

## Achieving Target Cholesterol Levels in Diabetic Patients: Potency of the Statin or Potency of the Physician?

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### Abstract

**Background:** The introduction of more potent statins such as atorvastatin and rosuvastatin in Israel was accompanied by massive advertising about their superiority.

**Objectives:** To assess the need for switching therapy from older statins to more potent ones among diabetic patients with uncontrolled hypercholesterolemia.

**Methods:** Data on all diabetic patients over 30 years old attending two urban clinics were extracted and analyzed. For each patient we checked the last low density lipoprotein-cholesterol measurements for the year 2006, the brand and the dose of cholesterol-lowering medications, prescriptions and actual purchasing over a 4 month period prior to the last LDL-C measurement, and whether treatment changes were necessary to achieve the LDL-C target (100 mg/dl or 70 mg/dl).

**Results:** The study population comprised 630 patients, age  $66.7 \pm 12.6$  years, of whom 338 (53.6%) were women. Of the 533 (84.6%) patients whose LDL-C was measured in 2006, 45 (8.1%) had levels < 70 mg/dl and 184 (33.3%) had levels of 70 mg/dl < LDL-C < 100 mg/dl. The reasons for LDL-C > 100 mg/dl were patients not prescribed cholesterol-lowering drugs (38.3%), partial compliance (27.2%), and under-dosage of statins (15.4%); only 7.7% needed to switch to a more potent statin. Reasons for LDL-C > 70 mg/dl were patients not prescribed cholesterol-lowering drugs (34.3%), partial compliance (22.0%), and under-dosage of statins (26.6%); only 8.7% needed to switch to a more potent statin.

**Conclusions:** Only a small minority of diabetic patients with uncontrolled hypercholesterolemia need one of the potent statins as the next treatment step. More emphasis on compliance and dose adjustment is needed to achieve the target LDL-C level.

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Diabetes mellitus causes a huge economic burden in western society. Thirteen percent of all hospitalization costs of Clalit Health Services (the largest health management organization in Israel, serving over 3,500,000 patients nationwide) were attributed to diabetic patients [1]. It has been estimated that in 2002 the direct medical expenditures in the United States for diabetics alone totaled 91.8 billion U.S. dollars [2]. Better diabetes control is associated with reduction of diabetes complications. Diabetes control relates to glucose, low density lipoprotein-cholesterol and blood pressure. Current recommendations by the American College of Physicians for diabetes control include maintaining

a LDL-C level of under 100 mg/dl [3,4]; if lifestyle modification and diet are not sufficient for achieving this goal, statins are considered the drug of choice. Treatment with simvastatin in patients at high risk for ischemic heart disease was found to be cost effective [5]. Hypertriglyceridemia and low high density lipoprotein contribute to the increased risk of ischemic heart disease in patients with diabetes, but high LDL-C level is the stronger predictor for cardiovascular morbidity and mortality among diabetic patients.

Most of the trials investigating hypercholesterolemia did not focus on diabetic patients, who usually constituted only a subgroup. Only two trials have been designed to evaluate the role of statins in patients with diabetes: CARDS [6] and ASPEN [7]. In CARDS the number needed to treat to prevent one acute cardiovascular event was 31 patients for 4 years, while in ASPEN statins were not superior to placebo. In other clinical trials where diabetic patients comprised at least 10% of the patients it was found that statins had a beneficial effect on cardiovascular endpoints [4]. It is important to note that in all these trials LDL-C levels at baseline were always above 100 mg/dl and end-of-study LDL levels were below 100 mg/dl.

Following these studies and the interpretation of their findings, several expert bodies issued their recommended guidelines. In 2004 the ATP-III (Adult treatment Panel) updated their recommendations adding an optional goal of LDL-C < 70 mg/dl for diabetic patients at "very high risk" for cardiovascular disease [8]. They used the results of the HPS and PROVE-IT trials as the basis of the recommendation. In 2007 the American Diabetes Association [9] recommended that individuals without overt cardiovascular disease should have a primary goal of less than 100 mg/dl LDL-C (level A evidence); all diabetic patients over the age of 40 should receive a statin regardless of baseline LDL-C level (level A evidence). While in individuals with CVD baseline, LDL-C should be reduced by 30–40% regardless of the baseline level, and the target of < 70 mg/dl LDL in this group is an option with B level evidence.

A summary of the literature as of the end of 2006, together with the expert guidelines, point to a universal reasonable target of LDL-C < 100 mg/dl for all diabetic patients. There is still debate regarding the LDL-C < 70 mg/dl target in selected "very high risk" populations of diabetic patients as well as about the recommendation for universal treatment to reduce baseline LDL-C by 30–40%.

LDL-C = low density lipoprotein-cholesterol  
CVD = cardiovascular disease

The introduction in Israel of more potent statins such as atorvastatin and rosuvastatin and the cholesterol absorption inhibitor ezetimibe has been accompanied by massive advertising attesting to their superior ability to achieve the target LDL levels according to the new guidelines. This has led to a demand by patients to receive them and pressure applied on their family physicians to prescribe these medications instead of the older ones. Clalit Health Services adopted a policy of costs containment since the prices of the new statins are considerably higher and there is little possibility of generic substitutions in the near future.

In order to assess the need for substituting treatment with more potent statins or adding ezetimibe to reduce lipid levels in our patients we conducted an audit among diabetic patients attending our clinics and chose the target of 100 mg/dl LDL-C for all diabetic patients. In another analysis we set a target of 70 mg/dl for diabetic patients with established CVD, and for all diabetics.

## Patients and Methods

Data on all diabetic patients over age 30 were extracted from two urban clinics of Clalit Health Services, Central District; these clinics together serve about 8000 patients. Clalit is the largest HMO in Israel, covering more than 50% of Israel's population and more than 70% of its elderly population (65 years and above). Every person insured by Clalit is allocated to a primary care physician, either a family physician or a pediatrician. Patients have one doctor to whom they are allocated. All community pharmacies used by the HMO are computerized and report to a central repository. We documented all prescriptions of statins and fibrates that were filled by our patients during the study period. The HMO issues statins and fibrates and requires nominal and almost equal co-payment for all the various statins. The system ensures that all prescriptions are documented and that drug selection by the patient is not influenced by financial factors. In view of the co-payment we assume that most of the medications that were filled were indeed used by the patients.

Calculated LDL-C levels were retrieved from the computerized records of the central laboratory, which performs all tests for the Central District. Patients' personal medical records have been completely computerized since 1999.

For each patient we checked the last total cholesterol, triglyceride, high density lipoprotein-cholesterol and calculated LDL-C measurements in 2006, the brand and the dose of cholesterol-lowering medications, whether a prescription for a cholesterol-lowering drug was actually prescribed in the patient's files, the actual number of tablets that were purchased by the patient over a 4 month period prior to the last lipid profile, and whether treatment changes were needed.

Compliance was defined as purchasing at least 75% of the expected tablets (3 months out of 4). This measure to define compliance in epidemiological database studies is based on purchasing data [10].

A need for a potent statin or ezetimibe was defined when a patient had taken 40 mg/day of simvastatin or more (or equivalent) for the 4 months prior to the lipid profile, with good

compliance and his/her last LDL-C above the target level. We ran three models:

- Model A – target LDL-C < 100 mg/dl for all patients
- Model B – target LDL-C < 70 mg/dl for all patients with established CVD and < 100 mg/dl for all the others.
- Model C – target LDL-C < 70 mg/dl for all patients.

A gap between prescription and purchasing of medications was defined when the patient did not buy any statin in the study period even though his/her physician prescribed statins at least once, as noted in the patient's electronic medical record. From the medical record we tried to determine why the patient stopped taking statins; for example, myopathy or abnormalities in creatine phosphokinase or transaminase levels.

## Statistics

STATA 8.0 TX USA was used for statistical analysis. Chi-square was used for comparison of groups.

## Results

The study population consisted of 630 diabetic patients. The average age was  $66.7 \pm 12.6$  years and 338 (53.6%) were women. In 2006 LDL-C was measured in 533 patients (84.6%) [Table 1]. There were no differences between the two clinics with regard to age, gender, or LDL-C measurements and levels.

We ran three models for target LDL levels. The lower the target the fewer the patients who reached it, and more patients needed higher doses of statins or switching to a more potent statin or ezetimibe. It is noteworthy that 124 patients with LDL-C above 100 were not prescribed any lipid-lowering medication and another 31 patients were prescribed statins but did not buy the medication. Table 2 presents the reasons why LDL-C target levels were not achieved in the three models.

A total of 229 patients had LDL-C levels lower than 100 mg/dl, and only 45 had an LDL-C level below 70 mg/dl. Table 3 compares the patients with different LDL-C levels. The proportion of men and of patients with CVD in the cohort increased as the LDL-C level decreased ( $P < 0.005$ ).

## Discussion

Despite the universal recommendation for a target LDL-C level below 100 mg/dl among diabetic patients, a significant number of patients do not reach this goal. Moreover, about 15% of our diabetic patients did not undergo a single LDL-C measurement during the previous calendar year.

Our study indicates that only a small minority of patients with uncontrolled hypercholesterolemia need, as the first step, to change to a more potent statin to achieve the target LDL-C level. Since we set lower target LDL-C levels, the compliance of physicians with the guidelines and the adherence of patients to their medication regimen are likely to be major problems. Of patients with elevated LDL-C levels, up to 38.3% were not prescribed statins by their physician at all and 27.2% bought only part of their medication. These rates, however, seem to be better than the rate of statin use among diabetic patients in Italy [11].

**Table 1.** Background medical and demographic characteristics of 630 patients

Gender	Men 44.4%
Age (yrs) (mean ± SD)	66.7 ± 12.6
Above 75	186 (29.5%)
Above 85	45 (7.1%)
Diabetes treatment	
Insulin	149 (23.7%)
Oral hypoglycemics	503 (79.8%)
Diet only	76 (12.1%)
Ischemic heart disease	213 (33.8%)
S/p CVA	80 (12.7%)
Peripheral vascular disease	66 (10.5%)
Carotid artery disease	28 (4.4%)
Any cardiovascular disease*	274 (43.5%)
Antilipemic treatment	
Any statin	346 (54.9%)
Simvastatin 20 mg or less	155 (24.6%)
Simvastatin 40 mg or more	74 (11.7%)
Potent statins	13 (2.1%)
Fibrates	38 (6.0%)
Ezetimibe	2 (0.3%)
Transaminases (ALT, AST) (measured in 470 patients, 74.6%)	
Normal	358 (76.2%)
Above upper limit	110 (23.4%)
At least 3 times above upper limit	2 (0.4%)
Creatine phosphokinase (measured in 406 patients, 64.4%)	
Normal	382 (94.1%)
Above upper limit	22 (5.4%)
At least 3 times above upper limit	2 (0.5%)
Lipid profile (measured in 553 patients, 84.6%, mean ± SD) (mg/dl)	
Total cholesterol	181.9 ± 40.7
Triglycerides	153.8 ± 77.9
HDL	42.5 ± 10.9
LDL (calculated)	108.6 ± 33.3

\* Some patients had more than one cardiovascular disease  
ALT = alanine aminotransferase, AST = aspartate aminotransferase

We chose to use the strict recommendation for LDL-C reduction rather than seek the specific reason why the specific patient did not receive the needed treatment since the aim of this study was to assess the need for changing treatment for more potent statins. It probably created a bias of the study results since the recommendation does not take into account the personal relationship that exists between the patient and the primary care physician, a very important factor. Patient's age, general condition, compliance, as well as drug interactions and side effects are important factors when making decisions about treatment. None of these factors was investigated in this study. The importance of clinical judgment is suggested by the larger proportion of CVD patients whose LDL-C levels are below 70 mg/dl. Cotton et al. [12] reported a variety of clinical reasons why physicians do not respond to elevated blood pressure in diabetic patients. Mottur-Pilson and colleagues [13] also found

**Table 2.** Reasons why LDL-C target levels\* were not achieved in 553 diabetic patients with lipid profile measured in 2006

	Model A No. of patients (%)	Model B No. of patients (%)	Model C No. of patients (%)
At target level	229 (41.4%)	129 (23.3%)	45 (8.1%)
Not at target levels	324 (58.6%)	424 (76.7%)	508 (91.9%)
Statins discontinued due to side effects	1 (0.3%)	1 (0.2%)	1 (0.2%)
Were not prescribed cholesterol-lowering drugs	124 (38.3%)	144 (34.0%)	174 (34.2%)
Physician prescribed cholesterol-lowering drugs but compliance was less than 75%	88 (27.2%)	98 (23.1%)	112 (22.0%)
Physician wrote a prescription but the patient did not buy the medication	31 (9.6%)	33 (7.8%)	34 (6.7%)
Need to increase statin dosage	50 (15.4%)	104 (24.5%)	135 (26.6%)
Need to switch to a more potent statin or to add ezetimibe	25 (7.7%)	37 (8.7%)	44 (8.7%)
Use of fibrates only	5 (1.5%)	7 (1.7%)	8 (1.6%)

\*Model A – All patients should achieve LDL < 100 mg/dl  
Model B – Only patients with established cardiovascular disease should achieve  
LDL < 70 mg/dl and the others LDL < 100 mg/dl  
Model C – All patients should achieve LDL < 70 mg/dl.

**Table 3.** Comparison between patients with different LDL-C levels (mg/dl)

	LDL ≤ 70	70 < LDL < 100	LDL ≥ 100	P
No. of patients	45	184	324	
Age (mean) (yrs)	67.6	68.1	66.9	NS
Gender (% men)	62.2%	47.8%	38.2%	0.003
Any CVD	64.4%	54.9%	37.0%	0.000
Were not prescribed cholesterol- lowering drugs	0%	27.1%	38.2%	0.000
Statins discontinued due to side effects	0%	0%	0.31%	NS
Physician wrote a prescription but the patient did not buy the medication	0%	1.6%	9.6%	0.000
Physician prescribed cholesterol-lowering drugs but compliance was less than 75%	13.6%	18.4%	19.9%	NS

that non-compliance with best practices among physicians in diabetes is common.

It is important to note that the proportion of patients with LDL-C < 100 mg/dl in the current study is almost similar to the 44% reported by Israel Ministry of Health 2005 statistics [14]. The percentage of patients without any LDL-C measurements in our group is similar to the rate among diabetic patients in U.S. academic medical centers, and the percentage of patients achieving LDL-C target levels is also similar [15].

Rosuvastatin has been shown to be more effective in reducing LDL-C level than simvastatin and atorvastatin [16]. Yet the results of the present study indicate that only a small minority of diabetic patients may really need one of the more potent statins or ezetimibe as the first change in their treatment. HMO decision makers and physicians should not be misled by heavy-handed and at times aggressive marketing of new treatment modalities.

In conclusion, our findings support the need for more emphasis on compliance and dosage adjustment rather than shifting to potent statins.

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