



## Hypertriglyceridemia and Cardiovascular Disease Management: The Role of Omega-3 Fatty Acids

### What We Know About Hypertriglyceridemia

- Elevated triglyceride (TG) levels are associated with increased cardiovascular (CV) risk
- Increased CV risk due to elevated TG levels is greater in women
- Approximately 30% of all heart attack patients have elevated TG levels

### Learning Objectives

After completing this activity, participants should be better able to:

- Discuss the etiology of hypertriglyceridemia and its potential impact on CV disease outcomes
- Develop treatment plans to help patients achieve low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride targets through diet, exercise, and drug therapy
- Assess the role of omega-3 acid ethyl esters in the management of hypertriglyceridemia with regard to efficacy, safety, and concomitant drug use

Control of hypertriglyceridemia can help reduce the risk of cardiovascular disease

Which common medications raise TGs?  
See page 57

### Risk Factors Come in Clusters

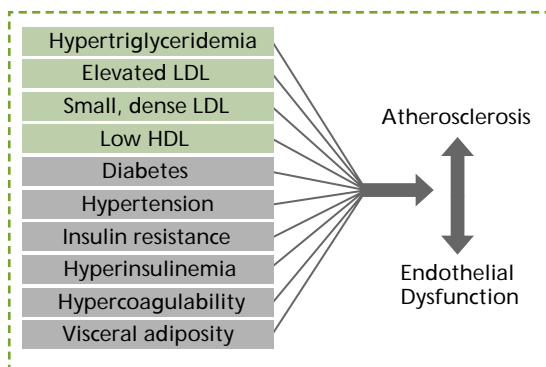
Cardiovascular disease is the leading cause of death in the United States. It is responsible for almost 2500 deaths every day.<sup>1</sup> In 2003, 37% of all deaths in the United States were related to CV disease. Unlike other leading causes of death, CV disease kills more women than men each year.<sup>1</sup> The death rate per 1000 women from CV disease is 273.4—more than 10 times as high as breast cancer (death rate of 25.6 per 1000 women).<sup>1</sup>

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- Risk score based on sum of graded risk factors that defines a 10-year hard CHD (MI + CHD death) risk percentage
- 10-year risk subcategories:

|                   |
|-------------------|
| >20% High         |
| 10%- 20% Moderate |
| <10% Low          |

**Figure 1. The Framingham point system for grading CVD risk.** ATP III risk assessment uses the Framingham point system to determine the 10-year CHD mortality risk. The 10-year CHD risk then is used to determine a patient's overall risk category. NCEP ATP III.<sup>2</sup>



**Figure 2. Risk factors rarely occur in isolation.** Dyslipidemias are risk factors for CV disease and usually occur in clusters with other risk factors, such as hypertension, diabetes, or the metabolic syndrome. Deedwania PC.<sup>3</sup>

Cardiovascular risk factors occur in clusters; that is, patients with 1 risk factor tend to have other risk factors, and risk of occurrence increases as the number of risk factors increases. The current guidelines from the National Cholesterol Education Program (NCEP) emphasize the importance of including other risk factors when selecting a treatment for dyslipidemia.<sup>2</sup> Clinicians should assess patients' "global" CV risk and intervene for all risk factors that are present.<sup>2</sup> The Framingham risk score is an excellent tool that provides an assessment of each patient's 10-year CV risk (Figure 1).<sup>2</sup> (See the *Hypertension* section for an example of a Framingham risk score.)

Dyslipidemias are a major CV risk factor that contribute to atherosclerosis and endothelial dysfunction (Figure 2).<sup>3</sup> Major risk factors are smoking, hypertension, family history of coronary heart disease (CHD), and age (men:  $\geq 45$  years; women:  $\geq 55$  years).<sup>2</sup> Other factors contribute to global CV risk.<sup>2</sup>

Dyslipidemias are prominent in the metabolic syndrome, characterized by abdominal obesity, low high-density lipoprotein (HDL), elevated TGs, atherogenic dyslipidemia, treated or untreated high blood pressure, and insulin resistance (Table 1).<sup>4</sup> This combination of factors is thought to predispose individuals to the development of CV disease and diabetes with enhanced prothrombotic and proinflammatory states (see the *Hypertension* section of this activity for more discussion).

Dyslipidemia is defined by type of lipid abnormality (Table 2). According to the latest NCEP Adult Treatment Panel (ATP III), the target total cholesterol (TC) is  $< 200$  mg/dL, LDL-C  $< 100$ , and HDL-C  $> 40$  mg/dL for men and

### Dyslipidemias Are Prominent in Metabolic Syndrome\*

| Risk Factor         | Defining Level (Adults) |
|---------------------|-------------------------|
| TG                  | $\geq 150$ mg/dL        |
| HDL-C               |                         |
| ➤ Men               | $< 40$ mg/dL            |
| ➤ Women             | $< 50$ mg/dL            |
| Waist circumference |                         |
| ➤ Men               | $> 102$ cm ( $> 40$ in) |
| ➤ Women             | $> 88$ cm ( $> 35$ in)  |
| Blood pressure      | $\geq 130/85$ mm Hg     |
| Fasting glucose     | $\geq 100$ mg/dL        |

\*Diagnosis is established when  $\geq 3$  of these risk factors are present. NCEP ATP III.<sup>2</sup>

>50 mg/dL for women.<sup>2</sup> Triglyceride levels <150 mg/dL are considered normal, levels 200 to 499 mg/dL are considered high, and levels >500 mg/dL are considered very high.<sup>2</sup>

### Triglycerides and CV Risk

Elevated TG levels (termed *hypertriglyceridemia*) are associated with increased CV risk, especially in women,<sup>5,6</sup> according to a multivariate analysis from the Framingham Heart Study (Figure 3).<sup>5</sup>

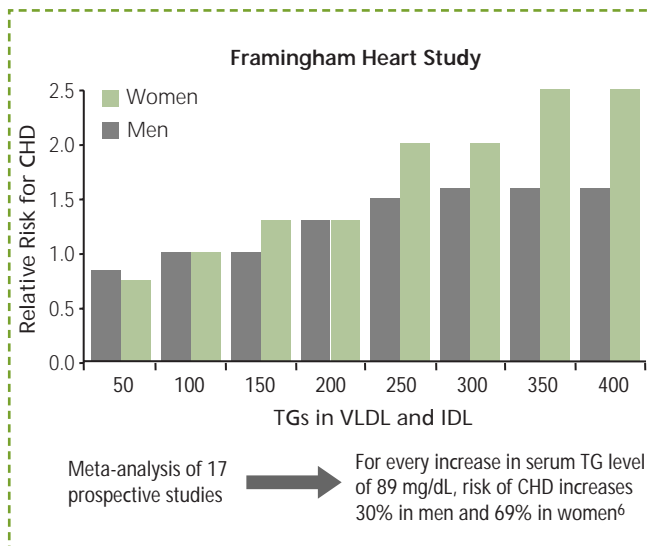
Elevated TG levels are present in an estimated 30% of all occurrences of myocardial infarction (MI).<sup>5</sup> Persons with the highest TG levels usually have the highest glucose levels and, thus, double the risk for diabetes.<sup>5</sup> An increase of 89 mg/dL (1 mmol/L) in the TG level is associated with a 30% increase in CHD risk for men and a 70% increase in risk for women. The increased CHD risk is highest when LDL-C levels are lower.<sup>6</sup>

As predictors of risk for CV disease, levels of plasma TG are independent of HDL-C and TC.<sup>7</sup> An analysis of lipid profiles of patients with a first-degree family history of CV disease who experienced MI or revascularization at an early age (<55 years for men and <65 years for women) found that TG levels 200 to 800 mg/dL were associated with a significantly higher CV disease risk than TG levels <100 mg/dL.<sup>7</sup> The odds ratio (OR) for CV disease was 11.4 (95% CI: 3.4-38.0;  $P < .0001$ ) for patients with TG levels of 500 to 799 mg/dL.<sup>7</sup> This risk was not offset by higher levels of HDL-C (Figure 4). Patients with TG levels >200 mg/dL were at increased risk even when the HDL-C levels were >40 mg/dL.<sup>7</sup> This differs from the

### ATP III Lipid Classifications

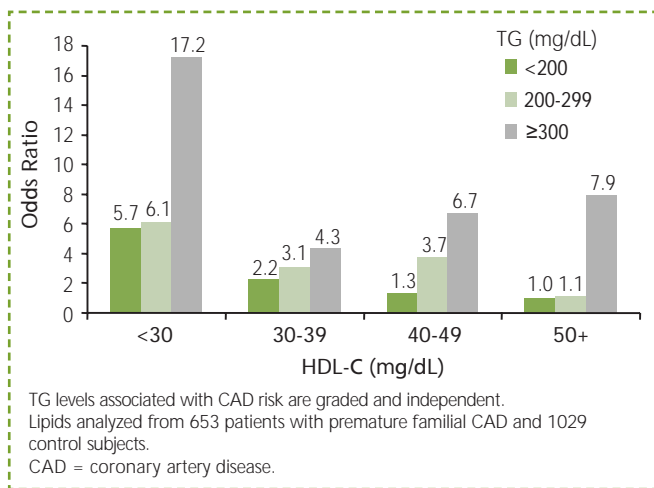
| TC (mg/dL)  |                  | HDL (mg/dL) |                 |
|-------------|------------------|-------------|-----------------|
| <200        | <i>Desirable</i> | <40 (M)     | <i>Low</i>      |
| 200-239     | Borderline high  | <50 (F)     | <i>Low</i>      |
| ≥240        | High             | ≥60         | High            |
| LDL (mg/dL) |                  | TG (mg/dL)  |                 |
| <100        | <i>Optimal</i>   | <150        | <i>Normal</i>   |
| 130-159     | Borderline high  | 150-199     | Borderline high |
| 160-189     | High             | 200-499     | High            |
|             |                  | ≥500        | Very high       |

Adapted from NCEP ATP III.<sup>2</sup>



**Figure 3.** Relative risk by TG levels in men and women in the Framingham study population. An analysis of the Framingham Heart Study data shows a significant relationship of TG with CHD risk in women, but not in men. The follow-up period was 30 years. A separate meta-analysis found elevated TG levels are a much larger risk for women than for men, even after adjustment for HDL-C levels (RR = 1.37 [95% CI: 1.13-1.66] for each 1 mmol [88.6 mg/dL] increase in triglyceride level). VLDL = very low-density lipoproteins. IDL = intermediate-density lipoproteins. Adapted from Castelli WP<sup>5</sup>; Hokanson JE.<sup>6</sup>

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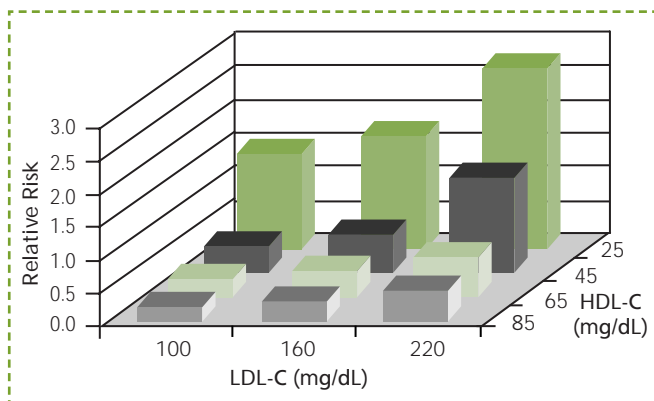


**Figure 4.** Elevated TG levels are associated with increased CV risk independent of HDL-C levels. Patients with TG  $\geq 300$  mg/dL were at much higher risk for CV disease even when HDL-C levels were  $>50$  mg/dL. Hopkins PN et al.<sup>7</sup>

pattern of interaction between HDL-C and LDL-C levels, where higher levels of HDL-C offset some of the risk associated with high LDL-C levels (Figure 5).<sup>8</sup> Although hypertriglyceridemia is an independent risk factor for CV disease, elevated TG levels rarely exist independently of other dyslipidemias, insulin resistance, and inflammatory states.<sup>6</sup>

### Guidelines for Lipid Profiles

The NCEP ATP III guidelines base LDL-C targets on risk factor profiles. According to the guidelines, comorbidities such as diabetes, carotid artery and peripheral vascular disease, and aortic aneurysms are coronary risk equivalents.<sup>2</sup> Patients with CHD/CHD equivalents or multiple risk factors that produce a 10-year risk of  $>20\%$  are candidates for intensive therapy to lower LDL-C levels to  $<100$  mg/dL.<sup>2</sup> Those with 2 or more risk factors and a 10-year risk of  $\leq 20\%$  have an LDL-C target level of  $<130$  mg/dL, and those with no or 1 risk factor and a 10-year risk of  $<10\%$  have an LDL-C target level of  $<160$  mg/dL.<sup>2</sup> Additional therapy beyond lowering LDL-C levels is recommended for patients with TG levels  $>199$  mg/dL.<sup>2</sup>



**Figure 5.** High levels of HDL-C offset some of the CV risk associated with high levels of LDL-C. Patients with the highest levels of HDL-C and LDL-C (lower right) were at lower risk than those with low levels of both (upper left). This is in contrast to Figure 4 where HDL-C levels do not offset the risk of elevated TG levels. Data from Framingham Heart Study (men). Kwiterovich PO Jr.<sup>8</sup>

A complete lipid profile (TC, HDL, LDL, TG) is recommended for assessment of lipids. Persons >20 years of age should have a lipid profile performed and repeated more frequently if CV risk factors are present.<sup>2</sup>

### Treatment of Dyslipidemia

A summary of the NCEP 2001 treatment guidelines for dyslipidemia follows<sup>4</sup>:

- ▶ Stratify each patient's CV risk (ie, using Framingham score)
- ▶ Initiate primary prevention through modification of risk factors with diet and therapeutic lifestyle changes (TLC)
- ▶ Treat individual lipid abnormalities aggressively and proactively
- ▶ Treat associated lipid and nonlipid CV risk factors with therapeutic TLC and pharmacotherapy

Commonly used pharmacologic interventions to reduce CV risk or other risk factors are shown in Table 3, which differentiates treatments that modify CV risk and those that modify lipid levels. Low-dose aspirin does not affect lipid levels, but does reduce risk for CV disease. Statins may reduce risk for CV disease independently of their LDL-lowering effect, and evidence suggests that angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors have beneficial effects on CV disease risk in addition to specific effects on blood pressure. Diets rich in omega-3 fatty acids also attenuate CV risk.

Statins are the first choice of therapy for reducing LDL-C levels. Statins, fibrates, and niacin have the best efficacy for increasing HDL-C levels. Although niacin is the most effective, the side effects of niacin may limit adherence. Hypertriglyceridemia can be treated with fibrates, niacin, omega-3 acid ethyl esters, and statins, especially rosuvastatin, atorvastatin, and simvastatin. Omega-3 acid ethyl esters are pharmaceutical agents and must be differentiated from omega-3 fatty acids that are dietary supplements. Lowering TG levels significantly with daily dietary supplements is difficult because of the large number of pills required. Orlistat is an option for weight loss, but side effects may limit its effectiveness. Finally, for insulin resistance, thiazolidinediones and biguanides enhance adipocyte, skeletal muscle, and hepatic insulin sensitivity.

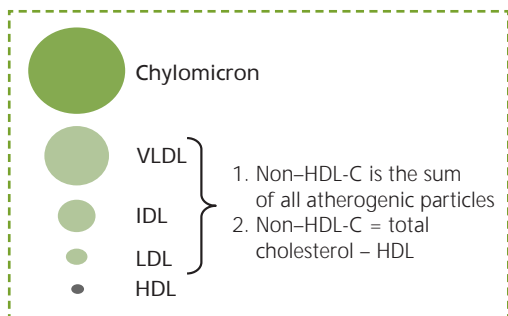
### Hypertriglyceridemia

Triglycerides are transported inside 5 types of lipoproteins, which vary in content (Figure 6):

- ▶ Chylomicrons (85%-90%)
- ▶ VLDL (50%-60%)
- ▶ IDL (20%-25%)
- ▶ LDL (<10%)
- ▶ HDL (<10%)

#### Pharmacotherapy Commonly Used to Reduce CVD Risk and/or Alter Risk Factors

| Therapeutic Target                   | Drug Class/Examples   |
|--------------------------------------|---|
| Preventive CV disease risk reduction | <ul style="list-style-type: none"> <li>▶ Aspirin (low-dose)</li> <li>▶ Omega-3 fatty acids</li> <li>▶ Statins</li> <li>▶ Thiazolidinediones</li> <li>▶ ACE inhibitors (ramipril)</li> </ul> |
| LDL-C                                | <ul style="list-style-type: none"> <li>▶ Statins</li> </ul>   |
| HDL-C                                | <ul style="list-style-type: none"> <li>▶ Fibrates</li> <li>▶ Niacin</li> </ul>  |
| TG                                   | <ul style="list-style-type: none"> <li>▶ Fibrates</li> <li>▶ Omega-3 acid ethyl esters</li> <li>▶ Niacin</li> </ul>   |
| Weight loss/management (long-term)   | <ul style="list-style-type: none"> <li>▶ Orlistat</li> </ul>  |
| Insulin resistance                   | <ul style="list-style-type: none"> <li>▶ Thiazolidinediones</li> <li>▶ Metformin</li> </ul>   |



**Figure 6.** Relative sizes of lipid particles. Chylomicrons are not measured in a standard fasting lipid profile. VLDLs are the primary particles carrying TG; the number of VLDLs in plasma is a marker for TG. HDLs are the smallest particles. Non-HDL-C is measured rather than just LDL-C for a more complete picture of the patient's atherogenic lipid profile.

The largest particles are the chylomicrons, which are formed in the intestine from dietary fat.<sup>4</sup> These particles are too large to infiltrate the vascular epithelium, but chylomicron remnants generated from the depletion of the TG core are atherogenic, binding to specific sites on macrophages, stimulating their conversion to foam cells and initiating atherogenic development. VLDL particles are smaller than chylomicrons and are produced in the liver from cholesterol and hepatic TGs. Lipoprotein lipase in the muscle and adipose tissues act on VLDL, reducing the TG core. As the core becomes depleted of TG, VLDL remnants or IDLs are formed. These IDL particles are further processed into LDL by hepatic lipase. IDL is included in the measurement of LDL-C.<sup>4</sup> LDL-C is the primary particle carrying cholesterol in the plasma, the most atherogenic, and the target of most lipid-lowering strategies.<sup>4</sup> Levels of HDL-C, the smallest particle, are inversely correlated with CV risk, and higher levels are considered beneficial.

Hypertriglyceridemia can result from an increase in the number of VLDL particles or an increase in TG within each VLDL particle. It typically is associated with low levels of HDL-C.<sup>6</sup>

Recent recommendations emphasized the importance of measuring the non-HDL-C component. Together, the VLDL, IDL, and LDL make up the non-HDL-C component of a TC measurement. All are atherogenic and promote vascular damage. Optimum non-HDL-C levels are 30 mg/dL higher than the LDL-C target level.<sup>2</sup> Thus, patients in the

highest risk category whose LDL-C target is <100 mg/dL would have a non-HDL-C target of <130 mg/dL.<sup>2</sup>

Elevated TG levels result from a variety of primary (inherited) and secondary causes, including lifestyle factors, disease states, and medications (Table 4).<sup>4</sup>

### Treatment of Hypertriglyceridemia

The cause, type of lipoprotein disturbance, and severity will determine the therapy for hypertriglyceridemia.

**Causes of Elevated TG Levels**

| Acquired Causes   | Secondary Causes  |
|---|---|
| <ul style="list-style-type: none"> <li>➤ Overweight/obesity</li> <li>➤ Physical inactivity</li> <li>➤ Smoking</li> <li>➤ Excess alcohol intake</li> <li>➤ High carbohydrate intake (&gt;60% of total energy)</li> </ul> | <ul style="list-style-type: none"> <li>➤ Diabetes mellitus</li> <li>➤ Chronic renal failure</li> <li>➤ Nephrotic syndrome</li> <li>➤ Cushing's disease</li> <li>➤ Lipodystrophy</li> <li>➤ Pregnancy</li> <li>➤ Medication use (eg, corticosteroids, beta-blockers, retinoids, thiazide diuretics, antiretroviral therapy)</li> </ul> |

NCEP ATP III.<sup>2</sup>

Therapeutic lifestyle changes, including weight loss, reduction in carbohydrate ingestion, decreased alcohol consumption, exercise, glycemic control, and medication adjustment are critical. Table 5 shows the efficacy of current treatments for hypertriglyceridemia.

### Statins

Statins are the most potent LDL-lowering drugs and have proven efficacy in the reduction of major CV events. They are not the first choice for treatment of severe hypertriglyceridemia because it is unlikely to be controlled by statins alone. The triglyceride-lowering effects of statins increase at higher doses, with reductions up to 30% with rosuvastatin, atorvastatin, and simvastatin.

### Fibrates

Fibrates lower TG levels effectively and, less robustly, raise HDL-C levels.<sup>9</sup> Fibrates act as peroxisome proliferator-activated receptor (PPAR)-alpha agonists, enhance lipoprotein lipase activity, and increase ApoA-I. They possess antiatherogenic effects as well as exert effects on lipid metabolism.<sup>9</sup>

In a large study, treatment with gemfibrozil reduced TG levels up to 30%, increased HDL-C levels up to 8%, and decreased the incidence of CV events.<sup>9</sup> The effect on CV events was more pronounced in patients with higher baseline levels of TG and lower levels of HDL-C, as well as in patients with insulin resistance compared with those without.<sup>9</sup> The Fenofibrate Intervention and Endpoint Lowering in Diabetes (FIELD) study, however, found a nonsignificant 11% reduction in CV events in patients with diabetes at low risk.<sup>10</sup> Fenofibrate will not increase the risk for clinical myopathy in combination with moderate-dose statins.<sup>11</sup> The FIELD study also provided additional evidence of the safety of fenofibrate/statin combination therapy.<sup>10</sup>

A combination of ezetimibe and fenofibrate is a reasonable consideration for patients who cannot tolerate statins.

### Niacin

Niacin (nicotinic acid) increases HDL-C levels when used alone<sup>12</sup> and reduces CV risk when used in combination with statins.<sup>13</sup> At the end of a 15-year study, patients treated with niacin demonstrated a significant ( $P = .0012$ ) survival benefit compared with placebo.<sup>12</sup> A combination of niacin and simvastatin significantly improved all lipid measures ( $P < .001$ ) and reduced the rate of major CV events by 90% ( $P = .03$ ) over a 38-month follow-up period.<sup>13</sup> A combination of niacin and lovastatin was significantly ( $P < .001$ ) more effective than atorvastatin or simvastatin monotherapy in raising HDL-C and lowering TG levels.<sup>14</sup> Niacin/statin combinations are recommended by NCEP for patients with high TG or low HDL-C levels.<sup>11</sup>

### Efficacy of Pharmacotherapy

| Drug                            | Reduction in TG Level |
|---------------------------------|-----------------------|
| Statins <sup>2</sup>            | Up to 30%             |
| Fibrates <sup>2</sup>           | 20%-50%               |
| Niacin <sup>2</sup>             | 20%-50%               |
| Fish oil (omega-3) <sup>2</sup> | 30%-40%               |
| Fibrate + statin <sup>26*</sup> | ~40%                  |
| Niacin + statin <sup>2</sup>    | ~40%                  |

\*Administer with caution due to risk of myopathy and rhabdomyolysis.  
NCEP ATP III<sup>2</sup>; Wierzbicki AS et al.<sup>26</sup>

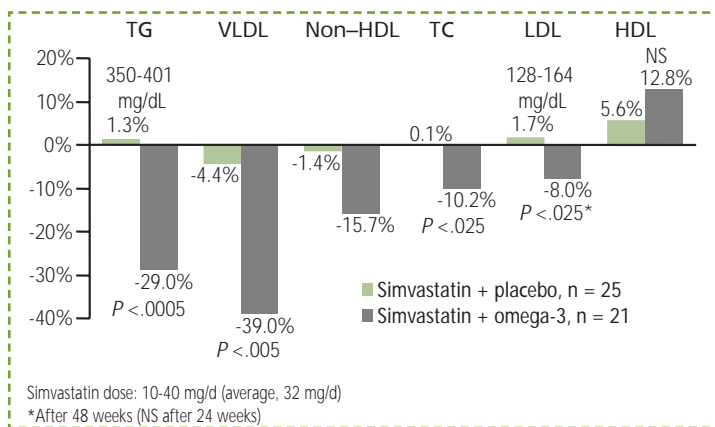
Although niacin is the most potent medication available for increasing HDL-C levels, its use often is affected by side effects, including flushing, dizziness, palpitations, nausea, hyperglycemia, gout, and tachycardia.<sup>4,15</sup> Pharmaceutical preparations of niacin (extended release) address many of these side effects and a preparation in development should block the prostaglandin-mediated mechanism that leads to flushing. This mechanism also can be reduced with aspirin.

### Omega-3 Fatty Acids: Clinical Benefit

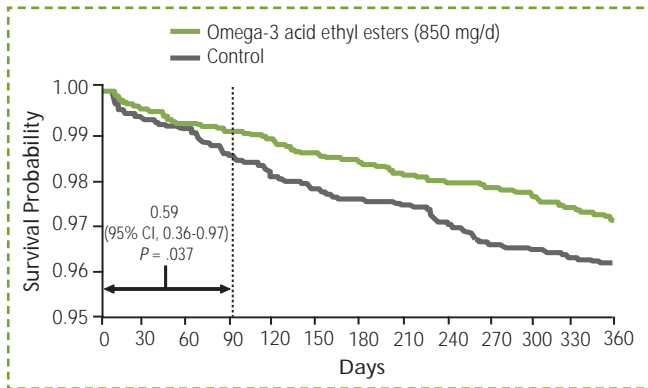
Omega-3 fatty acids lower TG levels by activating PPAR-alpha, inhibiting the synthesis of VLDL and TG in the liver,<sup>16</sup> enhancing VLDL and TG clearance, and increasing the rate of hepatic fatty acid oxidation.<sup>17,18</sup> A dose of 4 g/d of omega-3 fatty acids reduced TG levels by 35%, reduced VLDL by 42% (both,  $P < .05$ ), caused a small increase in HDL-C, and increased LDL-C by 25%.<sup>19</sup> In treating severe hypertriglyceridemia, this increase in LDL is associated with a change from more atherogenic, small, dense LDL to the less atherogenic, larger LDL and a concomitant reduction in the total number of LDL particles.<sup>20</sup>

Omega-3 fatty acids are not synthesized in the human body and must be obtained through food or supplements. The 2 major omega-3 fatty acids present in fish are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The omega-3 fatty acid in plants (eg, flaxseed oil) is alpha-linolenic acid (ALA).<sup>16</sup> Omega-3 fatty acids are precursors of prostaglandins, thromboxanes, and leukotrienes and have anti-inflammatory, antithrombotic, and antiarrhythmic properties.<sup>16,21</sup> The benefits of omega-3s include reduced serum TG, lower risk of sudden cardiac death and all-cause mortality, and reduced inflammatory and thrombotic risk.<sup>16</sup>

The American Heart Association (AHA) recommends dosing to achieve a level of 0.9 g/d of EPA.<sup>16,22</sup> Commercial supplements usually contain 180 mg of EPA.<sup>16</sup> The typical dose of omega-3s necessary to achieve a reduction in TG levels is 1 to 4 g/d alone or in combination with a statin; evidence suggests that 4 g/d is preferable. There are no known drug interactions or clinically important adverse effects associated with omega-3 fatty acids. A dose-related effect on bleeding time is seen with omega-3s, but no abnormal bleeding has been reported even at high doses or in combination with anticoagulants.<sup>16</sup> Fishy aftertaste, nausea, and bloating appear to be dose-related.<sup>16</sup>



**Figure 7.** Omega-3 acid ethyl esters in combination with simvastatin improves the lipid profile in patients with high TG. Combination therapy was significantly more effective for lowering atherogenic lipids than therapy with simvastatin alone. Durrington et al.<sup>23</sup>



**Figure 8.**

All-cause mortality from the GISSI-Prevenzione trial. This trial enrolled 11,323 patients with a recent history of MI and followed them for 1 year. The reduction in mortality associated with omega-3 acid ethyl esters was significant after only 3 months and remained throughout the study. From Marchioli R et al.<sup>21</sup>

The pharmaceutical preparation of omega-3 acid ethyl esters contains 90% omega-3 fatty acid and a defined dose of EPA 465 mg plus DHA 375 mg per capsule.<sup>23</sup> It is indicated for treatment of TG levels >500 mg/dL at a dose of 4 g/d, which can be taken once a day or divided as 2 capsules in the morning and 2 in the evening. Dietary supplement preparations of omega-3 fatty acids are inexpensive, but have much lower concentrations of the active ingredients. In some cases, more than 12 capsules per day may be needed to achieve the recommended dose. This requirement carries a high number of calories and leads to problems with adherence, as well as increased risk of gastrointestinal disturbances.

Omega-3 acid ethyl esters have been studied in combination with statins and found to further improve lipid profiles (Figure 7).<sup>23</sup> A study of treatment for lowering TG levels compared combined 4 g/d omega-3 acid ethyl esters and 10 to 40 mg/d simvastatin with simvastatin plus placebo.<sup>23</sup> Patients who were taking simvastatin were randomly assigned to receive omega-3 acid ethyl esters or placebo; assessments were made at 12, 24, and 48 weeks.<sup>23</sup> The combination therapy resulted in a sustained 20% to 30% decrease in TG levels and a 30% to 40% decrease in VLDL levels compared with placebo.<sup>23</sup> At each assessment, serum TG and VLDL levels were significantly lower in the patients who received omega-3 acid ethyl esters plus simvastatin ( $P < .0005$  and  $P < .005$ , respectively).<sup>23</sup> The combination was well tolerated.<sup>23</sup>

The GISSI-Prevenzione Trial randomly assigned 11,323 patients with a recent MI (within 3 months of study entry) to receive 300-mg vitamin E, 1 g/d of omega-3 acid ethyl esters (1 capsule), both, or neither.<sup>21</sup> This was a prevention trial, not a trial designed to lower TG levels. The combined efficacy end points of this study were (1) the cumulative rate of all-cause mortality, nonfatal MI, and nonfatal stroke, and (2) the cumulative rate of CV death, nonfatal MI, and nonfatal stroke.<sup>21</sup> After follow-up of 1 year, treatment with omega-3 alone resulted in a 45% reduction in sudden death and a 20% reduction in all-cause mortality (Figure 8).<sup>21</sup> This benefit occurred 3 months after the start of treatment<sup>21</sup> and continued throughout the study. Significant reductions in sudden cardiac death were seen at 4 months ( $P = .048$ ), in cardiac death at 6 months ( $P = .036$ ), in coronary death at 8 months ( $P = .040$ ), and CV death at 8 months ( $P = .024$ ).<sup>21</sup> Total cholesterol and LDL-C levels increased slightly early in the trial, but returned to near baseline levels by the end of the study.<sup>23</sup> This study showed that a low dose of omega-3 (the equivalent of about 2 oz of salmon) daily could prevent sudden cardiac death in patients with a previous MI.

**Clinical Recommendations: AHA and ADA**

The AHA recommendations for the use of omega-3 fatty acids in CV disease prevention focuses on 3 groups of patients: those with no documented CV disease, those with documented CV disease, and those with hypertriglyceridemia (Table 6).<sup>22</sup> The recommendation for those with no documented CV disease is to eat a variety of fish, preferably oily fish, including salmon, sardines, mackerel, herring, albacore tuna, and oysters at least twice a week. For those with documented disease, 1 g of EPA plus DHA per day is recommended from oily fish or a supplement. For patients with hypertriglyceridemia, 2 to 4 1-g capsules of EPA plus DHA per day are recommended.<sup>22</sup>

New guidelines for assessment of CV risk for women were published in 2007.<sup>24</sup> The authors emphasized that as many as 20% of all CV events in women occur in the absence of traditional (ie, identified in men) risk factors.<sup>24</sup> By including alternative risk factors, such as non-HDL-C levels, inflammatory biomarkers, measures of glycemic control, and creatinine and homocysteine levels, the new algorithm could more specifically assess women’s risk for CV disease.<sup>24</sup> Using this algorithm, 40% to 50% of women in the intermediate risk category (using ATP III measures) were reclassified into higher or lower risk categories.<sup>24</sup> For example, women with the same lipid profile and level of hypertension that led to an 11.5% 10-year risk of CV disease by the ATP III covariates could be reclassified as having a 4.9% to 18.4% 10-year risk when parental history and high-sensitivity C-reactive protein levels were included.<sup>24</sup>

The American Diabetes Association recommends lowering TG levels to <150 mg/dL for persons with diabetes<sup>25</sup> and endorses fibrates or niacin alone or in combination with statins for patients who have achieved LDL-C target goals but continue to have high TG levels or low HDL levels.<sup>25</sup> In addition, combination therapy of omega-3 acid ethyl esters with a statin in patients with TGs >500 mg/dL should be considered.

Table 7 provides an overview of focused treatment for hypertriglyceridemia. In all cases the primary task is to lower LDL-C levels as much as possible. However, there are different goals for each category of TG level. The secondary goal at TG levels between 200 and 499 mg/dL is to lower the non-HDL-C component, which is based on the TG level. For persons with severe hypertriglyceridemia, the primary goal is to reduce TG levels below 500 mg/dL, thereby reducing the risk of pancreatitis.

**American Heart Association Recommendations**

| Patient Population             | Recommendation  |
|--------------------------------|---|
| No documented coronary disease | Eat a variety of fish (preferably oily) at least twice weekly (salmon; mackerel; trout; herring; sardines; fresh, not canned, tuna; swordfish; anchovies; carp) Include foods rich in alpha-linolenic acid (flaxseed, canola, soybean, walnuts) |
| Documented coronary disease    | Consume approximately 1g of EPA plus DHA daily, preferably from oily fish EPA/DHA supplements may be used in consultation with a healthcare provider  |
| Hypertriglyceridemia           | Consume 2-4 g of EPA plus DHA daily in capsules by prescription   |

Kris-Etherton PM et al.<sup>22</sup>

### Focused Treatment for Hypertriglyceridemia

| Serum TG (mg/dL) | Primary Goal                                 | Secondary Goal  | Intervention  |
|------------------|--|-----------------|---|
| <150             | Lower LDL                                    | None            | ➤ None  |
| 150-199          | Lower LDL                                    | None            | ➤ Lifestyle changes<br>➤ Evaluate for metabolic syndrome  |
| 200-499          | Lower LDL                                    | Lower non-HDL-C | ➤ Modify lifestyle<br>➤ Evaluate for metabolic syndrome<br>➤ Consider drug therapy  |
| >500             | Lower serum TG level to prevent pancreatitis | Prevent CHD     | ➤ Modify lifestyle<br>➤ Omega-3 acid ethyl esters, fibrates, niacin<br>➤ Re-evaluate LDL-lowering efforts when TG <500 mg/dL<br>➤ In extreme cases, no alcohol, very low-fat diet |

NCEP ATP III.<sup>2</sup>

### Summary

Dyslipidemias are risk factors for CV disease and are important components of the metabolic syndrome. Elevated TG levels play an important role in patients' global CV risk and have been associated with increased risk for CV disease. Pharmacologic interventions for hypertriglyceridemia include fibrates, niacin, statins, and omega-3 fatty acids.

Omega-3 acid ethyl esters, available only by prescription, represent a purified form of these essential fatty acids with a predictable, standard amount of active ingredient. Studied alone and in combination with statins, they have been shown to be safe with no clinically important side effects or drug interactions. Although omega-3 fatty acids may prolong bleeding time, a meta-analysis of 15 trials of omega-3 fatty acids combined with aspirin, heparin, warfarin, or other antiplatelet agents found no evidence of increased, clinically significant bleeding. These agents are not contaminated with mercury and their use for treatment of hypertriglyceridemia is endorsed by the AHA.

## CASE STUDY

### A 63-Year-Old Woman With History of Hypertension and Hypercholesterolemia

#### Presentation

A 63-year-old woman presents with a history of hypertension and dyslipidemia. Her medications include an ACE inhibitor (ramipril 10 mg/d) for hypertension and simvastatin (40 mg/d) for cholesterol. On physical examination, her blood pressure appears well controlled and her blood glucose is normal. Her LDL is well controlled, but she has high TG levels and low HDL levels.

#### Physical Examination

- Body mass index: 33 kg/m<sup>2</sup>; waist 36 in
- Blood pressure: 128/82 mm Hg
- Fasting blood glucose: normal
- Thyroid: normal

#### Laboratory Values

- TC: 165 mg/dL
- HDL: 35 mg/dL
- LDL: 100 mg/dL
- TG: 392 mg/dL

#### Comment

This woman's Framingham Risk Score is 4% because she is a nonsmoker (it would be 8% if she smoked). In theory, she has a low 10-year risk of CV disease. The question is whether her elevated TG levels represent a particular risk that should be treated with lipid-lowering drugs.

#### Clinical Decision Point

*How could this patient's treatment be modified to focus management on hypertriglyceridemia?*

- Add gemfibrozil
- Add fenofibrate
- Add niacin
- Add omega-3 acid ethyl esters
- Advise diet modification and exercise only

#### Comment

Adding gemfibrozil with a statin is associated with an increased risk of muscle toxicity and is not a good choice in this case (Table 8). Although there is less risk with fenofibrate, outcomes with this combination have been disappointing. Niacin has demonstrated improved outcomes data in combination with a statin, but is associated with uncomfortable side effects that often limit adherence. It is the most potent agent for increasing HDL-C levels and a first-line choice for a patient who tolerates the side effects. Omega-3 acid ethyl esters also can be considered, but they are not FDA approved for these levels of TG and would be an off-label use. It is always important to emphasize diet and exercise.

**Table 8.**  
**Pros and Cons of Therapies to Lower TG Level**

| Agent                     | ↓TG | ↑HDL | ↑ Risk of Muscle Toxicity if Used With Statin |
|---------------------------|-----|------|---|
| Gemfibrozil               | +   | +    | ++++  |
| Fenofibrate               | +   | +    | +   |
| Niacin                    | +   | +++  | +   |
| Omega-3 acid ethyl esters | +   | +    | —   |

## CASE STUDY

### A 40-Year-Old Man With Family History of MI

#### Presentation

A 40-year-old man presents with a family history of MI. He is slightly overweight. His father had an MI at age 40. The patient's blood pressure, fasting blood glucose, and thyroid levels are normal. His lipid profile shows low HDL-C levels and slightly elevated LDL-C levels. His calcium score is 125. He had a thallium stress test, which showed a small, significant, reversible abnormality of the anterior wall.

#### Physical Examination

- ➔ Body mass index: 25 kg/m<sup>2</sup>
- ➔ Blood pressure: 128/82 mm Hg
- ➔ Electron beam computed tomography (EBCT): calcium score 25

#### Laboratory Values

- ➔ TC: 177 mg/dL
- ➔ HDL: 27 mg/dL
- ➔ LDL: 120 mg/dL
- ➔ TG: 151 mg/dL

#### Clinical Decision Point

*Which of the following would you advise for the patient to manage his dyslipidemia and improve his cardiovascular risk profile?*

- ➔ Gemfibrozil
- ➔ Fenofibrate
- ➔ Fenofibrate/ezetimibe
- ➔ Omega-3 acid ethyl esters
- ➔ Fenofibrate/omega-3 acid ethyl esters
- ➔ Ezetimibe/low-dose statins

#### Comment

This patient has tried several therapies because of his family history of premature heart disease and the abnormal result of his thallium stress test. He experienced severe flushing and gout with extended-release niacin and had back-ache with simvastatin.

For this patient, the question is whether to be concerned about his TG level of 151 mg/dL, given that his total cholesterol is 177 mg/dL. Should the patient receive drug therapy in addition to the diet and exercise program he will continue or implement? Several options are possible, including gemfibrozil, fenofibrate, and the combination of fenofibrate with ezetimibe. Another option may be to combine ezetimibe and a low-dose statin. In this case, the choice of therapy should involve the patient and clinician in a discussion of the potential benefits of therapy versus the risk of side effects and costs.

## QUESTIONS FROM SYMPOSIUM PARTICIPANTS

➔ **Q:** What should be done for a patient whose HDL decreases with statin therapy?

**A:** Clinicians must look at the patient's LDL-C goal first. Only after the LDL-C goal has been reached can they proceed to the TG and the HDL-C goals. Clinicians may also consider the ratios of LDL to HDL (with <2 being optimal) and other risk factors, as well as assess the TGs going up. Is the patient on other medications that would lower HDL? Could patients be taking anabolic steroids, beta-blockers, or other drugs?

There are 3 factors that correlate with atherosclerotic disease of the carotid artery: postprandial blood glucose, LDL-C level, and systolic hypertension. High HDL-C levels do not protect against carotid atherosclerotic vascular disease.

➔ **Q:** When should Vertical Analysis Profile (VAP) testing be used instead of the standard fasting lipid profile?

**A:** The NCEP guidelines do not recommend initial use of the VAP for all patients. The guidelines do recommend HDL, TG, TC, and LDL. The VAP can determine whether patients have small, dense LDL-C or what proportion of their HDL-C is HDL-2, while directly measuring the atherogenic lipoproteins, VLDL, IDL, and LDL.

➔ **Q:** Does vitamin E negate the effect of statins?

**A:** There is no evidence that vitamin E lowers CV risk. It has been shown to lower HDL levels in the HDL-Atherosclerosis Treatment Study (HATS) trial.

➔ **Q:** If a patient has normal TG and LDL-C levels but a low HDL, what dose of omega-3s would increase the HDL?

**A:** Omega-3s will not significantly increase the HDL independently of a TG-lowering effect. Although it is clear that baseline HDL-C predicts risk, the evidence is not clear whether changes in HDL-C induced with treatment parallel changes in risk. Torcetrapib, which was found to double HDL-C levels, was also found to increase mortality. The increase in HDL-C did not translate into an outcomes benefit. Niacin is the most effective drug for raising HDL-C levels.

➔ **Q:** How should dyslipidemia be approached in a patient who has abnormal liver function?

**A:** If the aspartate aminotransferase (AST; formerly serum glutamic-oxaloacetic transaminase [SGOT]) is <3 times the upper limit of normal, a patient can be started cautiously on a statin. However, patients should be assessed after 4 weeks of therapy rather than the usual 12 weeks.

➔ **Q:** Once patients are stabilized and have achieved good lipid profiles with statins and omega-3s, can medication be discontinued and normal lipid profile maintained with adequate exercise and diet?

**A:** No. Once therapy is stopped, lipid levels will return to baseline, untreated status within 2 to 4 weeks.

- ➔ **Q:** Which fibrates decrease TGs?  
**A:** All fibrates reduce TG levels effectively and to a similar extent. One of the benefits of fibrates is that the higher the TG levels, the greater the percent reduction obtained with fibrate therapy.
- ➔ **Q:** Can high doses of omega-3s be used in patients on warfarin?  
**A:** Omega-3s do not change the international normalized ratio (INR), but bleeding times can be prolonged. Clinicians should emphasize that patients must report any changes in bleeding.
- ➔ **Q:** Is severe allergy to fish or fish oils an issue in therapeutic use of omega-3 acid ethyl esters?  
**A:** Fish oil has no proteins, which are the allergens. Omega-3 acid ethyl esters are highly purified. Nonetheless, these products should be used with caution in patients with documented fish allergies.
- ➔ **Q:** In familial hypertriglyceridemia, should omega-3s be started in adolescents with borderline lipid panels?  
**A:** Omega-3s have not been studied well in adolescents and are not recommended for patients <18 years of age.
- ➔ **Q:** Is flaxseed oil effective in the management of hypertriglyceridemia or as a protectant for heart disease?  
**A:** Flaxseed oil has not been shown to be effective in this setting. Flaxseed oil has a short-chain omega-3, ALA, which is different from fish oil and doesn't lower TG levels. Randomized trials have not shown that flaxseed oil protects against heart disease. Flaxseed oil should be reserved for people who will not or cannot take fish oil capsules.
- ➔ **Q:** Can omega-3s be used during pregnancy?  
**A:** Omega-3 acid ethyl esters are not approved for use in pregnancy because they haven't been studied.
- ➔ **Q:** Do medicines such as beta-blockers, thiazide diuretics, and hormone replacement therapy have an effect on TGs?  
**A:** They all raise TGs. Carvedilol, a beta-blocker with alpha-blocking capability, will not have a significant effect on TGs.
- ➔ **Q:** Are fiber supplements effective in reducing TGs?  
**A:** Supplementing with fiber does not affect TGs. If fiber has any effect outside the bowel, it is a small effect on LDL-C—maybe a 5% drop—but no effect on TGs.

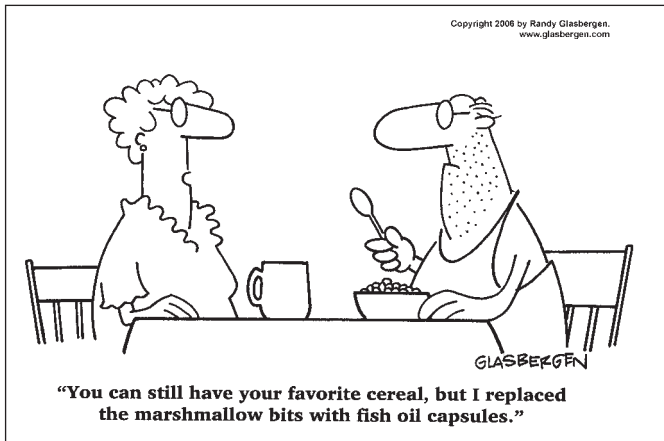
## Hypertriglyceridemia and Cardiovascular Disease Management: The Role of Omega-3 Fatty Acids

➔ **Q:** Is there any difference in mercury content between the pharmaceutical products and the supplement formulations of omega-3s?

**A:** None of the fish oil formulations have been shown to have mercury. Mercury is a water-soluble component that is eliminated with the proteins and the water when the oil is separated from the fish. The prescription brand omega-3 acid ethyl esters are free of mercury and PCBs as certified by the FDA.

➔ **Q:** Is there a chance that using omega-3s can increase LDL-C levels?

**A:** Yes. When patients have very high TG levels (>500 mg/dL), LDL-C levels will increase as the TGs decrease. However, the total number of LDL particles decreases and there is a shift from the smaller, more atherogenic LDL to the larger, less atherogenic LDL.



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