

Updates in Dyslipidemia

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Assessing Global Cardiometabolic Risk: The Role of Lipid Abnormalities

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Target Audience

Nurse practitioners (NPs) and physician assistants (PAs) in primary care practice.

Activity Goal

To familiarize NPs and PAs in primary care practices with the emerging concept of cardiometabolic risk, the lipid

abnormalities and other factors that contribute to this risk, and practical strategies for risk assessment.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Assess an individual patient's global coronary heart disease (CHD) risk based on cardiometabolic risk factors.
- Compare the clinical utility of low-density lipoprotein cholesterol, apolipoprotein B, and non-high-density lipoprotein cholesterol in determining a patient's CHD risk level.
- Use physical findings, laboratory studies, and current practice guidelines to identify patients with mixed dyslipidemia who have residual CHD risk despite statin monotherapy.

Accreditation Information

The University of Nebraska Medical Center College of Nursing Continuing Nursing Education is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is provided for 1.0 contact hour under ANCC criteria.

Provided for 1.2 contact hours under Iowa Provider #78. Provider approved by the California Board of Registered Nursing, Provider #13699 for 1.2 contact hours.



This program has been reviewed and is approved for a maximum of 1.0 hour of AAPA Category I CME credit by the Physician Assistant Review Panel. Approval is valid for 1 year from the issue date of April 1, 2010. Participants may submit the self-assessment at any time during that period.

This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

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The estimated time to complete this activity is 1 hour.

Release date: April 1, 2010

Expiration date: April 1, 2011

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High blood cholesterol is a prominent, modifiable risk factor for atherosclerosis, which can lead to the development of coronary heart disease (CHD).^{1,2} In the United States, CHD accounts for approximately 1 in every 5 deaths; the lifetime risk of developing CHD after age 40 years is 49% for men and 32% for women.² The Centers for Disease Control and Prevention estimates that a 10% decrease in total cholesterol (TC) levels would result in a 30% reduction in the incidence of CHD.³

During the past 2 decades, primary and secondary prevention of CHD has focused on lowering low-density lipoprotein cholesterol (LDL-C) levels, primarily with statins.⁴ Statin therapy is estimated to have prevented or postponed 16,580 CHD deaths from 1980 through 2000.⁵ However, there is a growing recognition that CHD risk persists even in patients with optimal LDL-C levels.⁶ Despite improvements in LDL-C levels, management of patients with dyslipidemia in the United States remains suboptimal. Of the estimated 101 million US adults with dyslipidemia, only about 35.3 million are receiving lipid therapies, and less than one third of treated patients are achieving their risk-stratified lipid goals.⁷

Consequently, other modifiable markers for CHD risk, beyond elevated LDL-C levels, are being examined. Attention is turning to elevated apolipoprotein B (apo B) and non-high-density lipoprotein cholesterol (non-HDL-C) levels, hypertriglyceridemia, low HDL-C levels, inflammation, metabolic syndrome, and the contribution of these risk factors to global cardiometabolic risk (CMR). The benefits of combination therapy for multifactorial cardiovascular risk reduction also are being examined.^{1,8}

This issue of *Updates in Dyslipidemia* is the first of 2 continuing education newsletters on managing dyslipidemia.

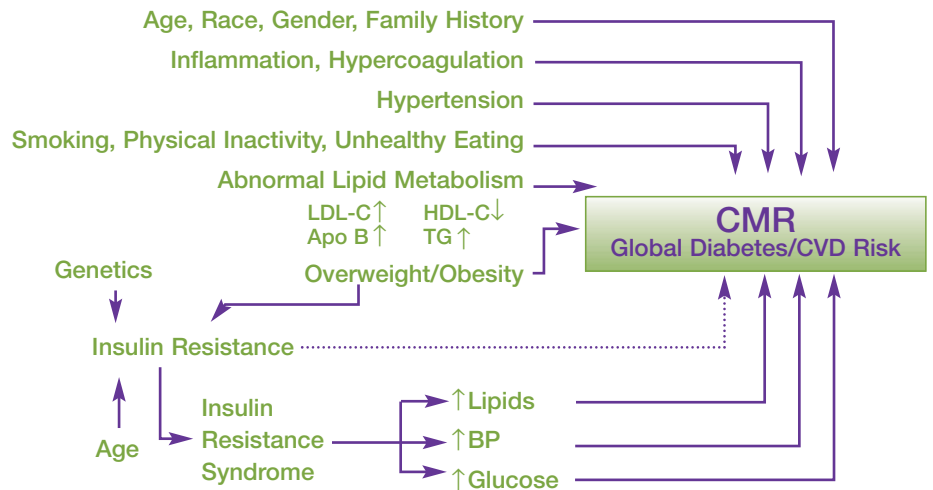


Figure 1. Factors contributing to CMR. BP = blood pressure. Brunzell JD, et al.³⁵

This issue focuses on the emerging concept of global CMR, the lipid abnormalities and other factors that contribute to this risk, and strategies for risk assessment. For a case-based discussion of CMR in a patient with dyslipidemia, see *Case: 68-Year-Old Man With Dyslipidemia*, page 9.⁹

What Is Cardiometabolic Risk?

CMR is a constellation of risk factors, including hypertension, insulin resistance, mixed (atherogenic) dyslipidemia, abdominal obesity, and physical inactivity, that increase an individual's

risk of developing cardiovascular disease (CVD) and type 2 diabetes (Figure 1).¹ Although these risk factors tend to cluster in individuals with CMR, each of these risk factors can occur in isolation.

Metabolic syndrome is a subset of CMR characterized by hypertension, impaired glucose metabolism, lipoprotein abnormalities (elevated triglycerides [TGs] and decreased HDL-C), and central obesity (see *How to Recognize Metabolic Syndrome*, page 3).¹⁰ Metabolic syndrome affects at least 20% to 25% of the world's adult population.¹¹ In the United States, an estimated 76 million adults aged ≥20 years and 2.9 million

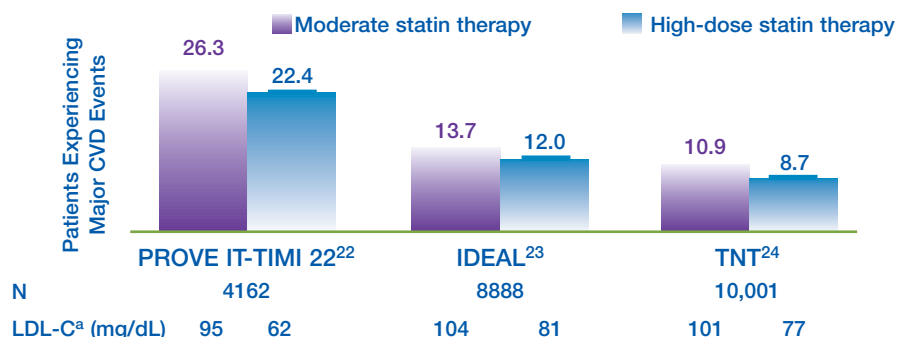


Figure 2. Residual CVD risk in patients treated with intensive statin therapy. ^aMean or median LDL-C after treatment. Cannon CP, et al.²²; Pedersen TR, et al.²³; LaRosa JC, et al.²⁴

adolescents aged 12 to 19 years have metabolic syndrome.¹²

A systematic review and meta-analysis of longitudinal studies concluded that metabolic syndrome increases the risk of incident cardiovascular events and death approximately 2-fold (relative risk [RR], 1.78; 95% confidence interval [CI], 1.58-2.00) and that the risk is higher in women than in men (RR 2.63 vs 1.98, $P = .09$). Even after adjustment for its component risk factors, metabolic syndrome remains a predictor of cardiovascular events and death (RR, 1.54; 95% CI, 1.32-1.79).¹³ The cardiovascular mortality rate associated with metabolic syndrome increases as more components of the syndrome are present.¹⁴ Metabolic syndrome, in addition, increases the risk of developing type 2 diabetes 5-fold.¹⁵

Are You Overlooking Residual CHD Risk After Statins?

LDL has a central role in the initiation and progression of atherosclerosis and thus is the most important atherogenic lipoprotein (see *Role of LDL in Atherogenesis*, page 5).^{1,16-19} Although LDL-C is the primary target of dyslipidemia management, evidence from several lipid-lowering trials have indicated that CHD events occur despite patients having on-treatment LDL-C levels within recommended limits.

A recent analysis of the Get With The Guidelines database showed that approximately half of the almost 137,000 patients hospitalized for coronary artery disease (CAD) had admission LDL-C levels <100 mg/dL.²⁰ In a meta-analysis of 14 statin studies that included more than 90,000 patients, lowering LDL-C by 39 mg/dL was associated with about a 20% reduction in the 5-year incidence of major cardiovascular events.²¹ However, the 5-year residual risk of vascular events remained high, with 14% of statin-treated patients experiencing vascular events

How to Recognize Metabolic Syndrome

Common criteria for the clinical diagnosis of metabolic syndrome were recently proposed in a joint statement from the International Diabetes Federation (IDF); the National Heart, Lung, and Blood Institute (NHLBI); the American Heart Association (AHA); the World Heart Federation (WHF); the International Atherosclerosis Society (IAS); and the International Association for the Study of Obesity (IASO). According to this statement, the clinical diagnosis of metabolic syndrome is made when ≥ 3 of 5 risk factor components are present. These updated recommendations use a single cut point for all components except waist circumference, for which population- or country-specific cut points are recommended until more data become available.¹⁰

Criteria for the Clinical Diagnosis of Metabolic Syndrome

| Measure | Cut Points |
|---|--|
| Elevated waist circumference | Population- and country-specific definitions |
| Elevated TGs (or drug treatment of elevated TGs) | ≥ 150 mg/dL |
| Reduced HDL-C (or drug treatment of reduced HDL-C) | <40 mg/dL (men); <50 mg/dL (women) |
| Elevated blood pressure (or antihypertensive treatment in a patient with a history of hypertension) | Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg |
| Elevated fasting glucose (or drug treatment of elevated glucose) | ≥ 100 mg/dL |

| Recommended Waist Circumference Thresholds by Population | Cut Points | |
|--|--------------------------------|--------------------------------|
| | Men | Women |
| Europid | | |
| AHA/NHLBI | ≥ 102 cm (≥ 40 in) | ≥ 88 cm (≥ 35 in) |
| IDF | ≥ 94 cm (≥ 37 in) | ≥ 80 cm (≥ 31.5 in) |
| Non-Europid (IDF Cut Points) | | |
| Asian | ≥ 90 cm (≥ 35.4 in) | ≥ 80 cm (≥ 31.5 in) |
| Middle East, Mediterranean | ≥ 94 cm (≥ 37 in) | ≥ 80 cm (≥ 31.5 in) |
| Sub-Saharan African | ≥ 94 cm (≥ 37 in) | ≥ 80 cm (≥ 31.5 in) |
| Ethnic Central and South American | ≥ 90 cm (≥ 35.4 in) | ≥ 80 cm (≥ 31.5 in) |

Alberti KG, et al.¹⁰

compared with 18% of control subjects, representing a residual RR of 79% in statin-treated patients. High-dose statin therapy has been shown to decrease some of this residual risk. In the Pravastatin or

Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22), Incremental Decrease in End Points Through Aggressive Lipid Lowering

Table 1. Residual CVD Risk After Statin Treatment

| Trial | Event Rate (No Diabetes) | | Event Rate (Diabetes) | |
|-----------------------------------|--------------------------|------------|-----------------------|------------|
| | On Statin | On Placebo | On Statin | On Placebo |
| HPS ^{25a} (CHD patients) | 19.8% | 25.7% | 33.4% | 37.8% |
| CARE ^{26b} | 19.4% | 24.6% | 28.7% | 36.8% |
| LIPID ^{27c} | 11.7% | 15.2% | 19.2% | 22.8% |
| PROSPER ^{28d} | 13.1% | 16.0% | 23.1% | 18.4% |
| ASCOT-LLA ^{29c} | 4.9% | 8.7% | 9.6% | 11.4% |
| TNT ^{30e} | 7.8% | 9.7% | 13.8% | 17.9% |

^aCHD death, nonfatal MI, stroke, revascularizations; ^bCHD death, nonfatal MI, CABG, PTCA; ^cCHD death and nonfatal MI; ^dCHD death, nonfatal MI, stroke; ^eCHD death, nonfatal MI, resuscitated cardiac arrest, stroke (80-mg vs 10-mg atorvastatin).

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty. HPS Collaborative Group²⁵; Sacks FM, et al²⁶; LIPID Study Group²⁷; Shepherd J, et al²⁸; Sever PS, et al²⁹; Shepherd J, et al.³⁰

(IDEAL), and Treating to New Targets (TNT) trials, an intensive LDL-C-lowering strategy (statin therapy at 40-80 mg/d) for secondary prevention of cardiovascular events showed statistically significant reductions in major events compared with that achieved with a moderate LDL-C-lowering strategy (statin therapy at 10-40 mg/d). Nonetheless, despite intensive statin therapy, a significant 2- to 5-year residual cardiovascular risk (9%-22%), remained in these patients (Figure 2).²²⁻²⁴

In patients with type 2 diabetes, the residual CVD risk seems to be higher. Data from the Heart Protection Study (HPS), Cholesterol and Recurrent Events (CARE), Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID), PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA), and TNT statin trials have indicated that patients with type 2 diabetes have a residual 5-year cardiovascular risk of 10% to 33% after statin treatment (Table 1). This on-treatment residual risk was comparable to the risk in patients without

diabetes who were receiving placebo.²⁵⁻³⁰

Because of the high level of cardiovascular residual risk identified in these statin trials, there have been increased efforts to identify other lipid abnormalities that may impact the incidence of events.

Why Look Beyond LDL-C in Assessing Risk?

Individuals with type 2 diabetes or

CMR have a type of dyslipidemia, termed mixed dyslipidemia, that is characterized by low levels of HDL-C; elevated levels of TGs and atherogenic apo B-containing lipoproteins, including very low-density lipoproteins (VLDLs) and VLDL remnants (VLDL_R); and increases in small, dense LDL (sdLDL).³¹ Measurement of LDL-C levels, however, may be normal or only modestly elevated in these patients. Given the increased number of atherogenic LDL and cholesterol-enriched remnant particles, the near normal LDL-C levels may be misleading. For this reason, LDL-C is not considered a good predictor of cardiovascular risk in patients with CMR or diabetes.³² (See *LDL-C Measurement May Not Reflect Atherogenic Burden in Mixed Dyslipidemia*, page 6.) Insulin resistance is frequently associated with the abnormal lipid profile of patients with mixed dyslipidemia.^{33,34} In addition, each of the lipid abnormalities are independently predictive of CHD risk.³⁵

Low HDL-C: Strong Predictor of CVD Risk

Large-scale observational and epidemiologic studies have demonstrated

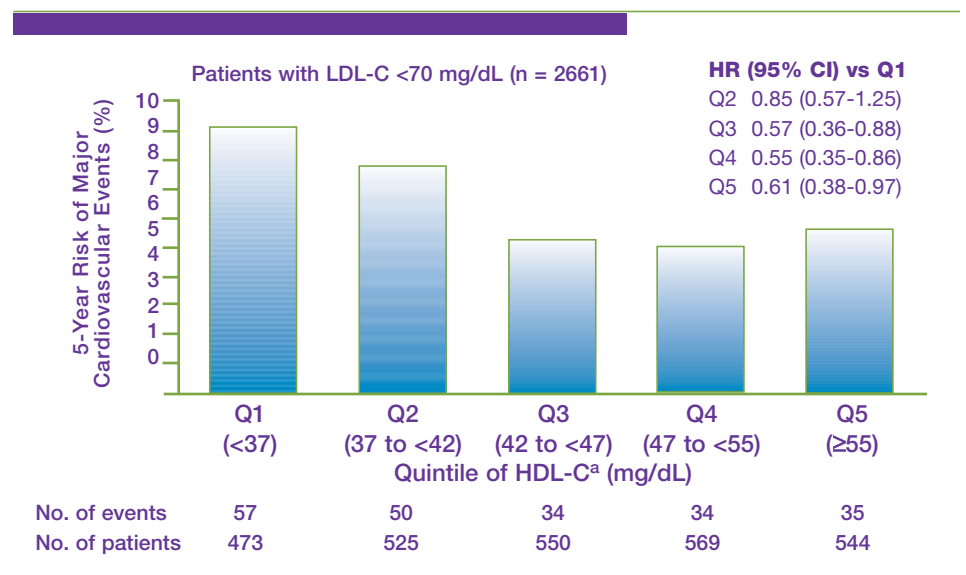


Figure 3. Low HDL-C predicts CVD risk in patients with LDL-C at target level. ^aOn-treatment level (3 months). Barter P, et al.⁶ Reproduced with permission of Massachusetts Medical Society © 2007. All rights reserved.

that low HDL-C levels are a strong predictor of cardiovascular events.³⁶ It has been estimated that for every 1% reduction in HDL-C level, the cardiovascular risk increases by 1% to 3%.³⁷ The cardiovascular risk with low HDL-C levels persists even in patients receiving statin therapy. This was shown in the HPS and CARE/LIPID studies in which patients with low HDL-C levels treated with statins had an approximately 35% higher rate of CVD events than patients with high HDL-C levels treated with statins.^{38,39} Controlling LDL-C levels with intensive statin therapy does not reduce the heightened risk of CHD conferred by low HDL-C. In the TNT study, patients with LDL-C levels <70 mg/dL who received high-dose statin therapy had a significantly increased 5-year risk of CHD events directly related to HDL-C levels (Figure 3). Patients in the highest HDL-C quintile (Q5 \geq 55 mg/dL) had a significantly lower risk of major cardiovascular events than patients in the lowest HDL-C quintile (Q1 <37 mg/dL; $P = .03$).⁶ Despite the increased cardiovascular risk associated with low HDL-C levels, therapeutic interventions to increase plasma levels of HDL-C have not been shown to improve cardiovascular outcomes.⁴⁰

Estimates from the National Health and Nutrition Examination Survey (NHANES) III indicate that greater than one third of the US adult population has low HDL-C.⁴¹

Elevated TG: Independent Predictor of CHD Risk

The association between elevated TG levels and CHD risk was demonstrated in a recent meta-analysis of 29 prospective studies involving approximately 263,000 individuals. The study results revealed an adjusted odds ratio of 1.72 (95% CI, 1.56-1.90) for incident CHD cases in individuals in the highest third of TG values compared with those in the lowest third of TG values.⁴² The Prospective Cardiovascular Münster (PROCAM) study provided additional evidence for elevated TG as an independent

Role of LDL in Atherogenesis

Lipoproteins transport lipids and lipid-soluble substances, such as cholesterol, through the blood. Lipoproteins are composed of an outer membrane consisting of phospholipids, unesterified cholesterol, and various surface apolipoproteins and an inner core consisting of cholesteryl ester, TG, and other neutral lipids.¹⁸ Lipoproteins vary with respect to their density, particle size, surface apolipoproteins, and TG and cholesterol content.¹⁹ They are classified according to their particle density as very low-density, low-density, intermediate-density, or high-density. Apo AI and apo B are structural proteins for HDL and the VLDL spectrum (VLDL-LDL), respectively. The suffix “-C” is added to the lipoprotein acronym when referring to the cholesterol component of the lipoproteins. Non-HDL-C is a measure of the TC carried by VLDL, IDL, LDL, and sdLDL particles and is calculated as TC minus HDL-C. VLDL and IDL are the main carriers of TGs.

A reduction in the TG content of VLDLs can occur in the circulation by the hydrolytic action of lipoprotein lipase to form VLDL_Rs and IDLs. IDLs can be cleared from the circulation by hepatic LDL receptors or converted to LDLs by further depletion of TGs through the action of hepatic lipases. LDLs can, in turn, exchange core lipids with VLDLs to become TG rich and undergo lypolysis, resulting in sdLDLs. All of the LDLs (VLDL, VLDL_R, IDL, LDL, and sdLDL) are atherogenic, as they migrate into the intima of vessels and initiate the cascade of events resulting in progression of atherosclerotic lesions.¹ However, sdLDLs are particularly atherogenic because they can more easily penetrate vessel walls (due to their small size), are more easily oxidized and glycated, and are more able to bind to proteoglycans in the vessel wall.¹ In a hypertriglyceridemic state (including metabolic syndrome or type 2 diabetes), plasma VLDL levels increase due to increased hepatic production and decreased clearance. This shifts the LDL particle distribution, resulting in higher levels of VLDL_R, IDL, and sdLDL.^{1,16,17}

LDL-C Measurement May Not Reflect Atherogenic Burden in Mixed Dyslipidemia

Lipoproteins are the atherogenic culprits that interact with the arterial wall and set in motion the cascade of events that leads to atherosclerosis.

Measurements of cholesterol levels are indirect estimates of the lipoproteins that transport cholesterol in plasma. However, the cholesterol content of LDL particles varies from person to person and is influenced by metabolic abnormalities such as insulin resistance and hyperglycemia. Hence, measurement of LDL-C may not accurately reflect the true burden of atherogenic LDL particles, especially in patients with mixed dyslipidemia who have elevated levels of apo B-containing lipoproteins. For this reason, measurement of serum apo B is a better approximation of the total atherogenic burden in patients with CMR.¹

predictor of CHD risk, regardless of HDL-C or LDL-C levels. This study followed middle-aged men with no history of myocardial infarction (MI) for 8 years. During this period, there was a 6-fold increased CHD risk in men whose TG levels were >200 mg/dL with an LDL-C to HDL-C ratio of >5.0.⁴³

Elevated TG and LDL-C: Potent Combination for CVD Risk

The combination of elevated TG and LDL-C levels is believed to pose a greater cardiovascular risk than elevated LDL-C alone. This is supported by data from the PROVE IT-TIMI 22 trial that evaluated a combination of LDL-C and TG levels on CVD risk in patients with acute coronary syndrome (ACS). The combination of on-treatment elevated TGs and LDL-C (≥ 150 mg/dL and ≥ 70 mg/dL, respectively) was associated with the highest risk of death, MI, and recurrent ACS (17.9%). In comparison, the most favorable prognosis (death, MI, or recurrent ACS event rate of 11.7%) was observed in patients who had the lowest on-treatment TG and LDL-C levels (<150 mg/dL and <70 mg/dL, respectively)

(hazard ratio [HR], 0.72; 95% CI, 0.54-0.94; $P = .017$).⁴⁴ Nonetheless, there are no outcomes data demonstrating that lowering elevated TGs improves cardiovascular risk beyond LDL-C goal attainment with statins.

Non-HDL-C: Predictor of Atherogenic Burden

Non-HDL-C is a better estimate of the total atherogenic burden than LDL-C. Non-HDL-C (TC minus HDL-C) is the sum of the concentration of cholesterol

within all lipoprotein particles considered to contribute to atherogenesis—the apo B-containing lipoproteins (LDL, sdLDL, VLDL, VLDL_R, intermediate-density lipoprotein [IDL], and lipoprotein(a)).¹⁶ Apo B can be measured directly from nonfasting blood samples, but the assay is not widely available. Thus, measurement of non-HDL-C is accepted as a surrogate marker for apo B in routine clinical practice.^{19,45}

Non-HDL-C has several practical advantages, including the ability to be assessed in patients with TG levels >400 mg/dL and patients who are not fasting.

Several studies have shown that non-HDL-C is a stronger predictor of CHD risk than LDL-C.⁴⁶⁻⁴⁸ Analyses of data from the Framingham Heart Study (N = 5794) indicated that in individuals free of CHD at baseline, within all non-HDL-C levels (<160, 160-189, and ≥ 190 mg/dL), no association between LDL-C and incident CHD risk was found, but within every level of LDL-C, a strong, positive, graded association between non-HDL-C and CHD risk was seen (Figure 4). The risk pattern did not change regardless of whether TG levels were <200 or ≥ 200 mg/dL.⁴⁶

In patients with diabetes, non-HDL-C may be a stronger predictor of CVD than

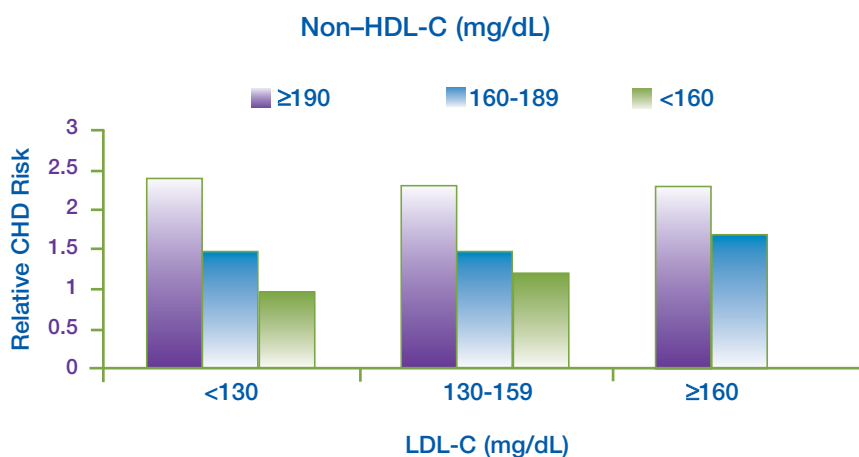


Figure 4. Value of non-HDL-C in predicting CHD risk. ^aReferent for comparison. Liu J, et al.⁴⁶

Table 2. On-Treatment LDL-C, Non-HDL-C, and Apo B Levels as Predictors of Cardiovascular Outcome: IDEAL, TNT

| Single-Measure Comparisons | HR | 95% CI | P Value |
|----------------------------|------|-----------|---------|
| LDL-C | 0.90 | 0.82-0.99 | .04 |
| Non-HDL-C | 1.31 | 1.19-1.44 | .001 |
| LDL-C | 0.95 | 0.87-1.05 | .33 |
| Apo B | 1.24 | 1.13-1.36 | .001 |
| Non-HDL-C | 1.14 | 1.00-1.30 | .06 |
| Apo B | 1.05 | 0.92-1.20 | .47 |

Kastelein JJ, et al.⁴⁹

LDL-C or TG. Among patients with diabetes in the Strong Heart Study, having a non-HDL-C level in the highest tertile (>161 mg/dL) compared with the lowest tertile (<127 mg/dL) carried a higher risk for MI (HR, 3.17) than having the highest tertile level compared with the lowest

tertile level of LDL-C (>115 mg/dL vs <91 mg/dL; HR, 1.96) or TG (>175 mg/dL vs <111 mg/dL; HR, 2.04).⁴⁷






Apo B and LDL-P: Other Markers of CVD Risk

Recent studies also suggest that apo B

and LDL particles (LDL-P) are equal or better indices of CVD risk than non-HDL-C—and clearly better than LDL-C—and may be more reliable indices of on-treatment residual CVD risk.¹ Using data from the TNT and IDEAL trials, Kastelein and colleagues compared apo B, LDL-C, and non-HDL-C as markers of cardiovascular risk in patients receiving statin therapy. On-treatment levels of non-HDL-C and apo B were more closely associated with cardiovascular outcome than LDL-C levels.⁴⁹ In pair-wise comparisons, the positive relationship between LDL-C and major cardiovascular events was lost, whereas non-HDL-C and apo B retained a positive association with the occurrence of major cardiovascular events (Table 2).

In a study of the Framingham Offspring cohort, LDL-P was shown to be a more sensitive indicator of low CVD risk than LDL-C or non-HDL-C,

Table 3. Lipoproteins and CMR: Key Clinical Practice Points

| Lipoprotein | Lipid Treatment Goals (mg/dL) in Patients With CMR | | Key Points | |
|---|--|---|---|---------------------------|
|  VLDL  IDL  LDL  sdLDL | TG-rich lipoproteins | Highest Risk • Known CVD; or • Diabetes plus ≥1 major CVD risk factor | <ul style="list-style-type: none"> All the lower density lipoproteins are atherogenic Non-HDL comprises all lipoproteins containing apo B In hypertriglyceridemia, VLDL levels increase, resulting in increased LDL and IDL levels Insulin resistance and hyperglycemia affect the cholesterol content of LDL; thus, in patients with CMR, serum apo B indicates total atherogenic burden better than LDL-C An apo B assay is not widely available; non-HDL-C is a surrogate marker for apo B in clinical practice | |
| | | High Risk • No CVD or diabetes but ≥2 major CVD risk factors; or • Diabetes but no other major CVD risk factor | | |
| | | Non-HDL-C: <100 (Note: Non-HDL-C goal should be 30 mg/dL higher than LDL-C goal) | | Non-HDL-C: <130 |
| | | Apo B: <80 | | Apo B: <90 |
| | | LDL-C: <70 | LDL-C: <100 | |
|  HDL | | HDL-C No specific treatment goals have been identified Cut point HDL-C values in patients with the metabolic syndrome are: • 40 (in men) • 50 (in women) | <ul style="list-style-type: none"> HDL levels are inversely correlated with CHD risk Low HDL-C levels often reflect presence of other atherogenic factors | |

Brunzell JD, et al¹; Grundy SM, et al⁴; NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATPIII]).¹⁹

Table 4. Effects of Major Drug Classes on Lipid Levels

| Drug Class | LDL-C Effects | HDL-C Effects | TG Effects |
|--|---------------|---------------|------------------|
| Statins (HMG-CoA reductase inhibitors) | ↓ 18%-55% | ↑ 5%-15% | ↓ 7%-30% |
| Bile acid sequestrants | ↓ 15%-30% | ↑ 3%-5% | None or increase |
| Niacin (nicotinic acid) | ↓ 5%-25% | ↑ 15%-35% | ↓ 20%-50% |
| Fibrates (fibric acid derivatives) | ↓ 5%-20% | ↑ 10%-35% | ↓ 20%-50% |

HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.
NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATPIII]).¹⁹

suggesting a potential clinical role for LDL-P as a goal of LDL management. In this study, subjects with a low level of LDL-P (<25th percentile) had a lower CVD event rate (59 events/1000 person-years) than those with an equivalently low level of LDL-C or non-HDL-C (81 and 74 events/1000 person-years, respectively).⁵⁰ LDL-P can be measured directly using nuclear magnetic resonance; however, the technique is not widely available, is relatively expensive, and its accuracy needs to be established. Moreover, the consistent CVD predictive power of LDL-P across various ethnicities, ages, and conditions that affect lipid metabolism has not been confirmed.¹

A recent population-based, observational study has identified another measure for predicting cardiovascular risk. In the INTERHEART study, apolipoprotein and cholesterol ratios were compared as indices of risk for acute MI in 12,461 case patients and 14,637 sex- and age-matched controls in 52 countries. Study results showed that the nonfasting apo B/apo AI ratio was a better marker of acute MI risk than the TC/HDL-C ratio, the non-HDL-C/HDL-C ratio, and the LDL-C/HDL-C ratio. The better predictive

value of the apo B/apo AI ratio was maintained across all ethnic groups in both sexes and at all ages.⁵¹

What Do Guidelines Recommend for Treating Beyond LDL-C?

To continue reducing the risk of cardiovascular events after optimal LDL-C lowering, additional lipoprotein abnormalities need to be addressed in patients with CMR. Because many patients with elevated TGs and low HDL-C have elevated levels of apo B, non-HDL-C serves as a better, cost-efficient surrogate of residual risk than LDL-C. Consequently, the National Cholesterol Education Program recommends non-HDL-C as a secondary target of therapy (after LDL-C) if the TG level is ≥ 200 mg/dL.⁴ The non-HDL-C goal is 30 mg/dL higher than the LDL-C goal.

In a paradigm shift in lipid management, the 2008 American Diabetes Association (ADA)/American College of Cardiology (ACC) Foundation Consensus Statement on lipoprotein management in patients with CMR not only endorses the non-HDL-C target goal, but adds apo B target levels to the recommended lipid treatment goals.¹

Although it still recommends measuring and using LDL-C to guide therapy, the ADA/ACC consensus panel notes that routine calculation and use of non-HDL-C constitute a better index than LDL-C for identifying high-risk patients.¹ This is especially important in patients with diabetes, in whom LDL-C levels may not be significantly elevated. In the presence of the elevated TG levels that usually accompany diabetes, non-HDL-C is particularly atherogenic.^{19,52} Lipid treatment goals for patients with CMR and key clinical practice points are summarized in Table 3.^{1,4,19}

The ADA/ACC also emphasizes the importance of assessing the presence and severity of major prognostic factors other than lipoprotein abnormalities that may contribute to the global risk of first or recurrent CVD events.¹ Risk factors including high blood pressure, smoking, hyperglycemia, obesity, adverse dietary habits, and physical inactivity are modifiable, most with lifestyle changes, and therapeutic interventions should be considered to reduce the risk associated with each of these risk factors. Risk factors such as age, gender, ethnicity, and family history are nonmodifiable, but their contribution to global cardiovascular risk should not be overlooked in risk assessment.¹

The current approach to lipid management recognizes that while statin monotherapy is standard of care for high-risk patients, it often is not sufficient. In individuals with persistent low HDL-C or high non-HDL-C levels despite statin therapy, especially if apo B levels remain elevated, combination therapy (eg, with a statin and niacin or a fibrate) is recommended.¹ This recognition is driving investigations of combined agents.⁵³⁻⁵⁷ The effects of major drug classes on lipid levels are summarized in Table 4.¹⁹



CASE: 68-Year-Old Man With Dyslipidemia

A 68-year-old man with dyslipidemia presents for a routine office visit to his primary care clinician. He has no anginal

symptoms or other complaints. He denies any shortness of breath or dyspnea on exertion, palpitations, lightheadedness, syncope, or symptoms consistent with paroxysmal nocturnal dyspnea. He currently does not follow a daily exercise program and is a nonsmoker.

Medical History

- CAD
- Acute inferior wall MI (July 1995), with percutaneous transluminal coronary angioplasty (PTCA) to distal right coronary artery (RCA)
- PTCA with stenting of mid-RCA (August 2006)
- Hypertension of 10 years' duration
- Mild aortic stenosis on echocardiogram, with aortic valve area 1.4 cm² (September 2006)
- Peripheral vascular disease (PVD); right carotid endarterectomy (October 2009)
- Obstructive sleep apnea (treated with continuous positive airway pressure)
- Renal stones

Physical Findings

- Weight: 212 lb; height: 5 ft 7 in; body mass index (BMI): 33.2 kg/m²; waist circumference: 43 in
- Blood pressure: 142/86 mm Hg (right arm, sitting)
- Pulse: 82 beats/min, regular; respirations: 18 breaths/min; afebrile
- Neck: no carotid bruits, carotid pulsations 2+

- Lungs: clear to auscultation
- Heart: regular rate and rhythm; S₁ and S₂; no S₃ or S₄; grade 3/6 systolic murmur at right sternal border
- Abdomen: Nontender, nondistended, no masses
- Extremities: distal pulses, 2+; mild bilateral lower-extremity edema

Laboratory Findings

- TC: 177 mg/dL
- TG: 248 mg/dL
- HDL-C: 36 mg/dL
- LDL-C: 91 mg/dL
- Non-HDL-C: 141 mg/dL
- Aspartate aminotransferase: 20 U/L
- Alanine aminotransferase: 36 U/L
- Glucose: 99 mg/dL

Current Medications

- Aspirin: 81 mg daily
- Clopidogrel: 75 mg daily
- Metoprolol tartrate: 25 mg twice a day
- Lisinopril: 20 mg daily
- Simvastatin: 40 mg daily
- Fish oil supplement: eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) 1 g daily

What is this patient's CMR level? Why? What would you do next? For an expert opinion, read the *Case Commentary* below by Peter H. Jones, MD, and John G. McGinnity, MS, PA-C, DFAAPA.

CASE | **Commentary**

PJ: This man has established CHD as well as metabolic syndrome (meeting 4 of 5 criteria: elevated BP, elevated waist circumference, low HDL-C, and high TG). This combination places him at very high risk for a recurrent event. As a result, he has a “reasonable” LDL-C goal of <70 mg/dL and a non-HDL-C goal of <100 mg/dL. Obtaining an apo B measurement may help us decide how intensively to modify his lipid therapy. His apo B level should be <80 mg/dL.

Lifestyle change, including weight reduction and exercise, is very important to prevent progression to diabetes as well as to reduce his BP and TG levels and increase his HDL-C level. However, it is unlikely that these lifestyle changes alone can achieve his lipid goals.

One potential therapeutic choice would be to add an intestinally-acting drug (eg, colesevelam or ezetimibe), which can reduce LDL-C by 15% to 20% (putting him near his LDL-C goal), but these agents will not change his HDL-C level. Niacin at a dose of at least 1000 mg/d should be strongly considered because it is the best drug for raising HDL-C and can further reduce LDL-C, non-HDL-C, and apo B levels. While the omega 3 fatty acids at 1 g/d should be continued, a case could be made for increasing the dosage to 4 g/d.

JM: I agree with Dr Jones. This patient is at very high risk for an adverse cardiac event. I would have a long talk with the patient about each of the factors that increase his CMR. He has established CHD and PVD. His BP is not at goal, and he meets the criteria for metabolic syndrome. His LDL-C level, despite

simvastatin therapy, is still too high for someone at his risk level. His target LDL-C goal should be <70 mg/dL, the level recommended for patients in the highest CMR category. His non-HDL-C level too is more than 40 mg/dL above the recommended target.

I would urge the patient to start a heart healthy diet and a daily exercise program of walking or other appropriate activities. I also agree with Dr Jones that niacin would be an excellent choice for addressing this patient's residual dyslipidemia risks. Niacin could benefit him by raising his HDL-C level and lowering both his TG and LDL-C levels. However, many patients will experience flushing/hot flashes with this medication. Titrating the dose slowly and recommending that the patient take the niacin at bedtime, shortly after taking his aspirin and after eating a snack, can sometimes lessen this side effect. An intestinally-acting drug (eg, colesvelam or ezetimibe) would be a possible choice for improving his LDL-C, but the lack of hard outcomes data on reducing cardiac events would make this choice less attractive.

Fibrates also could be added to this patient's current statin regimen to lower his TGs. I would not use gemfibrozil in combination with a statin because of the significantly increased risk of rhabdomyolysis. The risk of rhabdomyolysis is much lower with fenofibrate or fenofibric acid. If a fibrate is added, increasing the statin dose or changing to a more potent statin also may be considered to help achieve an LDL-C level <70 mg/dL.

Increasing the fish oil supplement dosage from 1 g daily to 3 to 4 g daily will improve the patient's TGs. Fish oil at a dose of 1 g daily has been shown to lower the risk of sudden cardiac death,⁹ but higher doses are needed to lower TG levels.

PCE Takeaways

- Risk factors for CVD and type 2 diabetes often cluster and increase global CMR; a multifactorial approach to risk assessment, prevention, and treatment is needed.
- Intensive therapy for all components of abnormal lipid metabolism that occur in people with CMR (increased TG, LDL-C, non-HDL-C; decreased HDL-C levels) is recommended.
- Target levels for non-HDL-C and apo B have been added to LDL-C treatment goals for patients with CMR.
- Combination therapy is recommended for patients receiving statin therapy who continue to have low HDL-C and high non-HDL-C levels.
- Niacin or fibrates may be used with statins to achieve these lipid goals.

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