Prevalence and Treatment of Low HDL Cholesterol Among Primary Care Patients With Type 2 Diabetes

An unmet challenge for cardiovascular risk reduction

RICHARD W. GRANT, MD, MPH
JAMES B. MEIGS, MD, MPH

OBJECTIVE — Patients with diabetes remain at high risk for cardiovascular events despite aggressive blood pressure, LDL cholesterol, and blood glucose control. We identified prevalence and predictors of low HDL cholesterol, characterized current lipid therapy, and estimated the theoretical benefit of more effective HDL cholesterol–raising methods among patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — We analyzed a primary care–based population of patients with type 2 diabetes (n = 7,692) in 12 eastern Massachusetts outpatient practices. We grouped fibrates, niacins, and n-3 fatty acid preparations as nonstatin HDL cholesterol–raising medicines, and we used published studies to estimate the potential benefit of raising HDL cholesterol levels in this population.

RESULTS — Nearly half (49.5%) of patients had low HDL cholesterol (<40 mg/dl for men, <50 mg/dl for women). Low HDL cholesterol was independently associated with prevalent cardiovascular disease (CVD), younger age, and higher A1C levels. Nearly two-thirds of patients (63.0%) were prescribed a statin (67.6% of patients below the HDL cholesterol goal, 80.5% of patients with CVD). In contrast, only 7.9% of patients were prescribed a nonstatin HDL cholesterol–raising medication, including 16.4% of patients below the HDL cholesterol goal with CVD. Based on published studies, normalizing low HDL cholesterol in this primary care cohort would correspond to an estimated CVD mortality reduction of 42% in women and 23% in men.

CONCLUSIONS — Nearly half of the patients in this large primary care cohort had low HDL cholesterol levels. In contrast to frequent statin use, few patients were prescribed currently available medicines to raise HDL cholesterol. Low HDL cholesterol represents a highly prevalent and potentially modifiable risk factor for CVD prevention in type 2 diabetes.

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Cardiovascular disease (CVD) remains a primary cause of morbidity and mortality among patients with type 2 diabetes despite the availability of effective therapies to treat major risk factors such as elevated blood pressure and cholesterol levels (1,2). Current evidence-based treatment guidelines for cholesterol management focus on prescription of hydroxymethylglutaryl-CoA reductase inhibitors (statins) to reduce LDL cholesterol levels (3–5). However, among patients with diabetes, substantial residual CVD risk remains even with high-dose statin therapy (6).

Many patients with diabetes have an atherogenic pattern of dyslipidemia characterized by relatively normal levels of dense LDL cholesterol particles coupled with low levels of HDL cholesterol (7,8). Low HDL cholesterol has been shown to be independently associated with increased CVD risk (9). Conversely, each 1-mg/dl increase in HDL cholesterol is associated with significant reductions of CVD mortality rates (3.7% in men and 4.7% in women) (10).

Therapeutic options to increase HDL cholesterol levels include lifestyle modifications such as increased exercise, smoking cessation, moderate alcohol consumption, and adoption of a Mediterranean diet (5,11). Among patients already prescribed statins, additional medications to correct dyslipidemia (fibrates, niacin, and high-dose n-3 fatty acids) have each been shown to further raise HDL cholesterol by 5–30% (12). However, clinical trial evidence (3,5,13) for the reduction of CVD end points by adding HDL cholesterol–raising therapy remains sparse.

To determine the scope of the "low HDL cholesterol problem" in type 2 diabetes, we conducted a multiclinic analysis among a large cohort of primary care patients with type 2 diabetes to *1*) identify prevalence and predictors of low HDL cholesterol levels, *2*) characterize current patterns of single and combination lipid-related pharmacotherapy, and *3*) estimate the theoretical cardiovascular benefit to our population of more effective HDL cholesterol management.

RESEARCH DESIGN AND METHODS

— We identified all patients with type 2 diabetes receiving regular primary care from a diverse network of 12 outpatient practices in eastern Massachusetts. These practices were part of the Massachusetts General Hospital Primary Care Practice-Based Research Network and shared a common electronic

From the General Medicine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

Address correspondence and reprint requests to Richard W. Grant, MD, MPH, 50-9 Staniford St., Boston, MA 02114. E-mail: rgrant@partners.org.

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Abbreviations: CVD, cardiovascular disease; EMR electronic medical record; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; MI, myocardial infarction; VA-HIT, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Demographic, clinical, and treatment characteristics of patients with diabetes in the 12 primary care practices of the Massachusetts General Hospital practice–based research network*

	Community health centers	Hospital-based practices	Private practices	Total
Clinics	4	3	5	12
n	3,104	3,459	1,129	7,692
Patient demographics				
Women (%)	53.2	45.6	45.5	48.6
Age (years)	61.6 (15)	64.7 (13)	64.1 (14)	63.3 (14)
Insurance (%)				
Commercial	27.5	36.6	45.6	34.4
Medicare	46.6	50.0	45.0	47.9
Medicaid	14.9	8.4	5.9	10.6
Uninsured	11.1	3.7	3.5	7.1
Household income ($)*	45,046 (28,260)	72,956 (68,653)	86,376 (84,376)	63,028 (60,917)
Nonwhite race (%)	34.3	24.0	23.3	28.1
English speaking (%)	76.7	95.1	97.8	88.1
Clinical characteristics				
CVD (%)	23.6	29.6	26.7	26.7
BMI (kg/m^2)	32.3 (7)	32.4 (7)	31.1 (7)	32.2 (7)
Current smoking (%)	16.4	15.8	7.4	14.8
Clinical management				
Visits in prior year	7.8 (6)	9.8 (6)	7.5 (7)	7.9 (6)
Total medications	9.2 (5)	10.3 (6)	8.8 (5)	9.6 (5)
Mean A1C (%)	7.66 (1.7)	7.38 (1.5)	7.45 (1.4)	7.51 (1.6)
A1C <7.0 (%)	40.3	45.1	43.9	43
Glycemic treatment (%)				
Diet only	17.3	23.1	18.7	20.1
Oral medicines	58.4	48.1	59.4	56.2
Any insulin	24.3	28.8	21.9	23.7
Mean blood pressure	129/74 (19/11)	132/74 (20/11)	130/73 (19/12)	130/74 (19/11)
Blood pressure <130/80 (mmHg) (%)	37.6	36.7	40.0	37.7
Hypertension treatment (%)	80.6	81.0	78.5	89.2
Mean LDL cholesterol level (mg/dl)	91.3 (33)	89.2 (31)	87.3 (32)	89.2 (32)
LDL cholesterol <100 (%) (mg/dl)	66.2	70.8	68.3	68.7
All three risk factors at goal (%)†	7.8	6.3	11.2	7.6

Data are *n* and proportions or means (SD). *Household income based on federal tax returns from patients' home zip code. †Three risk factors: A1C, blood pressure, and LDL cholesterol.

medical record (EMR) and clinical data repository. Study practices included three hospital-affiliated academic practices, four community health centers, and five private offices serving a wide range of communities and patient populations (Table 1). The study was approved by the Massachusetts General Hospital/Partners Health Care System institutional review board.

Patients with type 2 diabetes were identified from our electronic clinical database using a previously validated algorithm that included EMR problem lists, diabetes-specific medications, and/or A1C results >7.0%. This algorithm has 98% sensitivity and specificity when compared with the gold standard of manual chart review by a trained research nurse (14). Patients aged >18 years with at least one outpatient visit between 1 July 2004 and 30 June 2005 were included in this study.

Clinical variables

For the cohort of eligible patients, we collected the following demographic data: age, sex, insurance status (private, Medicare/Medicaid, or self-pay), race, and median household income based on Federal tax returns from patient's home zip code. We used billing, EMR, laboratory, and appointment data to define clinical variables. We defined CVD diagnosis by any one of the following three criteria: *1*) one inpatient diagnosis code or two outpatient diagnosis codes for either coronary artery disease or myocardial infarction (MI) (including ICD-9 codes 410.x through 414.x and 429.x), *2*) current procedural terminology billing codes for coronary artery bypass grafting or percutaneous insertion of an intracoronary stent, and/or *3*) evidence of MI by elevated troponin T (>0.09 ng/ml on one or more occasions) among patients with normal renal function. When compared with the standard of detailed manual chart review, this approach using administrative and laboratory data to define CVD had a sensitivity of 100% and specificity of 97% (15).

Practices in this study relied almost exclusively on the EMR to generate and print medication prescriptions. Currently prescribed medication lists were downloaded from the EMR for all eligible cohort patients on a single day (30 June 2005). We grouped each patient's lipid-specific medications into statins (atorva-

Table 2—*Variables associated with low HDL cholesterol levels in men and women*

Characteristics	Male HDL cholesterol <40 mg/dl	Female HDL cholesterol <40 mg/dl	Female HDL cholesterol <50 mg/dl
n	1,512	706	1,654
CVD	1.5 (1.3–1.8)	1.7 (1.4–2.1)	1.7 (1.3–2.2)
Smoking	1.3 (1.1–1.6)	1.4 (1.1–1.8)	NS
White race	1.5 (1.2–1.7)	1.5 (1.2–1.8)	NS
Age (by decade)	0.9 (0.8–0.96)	0.9 (0.8–0.9)	0.9 (0.8–0.97)
A1C (%)	1.06 (1.01–1.12)	1.09 (1.03–1.15)	1.1 (1.02–1.20)
BMI (kg/m^2)	NS	NS	1.02 (1.01–1.04)

Data are adjusted odds ratio (95% CI) calculated by logistic regression. NS, nonsignificant association in the multivariate model.

statin, cerivastatin, lovastatin, fluvastatin, rosuvastatin, simvastatin, and pravastatin) and nonstatins (fibrates [gemfibrozil and fenofibrate], niacins, and n-3 fatty acid preparations). All drugs in the nonstatin class are known to raise HDL cholesterol levels (in addition to any other effects on the lipid profile) and each has been studied in combination with statin therapy. Very few patients (0.6% of the cohort, 45 patients) were prescribed bile resins (cholestyramine, colestipol, or colesevelam), and, thus, these agents were not considered further in our analyses. Similarly, while ezetimibe prescription was somewhat more prevalent (2.7%), this agent is clinically used to further reduce LDL cholesterol rather than specifically raise HDL cholesterol and, thus, was not included in our analysis of HDL cholesterol–directed therapy.

We also determined the total number of prescribed medications and specifically identified those for treatment of hypertension (α-blockers, ACE inhibitors, angiotensin II receptor antagonists, β-blockers, calcium channel blockers, and thiazide diuretics) and hyperglycemia (metformin, sulfonylureas, glitazones, other oral hypoglycemics, and insulin). Unique pharmacologic agents prescribed as combination pills were each counted separately.

We looked back from the medication ascertainment date to obtain the most recently measured lipid panel, A1C, and blood pressure results in the preceding 12-month period. We used the preceding lipid result to capture the physician's intended lipid therapy for a given lipid profile. BMI was calculated from last-measured weight and any documented height in the EMR.

Risks of therapy

To detect prior adverse events associated with lipid-lowering therapy, we searched billing codes and discharge summaries for the preceding 9 years (1997–2005) for any inpatient claims for drug-related rhabdomyolysis, myopathy, or myositis (ICD-9 codes 359.4, 359.81, 359.9, 728.88, and 729.1). In 1997, 63% of the current study cohort ($n = 4,839$) was receiving care in our system, a proportion that increased incrementally each year until the analysis year. This period of review represents 59,174 patient-years of available hospitalization surveillance (but does not include missing data for hospitalizations outside of our system). Any potential drug-related events were subsequently verified by manual chart review.

Statistical analysis

We characterized the population according to the following parameters: *1*) LDL cholesterol goal status (<100 mg/dl), *2*) HDL cholesterol goal status (≥40 mg/dl for men, ≥50 mg/dl for women, based on 2005 American Diabetes Association guidelines), *3*) statin prescription, *4*) prescription of nonstatin HDL cholesterol–raising medications (fibrates, niacins, or n-3 fatty acid preparations), and *5*) presence of diagnosed CVD. We modeled predictors of low HDL cholesterol in our population using separate multivariate logistic regression models for men and women (SAS version 9.1; SAS Institute, Cary, NC). Model covariates were selected by including all significant variables ($P < 0.1$) from univariate analyses and then using stepwise elimination to identify a subset of clinically and statistically relevant variables (CVD status, smoking, race, age, A1C level, and BMI) that were used for all models (men, HDL cholesterol <40 mg/dl; women, HDL cholesterol <40 mg/dl; women, HDL cholesterol <50 mg/dl).

RESULTS — There were 7,692 eligible patients analyzed, with a mean of 895 patients from each clinic (range 94–2,282). The mean age was 63.3 ± 14 years, 51.4% were men, 80.5% were prescribed antihypertensive therapy, and 79.7% were prescribed antihyperglycemic therapy, including 23.0% prescribed insulin. The clinic populations varied appreciably by demographic factors, particularly insurance status, race, and median estimated household incomes, but less markedly by A1C or blood pressure control (Table 1).

Dyslipidemia

The mean LDL cholesterol for the cohort was 89.2 ± 32 mg/dl, with 68.7% of patients having LDL cholesterol <100 mg/dl (73.5% of men, 63.5% of women, $P < 0.001$). The mean HDL cholesterol level was 43.4 ± 12.4 mg/dl for men and 51.5 ± 14.9 for women ($P < 0.001$). Nearly half of men (45%) had HDL cholesterol levels <40 mg/dl, whereas 23% of women had HDL cholesterol levels <40 mg/dl and 54% had HDL cholesterol levels <50 mg/dl. Prevalence of CVD was 30.5% among patients with low HDL cholesterol versus 24.2% among patients with normal or elevated HDL cholesterol ($P < 0.001$). CVD, younger age, current smoking, white race, and higher A1C levels were each independently associated with HDL cholesterol <40 mg/dl among men (Table 2). The same set of variables was independently associated with HDL cholesterol <40 mg/dl in women, whereas CVD, younger age, elevation of A1C, and BMI but not race or smoking status were associated with women's HDL cholesterol <50 mg/dl (Table 2).

Pharmacologic management

Nearly two-thirds of the overall cohort was receiving statin therapy ($n = 4,845$, 63.0%), including 80.5% of patients with CVD. In contrast, 7.9% of the cohort ($n = 609$) was receiving nonstatin lipid-modifying therapy, including 11.6% with CVD. The most commonly prescribed agents in this class were gemfibrozil (3.8% of the cohort), fenofibrate (1.8%), n-3 fatty acid preparations (1.5%), and niacin (1.3%). Most of these agents were coprescribed with statins ($n = 416$; 68% of patients prescribed HDL cholesterol–raising therapy, corresponding to 5.4% of the overall cohort); 190 (45.7%) of these patients on dual therapy were at HDL cholesterol goal.

Figure 1 illustrates the proportion of patients with low HDL cholesterol (<40 mg/dl for men, <50 mg/dl for women)

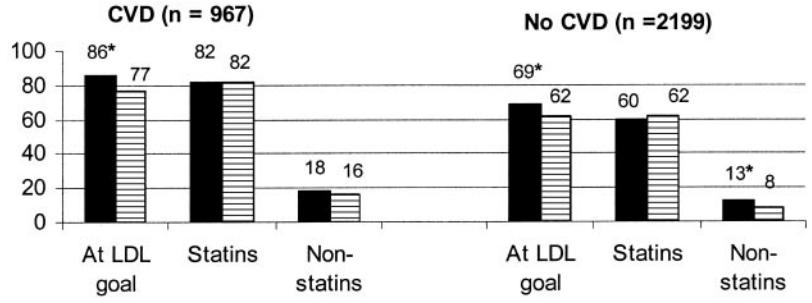

Figure 1—*Proportion of male (■) and female (▤) patients at LDL cholesterol goal (at LDL goal) (<100 mg/dl), prescribed statin therapy (statins), and prescribed nonstatin HDL cholesterol–raising therapy (nonstatins [fibrates, niacins, and n-3 fatty acids]) stratified by sex and diagnosed by CVD. Low HDL cholesterol levels were defined as <40 mg/dl for men and <50 mg/dl for women. *P < 0.01 for comparison between sexes.*

who were at LDL cholesterol goal, on statins, and on nonstatin HDL cholesterol–raising therapy, stratified by sex and CVD status. Patients with CVD were more likely to be receiving HDL cholesterol–raising therapy (generally in combination with statins). However, absolute prevalence of HDL cholesterol–raising therapy was low for all strata, particularly when compared with prevalence of statin prescription. Women were less likely to be at LDL cholesterol goal than men, regardless of CVD status ($P < 0.001$), and among low HDL cholesterol patients without CVD, women with low HDL cholesterol were less likely to be receiving nonstatin HDL cholesterol–raising therapy ($P = 0.016$).

American Diabetes Association guidelines (5) recommend additional therapy for patients at LDL cholesterol goal with low HDL cholesterol. In our cohort, just under one-half (49.8%) of patients already at LDL cholesterol goal were not at HDL cholesterol goal. Among these patients with normal LDL cholesterol levels and low HDL cholesterol, 73% were on statins and 10.5% were on additional HDL cholesterol–raising therapy.

Risks of therapy

Over the 59,174 patient-years of available observation, we found three cases of chart-confirmed rhabdomyolysis and four cases of myositis, only one of which was attributable to lipid-lowering therapy (statin therapy alone).

CONCLUSIONS — In this study, we present detailed dyslipidemia prevalence and current care practices for a large, multiclinic primary care cohort of patients with type 2 diabetes. We found that nearly one of every two patients with type 2 diabetes has low HDL cholesterol levels and that low HDL cholesterol was more prevalent in patients with existing CVD and those with worse glycemic control. Prevalence of statin prescription was high, but few patients were prescribed additional medicines that might further raise HDL cholesterol (e.g., fibrates, niacins, or n-3 fatty acids). Use of nonstatin HDL cholesterol–raising medication was uncommon in all low HDL cholesterol–subgroups analyzed, including patients with existing CVD and patients with LDL cholesterol treated to goal. In the highest-risk patients with existing CVD, women were less likely than men to receive specific HDL cholesterol–raising therapy, a pattern of less-aggressive risk factor treatment previously found in LDL cholesterol, antiplatelet, and ACE/angiotensin receptor blocker therapy (16).

The current practice described in our analysis reflects the contrast between the robust and well-publicized clinical trial evidence for LDL cholesterol–lowering therapy versus the more nebulous area of HDL cholesterol–raising therapy. Given the paucity of outcome data supporting combination therapy, these results likely reflect a general reluctance to treat low HDL cholesterol in current practice. However, even with aggressive LDL cholesterol lowering, as in the Treating to New Targets Study in which intervention patients received 80 mg atorvastatin (mean LDL 77 mg/dl), the "residual" absolute risk of CVD events among patients with diabetes remains high (14% over 5 years, compared with an 18% event rate among patients treated with 10 mg atorvastatin, mean LDL 99 mg/dl) (17). Indeed, statin-treated patients with low HDL cholesterol have cardiovascular event rates that exceed those of placebo-treated patients with normal HDL cholesterol (6). Our results underscore the extent of this residual risk in the general diabetic population.

Interpolating from population-based studies provides a rough estimate of the residual risk from low HDL cholesterol and underscores the potential impact of improving HDL cholesterol levels on cardiovascular risk reduction among patients with type 2 diabetes (18). Bringing all patients in our cohort with low HDL cholesterol levels to HDL cholesterol goal would require raising HDL cholesterol by 6.4 mg/dl in men and 8.9 mg/dl in women. According to epidemiologic estimates (10), such a change is estimated to correspond to a CVD mortality reduction of 42% in women and 23% in men.

Population-based estimates are limited by the observational nature of the data and the potential for unmeasured confounding. Randomized clinical trials, by comparison, provide higher quality evidence for the effect of clinical interventions but have limited generalizability to "real work" cohorts such as ours. Two of the most prominent trials of HDL cholesterol–raising interventions are the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) (19) and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial (20).

VA-HIT enrolled men with existing CVD and low HDL cholesterol in a placebo-controlled trial of gemfibrozil. Among the subgroup of patients with diabetes, 10 patients needed to be treated for 5 years in order to prevent one major cardiovascular event (number needed to treat = 10) (21). In our population, only 436 patients (5.7% of cohort, mean HDL cholesterol 33.4 ± 5.6 mg/dl) met the major study eligibility criteria of men with CVD and low HDL cholesterol. Applying the results of VA-HIT to this subset of our cohort would be predicted to prevent 44 major CVD events over 5 years.

FIELD specifically enrolled men and women with type 2 diabetes in a 5-year placebo-controlled trial of fenofibrate therapy. The somewhat disappointing lack of difference in the primary end point may in part have been due to the disproportionately higher rate of statin use in the placebo group. Nonetheless, there was a significant 1.4% absolute risk reduction in total CVD events among the 2,131 treated patients over 5 years (due mostly to fewer nonfatal MI and revascularizations), which corresponds to the

number needed to treat 71 patients over 5 years. Treating the 5,670 FIELD-eligible patients in our cohort (73.7% of the cohort, mean HDL cholesterol 47.8 ± 14.3 mg/dl) would be predicted to prevent 80 major CVD events over 5 years.

Most published studies of nonstatin lipid therapies were performed in the setting of no or infrequent statin prescription, which stands in marked contrast to our patient cohort and may therefore limit their applicability to current patient populations. Results from the recently initiated Action to Control Cardiovascular Risk in Diabetes trial to specifically evaluate fibrate treatment in the setting of statin therapy among 10,000 patients with type 2 diabetes may be more relevant to populations such as ours but are not expected before the year 2010 (22). In addition, estimates based on HDL cholesterol–raising results from clinical trials may be misleading if the intervention drugs alter CVD risk via additional mechanisms independent of their effect on HDL levels (23).

This study of current primary care–based dyslipidemia management involves one of the largest of such cohorts of type 2 diabetes published in the recent literature. Although patients in this study were analyzed from a single geographic region, the study cohort was similar to the U.S. national population in terms of demographics, smoking rates, and prevalence of comorbid conditions (24) and had somewhat better risk factor control (25). The relatively large cohort size allowed sufficient power to detect differences in treatment within sex, HDL cholesterol goal level, and CVD strata. Moreover, unlike many other studies that have ascertained medication information from patients' pharmacy claims data, our picture of medication use was based on actual physician prescription orders in the EMR (used exclusively for all medication orders in the 12 study practices). Each approach has relative benefits and limitations; the pharmacy claims method more accurately reflects what patients are actually taking, whereas the EMR method represents physician intent. Because of the cross-sectional nature of our medication ascertainment, we were unable to show temporal relationships between treatment and HDL cholesterol levels.

The high rates of treatment for the "big three" risk factors, hyperglycemia, hypertension, and LDL cholesterol, and the comparatively good rates of risk factor control in this cohort relative to national rates underscore the fact that the patients in these 12 practices were receiving high-quality evidence-based care. Given the high prevalence of low HDL cholesterol and the substantial residual risk for CVD events in patients with low HDL cholesterol, development of more potent HDL cholesterol–raising therapies or publication of more compelling evidence for current combination therapy has the potential to result in substantially reduced cardiovascular morbidity and mortality among patients with type 2 diabetes.

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