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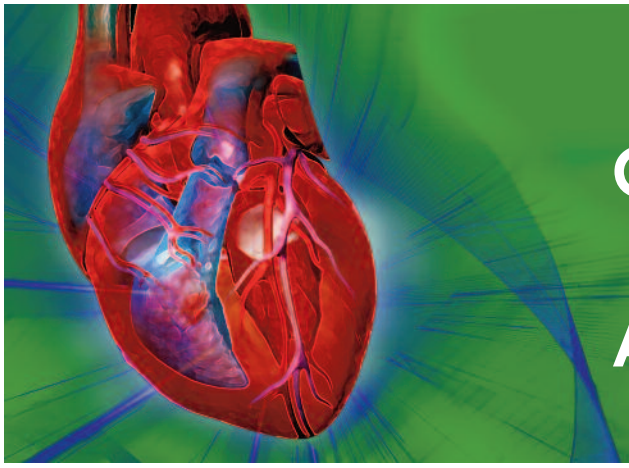

Reducing Residual CARDIOVASCULAR RISK in Patients With ATHEROGENIC DYSLIPIDEMIA

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Special Edition

HIGHLIGHTS FROM A SYMPOSIUM HELD AT THE AMERICAN HEART ASSOCIATION SCIENTIFIC SESSIONS 2008

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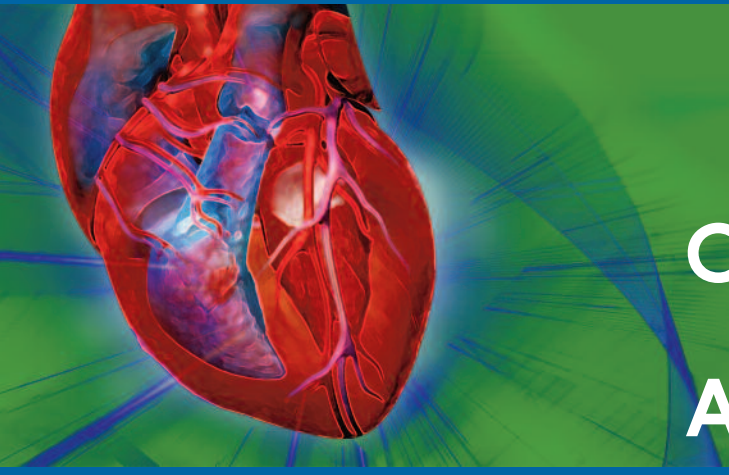

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Abbott A Promise for Life

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Reviewer

Michael H. Davidson, MD

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Intended Audience

This activity is intended for physicians and other healthcare professionals with an interest in managing patients with atherogenic dyslipidemia.

Statement of Need

This program will provide updated information about the role of elevated triglycerides and low HDL-C in residual cardiovascular risk that remains after statin therapy. This program will review the national guideline recommendations for treating beyond LDL-C and the clinical trial evidence that supports treating atherogenic lipid abnormalities beyond LDL-C in high-risk patient populations. Current therapeutic options will be discussed, and the efficacy and safety of using combination lipid-modifying therapies to manage atherogenic dyslipidemia and reduce residual cardiovascular risk will also be addressed.

Learning Objectives

Upon completion of this activity, participants will

- Evaluate the importance of elevated triglycerides and low HDL-C in CVD risk
- Explain how to calculate non–HDL-C and relate its value in predicting CVD risk
- Determine which patients will benefit from combination lipid-modifying therapies to reduce residual CVD risk

Method of Participation

It has been determined that this activity can be completed in 1 hour. The participant should review the learning objectives and faculty disclosure, read the monograph, reflect on the content, answer the posttest questions, and complete the evaluation form. A minimum score of 70% must be achieved on the posttest. A certificate of credit will be mailed to participants within 6 weeks of receipt of mailed or faxed forms. (Certificates will be immediately available if the completed posttest and forms are submitted online at www.accessCME.org.) There is no fee to participate in the program or for the generation of the certificate.

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Dean A. Bramlet, MD, has been a speakers bureau participant for Abbott, AstraZeneca, Merck, Sankyo, and Schering-Plough.

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Reducing Residual Cardiovascular Risk in Patients With Atherogenic Dyslipidemia

Introduction

A symposium entitled "Reducing Residual Cardiovascular Risk in Patients With Atherogenic Dyslipidemia," held at the American Heart Association's Scientific Sessions on Monday November 10, 2008, addressed the use of lipid-modifying therapies to reduce cardiovascular disease (CVD) risk. This newsletter presents highlights of this symposium, which was chaired by Michael H. Davidson, MD, Clinical Professor and Director of Preventive Care for the University of Chicago Pritzker School of Medicine and Executive Medical Director for Radiant Research in Chicago, Illinois. The newsletter opens with an overview of the role of elevated triglycerides and low HDL-C in residual risk, which was presented by Dean A. Bramlet, MD, Diplomate of Clinical Lipidology, Assistant Consulting Professor of Medicine, Cardiology, Duke University, Durham, North Carolina and Founder and Medical Director, The Heart and Lipid Institute of Florida, St. Petersburg, Florida. This is followed by a review of national guidelines for treating beyond LDL-C and examination of clinical trial results with lipid-modifying agents, which was presented by Sergio Fazio, MD, PhD, Professor of Medicine and Pathology and Director, Preventative Cardiology Services/Atherosclerosis Research Unit, Vanderbilt University Medical Center, Nashville, Tennessee. This newsletter closes with an overview of the efficacy and safety of combination lipid-modifying therapies, presented by Michael H. Davidson, MD.

What Is the Role of Elevated Triglycerides and Low HDL-C in Residual CVD Risk Remaining After Statin Therapy?

Presented by
Dean A. Bramlet, MD, FACC, FACP, FAHA

The Metabolic Syndrome Increases CVD Risk

In the United States, there are approximately 47 million adults with the metabolic syndrome, and the prevalence of this disorder continues to steadily increase.[1,2] The most recent definition from the American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI) update of the National Cholesterol Education Program (NCEP) criteria indicate that the metabolic syndrome is diagnosed by any 3 of the following characteristics: waist circumference ≥102 cm (≥40 in) in men (≥90 cm for Asian men) or ≥88 cm (≥35 in) in women (≥80 cm for Asian women), triglycerides ≥150 mg/dL, HDL-cholesterol (HDL-C) <40 mg/dL (men) or <50 mg/dL (women), systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, and fasting plasma glucose (FPG) ≥100 mg/dL.[3] Furthermore, patients receiving drug therapy to reduce triglycerides, raise HDL-C, lower blood pressure, or decrease glucose levels are considered to have the corresponding component of the metabolic syndrome.[3]

A recent study examined the predictive power of the presence of a hypertriglyceridemic waist phenotype (waist circumference >35.4 in in men or >33.5 in in women and a plasma triglyceride level >177 mg/dL) for coronary artery disease (CAD) in patients (N = 592) with glucose intolerance or type 2 diabetes (**Figure 1**).[4] Patients who had the hypertriglyceridemic waist phenotype had a significant 2-fold increase in risk of CAD (*P*=.02) and on average experienced the first symptoms of CAD 5 years earlier than patients without the phenotype (**Figure 1**).[4] Thus, the presence of the hypertriglyceridemic phenotype predisposes high-risk patients, especially those with glucose intolerance or type 2 diabetes, to CAD.

The effect of the metabolic syndrome on atherosclerotic risk was also examined by Espinola-Klein et al in 811 patients with coronary heart disease (CHD) and either low or high atherosclerotic burden.[5] Those patients with only CHD were classified as having low atherosclerotic burden, whereas those patients with CHD plus cardiovascular disease (CVD) and/or peripheral arterial disease (PAD) were classified as having high atherosclerotic burden. In patients with the metabolic syndrome who had low atherosclerotic burden, there was an increased CVD event rate and mortality compared with those who did not have the metabolic syndrome (21.2% versus 12.9%, *P*=.02; and 10.0% versus 5.1%, *P*=.04; respectively).[5] Furthermore, the increase in CVD event rate and mortality was even more dramatic in patients with the metabolic syndrome and high atherosclerotic burden compared with those with only high atherosclerotic burden (34.3% versus 26.5%, *P*=.01; and 26.4% versus 10.3%, *P*<.0001; respectively).[5] Thus, the presence of the metabolic syndrome worsens cardiovascular prognosis regardless of atherosclerotic burden. Those patients who have both the metabolic syndrome and high atherosclerotic burden have the highest risk of CVD events and mortality.[5]

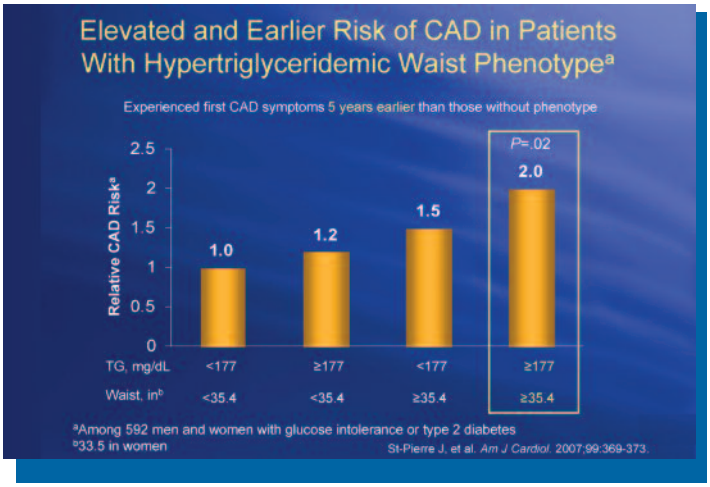

Figure 1. Elevated and Earlier Risk of CAD in Patients With Hypertriglyceridemic Waist Phenotype.

The predictive power of the presence of a hypertriglyceridemic waist phenotype (waist circumference >35.4 in. in men or >33.5 in. in women and a plasma triglyceride level >177 mg/dL) for CAD was examined in patients (N = 592) with glucose intolerance or type 2 diabetes. Patients who had the hypertriglyceridemic waist phenotype had a significant 2-fold increase in risk of CAD (*P*=.02) and on average experienced the first symptoms of CAD 5 years earlier than patients without the phenotype.[4]

Diabetes Increases CVD Risk

Diabetes is also a prevalent condition in the United States affecting 23.6 million Americans with 1.6 million new cases diagnosed in adults each year.[6] The number of people affected with diabetes continues to rise, and it is thought that the increase in cases of diabetes is linked to the increase in obesity, with the latest statistics indicating that 32.9% of adults are obese.[7] In patients with diabetes, CVD is a serious comorbidity with the diagnosis of some form of CVD reported by 38.1% of adults with diabetes.[8]

Analysis of data from the Multiple Risk Factor Intervention Trial (MRFIT) examined the relationship of diabetes and/or prior-myocardial infarction (MI) to the 25-year trend in cardiovascular and noncardiovascular mortality in men with diabetes (n = 4809) and men with a prior MI (n = 4625).[9] There were higher rates of CVD death and CHD death in men with a prior MI compared with those with diabetes, and the presence of diabetes further increased the rate of mortality in men with MI.[9] Overall, both diabetes and MI were strong predictors of CVD and CHD mortality.

It is estimated that heart disease and stroke are responsible for approximately 68% of deaths in people with diabetes.[10] In fact, adults who have diabetes have a 2- to 4-fold increase in heart disease death rates compared with adults without diabetes.[10] The NCEP

Adult Treatment Panel III (ATP III) guidelines recognize that diabetes is a major, independent risk factor for CVD and recommend that diabetes be aggressively managed as a CHD risk equivalent.[11]

Microvascular and macrovascular complications that accompany diabetes have significant impact on the quality of life for patients with diabetes. When patients (N = 1257) with type 2 diabetes were administered a questionnaire to assess diabetes complications and comorbidities and the Self-Administered Quality of Well Being (QWB-SA) index was used to calculate a health utility score the results indicated that major complications of diabetes were associated with worse health-related quality of life.[12] The QWB-SA health utility scores for nonobese, diet-controlled men and women with type 2 diabetes and no microvascular, neuropathic, or cardiovascular complications were used as baseline measurements (0.69 for men and 0.65 for women). Congestive heart failure (CHF), stroke, dialysis, foot ulcers, amputation, and blindness were associated with the most substantial reductions in QWB-SA health utility scores (-0.052, -0.072, -0.078, -0.099, -0.105, and -1.170; respectively).[12] Interestingly, microvascular complications of diabetes (dialysis, foot ulcers, amputation, and blindness) were associated with greater reductions in patient evaluation of heath-related quality of life than macrovascular complications (CHF and stroke).[12] Thus, microvascular complications are not benign events but rather have a substantial impact on patient quality of life.

Not only do the macrovascular and microvascular complications of diabetes have substantial impact on quality of life for affected patients, but healthcare for these complications is also associated with a significant economic burden. A study by O'Brien et al estimated the direct medical costs of managing microvascular and macrovascular complications of T2DM diabetes in the United States in 2000.[13] The study reported that the annual costs of managing microvascular complications were as significant as those associated with macrovascular complications. The acute costs of major CVD and cerebrovascular events resulted in a greater financial burden ($39 622 and $57 644, respectively) than early-stage microvascular complications (eg, microalbuminuria $78).[13] However, microvascular complications that are initially relatively low in cost (eg, microalbuminuria $78) can progress to more costly advanced stages (eg, end-stage renal disease $37 022).[13] The progression of microvascular complications was associated with a substantial economic burden, which exceeded that attributed to macrovascular complications.[13] Thus, the complications of diabetes are associated with both a reduction in patient quality of life and substantial financial burden.

Residual Risk Remains Even After Statin Treatment

Although statin treatment significantly reduces the risk of CHD events, a substantial number of residual events continues to occur. Major statin trials across diverse patient populations have demonstrated that regardless of the patient population studied, residual CVD risk is a serious concern with two-thirds of events continuing to occur after statin monotherapy (**Figure 2**).[14-19] Furthermore, intensive statin treatment to aggressively reduce LDL-C to <100 mg/dL is not sufficient to eliminate residual CVD risk; therefore, it seems likely that factors other than LDL-C contribute to CVD risk.[20-22] In high-risk patients with diabetes, residual risk is an even greater problem for patients with diabetes who receive statin therapy, having a greater number of events than patients without diabetes who receive placebo.[23]

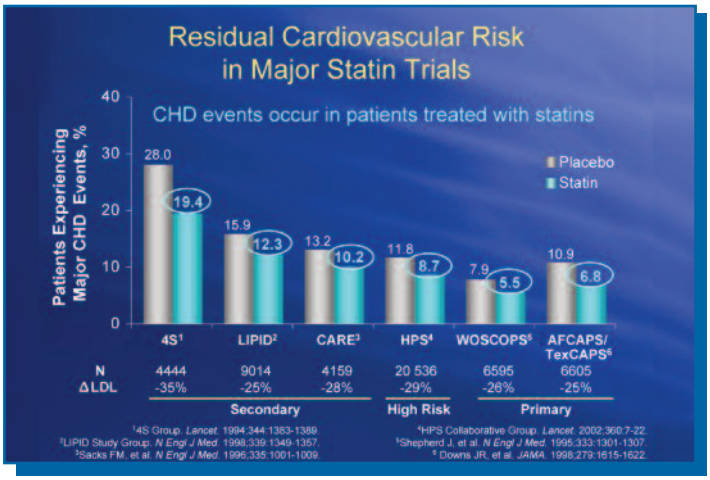

Figure 2. Residual Cardiovascular Risk in Major Statin Trials.

These major statin trials, which included diverse patient populations, demonstrated that regardless of the patient population studied, residual CVD risk is a serious concern with two-thirds of events continuing to occur after statin monotherapy.[14-19]

High Triglycerides and Low HDL-C Increase CVD Risk

Many patients with diabetes and/or the metabolic syndrome have atherogenic dyslipidemia, which refers to the presence of elevated triglycerides; low HDL-C; and an excess of small, dense LDL particles.[24,25] The observed increase in triglycerides is the result of an increase in triglyceride rich remnant lipoproteins (eg, VLDL) for which triglycerides are a surrogate marker.[24,25] This mixed dyslipidemia profile is referred to as the atherogenic triad or atherogenic dyslipidemia and contributes to an increase in CVD risk.

The Copenhagen Male Study examined 2906 men aged 53 to 74 years and free of ischemic heart disease.[26] During the 8-year follow-up 229 subjects developed ischemic heart disease and after stratification by LDL-C levels (≤170 mg/dL or >170 mg/dL), the incidence of ischemic heart disease was highest in men with high triglycerides (≥142 mg/dL) and low HDL-C levels (≤48 mg/dL). There was a clear gradient of ischemic heart disease risk, with an approximately 2 to 3 times higher risk of ischemic heart disease in the high triglyceride and low HDL-C group compared with the low triglyceride and high HDL-C group (triglycerides ≤97 mg/dL and HDL-C ≥57 mg/dL, $P<.001$).[26] Interestingly, there was a significant increase in the incidence of ischemic heart disease in patients with low LDL-C (≤170 mg/dL), high triglycerides, and low HDL-C compared with patients with high LDL-C (>170 mg/dL), low triglycerides, and high HDL-C ($P=.01$).[26] These data indicate that regardless of LDL-C level, the risk for ischemic heart disease was lowest in patients with low triglycerides and high HDL-C.

The NCEP ATP III guidelines identify low HDL-C as an independent risk factor that is inversely associated with CHD risk.[11] The independent association between HDL-C and CVD risk remains even after correction for other risk factors on multivariate analysis.[11] Epidemiological data indicates that increasing HDL-C by 1 mg/dL, a clinically attainable goal, results in a dramatic 2% risk reduction in men and 3% risk reduction in women.[11,27] In addition, reductions in HDL-C are frequently correlated with elevated levels of triglycerides and remnant lipoproteins, which further increases CVD risk.[11]

Although the mechanism through which HDL exerts its antiatherogenic actions has not been fully elucidated, HDL plays a central role

in reverse cholesterol transport from the arterial wall to the liver.[28] In addition, HDL has other proposed antiatherogenic activities including antiinflammatory activity, antioxidative activity, antiinfectious activity, antithrombotic activity, antiapoptotic activity, and vasodilatory activity.[29,30] Any or all of these actions may be involved in the association between low levels of HDL-C and increases in CVD risk.

A study by Alsheikh-Ali et al demonstrated that low HDL-C is highly prevalent, even in patients who have well-controlled LDL-C.[31] Data from high-risk patients with documented CHD (n = 635) or CHD risk equivalents (n = 877) were examined for the presence of low HDL-C (<50 mg/dL in men or <40 mg/dL in women).[31] In these patients LDL-C was on average 108 mg/dL and 65% of the population was receiving statin therapy. Low HDL-C was prevalent across all levels of LDL-C, regardless of gender but most prevalent in patients with well-controlled LDL-C ≤70 mg/dL (79% versus 66% in patients with LDL-C 71-100 mg/dL and 64% in patients with LDL-C >100 mg/dL, *P*<.01).[31] Therefore, in high-risk patients with CHD or CHD risk equivalents, low HDL-C is a frequent comorbidity despite statin treatment and the achievement of aggressive LDL-C goals.

Furthermore, the Treating to New Targets (TNT) study revealed that having low HDL-C increases CVD risk even in those patients with well-controlled LDL-C. Patients who received statin therapy for 3 months and were in the lowest stratum of LDL-C (n = 2661, mean LDL-C 58 mg/dL) had a increased 5-year risk of major CVD events associated with a low HDL-C.[32] Patients in the highest HDL-C quintile (Q5 ≥55 mg/dL) had significantly lower risk for major CVD events than patients in the lowest quintile (Q1 <37 mg/dL, *P*=.03; Q5 hazard ratio versus Q1 = 0.61).[32] Thus, the increased risk of CVD events imparted by low HDL-C is not eliminated by aggressive statin therapy.

Elevated triglycerides are also a CVD risk factor. This was recently demonstrated in a meta-analysis of 29 prospective studies, the largest and most comprehensive epidemiological assessment of the association between triglyceride values and CHD risk in Western populations (262 525 participants; 10 158 CHD cases).[33] The combined analysis of all 29 studies resulted in an adjusted odds ratio of 1.72 (95% CI, 1.56-1.90) in a comparison of extreme thirds of usual triglyceride values (ie, individuals with usual log-triglyceride values in the top third of the population compared with those in the bottom third).[33] The odds ratio was adjusted in all but one study for age, sex, smoking status, lipid concentrations, and most studies also adjusted for blood pressure. Adjustment for HDL-C attenuated the magnitude of the association between triglyceride level and CHD risk.[33] The authors of the study concluded that there is a strong and highly significant association between triglyceride value and CHD risk.

The Metabolic, Lifestyle, and Nutrition Assessment in Young Adults (MELANY) study evaluated the effect of variations in triglyceride levels over time on CHD risk. Men aged between 26 to 45 years (N = 13 953) with baseline fasting triglyceride levels <300 mg/dL were followed for 5 years and had triglyceride measurements taken at 2 time points.[34] Coronary heart disease was diagnosed by angiography-proven stenosis >50% in at least 1 coronary artery or fatal or nonfatal MI. Men with low triglyceride levels (≤93 mg/dL) at the first time point experienced a 3.81-fold or 6.76-fold greater CHD risk if their triglyceride levels increased to intermediate (94-147 mg/dL) or high levels (≥148 mg/dL), respectively, at the second time point compared with men who maintained low triglyceride levels over the 5 years.[34] Furthermore, men with low triglyceride levels at the second time point had a 3.88-fold and 4.90-fold increased CHD risk if their triglyceride levels were intermediate or high, respectively, at the first time point compared with men who maintained low triglyceride levels for the duration of the study.[34] Men with high triglyceride levels at both time points had a 8.23-fold greater CHD risk compared to men who maintained low triglyceride levels, whereas men with high triglyceride levels initially, but intermediate or low levels at the second time point, experienced a 6.84-fold or 4.90-fold increased risk as compared to men who continually had low triglycerides.[34] Thus, reducing elevated triglycerides from baseline results in a reduction in CHD risk compared with stable high triglyceride levels; however, CHD risk is still greater than that of those who maintain consistently low triglyceride levels.[34] These data demonstrate that in addition to being an independent CHD risk factor, triglyceride levels may have a cumulative effect on CHD risk.

Analysis of the PROVE IT-TIMI 22 study data demonstrated that low on-treatment levels of triglycerides in combination with low LDL-C were superior to low LDL-C alone for reducing CHD events following an acute coronary syndrome (ACS).[35] Patients (N = 4162) with total cholesterol <240 mg/dL, or <200 mg/dL if receiving lipid-lowering therapy, were randomized to intensive statin therapy (atorvastatin 80 mg) or standard therapy (pravastatin 40 mg) with a mean follow-up of 2 years. A Cox proportional hazards model revealed that each 10 mg/dL reduction in triglycerides was associated with a 1.8% reduction in CHD risk (*P*<.001). Triglyceride level remained significantly associated with death, MI, and recurrent ACS even after covariate adjustment that included LDL-C (*P*<.001) or non–HDL-C (*P*=.010).[35]

Additional analysis of the PROVE IT-TIMI 22 data focused on NCEP ATP III recommended cutpoints for LDL-C and triglycerides.[35] Significantly fewer events occurred in patients with LDL-C <70 mg/dL (13.0%) compared with patients with LDL-C ≥70 mg/dL (16.2%, HR 0.81, *P*=.015) from 30 days to the 2 year follow-up.[35] Fewer events also occurred in those patients with triglycerides <150 mg/dL (13.2%) compared with those with triglycerides ≥150 mg/dL (17.6%, HR 0.73, *P*<.001) in univariate analysis and after adjustment for age, gender, high LDL-C, low HDL-C, smoking, ACS, peripheral vascular disease, and treatment effect (HR 0.80, *P*=.025).[35] A Cox proportional model further examined the relationship between on-treatment LDL-C and triglyceride levels at 30 days and risk of recurrent events and determined that compared with LDL-C ≥70 mg/dL and triglycerides ≥150 mg/dL, significantly lower CHD risk was found with triglycerides <150 mg/dL and LDL-C <70 mg/dL (HR 0.72, *P*=.017). Graded responses were observed among patients with LDL-C ≥70 mg/dL and triglycerides <150 mg/dL (HR 0.85, *P*=.18). These data indicate that therapeutic strategies for lowering both LDL-C and triglycerides may be most effective after ACS to reduce residual CHD risk.[35]

Conclusions

The presence of diabetes or the metabolic syndrome significantly increases a patient's CVD risk. Although statin therapy is an effective strategy to reduce CHD risk, a large number of residual CVD events continue to occur, especially in patients with diabetes. Diabetes and the metabolic syndrome are frequently accompanied by the presence of atherogenic dyslipidemia characterized by elevated triglycerides, low HDL-C, and a preponderance of small, dense LDL particles. Both elevated triglycerides and low HDL-C are independent risk factors for CVD. Thus, in addition to targeting LDL-C with statin therapy, these risk factors may provide additional targets for clinical intervention.

Treating Beyond LDL-C: National Guideline Recommendations and Clinical Trial Evidence

Presented by
Sergio Fazio, MD, PhD

National guidelines have begun acknowledging that factors other than LDL-C contribute to a patient's CVD risk. The NCEP ATP III guidelines report that elevated triglycerides are an indicator of elevated levels of atherogenic lipoproteins.[11] Thus, when triglycerides are elevated the measurement of LDL-C may not accurately reflect total CVD risk. Therefore, measurement of non–HDL-C, which is the sum of LDL-C, VLDL-C, IDL-C, and lipoprotein(a) (Lp(a)) (non–HDL-C is easily calculated by subtracting the HDL-C measure from the total cholesterol measure), is a better indicator of atherogenic lipoproteins when triglycerides are elevated.[11] The NCEP ATP III guidelines recommend that when triglyceride levels are ≥200 mg/dL that non–HDL-C be a secondary target of therapy.[11] The NCEP ATP III guidelines define the threshold for normal triglycerides as 150 mg/dL, and at this value VLDL-C content is ≤30 mg/dL.[11] As a result, the goal for non–HDL-C is <30 mg/dL above the goal for LDL-C.[11]

In addition to their association with elevated atherogenic remnant lipoproteins, elevated triglycerides are correlated with increased small, dense LDL particles, which are also inaccurately measured by LDL-C.[11] Small, dense LDL particles are cholesterol poor and as a result it takes more small, dense LDL-C particles to reach a given LDL-C value.[36] The LDL-C measurement does not provide information about the size or atherogenicity of LDL particles, and therefore, it is possible for 2 patients to have identical LDL-C values but very different CVD risk.[36] Thus, measurement of non–HDL-C also more accurately reflects risk when small, dense LDL particles are present.[36]

The relationship between elevated triglycerides and increases in small, dense LDL particles was examined in participants (N = 2993) from the Framingham Offspring Study (**Figure 3**).[37] As triglyceride levels increased in these patients, an increase in total number of LDL particles was also observed.[37] In contrast, levels of LDL-C remained low.[37] Thus, reinforcing the notion that in patients with high triglyceride levels there is often a corresponding increase in LDL particle number and LDL-C levels may not accurately predict CVD risk.

Several studies have validated the use of non–HDL-C as a better predictor of CVD risk than LDL-C. A study of healthy participants from the Women's Health Study (WHS, N = 15 632, age ≥45 years) demonstrated that non–HDL-C was better than LDL-C for prediction of a first CVD event.[38,39] Similarly, data from the Framingham Heart Study (1562 men and 1760 women, age ≥30 years, free of CHD at baseline) revealed that non–HDL-C was superior to LDL-C and comparable to apolipoprotein B (Apo B) for predicting CHD risk.[40]

A recent retrospective analysis also compared the predictive power of LDL-C, non–HDL-C, and Apo B for CVD events in patients

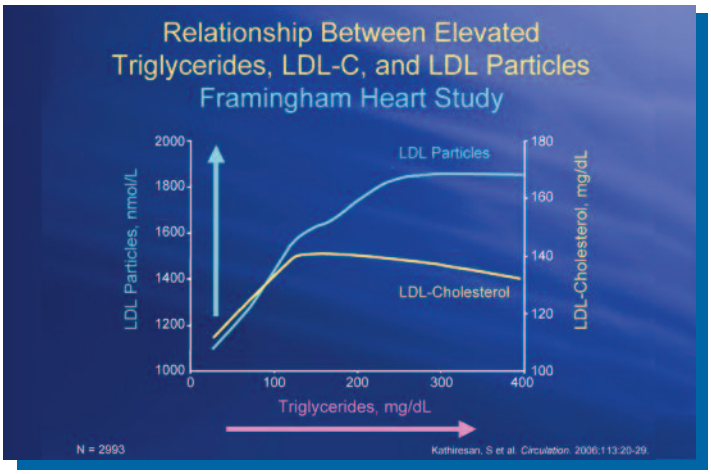

Figure 3. Relationship Between Elevated Triglycerides, LDL-C, and LDL Particles.
In the Framingham Heart Study, as triglyceride levels increased, an increase in total number of LDL particles was also observed. However, levels of LDL-C remained low despite the increase in LDL particle number.[37] Reprinted with permission from Lippincott, Williams, and Wilkins.

receiving statin therapy through analysis of the TNT and the IDEAL data sets.[41] A Cox proportional hazards model was used to compare the strength of association of each variable with major CVD event (CHD death, nonfatal MI, resuscitation after cardiac arrest, and fatal or nonfatal stroke) risk. When LDL-C and non–HDL-C were compared directly, the positive relationship between LDL-C and CVD events disappeared, whereas non–HDL-C continued to be positively associated with CVD events (HR 1.31, *P*<.001). Similarly, when LDL-C and Apo B were compared directly in the same regression model, LDL-C lost its positive association with CVD event risk; however, Apo B remained a significant predictor of CVD event risk (HR 1.24, *P*<.001).[41] When non–HDL-C and Apo B were compared directly, both lost significance due to a colinear relationship (HR 1.14, *P*=.06 and HR 1.05, *P*=.47; respectively). Thus, in the IDEAL and TNT study populations, on-treatment levels of non–HDL-C and Apo B were more strongly related to CVD outcome than LDL-C, validating the CVD predictive power of measuring non–HDL-C or Apo B.[41]

National Guideline Recommendations for Lipoprotein Management

In 2004 an update to the NCEP ATP III guidelines was released that reaffirms that the primary goal of lipid-modifying therapy is LDL-C and the secondary target of therapy is non–HDL-C (when triglycerides are ≥200 mg/dL), with a non–HDL-C goal 30 mg/dL higher than the LDL-C goal.[11,42] However, the 2004 update to the NCEP

ATP III guidelines proposed new optional treatment goals for LDL-C stratified by CVD risk.[42] For high-risk patients, the recommended LDL-C treatment goal is <100 mg/dL. However, for patients considered to be at very high risk, which include those with CVD and multiple major risk factors (especially diabetes), severe or poorly controlled risk factors, multiple risk factors for the metabolic syndrome (especially high triglycerides plus elevated non–HDL-C with low HDL-C), or ACS an LDL-C target of <70 mg/dL is a therapeutic option for further reducing CVD risk.[42] Furthermore, for moderately high-risk patients (2 risk factors and 10-year risk of 10% to 20%), the recommended LDL-C goal is <130 mg/dL, but an LDL-C goal of <100 mg/dL can be considered as a therapeutic option.[42]

The NCEP ATP III guidelines also specify risk classifications for triglycerides and HDL-C. According to the NCEP ATP III guidelines, normal triglycerides are <150 mg/dL, borderline-high triglycerides are 150 to 199 mg/dL, high triglycerides are 200 to 499 mg/dL, and very high triglycerides are ≥500 mg/dL. Additionally, the NCEP ATP III guidelines define low HDL-C as <40 mg/dL (<50 mg/dL for women) and high HDL-C as ≥60 mg/dL.[11,42] The update recommends, "For those high-risk patients who have elevated triglycerides or low HDL-C, addition of a fibrate or nicotinic acid to LDL-lowering therapy can be considered."[42]

In 2007, the ADA and the American Heart Association (AHA) published a joint scientific statement for primary prevention of CVD in patients with diabetes that harmonized the recommendations of both organizations and highlighted key differences. Both organizations recommend LDL-C as the primary target of lipid-lowering therapy (LDL-C goal <100 mg/dL).[43] However, the joint statement acknowledges that triglyceride-rich atherogenic lipoproteins, especially VLDL, are often elevated in patients with diabetes and are therefore a secondary target of lipid-lowering therapy (after attaining the LDL-C goal). The ADA recognizes serum triglycerides are a marker for atherogenic triglyceride-rich lipoproteins and recommends lowering triglycerides to <150 mg/dL, if possible.[43] The AHA designates non–HDL-C as the secondary target of therapy in patients with elevated triglycerides (200-499 mg/dL) with a non–HDL-C goal of ≤130 mg/dL (30 mg/dL above the goal for LDL-C, similar to the NCEP ATP III guidelines). The AHA further recommends that if triglycerides are ≥500 mg/dL, lowering triglycerides is the first priority (with pharmacotherapy such as niacin or fibrate treatment), followed by reduction of non–HDL-C to a goal of ≤130 mg/dL.[43] The ADA recommends raising HDL-C to a goal of >40 mg/dL in men and >50 mg/dL in women, whereas the AHA advocates efforts to increase HDL-C but does not set specific therapeutic goals.[43] Finally, the joint statement acknowledges that combination therapy of LDL-C–lowering drugs (statins) with niacin or fibrates may be necessary to achieve all lipid targets.[43]

The American Diabetes Association (ADA) and American College of Cardiology (ACC) released a consensus statement that sets specific goals for patients with cardiometabolic risk (CMR) and lipoprotein abnormalities based on their risk for CVD.[44] The consensus panel concluded that routine measurement of non–HDL-C is a better indicator of CVD risk than LDL-C. The panel also addressed the utility of measuring Apo B and noted that the assay for Apo B is not yet widely available. However, measurement of Apo B is recommended for guiding adjustments to lipid-modifying therapy.[44]

All patients with CMR have a high lifetime risk for CVD, but there are patients that the ADA/ACC consensus statement defines as highest-risk patients over the short or intermediate term.[44] Highest-risk patients are those with established CVD and those who do not have clinical CVD but who have diabetes and 1 or more major CVD risk factor beyond their dyslipidemia (eg, smoking, hypertension, or family history of premature CHD; **Figure 4**). Highest-risk patients should be treated to an LDL-C goal <70 mg/dL, a non–HDL-C goal <100 mg/dL, and an Apo B goal <80 mg/dL (**Figure 4**).[44] Among patients with CMR and lipoprotein abnormalities, high-risk patients are those without diabetes or clinical CVD but with 2 or more major CVD risk factors (eg, smoking, hypertension, and family history of premature CHD) and those with diabetes but no other CVD risk factors (**Figure 4**). Recommended goals for high-risk patients are LDL-C <100 mg/dL, non–HDL-C <130 mg/dL, and Apo B <90 mg/dL (**Figure 4**).[44] Statins are recommended as the first line of therapy for all patients with CMR; however, combination therapy is recommended for patients on statin therapy who continue to have low HDL-C or elevated non–HDL-C, especially in the presence of elevated Apo B levels (**Figure 4**).[44] Niacin is recommended as the preferred agent for use in combination with statins because there is currently better evidence for a reduction in CVD events with niacin, as monotherapy or in combination, than there is for fibrates.[44]

Patients Are Not Achieving Lipid Goals

Despite the publication of treatment guidelines, many high-risk patients fail to reach treatment goals. The NCEP Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II was a national survey of 4885 patients that examined achievement of lipid targets.[45] Of the 728 hypertriglyceridemic patients (triglycerides ≥200 mg/dL) who had CHD, diabetes, or other CHD risk equivalents the majority of patients failed to achieve the combined LDL-C and non–HDL-C goal (67%, 75%, and 83%; respectively).[45]

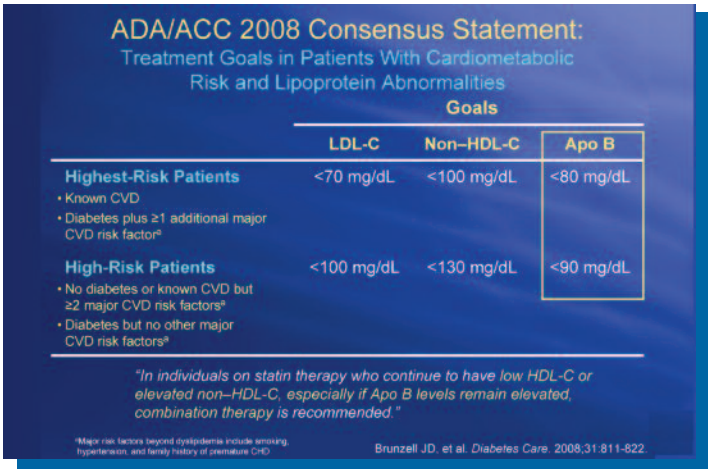

Figure 4. The ADA/ACC 2008 Consensus Statement.

The ADA/ACC consensus statement defines highest-risk patients as those with established CVD and those who do not have clinical CVD but who have diabetes and 1 or more major CVD risk factor beyond their dyslipidemia. Highest-risk patients should be treated to an LDL-C goal <70 mg/dL, a non–HDL-C goal <100 mg/dL, and an Apo B goal <80 mg/dL. High-risk patients are those without diabetes or clinical CVD but with 2 or more major CVD risk factors and those with diabetes but no other CVD risk factors. Recommended goals for high-risk patients are LDL-C <100 mg/dL, non–HDL-C <130 mg/dL, and Apo B <90 mg/dL. Statins are recommended as the first line of therapy for all patients with CMR; however, combination therapy is recommended for patients on statin therapy who continue to have low HDL-C or elevated non–HDL-C, especially in the presence of elevated Apo B levels.[44]

A similar study by Alsheikh-Ali et al examined whether patients with CHD risk equivalents (n = 877; 96% had diabetes) and patients with documented CHD (n = 635) were meeting lipid goals of LDL-C <100 mg/dL, HDL-C ≥40 mg/dL in men and ≥50 mg/dL in women, and non–HDL-C <130 mg/dL (if triglyceride levels were ≥200 mg/dL). The majority of patients with CHD risk equivalents did not achieve the targets for LDL-C (67%), HDL-C (66%), and non–HDL-C (71%) and also had at least 1 suboptimal lipid level (88%) regardless of age and gender.[46] Compared with patients with established CHD, patients without documented CHD were significantly less likely to have met LDL-C goals (*P*<.001) and equally as likely to have at least 1 suboptimal lipid parameter. Of those patients with CHD risk equivalents, 57% were taking statins, which increased the likelihood of meeting LDL-C goals. Of patients with low HDL-C (n = 577), only 4.7% were taking niacin and 4.9% were taking fibrates. Further, the use of combination therapy was rare, with only 4.9% of patients prescribed a statin in combination with another lipid-modifying drug.[46] Thus, taken together, these studies indicate that a large number of patients with significant CHD risk fail to meet lipid goals for CHD prevention advocated by national guidelines.

Lipid-Modifying Therapies Beyond Lowering LDL-C

Omega-3 Fatty Acids

In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenezione (GISSI-P) trial patients who had a recent MI (≤3 months) were assigned to receive supplements of omega-3 fatty acids (1 g, n = 2836), vitamin E (n = 2830), the combination of omega-3 fatty acids and vitamin E (n = 2830) or placebo (n = 2828).[47] Patients who received omega-3 fatty acid supplementation had a significant 15% reduction in the risk of death, nonfatal MI, and stroke compared with patients who received placebo after 3.5 years (*P*=.023).[47] When CVD death, nonfatal MI, and nonfatal stroke were analyzed there was a significant 20% reduction observed in the omega-3 fatty acid group (*P*=.008).[47]

The Japan Eicosapentaenoic Acid (EPA) Lipid Intervention Study (JELIS) evaluated patients with total cholesterol levels that exceeded 250 mg/dL who were randomly assigned either statin monotherapy (n = 9319) or 1.8 g daily of EPA (an omega-3 fatty acid) in combination with a statin (n = 9326).[48] After a mean follow-up of 4.6 years, significantly more patients (3.5%) in the statin monotherapy group experienced a major CHD event compared with patients in the EPA and statin combination group (2.8%), a 19% relative risk reduction in major CHD events with the omega-3 fatty acid combination therapy (*P*=.011). The reductions in LDL-C were similar (approximately 25%) in both groups, indicating reductions in serum LDL-C levels were not responsible for the observed risk reduction in major CHD events. However, addition of EPA to statin therapy significantly reduced triglycerides by 9%, compared with statin monotherapy (4%, *P*<.001). Similar, modest changes in HDL-C were observed in both treatment groups. The study included exclusively Japanese hypercholesterolemic patients and therefore it is uncertain whether the results can be generalized to broader populations.[48] However, taken together these studies suggest a potential role for omega-3 fatty acid therapy in reducing CVD events.

Niacin

The Coronary Drug Project (CDP), conducted over 30 years ago, demonstrated a reduction in clinical events with niacin. The CDP was a placebo-controlled study that examined the effects of 5 lipid-modifying agents (low-dose and high-dose estrogen, clofibrate, dextrothyroxine, and niacin) in 6341 men with a history of MI.[49] The estrogen groups and the dextrothyroxine groups were prematurely discontinued due to an excess of adverse effects; however, the niacin and clofibrate groups completed the study with a mean follow-up of 6.2 years. Total mortality was similar in the niacin group (24.4%) and the placebo group (25.4%). However, there was a significant reduction in the combined outcome of CHD death and nonfatal MI (15%, *P*<.05), nonfatal MI (26%, *P*<.05), and cerebrovascular events (stroke or transient ischemic attack; 24%, *P*<.05) with niacin therapy. In addition, the incidence of cardiovascular surgery from trial entry to 5-year follow-up was reduced 47% with niacin therapy compared with placebo (*P*<.05).[49]

A post hoc analysis of CDP data compared rates of nonfatal MI in patient subgroups defined by baseline FPG.[50] Compared with placebo, niacin reduced the 6-year risk of recurrent MI similarly in patients at all levels of baseline FPG, including those with FPG levels ≥126 mg/dL (the current ADA definition of diabetes).[50] Furthermore, niacin also reduced the 6-year risk of the combined end point of CHD death or nonfatal MI similarly in patients at all levels of baseline FPG compared with placebo. Notably, the beneficial effect of niacin for reducing recurrent nonfatal MI and CHD events was not significantly diminished with increased baseline FPG, even in those patients with the highest baseline FPG levels.[50] The use of niacin has previously been cautioned in patients with abnormal glucose metabolism or overt diabetes, but this caution is not supported by post hoc analysis of the CDP data. The results from the CDP demonstrate that any increase in FPG levels with niacin use did not translate into a disadvantage with respect to CHD events.[50]

The HDL-Atherosclerosis Treatment Study (HATS) was a double-blind study that examined the effects of simvastatin and niacin combination therapy compared with double placebo in patients with CHD, low HDL-C (≤35 mg/dL in men or ≤40 mg/dL in women), and LDL-C levels ≤145 mg/dL over 3 years.[51] The end points of the study were defined as angiographic evidence of a change in coronary stenosis, measured by quantitative coronary angiography, and the occurrence of a CVD event (death, MI, stroke, or revascularization). Patients who received placebo experienced overall progression of the most severe coronary stenosis (+3.9%), whereas patients who received niacin and simvastatin combination therapy experienced slight regression (-0.4%, *P*<.001; **Figure 5**). In addition, there was a dramatic reduction (90%) in the composite end point of CVD events with simvastatin and niacin combination therapy compared with placebo treatment (*P*=.03, **Figure 5**).[51]

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 3) was an extension study of ARBITER 2, a placebo-controlled study that examined the addition of niacin ER to pre-existing statin therapy in patients with known CHD and low HDL-C (defined as <45 mg/dL).[52,53] In ARBITER 3, patients taking placebo (statin monotherapy) were allowed to cross over to niacin ER. In patients who were treated with statin and niacin ER combination therapy for 12 to 24 months, there was a

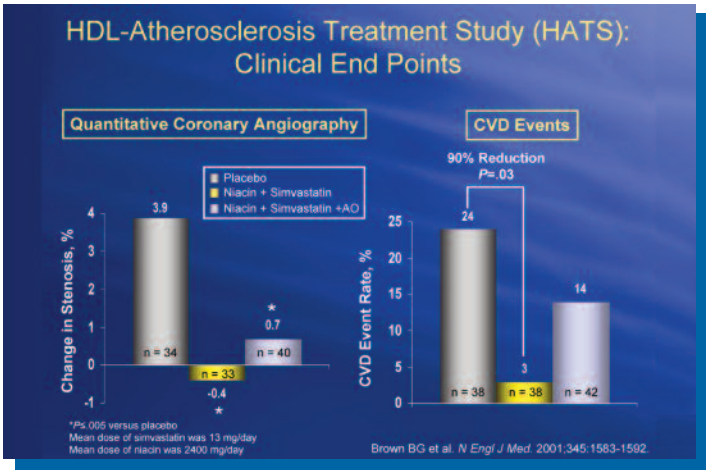

Figure 5. HDL-Atherosclerosis Treatment Study (HATS): Clinical End Points.

In HATS, patients who received placebo experienced overall progression of the most severe coronary stenosis (+3.9%), whereas patients who received niacin and simvastatin combination therapy experienced slight regression (-0.4%, *P*<.001). There was also a dramatic reduction (90%) in the composite end point of CVD events with simvastatin and niacin combination therapy compared with placebo treatment (*P*=.03).[51]

significant regression of atherosclerosis as measured by carotid intima-media thickness (CIMT; -0.027 and -0.041, respectively; *P*<.001 versus statin monotherapy).[52] High-risk patients with diabetes or the metabolic syndrome also experienced significant regression of CIMT with statin and niacin ER combination therapy for 12 to 24 months compared with statin monotherapy (-0.046, *P*<.001).[52] Further analysis of data from the ARBITER 3 study revealed a statistically significant inverse correlation between increases in HDL-C and CIMT regression (*P*=.002), suggesting that increasing HDL-C with niacin ER therapy may contribute to the beneficial regression of atherosclerosis.[52]

Fibrate Therapy

Subgroup analysis of data from the Department of Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) was designed to determine the efficacy of gemfibrozil in patients with diagnosed diabetes (n = 627), undiagnosed diabetes (n = 142), impaired FPG (n = 323), or normal patients (n = 1425).[54] Participants with diabetes had a significantly higher cumulative incidence of major CVD events (36.5% and 34.3% for patients with diagnosed and undiagnosed diabetes, respectively) compared with subjects without diabetes (23.8% and 21% for subjects with impaired FPG and normal FPG, respectively; *P*<.001 for diabetic versus nondiabetic groups).[54] Patients with and without diabetes had similar reductions in the 5-year incidence of nonfatal MI (22% and 21%, respectively). However, in patients with diabetes there were significant reductions in the 5-year incidence of CHD death and stroke (41%, *P*=.02 and 40%, *P*=.046; respectively) compared with nonsignificant reductions in patients without diabetes (3%, *P*=.88 and 10%, *P*=.67; respectively).[54] Thus, patients with diabetes did as well (nonfatal MI) or much better than (CHD death or stroke) patients without diabetes with gemfibrozil therapy.[54]

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study investigated the long-term effects of fenofibrate in a large patient population with type 2 diabetes (N = 9795; 5-year follow-up).[55] Fenofibrate treatment resulted in a nonsignificant 11% reduction in the primary end point of CHD events (ie, nonfatal MI or CHD death; *P*=.16); however, further analysis revealed a significant 24% reduction in nonfatal MI (*P*=.01) in fenofibrate-treated patients. The FIELD trial also examined total CVD events (CHD events, stroke, death due to CVD, and revascularization) and reported that fenofibrate treatment resulted in a significant 11% reduction in the secondary end point of total CVD events compared with placebo (*P*=.035) and a significant 21% reduction in coronary revascularizations (*P*=.003).[55] Furthermore, fenofibrate treatment had a particularly beneficial effect in the subgroup of patients with no prior CVD. In this primary prevention population (78% of the total population, n = 7664), fenofibrate reduced the incidence of total CVD events by 19% (*P*=.004) and CHD events by 25% (*P*=.014).[55]

The FIELD trial also examined the effects of fenofibrate on microvascular complications of diabetes, such as the progression of nephropathy (indicated by microalbuminuria), amputations, and retinopathy as predetermined tertiary outcomes of the study.[55] Treatment with fenofibrate reduced the number of nontraumatic amputations by 38% (*P*=.01).[56] In the overall analysis of albuminuria progression and regression, there were 14% fewer patients progressing and 15% more patients regressing in the fenofibrate group compared with the placebo group (*P*=.002 for the combined effect). Furthermore, fenofibrate-treated patients experienced a 31% reduction in the need for laser therapy for retinopathy compared with placebo-treated patients (*P*=.0002) with the retinal benefits evident within 8 months of initiating treatment with fenofibrate.[57]

Conclusions

Despite our best efforts with statin therapy, factors beyond LDL-C, including elevated triglycerides and low HDL-C, contribute to CVD risk. When triglycerides are elevated (≥200 mg/dL), LDL-C may not accurately assess CVD risk and non–HDL-C and Apo B have been validated as better predictors of CVD risk. National guidelines agree that LDL-C should be the primary target of lipid-lowering therapy but recognize that combination therapy may be necessary to achieve all lipid targets. Combination therapy with omega-3 fatty acids, niacin, and fibrates are effective strategies for reducing CVD risk and can be considered as additional treatment options.

Combination Lipid-Modifying Therapies: Efficacy and Safety

Presented by
Michael H. Davidson, MD

Recent studies have demonstrated the safety and efficacy of using combination lipid-modifying regimens. The COMBination of prescription Omega-3 with Simvastatin (COMBOS) study examined the lipid efficacy of the addition of omega-3 fatty acids to background statin therapy in hypertriglyceridemic patients (triglycerides ≥200 mg/dL and <500 mg/dL).[58] All patients (N = 254) received 8 weeks of simvastatin therapy followed by randomization to simvastatin plus omega-3 fatty acids or simvastatin plus placebo for an additional 8 weeks. After omega-3 fatty acid treatment, there was a significant reduction in non–HDL-C (-9.0%), triglycerides (-29.5%), and VLDL-C (-27.5%) and a significant increase in HDL-C (+3.4%) compared with placebo (-2.2%, -6.3%, -7.2%, and -1.2%, respectively; *P*<.001 for all comparisons).[58] Thus, the COMBOS study demonstrated that adding omega-3 fatty acid therapy to background statin therapy was an effective strategy for improving atherogenic lipid abnormalities.

The 2007 National Lipid Association (NLA) Safety Task Force concluded that omega-3 fatty acid therapy is a safe option for lowering triglycerides.[59] Although there are documented antithrombotic effects of omega-3 fatty acids, the NLA Safety Task Force found no evidence of an increased bleeding risk with omega-3 fatty acid therapy, even in patients taking anticoagulants such as aspirin or warfarin.[59] The risks of patient intolerance and toxicity, exposure to environmental toxins, and hypervitaminosis due to omega-3 fatty acid oxidation are minimized by the rigorous purification processes used in the production of fish oil supplements and prescription preparations.[59] Dietary supplements are not subject to FDA approval; therefore, the NLA Safety Task Force recommends patient education regarding variations in the purification processes among fish oil manufacturers.[59] Patients should be advised that efficacy of therapy is directly related to the amount of omega-3 fatty acids, and higher doses of a fish oil supplement may be necessary to achieve an omega-3 fatty acid intake equivalent to that in prescription fish oil preparations.[59]

The lipid efficacy of niacin ER and statin combination therapy has been evaluated in several recent clinical trials. The Safety and Efficacy of a Combination of Niacin ER and Simvastatin in Patients with Dyslipidemia (SEACOAST) study evaluated niacin ER/simvastatin combination therapy versus simvastatin monotherapy in patients with elevated non–HDL-C.[60,61] Patients assigned to SEACOAST I were randomized to receive simvastatin 20 mg, niacin ER/simvastatin 1000/20 mg, or niacin ER/simvastatin 2000/20 mg.[61] Alternatively, patients who were assigned to SEACOAST II were randomized to either simvastatin 80 mg, niacin ER/simvastatin 1000/40 mg, or niacin ER/simvastatin 2000/40 mg.[60]

In SEACOAST I, treatment with niacin ER/simvastatin 1000/20 mg or 2000/20 mg resulted in significantly greater reductions in non–HDL-C (-14% and -23%, *P*<.01 and *P*<.001; respectively) and triglycerides (-27% and -38%, respectively; *P*<.001 for both comparisons) compared with patients receiving simvastatin 20 mg (-7% and -15%).[61] In addition, significantly greater increases in HDL-C were observed with niacin ER/simvastatin 1000/20 mg (+18%) and 2000/20 mg (+25%) therapy compared with simvastatin 20 mg (+7%; *P*<.001 for both comparisons). All treatment groups experienced similar reductions in LDL-C.

In SEACOAST II, reductions in LDL-C and non–HDL-C were similar among groups. However, niacin ER/simvastatin 1000/40 mg and 2000/40 mg significantly increased HDL-C (+15% and +22%, respectively) compared with a slight reduction in HDL-C (-1%, *P*<.001 for both comparisons) observed with simvastatin 80 mg.[60] Triglycerides increased slightly with simvastatin 80 mg (+0.3%), whereas triglycerides were significantly reduced with niacin ER/simvastatin 1000/40 mg (-23%, *P*<.001) and 2000/40 mg (-32%, *P*<.001).[60]

The Open-Label Evaluation of the Safety and Efficacy of a Combination of Niacin ER and Simvastatin in Patients With Dyslipidemia (OCEANS) study also examined the efficacy of niacin ER/simvastatin 2000/40 mg in patients with elevated non–HDL-C.[62] The proportion of patients achieving lipid targets (HDL-C ≥40mg/dL, triglycerides <150mg/dL, or CHD risk-adjusted goals for non-HDL-C and LDL-C) after 24 weeks of treatment were analyzed. Of those patients who failed to achieve lipid goals after a simvastatin 40 mg run-in (baseline), 82% achieved their non–HDL-C goal, 67% achieved their HDL-C goal, 64% achieved their triglyceride goal, and 65% achieved the combined goals for LDL-C, HDL-C, and triglycerides with niacin ER/simvastatin 2000/40 mg therapy.[62] Thus, the combination of niacin ER and simvastatin was efficacious and resulted in more patients reaching lipid targets than simvastatin monotherapy.

Flushing is a common side effect of niacin therapy. A new formulation of niacin ER is associated with an improved overall flushing profile and has demonstrated a significant 42% reduction in median severity of flushing and a significant 43% reduction in median duration of flushing, compared with the previously available formulation of niacin ER (*P*<.0001 for both comparisons).[63,64] In fact, the new formulation of niacin ER reduced the duration of the first flushing event by more than 1 hour.[64] Thus, the new formulation of niacin ER represents an improved niacin therapy option.

Furthermore, a recent study by Cefali et al demonstrated the utility of coadministering aspirin with the new formulation of niacin ER

for a further reduction in flushing severity.[63] Patients receiving the new formulation of niacin ER (2000 mg) were randomized to treatment with 650 mg aspirin 30 minutes prior to niacin therapy, 650 mg of aspirin concomitant with niacin therapy, or placebo. Patients receiving aspirin with niacin ER (both regimens) experienced a significant reduction in the incidence of flushing.[63] In addition, treatment with aspirin (both regimens) resulted in a further 42% reduction in median severity of flushing compared with the new formulation of niacin ER alone (*P*<.001).[63] These data demonstrate that adding aspirin is an effective strategy to further minimize the incidence and intensity of cutaneous flushing with the new formulation of niacin ER therapy.

Flushing may actually indicate a positive response to niacin therapy. The relationship between niacin ER-induced flushing and HDL-C response was analyzed in 77 patients who were randomized to niacin ER and completed the 12-month end point assessment of the ARBITER 2 study (**Figure 6**).[65] Flushing was reported by 68.8% subjects (n = 53) over 12 months. Those patients who reported flushing had a significantly greater increase in HDL-C, with progressive increases observed during the trial period versus patients who did not report flushing (**Figure 6**).[65] Mean increases in HDL-C at 3, 6, and 12 months among subjects with flushing were 4.2 mg/dL (11.1%), 5.8 mg/dL (15.5%), and 7.3 mg/dL (18.8%; *P*<.001 for trend) versus 3.5 mg/dL (9.3%), 4.0 mg/dL (10.5%), and 4.0 mg/dL (9.9%; *P*=.89 for trend) in those without flushing (**Figure 6**).[65] In addition, the change in HDL-C on repeated measures (*P*=.028) and at the 12-month study end point (*P*<.05) was statistically significantly greater in the flushing group.[65] Furthermore, multivariable analysis controlling for age, gender, diabetes, baseline HDL-C, baseline triglycerides, aspirin use, and medication adherence found that the HDL-C increase was significantly associated with self-reported flushing (*P*=.019).[65] Although there was no significant difference in the rate of CIMT progression between those with (0.011 mm) and without flushing (0.033 mm; *P*=.38), there was a directional trend for less progression of CIMT among subjects with flushing.[65] These data indicate that flushing may be a clinical marker of lipid response to niacin ER therapy, and provide clinicians with additional rationale for encouraging patients to continue niacin therapy despite the often transient side effect of flushing with treatment.

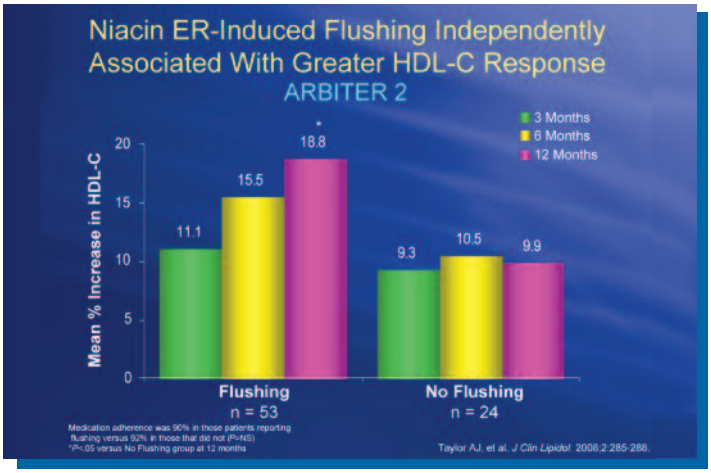

Figure 6. Niacin ER-Induced Flushing Independently Associated With Greater HDL-C Responses.

Patients in the ARBITER 2 who reported flushing had a significantly greater increase in HDL-C, with progressive increases observed during the trial period, versus patients who did not report flushing. Mean increases in HDL-C at 3, 6, and 12 months among subjects with flushing were 4.2 mg/dL (11.1%), 5.8 mg/dL (15.5%), and 7.3 mg/dL (18.8%; *P*<.001 for trend) versus 3.5 mg/dL (9.3%), 4.0 mg/dL (10.5%), and 4.0 mg/dL (9.9%; *P*=.89 for trend) in those without flushing.[65] Reprinted from the *Journal of Clinical Lipidology*, Volume 2, Taylor AJ, et al., Flushing and the HDL-C response to extended-release niacin, pp. 285-288, 2008, with permission from Elsevier.

In 2007, the NLA Safety Task Force concluded that the accumulated data from 2 decades of clinical evidence since the introduction of statins do not support a general myopathic effect of niacin either alone or in combination with statins.[66] The statement affirms that no major clinical trial has suggested a potential drug interaction between statins and niacin, and there is no proposed theoretic mechanistic reason to expect one.[66] Furthermore, niacin is also safe for use in combination with statin therapy in high-risk patients with diabetes.[66]

Fenofibrate Combination Therapy

Treatment with fenofibrate has been demonstrated to increase the number of patients with diabetes achieving ADA goals. Combination therapy with atorvastatin and fenofibrate was evaluated in 120 patients with type 2 diabetes and combined hyperlipidemia (total cholesterol >220 mg/dL, LDL-C >130 mg/dL, triglycerides between 200 mg/dL to 399 mg/dL, and Apo B >150 mg/dL) but free of CHD at baseline.[67] Patients were randomized to treatment with atorvastatin, fenofibrate, or atorvastatin and fenofibrate combination therapy. Combination therapy with atorvastatin and fenofibrate was significantly more effective at reducing total cholesterol, LDL-C, and triglycerides, and increasing HDL-C after 24 weeks, compared with either monotherapy (*P*<.0001). In addition, more patients in the combination therapy group than either of the monotherapy groups met the ADA recommended goals of LDL-C <100 mg/dL, triglycerides <150 mg/dL, and HDL-C >40 mg/dL (*P*<.05 versus both monotherapies).[67]

The safety and efficacy of a new formulation of fenofibrate (fenofibric acid) has been examined in several recent clinical trials. A 12-week randomized trial compared the efficacy of fenofibric acid, rosuvastatin 10 mg, rosuvastatin 20 mg, and combinations of fenofibric acid and rosuvastatin (10 mg or 20 mg) in patients with type 2 diabetes and mixed dyslipidemia (n = 276; LDL-C ≥130 mg/dL, triglycerides ≥150 mg/dL, and HDL-C <40 mg/dL in men and <50 mg/dL in women).[68] Compared with fenofibric acid monotherapy, treatment with fenofibric acid/rosuvastatin combination therapies resulted in a significantly greater reduction in LDL-C (*P*<.001).[68] Furthermore, the fenofibric acid/rosuvastatin combination therapies resulted in significantly greater increases in HDL-C (*P*<.001) and reductions in triglycerides compared with the corresponding rosuvastatin monotherapy (*P*=.002).[68] Importantly, after 12 weeks, fenofibric acid and rosuvastatin combination therapy resulted in mean values of LDL-C, triglycerides, and HDL-C within or close to the lipid targets suggested by the ADA treatment guidelines.[68]

In another study, patients with mixed dyslipidemia (LDL-C ≥130 mg/dL, TG ≥150 mg/dL, and HDL-C <40 mg/dL in men and <50 mg/dL in women, N = 1445) receiving fenofibric acid/rosuvastatin combination therapy (135/10 mg) for 12 weeks experienced significant reductions in triglycerides and significant increases in HDL-C (-47.1% and +20.3%, respectively) compared with patients receiving rosuvastatin monotherapy (-24.4% and +8.5%, respec-

tively; *P*<.001 for both comparisons).[69] Furthermore, a significant reduction in LDL-C was observed in patients receiving combination therapy compared with patients receiving fenofibrate monotherapy (-37.2% versus -6.5%, *P*<.001).[69] In addition, the combination of fenofibric acid and rosuvastatin therapy resulted in a favorable shift in the percentage of patients with large, buoyant LDL particles from 13.3% at baseline to 51.8% following 12 weeks of combination therapy (**Figure 7**).[70] In contrast, patients on rosuvastatin monotherapy experienced a more modest shift, with only 18.2% of patients with large, buoyant LDL particles post-treatment compared with 6.8% observed at baseline (**Figure 7**).[70] The combination of fenofibric acid and rosuvastatin was well-tolerated; no rhabdomyolysis or unexpected hepatic, renal, or muscle safety signals were identified.[71] Fenofibric acid has also been investigated in combination with simvastatin and atorvastatin. Interestingly, in patients with prediabetes, fenofibric acid used in combination with simvastatin, atorvastatin, or rosuvastatin significantly lowered mean blood glucose levels by 3.1 mg/dL from baseline compared with statin monotherapy (*P*<.001).[72]

The risk of adverse events has been a concern when using statin and fibrate combination therapy. It has been determined that the adverse effects of statin and fibrate combination therapy are dependent on pharmacokinetic interactions that alter statin metabolism and clearance.[73-82] The UGT 1A9 and UGT 2B7 glucuronidation pathways are utilized in fenofibrate metabolism, whereas the UGT 1A1 and UGT 1A3 pathways are used by both gemfibrozil and the statins thus explaining the competitive inhibition of statin metabolism observed in the presence of gemfibrozil but not fenofibrate.[83] In 2007 the NLA Safety Task Force declared that the use of gemfibrozil and statin combination therapy should be avoided. However, because fenofibrate does not interfere with statin metabolism the NLA Safety Task Force concluded that fenofibrate is the preferred fibrate for use in combination with statins.[84]

Ongoing Clinical Trials With Combination Therapy

Several clinical trials underway will further clarify the efficacy and safety of combination lipid-modifying therapy. The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) study enrolled an estimated 3300 men and women with vascular disease (CHD, CVD, and PAD) and atherogenic dyslipidemia (triglycerides >150 mg/dL and HDL-C <40 mg/dL). Patients will receive niacin ER and simvastatin combination therapy or simvastatin monotherapy with a treatment goal of LDL-C <80 mg/dL (average). The study began in September 2005, and a 4-year median follow-up is planned with the first major CVD event as the primary outcome.

The Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) enrolled approximately 20 000 patients with pre-existing atherosclerotic vascular disease (CVD, CHD, PAD). Patients will be treated with ER niacin/laropiprant and simvastatin combination therapy or simvastatin monotherapy. All groups will have a treatment goal of LDL-C <77 mg/dL (average). The study was initiated in January 2007, and the primary outcome is the first major vascular event with a 4-year follow-up planned.

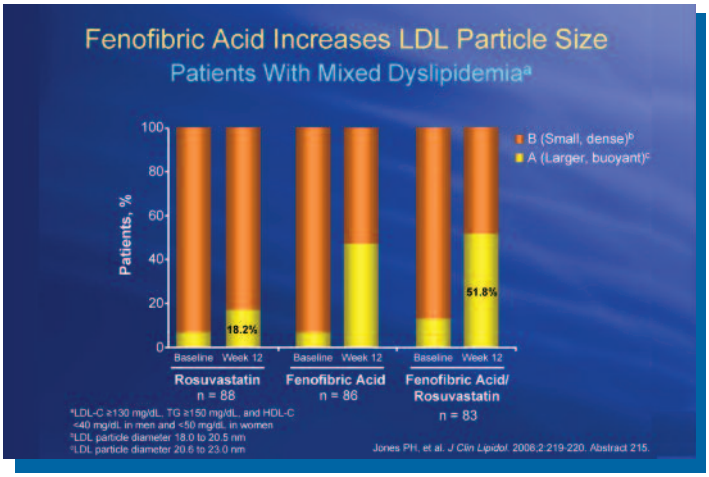

Figure 7. Fenofibric Acid Increases LDL Particle Size.
The combination of fenofibric acid and rosuvastatin therapy resulted in a favorable shift in the percentage of patients with large, buoyant LDL particles from 13.3% at baseline to 51.8% following 12 weeks of combination therapy. Patients who received rosuvastatin monotherapy experienced a more modest shift, with only 18.2% of patients with large, buoyant LDL particles posttreatment compared with 6.8% observed at baseline.[70]

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol-HDL and LDL Treatment Strategies (ARBITER 6-HALTS) is a randomized, parallel group, open-label study comparing HDL-C–focused and LDL-C–focused lipid treatment strategies for their effects on atherosclerosis. A maximum of 400 subjects with CHD or CHD equivalents who are at goal for LDL-C (<100 mg/dL) with low HDL-C (<50 mg/dL for men and <55 mg/dL for women) on statin monotherapy will be assigned to either intensified LDL-C–lowering therapy with ezetimibe (10 mg/day) or HDL-C–raising therapy with ER niacin. The primary end point is mean change in CIMT after 14 months. Enrollment in ARBITER 6-HALTS began in November 2006, and results are anticipated in early 2009.

The ACCORD trial is a randomized, multicenter, double 2 x 2 design trial being conducted in 10 000 patients with type 2 diabetes. The trial was designed to test the effects of intensive glycemic control, therapy to increase HDL-C and lower triglycerides, and intensive blood pressure control on major CHD events. All participants will be in the glycemic control trial; however, in February 2008 the intensive glucose-lowering arm was stopped due to safety concerns.[85] One arm of the trial will address the effects of lipid control using simvastatin monotherapy or in combination with fenofibrate in 5800 of the participants. The trial began enrolling patients in February 2003 and is expected to be completed in June 2009.

Conclusions

National guidelines indicate that combination therapy may be necessary to meet recommended lipid targets. Clinical trial data with omega-3 fatty acids, niacin, and fenofibrate indicate that these are safe and efficacious treatment options for improving the profile of atherogenic lipid abnormalities. Ongoing clinical trials will further clarify the safety and efficacy of combination therapy for reducing CVD events.

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Posttest Questions

1. **The presence of hypertriglyceridemic waist phenotype (waist circumference >35.4 in. in men or >33.5 in. in women and a plasma triglyceride level >177 mg/dL) had a significant ___________ increase risk of CAD (*P*=.02).**
   a. 2-fold b. 4-fold
   c. 5-fold d. 6-fold

2. **A study by Alsheikh-Ali et al demonstrated that low HDL-C was prevalent across all levels of LDL-C, regardless of gender, but most prevalent in patients with _____________.**
   a. Poorly controlled LDL-C >100 mg/dL
   b. Well-controlled LDL-C ≤70 mg/dL
   c. Poorly controlled triglycerides >150 mg/dL
   d. Well-controlled triglycerides <150 mg/dL

3. **When triglycerides are elevated, LDL-C may not accurately reflect total CVD risk, and the NCEP ATP III guidelines recommend that when triglyceride levels are ≥200 mg/dL that ___________ be a secondary target of therapy**
   a. Apo B b. CRP
   c. Triglycerides d. Non–HDL-C

4. **The 2008 consensus statement issued by the ADA and ACC recommends measurement of LDL-C, non–HDL-C, and _____________ in patients with cardiometabolic risk to more accurately assess their CVD risk.**
   a. CRP b. Apo A-I
   c. Apo B d. Lp(a)

5. **The JELIS study revealed that combination therapy with ____________ provided a 19% relative risk reduction in major CHD events.**
   a. Fenofibrate/statin
   b. Omega-3 fatty acid (EPA)/statin
   c. Niacin/statin
   d. Colestipol/statin

6. **In the ARBITER 3 study, there was a significant, inverse correlation between the increase in HDL-C and regression of CIMT.**
   a. True
   b. False

7. **In the FIELD trial, fenofibrate treatment had a particularly beneficial effect in the subgroup of _____________.**
   a. Patients with a prior MI
   b. Patients with well-controlled LDL-C
   c. Male patients
   d. Patients with no prior CVD

8. **In the COMBOS trial, the addition of omega-3 fatty acids to background statin therapy had what effect on triglyceride levels?**
   a. A 29.5% increase
   b. A 29.5% reduction
   c. A 70% reduction
   d. No change

9. **In SEACOAST I, patients treated with niacin ER/simvastatin had significantly greater reductions in_____________ compared with patients receiving simvastatin monotherapy.**
   a. LDL-C and triglycerides
   b. Non–HDL-C and LDL-C
   c. Non–HDL-C and triglycerides
   d. Apo B and LDL-C

10. **The combination of fenofibric acid and rosuvastatin in patients with mixed dyslipidemia resulted in a shift in resulted in a favorable shift in the percentage of patients with large, buoyant LDL particles.**
    a. True
    b. False

POSTTEST ANSWER SHEET

1. ______ 2.______ 3.______ 4.______ 5.______ 6. ______ 7.______ 8.______ 9.______ 10.______

Participant name: [ ]

Phone number: [ ][ ][ ] – [ ][ ][ ] – [ ][ ][ ][ ]

Date: [ ][ ] – [ ][ ] – [ ][ ][ ][ ]
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EVALUATION FORM

Reducing Residual Cardiovascular Risk in Patients With Atherogenic Dyslipidemia

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(Scale: 1=Poor, 2=Fair, 3=Average, 4=Good, 5=Excellent) Using this scale, please rate the following:

ACTIVITY EVALUATION			
Quality of educational content	1 2 3 4 5	Level of instruction	1 2 3 4 5
Objective and balanced material	1 2 3 4 5	Usefulness of course materials	1 2 3 4 5
Scientifically rigorous	1 2 3 4 5	Appropriate teaching method used	1 2 3 4 5

Please indicate whether the following objectives were met:

LEARNING OBJECTIVES	Yes	No
Evaluate the importance of elevated triglycerides and low HDL-C in CVD risk	◯	◯
Explain how to calculate non–HDL-C and relate its value in predicting CVD risk	◯	◯
Determine which patients will benefit from combination lipid-modifying therapies to reduce residual CVD risk	◯	◯

This activity was free of commercial bias. (If not, please explain below.)	◯	◯
This activity increased your knowledge in delivering patient care. (May comment below.)	◯	◯
This activity will change your practice behavior. (If so, how? May comment below.)	◯	◯
If yes, how soon will you implement a change? ◯ Immediately ◯ 1 month ◯ 6 months ◯ 12 months		
Facilities, technical arrangements, etc, efficiently supported this educational activity (May comment below.)	◯	◯

Would you recommend this activity to a colleague?	◯	◯

How did you hear about this activity? (Please select all that apply)
◯ Brochure ◯ E-mail ◯ Colleague ◯ Telephone
◯ Web site ◯ Fax ◯ Other_____

EDUCATIONAL NEEDS – YOUR COMMENTS ARE APPRECIATED AND WILL HELP TO IMPROVE FUTURE ACTIVITIES

1) What topics do you need for future activities? _____

2) How can we improve this activity?_____

Comments:_____