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ORIGINAL RESEARCH

Impact of Change in High-Density Lipoprotein Cholesterol from Baseline on Risk for Major Cardiovascular Events

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ABSTRACT

Introduction: Low concentration of high-density lipoprotein cholesterol (HDL-C) has increasingly been recognized as a strong and independent predictor of cardiovascular risk. The aim of this study was to determine the association between change in HDL-C concentration from baseline and risk of a major cardiovascular event in a commercially insured population cohort with suboptimal HDL-C and low-density lipoprotein cholesterol (LDL-C) concentrations at baseline. ***Methods:*** A retrospective longitudinal survival analysis was conducted using claims data from a large, commercial US health plan. To be included, patients had to be ≥50 years of age on the index date (laboratory test date between January 1, 2000 and December 31, 2003 on which both their LDL-C and HDL-C were not at goal), be continuously enrolled for a minimum of 6 months prior to and 12 months after the index date, and had to have at least one other laboratory panel result within 1 year prior to the cardiovascular event or study disenrollment. Cox proportional hazards analysis was conducted to assess the association between change in HDL-C concentrations and risk of a major cardiovascular event (defined as a ≥1-day hospitalization for a cardiovascular disease [CVD] diagnosis or an invasive cardiovascular procedure) within 5 years of the index date, after adjusting for covariates. ***Results:*** A 0.026 mmol/L (1 mg/dL) increase in HDL-C from baseline was associated with a statistically significant 1.9% decreased risk of a major cardiovascular event ($P<0.0001$; hazard ratio: 0.981; 95% CI: 0.974, 0.989), after adjustment for covariates. ***Conclusion:*** Our finding of an inverse association between change in HDL-C concentrations and risk of a major cardiovascular event confirms previously reported results. Increasing HDL-C concentrations may serve as an effective measure for preventing future cardiovascular events.

Keywords: cardiovascular diseases; cholesterol; coronary heart disease; HDL; LDL

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INTRODUCTION

Researchers have studied numerous underlying risk factors associated with the occurrence of major cardiovascular events, including suboptimal lipid concentrations, obesity, hypertension, the presence of comorbidities, and smoking.[1-4] It has been well established that dyslipidemia is associated with excess risk of developing cardiovascular disease (CVD). A low concentration of high-density lipoprotein cholesterol (HDL-C), the second most common lipid abnormality in patients with CVD (~35%, incidence among men and ~40% among women),[4-6] has increasingly been recognized as a strong and independent predictor of cardiovascular risk.[6-17]

HDL-C, a complex of Apo-A lipoproteins, has antioxidative, antiproliferative, antithrombotic, and anti-inflammatory properties,[18,19] and is known to be protective against CVD by mediating the process of reverse cholesterol transport, which involves the transfer of excess cholesterol from macrophages in the peripheral tissues through the blood stream to the liver, where it metabolizes the cholesterol and excretes it into the bile.[19-21]

The Framingham Heart Study (FHS) was the first major study to demonstrate the inverse association between HDL-C concentration and cardiovascular risk, in a cohort of 2815 individuals 49 to 82 years of age who were followed up for approximately 4 years. This relationship was present at all concentrations of low-density lipoprotein cholesterol (LDL-C), but the highest risk of coronary heart disease (CHD) was associated with low HDL-C coupled with high LDL-C.[22] The FHS investigators also found that HDL-C was the strongest lipid predictor of coronary artery disease risk in men and women >49 years of age.[17]

Since the FHS was conducted, numerous epidemiological, mechanistic, and intervention studies have demonstrated that low HDL-C is a major cardiovascular risk factor and that raising HDL-C concentrations may be beneficial in terms of reducing this risk.[11-17] In prospective observational studies and retrospective case-control studies, low HDL-C concentrations have been consistently associated with increased risk for all forms of atherosclerotic disease and its clinical sequelae, including myocardial infarction, stroke, and sudden death. By contrast, high serum levels of this lipoprotein are associated with reduced risk for these outcomes.[18] In fact, it is estimated that >40% of coronary events occur in individuals with HDL-C <40 mg/dL.[20]

Data from several epidemiological studies emphasize that the risk factor associated with low HDL-C concentration is totally independent of LDL-C, ie, regardless of how low the LDL-C concentration is, a decrease in HDL-C increases the risk of CVD.[18,20,23] The results of a Cox regression analysis using data from the Framingham Offspring Study showed that the lower the pretreatment LDL-C level, the greater the impact of raising the HDL-C.[24] Results of prospective epidemiological studies,[12,25] as well as those reported in a meta-analysis of two major North American population-based studies and two randomized clinical trials,[26] demonstrate that every 0.026 mmol/L (1 mg/dL) increase in HDL-C was associated with a 2% to 3% decrease in CVD risk, independent of LDL-C and triglyceride concentrations. The importance of HDL-C as an independent and predictive risk factor for CVD and CHD also has been increasingly recognized in national and international treatment guidelines,[27] which recommend combining statin therapy with niacin or a fibrate to treat patients with multiple lipid abnormalities, particularly those with suboptimal HDL-C.[28-30] Fibrates reportedly increase HDL-C concentrations by 10%, and

nicotinic acid—the most effective agent to date—has been shown to increase HDL-C by 20% to 26%.[11,31]

All of the commonly used risk equations that have been adopted to predict the risk of CHD/CVD incorporate HDL-C concentrations as a predictor. These include the Framingham Risk Equation[32] (and the Adult Treatment Panel III, which calculates the 10-year risk of coronary events based on an adaptation of the original Framingham function),[33] SCORE (Systematic Coronary Risk Evaluation),[34] PROCAM (Prospective Cardiovascular Münster),[35] QRISK,[36,37] and the Joint British Societies Coronary Prediction Risk charts.[38] These established CVD risk equations, as well as modified versions of them incorporating additional risk factors, have been validated in community-based populations.[39-44] Incorporation of HDL-C into CVD risk assessment equations has proven to be of independent predictive value, and may appropriately guide classification of some patients from a lower- to a higher- risk grouping.[45]

Study Objective

The primary objective of the present study was to determine the association between change in HDL-C concentrations from baseline and risk of a major cardiovascular event in a commercially insured population cohort with suboptimal HDL-C and LDL-C concentrations at baseline.

MATERIALS AND METHODS

Study Design

A retrospective, longitudinal study was conducted using enrollment information and medical and pharmacy claims data from the i3 Ingenix LabRx administrative claims database of a large US health plan. The health plan comprises discounted fee-for-service independent practice association plans throughout the US, with a preponderance of members in the south and midwest. At the time the study was conducted, medical and pharmacy data were available for approximately 14 million health plan enrollees. The data were de-identified and accessed using techniques that are in compliance with the Health Insurance Portability and Accountability Act.[46] As no identifiable protected health information was extracted during the course of the study, institutional review board approval was not required.

Study Population Identification

Commercial health plan members were enrolled in the study if they met the following inclusion criteria: (1) ≥50 years of age on the index date (defined as the laboratory test date between January 1, 2000 and December 31, 2003 on which both their LDL-C and HDL-C were not at goal); (2) continuously enrolled for a minimum of 6 months prior to the index date and 12 months after the index date; and (3) at least one other complete lipid laboratory panel result within 1 year before the cardiovascular event or, if no event occurred, within 1 year before the end of their study enrollment (censorship).

Study Measures

Patient demographics and baseline clinical characteristics were derived from the enrollment and medical claims data. Baseline characteristics included continuous variables (age at index date, baseline HDL-C, LDL-C, triglycerides, total cholesterol, change in HDL-C, change in LDL-C, change in triglyceride, and change in total

cholesterol concentrations from baseline), and categorical variables (gender, presence of selected comorbidities, and occurrence of a major cardiovascular event prior to the index date). A major cardiovascular event was defined as a hospitalization with at least a one-night stay for any of the following CVD-related diagnoses (myocardial infarction, ischemic heart disease, cerebrovascular disease, atherosclerosis, aortic aneurysm, peripheral vascular disease) or any of the invasive cardiovascular procedures (angioplasty/stenting, cardiac catheterization, coronary artery bypass graft) coded with the International Classification of Diseases 9th Revision or Current Procedural Terminology 4th Edition codes listed in Table 1.

Analyses

A Cox proportional hazards model was used to assess the association between change in HDL-C concentrations from baseline and risk of the earliest future major cardiovascular event within 5 years of the date the lipid laboratory values were obtained (index date), adjusting for the following variables: LDL-C, HDL-C, and triglyceride concentrations; change in LDL-C and triglycerides from the index date; age; gender; and other covariates considered predictive of major cardiovascular events (ie, the presence of CVD, diabetes, angina, ischemic heart disease, hypertension, cardiac conduction disorder, congestive heart failure, or cerebrovascular disease at baseline).

RESULTS

Study Population Identification

A total of 1,388,813 individuals were identified who had at least one complete lipid panel result from the period January 1, 2000 to

Table 1. Definition of a major cardiovascular event.

Cardiovascular event	ICD-9 diagnosis and procedure codes, CPT-4 procedure codes
Myocardial infarction	ICD-9 diagnosis code 410.xx
Other ischemic heart diseases	ICD-9 diagnosis codes 411.xx, 414.xx
Angina	ICD-9 diagnosis codes 413.xx
Cerebrovascular disease	ICD-9 diagnosis codes 433.xx - 438.xx,
Atherosclerosis	ICD-9 diagnosis code 440.xx
Aortic aneurysm	ICD-9 diagnosis code 441.xx
Peripheral vascular disease	ICD-9 diagnosis code 443.9
CABG, angioplasty, catheterization, heart stenting (invasive cardiovascular procedures)	ICD-9 procedure codes: 36.1x, 36.2x, 36.01 - 36.09, 37.21 - 37.23, 38.12, 38.13, 38.18, 39.25, 39.26, 39.29, 39.50, 39.90, 88.48, 88.77
	CPT-4 procedure codes: 33510 - 33545, 33572, 34101, 34111, 34201, 34203, 35301, 35311- 35381, 35390, 35454, 35456, 35459, 35470, 35473, 35474, 35482, 35483, 35485, 35492, 35493, 35495, 35533, 35541, 35546, 35641, 35646, 35548, 35549, 35551-35571, 35654, 36230, 36240 - 36248, 75500, 75501, 75505 - 75507, 75509 - 75511, 75523, 75524, 75527, 75528, 75552-75556, 75710, 75716, 76499, 78460 - 78483, 92975, 92977, 92980 - 92984, 92995, 92996, 93501- 93536, 93542, 93543, 93539, 93540, 93545, 93547-93553, 93555, 93923, 93992

CABG=coronary artery bypass graft; CPT=Current Procedural Terminology; CVD=cardiovascular disease; ICD=International Classification of Diseases.

December 31, 2003. Of those, 312,279 patients had LDL-C and HDL-C concentrations that were not at goal. The flowchart in Figure 1 shows the numbers of patients who were excluded from participation in the study because they either did not meet the age requirement, were not enrolled in the health plan for at least 6 months pre-index and at least 12 months post-index, or did not have at least one other laboratory panel result within a year before the cardiovascular event, or within a year before the end of their study enrollment. The final study population comprised 21,257 patients.

Descriptive Statistics

The mean and median durations of follow-up were 1120 and 979 days, respectively (range, 18 to 2892 days). The mean time between baseline lipid profile assessment and the subsequent lipid measurement was 973.4 days (SD 601.7). Patients ranged from 50 to 84 years of age, and the mean age at index date was 59.3 years (Table 2). The majority (56.33%) of patients were female (Table 3). Mean baseline HDL-C was 1.02 mmol/L (39.4 mg/dL) (Table 2). The lowest HDL-C concentration was 0.59 mmol/L (23 mg/dL), and the highest was 1.27 mmol/L (49 mg/dL) (data not shown).

Hypertension was the most common comorbidity assessed at baseline, with a prevalence of 53.19%, and diabetes was the second most common, present in 22.75% of patients. Angina was the only other comorbidity that was present in more than 10% of the study patients (Table 3).

Figure 1. Sample selection schema. HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; pts=patients.

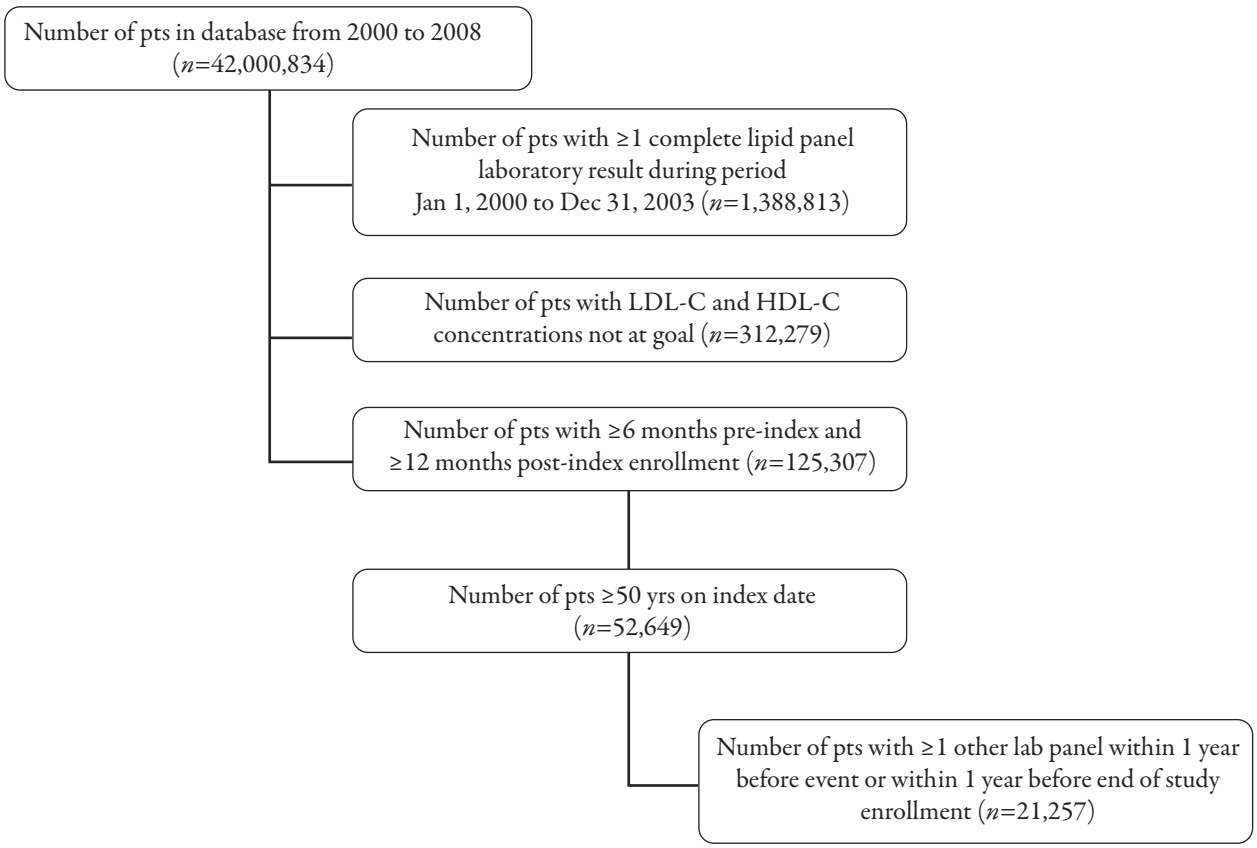

Table 2. Baseline characteristics: continuous variables (n=21,257).

Continuous variable	Mean	Lower CL (mean)	Upper CL (mean)	Range
Age at index date	59.3	59.1	59.4	50-84
Baseline HDL-C, mmol/L (mg/dL)	1.0 (39.4)	1.0 (39.3)	1.0 (39.5)	0.6-1.3 (23-49)
Baseline LDL-C, mmol/L (mg/dL)	3.5 (137.2)	3.5 (136.8)	3.6 (137.5)	2.6-5.8 (101-226)
Baseline triglycerides, mmol/L (mg/dL)	2.1 (187.0)	2.1 (186.0)	2.1 (188.0)	0.4-7.0 (35-619)
Baseline total cholesterol, mmol/L (mg/dL)	5.5 (214.1)	5.5 (213.7)	5.5 (214.6)	3.6-8.5 (141-330)
HDL-C change from baseline, mmol/L (mg/dL)	0.08 (3.2)	0.08 (3.1)	−0.09 (3.3)	−0.5-1.6 (−19-63)
LDL-C change from baseline, mmol/L (mg/dL)	−0.5 (−20.8)	−0.6 (−21.3)	−0.5 (−20.3)	−4.7-2.9 (−183-111)
Triglyceride change from baseline, mmol/L (mg/dL)	−0.2 (−19.0)	−0.2 (−20.0)	−0.2 (−18.0)	−5.7-5.4 (−508-479)
Total cholesterol change from baseline, mmol/L (mg/dL)	−0.6 (−21.5)	−0.6 (−22.0)	−0.5 (−20.9)	−5.2-3.2 (−202-123)

CL=confidence limit; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol.

Table 3. Baseline characteristics: categorical variables (n=21,257).

Categorical variable	Percentage of patients
Male	43.67
Diabetes	22.75
Myocardial infarction	1.79
Angina	14.42
Hypertension	53.19
Conduction disorder	8.75
Congestive heart failure	3.75
Cerebrovascular disease	0.57
Other ischemic heart disease	4.53
Baseline cardiovascular event	3.61

Risk Estimates

Parameter estimates and hazard ratios for all values are shown in Table 4, with upper and lower confidence limits provided for all variables.

Demographic Variables

A 1-year increase in age above 50 (at index date) was associated with a 3.9% increase in the probability of occurrence of a major cardiovascular event, after adjustment for other variables associated with cardiovascular risk (Table 4). Also, male gender was associated with a 33.1% increased risk of a major cardiovascular event compared with female gender. Both of these associations were statistically significant. With regard to comorbidities and their associated risks, patients with diabetes had a 73.1% increased risk of a major cardiovascular event compared with patients who did not have diabetes at baseline; and patients with hypertension had a 22.3% higher risk of a major cardiovascular event compared with patients who did not have hypertension at baseline.

Laboratory Values

There was a statistically significant association between change from baseline HDL-C and risk

Table 4. Cox proportional hazards model: odds of a major cardiovascular event.

Variable	Parameter estimate	Hazard ratio	HR lower CL	HR upper CL	*P*-value
HDL-C change from baseline	–0.01869	0.981	0.974	0.989	<0.0001
LDL-C change from baseline	0.00623	1.006	1.005	1.008	<0.0001
Triglyceride change from baseline	–0.0001190	1.000	0.999	1.001	0.7626
Gender	0.28574	1.331	1.169	1.515	<0.0001
Age at index date	0.03828	1.039	1.033	1.045	<0.0001
Baseline HDL-C	–0.03101	0.969	0.958	0.981	<0.0001
Baseline LDL-C	0.00834	1.008	1.006	1.010	<0.0001
Baseline triglycerides	0.00118	1.001	1.000	1.002	0.0027
Cardiovascular disease at baseline	0.64587	1.908	1.589	2.290	<0.0001
Diabetes at baseline	0.54866	1.731	1.562	1.919	<0.0001
Myocardial infarction at baseline	0.02233	1.023	0.818	1.278	0.8443
Angina at baseline	1.09163	2.979	2.642	3.359	<0.0001
Ischemic heart disease at baseline	0.12863	1.137	0.957	1.351	0.1432
Hypertension at baseline	0.20119	1.223	1.099	1.361	0.0002
Conduction disorder at baseline	0.12414	1.132	0.985	1.301	0.0798
Congestive heart failure at baseline	0.15837	1.172	0.988	1.389	0.0685
Cerebrovascular disease at baseline	0.52955	1.698	1.162	2.481	0.0062

CL=confidence limit; HDL-C=high-density lipoprotein cholesterol; HR=hazard ratio; LDL-C=low-density lipoprotein cholesterol.

of a major cardiovascular event occurring, as shown in Table 4. A 0.026 mmol/L (1 mg/dL) increase in HDL-C from baseline was associated with a significant 1.9% decrease in the odds of a major cardiovascular event occurring ($P<0.0001$; hazard ratio: 0.981; 95% CI: 0.974, 0.989), after adjustment for other variables associated with cardiovascular risk. Therefore, a 0.13 mmol/L (5 mg/dL) increase in HDL-C from baseline was associated with a 9.5% (1.9% multiplied by 5) decrease in risk of a major cardiovascular event.

Table 4 also shows that a 0.026 mmol/L (1 mg/dL) increase in LDL-C from baseline corresponded to a 0.6% increase in risk of a major cardiovascular event. Although higher baseline triglyceride concentrations were associated with a 0.1% increase in the risk of a major cardiovascular event, change from baseline triglyceride concentrations had no impact on the risk of a major cardiovascular event. Finally, Table 5 shows that a 0.026 mmol/L (1 mg/dL) increase from baseline in total cholesterol was associated with a 0.5% increase in the odds of a major cardiovascular event.

DISCUSSION

The primary objective of this study was to evaluate the association between change in HDL-C concentrations from baseline and risk of a major cardiovascular event in a cohort of patients with suboptimal HDL-C and LDL-C concentrations at baseline. To our knowledge, only one other claims-based analysis has evaluated this association; however, the focus of that study, by Nichols et al.,[47] was to examine whether the use of fibrate therapy in a general clinical setting provided cardiovascular benefits independent of changes in the traditional lipoprotein fractions.

Table 5. Cox proportional hazards model replacing HDL-C, LDL-C, and triglycerides with total cholesterol: odds of a major cardiovascular event.

Variable	Parameter estimate	Hazard ratio	HR lower CL	HR upper CL	*P*-value
Total cholesterol change from baseline	0.00453	1.005	1.003	1.006	<0.0001
Gender	0.56495	1.759	1.588	1.949	<0.0001
Age at index date	0.03750	1.038	1.032	1.044	<0.0001
Baseline total cholesterol	0.00719	1.007	1.005	1.009	<0.0001
Cardiovascular disease at baseline	0.62483	1.868	1.555	2.243	<0.0001
Diabetes at baseline	0.56867	1.766	1.595	1.955	<0.0001
Myocardial infarction at baseline	0.02719	1.028	0.823	1.284	0.8107
Angina at baseline	1.10392	3.016	2.675	3.400	<0.0001
Ischemic heart disease at baseline	0.13946	1.150	0.968	1.366	0.1129
Hypertension at baseline	0.20545	1.228	1.104	1.367	0.0002
Conduction disorder at baseline	0.12982	1.139	0.991	1.308	0.0667
Congestive heart failure at baseline	0.19250	1.212	1.022	1.437	0.0267
Cerebrovascular disease at baseline	0.55252	1.738	1.189	2.539	0.0043

CL=confidence limit; HDL-C=high-density lipoprotein cholesterol; HR=hazard ratio; LDL-C=low-density lipoprotein cholesterol.

Using Cox proportional hazards analysis, we determined that an inverse association between HDL-C concentration and cardiovascular risk does exist—and that it is statistically significant. After adjustment for other covariates, a 0.026 mmol/L (1 mg/dL) increase in HDL-C from baseline was associated with a 1.9% decrease in the risk of a major cardiovascular event (and a 0.13 mmol/L [5 mg/dL] increase in HDL-C from baseline was associated with a 9.5% decrease in the odds of a major cardiovascular event). The combination of this strong inverse HDL-C-risk relationship, along with the other significant risk findings involving LDL-C, age, gender, and comorbidities, is indicative of strong construct validity and serves as confirmation of earlier findings of an association between HDL-C concentration and cardiovascular risk, as reported in numerous epidemiological, mechanistic, and intervention studies.[11,12,15,17,18,20,23,25,26]

The only other retrospective claims-based analysis we identified that evaluated the association between HDL-C and cardiovascular risk (Nichols et al.[47]) reported findings consistent with ours, and, similar to our patient cohort, their study population also had low HDL-C concentrations at baseline. Nichols et al.[47] conducted a matched, retrospective cohort study using electronic records obtained from a large health maintenance organization in the northwestern United States. They used multivariate analysis to identify predictors of CVD incidence and to examine whether the use of fibrate therapy in a general clinical setting provided cardiovascular benefits independent of changes in the traditional lipoprotein fractions. These investigators found that, overall, cardiovascular risk was 26% lower for every 0.13 mmol/L (5 mg/dL) increase in HDL-C.

Low HDL-C concentration was the only significant predictor of coronary events in the multivariate Cox proportional hazards analysis by Koro et al.[14] They studied a cohort of 6928 patients in an urban primary care practice who had two or more lipid measurements obtained

between January 1985 and December 1997, and reported that a change in HDL-C from baseline was a significant (P<0.001) predictor of coronary events, with a hazard ratio of 0.93 (95% CI: 0.90, 0.97). After adjusting for covariates, a 0.26 mmol/L (10 mg/dL) higher baseline HDL-C was associated with an 11% (95% CI: 7%, 14%) lower risk of coronary events, and a 0.26 mmol/L (10 mg/dL) increase in HDL-C from baseline was associated with a 7% (95% CI: 3%, 10%) lower risk of coronary events, whereas neither baseline LDL-C/triglycerides nor change in LDL-C/triglycerides from baseline predicted subsequent coronary events. The present study supports their finding with regard to change in triglycerides from baseline, but in contrast to their study, we did find a significant association between change in LDL-C from baseline and risk of a major cardiovascular event. Our study population differs from the cohort studied by Koro et al.[14] in that their inclusion criteria did not require patients' lipid concentrations to be suboptimal, whereas all patients in the present study had poor HDL-C and LDL-C concentrations at baseline.

Our results with regard to other risk factors that are associated with a statistically significant increased risk of a major cardiovascular event, ie, high LDL-C concentration, high triglycerides, high total cholesterol concentration, older age, diabetes, and hypertension—also support findings reported in previous studies.[9,14,48,49]

Due to likely high colinearity with the predictor variable of interest (change in HDL-C concentration), we could not incorporate lipid-modifying therapy use in this model. However, almost half of the study population (46.3%; n=9638) received statin monotherapy between the index date and either the date of occurrence of the major cardiovascular event or the censor date, and 37.9% (n=8048) did not take any lipid-modifying therapy (data not shown). Much smaller percentages of patients took other lipid-modifying therapies, as follows: statin and fibrate, 6.8%; fibrate only, 3.7%; statin and niacin, 2.7%; statin and fibrate and niacin, 1.3%; niacin only, 0.9%; and fibrate and niacin, 0.4%. Future studies might consider lipid-modifying drug-use categories as the primary predictors in a model similar to this.

Study Limitations

Interpretation of the study findings must take into consideration certain limitations that are inherent to the use of claims data. Presence of a diagnosis code on a medical claim is not positive presence of disease, as the diagnosis code may be incorrectly coded or included as a rule-out criterion rather than actual disease. In addition, claims data do not reveal patient lifestyle information that could have an effect on study outcomes, such as smoking, obesity, exercise, and diet. As patients served as their own controls in this study, only large and sustained changes in these behaviors over time would impart significant bias. Research suggests that most patients are unable to sustain these types of changes over a long period of time.[50,51] Finally, results from this retrospective claims analysis may be less generalizable to populations that include persons without public health insurance.

CONCLUSION

Our finding, that a 0.026 mmol/L (1 mg/dL) increase in HDL-C from baseline was associated with a 1.9% decrease in the risk of a major cardiovascular event, provides further support for the previously reported association between low HDL-C concentrations and increased risk of major cardiovascular events. Based on the

findings of the present analysis and those reported in numerous previously published studies, physicians should consider prescribing pharmacologic or lifestyle changes that raise HDL-C as a preventative measure for future major cardiovascular events in patients with suboptimal HDL-C.

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