

## Non-HDL Cholesterol: When—and How—to Treat

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**ABSTRACT:** Reducing low-density lipoprotein cholesterol (LDL-C) levels does not eliminate cardiovascular risk; most patients obtain only a 25% to 35% risk reduction. When the triglyceride level is above 200 mg/dL, non-high-density lipoprotein cholesterol (non-HDL-C) is a more precise therapeutic target than LDL-C. It can serve as an excellent proxy for assessing the total number of circulating atherogenic particles. Non-HDL-C may be superior to LDL-C in predicting cardiovascular disease and should be used as the primary lipid target in persons with diabetes, who characteristically have a dyslipidemia that consists of decreased HDL-C levels, elevated triglyceride levels, and normal to elevated LDL-C levels.

Key words: low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, non-high-density lipoprotein cholesterol, type 2 diabetes mellitus

Over the past 4 decades, our understanding of the role of elevated cholesterol in cardiovascular disease (CVD) has undergone radical change. During that time, we have moved from a belief that cholesterol does not matter and that atherosclerosis is an irreversible process to a strong conviction that treating elevated cholesterol, especially elevated low-density lipoprotein cholesterol (LDL-C), can slow and perhaps halt the progression of atherosclerosis. But it has been a slow process for several reasons.

In the 1960s, the Framingham investigators demonstrated that ele-

vated serum cholesterol is a risk factor for CVD.<sup>1</sup> However, there was no compelling evidence that treating elevated cholesterol reduces cardiovascular events until the Lipid Research Clinics Coronary Primary Prevention Trial in 1984.<sup>2</sup> Cholestyramine resin was used in this trial. The results were not generally accepted by the medical community because the study included only middle-aged men; moreover, cholestyramine is difficult to tolerate.

In 1987 the first statin was introduced. This was a watershed moment because a better-tolerated drug was now available that lowered LDL-C more effectively than other pharmacological agents. But it was not until the late 1990s that studies clearly demonstrated a reduction in cardiovascular events across a broad range of patients. The results of the Heart Protection Study, one of the most influential trials, were not published until 2002.<sup>3</sup> This and other landmark studies conclusively demonstrated that elevated cholesterol, specifically elevated LDL, poses significant risk and that lowering it will reduce cardiovascular events.

However, lowering LDL-C does not completely eliminate risk. Most patients obtain only a 25% to 35% risk reduction. A patient treated with a statin therefore has a residual risk of 65% to 75% of his or her pre-treatment risk.<sup>4</sup> In many cases, additional drugs are required to reduce risk further.<sup>5</sup> This creates problems with cost, additional adverse effects, drug interactions, and patient acceptance. Here I present a case that demonstrates the challenges facing clinicians, and I dis-

**Table 1 – Achievement of LDL-C and non-HDL-C goals in high-risk patients<sup>a</sup> in the NEPTUNE II survey**

Patient category	Achieved LDL-C goal (%)	Achieved non-HDL-C goal (%)
Moderately high risk	38	23
Very high risk	23	4

<sup>a</sup> Patients had triglyceride levels of > 200 mg/dL.

LDL-C, low-density lipid cholesterol; HDL-C, high-density lipid cholesterol; NEPTUNE, National Cholesterol Education Program (NCEP) Evaluation Project Utilizing Novel E-Technology.

Data from Davidson MH et al. *Am J Cardiol.* 2005.<sup>16</sup>

cuss how these challenges can best be addressed.

**A PATIENT AT RISK:  
WOMAN WITH DIABETES,  
PREVIOUS MI,  
AND DYSLIPIDEMIA**

*Mrs S. is a 58-year-old postmenopausal Hispanic woman who comes to a primary care office because of increasing fatigue. She has a family history of diabetes. She has 3 children, and she thinks she had “a touch of diabetes” with her last pregnancy. One year earlier she had a myocardial infarction (MI), and her blood glucose level was found to be elevated.*

*Her examination is unremarkable except for a body mass index (BMI) of 28, blood pressure (BP) of 140/88 mm Hg, and decreased sensation in both feet. Laboratory studies reveal the following values: hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), 7.8%; fasting blood glucose, 185 mg/dL; normal complete blood cell count, creatinine, and blood urea nitrogen; triglycerides, 350 mg/dL; total cholesterol, 200 mg/dL; LDL-C, 105 mg/dL; high-density lipoprotein cholesterol (HDL-C), 25 mg/dL; and non-HDL-C, 175 mg/dL. She is treated with lifestyle changes, metformin, and an angiotensin-converting enzyme inhibitor.*

*When she returns 3 months later, she has lost 5 lb and now walks 3 days a week. Her BMI is 27, and BP is*

*130/78 mm Hg. HbA<sub>1c</sub> level is 6.3%; triglycerides, 250 mg/dL; total cholesterol, 200 mg/dL; LDL-C, 120 mg/dL; HDL-C, 30 mg/dL; and non-HDL-C, 170 mg/dL.*

**BEYOND LDL-C LOWERING**

This case raises several questions. Why did her LDL-C level increase instead of decrease? The LDL-C level obtained in most lipid profiles is calculated using the Friedewald formula<sup>6</sup>: total cholesterol minus HDL-C minus triglycerides divided by 5. Thus, to calculate this patient's initial LDL-C level: (200 – 25) – (350/5) = 105.

Although random variation (up to 19%) can influence numbers when retesting, the formula may create a false impression by underestimating the LDL-C level when the triglyceride level is high. As the level of triglycerides increases, the LDL-C level mathematically decreases, and as triglycerides decrease, LDL-C increases. So the change in LDL-C is a reflection of the change in triglycerides. This is why the National Cholesterol Education Program (NCEP) guidelines state that the LDL-C level is not a valid basis for therapeutic decisions when the triglyceride level is over 200 mg/dL.<sup>7</sup>

The next question is, How is the non-HDL-C level useful? Obtaining a non-HDL-C level does not require

additional testing. If the total cholesterol and HDL-C values are in the patient's chart, the non-HDL-C level can be calculated as follows: total cholesterol minus HDL-C. Thus, to calculate this patient's initial non-HDL-C level: 200 – 25 = 175.

Patients with type 2 diabetes characteristically have a dyslipidemia that consists of decreased HDL-C levels, elevated triglyceride levels, and normal to elevated LDL-C levels.<sup>8</sup> The NCEP recognizes hypertriglyceridemia as a risk factor for coronary artery disease; in its guidelines, non-HDL-C is identified as the therapeutic target rather than LDL-C if the triglyceride level is greater than 200 mg/dL.<sup>7</sup> Subsequent studies have demonstrated that the level of non-HDL-C predicts CVD in persons with diabetes.<sup>9</sup> Moreover, non-HDL-C may be superior to LDL-C in predicting CVD and should be used as the primary lipid target in persons with diabetes.<sup>10</sup> Non-HDL-C contains the highly atherogenic, small, dense lipoproteins that are associated with a high incidence of CVD.<sup>11</sup>

**A NEW THERAPEUTIC TARGET**

*For Mrs S., non-HDL-C is now the target. The goal for non-HDL-C is 30 mg/dL higher than the goal for LDL-C. For persons with diabetes, the goal for LDL-C is 100 mg/dL and the non-HDL-C goal is 130 mg/dL. Because Mrs S. has diabetes and a history of a cardiovascular event, her goals should be the optional NCEP targets of an LDL-C level of 70 mg/dL and a non-HDL-C level of 100 mg/dL.<sup>12</sup>*

*She is treated with atorvastatin, 10 mg/d. Three months later, her HbA<sub>1c</sub> level is 6.2%; triglycerides, 201 mg/dL; total cholesterol, 145 mg/dL; LDL-C, 70 mg/dL; HDL-C, 35 mg/dL; and non-HDL-C, 110 mg/dL. Treatment has significantly reduced total cholesterol, LDL-C, and non-HDL-C levels, but her triglyceride level re-*

mains over 200 mg/dL and her HDL-C level is 35 mg/dL. For women, the NCEP goal for triglycerides is 150 mg/dL or lower; and the goal for HDL-C is 50 mg/dL or higher.<sup>7,12</sup>

#### REDUCING RESIDUAL CARDIOVASCULAR RISK

Has this patient's risk of a cardiovascular event been reduced to an acceptable level? Should she receive any additional treatment? Her LDL-C level is at goal, but non-HDL-C is the therapeutic target when the triglyceride level is over 200 mg/dL. Her non-HDL-C is lower than the stan-

dard goal of 130 mg/dL but is not at the optional goal of 100 mg/dL.

When niacin is added to a statin, cardiovascular risk reduction can be increased to 80% to 90%.<sup>13,14</sup> Niacin increases HDL-C levels by 25% to 35% and decreases triglyceride levels by 20% to 30%. In studies, the patients who obtained the greatest risk reduction were similar to Mrs S. in that they had high triglyceride levels and low HDL-C levels before treatment was started.

Niacin does not increase statin-related side effects; however, it has its own adverse effects. About 5% of pa-

tients may not tolerate niacin because of flushing. One adult-strength aspirin taken with niacin in the evening significantly reduces this effect. Another adverse effect of niacin is a mild increase in levels of blood glucose and uric acid. The blood glucose elevation is usually small and is easily controlled in most cases. Closer monitoring of blood glucose levels and HbA<sub>1c</sub> is recommended when niacin is started. The newer formulation of niacin (Niaspan) has a more favorable side-effect profile. In my experience, the newer formulation produces less flushing and less elevation in blood glucose levels.

**Table 2 – Sample report card for a male patient with type 2 diabetes mellitus**

	Goal	Oct 2007	July 2007	Jan 2007
Weight (lb)		185	201	201
BMI		31	34	34
Waist size (in)	< 40	42	44	44
BP (mm Hg)	< 120/80	135/80	155/88	140/89
Eye check	Once a year	Done		
Foot check	Once a year	Done		
HbA <sub>1c</sub>	≤ 6	7.0	8.5	7.9
Total cholesterol (mg/dL)	≤ 135	185	222	222
LDL-C (mg/dL)	≤ 70	105	145	144
HDL-C (mg/dL)	≥ 40	44	33	35
Non-HDL-C (mg/dL)	≤ 100	141	189	187
Triglycerides (mg/dL)	≤ 150	144	188	200
Urinary microalbumin	Once a year	Not done		
Influenza vaccine	Once a year	Done		
Aspirin	Daily	Yes	No	Yes
Group visit		Yes	Yes	No
Pneumococcal vaccine	Once or twice if given before age 65	First one given		

BMI, body mass index; BP, blood pressure; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Table 3 – Sample report of achievement of LDL-C and non-HDL-C goals in 3 practices

Primary care practice	No. of patients with very high LDL-C (> 130 mg/dL)	No. of patients with high LDL-C ( $\geq 100 \leq 130$ mg/dL)	No. of patients with very high non-HDL-C (> 160 mg/dL)	No. of patients with high non-HDL-C (> 130 - $\leq 160$ mg/dL)
Clinic 5	60	88	70	150
Clinic 11	92	135	114	197
Clinic 15	140	208	158	389

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

*Niaspan, 500 mg in the evening, is prescribed for Mrs S., and the dose is increased monthly by 500 mg to 2000 mg total. She is able to tolerate the medication. She returns 6 months later, and her triglyceride level is 150 mg/dL; total cholesterol, 137 mg/dL; LDL-C, 60 mg/dL; HDL-C, 47 mg/dL; and non-HDL-C, 90 mg/dL. Her HbA<sub>1c</sub> level is 6.4%.*

She also could have been treated with a higher dose of a statin, a fibrate, or fish oil. Fish oil decreases triglyceride levels and has minimal effect on HDL-C. Fibrates have a significant effect on triglycerides, but they are not as effective as niacin in increasing HDL-C levels. Statins have some effect on both triglycerides and HDL-C, but not to the same degree as the other agents.

#### NON-HDL CHOLESTEROL: THE FORGOTTEN TARGET

Unfortunately, most physicians are not aggressive in treating elevated non-HDL-C.<sup>15</sup> **Table 1** compares the achievement of LDL-C goals with that of non-HDL-C goals in both moderately high-risk and very high-risk patients from a national survey.<sup>16</sup> This survey included patients with triglyceride levels over 200 mg/dL who were undergoing outpatient lipid management by physicians who were high prescribers (top 26%) of lipid-altering drugs. The percentage of patients who achieved the non-HDL-C

goal was lower than that of those who achieved the LDL-C goal, especially in the very high-risk group. These results are disappointing, but they are indicative of the time it takes for national guidelines to be adopted.

Physicians will not use non-HDL-C level as a goal if it is not part of the lipid profile report they receive. The Diabetes Master Clinician Program (DMCP) of the Florida Academy of Family Physicians through its Internet-based diabetes registry provides all of its members with an automatic calculation of non-HDL-C levels.<sup>17,18</sup> The registry contains several items, including the lipid values of all the patients in the database.

Physicians are provided with 2 types of reports for their patients with diabetes. The reports identify the level of goal achievement for diabetes quality indicators, including lipid goals. One report is used during the traditional office visit in managing an individual patient (**Table 2**), and the other aids the physician in identifying high-risk patients in the practice (**Table 3**). Teaching physicians how to use data from the registry is a key component of the DMCP.

Table 3 contains reports of the total number of patients who are above goal in 3 of the physician's offices that use the database. The reports show that fewer patients are at goal for non-HDL-C than for LDL-C. Positioning the cursor over one of the num-

bers produces a report of all the patients in that category for the practice. The physician can use this as a tool to identify high-risk patients who may have "fallen through the cracks" of an everyday busy office practice.

#### KEY TAKE-HOME POINTS

- The non-HDL-C level is a convenient, practical lipid value that can serve as an excellent proxy for assessing the total number of circulating atherogenic particles. It is a more precise therapeutic target than LDL-C when the triglyceride level is above 200 mg/dL.
- Patients who have an increased residual cardiovascular risk after maximal LDL-C reduction can be identified by their non-HDL-C level.
- Reaching ideal goals for non-HDL-C, especially in persons with diabetes, is one of the most significant means of reducing cardiovascular events.■

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#### Therapeutic Agents in This Article

Atorvastatin (Lipitor)  
Cholestyramine\* (Questran)  
Fish oil\*  
Metformin\* (Glucophage)  
Niacin\* (Niacor, Niaspan  
[extended-release])

\*Available in a generic formulation.

Filler