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SPECIAL EDITION

Treating Beyond LDL for Additional Reduction in CV Risk Results from Clinical Trials

CME-Certified Activity

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1. c. According to Dr. Cusi, patients with type 2 diabetes typically have high triglycerides, low HDL-cholesterol, and LDL-cholesterol of the small, atherogenic type that may only be moderately elevated.

Locator: Lipid Abnormalities in Type 2 Diabetes Patients

2. d. According to Dr. Grundy, in ATP-III, the primary target for diabetic patients is LDL cholesterol, which should be treated to a level of less than 100mg/dL. In patients with either diabetes or both diabetes and CVD, clinicians may consider lowering LDL to less than 70mg/dL.

Locator: Lipid Abnormalities in Type 2 Diabetes Patients

3. a. The first trial was the Helsinki Heart Study, which included 4,081 patients. The data on patients with diabetes were provocative because, although there were only a few patients with diabetes in the study, the reductions in coronary heart disease were impressive—beyond 50%. This led to the VA-HIT study, which examined gemfibrozil in coronary heart disease in 2,500 subjects, of which about one-quarter had diabetes.

Locator: Trial Data on Combination Therapy for Diabetic Dyslipidemia

4. c. According to Dr. Robertson, both the VA-HIT and Helsinki trials suggest that the best candidates for combination therapy are those patients with the metabolic syndrome, hyperinsulinemia, or other evidence of impaired fasting glucose, but who are not yet diabetic. In both trials, relatively little benefit was seen in patients with low HDL and high cholesterol in the absence of high triglycerides or impaired fasting glucose, but a substantial benefit was seen in the patients who had either frank diabetes or metabolic syndrome.

Locator: Clinical Implications of Trial Data

5. d. According to Dr. Grundy, niacin may worsen glucose tolerance in some patients, therefore, hemoglobin A1c and glucose levels should be monitored appropriately. With the administration of niacin, there is an initial suppression of free fatty acid released from adipose tissue that could be protective against insulin resistance. However, the free fatty acid release rebounds to even higher levels, negating the benefit of the suppression of free fatty acids.

Locator: Statins or Fibrates + Niacin

6. b. According to Dr. Grundy and Dr. Robertson, omega-3 fatty acids are suitable for lowering triglycerides, particularly in patients who do not tolerate fibric acids or niacin, or whose hypertriglyceridemia persists despite the fibrates and niacin. It has minimal impact on the remainder of the lipid profile, and there is little data to suggest any long-term effects on cardiovascular events. It was noted that omega-3 fatty acids are useful in a situation where a patient has extremely high triglycerides, such as 1,000 mg/dL. Available data does not prove omega-3 fatty acids to be a strong first choice for lowering triglycerides, and their lack of effect on HDL does not make them desirable for typical diabetic dyslipidemia.

Locator: Omega-3 Fatty Acids

7. d. The FIELD study is unique because, as Dr. Cusi noted, it was the first study to target patients with type 2 diabetes with a lipid lowering agent. In addition, the recommendations for lipids and cardiovascular management changed midstream once the importance of statin therapy was established. Finally, the FIELD study was comprised of patients at lower risk for cardiovascular events compared with the diabetes population included in earlier studies of cardiovascular risk reduction. Approximately 80% had no prior cardiovascular disease (average HDL of 42 mg/dL was substantially higher and average triglycerides of 153 was substantially lower than previously studied diabetes populations). In addition, about one-third of patients were not considered to be dyslipidemic at entry. Dr. Cusi noted that, "This unique population may have mitigated the expected benefits of therapy because their incidence of cardiovascular disease was likely one of the lowest considering a diabetic population."

Locator: FIELD Study: Key Findings and Implications/Study Design and Description

8. a. According to Dr. Robertson, the difficult aspect of the FIELD trial is the mixture of both primary prevention and secondary prevention patients. Death or non-fatal MI in the secondary prevention group of patients equates to a slightly different short-term risk as compared to the primary prevention group. While patients with type 2 diabetes are at a high lifetime risk for cardiovascular events, patients with type 2 diabetes and known coronary disease are at exceptional risk for short-term events.

Locator: FIELD Study: Key Findings and Implications/Study Design and Description

9. d. There was a very low rate of complications for patients receiving fibric acids in FIELD. Twenty-five percent of placebo-treated patients with a history of cardiovascular disease were placed on statin therapy. Also, approximately 20% of high-risk patients received statins plus fenofibrates. The adverse event rates did not seem to differ between these two groups.

Locator: FIELD Study: Key Findings and Implications/Fenofibrate Safety

10. c. According to Dr. Jones, myopathy issues are reported more often with gemfibrozil and statins because of the glucuronidation of statins, which gemfibrozil seems to inhibit. This causes higher statin plasma levels when given concomitantly. Fenofibrate does not affect that glucuronidation and does not affect statin plasma levels when given concomitantly.

Locator: FIELD Study: Key Findings and Implications/Fenofibrate Safety



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Medical Crossfire fuels physician education and learning as the only medical education program dedicated to medical debates and to authoritative peer exchange among health care thought leaders on clinical issues that directly impact the practice of medicine.

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Treating Beyond LDL for Additional Reduction in CV Risk

Results from Clinical Trials

CME-Certified Activity



Jointly Sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ)—Center for Continuing and Outreach Education and *Medical Crossfire*/Liberty Communications Network.



Release Date: February 2006 • Expiration Date: March 31, 2007

This activity is supported by an educational grant from Abbott Laboratories.

Educational Overview

Fibrate therapy has been available since the 1970s for the treatment of lipid abnormalities, specifically elevated triglycerides and low HDL-cholesterol. Several clinical trials have demonstrated the efficacy of fibrate therapy for the primary and secondary prevention of cardiovascular disease in patients with type 2 diabetes; however, until now there have been no large scale interventional studies conducted exclusively in this patient population. The recently published Fenofibrate Intervention Event Lowering in Diabetes (FIELD) study is the largest clinical outcomes study ever conducted with lipid therapy in patients with type 2 diabetes. Although there was no significant difference in the primary endpoint, significant benefits were observed in some secondary endpoints and patient subsets. These results are likely to have an impact on future clinical guidelines and practice for the management of cardiovascular disease as well as treatment decisions made in the clinical practice setting.

Through debate and authoritative peer exchange, this *Medical Crossfire*[®] activity, conducted in conjunction with UMDNJ, will discuss the implications of the recently published FIELD study on the management of cardiovascular disease in patients with type 2 diabetes.

Target Audience

This educational activity is designed for cardiologists and other health care professionals interested in or involved with lipid management in patients with type 2 diabetes.

Learning Objectives

- Review the lipid abnormalities in patients with type 2 diabetes.
- Consider the NCEP guidelines related to the prevention of cardiovascular disease in patients with type 2 diabetes.
- Discuss recent clinical data that support NCEP guidelines on combination therapy for lipid management.
- Appraise emerging data that may influence future guidelines on the management of patients at high risk for cardiovascular disease.

Method of Instruction

Participants should read the learning objectives and review either the print monograph or audio CD in its entirety. After reviewing the material, complete the self-assessment test consisting of a series of multiple-choice questions. The activity is complemented with references that contain the rationale for the correct answer to each question as well as a description identifying the section in the activity that contains the correct answer, allowing participants to review the material as needed, thus finalizing their educational participation.

Upon completing this activity as designed, participants will receive a letter of credit awarding AMA/PRA category 1 credit three to four weeks after receipt of the registration and evaluation materials. Estimated time to complete this activity as designed is 1.5 hours.

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of UMDNJ—Center for Continuing and Outreach Education and *Medical Crossfire*/Liberty Communications Network. UMDNJ—Center for Continuing and Outreach Education is accredited by the ACCME to provide continuing medical education for physicians.

UMDNJ—Center for Continuing and Outreach Education designates this educational activity for a maximum of 1.5 AMA PRA Category 1 Credits.[™] Physicians should only claim credit commensurate with the extent of their participation in the activity.

The print monograph was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by John B. Kostis, MD; Anthony Messina, MD; and Lisa Motavalli, MD. The audio CD was reviewed by John B. Kostis, MD; Liliana Cohen, MD; and Syed Hussain, MD.

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Disclosure Declarations

In accordance with the disclosure policies of UMDNJ and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity participants: 1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services, that relate to the content of their presentation/material, or the commercial contributors of this activity, that could be perceived as a real or apparent conflict of interest; and 2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

Faculty Disclosure Declarations

Dr. Cusi has received grant/research support from Abbott Laboratories and Takeda Pharmaceuticals North America; has served as a consultant for Abbott Laboratories, Merck & Co., Novo Nordisk, Pfizer Labs, and sanofi-aventis; and has been a member of the scientific advisory boards of Abbott Laboratories, Merck & Co., and Pfizer Labs.

Dr. Grundy has received grant/research support awarded to the University of Texas Southwestern Medical Center by Abbott Laboratories, Kos Pharmaceuticals, and Merck & Co.; has received honoraria from Abbott Laboratories, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Fournier Pharma, Kos Pharmaceuticals, Merck & Co., Pfizer Labs, Sankyo Pharma, and Schering-Plough Healthcare Products; and has been a member of the scientific advisory boards of AstraZeneca Pharmaceuticals, Pfizer Labs, and sanofi-aventis.

Dr. Jones has received grant/research support from Abbott Laboratories, AstraZeneca Pharmaceuticals, and Kos Pharmaceuticals; and has been a member of the scientific advisory boards of Abbott Laboratories and GlaxoSmithKline Pharmaceuticals.

Dr. Robertson has served as consultant for Abbott Laboratories and Eli Lilly, and has served on the speakers' bureaus of Abbott Laboratories, AstraZeneca Pharmaceuticals, Eli Lilly, Pfizer Labs, sanofi-aventis, and Takeda Pharmaceuticals North America.

Dr. Kostis has received grant/research support from Pfizer Labs; has been a consultant for Berlex Laboratories, Pfizer Labs, Schering-Plough Healthcare Products, and Taisho Pharmaceuticals Co.; has served on the speakers' bureaus of Bristol-Myers Squibb, Sanofi, Merck & Co., and Pfizer Labs; and is a member of the scientific advisory boards of Schering-Plough Healthcare Products and Pfizer Labs.

Dr. Cohen, Dr. Hussain, Dr. Messina, and Dr. Motavalli have no financial arrangements or affiliations to disclose.

Off-Label Usage Disclosure

This activity contains discussion of unlabeled use of commercial products or non-FDA approved use of investigational agents. The prescription agent fenofibrate is not indicated for the primary or secondary prevention of coronary heart disease in patients with diabetes. The prescription agent gemfibrozil is not indicated for the primary or secondary prevention of coronary heart disease in patients with diabetes. While simvastatin and atorvastatin are indicated for the primary or secondary prevention of coronary heart disease specifically in patients with diabetes, the other available HMG-CoA reductase inhibitors (statins) are not.

Disclaimer

The views expressed in this activity are those of the faculty. It should not be inferred or assumed that they are expressing the views of Abbott Laboratories, any other manufacturer of pharmaceuticals, UMDNJ, or *Medical Crossfire*/Liberty Communications Network.

It should be noted that the recommendations made herein, with regard to the use of therapeutic agents, varying disease states, and assessments of risk, are based upon a combination of clinical trials, current guidelines, and the clinical practice experience of the participating panelists. The drug selection and dosage information provided in this activity are believed to be accurate. However, the participants are urged to consult the full prescribing information on any drug mentioned in this activity for recommended dosage, indications, contraindications, warnings, precautions, and adverse effects before prescribing any medication. This is particularly important when a drug is new or infrequently prescribed.

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Treating Beyond LDL for Additional Reduction in CV Risk

Results from Clinical Trials

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Fibrate therapy has been used clinically since the 1970s, though its true mechanism of action on PPAR-alpha was not fully understood until the 1990s. The utility of fibrate therapy for the treatment of lipid abnormalities—specifically elevated triglycerides and low HDL cholesterol—is well known. Several clinical trials have demonstrated the efficacy of fibrate therapy for the primary and secondary prevention of cardiovascular disease in patients with type 2 diabetes.^{1,2,3} However, none of these trials have focused exclusively on patients with diabetes. The recently released Fenofibrate Intervention Event Lowering in Diabetes study (FIELD)⁴ investigated the effect of fibrate therapy on clinical outcomes in patients with type 2 diabetes. Although there was no significant difference in the primary endpoint, significant benefits were observed in some secondary endpoints and patient subsets. These findings may impact future clinical guidelines for the management of cardiovascular disease and help to guide treatment decisions made in the clinical practice setting. This **Medical Crossfire** discussion among national experts explores treating beyond LDL for additional reduction in CV risk as well as the potential impact of the recently released FIELD study on future clinical guidelines and practice.

Lipid Abnormalities in Type 2 Diabetes Patients

Type 2 diabetes and insulin resistance remain a major risk factor for cardiovascular disease morbidity and mortality. Observational studies indicate that lipid reduction plays a key role in the primary prevention of cardiovascular disease (CVD) in patients with diabetes.⁵ Peter H. Jones, MD, moderator of this **Medical Crossfire**, initiated discussion on this topic by asking the panel to review the lipid abnormalities typically seen in patients with type 2 diabetes.

“These patients usually have high triglycerides, low HDL-cholesterol, and LDL-cholesterol that may be only moderately elevated, but it is the small, very atherogenic type of LDL,” explained Kenneth Cusi, MD, noting that these abnormalities do not

happen by chance. Insulin resistance is associated with these abnormalities because “the liver received an excessive amount of free fatty acids (FFA) coming from adipose tissue that is resistant to the antilipolytic action of insulin. This provides the fuel (i.e., FFA) for an increased hepatic VLDL secretion. Excessive rates of VLDL secretion by the liver lower plasma HDL concentration by increasing its turnover and clearance,” he said.

Individuals with diabetes “face the challenge of responding to an excess of available calories,” added David D. Robertson, MD. “The calories of the blood sugar and the lipids that circulate are a metabolic issue; overprotection is one side of it, and adequate clearance is another.” He then described approaches to managing dyslipidemia, using the current armamentarium of agents.

“Agents that are currently available address the clearance of LDL or the breakdown of the triglyceride-rich particles, or affect the production of the triglyceride-rich particles. We have a variety of opportunities to impact both the excess production and the empiric clearance of lipid particles from the blood of the patient with diabetes,” he noted.

Agreeing with Dr. Robertson, Dr. Jones noted that dyslipidemia in diabetes is “usually not an LDL-cholesterol abnormality, but rather one that involves structural and compositional abnormalities in lipids such as small dense LDL, small dense HDL, and overproduction of triglycerides.” He pointed out that panelist Scott Grundy, MD, PhD, has served as chair of the National Cholesterol Education Program’s Adult Treatment Panel (NCEP ATP) over the past decade. The ATP-III update of 2001,⁶ Dr. Jones noted, “changed the role of diabetes as a risk.” He asked Dr. Grundy to discuss the recent guideline changes and provide his perspective.

Dr. Grundy commented that the ATP-III panel stated that diabetes is a coronary heart disease risk equivalent, placing individuals with diabetes at high risk for cardiovascular disease. “Subsequently, we modified that term in our update of the ATP-III in 2004 by calling diabetes a high-risk condition,” he explained. The primary target of lipid treatment is LDL cholesterol, which should be reduced to a level less than 100 mg/dL. In patients with both diabetes and CVD, clinicians may consider lowering LDL to less than 70 mg/dL. Several clinical trials now demonstrate that LDL lowering reduces risk effectively in patients with diabetes.⁷⁻¹⁰ Apart from LDL, patients may have elevated triglycerides and HDL levels that are too low, also known as atherogenic or diabetic dyslipidemia, Dr. Grundy noted. “This may require consideration of additional therapies after the LDL is controlled.”

Treating Beyond LDL

Dr. Jones acknowledged that treating triglycerides and HDL is important. “For typical

lipid abnormalities in patients who are insulin resistant—for instance, those patients with diabetes and the metabolic syndrome—the American Diabetes Association has published recommendations for lipid treatment.¹¹ Typically, the ADA follows the ATP in recommending lipid levels. Have they maintained that after the recent update?” he went on to ask the panel.

“The ADA acknowledges that the data for lowering LDL through statin therapy are very strong,” explained Dr. Cusi, “but it would also like to see triglycerides below 150 mg/dL, and HDL above 40 mg/dL in men and 50 mg/dL in women.” He admitted that these numbers can be difficult to achieve, and noted that lifestyle modification and pharmacological therapy are tools clinicians can use to reach treatment targets. What further complicates management “is how to target the residual dyslipidemia once target LDL levels have been reached,” he offered. “We have a major problem here, and many of our patients need combination therapy.”

“Targeting triglycerides and HDL is a critical issue in these patients,” agreed Dr. Jones, “and insulin resistance and central adiposity are likely strong drivers of the imbalance. Lifestyle likely impacts triglycerides more than LDL; therefore, therapeutic lifestyle change becomes a critical issue in patients who have hypertriglyceridemia along with insulin resistance, diabetes, or metabolic syndrome. Lifestyle changes along with exercise and weight loss are another important way of increasing HDL,” he concluded.

“Glucose control is also essential,” interjected Dr. Cusi. “For instance, if a patient has a blood sugar level of 250 mg/dL, this needs to be treated aggressively or lipid-lowering interventions will fail to control hypertriglyceridemia and increase HDL.”

Dr. Jones then asked the panelists to share their clinical experiences. “What are some challenges faced in the clinical setting when attempting to improve triglycerides or raise HDL through therapeutic lifestyle changes (TLC)?” he queried.

“Therapeutic lifestyle is an ongoing challenge,” lamented Dr. Robertson. “At each visit it is absolutely essential that we revisit the issue of TLC. We need to focus on improvements that have been made, on goals that have been set, and what has been achieved and what has not. Success varies from one patient to the next, but only with persistence do we see the benefits. Over the long term a substantial amount of improvement in triglycerides is going to be dependent on lifestyle changes, but the residual challenge and the intervening crisis is often one we can only meet with pharmacologic therapies. If we wait for three to four years to succeed with lifestyle changes and leave the triglycerides untreated, we know that the opportunity for disease to progress is quite evident,” he said.

Dr. Jones noted that the ATP-III has referred to targeting triglycerides and HDL in high-risk patients such as individuals with diabetes, but that the guidelines do not give specific targets for triglycerides or HDL. “Are there plans for setting those kinds of targets, or will the focus remain on non-HDL cholesterol?” he asked.

Dr. Grundy explained that non-HDL encompasses LDL and VLDL cholesterol, and “it is a simple target that extends the LDL target. If you can reduce the non-HDL down 30 milligrams above the LDL goal, then in most cases you will have achieved the ADA recommendations.” He illustrated this point with a patient example, one whose LDL goal is 100 mg/dL, and non-HDL is 130 mg/dL. “If you lower the non-HDL to 130 mg/dL, most of the time the triglycerides will be less than 150 mg/dL. Targeting non-HDL adds an element of simplicity to the treatment.” HDL is different, he noted, “because the ATP-III states that an effort should be made to raise HDL, which is a target after non-HDL is achieved.” Although the ADA has set goals for HDL in both men and women, there is not a simple way to achieve those goals. Dr. Grundy advised that clinicians should “make an effort to raise HDL as much as possible in a practical way, and not set a specific goal.”

Trial Data on Combination Therapy for Diabetic Dyslipidemia

Fibrates

Dr. Jones then asked the panel whether there are specific recommendations in the ATP-III update regarding high-risk patients such as those with diabetes, about combination lipid drug treatment, or specific recommendations about combining other drugs with statins.

“Certainly, adding other lipid-lowering agents to statins is an option once the patient has achieved the LDL goal first,” answered Dr. Grundy. “Alternately, depending on the patient’s lipoprotein pattern, the statin dose can be increased. Some of the recent statin trials such as TNT¹² and IDEAL¹³ demonstrate that this strategy would be a reasonable approach to achieve additional risk reduction. Other options include triglyceride-lowering agents like nicotinic acid and fibrates, both of which may be combined with statins. Fenofibrate in particular appears to be safe for use with statins,” he noted. “Depending on the patient’s lipoprotein profile and tolerance to the agents, any of these three approaches are reasonable options,” he concluded.

Dr. Jones remarked that data from the CARDS¹⁰ trial as well as the subgroup analysis from the Heart Protection Study⁸ show that statins do afford considerable risk reduction, including a reduction in stroke, in patients with diabetes. He asked the panel, “Prior to 2005, were any data available on the effects of agents besides statins in patients with diabetes or the metabolic syndrome?”

“We have learned a lot about the therapeutic potential of fibrates from clinical trials conducted during the 1990s,” claimed Dr. Cusi in addressing the question posed by Dr. Jones. The first trial was the Helsinki Heart Study,¹ which included 4,081 patients. The data on patients with diabetes were provocative because, although there were only a few patients with diabetes in the study, “the reductions in coronary heart disease were impressive—beyond 50%,” Dr. Cusi reported.

Dr. Cusi then addressed the VA-HIT² study, which was conducted in Veteran's Affairs medical centers across the United States. The researchers studied the effects of gemfibrozil therapy on coronary heart disease in approximately 2,532 patients, of which about one-quarter had diabetes. "There was a 22% reduction in the primary endpoint of death from coronary heart disease and fatal MI." In the BIP study, he went on, "bezafibrate demonstrated a reduction in cardiovascular events in the subgroup of subjects with plasma triglycerides ≥ 200 mg/dL,¹⁴ and more recently, in individuals with the metabolic syndrome.¹⁵ The Diabetes Atherosclerosis Intervention Study (DAIS), an angiographic trial, suggested that fenofibrate could prevent the progression of coronary artery disease in patients with pre-existing heart disease."¹⁶

Dr. Cusi added that an additional issue in the field of diabetes treatment is that many patients need combination therapy to reach lipid targets. "The ADA has provided some guidelines," he acknowledged, "but we need endpoint trial data about the effectiveness of combination therapy. Beyond good glycemic control and statins, many patients with diabetes require additional therapy to achieve triglyceride and HDL goals. Because we do not have endpoint trial data, the best drug to use in combination with statins remains controversial. However, in patients with the metabolic syndrome and/or diabetes, one may be inclined to avoid niacin since it may worsen insulin resistance while other pharmacological options such as fibrates or omega-3 fatty acids do not alter insulin sensitivity," Dr. Cusi concluded.

Niacin

"Combination therapy is going to be the wave of the future for high-risk patients, including those with diabetes," declared Dr. Jones. "However, more information is needed about the efficacy and safety of utilizing fibrates or even niacin in combination with statins." He mentioned that the evidence is

strong for the benefits of both gemfibrozil and niacin in balancing lipids, and noted that the Adult Treatment Panels over the past 15 years have recommended niacin as an optional therapy for all lipid parameters. Requesting that the panel review clinical trial data for niacin specifically in patients with type 2 diabetes with metabolic syndrome, Dr. Jones asked, "Does niacin show clinical benefit or, as was mentioned by Dr. Cusi, the possibility that it might worsen glucose levels?"

"In terms of outcome trials, niacin is the 'odd-man out' because we do not have a lot of outcome data," admitted Dr. Grundy. "There have been a large number of statin and fibrate trials, and we have a fairly good idea of the efficacy of these drugs for reducing CHD risk. However, there have not been many large-scale clinical trials with niacin." He mentioned the Coronary Drug Project,¹⁷ a secondary prevention trial in which niacin produced a reduction in risk and in long-term total mortality. A follow-up analysis of the Coronary Drug Project showed impressive results—that niacin was as effective in reducing risk in patients with diabetes and metabolic syndrome. He added that niacin can worsen glucose tolerance in some patients, and therefore hemoglobin A1C and glucose levels should be monitored appropriately in patients with diabetes who use niacin. "Niacin is extremely effective in patients with diabetes for improving their dyslipidemia, and we like to use it when we can," he observed. "But for some patients, side effects do limit its use. In patients with diabetes the dose should be relatively low—around 1 to 2 grams per day."

Dr. Cusi offered a diabetologist's angle to the discussion. "This is the dilemma that we face on a daily basis. As diabetologists we are in general uncomfortable when using niacin because it may worsen diabetes control. The real question, for which we do not have a good answer, is if you put a diabetic on low-dose niacin or a fibrate, is there potential for that patient to have less cardio-

vascular events over the next five years? We need a controlled clinical trial to answer this. In the meantime, as director of an endocrinology, diabetes, and lipid clinic, I would maintain that diabetologists are uncomfortable using niacin. Which would lower cholesterol more effectively in patients with diabetes over five years? Niacin or fibrates? Again, we do not have an answer for that. The ADA recommends that clinicians use niacin with caution in patients with diabetes, and the reason behind this suggestion may be the rebound in plasma free fatty acid concentration associated with its use.^{18,19} A number of studies that looked at insulin sensitivity using the gold-standard hyperinsulinemic euglycemic clamp technique, have found that niacin worsens insulin resistance.²⁰ Dr. Cusi then referred to a study that Dr. Vega, Dr. Grundy, and colleagues performed recently¹⁹ that demonstrated a rebound in free fatty acids after chronic use of extended-release niacin, and asked him to comment further.

“It is an interesting phenomenon,” reported Dr. Grundy. “When niacin is administered, there is an initial suppression of free fatty acid released from adipose tissue that could be protective against insulin resistance. Unfortunately, the free fatty acid release rebounds to even higher levels, especially with crystalline niacin. The levels can be quite high, and this negates the benefit of the suppression of free fatty acids. We tried using an extended release formulation of niacin that seemed to mitigate or reduce the rebound somewhat, but it still occurred to some extent.”

Omega-3 Fatty Acids

Dr. Jones returned to the subject of balancing the non-LDL lipids, and mentioned another option that was recently approved by the FDA for lowering triglycerides—a very concentrated form of omega-3 fatty acids. “Do these play a role in managing triglycerides in patients with diabetes?” he asked the panel.

Dr. Robertson responded that the role of the omega-3 fatty acids in reducing triglyc-

erides has been evaluated in a number of situations. “For patients who either do not tolerate fibric acids or niacin, or who still persist with more severe hypertriglyceridemia despite the fibrates and niacin, the role of the omega-3s is quite consistent. It is rare that a patient would not respond to them when they are taken in adequate doses. These agents have a minimal impact on the remainder of the lipid profile, however, and there is very little data to suggest any long-term effects on cardiovascular events. They are adjunct therapy for patients with more severe hypertriglyceridemia, and in that capacity they work quite well,” he offered.

For the treatment of post-MI patients, the American Heart Association advocates a moderate amount of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)—about 800 to 1,000 milligrams a day;²¹ however, this is not a lipid-modifying dose. Between 3,000 and 4,000 milligrams per day of DHA and EPA are needed to impact triglycerides.²² Dr. Robertson went on to explain, “I see the use of omega-3 fatty acids as a focused mechanism for addressing more severe dyslipidemia, and not as an obvious risk factor-modifying and risk-reducing strategy for patients in terms of cardiovascular disease. I am sure it is helpful, but we cannot really be sure of the benefits.”

Dr. Grundy agreed with his colleague and stated that he uses omega-3 fatty acids in the unusual patient with diabetes whose triglycerides are extremely high—usually more than 1,000 mg/dL. “In such a patient, you are going to need multiple drugs, including fibrates and, likely, niacin and omega-3 fatty acids, in an attempt to lower triglycerides to a range that at least removes the short-term risk of acute pancreatitis,” he maintained.

Dr. Robertson pointed out that unconcentrated fish oil adds significant calories to the diet versus concentrated fish oils. He added, “there were historically some concerns about worsening insulin resistance and glycemic control, but with the newer preparations that really does not seem to be an issue.”

Clinical Implications of Trial Data

Seeking the panelists' perspective on the implications of the studies discussed in this *Medical Crossfire*, Dr. Jones directed the next question to Dr. Grundy and asked, "In your view, how might these major studies impact therapy?"

"The VA-HIT trial was extremely impressive, and it certainly provides a rationale for the use of fibrates in combination therapy," replied Dr. Grundy. "Some believe that if the LDL is very low, fibrates can be used alone, although there remains strong evidence for first-line therapy with statins as seen in the Heart Protection Study." He added that, "The results of the VA-HIT trial should be aligned with the FIELD study to see how they compare. Nevertheless, the VA-HIT trial does provide a rationale for combination therapy."

Dr. Robertson mentioned that both VA-HIT and the Helsinki Heart Study suggest that patients who are the best candidates for combination therapy are those with the metabolic syndrome, hyperinsulinemia, or other evidence of impaired fasting glucose, but who do not yet have diabetes. "In both trials, we saw relatively little benefit for patients with low HDL and high cholesterol in the absence of high triglycerides or impaired fasting glucose, but a substantial benefit was demonstrated in the patients who had either frank diabetes or metabolic syndrome." It appears that, whether through specific changes in the lipids or other effects that PPAR activation might have, there is a substantial opportunity for the patient with a combination of insulin resistance and dyslipidemia to improve, he acknowledged. "In the absence of that situation, we were seeing only modest reductions in coronary death versus about a 40% reduction in VA-HIT where the patients were diabetic or pre-diabetic; for reduction in risk of stroke there was also a stronger benefit in the group with either pre-diabetes or diabetes."

Trials such as the IDEAL trial and the TNT trial with atorvastatin show incremental benefit of aggressive LDL reduction, but further reduction is moderate, he continued. The relative risk reduction of 30% to 35% increased to about 40% to 45% reduction at best, leaving a 50% to 55% residual risk. "When we see the high absolute risk for a patient with diabetes still at 50% to 60% of baseline risk, despite intensive treatment with statins, it makes us very aware that there are other options we need to consider." He agreed with Dr. Grundy's emphasis on the non-HDL cholesterol and urged practitioners to learn from that point. "If we are pushing statins and we are seeing improvement in both the non-HDL and the LDL, then further effort with statins may be appropriate. However, if we increase the statin and see only reduction in LDL but little change in the non-HDL, then we realize we are dealing with the type of mixed dyslipidemia that may benefit from a combined therapy approach."

FIELD Study: Key Findings and Implications

Study Design and Description

The FIELD study was published in November 2005 in *The Lancet* and presented simultaneously at the 2005 American Heart Association meeting in November in Dallas.

The FIELD study was conducted in Australia, New Zealand, and Finland and included 9,795 patients between age 50 and 75 who were not on statin therapy at study entry. The primary outcome was coronary events. The majority of the patients, approximately 7,664, did not have previous cardiovascular disease. The structure of the trial allowed for observations of both short-term and long-term effects with fenofibrate.²³ Before randomization to fenofibrate or placebo arm, patients had a run-in phase that included a six-week single-blind active run-in on 200 mg fenofibrate daily.

FIELD SYNOPSIS

Patient Population

- 9,795 participants aged 50-75 years, with type 2 diabetes mellitus, and not taking statin therapy at study entry
 - 2,131 with previous cardiovascular disease; 7,664 without (at randomization)
 - Subjects were not to be obvious candidates for lipid-lowering therapy; only 37% to 39% of the patients met the definition of dyslipidemia (TG >150 and HDL <40 mg/dL for men or <50 mg/dL for women).
 - Baseline LDL-C: 119 mg/dL; HDL-C: 42 mg/dL; triglycerides 154 mg/dL
 - Average duration of T2DM was five years (A1C 6.9%)

Outcomes Assessed

- Primary outcome
 - All coronary events (coronary heart disease death or non-fatal myocardial infarction)
- Secondary outcome for prespecified subgroup analyses
 - Total cardiovascular events (the composite of cardiovascular death, myocardial infarction, stroke, and coronary and carotid revascularization)

Efficacy and Safety Results

- On average, more patients allocated to placebo (~40%) than fenofibrate (~20%) started statin therapy at some point during the study period. The mean exposure of each group to statin therapy over five years was 17% for the placebo group and 8% ($P<0.0001$) for the fenofibrate group.
- Fenofibrate patients experienced a coronary event rate of 5.2% while patients on placebo had a rate of 5.9% with fenofibrate, which corresponded to a relative reduction of 11% ($P=0.16$) for patients on fenofibrate.
 - This finding corresponded to a significant 24% reduction in non-fatal myocardial infarction ($P=0.010$) and a non-significant increase in coronary heart disease mortality ($P=0.22$).
 - Total cardiovascular disease events were significantly reduced from 13.9% to 12.5% ($P=0.035$) with fenofibrate.

- The reduction included a 21% decrease in coronary revascularization ($P=0.003$).
- In subjects without prior cardiovascular disease ($n = 7664$), fenofibrate reduced the primary end point (any coronary event) by 25% ($P=0.014$) and total cardiovascular disease events by 19% ($P=0.004$).
 - Total mortality was 6.6% in the placebo group and 7.3% in the fenofibrate group ($P=0.18$).
 - Fenofibrate was associated with less albuminuria progression (10% vs 11%, $P=0.002$), and less retinopathy needing laser treatment (5.2% vs 3.6%, $P=0.0003$).
 - There were no differences in incidence of myositis or hepatic transaminase elevations between treatment groups. There was an increase in pancreatitis (0.5% vs 0.8%, $P=0.031$) and pulmonary embolism (0.7% vs 1.1%, $P=0.022$) with fenofibrate. No other significant differences in adverse effects were noted.

Summary

- Fenofibrate did not significantly reduce the pre-established primary endpoint of coronary events ($P=0.16$), although total cardiovascular events were significantly decreased by 11% ($P=0.035$). Higher statin use in the placebo arm, low coronary event rates and moderate dyslipidemia at study entry could have limited treatment effects. After adjustment for crossover of placebo to other lipid-lowering, coronary events were significantly reduced by fenofibrate. In subjects without prior cardiovascular disease ($n=7664$), fenofibrate reduced significantly coronary events by 25% and total cardiovascular disease events by 19%. Microvascular disease was also reduced with treatment. There were no significant differences in rates of hepatic transaminase elevations or myositis (either alone or in combination with statins) between fenofibrate and placebo.

The panelists noted that the FIELD study was unique in its patient population for a study in diabetes and the era in which it was conducted, explaining that the patient population in FIELD was a comparatively lower-risk population in terms of prior cardiovascular events and lipid abnormalities than the patient populations in previous studies that looked at cardiovascular risk reduction in patients with diabetes. In addition, the panel explained that, during the time the study was conducted, the importance of statin therapy for cardiovascular risk reduction emerged, changing recommendations for lipid and cardiovascular management.²⁴ Consequently, statin therapy was initiated during the study and may have influenced the results. Dr. Jones asked the panelists to discuss the design of the study and its outcomes.

“This was a long-awaited study because it was really the first to target patients with type 2 diabetes with a lipid-lowering agent,” declared Dr. Cusi. “For three out of four subjects this was a primary prevention trial, that is, patients with no prior CVD.” The primary endpoint of the trial was death from coronary heart disease or non-fatal myocardial infarction. Other pre-specified subgroup analysis incorporated total cardiovascular events, which included all myocardial infarction events (fatal and non-fatal), stroke, carotid revascularizations, and cardiac death. “A rather unique population was selected,” said Dr. Cusi. “The VA-HIT study set the stage for treating patients with an average triglyceride level of about 160 mg/dL, and an HDL of about 32 mg/dL. However, the FIELD study largely recruited patients without prior cardiovascular disease, with an average plasma HDL concentration of 42 mg/dL—substantially higher—and slightly lower triglycerides of 153 mg/dL. In addition, about one-third of patients were not considered to be dyslipidemic at entry. This unique population may have mitigated the expected benefits of therapy, because the incidence of cardiovascular

disease was one of the lowest for a clinical trial composed exclusively of individuals with diabetes,” he contended.

The results of the FIELD study show a non-significant 11% reduction in the primary endpoint of coronary heart disease, death, and non-fatal myocardial infarction. “This may have been disappointing to clinicians expecting more out of fibrates as monotherapy in these patients whose HDL was 42 mg/dL and whose LDL was averaging about 119 mg/dL,” remarked Dr. Jones. “However, the secondary endpoints of total cardiovascular disease events were significantly reduced by 11%.”

“The difficult aspect of this study is the mixture of both primary prevention and secondary prevention patients,” remarked Dr. Robertson. “Death or non-fatal MI in the secondary prevention group of patients equates to a slightly different short-term risk as compared to the primary prevention group.²³ Clearly, patients with type 2 diabetes are at high lifetime risk for cardiovascular events. But patients with type 2 diabetes and known coronary disease are at exceptional risk for short-term events. The opportunity to impact the risk in the near future is relatively low without an aggressive treatment plan.” He explained that this has been demonstrated with the more-aggressive statin therapy that Treat to New Targets Trial recently presented.²⁵ In that trial, the most intensive therapy offered greater benefit in the shortest period of time for the highest-risk patients. “The total cardiovascular event picture, perhaps, is a fair evaluation,” he suggested. “One opportunity is to look at the Kaplan-Meier curves for the study as a whole. There was very little impact on the primary endpoint in the beginning, but there is some suggestion of separation of the curves at the second, third, and fourth year. Again, this is complicated by the mixed group of primary and secondary prevention patients. What we may be seeing is a cohort of primary prevention benefits beginning in

the third and fourth year, where the secondary prevention group probably needs more aggressive treatment up front.”

Dr. Jones reiterated that there was a significant reduction in non-fatal MI but not in coronary heart disease death. “This is what potentially drove the primary endpoint to non-significance—the unfortunate lack of benefit in coronary heart disease death despite the benefit in non-fatal MI. There was a significant reduction in coronary revascularizations, which was important as well. Although VA-HIT did show a reduction in coronary heart disease death, those men were all secondary prevention patients and they were characterized by very low HDL levels, which was not the case in the FIELD patient population. In the patients considered free of cardiovascular disease at baseline, which constituted 75% to 80% of the patient population, there was a significant reduction in total cardiovascular disease events, which was very important in those patients less than age 65.”

A Midstream Change: Statin Drop In

“What was quite remarkable about the FIELD study is that the recruitment began in 1998 and ended in 2000, prior to the ATP-III guidelines, which made diabetes a very high-risk state for cardiovascular disease,” pointed out Dr. Jones. Initially, patients were randomized to fenofibrate or placebo with no lipid treatment. During the study, the ATP-III guidelines were updated. The newer guidelines considered diabetes to be a very high-risk state that required more aggressive goals for lipid management, particularly for LDL lowering. Soon after came the results of the Heart Protection Study, which recommended the use of statins in high-risk patients regardless of baseline LDL. Consequently, statin therapy was initiated or “dropped in” as the trial was being conducted.

“Statin drop-in had a definite effect,” proclaimed Dr. Grundy. “This study began in

one era and ended in another. At the time it started, we did not have the evidence for the benefit of statin therapy in patients with diabetes. It was still open to question at that point; after it was proven, many patients were started on statins. The patients in the placebo group received more statins than those in the treatment group, because the fenofibrate already had some lipid benefit. This crossover effect blurred the endpoint to some extent. When the authors attempted to analyze the data, a greater effect emerged for fenofibrate, which I think is quite reasonable.”

Put in the context of other clinical trials which generally show a risk reduction by fibrates of approximately 15% to 20% for cardiovascular events, this trial shows that fenofibrate provides a similar benefit. “With the appropriate corrections and taking all the events into account for a trial that had limited power, the results from FIELD are the same: a 15% to 20% reduction in events. That is not trivial, but these drugs are not statins either,” acknowledged Dr. Grundy. “They do not have the power to reduce risk as much as statins—particularly high doses of statins. But they certainly could be valuable agents for incremental risk reduction. When trials are broken up into primary prevention, secondary, and subgroup analysis, I believe it weakens the conclusions.”

Dr. Cusi agreed with Dr. Grundy’s assessment and summarized an important message for the practicing clinician. “One may expect a 15% to 20% reduction in coronary heart disease events or total cardiovascular disease with fibrate use. “In the FIELD study, the overall 11% reduction of the primary outcome of total CHD events ($P<0.16$) and the secondary endpoint of total CVD events ($P<0.035$) increased to 19% ($P<0.01$) and 15% ($P<0.004$), respectively, after adjusting for the greater use of statins in the placebo arm. As a primary prevention intervention, fenofibrate in FIELD significantly reduced CHD events by 25% and total CVD events 19%.” To some extent, Dr. Cusi went

on, “patient selection in FIELD may have limited the impact of fenofibrate therapy. For example, patients had a more ‘mild dyslipidemia’ compared to other trials including patients with diabetes, and compared to what we usually see in our clinics in patients with the metabolic syndrome or diabetes. Clinicians may typically encounter HDL levels well below 40 mg/dL and triglycerides much higher than 150 mg/dL, as compared to the average levels of patients recruited in FIELD. More importantly, the blood pressure (140/80 mmHg) and hemoglobin A1C control (6.9%) in this trial was better than in most previous lipid or diabetes intervention trials.”

Fenofibrate Safety

“Safety is another issue that arose from the results of the FIELD study,” mentioned Dr. Jones. “The study authors suggested that fenofibrate use is generally safe as monotherapy. Although the authors did not give specifics about those patients that took statins in combination, it is suggested that combination therapy was safe as well.”

“The very low rate of complications for the patients receiving fibric acids in the trial was reassuring,” agreed Dr. Robertson. In the FIELD study, 25% of the placebo-treated patients with a history of cardiovascular disease were placed on statin therapy. There were also a substantial number of high-risk patients who received statins plus fenofibrate—just under 20%. “The adverse event rates did not seem to differ between these two groups,” he noted. Other studies, such as the Lipids and Diabetes Study, or LDS trial, also suggest that fenofibrate and statin therapy in combination could provide safety benefits, although the data have not been published. In addition, NIH-sponsored protocols in the United States, such as the BARI-2D protocol and the ACCORD trial, are long-term studies that are collecting many years of experience. These protocols are utilizing fenofibrates and statins in com-

bination in a large number of patients without any need for the data and safety monitoring committee to point out any increased risk, Dr. Robertson added. “They are creating an opportunity for physicians to see the fenofibrate-statin combination as one of appropriate risk.” Dr. Robertson then alluded to Dr. Jones’ work, which focuses on the gemfibrozil-statin combination versus the fenofibrate-statin combination and the risk of adverse events.²⁶

“We did tend to find that there was a higher incidence of the severe issues of rhabdomyolysis associated with gemfibrozil-statin use as opposed to fenofibrate-statin use, as reported to the adverse event reporting system of the FDA,” acknowledged Dr. Jones. “There are some mechanistic reasons why there may be more potential for less reported myopathy issues with fenofibrate-statin versus gemfibrozil-statin. It relates to the glucuronidation of statins, which gemfibrozil seems to inhibit, and which causes higher statin plasma levels when given concomitantly. Fenofibrate does not affect that glucuronidation and does not affect statin plasma levels when given concomitantly.”

“In today’s world we have to accept that any use of fibric acid in a patient with diabetes is going to be in conjunction with statins,” asserted Dr. Robertson. “The absolute event rate for patients with previous cardiovascular events in the FIELD study was two- to three-fold higher. While the conclusions may not be appropriate to distinguish, we do have higher- and lower-risk patients. Realistically, even in the primary prevention or in the patients whose cumulative risk may be, over five years, less than 3% or 4%, we are still going to be looking at statin plus fibric acid for the vast majority of those patients. The previous cardiovascular disease absolute risk of either a fatal MI or death was 6% at six years, so obviously there is a critical need for a statin in that group of patients with or without the fibric acid.”

Influence Of Field On Future Guidelines

Dr. Grundy reiterated a point he had made earlier about considering the results of the FIELD study in the context of previously conducted fibrate studies. He emphasized that “the FIELD study must be integrated into the perspective of all the clinical trials that have been done with fibrates over the years. There is a tendency to take the most recent trial that has been done and believe that it is the last word on the subject. For fibrates, I do not believe that is the case.”

Dr. Jones directed his next question to Dr. Grundy, and asked, “Is there a potential for the results of the FIELD study to influence future updates by the ATP-III with regard to fibrates, either as monotherapy or in combination therapy with statins, in patients with diabetes?”

“Every clinical trial has its influence, and I think the FIELD study will as well,” answered Dr. Grundy, who mentioned that other evidence—such as the subgroup analysis of the TNT and IDEAL trials—will be taken into account. It also remains to be seen how patients improve on high doses of statins. In addition, results from trials on nicotinic acid should be available in the future, he reported.

“I do not think the FIELD study negates the value of fenofibrate in combination with a statin in patients with diabetes who have cardiovascular disease,” said Dr. Grundy. To clarify his position, he stated, “If we label individuals with diabetes without cardiovascular disease as high-risk, they would be candidates for combination therapy. Most of the patients that clinicians see with diabetes, even those without heart disease, have a much higher risk for developing future heart disease. We have a fairly high-risk group in the US who are candidates for combination therapy, regardless of whether or not they have heart disease. However, if a patient has an abnormality with only LDL and not with triglycerides and HDL, I do not see much advantage to adding a fibrate,” he stated.

Pressing the panel to comment further, Dr. Jones sought opinions as to whether the FIELD results may influence what the American Diabetes Association recommends for lipid treatment in terms of monotherapy or combination therapy.

“It does appear that once statin therapy has lowered the LDL to goal, fibrates have the potential in certain patients to provide additional benefit,” claimed Dr. Cusi, “for example, in patients with diabetes.” He mentioned the positive effect fenofibrate had on microvascular complications in the FIELD study and remarked specifically that retinopathy was reduced markedly from 5.2% in the placebo group to 3.6% in the group on fenofibrate. Dr. Cusi also added that fenofibrate-treated patients experienced a reduced progression of albuminuria. Investigators reported that other important risk factors for the development of these microvascular endpoints were well matched between groups, particularly glucose control and blood pressure control. “These are provocative findings, and we are very eager to look deeper into these data, which could open up a new paradigm,” he exclaimed. “As Dr. Grundy mentioned, statin therapy is the cornerstone of treatment to reduce cardiovascular disease in patients with diabetes. But the point to be made is that when triglyceride levels are 150 mg/dL to 160 mg/dL and HDL falls between 30 mg/dL and 40 mg/dL, then further pharmacological therapy may be warranted if lifestyle changes fail. In the FIELD study, there was a trend for those who had lower HDL and higher triglycerides to benefit. More importantly, it has been overlooked that when the LDL and the total cholesterol were low, those patients tended to also have greater benefit,” he concluded.

Final Thoughts

In offering a concluding message from this *Medical Crossfire*, Dr. Robertson described the treatment of cardiovascular risk in

patients with diabetes as a multifaceted approach that must include the treatment of dyslipidemia. “We certainly have learned that statins are very effective, but we also know that more intensive treatment of other aspects of the disease—blood pressure, blood sugar, and other areas of lipid therapy in addition to lifestyle changes—all provide an opportunity for benefit. If non-HDL levels are not improving to the same degree that LDL is improving, looking at other treatments is a perfectly valid approach. The FIELD study provides us with strong evidence that the patients with the lowest HDL, perhaps the patients who have had diabetes for a less complicated course without cardiovascular disease, may benefit from this therapy even in the absence of a statin. In the future, the ACCORD trial will help us know the benefits of statins and fibrates together.”

“Statins are the cornerstone of therapy,” remarked Dr. Cusi, who advised practicing clinicians to target triglycerides when they remain above 150 mg/dL and the HDL is not at goal. “Consider additional pharmacological therapy, and if used with caution and good follow-up, I think our patients are going to reap additional benefits. It remains uncertain which is the best combination therapy, but I feel inclined to say that in the absence of head-to-head studies, the current evidence points to fibrate therapy. In that sense, fenofibrate appears to be safer than gemfibrozil. Above all, close follow-up of these patients is needed. We are in a very exciting time, and these guidelines are going to evolve as new trials come out,” he concluded.

Dr. Grundy characterized type 2 diabetes as a high-risk condition for cardiovascular disease, particularly in middle-aged patients as they begin to accumulate clustering of metabolic risk factors. Regarding this patient

population, Dr. Grundy maintained that, “They require attention to all of these risk factors for risk reduction, and certainly the lipids offer the best opportunity right now for reducing risk—both LDL and dyslipidemia.” Blood pressure control is also extremely important, he noted, as are the prevention of microvascular and macrovascular disease. “Lifestyle changes can add additional benefit, and aspirin therapy can reduce thrombotic events. Patients with diabetes deserve a broad approach to reducing their risk, and all of the risk factors need attention,” he stated.

“Those are all excellent comments, and I would like to conclude with a few of my own,” offered Dr. Jones. “I believe everything that has been said during this *Medical Crossfire* favoring statins in a broad range of high-risk patients for the prevention of cardiovascular disease in patients with diabetes clearly fits. The vast majority of clinicians will likely turn to statins for the reduction of first cardiovascular event, as well as recurrent cardiovascular events, in diabetic patients. The FIELD study has given us an option of monotherapy over statins for the patient with diabetes and without cardiovascular disease whose LDL cholesterol may already be at a target range. One group of patients that we all face in clinical practice that may be significant in number is that which is intolerant to statins. While we may want to use statins in most patients, they may not be tolerable at the doses that are most effective, if at all. Perhaps the FIELD study will give us some reassuring evidence that fibrates as monotherapy would be a reasonable option in those patients with diabetes and without manifest cardiovascular disease who are statin intolerant.” ■

REFERENCES

1. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;317:1237-1245.
2. Rubins HB, Robins SJ, Collins D, et al., for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med*. 1999;341:410-418.
3. Steiner G. The Diabetes Atherosclerosis Intervention Study (DAIS): a study conducted in cooperation with the World Health Organization. The DAIS Project Group. *Diabetologia*. 1996;39:1655-1661.
4. The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005;366:1849-1861.
5. Stamler J, Vaccaro O, Neaton JD, et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16:434-444.
6. National Cholesterol Education Program. Third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). NIH Pub. No. 02-5215. Bethesda, MD: National Heart, Lung, and Blood Institute, 2002.
7. Keech AC, Colquhoun D, Best J, et al., for the LIPID study group. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. *Diabetes Care*. 2003;26:2713-2721.
8. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol-lowering with Simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361:2005-2016.
9. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial: Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs. usual care. *JAMA*. 2002;288:2998-3007.
10. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685-696.
11. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*. 2005;28(suppl 1):S1-S36.
12. LaRoza JC, Grundy SM, Waters DD, et al., for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425-1435.
13. Pedersen TR, Faergeman O, Kastelein JJP, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction. The IDEAL Study: a randomized controlled trial. *JAMA*. 2005;294:2437-2445.
14. The BIP Study Group. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. *Circulation*. 2000;102:21-27.
15. Tenenbaum A, Motro M, Fisman EX, et al. Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. *Arch Intern Med*. 2005;165:1154-1160.
16. DAIS Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet*. 2001;357:905-910.
17. Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA*. 1975;231:360-381.
18. Shepherd J, Betteridge J, Van Gaal L; European Consensus Panel. Nicotinic acid in the management of dyslipidaemia associated with diabetes and metabolic syndrome: a position paper developed by a European Consensus Panel. *Curr Med Res Opin*. 2005;21:665-682.
19. Vega GL, Cater NB, Meguro S, et al. Influence of extended-release nicotinic acid on nonesterified fatty acid flux in the metabolic syndrome with atherogenic dyslipidemia. *Am J Cardiol*. 2005;95:1309-1313.
20. Alvarsson M, et al. *Scand J Clin Invest*. 1996;56:563-570.
21. AHA Scientific Statement: Fish consumption, fish oil, omega-3 fatty acids and cardiovascular disease, #71-0241 *Circulation*. 2002;106: 2747-2757.
22. Harris WS. n-3 Fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr*. 1997; 65(5 Suppl): 1645S-1654S.
23. Scott R, Best J, Forder P, et al. Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study: baseline characteristics and short-term effects of fenofibrate. *Cardiovasc Diabetol*. 2005;4:13.
24. The FIELD Study Investigators. The need for a large-scale trial of fibrate therapy in diabetes: the rationale and design of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Cardiovascular Diabetology*. 2004;3:9.
25. Shepherd J. Latebreaking clinical trials, Treat to New Targets Trial. Presented at the American Diabetes Association 65th Scientific Sessions. June 10-14, 2005. San Diego, California.
26. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol*. 2005;95(1):120-122.

Treating Beyond LDL for Additional Reduction in CV Risk

Results from Clinical Trials

CME Test

1. Patients with type 2 diabetes typically have which of the following in their lipid profile?
 - a. high HDL-cholesterol, low triglycerides, and high LDL-cholesterol
 - b. high HDL-cholesterol, high triglycerides, and high LDL-cholesterol
 - c. low HDL-cholesterol, high triglycerides, and LDL-cholesterol that is only slightly elevated but is the small, atherogenic type
 - d. low HDL-cholesterol, low triglycerides, and low LDL-cholesterol
2. What lipid level does the ATP-III recommend clinicians aim for in type 2 diabetes patients?
 - a. Keep triglycerides below 150mg/dL and HDL above 40mg/dL in men and 50mg/dL in women.
 - b. Keep LDL lower than 70mg/dL in all patients.
 - c. Get non-HDL down to 130mg/dL, which usually lowers triglycerides to less than 150mg/dL.
 - d. Treat to get LDL less than 100mg/dL in diabetes patients; in patients with diabetes and CVD, consider lowering LDL to 70mg/dL.
3. Which of the following trials was the first to show a reduction in coronary heart disease with fibrate therapy?
 - a. Helsinki Heart Study
 - b. TNT
 - c. IDEAL
 - d. CARDS
4. Based on the findings from the VA-HIT and Helsinki trials, which patients are most likely to receive the greatest benefit from combination therapy with fibrates?
 - a. patients who are hypercholesterolemic but have no signs of insulin resistance
 - b. high-risk patients with diabetes who also have previous cardiovascular disease
 - c. patients with the metabolic syndrome, hyperinsulinemia, or other evidence of impaired fasting glucose
 - d. patients who have type 2 diabetes but are not hypercholesterolemic
5. Niacin has been shown to do all of the following except
 - a. worsen glucose tolerance.
 - b. suppress free fatty acid release from adipose tissue.
 - c. cause a rebound in free fatty acids.
 - d. decrease LDL-cholesterol particle size.
6. In which case might omega-3 fatty acids be useful?
 - a. a patient with elevated LDL but normal HDL and triglycerides
 - b. a patient with extremely high triglycerides taking fibrates and niacin
 - c. a patient with diabetes whose LDL is being controlled effectively with statins, but whose HDL is too low
 - d. a patient with diabetes and dyslipidemia characterized by moderate elevations in LDL and normal triglycerides who has a high risk of future cardiovascular events
7. The FIELD trial was noteworthy for all of the following except:
 - a. It was the first study to investigate cardiovascular risk reduction with lipid lowering therapy specifically exclusively in patients with diabetes.
 - b. Recommendations for lipids and cardiovascular management changed during the course of the trial and the importance of statin therapy emerged, leading to the incorporation of statin therapy.
 - c. The patient population was at lower risk for cardiovascular events than patients with diabetes included in previous cardiovascular risk reduction studies in diabetics.
 - d. It included younger patients (i.e., below the age of 50 years) who were at high risk for cardiovascular events.
8. What aspect of the FIELD study design makes straightforward analysis difficult?
 - a. the inclusion of both primary and secondary prevention patients
 - b. the dose of fenofibrate used
 - c. the inclusion of a placebo-controlled arm
 - d. the age group studied
9. What did the FIELD study demonstrate with regard to the safety of fibrates?
 - a. Fibrates caused an assortment of adverse events in study patients that led to a high withdrawal rate.
 - b. Patients on fibrate monotherapy had minimal adverse events, but those on combination therapy with a statin reported significantly more adverse events.
 - c. Patients on fibrate monotherapy had significant adverse events.
 - d. Adverse event rates did not differ between patients on fibrate monotherapy and patients on combination therapy with fibrates and statins.
10. What could account for the higher incidence of severe rhabdomyolysis associated with gemfibrozil-statin use as opposed to fenofibrate and statin use?
 - a. rebound of free fatty acids with gemfibrozil
 - b. twice-daily dosing is recommended for gemfibrozil, versus once-daily dosing with fenofibrate
 - c. elevated plasma statin levels due to inhibition of statin glucuronidation with gemfibrozil
 - d. shorter half-life of gemfibrozil versus fenofibrate

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Treating Beyond LDL for Additional Reduction in CV Risk
Results from Clinical Trials

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In order to obtain AMA/PRA category 1 credit(s), participants are required to:

1. Read the learning objectives, review the activity, and complete the self-assessment test.
2. Complete both the activity registration and evaluation forms, and record your answers in the box below.
3. Send the activity registration and evaluation forms to:

UMDNJ–Center for Continuing and Outreach Education
via mail: PO Box 1709, Newark, NJ 07101-1709 or via fax: (973) 972-7128

Self-Assessment Test

Circle the best answer for each question on the CME test.

- | | | | | | | | | | |
|----|---|---|---|---|-----|---|---|---|---|
| 1. | A | B | C | D | 6. | A | B | C | D |
| 2. | A | B | C | D | 7. | A | B | C | D |
| 3. | A | B | C | D | 8. | A | B | C | D |
| 4. | A | B | C | D | 9. | A | B | C | D |
| 5. | A | B | C | D | 10. | A | B | C | D |

(Please print)

First Name _____ MI _____ Last Name _____

Degree _____ Affiliation _____

Specialty _____

Day Phone _____ Evening Phone _____

Fax _____ E-Mail _____

Preferred Mailing Address: Home Business

City _____ State _____ Zip _____

Please select version reviewed: Print monograph [08MC05/JE01] Audio CD [08MC05/JE02]

I certify that I have completed the “Treating Beyond LDL for Additional Reduction in CV Risk: Results from Clinical Trials” activity as designed and I am claiming [up to 1.5 credits] _____ AMA/PRA category 1 credit(s).

Signature _____

Date _____

A continuing education credit letter will be mailed to you within 3 to 4 weeks.

Credit for this activity is available until March 31, 2007.

UMDNJ–Center for Continuing and Outreach Education, PO Box 1709, Newark, NJ 07101-1709
Phone: (973) 972-4267 or (800) 227-4852

Treating Beyond LDL for Additional Reduction in CV Risk

Results from Clinical Trials

Activity Evaluation Form

The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. **Please note: CME credit letters will be issued only upon receipt of a completed evaluation form.** Thank you for your cooperation!

Program Objectives

	Strongly Agree		Strongly Disagree		
Having completed this activity, are you better able to:					
Review the lipid abnormalities in patients with type 2 diabetes.	5	4	3	2	1
Consider the NCEP guidelines related to the prevention of cardiovascular disease in patients with type 2 diabetes.	5	4	3	2	1
Discuss recent clinical data that support NCEP guidelines on combination therapy for lipid management.	5	4	3	2	1
Appraise emerging data that may influence future guidelines on the management of patients at high risk for cardiovascular disease.	5	4	3	2	1

Overall Evaluation

	Strongly Agree		Strongly Disagree		
The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
The information presented will influence how I practice.	5	4	3	2	1
The information presented will help me improve patient care.	5	4	3	2	1
The faculty demonstrated current knowledge of the subject.	5	4	3	2	1
The activity was educationally sound and scientifically balanced.	5	4	3	2	1
The activity avoided commercial bias or influence.	5	4	3	2	1
Overall, the activity met my expectations.	5	4	3	2	1
I would recommend this activity to my colleagues.	5	4	3	2	1

Based on information presented in the program, I will (check one):

- Do nothing, as the content was not convincing
- Change my practice
- Seek additional information on this topic
- Do nothing, as current practice reflects program's recommendations

If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide us with a brief description of how you plan to do so.

Please provide any additional comments pertaining to this activity (positives and negatives) and suggestions for improvement.

Please list any topics that you would like to be addressed in future educational activities.
