Clinical Relevance of Non-HDL Cholesterol in Patients With Diabetes

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It is well known that people with type 2 diabetes have elevated cardiovascular risk. Adults with diabetes have a two to four times higher risk of experiencing cardiovascular events than adults without diabetes,[1,2] and their relative risk of dying from cardiovascular disease (CVD) is about twice as high.[3] Many factors account for increased CVD risk in diabetes, but lipid abnormalities are major contributors. The common lipid abnormality of diabetes, diabetic dyslipidemia, is characterized by elevated triglycerides, low levels of HDL cholesterol, and increased presence of small, dense LDL particles (Table 1).[4] Although LDL cholesterol is not typically elevated in patients with diabetes, the changes in LDL composition that can accompany the disease make the LDL exceptionally atherogenic.[5,6] In fact, once triglyceride levels exceed 100 mg/dl, the atherogenic small, dense LDL particles predominate.[7]

Clinical trial evidence has demonstrated that CVD risk in diabetes can be significantly reduced through lipid-lowering therapy with HMG-CoA reductase inhibitors (statins).[8,9] A meta-analysis of > 90,000 patients in randomized statin trials found that in people with a history of diabetes, the 5-year incidence of major coronary events was reduced by ~ 25% for each 39 mg/dl reduction in LDL cholesterol ($P < 0.0001$).[9] Nevertheless, despite current guidelines recommending statins as first-line lipid-lowering therapy in diabetes,[10] many diabetic individuals do not achieve recommended cholesterol goals of LDL < 100 mg/dl and, for those with hypertriglyceridemia, non-HDL cholesterol < 130 mg/dl.

According to a recent survey, the second National Cholesterol Education Program (NCEP) Evaluation Project Utilizing Novel E-Technology (NEPTUNE II), which assessed the success of prescribers of lipid-lowering therapy in treating patients to their NCEP Adult Treatment Panel (ATP) III cholesterol targets, only 55% of patients with diabetes reached their LDL cholesterol goals (compared with 62% of patients with

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IN BRIEF

Patients with type 2 diabetes have high rates of cardiovascular disease (CVD), much of which may be preventable with appropriate treatment of lipid abnormalities. Diabetic dyslipidemia most commonly manifests as elevated triglycerides and low levels of HDL cholesterol, with a predominance of small, dense LDL particles amid relatively normal LDL cholesterol levels. In diabetic patients, non-HDL cholesterol may be a stronger predictor of CVD than LDL cholesterol or triglycerides because it correlates highly with atherogenic lipoproteins. Target goals for LDL and non-HDL cholesterol in patients with diabetes are < 100 and < 130 mg/dl, respectively. Failure to consider the importance of non-HDL cholesterol in type 2 diabetes may result in undertreatment of patients with diabetes.

CVD).[11] Goal attainment was even lower for patients with hypertriglyceridemia, in whom reduction of both LDL and non-HDL cholesterol is recommended; only 25% of hypertriglyceridemic patients with diabetes reached goals for both LDL and non-HDL cholesterol, compared with 33% of those with CVD.[11] These treatment gaps suggest that physicians and their patients may not fully appreciate the importance of controlling dyslipidemia in the presence of diabetes.

What Is Non-HDL Cholesterol?
Non-HDL cholesterol measurement (calculated as total cholesterol minus HDL cholesterol) provides a single index of all the atherogenic, apolipoprotein (apo) B–containing lipoproteins—LDL, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and lipoprotein(a). Although apo B can be assessed directly, measurement of non-HDL cholesterol is more practical, reliable, and inexpensive and is accepted as a surrogate marker for apo B in routine clinical practice.[10,12] Unlike LDL cholesterol, which can be incorrectly calculated in the presence of postprandial hypertriglyceridemia, non-HDL cholesterol is reliable when measured in the nonfasting state.[10]

Because non-HDL cholesterol measures the apo B–containing lipoproteins, it can serve as an additional tool to assess cardiovascular risk in people whose risk is not accurately identified by LDL cholesterol alone.[6,13] This is especially important in patients with diabetes, in whom LDL levels may

Table 1. Typical Lipid Profile of Diabetes Compared With Nondiabetic, Healthy People	
Lipid Component	**Status**
• LDL	• Normal, with greater number of small, dense particles
• HDL	• Low
• Triglycerides	• Elevated

not be significantly elevated. Moreover, non-HDL cholesterol is particularly atherogenic in the presence of the hypertriglyceridemia that usually accompanies diabetes.[10,13]

Atherogenicity of Non-HDL Cholesterol and Triglyceride-Rich Lipoproteins

Just as LDL is the primary carrier of cholesterol in plasma, two remnant lipoproteins—VLDL and IDL—are the main carriers of triglycerides. These triglyceride-rich lipoproteins (TGRLPs) also carry cholesterol.[13] In the presence of hypertriglyceridemia, TGRLPs may be partly depleted of their triglyceride content and become enriched with cholesterol from LDL. The modified remnant lipoproteins that result are believed to be highly atherogenic because of their small size, high cholesterol content, and increased residence time in plasma.[12–14] They are able to deliver more cholesterol to macrophages than LDL particles[15] because they can penetrate the arterial wall with ease, be taken up directly by macrophages, and participate in foam cell formation,[4,16] thus initiating the lipid-laden plaque.

At the same time, LDL exchanges core lipids with VLDL to become triglyceride rich and undergoes lypolysis, resulting in a smaller and denser LDL particle.[14] These compacted, lipid-depleted LDL particles are more atherogenic because they are more easily oxidized and readily penetrate the artery wall. However, even though the small, dense LDL particles are greater in both number and atherogenicity than normal-sized LDL, LDL cholesterol levels appear "normal" rather than "high" on standard measurements because small, dense particles are lipid poor.[14]

Therefore, the measurement of LDL cholesterol alone does not provide sufficient measure of atherogenic risk[10] in hypertriglyceridemic patients, and a second measure of atherogenic risk is warranted.

Non-HDL Cholesterol and CVD Risk Prediction

Elevated non-HDL cholesterol signifies increased CVD risk, even if LDL cholesterol levels are at or below the NCEP goal or appear "normal."[12] In clinical trials, non-HDL cholesterol has been shown to independently predict CVD.[17,18] In patients with diabetes, non-HDL cholesterol may be a stronger predictor of CVD than either LDL cholesterol or triglycerides.[6] In the Strong Heart Study, patients with diabetes in the highest tertile of non-HDL cholesterol had a higher hazard ratio for myocardial infarction (3.17) than they did with any other lipid parameter (1.96 for LDL cholesterol and 2.04 for triglycerides) compared with those in the lowest tertile. They also had the second highest hazard ratio for coronary heart disease (CHD) (2.75 vs. 1.90 for LDL, 2.12 for triglycerides, and 3.06 for the total/HDL cholesterol ratio).[6] This finding was noted after adjustment for covariates including age, sex, BMI, and systolic blood pressure.

There is also evidence to suggest that, in patients with diabetes, non-HDL cholesterol is a stronger predictor of mortality from coronary disease than LDL cholesterol. In a post hoc analysis of patients with diabetes from four prospective cohort studies—the Framingham Cohort Study, the Framingham Offspring Study, the Lipid Research Clinics Prevalence Follow-Up Study, and the usual-care group of the Multiple Risk Factor Intervention Trial—the relative risk of death for diabetic (compared with nondiabetic) patients was 7.2 for those with elevated non-HDL cholesterol ≥ 130 mg/dl) and low LDL (< 100 mg/dl) and 5.7 for those with low non-HDL cholesterol (< 130 mg/dl) and elevated LDL (≥ 100 mg/dl).[3]

Guidelines for Setting Non-HDL Cholesterol Goals in Diabetes

Although LDL cholesterol remains the primary target of therapy in dyslipidemic patients, the NCEP considers non-HDL cholesterol a secondary target in people with elevated triglycerides ≥ 200 mg/dl), many of whom are diabetic.[4,12] The recommended non-HDL cholesterol goal is 30 mg/dl above the LDL goal (Table 2).[10] Both the NCEP and the American Diabetes Association recommend reducing LDL cholesterol to a goal of < 100 mg/dl in patients with diabetes.[10,19] Thus, a person with diabetes would have an LDL cholesterol target of < 100 mg/dl and a non-HDL cholesterol target of < 130 mg/dl.

Using Non-HDL Cholesterol to Assess Risk in a Typical Patient With Diabetes

The following case illustrates how failure to consider the importance of

Table 2. NCEP ATP III Goals for LDL Cholesterol and Non-HDL Cholesterol in High-Risk Patients		
Risk Category	**Primary Target: LDL Cholesterol**	**Secondary Target: Non-HDL Cholesterol**
• CHD or CHD risk equivalents, including diabetes	< 100 mg/dl	< 130 mg/dl

non-HDL cholesterol may result in the undertreatment of patients with diabetes.

R.R. is a 55-year-old man with a recent diagnosis of type 2 diabetes. He was previously noted to have impaired fasting glucose, for which he was prescribed a program of weight reduction and increased physical activity, as well as hypertension (140/85 mmHg), for which he was treated with an angiotensin receptor blocker. However, lifestyle changes are extraordinarily difficult for most people, and R.R. remained sedentary and obese (280 lb, 5 feet, 11 inches tall, BMI 39 kg/m²). His fasting blood glucose level at diabetes diagnosis was 177 mg/dl.

R.R.'s lipid profile was:
- Total cholesterol: 207 mg/dl
- Triglycerides: 364 mg/dl
- HDL cholesterol: 36 mg/dl
- LDL cholesterol: 98 mg/dl
- Non-HDL cholesterol: 171 mg/dl

Because the patient's LDL level was already at goal, no steps were taken to start him on statin therapy to achieve further reductions. In addition, although the NCEP ATP III guidelines recommend lowering non-HDL cholesterol as a secondary goal when hypertriglyceridemia (triglycerides > 200 mg/dl) is present,[10] this patient's non-HDL level was not targeted for therapy. Not surprisingly, several years later, the patient was found to have severe coronary artery disease and required coronary artery bypass grafting.

This case illustrates a mistake too often made with patients with diabetes: LDL status is used exclusively to guide cholesterol management, and an opportunity to lower cardiovascular risk is missed. Had the NCEP ATP III recommendations of aggressive reduction of LDL cholesterol and non-HDL cholesterol been applied to R.R., his outcome would probably have been more favorable. His triglyceride level of 364 mg/dl would have drawn attention to TGRLP-related atherogenic risk and to the necessity of lowering his

non-HDL cholesterol to < 130 mg/dl, well below his initial level of 171 mg/dl. Statin therapy would have been started promptly with the express purpose of reducing atherogenic cholesterol and CVD risk. A fibrate also may have been warranted to treat his triglycerides.

Treating Non-HDL Cholesterol in Patients With Diabetes: Recent Findings

Reduction of non-HDL cholesterol can be accomplished with intensification of statin therapy, use of a statin with greater LDL-lowering efficacy, or the addition of a fibrate or niacin specifically to enhance VLDL reduction.[10,20] Overall, statins have a greater ability than other lipid-lowering drugs to beneficially affect the entire range of atherogenic lipoproteins, including the atherogenic components of non-HDL cholesterol.[4,10,13] Statins slow the secretion of VLDL from the liver and attenuate the subsequent formation of IDL and LDL. They also increase the clearance of IDL and LDL from plasma.[4,13] Generally, statins lower non-HDL and LDL cholesterol by similar percentages.[21] More efficacious statins can also adequately lower triglycerides, especially in combination with aggressive therapeutic lifestyle changes, including weight reduction and increased physical activity.[10,19]

Recent clinical trials support the use of statin therapy in patients with type 2 diabetes. An analysis of 5,963 diabetic adults in the Heart Protection Study showed that simvastatin reduced the rate of first major cardiovascular events by 22% ($P < 0.0001$) in all patients with diabetes, by 33% ($P = 0.0003$) in those without occlusive vascular disease, and by 27% ($P = 0.0007$) in those without elevated LDL cholesterol.[22] The 2,532 patients with diabetes receiving atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm study had a significant 23% reduction in total cardiovascular events and procedures compared with

those given placebo (116 vs. 152 events; $P = 0.036$).[23]

The primary prevention Collaborative Atorvastatin Diabetes Study assessed whether statin therapy could make a significant difference in CVD outcomes in 2,838 patients with type 2 diabetes but without elevated levels of LDL cholesterol (< 130 mg/dl in two-thirds of the group).[24] Compared with placebo, atorvastatin, 10 mg, was associated with a 37% reduction in risk of first CVD events ($P = 0.001$) and a nonsignificant yet robust 27% decrease in all-cause mortality ($P = 0.059$). Atherogenic lipids and lipoproteins were significantly decreased relative to baseline as follows: LDL cholesterol (40%; $P < 0.0001$), non-HDL cholesterol (36%; $P < 0.0001$), and triglycerides (19%; $P < 0.0001$).[24]

Three non-outcomes studies investigated intensive lipid lowering in patients with diabetes with varying dose levels of rosuvastatin. In A Randomized Double-blind Study to Compare Rosuvastatin and Atorvastatin in Patients with Type 2 Diabetes, 509 patients were treated with either statin at 10 and 20 mg/day for 8 weeks at each dosage. By 16 weeks, mean LDL and non-HDL cholesterol reductions with rosuvastatin were 57.4 and 50.6%, respectively, compared with 46 and 41.5% with atorvastatin ($P < 0.001$).[20] The Compare Rosuvastatin with Atorvastatin on ApoB/ApoA1 Ratio in Patients With Type 2 Diabetes Mellitus and Dyslipidemia study used a wider dose range of rosuvastatin (10–40 mg) and atorvastatin (20–80 mg) over 18 weeks in 263 patients with diabetes. Rosuvastatin was associated with significantly greater reductions than atorvastatin in a variety of lipid parameters, including LDL cholesterol (53.6 vs. 47.8%; $P < 0.01$), non-HDL cholesterol (49.6 vs. 44.4%; $P < 0.05$), and the apoB/apoA1 ratio (40.5 vs. 35.8%; $P < 0.05$).[25] The full benefit of these differences in lipid lowering will need to be confirmed with cardiovascular outcomes studies, as well as the benefit

of combination therapy with simvastatin plus ezetimibe. In one intermediate outcomes study comparing rosuvastatin to placebo in lower-risk patients with subclinical atherosclerosis, rates of progression of plaque as measured by carotid intimal medical thickness were reduced by the drug.[26,27]

Results With Non-Statin Treatments

Fibrates lower triglycerides and raise HDL cholesterol; however, they are not considered first-line lipid-lowering therapy in diabetes,[10] possibly because convincing evidence does not yet exist that fibrates prevent CVD in patients with diabetes.[28] In the 5-year Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study of almost 10,000 patients with type 2 diabetes, fenofibrate did not significantly reduce the primary outcome of first myocardial infarction or CHD death (11% relative risk reduction, $P = 0.16$). However, it did decrease the secondary outcome, risk of total CVD events, through significant reductions of 24% in nonfatal myocardial infarction ($P = 0.01$) and 21% in coronary revascularizations ($P = 0.003$). Compared with placebo, fenofibrate achieved a 14.7% reduction in LDL cholesterol, a 27.3% reduction in triglycerides, and a 15.7% reduction in apo B.[29] One possible explanation for the nonsignificant reduction in the primary end point in FIELD is the high use of statins in the placebo arm.[30]

Recent data have emerged suggesting that fibrates may confer additional cardiometabolic risk protection. For example, the 18-year follow-up data from the Helsinki Heart Study have revealed a 33% reduction in all-cause mortality ($P = 0.03$) and a 71% reduction in CHD mortality ($P < 0.001$) in patients receiving gemfibrozil who were in the highest tertile of both BMI and triglyceride level at baseline.[31] Additionally, a recent analysis of the Bezafibrate Infarction Prevention study has shown that worsening of insulin resistance was attenuated by bezafibrate compared with placebo.[32]

Another potential approach to risk reduction in diabetes is the use of pioglitazone, which, in addition to lowering blood glucose, has been shown to favorably affect lipids, blood pressure, and other cardiovascular risk factors in patients with diabetes.[33] The secondary-prevention Prospective Pioglitazone Clinical Trial in Macrovascular Events study randomized 5,238 patients with diabetes to placebo or pioglitazone in addition to their usual diabetes, hypertension, or lipid (primarily statins) medications for almost 3 years. Compared with placebo, pioglitazone reduced the primary end point, a composite of cardiovascular events, by a nonsignificant 10% ($P = 0.095$), although the main secondary end point, a composite of all-cause mortality, nonfatal myocardial infarction, and stroke, was significantly reduced by 16% ($P = 0.027$).[34] Heart failure hospitalizations were significantly increased with pioglitazone (6 vs. 4% with placebo; $P = 0.007$), yet heart failure mortality was not significantly different between the pioglitazone and placebo groups. Lipid changes were as expected, with a reduction in triglycerides and an increase in HDL cholesterol, with a small but significant increase in LDL cholesterol (7.2 with pioglitazone vs. 4.9 with placebo; $P = 0.003$).

Conclusions

Current treatment guidelines consider non-HDL cholesterol to be an important CVD risk predictor and therapeutic target in patients with diabetic dyslipidemia. Reflecting the full complement of atherogenic lipoproteins, rather than LDL cholesterol alone, non-HDL cholesterol is responsive to statin therapy in patients with type 2 diabetes, both with and without elevated LDL. Although non-HDL cholesterol is considered a secondary target of therapy, it is associated with increased CVD risk in patients with diabetes with hypertriglyceridemia, even if the LDL cholesterol goal of < 100 mg/dl has been reached. A recent update to the NCEP guidelines[21] has endorsed an even lower LDL cholesterol goal (< 70 mg/dl) for very-high-risk patients, such as those with type 2 diabetes and CVD. Intensive treatment with statin therapy has provided dramatic cardiovascular risk reduction through tenacious lowering of LDL, non-HDL, and other atherogenic lipoproteins in these and other high-risk groups. Appropriate attention to measuring, targeting, and treating non-HDL cholesterol in patients with diabetes can help to limit instances in which high-risk lipid profiles remain unrecognized and unaddressed.

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