event or death or, otherwise, until censor date 31 December 2012. Mean (SD) follow-up was 6.0 (1.0) years, with 146,553 person-years of follow-up.

Statistical Methods

A propensity score for treatment with lipid-lowering medication was estimated with logistic regression using all 32 baseline variables. The propensity score is the conditional probability of being treated, given the baseline characteristics. It is used to balance the covariates in the two groups in order to allow for causal inference (14). All continuous variables were modeled using restricted cubic splines with 3 df. Missing data were handled by means of multiple imputation; we used the multiple imputation by chained equations algorithm to impute 10 complete data sets and then calculated a propensity score in each complete data set (15). The average of the 10 propensity scores was used in the analysis.

We used the propensity score to perform a stratified analysis in the overall cohort and to perform a matched analysis. The matched procedure provides estimates of the mean treatment effect on the treated individuals (i.e., the mean effect of LLT on subjects who received LLT), while the analysis in the overall cohort provides estimates of the mean treatment effect (i.e., the mean effect of moving the entire population with type 1 diabetes from untreated to treated with lipid-lowering medication). We emphasize the stratified analysis, since it explores our main research question, namely, the benefit of prescribing LLT to individuals with type 1 diabetes not on such treatment.

Matching was done without replacement using a caliper width of 0.01. This caliper yielded the greatest overlap between the two groups in the distribution of propensity score (Supplementary Fig. 2). The matching procedure excluded 1,362 treated patients, leaving 4,025 treated individuals, who were matched to 1 control subject (not treated with lipid-lowering medication) each. Using a wider caliper (we tested calipers from 0.5 to 0.01) did not substantially reduce the number of excluded individuals but affected covariate balance, as judged by distribution of the propensity score. As evident from Supplementary Fig. 2, the distributions of propensity scores among treated and untreated in the matched cohort are perfectly aligned.

The ability of the propensity score to balance baseline characteristics was assessed by standardized differences, which is the difference in percentage between the means for the groups divided by the mutual SD. Standard differences of $<$10% (in absolute values) were considered nonsignificant (16). Standardized mean differences are additionally presented for a one-to-one matched cohort (with replacement) without a caliper defined. As a measure of balance, we have calculated a variance ratio, which is the mean ratio of the variance of a variable in treated subjects to the variance of the variable in the untreated subjects. The variance ratio should equal 1.0 if there is a perfect balance. Survival analyses were performed by Cox regression.

Crude event rates per 1,000 person-years, with exact Poisson CIs of 95%, were calculated for each outcome. Kaplan-Meier plots for all outcomes were obtained in the matched cohort. Cox regression was also performed in the overall cohort (n = 24,230) by stratifying on the propensity score, using eight strata.

RESULTS

Patient Characteristics at Baseline

Table 1 gives baseline characteristics for the overall cohort and the matched cohort. In the overall cohort, 18,843 did not have LLT, while 5,387 were treated with such medication. People with LLT were older, had longer diabetes duration, more often used antihypertension medication, and had a slightly higher HbA_{1c}. There were crude differences between the groups at baseline, but the propensity score allowed for satisfactory balancing of all 32 covariates, and there were no differences between treated and untreated in the matched cohort.

Absolute Risk of Events

The absolute risks of events in the overall and the matched cohort are given in Table 2. In the overall cohort, people on LLT had roughly four times higher crude event rates than the untreated patients. In the matched cohort, there were 17.3 and 18.2 fatal/nonfatal CVD events per 1,000 person-years among untreated and treated patients, respectively. For all-cause death, there were 13.2 and 9.9 deaths per 1,000 person-years among untreated and treated, respectively. These differences were reflected in the Kaplan-Meier curves (Fig. 1 and Supplementary Figs. 3–7).

Hazard Ratios for Events

Hazard ratios (HRs) for treated versus not treated with lipid-lowering medication in the overall and in the matched cohort with type 1 diabetes are given in Fig. 2. HRs in the overall cohort (lipid-lowering medication vs. no lipid lowering medication) were significant for all outcomes: for cardiovascular death, 0.60 (95% CI 0.50–0.72); for all-cause death, 0.56 (0.48–0.64); for fatal/nonfatal stroke, 0.56 (0.46–0.70); for fatal/nonfatal AMI, 0.78 (0.66–0.92); and for fatal/nonfatal CHD 0.85 (0.74–0.97).

HRs in the matched cohort (lipid-lowering medication vs. no lipid lowering medication) were significant only for all-cause death 0.74 (95% CI 0.62–0.88) (Fig. 2).

Table 1—Baseline data from the overall and one-to-one matched cohort

	Overall cohort						Matched cohort: one to one matched with a caliper of 0.01			
			Before matching†		One-to-one default matching‡					
	Untreated with lipid-lowering medication	Treated with lipid-lowering medication	SMD	Variance ratio	SMD	Variance ratio	Untreated with lipid-lowering medication	Treated with lipid-lowering medication	SMD	Variance ratio
n	18,843	5,387					4,025	4,025		
Patient characteristics										
Male sex, *n* (%)	9,984 (53.0)	3,051 (56.6)	10.36	0.99	−0.27	1.00	2,174 (54.0)	2,243 (55.7)	3.79	0.99
Age, years	36.3 (12.7)	50.4 (11.7)	144.65	0.84	−4.75	0.99	49.1 (12.0)	48.4 (11.7)	−5.92	1.01
Diabetes duration, years	21.0 (13.2)	34.0 (12.8)	129.44	0.93	−2.08	1.04	32.8 (12.7)	32.1 (12.8)	−5.67	1.02
Age at diagnosis, years	15.3 (7.6)	16.5 (7.9)	21.08	1.08	−3.65	0.97	16.2 (7.9)	16.3 (7.9)	0.44	0.99
Smoker, *n* (%)	2,275 (12.1)	689 (12.8)	3.09	1.05	2.09	1.05	521 (12.9)	512 (12.7)	−0.52	0.99
BMI (kg/m^2)	25.3 (4.3)	26.8 (4.5)	48.55	1.13	0.74	0.96	26.3 (4.4)	26.4 (4.4)	0.02	0.95
Weight (kg)	76.1 (14.9)	79.6 (15.9)	32.55	1.14	0.58	1.00	78.3 (15.6)	78.4 (15.3)	0.91	0.96
Height (m)	173.4 (9.6)	172.2 (9.6)	−16.93	0.99	−0.43	1.00	172.1 (9.5)	172.3 (9.5)	1.81	1.00
Waist (cm)	87.9 (12.5)	94.6 (13.0)	73.61	1.08	3.49	0.99	92.9 (12.9)	92.8 (12.6)	−0.76	0.96
Biomarkers										
HbA_{1c} (mmol/mol) / (%)	63.7 (14.9) / 8.0 (1.4)	65.7 (13.6) / 8.2 (1.3)	19.72	0.83	1.24	1.00	65.2 (13.7) / 8.1 (1.3)	65.1 (13.7) / 8.1 (1.3)	−0.13	0.98
eGFR (mL/min)	96.5 (26.5)	79.9 (27.3)	−84.87	1.06	−1.55	0.98	83.2 (25.9)	83.7 (26.4)	2.28	1.06
Systolic BP (mmHg)	124.5 (14.7)	134.8 (16.7)	91.57	1.29	−1.56	1.00	133.4 (16.4)	133.2 (16.5)	−1.59	0.99
Diastolic BP (mmHg)	73.1(8.9)	74.3 (9.7)	17.31	1.19	−2.77	1.03	74.3 (9.4)	74.4 (9.5)	0.39	1.03
Triglycerides (mmol/L)	1.07 (0.80)	1.34 (1.08)	45.01	1.82	−3.50	0.69	1.23 (0.95)	1.25 (0.96)	0.85	0.92
HDL (mmol/L)	1.62 (0.49)	1.65 (0.52)	7.35	1.14	1.58	0.92	1.69 (0.52)	1.67 (0.52)	−3.06	0.99
Total cholesterol (mmol/L)	4.70 (0.91)	4.89 (1.03)	29.63	1.28	−8.64	0.99	4.98 (0.98)	4.93 (0.98)	−5.91	1.01
LDL cholesterol (mmol/L)	2.60 (0.77)	2.66 (0.89)	9.70	1.36	−9.26	1.02	2.76 (0.85)	2.71 (0.86)	−5.42	1.02
Non-HDL cholesterol (mmol/L)	3.07 (0.88)	3.24 (1.03)	26.41	1.37	−9.42	0.99	3.30 (0.98)	3.26 (1.00)	−4.21	1.04
Physical activity, *n* (%)										
Never	5,081 (27.0)	1,441 (26.7)	−0.69	1,00	−0.02	1.00	1,159 (28.8)	1,162 (28.9)	0.81	1.01
<1 time/week	1,715 (9.1)	687 (12.8)	17.28	1.35	2.30	1.05	460 (11.4)	415 (10.3)	−3.97	0.91
1–2 times/week	2,015 (10.7)	641 (11.9)	5.46	1.10	−5.24	0.89	482 (12.0)	501 (12.4)	2.10	1.05
3–5 times/week	5,146 (27.3)	1,366 (25.4)	−6.23	0.95	−0.51	0.99	1,154 (28.7)	1,215 (30.2)	2.91	103
Daily	5,127 (27.2)	1,358 (25.2)	−6.39	0.95	2.07	1.02	856 (21.3)	841 (20.9)	−1.17	0.98
Treatment, *n* (%)										
Insulin pump	2,828 (15.0)	666 (12.4)	−10.65	0.85	0.17	1.00	544 (13.5)	516 (12.8)	−2.84	0.94
Antihypertensives	3,802 (20.2)	3,591 (66.7)	142.76	1.38	−1.54	1.01	2,314 (57.5)	2,292 (56.9)	−1.17	1.00
Aspirin	1,223 (6.5)	2,034 (37.8)	129.63	3.87	0.26	1.00	1,001 (24.9)	1,025 (25.5)	1.79	1.02
Coexisting conditions, *n* (%)										
Heart failure	66 (0.4)	83 (1.5)	21.54	4.35	−2.73	0.82	46 (1.1)	43 (1.1)	−2.36	0.82
Atrial fibrillation	60 (0.3)	63 (1.2)	16.94	3.64	−1.10	0.91	37 (0.9)	34 (0.8)	−2.50	0.79
Liver disease	43 (0.2)	12 (0.2)	−0.16	0.98	1.01	1.27	10 (0.2)	10 (0.2)	0.24	1.05
Cancer	176 (0.9)	100 (1.9)	12.29	1.97	0.26	1.02	82 (2.0)	69 (1.7)	−2.96	0.82
Psychiatric disease	387 (2.1)	130 (2.4)	3.52	1.17	0.32	1.02	102 (2.5)	102 (2.5)	0.20	1.01
Amputation	37 (0.2)	47 (0.9)	16.27	4.41	2.36	1.33	26 (0.6)	28 (0.7)	1.39	1.20

Continued on p. 5

Table 1—Continued

	Overall cohort						Matched cohort: one to one matched with a caliper of 0.01			
			Before matching†		One-to-one default matching‡					
	Untreated with lipid-lowering medication	Treated with lipid-lowering medication	SMD	Variance ratio	SMD	Variance ratio	Untreated with lipid-lowering medication	Treated with lipid-lowering medication	SMD	Variance ratio
Stage 5 kidney disease	177 (0.9)	195 (3.6)	30.83	3.75	−0.33	0.98	113 (2.8)	121 (3.0)	1.16	1.07
No albuminuria	15,925 (84.5)	3,257 (60.5)	−83.76	1.83	−2.18	1.01	2,686 (66.7)	2,673 (66.4)	−1.62	1.01
Microalbuminuria	2,184 (11.6)	1,243 (23.1)	46.60	1.73	0.80	1.01	894 (22.2)	893 (22.2)	0.90	1.01
Macroalbuminuria	766 (4.1)	892 (16.6)	69.98	3.54	1.95	1.04	445 (11.1)	464 (11.5)	1.61	1.04
Socioeconomic status										
Income (hundred kronor), *n* (%)	1,756 (1,953)	1,924 (1,865)	12.23	0.91	−0.56	0.94	1,955 (1,711)	1,958 (1,956)	0.20	1.26
Education ≤9 years, *n* (%)	2,738 (14.5)	1,207 (22.4)	30.17	1.40	0.01	1.00	840 (20.9)	810 (20.1)	−1.76	0.97
Education 10–12 years, *n* (%)	10,004 (53.1)	2,837 (52.7)	−1.21	1.00	1.50	1.00	2,063 (51.3)	2,125 (52.8)	3.42	1.00
College/university, *n* (%)	6,115 (32.5)	1,344 (24.9)	−22.99	0.85	−1.85	0.98	1,122 (27.9)	1,090 (27.1)	−2.26	0.98
Single, *n* (%)	11,293 (59.9)	1,771 (32.9)	−76.76	0.92	0.78	1.01	1,427 (35.5)	1,454 (36.1)	2.88	1.02
Divorced, *n* (%)	1,482 (7.9)	743 (13.8)	29.03	1.64	0.86	1.02	529 (13.1)	524 (13.0)	−0.63	0.99
Married, *n* (%)	5,905 (31.3)	2,750 (51.0)	58.17	1.16	−0.74	1.00	1,978 (49.1)	1,962 (48.7)	−1.49	1.00
Widowed, *n* (%)	164 (0.9)	124 (2.3)	18.68	2.61	−1.83	0.90	92 (2.3)	85 (2.1)	−3.13	0.83
Immigrant, *n* (%)	1,164 (6.2)	332 (6.2)	−0.08	1.00	−1.33	0.95	228 (5.7)	246 (6.1)	0.92	1.03

Data are means (SD) for continuous variables and frequencies (percent) for categorical variables. Income is given in hundred kronor (Swedish currency). SMD, standardized mean difference: difference between the means for the two groups divided by the mutual SD. Standard differences of <10 (absolute value) are considered nonsignificant. Variance ratio: the mean ratio of the variance of a variable in treated subjects to the variance of the variable in untreated subjects; should equal 1.0 if there is perfect balance. †Standardized mean differences in the unmatched overall cohort. ‡Standardized mean differences in the overall cohort after 1-to-1 matching without use of caliper. For the matched analysis we use the cohort obtained with a caliper of 0.01.

CONCLUSIONS

This nationwide observational study of patients with type 1 diabetes in Swedish clinical practice with a mean follow-up of 6 years shows that treatment with lipid-lowering medication in primary prevention reduces the incidence of cardiovascular death, all-cause death, CVD, stroke, CHD, and AMI among individuals with type 1 diabetes. To our knowledge, this is the first study to explore the effect of lipid-lowering medication among persons with type 1 diabetes with no previous CVD. We report that the risk of all-cause death and stroke in the overall cohort was almost halved for persons on LLT. The risk of cardiovascular death was reduced by 40%, while the reduction for AMI and CHD was 22% and 15%, respectively.

From the NDR, we can retrieve information on whether the individuals included in the study are treated with lipid-lowering medication but we cannot differentiate what kind of medication, although a previous study from the NDR has shown that >97% of lipid-lowering medication consists of statins (8).

We have estimated the effect of LLT in the overall cohort as well as in a one-to-one matched cohort. We think both analyses add valuable information; however, the analysis in the overall cohort addresses the more difficult clinical question of whether individuals who today are not treated with LLT would benefit from treatment. The results from the overall cohort describe the effect for the whole population if everyone had been allocated to LLT and clearly shows that such treatment markedly reduces the risk for all outcomes.

We observed these findings among rather young persons with type 1 diabetes (overall mean age 39.4 years). The analysis in the overall cohort indicates that treating such a population with diabetes with LLT could substantially reduce cardiovascular morbidity and mortality. This is noteworthy, since current guidelines recommend prescribing LLT to patients aged 40 years or older. However, our analyses did not specifically examine patients aged 40 years or younger due to the relatively few events in that age range (there were 92 deaths among patients aged 40 years or below).

Results from the matched cohort, on the other hand, show the effect of lipid-lowering medication among those who

Table 2—Incidence rates of all outcomes in the overall and matched cohort

	Fatal/nonfatal CVD		Fatal/nonfatal CHD		Fatal/nonfatal AMI		Fatal/nonfatal stroke		CV death		Total death	
	*n**	Rate (95% CI)†	*n*	Rate (95% CI)	*n*	Rate (95% CI)	*n*	Rate (95% CI)	*n*	Rate (95% CI)	*n*	Rate (95% CI)
Overall cohort												
Untreated	645	5.72 (5.29, 6.18)	477	4.23 (3.86, 4.63)	315	2.8 (2.5, 3.12)	206	1.83 (1.59, 2.1)	253	2.25 (1.98, 2.54)	493	4.38 (4.0, 4.78)
Treated	707	22.98 (21.32, 24.74)	568	18.46 (16.98, 20.05)	374	12.16 (10.96, 13.45)	188	6.11 (5.27, 7.05)	276	8.97 (7.94, 10.09)	412	13.39 (12.13, 14.75)
Matched cohort												
Untreated	405	17.31 (15.67, 19.08)	307	13.12 (11.69, 14.67)	202	8.63 (7.48, 9.91)	124	5.30 (4.41, 6.32)	178	7.61 (6.53, 8.81)	310	13.25 (11.82, 14.81)
Treated	428	18.25 (16.56, 20.06)	339	14.45 (12.96, 16.08)	209	8.91 (7.74, 10.2)	117	4.99 (4.13, 5.98)	149	6.35 (5.37, 7.46)	232	9.89 (8.66, 11.25)

*Number of events. †Rate denotes incidence rate per 1,000 patient-years; exact Poisson CIs of 95% were used.

actually received treatment compared with untreated control subjects. The protective effect of LLT was much less evident in the matched cohort. We believe this is due to exclusion of treated patients who were at the highest risk of events and would thus have had greatest benefit from treatment. Hence, the matched cohort constitutes subgroups of the original groups, since the matching procedure excluded a substantial proportion of individuals in both the treated and untreated populations. This explanation is confirmed by Supplementary Fig. 8, which shows that those who were excluded from the matched analysis had very high propensity scores. Nevertheless, this analysis showed a 26% reduction in risk of all-cause death for persons with type 1 diabetes on primary prevention with LLT. Treated and untreated patients had similar LDL cholesterol levels at baseline, but the fact that patients on LLT have presumably been exposed to higher LDL cholesterol levels prior to inclusion in the study could explain the findings that LLT was not associated with a reduced risk of cardiovascular outcomes in all analyses.

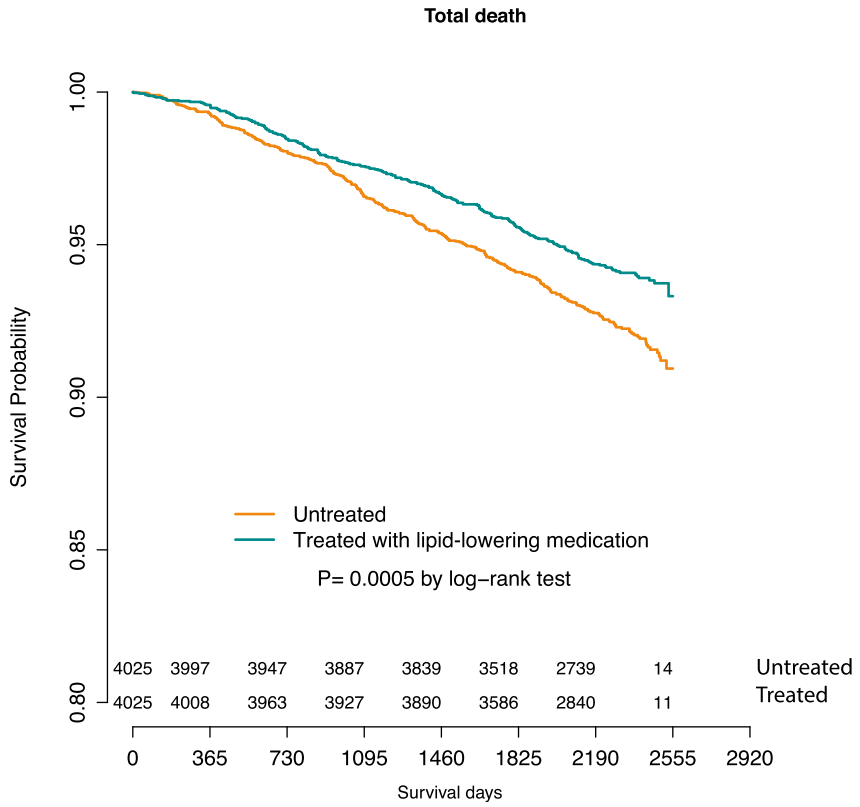

Figure 1—Kaplan-Meier curves for all-cause death in the matched cohort.

There are studies, both interventional and observational, proving that hyperlipidemia has a crucial role in the process of atherosclerosis and development of CVD (17,18). There is convincing support for LLT with statins in reducing the incidence of cardiovascular events in the general population and in people with type 2 diabetes, with a history of CVD, but also in primary prevention (19–21). An updated Cochrane review from 2013 including 18 randomized control trials of statin treatment in primary prevention showed statistically significant reductions in all-cause mortality, CVD, and stroke. It concludes that statins, even in the primary prevention setting, are likely to be cost-effective with the potential to improve patient quality of life (4). Current guidelines for LLT in type 1 diabetes are based on extrapolations from randomized controlled trials in individuals with type 2 diabetes, sometimes including a small cohort of patients with type 1 diabetes, or the general population, and often not representative in other aspects such as age and concurrent diseases (4,5).

Since trial-based data on the effect of LLT for primary prevention of CVD and cardiovascular death in individuals with type 1 diabetes are scarce, we believe that this observational study adds important information. Our study shows convincing effects of LLT in preventing all cardiovascular end points, even if the effect on reducing cardiovascular

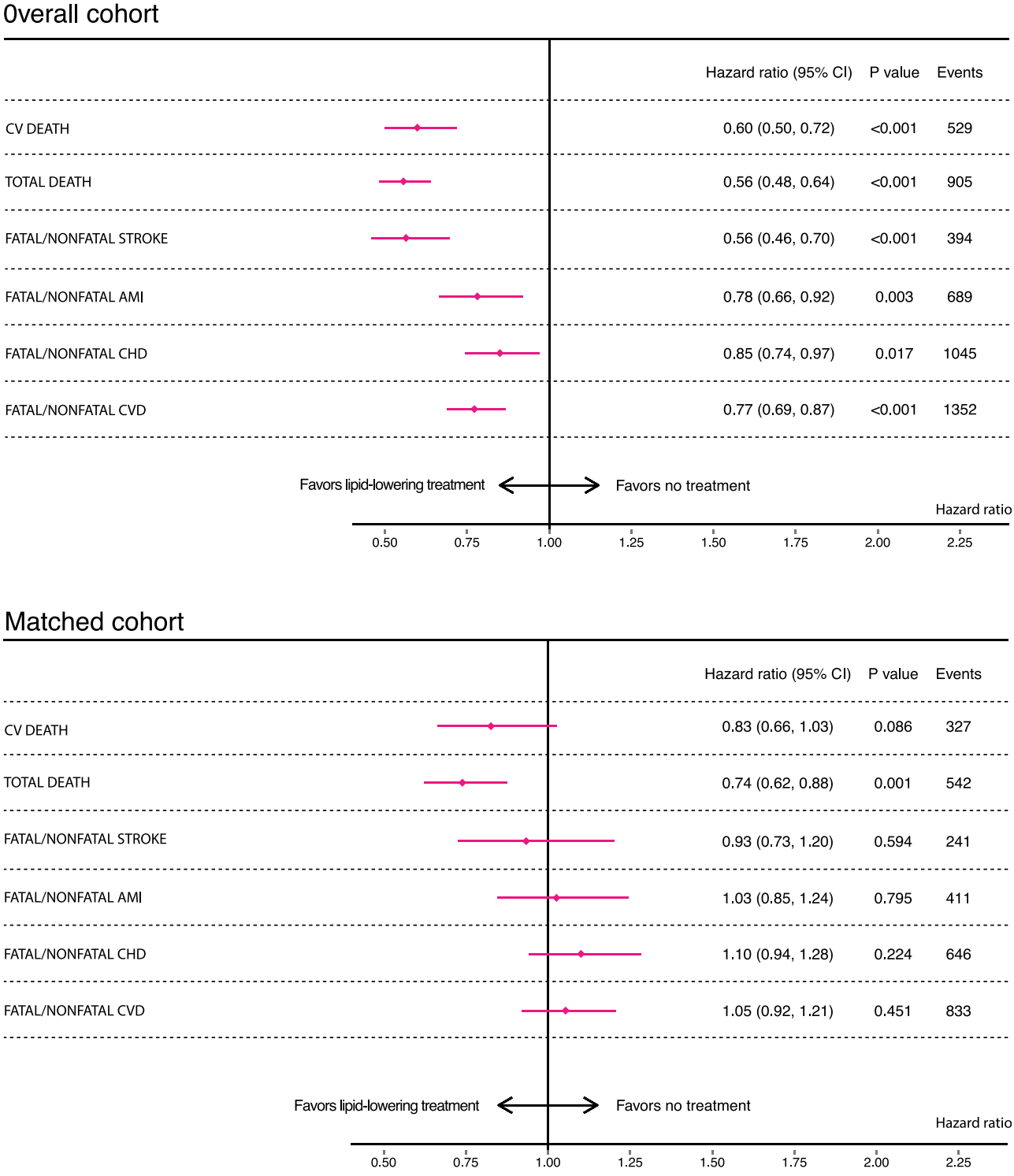

Figure 2—Effect of LLT in the overall cohort (n = 24,230) and in the matched cohort (n = 8,050). CV, cardiovascular. (A high-quality color representation of this figure is available in the online issue.)

morbidity, except for stroke, was lesser than the effect on cardiovascular death and all-cause death. The mean age of the individuals with treatment in the overall cohort and the matched cohort was 50 and 48 years and diabetes duration 34 and 32 years, respectively, and perhaps we need to start to take preventive measures earlier to be able to prevent cardiovascular morbidity. Could it be that we are mitigating the fatal effects of CVD but that we are too late in protecting against the effects of early development of atherosclerosis in our patients with type 1 diabetes? Studies examining benefit of statins in younger patients with type 1 diabetes are lacking, and we need more research in this area. Meanwhile, an emphasis on good risk factor control also in young patients seems warranted.

The strength of this study is the large sample size of patients with type 1 diabetes in clinical practice studied in a real-life setting and with a prospective approach, with detailed information on clinical characteristics as well as socioeconomic factors and laboratory measures. Obvious limitations are its nature as an observational study and the possibility of unknown confounders that we have not controlled for. There is always a risk for residual confounding; however, we have adjusted for most of the established CVD risk factors in our model and also balanced the cohort according to socioeconomic status. Also, we did not in this study examine the statin doses or degrees of LDL cholesterol lowering.

Summary

This observational study shows that LLT is associated with 22–44% reduction in the risk of CVD and cardiovascular death among individuals with type 1 diabetes without history of CVD. This is the first large observational study underlining the importance of intervention with LLT in primary prevention to reduce cardiovascular risk in type 1 diabetes.

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