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**TARGET AUDIENCE**

This activity is designed for hospital- and office-based physicians involved in adult patient care.

**STATEMENT OF NEED**

Hypertriglyceridemia is a common lipid disorder observed in approximately 33% of adults living in the United States. While hypertriglyceridemia is frequently associated with other lipid abnormalities and the metabolic syndrome, numerous studies have shown that elevated triglyceride levels are an independent risk factor for coronary artery disease.

Lifestyle changes, dietary supplements, and pharmacologic therapy, including statins, niacin, fibrates, and omega-3 fatty acid preparations containing eicosapentaenoic acid and docosahexaenoic acid, are current strategies used to lower triglyceride levels.

The purpose of this program is to provide comprehensive education on the relation between elevated triglycerides and cardiovascular risks factors and a rationale for treatment strategies that will improve patient outcomes.

**SPECIFIC OBJECTIVES**

Following completion of this program, the participant should be better able to:

- Discuss the relation between hypertriglyceridemia and coronary heart disease
- Describe the etiology and pathophysiology of hypertriglyceridemia
- Understand the available antihypertriglyceridemic options regarding mechanism of action, efficacy, and patient safety
- Identify appropriate combination therapies for dyslipidemia through practical case study discussions

**FACULTY**

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**STATEMENT AND INDIVIDUAL**

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## Strategies for Reducing Cardiovascular Risk in Patients With Hypertriglyceridemia

The obesity epidemic in the United States has generated a number of related health issues, such as increased prevalence of the metabolic syndrome and its comorbidities, including hypertriglyceridemia.<sup>1</sup> The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP/ATP III) describes hypertriglyceridemia as a key clinical feature of the metabolic syndrome.<sup>2</sup> A 2005 study that examined data from the National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999-2000 cited increases in high blood pressure, waist circumference, and hypertriglyceridemia as major factors in the rise in prevalence of the metabolic syndrome, especially among women.<sup>1</sup> It is not surprising that an increased prevalence of hypertriglyceridemia among men and women parallels an increased prevalence of obesity, the metabolic syndrome, and cardiovascular disease (CVD).<sup>3</sup> Based on meta-analyses of prospective studies indicating that elevated triglycerides (TGs) are an independent risk factor for coronary heart disease (CHD), the NCEP/ATP III (2002) *Classification of Serum Triglycerides—Standards for Hypertriglyceridemia* were revised substantially downward from ATP II levels<sup>2,4</sup>:

- Normal TGs: <150 mg/dL
- Borderline-high TGs: 150-199 mg/dL
- High TGs: 200-499 mg/dL
- Very high TGs: ≥500 mg/dL

A further complication is a lack of patient knowledge about hypertriglyceridemia and associated cardiovascular (CV) risks. Results from a survey of 2089 patients and 510 physicians by the National Lipid Association revealed that an overwhelming majority of physicians thought that patients had a poor understanding of TGs, including the independent risks that elevated levels of TGs pose to CV health.<sup>5</sup>

### Triglyceride levels and CVD risk

Historically, establishing an association between elevated TGs and CVD risk was complicated by the interrelation of hypertriglyceridemia and other well-established risk factors, such as low levels of high-density lipoprotein cholesterol (HDL-C), obesity, and diabetes. The Framingham Heart Study provided some of the first evidence suggesting that elevated TGs increase the risk for



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**Table 1**

**Tolerability and Safety Considerations for Current TG-Lowering Agents**

Agent	Tolerability	Safety Considerations
Fibrates	Generally well tolerated	<ul style="list-style-type: none"> <li>• Slightly increased risk for myopathy, cholelithiasis, venous thrombosis</li> <li>• Avoid using gemfibrozil in combination with statins</li> <li>• May increase creatinine, but routine monitoring not required in asymptomatic patients</li> </ul>
Niacin	5%-10% of patients will not tolerate niacin because of flushing	<ul style="list-style-type: none"> <li>• Infrequent reports of serious hepatic toxicity, mainly with slow-release formulations</li> <li>• Requires regular monitoring of liver enzymes</li> <li>• Rare retinal macular edema, nausea, vomiting, gout</li> <li>• Palpitations, tachycardia, and atrial fibrillation are potential adverse events</li> <li>• Can induce insulin resistance</li> </ul>
Prescription EPA + DHA	Taste perversion (principally fishy taste) experienced by <3%	<ul style="list-style-type: none"> <li>• No evidence to support an increased bleeding risk</li> <li>• Rigorous purification process reduces risk of hypervitaminosis, fatty acid oxidation, and exposure to environmental toxins</li> </ul>
Statins	Generally well tolerated	<ul style="list-style-type: none"> <li>• Myopathy and rhabdomyolysis are rare at standard doses</li> <li>• Asymptomatic increases in liver transaminases</li> </ul>

EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid. McKenney JM, Sica D. *Am J Health Syst Pharm.* 2007;64:595-605<sup>30</sup>; Guyton JR, Bays HE. *Am J Cardiol.* 2007;99(suppl):S22-S31<sup>46</sup>; Davidson MH, et al. *Am J Cardiol.* 2007;99:3C-18C<sup>47</sup>; Bays HE. *Am J Cardiol.* 2007;99(suppl):35C-43C<sup>48</sup>; Armitage J. *Lancet.* 2007.doi:10.1016/S0140-6736(07)60716-8<sup>49</sup>.

heart disease, particularly among women.<sup>6,7</sup> A number of studies prior to the late 1990s examined the association between serum TGs and CV risk, although no single study provided enough strength of evidence to demonstrate a definite causal relation.<sup>8</sup> To make an inclusive assessment, a meta-analysis of 17 population-based studies of TGs and CV risk was conducted. After adjustment for other risk factors, results showed a relative risk (RR) estimate associated with a 1 mmol/L (88.5 mg/dL) increase in TGs of 1.32 for men (95% confidence interval [CI], 1.26-1.39) and 1.76 for women (95% CI, 1.50-2.07).<sup>8</sup>

The Baltimore Coronary Observational Long-Term Study (N=740) showed that serum TG levels >100 mg/dL are an independent predictor of new cardiac events in patients diagnosed with CHD (RR=1.5; 95% CI, 1.1-2.1).<sup>9</sup> In addition, Kaplan-Meier analysis showed that survival after CHD events was lower in patients with TG ≥100 mg/dL than in those with TG <100 mg/dL (P=.008). A recent meta-analysis of 29 prospective studies involving general Western populations indicated highly significant associations between TGs and CHD.<sup>10</sup> Comparison between subjects in the highest and the lowest third of TG levels yielded an adjusted odds ratio of 1.72 (95% CI, 1.56-1.90) for CHD, with adjustment for age, sex, smoking, and other lipid concentrations in all but one study, and adjustment for blood pressure in most studies.<sup>10</sup>

An increase in CV risk with increased TGs has been shown to persist especially at higher levels of low-density lipoprotein cholesterol (LDL-C).<sup>11,12</sup> The independent risk of TGs in relation to HDL-C has also been demonstrated in the Copenhagen Male Study, which documented the incidence of ischemic heart disease in 2906

initially disease-free men aged 53 to 74 years over an 8-year follow-up period.<sup>12</sup> Results showed that increasing TGs increased the risk for ischemic heart disease, even in men with HDL-C of 57 to 134 mg/dL, which are levels considered to be cardioprotective. The Helsinki Heart Study, a 5-year, randomized, primary prevention trial, investigated the joint effect of TG and lipoprotein cholesterol levels on cardiac endpoints in 4081 Finnish men with dyslipidemia.<sup>13</sup> Results revealed that analyzing TG concentrations in combination with HDL-C and LDL-C information was highly prognostic for CHD risk. Subjects with an LDL-C-to-HDL-C ratio >5 and a TG concentration >2.3 mmol/L (205 mg/dL) were identified as a subgroup with exceptionally high risk (RR=3.8; 95% CI, 2.2-6.6).<sup>13</sup>

**Primary and secondary causes of hypertriglyceridemia**

Hypertriglyceridemia can result from a number of single or combined factors, including primary hereditary syndromes and secondary causes such as lifestyle, diseases/conditions, and medication side effects.<sup>14,15</sup>

The primary causes of hypertriglyceridemia are familial disorders of lipid or lipoprotein metabolism. The most common familial dyslipidemia (1 in 200 individuals) leading to hypertriglyceridemia is familial combined hyperlipidemia, which is characterized by a family history of high LDL-C, very low-density lipoprotein cholesterol (VLDL-C), and apolipoprotein (apo B).<sup>14</sup> Serum TGs are typically elevated to a range of 150 mg/dL to 500 mg/dL, and early CVD occurs at a 2- to 5-fold higher rate in this phenotype.<sup>14,15</sup>

A rarer primary cause of hypertriglyceridemia is familial dysbetalipoproteinemia (type III or remnant

removal disease), which has a prevalence rate in the general population of 0.2% to 1.0%.<sup>15</sup> A secondary exacerbating condition, such as obesity or diabetes, is required for expression of this phenotype. Patients with dysbetalipoproteinemia present with moderately severe TGs and total cholesterol (TC) (both lipids at 300-400 mg/dL), although HDL-C is usually normal.<sup>15</sup>

Familial hypertriglyceridemia occurs in families with a pervasive history of hypertriglyceridemia among first-degree relatives, and can present with or without chylomicronemia.<sup>14,15</sup> High levels of large, TG-rich VLDL and low HDL-C are typical of this syndrome, with near-normal LDL-C and apo B.<sup>15</sup> People with this phenotype can present with hypertriglyceridemia that is either mild to asymptomatic (>200 mg/dL) or severe (>1000 mg/dL), depending on whether secondary risk factors exist.<sup>14,15</sup> Patients with more severe disease may develop eruptive xanthomas and pancreatitis.<sup>14,15</sup>

Deficiency of lipoprotein lipase or its cofactor apo C-II results in familial chylomicronemia, a very rare recessive condition that occurs in about 1.1 million individuals.<sup>16</sup> TG levels are highly elevated, ranging from 1000 to 10,000 mg/dL.<sup>15</sup> This disorder is usually apparent from childhood due to development of eruptive xanthomas, pancreatitis, and in severe cases, visibly lipemic plasma.<sup>16</sup> The risk of early CVD is unclear, since the large, nonmetabolized chylomicrons that accumulate in this condition are not known to be atherogenic.<sup>15,16</sup>

Far more common than primary causes of hypertriglyceridemia are secondary causes, especially lifestyle factors.<sup>14</sup> Excessive caloric intake, inactivity, high carbohydrate intake (>60% of energy intake), and excessive alcohol consumption contribute to an “atherogenic lifestyle,” which leads to a number of CVD risk factors, including hypertriglyceridemia. High caloric intake stimulates production of VLDL and also can lead to decreased HDL-C and increased small, dense LDL. The effects of alcohol consumption are more variable, although TGs are more often affected than cholesterol.<sup>14</sup>

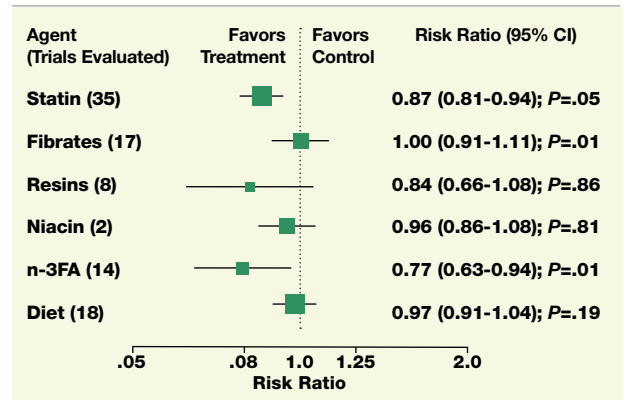
Besides lifestyle factors, other secondary causes of hypertriglyceridemia include overweight and obesity, the metabolic syndrome, type 2 diabetes mellitus, kidney disease and nephrotic syndrome, Cushing syndrome, hypothyroidism, and pregnancy.<sup>14</sup> Some medications also can induce hypertriglyceridemia, including estrogen replacement therapy, oral contraceptives, tamoxifen, corticosteroids, beta-blockers, thiazide diuretics, retinoids, protease inhibitors, atypical antipsychotics (chlorpromazine, clozapine, fluperlapine, olanzapine, perphenazine, risperidone), and immunosuppressants.<sup>14</sup>

### TGRLs, atherogenesis, and endothelial dysfunction

The atherogenicity of TG-rich lipoproteins (TGRLs) is determined largely by particle size and apolipoprotein composition.<sup>16,17</sup> Whereas chylomicrons and large

Figure 1

### Estimate of Effect of Lipid-Lowering Interventions on Overall Mortality



CI = confidence interval; n-3FA = n-3 fatty acids. Adapted with permission from Studer M, et al. *Arch Intern Med.* 2005;165:725-730.<sup>20</sup>

VLDLs are unable to enter the arterial intima due to their large size, small VLDLs and intermediate-density lipoproteins can penetrate the arterial intima readily and have been shown to be associated with the presence, severity, and progression of atherosclerosis.<sup>16</sup> The most abundant lipoprotein in TGRLs, apo C-III slows the clearance and metabolism of TGRLs by interfering with lipoprotein binding to cell-surface receptors and inhibiting lipoprotein lipase activity.<sup>16</sup> Abnormalities in TGRL metabolism are common in persons with insulin resistance, and include increased VLDL and chylomicron secretion into plasma; small-cholesteryl, ester-depleted, dense LDL; and decreased HDL-C.<sup>17</sup> This combination of abnormalities is particularly predictive of CVD.<sup>16,17</sup>

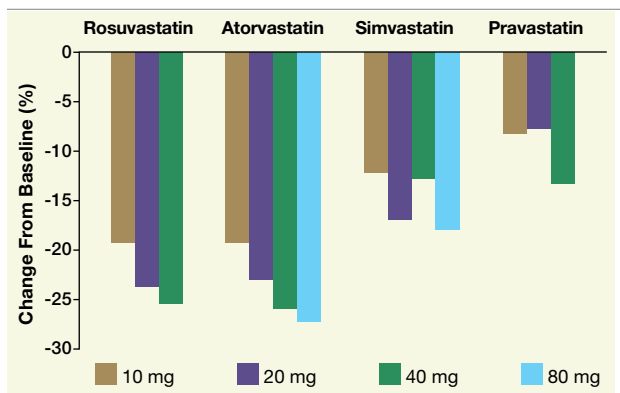
High TGRLs are associated with other negative CV effects, including severe impairment of endothelial function during postprandial hypertriglyceridemia. Results from a recent study in individuals with type IV hypertriglyceridemia showed that endothelial impairment seen during the postprandial phase may be related to increased expression of genes associated with inflammation in endothelial cells.<sup>18</sup> This evidence suggests that elevated TGRLs are proinflammatory and atherogenic, and induce endothelial dysfunction.

### Management of hypertriglyceridemia

Individual risk assessment is the first step in determining treatment for a patient with hypertriglyceridemia. The NCEP/ATP III identified LDL-C as the primary target of therapy for the prevention of CHD.<sup>4</sup> In patients with high TGs, non-HDL-C (TC minus HDL-C or the sum of LDL-C plus VLDL-C) is identified as the secondary risk target. Specifically, when TGs are >200 mg/dL, the goal for non-HDL-C should be set at the recommended LDL-C plus 30 mg/dL. When TGs are at levels considered borderline-high (150 to 199 mg/dL), weight loss and

**Figure 2**

### Effect of Statins on TG Levels After 6 Weeks of Therapy



TG = triglyceride. Patients with hypercholesterolemia (N=2431). Jones PH, et al. *Am J Cardiol.* 2003;92:152-160.<sup>21</sup>

lifestyle factors, including physical activity, are the recommended treatment strategies.<sup>4</sup> For higher levels of TG (>200 mg/dL), non-HDL-C becomes a secondary target of therapy and pharmacologic treatment is appropriate.<sup>4</sup>

The treatment approaches for hypertriglyceridemia are diverse and involve most of the available therapies: fibrates (gemfibrozil, fenofibrate, clofibrate), statins (lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin), niacin (immediate release, sustained release, and extended release), and omega-3 fatty acids, especially eicosapentaenoic

acid (EPA) and docosahexaenoic acid (DHA).<sup>4,19</sup> All of these treatments are effective as well as generally safe and well tolerated (TABLE 1). The results of a meta-analysis suggested that statins and omega-3 fatty acids may reduce the risk of overall mortality more than do other lipid-lowering interventions.<sup>20</sup> This analysis examined the effects of lipid-lowering interventions on mortality in 97 randomized and controlled studies (FIGURE 1).<sup>20</sup>

#### Statins

In addition to the well-known LDL-C-lowering effects of statins, TG reductions of 7% to 30% also are achieved with statin therapy.<sup>4</sup> The efficacy of 4 statins was examined in 2431 adults with LDL-C levels  $\geq 160$  mg and <250 mg/dL and TG levels <400 mg/dL in a randomized, parallel-group, multi-center trial (FIGURE 2).<sup>21</sup> Subjects were treated with 10, 20, 40, or 80 mg of atorvastatin or simvastatin or 10, 20, or 40 mg of rosuvastatin or pravastatin. Results showed that rosuvastatin and atorvastatin had a more robust TG-lowering effect, which appeared to be dose dependent (eg, -26.1% for atorvastatin 40 mg, and -28.2% for atorvastatin 80 mg). Simvastatin and pravastatin lowered TGs to a lesser degree (-18.2% for simvastatin 80 mg, and -13.2% for simvastatin 40 mg), and it was unclear whether there was a dose-dependent effect.

#### Fibrates

Fibrate therapy reduces TGs by 20% to 50%.<sup>4</sup> Fibrates are peroxisome proliferator-activated receptor- $\alpha$  ago-

#### A CASE STUDY

### Managing patients with mixed dyslipidemia

**This case study presents a woman with mixed dyslipidemia and the treatment strategies used to normalize her TG levels.**

Mary is a 50-year-old obese woman, with a body mass index of 32, a waist circumference of 96 cm, and a medical history of borderline-high TC. Simvastatin (20 mg/d) was started 8 months ago to lower LDL-C (165 mg/dL) and TGs (300 mg/dL). She was also treated with lisinopril for hypertension (159/90 mm Hg). Mary claims to be physically active and diet conscious, although her presenting conditions lead her physician to be skeptical. She consumes 6 to 8 glasses of wine per week

and quit smoking about 3 years ago. Her current laboratory values are TC, 264 mg/dL; LDL-C, 165 mg/dL; HDL-C, 43 mg/dL; TGs, 280 mg/dL; and fasting glucose, 98 mg/dL. All other laboratory values are normal.

Mary's CV risk factors include age, hypertension, and obesity. Another potential risk factor is her waist circumference, indicating abdominal obesity (AO), which may be a better predictor of disease risks and mortality than overall obesity.<sup>41</sup> Mary also has hypertriglyceridemia, high levels of LDL-C and TC, and low HDL-C levels.

Mary's physician must decide which lipid factor is most important to treat—and both cholesterol and TGs should be treated. Mary's response to statin therapy has been inadequate for lowering LDL-C and TGs. If noncompliance with the simvastatin regimen can be ruled out, a reasonable approach would be to increase her dose of simvastatin and prescribe therapeutic lifestyle changes, such as

diet and exercise. The AHA *Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update* recommends exercise (30 min of moderate-intensity activity on most or all days of the week for all women, and 60 to 90 min for those who need to lose weight), and EPA plus DHA in a capsule form as an adjunct to diet for women with CHD (0.85-1.0 g/d) and women with high TGs (2-4 g/d).<sup>42</sup>

Additional recommendations for women with a 10% to 20% 10-year risk for MI include starting a statin if LDL-C  $\geq 130$  mg/dL, then initiating niacin or a fibrate for low HDL-C after the LDL-C goal has been reached. For women considered to be at higher risk, the AHA recommends initiating a statin if LDL-C is  $\geq 100$  mg/dL, and to achieve a target of <70 mg/dL for very-high-risk women.<sup>42</sup>

After following a diet and exercise regimen for 4 months, Mary's waist circumference has decreased to 93 cm, her

nists that increase expression in genes involved in lipid homeostasis, including those that enhance fatty acid uptake and oxidation.<sup>22</sup> Increased metabolism reduces the availability of fatty acids required for VLDL synthesis in the liver. In addition, intravascular lipolysis of TGs in chylomicrons and VLDL is enhanced because of increased lipoprotein lipase activity.<sup>23</sup>

The CV benefit of fibric acids has shown in a study of 2531 men with CHD and a primary lipid defect of low HDL-C (<40 mg/dL). Long-term treatment with gemfibrozil reduced TGs by 31% and increased HDL-C by 6%.<sup>23</sup> Moreover, the RR for any CHD event was reduced by 22% ( $P=.006$ ) and the combined outcome of death from CHD, nonfatal myocardial infarction (MI), and stroke was reduced by 24% ( $P<.001$ ) compared with placebo. In another study, treatment with fenofibrate for 24 weeks reduced TGs by 38% in patients with type IIa hypercholesterolemia (baseline TG level <250 mg/dL) and by 45% in patients with type IIb hypercholesterolemia (baseline TG level >250 mg/dL).<sup>24</sup>

### Niacin

The substantial lipid-lowering properties of niacin (reductions of 20% to 50%) have been well known for more than 50 years.<sup>4,19</sup> Treatment with niacin low-

LDL-C is still 165 mg/dL, and her TGs have decreased to 220 mg/dL. Her fasting blood glucose level has decreased to 95 mg/dL. Mary has been evaluated for primary causes of her continued hypertriglyceridemia, but none was apparent. Her physician concludes that the metabolic syndrome, diagnosed at the time lisinopril and statin therapy were initiated, is responsible for her persistent hypertriglyceridemia. She has 3 of the risk factors described by NCEP/ATP III for identification of the metabolic syndrome in women: high TGs ( $\geq 150$  mg/dL), low HDL-C (<50 mg/dL), and AO (waist circumference >88 cm).<sup>4</sup>

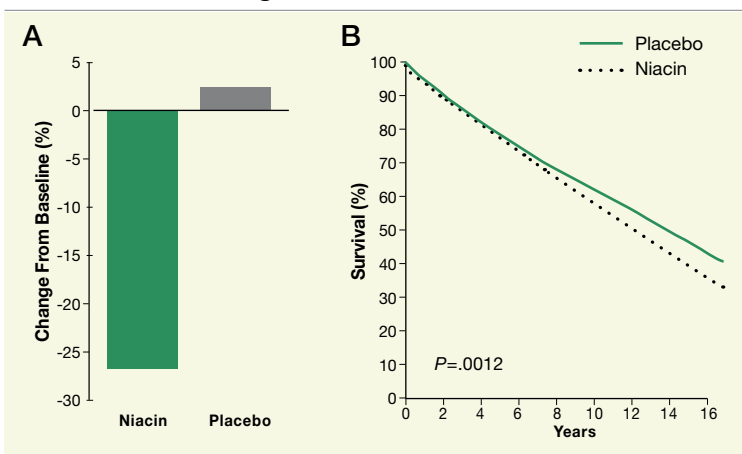
Clearly, Mary needs an adjustment to her pharmacologic therapy for TG lowering, such as adding a fibrate, niacin, or EPA/DHA to her statin therapy. The addition of fenofibrate to simvastatin therapy for men and women with combined hyperlipidemia has been shown to lower TGs by 43%, a difference of -23.6%

( $P<.001$ ) compared with simvastatin alone over an 18-week study period.<sup>43</sup> Similarly, prescription EPA/DHA in combination with statin therapy was shown to improve hypertriglyceridemia in patients with combined hyperlipidemia and in patients with persistent hypertriglyceridemia and established CHD.<sup>44</sup> The lipid-lowering effect of prescription EPA/DHA (4 g/d) combined with simvastatin therapy (20 mg/d) was investigated in patients with combined hyperlipidemia.<sup>44</sup> Results showed that, after 5 weeks of treatment, the addition of EPA/DHA resulted in further reduction of TG levels ( $P=.007$ ), TC ( $P=.052$ ), and apo E ( $P=.035$ ) compared with simvastatin alone.<sup>44</sup> Another study examined the TG-lowering effectiveness of prescription EPA/DHA (2 g/d) added to existing simvastatin therapy (10-40 mg/d) in patients with persistent hypertriglyceridemia and documented CHD.<sup>45</sup> Results showed a significant decrease in TC levels of 20% to 30% ( $P<.005$ ) that was sus-

tained over the 24-week, double-blind study period compared with baseline and placebo.<sup>45</sup>

Mary is likely to achieve safe TG lowering by adding niacin, a fibrate, or prescription EPA/DHA to her statin regimen. When several agents are effective, final treatment decisions may be based on relative tolerability. Fibrates and prescription EPA/DHA are generally well tolerated, although "fishy taste" can occur with EPA/DHA at an incidence of 2.7%.<sup>30</sup> Up to 5% to 10% of patients will not tolerate niacin for long-term use because of flushing.<sup>46</sup> Safety issues associated with fibrates (ie, slight increase in risk for myopathy, cholelithiasis, and thrombosis) and niacin (ie, macular edema, nausea, vomiting) are rare.<sup>46,47</sup> No serious safety concerns are associated with prescription EPA/DHA and, based on FDA regulatory requirements, its highly purified form eliminates concerns about environmental contaminants.<sup>48</sup> ■

**Figure 3**  
Effect of Niacin on TG Levels and Mortality Among Men With Previous MI

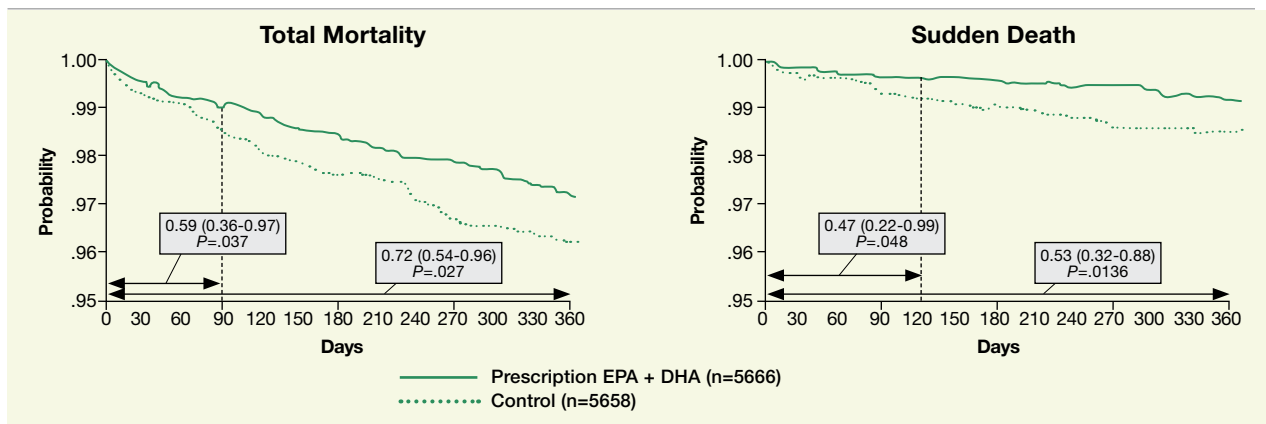


MI = myocardial infarction; TG = triglyceride. **A:** TG levels after 1 year of treatment. **B:** All-cause mortality during 16 years of treatment and follow-up. Adapted with permission from Canner PL, et al. *J Am Coll Cardiol.* 1986;8:1245-1255.<sup>26</sup>

ers plasma TGs mainly by 2 mechanisms: inhibition of lipolysis in adipose tissue and inhibition of hepatic TG synthesis.<sup>25</sup> Doses of 1500 to 3000 mg/d lower TGs by approximately 20% to 50% and increase HDL-C.<sup>4</sup> The long-term CV benefit of niacin treatment on mortality was demonstrated in 8341 men with documented history of MI in the Coronary Drug Project (FIGURE 3).<sup>26</sup> Treatment with niacin resulted in a 26.9% reduction in TGs from baseline after

**Figure 4**

### Early Effects of Prescription EPA Plus DHA on Mortality in Patients With Previous MI



DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; MI = myocardial infarction. Relative risk and 95% confidence intervals shown in boxes. Total mortality (left); sudden death (right). Adapted with permission from Marchioli R, et al. *Circulation*. 2002;105:1897-1903.<sup>36</sup>

1 year, whereas the placebo group experienced a 2.1% increase. After a mean follow-up of 15 years, treatment with niacin reduced all-cause mortality by 11% compared with placebo ( $P=.0004$ ).<sup>26</sup>

#### Omega-3 fatty acids

The relevant omega-3 fatty acids are EPA and DHA, which are derived from marine sources (eg, fatty fish)<sup>27-29</sup> and are available as a prescription formulation and as dietary fish oil supplements. The prescription formulation of EPA and DHA is a highly purified and concentrated ethyl ester product (approximately 840 mg/g), and is approved by the US Food and Drug Administration (FDA) and as an adjunct to diet for treatment of very high TGs ( $\geq 500$  mg/dL) in adults.<sup>30</sup> This product is considered a tier-3 drug for most payers, and although EPA/DHA dietary supplements are less costly, up to 3 times as many capsules are required to achieve the same dosage.<sup>31</sup> The difference in concentration depends on whether EPA and DHA are available as TGs or the more concentrated methyl ester or ethyl ester.<sup>32</sup> Both the TG and methyl ester forms have shown equally effective antihypertriglyceridemic activity in patients with type IV hyperlipidemia, the most common form of familial hypertriglyceridemia.<sup>15,33</sup>

Unlike the prescription formulation of EPA/DHA, dietary supplements are unregulated. Manufacturing standards are much less rigorous, so they are more likely to contain environmental contaminants, such as heavy metals or pesticides.<sup>30</sup> Also unlike prescription EPA/DHA, no clinical trial evidence has shown that dietary supplement formulations of EPA and DHA are effective for lowering TGs or reducing CHD risk.<sup>30</sup>

Clinical studies with EPA and DHA have reported dose-dependent TG reductions of 40% to 79% among persons with severe hypertriglyceridemia.<sup>34</sup> Treatment with EPA/DHA achieves TG reductions at rates similar to those seen with fibrates in patients with hypertri-

glyceridemia, and reduces CV risk within a few months of initiating therapy.

The mechanism of action by which EPA and DHA lower TGs is not well understood. One working model suggests the involvement of 4 or more metabolic nuclear receptors that are controlled by sterol regulatory element binding protein-1c;<sup>35</sup> another theory is that EPA and DHA activate lipoprotein lipase, by activation of the PPAR- $\alpha$  nuclear receptor, which could increase chylomicron clearance.<sup>35</sup>

The effectiveness of a low dose of highly purified prescription EPA/DHA (850-882 mg/d) for early protection against total mortality and sudden death was demonstrated in 11,323 subjects who had experienced a recent MI (FIGURE 4).<sup>36</sup> After 3 months of treatment, total mortality was significantly reduced in the EPA/DHA group (RR=0.59; 95% CI, 0.36-0.97;  $P=.037$ ) compared with the control group. Similarly, the risk for sudden death was sharply reduced by 4 months (RR=0.47; 95% CI, 0.219-0.995;  $P=.048$ ). These data support the hypothesis for antiarrhythmic properties of EPA/DHA.<sup>36</sup>

The American Heart Association (AHA) recommends that individuals with CHD consume approximately 1 g/d of EPA and DHA, preferably from oily fish, and that those without CHD eat a variety of oily fish at least twice weekly.<sup>37,38</sup> Additionally, children older than 2 years and adolescents are encouraged to increase their intake of broiled or baked oily fish.<sup>39</sup> Eating fish is not hazardous to the health of the general population, but some people are at greater risk from exposure to environmental contaminants.<sup>33</sup> Although trace amounts of methylmercury can be found in nearly all fish, some fish contain higher amounts that may harm an unborn baby or a child.<sup>40</sup> The Institute of Medicine, the FDA, and the Environmental Protection Agency advise women who are or may become pregnant, those who are breast-feeding, and young children to avoid certain fish and shellfish.<sup>40</sup>

## Summary

The prevalence of hypertriglyceridemia—a key clinical feature of the metabolic syndrome and an independent risk factor for CHD—is increasing among US men and women. As a result, the NCEP/ATP III has revised its classification of serum TGs downward to establish goals for TG lowering. Because hypertriglyceridemia can result from single or combined factors (eg, primary, hereditary syndromes, lifestyle, diseases, medication

side effects), physicians should base treatment strategies on individual patient profiles. Current treatments utilized to normalize TGs include lifestyle modification (eg, weight loss, exercise), fibrates, statins, niacin, and omega-3 fatty acids (ie, EPA and DHA). Patient education regarding TGs and CV risk is also needed to improve patient–physician communication, aid treatment adherence, and improve outcomes. ■

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## CME Posttest

Select the single-letter response that best completes each sentence.

- A study published in 2005 examining data from the National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999-2000 cited increases in \_\_\_\_\_ as accounting for much of the increase in prevalence of the metabolic syndrome, especially among women.
  - High blood pressure
  - Large waist circumference
  - Hypertriglyceridemia and high blood pressure
  - Hypertriglyceridemia, high blood pressure, and large waist circumference
- According to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP/ATP III) (2002) *Classification of Serum Triglycerides—Standards for Hypertriglyceridemia* are:
  - Normal triglycerides (TG) <150 mg/dL; borderline-high TGs 150-199 mg/dL; high TGs 200-499 mg/dL; very high TGs ≥500 mg/dL
  - Normal TGs <200 mg/dL; borderline-high TGs 200-300 mg/dL; high TGs 300-499 mg/dL; very high TGs ≥500 mg/dL
  - Normal TGs <100 mg/dL; borderline-high TGs 100-199 mg/dL; high TGs 200-499 mg/dL; very high TGs ≥500 mg/dL
  - Normal TGs <200 mg/dL; borderline-high TGs 200-400 mg/dL; high TGs 400-599 mg/dL; very high TGs ≥600 mg/dL
- Miller and colleagues conducted a retrospective study that examined risk factors for the development of new coronary events in 740 patients who were diagnosed with coronary heart disease from 1977 through 1978. Results from multiple logistic regression analyses of data indicated that the presence of diabetes, HDL-C <35 mg/dL, or \_\_\_\_\_ were independent predictors of coronary artery disease events.
  - Waist circumference >90 cm
  - TG >100 mg/dL
  - LDL-C >150 mg/dL
  - Hypertension
- The independent risk of TG levels for ischemic heart disease in relation to \_\_\_\_\_ levels was clearly demonstrated in the Copenhagen Male Study.
  - HDL-C
  - IDL-C
  - VLDL-C
  - Chylomicrons
- The most common form of inherited hypertriglyceridemia is familial combined hyperlipidemia, which occurs in about 1 in 200 individuals. The phenotype is characterized by serum TG levels of \_\_\_\_\_ and a 2- to 5-fold higher rate of early cardiovascular disease.
  - 200 mg/dL to 1000 mg/dL
  - 250 mg/dL to 500 mg/dL
  - 150 mg/dL to 500 mg/dL
  - 500 mg/dL to 1000 mg/dL
- Whereas the TG-rich lipoprotein chylomicrons and large VLDL \_\_\_\_\_ the arterial intima due to their large size, small VLDL and LDL can penetrate the arterial intima readily, and have been shown to be associated with the presence, severity, and progression of atherosclerosis.
  - Can undergo proteolysis within
  - Can undergo lipid exchange within
  - Are able to enter
  - Are unable to enter
- According to the NCEP/ATP III, when TG levels are >200 mg/dL, the goal for non-HDL-C should be set at the recommended LDL-C level \_\_\_\_\_.
  - Minus 50 mg/dL
  - Minus 30 mg/dL
  - Plus 30 mg/dL
  - Plus 50 mg/dL
- Although the statin class of lipid-lowering drugs is best known for cholesterol lowering, reductions of \_\_\_\_\_ in TG levels are also obtained with statin therapy.
  - 50%-60%
  - 30%-60%
  - 5%-10%
  - 7%-30%
- Clinical studies with eicosapentaenoic acid and docosahexaenoic acid have reported dose-dependent TG lowering of \_\_\_\_\_, with reductions of \_\_\_\_\_ in subjects with severe hypertriglyceridemia.
  - 40%, up to 79%
  - 7%-30%, up to 43%
  - 7%-30%, less than 20%
  - 43%, less than 20%
- The American Heart Association *Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update* recommends at least 30 minutes of moderate-intensity exercise daily or on most days and \_\_\_\_\_ in a capsule form as an adjunct to diet for all women, regardless of cardiovascular risk level.
  - Niacin
  - Omega-3 fatty acids
  - A multivitamin
  - Olive oil

## CME Registration

NAME (FIRST)	(LAST)
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ADDRESS	
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To obtain credit, 70% or more of your answers must be correct. Complete the posttest answers and activity evaluation, and send them to:

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## Activity Evaluation

Your frank and considered evaluation will be helpful in improving our CME activities. Please circle your number choice.

**5 = Excellent 4 = Good 3 = Fair 2 = Poor 1 = Unsatisfactory**

1. Please rate this activity in meeting its stated learning objectives:	
• Discuss the relation between hypertriglyceridemia and coronary heart disease.	5 4 3 2 1
• Describe the etiology and pathophysiology of hypertriglyceridemia.	5 4 3 2 1
• Understand the available antihypertriglyceridemic options regarding mechanism of action, efficacy, and patient safety.	5 4 3 2 1
• Identify appropriate combination therapies for dyslipidemia through practical case study for discussions.	5 4 3 2 1
2. CME activities must be "free of commercial bias for or against any product." In this regard, how would you rate this activity?	5 4 3 2 1
3. How would you rate this activity in comparison to other activities?	5 4 3 2 1
4. What percentage of the material was new to you? <input type="checkbox"/> 90% <input type="checkbox"/> 70% <input type="checkbox"/> 50% <input type="checkbox"/> 30% <input type="checkbox"/> 10%	
5. Will you make changes that will benefit patient care as a result of information received today? If yes, please describe. <input type="checkbox"/> Yes <input type="checkbox"/> No	
6. I have read this article and completed this activity in _____ hour(s).	