REVIEW TOPIC OF THE WEEK

Fasting or Nonfasting Lipid Measurements
It Depends on the Question

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ABSTRACT

In the 2013 American College of Cardiology (ACC)/American Heart Association Guideline (AHA) on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, low-density lipoprotein cholesterol treatment thresholds have been replaced with a focus on global risk. In this context, we re-examine the need for fasting lipid measurements in various clinical scenarios including estimating initial risk for atherosclerotic cardiovascular disease in a primary prevention patient; screening for familial lipid disorders in a patient with a strong family history of premature atherosclerotic cardiovascular disease or genetic dyslipidemia; clarifying a diagnosis of metabolic syndrome so it can be used to make lifestyle counseling more effective; assessing residual risk in a treated patient; diagnosing and treating patients with suspected hypertriglyceridemic pancreatitis; or diagnosing hypertriglyceridemia in patients who require therapy for other conditions that may further elevate triglycerides. Posing a specific question can aid the clinician in understanding when fasting lipids are needed and when nonfasting lipids are adequate.

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Manuscript received November 20, 2015; accepted December 1, 2015.

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ABBREVIATIONS AND ACRONYMS

ACC/AHA = American College of Cardiology/American Heart Association
apoB = apolipoprotein B
ASCVD = atherosclerotic cardiovascular disease
CRP = C-reactive protein
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol

Practice patterns favoring fasting lipid panels were likely influenced by the historical context in which cholesterol management developed over the past half century. The initial classifications of hyperlipidemia proposed in 1967 were genetic and required fasting triglycerides (2). The Friedewald formula was subsequently introduced to allow calculation of a low-density lipoprotein cholesterol (LDL-C) level using fasting data (3). In addition, the first 2 National Cholesterol Education Program (NCEP) guidelines, released in 1988 and 1993, focused on primary and secondary prevention of coronary heart disease and established specific LDL-C goals. The third NCEP report (Adult Treatment Panel III [ATP III]) broadened the focus by using 10-year coronary heart disease risk estimation, but still relied on specific LDL-C goals to set treatment thresholds (4). These guidelines therefore reinforced the use of fasting lipids.

Rather than emphasizing specific LDL-C goals, the 2013 guidelines sought to match the intensity of LDL-C–lowering therapy to the baseline ASCVD risk. More specifically, they found strong evidence for statins as first-line therapy in patients: 1) with clinical ASCVD; 2) 40 to 75 years of age with diabetes and an LDL-C of 70 to 189 mg/dl; 3) with an LDL-C ≥190 mg/dl; and 4) 40 to 75 years of age without clinical ASCVD or diabetes, but with an LDL-C of 70 to 189 mg/dl and estimated 10-year ASCVD risk of 7.5% or higher (1). With this latter group, use of statins was not meant to be automatic, but rather was to be considered after a clinician-patient risk discussion (5).

The 2013 guidelines also identified additional factors to consider for those who do not belong to a statin benefit group, or for whom, after quantitative risk assessment, a risk-based treatment decision is uncertain. These include: 1) a primary elevation of fasting LDL-C ≥160 mg/dl or other evidence of genetic hyperlipidemias; 2) a family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; 3) a high-sensitivity C-reactive protein (CRP) ≥2 mg/l; 4) a coronary artery calcium score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity; 5) an ankle brachial index <0.9; and 6) an elevated lifetime risk of ASCVD.

Except for helping to identify genetic hyperlipidemia, the use of LDL-C values as decision points in the current guideline is limited. Indeed, a recent study in non-diabetic primary prevention patients noted that the new guidelines more accurately identified atherosclerotic burden on computed tomography angiography, as compared with the older ATP III guideline. They found that the predictive value of LDL-C targets were strikingly inferior to assessment of risk alone in approximately 3,000 subjects undergoing computed tomography coronary angiography (6).

In addition, although the guidelines appropriately emphasize the general utility of a fasting lipid panel, they also indicate that obtaining lipids in the fasting state is preferred, rather than mandatory, depending on the clinical scenario (see Figures 3, 4, and 5 of the guidelines [1]). For practical purposes, the traditional reliance on fasting lipids to answer most questions may no longer be necessary.

QUESTION #1: WHAT IS THE INITIAL RISK FOR MY UNTREATED, PRIMARY PREVENTION PATIENT?

Estimating baseline risk is an important step in determining who may benefit from initiation of cholesterol-lowering therapy. Higher LDL-C levels are associated with higher rates of cardiovascular and all-cause mortality, and a recent, nationally representative cohort study showed similar prognostic value for LDL-C results obtained in either the fasting or nonfasting state (7). Given this, a careful reader may wonder why the new cholesterol guidelines do not use LDL-C to predict risk, instead relying on total cholesterol and high-density lipoprotein cholesterol (HDL-C). This is largely due to inaccuracy of the Friedewald formula at low LDL-C (<70 mg/dl) and high triglyceride (>400 mg/dl) levels (8).
Direct LDL-C can be measured regardless of triglyceride levels and would intuitively seem to simplify LDL-C estimation. However, this is a common misconception, as the accuracy of directly measured LDL-C across the spectrum of possible values has not been shown. Importantly, the Centers for Disease Control and Prevention (CDC) Lipid Standardization Program standardizes assays for total cholesterol, HDL-C, and triglycerides. The CDC Lipid Standardization Program does not monitor the accuracy of direct LDL-C determined by commercially available chemical assays, and results have been shown to deviate significantly from the gold standard (9). In addition, the definition of LDL-C estimated by the traditional Friedewald formula includes cholesterol contained in biological low-density lipoprotein (LDL), intermediate-density lipoprotein, and lipoprotein(a). There is evidence that certain commonly used commercial direct LDL assays measure cholesterol associated with LDL and intermediate-density lipoprotein, but not lipoprotein(a) (10). In addition, relatively small absolute reductions in non-HDL-C cut-points result in substantial reclassification of patients to higher-risk categories (11,12). Biological variability and seasonal LDL-C variations have also been noted (13). These factors combined could lead to substantial overtreatment on the basis of guidelines aimed at achieving arbitrary fixed targets. Instead, the purpose of lowering LDL-C in primary prevention is to reduce the risk of a first heart attack or stroke. Randomized controlled trials have shown that across a broad range of LDL-C levels, there is an approximate 20% relative risk reduction in adverse cardiovascular events for each 1 mmol/l (39 mg/dl) lowering of LDL-C with statin therapy (14). Excluding patients 40 to 75 years of age with diabetes and an LDL-C ≥70 mg/dl or those with an LDL-C ≥190 mg/dl, some primary prevention patients may not have sufficient absolute risk to justify starting a statin. For example, low-risk patients can avoid the expense and potential risk associated with a statin if it would only reduce their 10-year risk of a heart attack or stroke by a very small amount. One could understand
that going from a 1% risk to a 0.5% risk is akin to a half-the-distance to the goal penalty on first down at the 1-yard line—yes, the result is theoretically better, but really is quite modest.

Several risk estimators have been developed, including the Systematic Coronary Risk Evaluation, Framingham Score, Reynolds Risk Score, QRISK2, and the ASCVD Pooled Cohort Risk Estimator. Although each of these incorporates age, sex, smoking status, and hypertension into their risk models (Table 1), the only lipid components included are total cholesterol and HDL-C (1,15). Acknowledging that these measures were generally obtained in the fasting state in cohorts used to derive the risk scores, they actually vary little between fasting and nonfasting states. Therefore, for risk estimation alone, either fasting or nonfasting lipids suffice.

**QUESTION #2: HOW SHOULD I SCREEN AND FOLLOW PATIENTS WITH A FAMILY HISTORY OF GENETIC HYPERLIPIDEMIA OR PREMATURE ASCVD?**

Notwithstanding other risk factors, familial hypercholesterolemia is an important contributor to premature ASCVD (16). The most common lipid abnormality suggestive of familial hypercholesterolemia is a fasting LDL-C level ≥190 mg/dl. Premature ASCVD is generally defined by occurrence in a first-degree male relative <55 years of age or female relative <65 years of age. For first-degree relatives of patients with either condition, a fasting lipid profile is preferred. However, as the ACC/AHA guidelines indicate, a nonfasting non-HDL ≥220 mg/dl could indicate genetic hyperlipidemia that requires further evaluation, including ruling out secondary causes (17).

Patients with significantly elevated triglycerides may also have a genetic disorder, such as familial combined hyperlipidemia, familial hypertriglyceridemia, or familial type III dyslipoproteinemia. Fasting lipids, especially if combined with an apolipoprotein B (apoB) level, may help to distinguish among these conditions and define the risk for pancreatitis (18).

As one example, familial type III dyslipoproteinemia can be instructive. It represents a genetic lipid disorder associated with premature ASCVD. Affected patients have elevated lipids, with total cholesterol and triglycerides often at approximately equal levels (≥300 mg/dl) (19). Diagnosis of familial type III is important because of a higher than previously thought prevalence (approximately 0.2% in women and 0.4% to 0.5% men older than 20 years of age) and high carbohydrate sensitivity (20). Characteristic skin lesions, such as palmar creases and tuberoeruptive xanthomas, may suggest the diagnosis (21). The disorder is caused by deficient/defective apolipoprotein E and manifests clinically when an additional metabolic disorder, such as diabetes or insulin resistance, results in either increased synthesis or decreased clearance of very-low-density lipoprotein. Whereas measurement of abnormal cholesterol-rich very-low-density lipoprotein makes the diagnosis, this initially required ultracentrifugation (20). A simpler method involves measuring fasting lipids and an apoB level (18,22).

**QUESTION #3: WHAT IF I WANT TO CLARIFY THE DIAGNOSIS OF METABOLIC SYNDROME?**

Metabolic syndrome is a clinical construct defined by the presence of at least 3 of the following risk factors: 1) waist circumference ≥102 cm (40 inches) for men or ≥89 cm (35 inches) for women; 2) blood pressure ≥130/≥85 mm Hg; 3) fasting blood glucose ≥100 mg/dl; 4) HDL-C <40 mg/dl for men and <50 mg/dl for women; and 5) triglycerides ≥150 mg/dl (23). Of note, simultaneous measurement of just 2 of the metabolic syndrome variables, waist circumference and fasting triglycerides, identifies men with an atherogenic metabolic triad (hyperinsulinemia, an elevated apoB level, and small dense LDL-C) who are at high risk for ASCVD (24). Patients

<table>
<thead>
<tr>
<th><strong>TABLE 1</strong> Comparison of Risk Estimator Components</th>
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<tbody>
<tr>
<td><strong>Total Cholesterol</strong></td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>SCORE</td>
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<tr>
<td>Framingham</td>
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<tr>
<td>ASCVD</td>
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<tr>
<td>Reynolds</td>
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<td>QRISK2</td>
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AF = atrial fibrillation; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; BP = systolic blood pressure; CHD = coronary heart disease; CKD = chronic kidney disease; DM = diabetes mellitus; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; HTN = hypertension; RA = rheumatoid arthritis; SCORE = Systematic Coronary Risk Evaluation, European Concerted Action Project pooled cohort tool.
with metabolic syndrome have an approximate 5-fold higher risk of developing diabetes, a roughly 2-fold higher risk of developing coronary artery disease, and a high likelihood of having nonalcoholic fatty liver disorder (25).

Whether metabolic syndrome is a surrogate for insulin resistance and whether it predicts ASCVD independent of the above risk factors remains controversial (26). However, sharing a diagnosis of metabolic syndrome with patients increases risk perception and motivation toward healthier behavior (27). Lifestyle modifications focused on diet, physical activity, and weight-related behaviors appear particularly effective in reducing metabolic risk. For example, among patients with impaired fasting glucose, the Diabetes Prevention Program found that intensive lifestyle intervention reduced the incidence of diabetes by 58% (28). More recent efforts have focused on the delivery of lifestyle interventions in community settings or via smartphone applications in an effort to make implementation less burdensome and more sustainable (29,30).

Therefore, it is important to identify patients with metabolic risk factors so that intensive lifestyle interventions can be emphasized. Yet, establishing the diagnosis can be a challenge when a patient is not fasting. In the previously presented patient, obtaining fasting labs at a later date from a laboratory closer to home would be a reasonable option, but should be balanced against added expenses and time costs. Another option in this situation is to measure waist circumference, blood pressure, and nonfasting labs. The presence of elevated triglycerides (using a 200 mg/dl threshold; see Question 6), a hemoglobin A1c above 5.6%, and a low HDL-C level (<40 mg/dl in men and <50 mg/dl in women) could allow a reasonable tally of metabolic risk factors and obviate the need for a return fasting visit. Such an approach could minimize a delay to diagnosis and expedite the implementation of lifestyle modification interventions at a time when the patient may be most ready for change.

**QUESTION #4: WHAT IS THE RESIDUAL RISK FOR MY TREATED PATIENT?**

When assessing residual risk, it is important to remember that other factors beyond cholesterol (e.g., lifestyle, smoking status, blood pressure, and blood glucose) play an important role (31). A discussion of non–HDL-C, whether or not it is focused on a specific target number, should first emphasize intensive lifestyle interventions with particular attention to medication adherence, improved diet, and healthy activity. Although it may seem logical to simply input on-treatment total cholesterol and HDL-C levels into the ASCVD risk estimator, such an approach is not advised because calculated risk estimates are based on those naïve to lipid-lowering therapy. The risk estimator does not differentiate between a patient who may have carried a higher risk factor burden over many decades before treatment and another patient off therapy who lived for years with a lower risk profile.

Instead, the impact of lipid-modifying therapy on residual risk is better framed by an understanding that there is a relative risk reduction of approximately 20% per 1 mmol/l (39 mg/dl) of LDL-C lowered with moderate- and high-intensity statin therapy. Accordingly, response to therapy is better gauged with a fasting lipid panel. Obtaining fasting lipids at follow-up also provides prognostic value, as a triglyceride level <150 mg/dl is associated with a lower incidence of statin-induced diabetes (32) and better outcomes after an acute coronary syndrome (33–35).

For some treated patients, however, a baseline LDL-C level may not be available against which to compare. In such individuals, the clinician may consider (as noted in the 2013 guidelines) that in randomized controlled trials, the LDL-C for patients receiving high-intensity statins was usually in the <100-mg/dl range. Similar to the U.S. guidelines, the update to the existing National Institute for Health and Care Excellence (NICE) guidelines does not recommend fixed targets for therapy, but does recommend nonfasting non–HDL-C to gauge adequacy of response (with at least a 40% decline) (36).

Because lifestyle change may result in improved LDL-C and non–HDL-C levels, clinicians may wish to share improvements in these values with patients (37). In addition, primary prevention data from the JUPITER (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial comparing rosvuastatin (20 mg/day) to placebo in individuals with a low LDL-C level and a high-sensitivity CRP ≥2.0 mg/l suggests that overall residual risk decreased among those achieving an on-treatment LDL-C <70 mg/dl, non–HDL-C <100 mg/dl, or apoB <80 mg/dl (38). In contrast, on-treatment triglycerides showed no association with cardiovascular disease (39). Thus, in this trial, nonfasting non–HDL-C or apoB levels were as useful as levels obtained in the fasting state.

In secondary prevention, good adherence and an appropriate response to statin therapy are especially
important. This is because high-intensity statin therapy has been shown to attenuate the expected progression of coronary atherosclerosis in all strata of patients with coronary artery disease, irrespective of baseline lipoprotein or CRP levels (40). Not surprisingly, angiographic data show that hyporesponders to statin therapy have greater progression of atherosclerosis (41). For this reason, obtaining repeat fasting lipids in the secondary prevention population can be helpful.

For patients without an expected response, gauging adherence is critical. For example, among patients with a myocardial infarction who had cost-sharing eliminated in the MI-FREE (Post-Myocardial Infarction Free Rx Event and Economic Evaluation) trial, adherence to statin therapy at 1 year was only 54.4% (42). In this case, rather than changing statins or adding additional lipid-lowering therapy, focusing on barriers to adherence may be the best therapeutic strategy.

**QUESTION #5: HOW SHOULD I ASSESS PATIENTS WITH OR AT RISK FOR PANCREATITIS?**

Patients with pancreatitis should have fasting lipids checked to assess whether hypertriglyceridemia (≥500 mg/dl) is the cause. After initiating treatment, a repeat fasting lipid profile should be rechecked to ensure that recurrent pancreatitis is unlikely.

Although screening the general population for elevated fasting triglycerides to identify those at risk for pancreatitis is neither practical nor warranted, certain subpopulations of patients may benefit from testing. Such patients at increased risk include those: 1) with human immunodeficiency virus (HIV) treated with highly active antiretroviral therapy; 2) treated with medications that can greatly elevate triglycerides, such as long-term high-dose steroids or retinoic acid derivatives; 3) with visceral adiposity or those with a family history of dyslipidemia before starting oral contraceptive or hormone replacement therapy; or 4) women planning to get pregnant with known dyslipidemia or a family history of a lipid disorder. The greatest elevations in triglyceride levels often occur in these scenarios when genetically predisposed patients are exposed to an unhealthy diet, drugs that raise triglycerides, diseases associated with hypertriglyceridemia, or certain metabolic disorders (Table 2) (1).

**QUESTION 6: CAN HYPERTRIGLYCERIDEMIA BE DIAGNOSED WITH NONFASTING TRIGLYCERIDES?**

A recent AHA statement on hypertriglyceridemia and coronary heart disease suggests that clinicians

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**TABLE 2** Common Causes of Secondary Hyperlipidemia

<table>
<thead>
<tr>
<th>Secondary Causes</th>
<th>Elevated LDL-C</th>
<th>Elevated Triglycerides</th>
</tr>
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<tbody>
<tr>
<td>Diet</td>
<td>Saturated or trans fats, weight gain, anorexia nervosa</td>
<td>Weight gain, very-low-fat diets, high intake of refined carbohydrates, excessive alcohol intake</td>
</tr>
<tr>
<td>Drugs</td>
<td>Diuretics, cyclosporines, glucocorticoids, amiodarone</td>
<td>Oral estrogen, glucocorticoids, bile acid sequestrants, retinoid acid, anabolic steroids, sirolimus, rapalofene, tamoxifen, beta-blockers (not carvedilol), thiazides</td>
</tr>
<tr>
<td>Diseases</td>
<td>Biliary obstruction, nephrotic syndrome</td>
<td>Nephrotic syndrome, chronic renal failure, lipodystrophies</td>
</tr>
<tr>
<td>Disorders and altered states of metabolism</td>
<td>Hypothyroidism, obesity, pregnancy</td>
<td>Diabetes (uncontrolled) hypothyroidism, obesity, pregnancy</td>
</tr>
</tbody>
</table>

Adapted with permission from Stone et al. (1)

LDL-C = low-density lipoprotein cholesterol.
can use a nonfasting triglyceride level of >200 mg/dl to identify hypertriglyceridemic states (43). Among normotriglyceridemic subjects (i.e., fasting triglyceride levels <150 mg/dl), consumption of a low-fat breakfast (typically <15 g of fat) before blood sampling should not induce an increase in postprandial triglyceride levels by more than 20%, and is unlikely to cause levels to exceed 200 mg/dl (44). Additional more recent data has suggested that a nonfasting triglyceride level of 175 mg/dl could also be reasonable (45). Follow-up fasting triglyceride testing in these cases is not needed, but this should not dissuade further discussion of lifestyle measures. In contrast, among those with a nonfasting triglyceride level >200 mg/dl, a follow-up fasting lipid panel in 2 to 4 weeks is helpful. Of note, if the nonfasting triglyceride level is >1,000 mg/dl, a diagnosis of severe hypertriglyceridemia is present, and the heightened risk of hyperlipidemic pancreatitis should be addressed promptly. The suggested algorithm from the AHA scientific statement on triglycerides and cardiovascular disease is shown in Figure 1.

**CONCLUSION**

We have shown that there are a number of clinical scenarios in which fasting lipids offer valuable clinical information, but that in others, nonfasting lipids will suffice. To assess the initial risk of ASCVD in an untreated patient, fasting or nonfasting total cholesterol and HDL-C levels provide all that is needed. Among those with a nonfasting non-HDL-C level >220 mg/dl, a familial cause of hyperlipidemia should be suspected and further evaluated. For patients with a family history of premature ASCVD or features suggestive of familial hyperlipidemia, screening and follow-up should ideally be performed with fasting lipid panels.

Understanding a patient’s metabolic burden can provide a useful baseline for lifestyle counseling. Although a diagnosis of metabolic syndrome requires a tally of metabolic risk factors measured in the fasting state, it can be approximated for practical purposes by nonfasting results. Among those with a nonfasting triglyceride level >200 mg/dl, a follow-up fasting lipid panel should be performed.

Those who present with secondary causes of hyperlipidemia (due to diet, drugs, diseases, or disorders of metabolism) should have a fasting lipid panel performed. Indeed, it may be important for those about to initiate therapy with estrogenic hormones, steroids, retinoic acid, or certain antineoplastic agents to understand their propensity for severe hypertriglyceridemia and subsequent risk of pancreatitis. When assessing a patient’s response to lipid therapy, the 2013 guidelines note that fasting lipids and calculation of the change in LDL-C allow estimation of therapeutic response and adherence to therapy. In other scenarios, however, including the one described in the introductory case, nonfasting lipids can provide requisite information without further inconvenience. Therefore, when attempting to answer whether fasting or nonfasting lipids are most appropriate, it is important to first think carefully about the clinical scenario and consider what question is to be answered with the results.

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**REFERENCES**


KEY WORDS atherosclerotic cardiovascular disease, cholesterol, primary prevention, secondary prevention, statins, triglycerides