The Challenge of Achieving National Cholesterol Goals in Patients With Diabetes

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OBJECTIVE — This study analyzed lipid results from a large community-based population of patients with diabetes to assess the feasibility of attaining the standard and new optional LDL-based lipid goals using currently available lipid-lowering medications.

RESEARCH DESIGN AND METHODS — Ambulatory patients with diabetes who were interviewed as part of the Vermont Diabetes Information System trial with a reported LDL were analyzed. Patients were categorized into high-risk and very-high-risk cardiovascular status. For patients not at the LDL goal, the required changes in therapy to achieve the goal were assessed.

RESULTS — Of the entire cohort, 49.4% (321 of 650) had LDL <100 mg/dl. According to the National Cholesterol Education Program, 29.4% (191 of 650) of patients were very high risk and have an optional LDL goal of <70 mg/dl. Only 15.7% (30 of 191) of very-high-risk patients had an LDL <70 mg/dl. Based on our analysis of high-risk patients, 17 of 459 (3.7%) would require more than two lipid-lowering drugs to achieve an LDL <100 mg/dl. In the very-high-risk group, we estimate that 26.2% (50 of 191) of patients will not reach LDL <70 mg/dl with two lipid-lowering medications.

CONCLUSIONS — In many patients with diabetes and cardiovascular disease, it will be difficult to attain an LDL goal of <70 mg/dl. Approximately 25% of patients will require more than two lipid-lowering drugs at maximal doses to attain this goal, assuming 100% tolerance of lipid-lowering medications.

Diabetes Care **28:1029–1034, 2005**

Cholesterol management is essential in the preventive care of patients with diabetes. In 2001, the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) was published to guide the management of hypercholesterolemia (1). The guideline considers patients with diabetes to be at high risk of cardiovascular events and recommends the same LDL goal as those for patients with established cardiovascular disease (CVD) (LDL <100 mg/dl).

Recently, the NCEP released a report providing updated recommendations, which includes an "optional" LDL goal of <70 mg/dl for patients who are at "very high risk" for cardiovascular heart disease (2). Very high risk is defined as patients with established CVD plus one or more of the following: patients with multiple risk factors (including diabetes), severe and poorly controlled risk factors, multiple risk factors of the metabolic syndrome, and acute coronary syndromes.

To effectively manage hypercholesterolemia, many patients require lipid-lowering medications. Potent lipid-lowering medications are available, including hydroxymethylglutaryl-CoA reductase inhibitors (i.e., statins), ezetimibe, fibrates, niacin, and bile acid sequestrants. Based on the updated report, statins should be prescribed using at least "standard" doses of LDL-lowering drugs, defined as doses that are expected to provide a 30–40% reduction in LDL levels (2).

Despite available therapies and increased attention to hypercholesterolemia, many patients fail to achieve LDL goals (3–4). Data from the third U.S. National Health and Nutrition Examination Survey (NHANES; 1988–1994) showed only 42% of patients with diabetes achieved an LDL <130 mg/dl (5). More recent data demonstrated only 22.5% of patients with diabetes in a managed care sample achieved an LDL <100 mg/dl (6). Further, data from 1996 to 1998 showed patients with diabetes were 26% less likely to have a lipid profile than patients without diabetes (7). Many patients with diabetes will meet the criteria for very high risk and be eligible for the new optional LDL <70 mg/dl goal. Given the few patients who achieve the current LDL goal of <100 mg/dl, we would expect a significant gap between current care and the optional goal of <70 mg/dl.

We analyzed lipid results from a large community-based population of patients with diabetes to assess the feasibility of attaining the new optional LDL-based lipid goal using currently available lipid-lowering medications.

RESEARCH DESIGN AND METHODS

— We performed a cross-sectional analysis of the laboratory and survey data from the Vermont Diabetes Information System (VDIS) trial. VDIS

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Received for publication 1 December 2004 and accepted in revised form 2 February 2005.

Abbreviations: CVD, cardiovascular disease; NCEP, National Cholesterol Education Program; NHANES, National Health and Nutrition Examination Survey; VDIS, Vermont Diabetes Information System.

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

was a randomized controlled trial of a decision-support system for primary care providers and their patients with diabetes. The design and methods of the study are described elsewhere (8). In brief, primary care practices and their patients with diabetes received decision support and reminders regarding diabetes-specific laboratory tests including HbA_{1c}, lipids, microalbumin screening, and creatinine testing. Laboratory tests were uploaded on a nightly basis from participating hospitals in the region. A random subsample of patients underwent a home interview that included measurement of height, weight, and blood pressure and collection of the current medication list by direct examination of all prescription and nonprescription containers.

In all, 13 hospitals, 69 practices, and 6,722 patients were enrolled in the study; 704 patients were interviewed since the study start date of 5 June 2003. To be eligible for this analysis, patients needed to be enrolled in the VDIS study, have a diagnosis of type 1 or type 2 diabetes confirmed by their primary care provider, and have a reported calculated LDL value. Thirteen patients with triglyceride levels >400 mg/dl, for whom LDL estimation was not accurate, were not included in this report. This project was approved by the Committees on Human Research at the University of Vermont.

Our goal was to study the lipid profiles and medications of patients with diabetes. We reviewed each patient's medication list for the presence of lipid medications. Medications from the following drug classes were considered lipid-lowering medications: statins, ezetimibe, fibrates, niacin, and bile acid sequestrants. Laboratory data included calculated LDL, HDL, total cholesterol, and triglycerides.

Patients were divided into two groups, high-risk and very-high-risk cardiovascular status, based on the new NCEP report (2). Because all patients in the cohort had confirmed diabetes, all patients were at least high risk. Patients were considered very high risk if they also had established CVD. Established CVD was defined as any of the following: history of myocardial infarction, peripheral vascular disease, or stroke or transient ischemic attack. The survey questions were adapted from questions used by the National Center for Health Statistics in NHANES (9).

In addition to data collection regarding CVD, we reviewed CVD risk factors including suboptimal diabetes control (HbA_{1c} ≥7%), cigarette smoking, HDL <40 mg/dl, triglycerides ≥200 mg/dl, age ≥45 years in men or age ≥55 years in women, and hypertension. The presence of hypertension was defined as either a blood pressure ≥140/90 at the time of the interview or as the subject responding positively to the question, "Are you currently taking medications for hypertension or high blood pressure?"

We analyzed the lipid-lowering therapies of all patients in the cohort and compared the therapies to patients' LDL values. We determined the proportion of patients taking any dose of any commercially available statin and those taking at least a standard dose of statin (i.e., atorvastatin 10 mg, fluvastatin 80 mg, lovastatin 40 mg, pravastatin 40 mg, rosuvastatin 5 mg, or simvastatin 20 mg) (2). Additionally, we counted the number of lipid-lowering medications each patient was prescribed.

For patients not at their LDL goal, we estimated the required changes in therapy to achieve the goal. We made several assumptions in prescribing lipid medications. We assumed a "best case" scenario, including no contraindications to statins or other lipid-lowering drugs and 100% medication adherence and tolerance. Statins were categorized into low (<30% LDL reduction), standard (34% LDL reduction), high (45% LDL reduction), and maximal dose (55% LDL reduction) using previously published LDL reduction comparison charts (10). Although rosuvastatin 40 mg may provide a more potent LDL reduction than atorvastatin 80 mg (11), we considered both regimens to be "maximal dose" with a corresponding 55% LDL reduction (only two patients were taking rosuvastatin).

We assumed adding a second agent would produce an additional 15% LDL reduction. We believed this assumption was reasonable, given previously published reported LDL percentage reductions for ezetimibe (18%) (12), fibrates (5–20%), niacin (5–25%), and bile acid sequestrants (15–30%) (1). We did not specify which second agent should be selected or at what intensity. Patients requiring more than the maximal dose of a statin in addition to a second agent were classified as "beyond two lipid-lowering drugs."

We used descriptive statistics to document proportions for each of the measures. We compared characteristics between high-risk and very-high-risk patients using Fisher's exact test. For the lipid medication analysis, we performed sensitivity analyses around the LDL percentage reduction of the second agent to determine how the second drug would influence the number of patients considered beyond two drugs. We used STATA 8.2 (STATA, College Station, TX) for statistical analyses.

RESULTS — A total of 650 (92.3%) of the 704 interviewed patients had a baseline LDL and triglycerides <400 mg/dl and therefore were included in the analysis. The characteristics of the cohort are described in Table 1. The mean duration of diabetes was 10.7 years, with a range from 3.7 months to 62.9 years (95% CI 9.9–11.5 years). The median medication burden for patients was 8, with a range of 0–29 medications. Most of the patients were elderly (mean age 65.3 years; 95% CI 64.4–66.2), married, and non-Hispanic white. More than half of patients (336 of 593; 56.7%) had an annual household income <$30,000/year. Nearly all of the patients had some form of health insurance, with 85.3% (547 of 641) of patients having partial or full prescription coverage. The majority of patients were obese (67.6%; 95% CI 64.0–71.2) and 52.6% of patients had an HbA_{1c} <7% (95% CI 48.7–56.5). In all, 69.7% of the cohort had a total cholesterol <200 mg/dl (95% CI 66.0–73.2).

Overall, ~30% (191 of 650) of patients responded to questions indicating they had known CVD, placing them in the very-high-risk category (Table 2). Of the very-high-risk patients, 60.7% (116 of 191) responded they had a history of myocardial infarction, 30.4% (58 of 191) indicated a history of peripheral vascular disease, and 39.3% (75 of 191) listed a history of stroke or transient ischemic attack. (Some patients cited more than one CVD event.). Diabetes at goal (HbA_{1c} <7%), cigarette smoking, low HDL, and high triglyceride levelswere not statistically different between high-risk and very-high-risk patients. However, very-high-risk patients were older ($P < 0.001$) and more likely to have hypertension compared with the high-risk patients in the cohort ($P < 0.02$).

Of the entire cohort, 49.4% (321 of

Table 1—*Characteristics of the cohort*

	n	%*
Total cohort	650	
Median duration of diabetes (years)	7.4	
Median number of medications per patient	8	
Age (years)		
18–44	38	5.9
45–64	259	39.9
>65 years	353	54.3
Female	338	52
Non-Hispanic white	611	96.2
Married	421	64.8
Obese (BMI ≥ 30)	432	67.6
Education		
< High school	151	23.4
High school	225	34.8
> High school	270	41.8
Annual household income		
<$30,000/year	336	56.7
>$30,000/year	257	43.3
Health insurance		
Private	359	55.5
Medicaid	122	18.9
Medicare only	113	17.5
Military	36	5.6
No insurance	15	2.3
Prescription coverage		
Covered or partially covered	547	85.3
Not covered	80	12.5
Met with a dietician in the last year	221	34.3
Met with a certified diabetes educator in last year	164	25.7

*Some percentages do not total 100% due to nonresponse.

650) were at a goal LDL <100 mg/dl (Table 2). Compared with 59.7% of very-high-risk patients, only 45.1% of high-risk patients achieved an LDL <100 mg/dl ($P < 0.001$). Very-high-risk patients were also more likely to be taking a statin ($P < 0.001$) and be taking at least a standard dose of statin ($P < 0.001$) than the high-risk patients. Only 15.7% (30 of 191) of very-high-risk patients and 8.1% (37 of 459) of high-risk patients had LDL <70 mg/dl.

From a therapeutic standpoint in the high-risk group, 40.3% (185 of 459) of patients will require an intensified single-agent regimen to attain LDL <100 mg/dl (Table 3). Fifty of the high-risk patients (10.9%) will require the addition of a second agent to attain an LDL goal of <100 mg/dl. Based on our analysis of high-risk patients, 17 of 459 (3.7%) patients in the cohort will require more than two lipid-lowering drugs to achieve LDL <100 mg/dl.

Therapeutic requirements in the very-high-risk group were even more substantial (Table 3). Compared with an estimated 4.2% (8 of 191) of patients that require more than two drugs when the LDL target is <100 mg/dl, we estimate that 26.2% (50 of 191) of patients will not reach an LDL <70 mg/dl with two drugs.

When the LDL percentage reduction of the second agent was varied from 15% to 10 and 5%, the percentage of very-high-risk patients beyond two drugs increased to 29.3 and 34.5%, respectively. When the LDL percentage reduction of the second agent was varied from 15% to 18, 20, 25, and 30%, the percentage of very-high-risk patients who used more than two drugs decreased from 26.2% to 20.9, 18.3, 15.2, and 11.0%, respectively.

CONCLUSIONS — Our data describe a cohort of patients with diabetes who receive primary care services. Nearly 33% of our cohort had CVD and therefore would be included in the very-high-risk category of the new NCEP report, with an optional LDL goal <70 mg/dl. This finding is similar to the U.S. prevalence of CVD among patients with diabetes of 38% reported by the Centers for Disease Control and Prevention in 2002 (13). If 30% is used as a conservative estimate and applied to the estimated 18.2 million Americans with diabetes (14), ~5.5 million patients with diabetes may be considered very high risk with an optional LDL goal <70 mg/dl.

Reducing patients' LDL values from 100 to 70 mg/dl is not a trivial undertaking. About 50% of our overall cohort is already receiving lipid-lowering therapy. Using optimistic assumptions, we estimate that 96% of patients could achieve a target LDL of <100 mg/dl with maximal therapy with two lipid-lowering drugs. However, using the same optimistic assumptions in very-high-risk patients, we estimate that 25% of patients could not achieve the optional LDL <70 mg/dl goal with maximal doses of two lipid-lowering drugs.

We made assumptions to estimate the effects of lipid-lowering therapy. Our best-case assumptions include no contraindications to treatment, no side effects necessitating limits on dose or discontinuation of medications, 100% medication adherence, typical LDL-lowering responses to statins, and additive LDL reductions with increased doses and the addition of a second drug. It is very likely that, in actual practice, even higher proportions of patients would be unable to reach the optional goal with two drugs.

Medication adherence is essential to obtaining benefit from statins. Although our analysis assumed 100% adherence, it is well known that medication adherence is suboptimal in both clinical trials and actual practice. Clinical trials of statin therapy have shown adherence rates of 80–87% over 3–4 years (15–17). "Real world" adherence rates may be substantially lower than in clinical trials. Ellis and associates (18) analyzed nearly 4 years of pharmacy claims data of 2,258 adults prescribed statins for secondary prevention. Patients were adherent to statins 78.5% of the time. However, one study of 36,106 elderly patients with coronary artery disease demonstrated that only 36.1% were adherent to statins at 2 years (19).

The average medication burden of these patients—eight medications—is al-

Table 2—*Comparison of characteristics between high-risk and very-high-risk patients*

	High risk	Very high risk	*P* value*
Total cohort	459	191	
Diabetes	459 (100)	191 (100)	
Self-reported CVD	0	191 (100)	
History of myocardial infarction	0	116 (60.7)	
History of pulmonary vascular disease	0	58 (30.4)	
History of stroke or transient ischemic attack	0	75 (39.3)	
Diabetes at goal (HbA_{1c} <7%)	238 (51.9)	104 (54.5)	0.6
CVD risk factors			
Current cigarette smoking	70 (15.3)	29 (15.2)	1
Hypertension	367 (80)	168 (88)	0.02
HDL <40 mg/dl	156 (34)	79 (41.4)	0.09
Age ≥45 years (men), ≥55 years (women)	383 (83.4)	183 (95.8)	<0.001
Triglycerides ≥200 mg/dl	145 (31.7)	61 (32.1)	0.9
LDL values and lipid drugs			
LDL <70 mg/dl	37 (8.1)	30 (15.7)	0.005
No lipid drugs	14	4	
One lipid drug	21	22	
Two or more lipid drugs	2	4	
LDL 70–99 mg/dl	170 (37)	84 (44)	0.1
No lipid drugs	66	23	
One lipid drug	96	55	
Two or more lipid drugs	8	6	
LDL 100–129 mg/dl	159 (34.6)	53 (27.8)	0.1
No lipid drugs	81	15	
One lipid drug	69	32	
Two or more lipid drugs	9	6	
LDL 130–159 mg/dl	66 (14.4)	20 (10.5)	0.2
No lipid drugs	39	11	
One lipid drug	25	6	
Two or more lipid drugs	2	3	
LDL >160 mg/dl	27 (5.9)	4 (2.1)	0.04
No lipid drugs	17	1	
One lipid drug	9	3	
Two or more lipid drugs	1	0	
Any dose of statin	219 (47.7)	130 (68.1)	<0.001
At least standard dose statin†	191 (41.6)	110 (57.6)	<0.001

Data are *n* (%). **P* values obtained using Fisher's exact test. †Standard dose is the dose required to achieve a 30–40% LDL reduction.

ready substantial. Adding more lipid medications may increase the risk of drug interactions and adverse effects, including increased risk of myopathy with combinations of statins and fibrates and other agents (20). Further, recent data suggest that the incidence of rhabdomyolysis in older patients with diabetes taking statins and fibrates may be as high as 1 in 484 (21). Newer lipid-lowering drugs such as ezetimibe have few drug interactions and appear to be safe in combination with statins (22). However, adding an expensive newer agent to an already costly medication regimen may prove difficult for patients. Additionally, many two- and three-drug combinations have not been adequately tested in clinical trials.

There are some important differences between our cohort and the rest of the nation. NHANES (1999–2000) provides data representative of the noninstitutionalized U.S. civilian population. Compared with NHANES data of patients with diabetes, our cohort is older, has had diabetes for a shorter duration, is less racially diverse, is more obese, and has a larger proportion of patients at both HbA_{1c} <7% and total cholesterol <200 mg/dl (23). These findings, particularly the proportion of patients achieving diabetes and total cholesterol targets, strengthen our conclusions. If it will be difficult for our well-controlled cohort to achieve lower LDL goals, it will likely be even more challenging for the rest of the nation to achieve these ambitious targets.

One strength of this study is that that the study population reflects a cohort of unselected patients with diabetes who are receiving primary care. They should be representative of patients cared for by primary care providers in similar settings in the U.S. Another strength is that the medication lists and doses were obtained by direct observation of the pill bottles and reviewed directly with the patient, not from an administrative source such as pharmacy or billing records.

Table 3—*Lipid medication requirements to achieve goal LDL*

		Very high risk	
Action required to achieve goal LDL	High risk: LDL <100 mg/dl	LDL <70 mg/dl	LDL <100 mg/dl
No action required (currently at goal)	207 (45.1)*	30 (15.7)†	114 (59.7)‡
Maximize one drug (statin)	185 (40.3)	75 (39.3)	51 (26.7)
Maximize two drugs (statin + other lipid drug)§	50 (10.9)	36 (18.9)	18 (9.4)
Beyond two drugs	17 (3.7)	50 (26.2)	8 (4.2)
Total	459 (100)	191 (100)	191 (100)

Data are *n* (%). *Eighty patients were taking zero lipid drugs, 117 one lipid drug, and 10 two lipid drugs. †Four patients were taking zero lipid drugs, 22 one lipid drug, and 4 two lipid drugs. ‡Twenty-seven were taking no lipid drugs, 77 one lipid drug, and 10 two lipid drugs. §We assumed that any second lipid drug added would produce an additional 15% reduction in LDL.

There are also several limitations to our analysis. The diagnosis of CVD used to classify patients into the high-risk and very-high-risk categories was based in part on self-report. Although we used questions based on those used in NHANES in an effort to maximize comparability, it would have been preferable to base the diagnosis of CVD on more objective data. Additionally, the patients with self-reported CVD were statistically more likely to have baseline LDL <100 mg/dl, suggesting that patients with diagnosed CVD are more likely to be treated with more aggressive regimens.

We did not have detailed dietary information for the cohort. Following the NCEP's Step I or Step II diet has been shown in a meta-analysis to lower LDL by 12–16% (24). Because we did not have dietary records for patients, we could not estimate additional LDL lowering to be gained by dietary intervention. However, the entire cohort was under care by a primary care physician. It is likely that dietary and other lifestyle changes recommended by the NCEP have already been implemented and are therefore reflected in patients' LDL values. This idea is supported by our data that over 33% of the cohort was under care by a dietitian in the last year alone. Therefore, it is unlikely that this cohort would gain an additional LDL-lowering benefit in excess of 10% with further dietary interventions that would be reasonably available and achievable.

Based on our analysis of primary care patients with diabetes using objective measures of LDL cholesterol and accurate medication lists, we have determined that it will be extremely difficult to attain new LDL goals of <70 mg/dl in patients with diabetes and CVD. Approximately 25% of patients will require more than two lipid-lowering drugs at maximal doses to attain this goal, with patients already taking an average of eight medications at baseline. Furthermore, at the highest doses of lipid-lowering drugs, additional patients will stop therapy due to side effects and nonadherence. Without the development of newer, more potent LDL-lowering drugs, clinicians may need to content themselves with attaining an LDL goal of <100 mg/dl in many very-high-risk patients.

Acknowledgments— This work was supported in part by Grant K08 HS013891 from the Agency for Healthcare Research and Quality and by Grant R01 DK061167 and K24 DK068380 from the National Institute of Diabetes and Digestive and Kidney Diseases.

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