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SPECIAL EDITION

Additional Reduction of CV Risk Beyond LDL-C

Applying the Data to Clinical Practice

CME-Certified Activity

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Jointly Sponsored by



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

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



VOL 7 • NO 4 • MARCH 2006



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1. **b.** The FIELD study was conducted in Australia, New Zealand, and Finland and included 9,795 patients between ages 50 and 75 who were not on statin therapy at study entry. The primary outcome was coronary events. The majority of the patients were low-risk—more than 2,000 had previous cardiovascular disease, and about 7,600 did not. The structure of the trial allowed for observations of both short-term and long-term effects with fenofibrate.

Locator: Case Study 1/FIELD Study Design and Treatment Implications

2. **a.** According to Dr. Robertson, in patients without previous cardiovascular events, the primary endpoints of non-fatal MI and also cardiovascular death were reduced. Dr. Cusi noted that additional findings from FIELD were important, including reduction in retinopathy of about 30% and some prevention in progression of microalbuminuria.

Locator: Case Study 1/FIELD Study Design and Treatment Implications

3. **d.** According to Peter Jones, MD, almost 80% of the patients in FIELD had no known cardiovascular disease at baseline. The average patient did not reach the very high-risk category.

Locator: Case Study 1/Gauging Risk in Patients with Type 2 Diabetes

4. **a.** Gemfibrozil increases the level of statin plasma levels, and a limiting factor for prescribing combination therapy in the hypercholesterolemic diabetic is fear of causing myositis. Pharmacokinetic studies have shown that fenofibrate does not increase the levels of statins in which it has been tested.

Locator: Case Study 1/Fibrate Safety

5. **c.** According to Dr. Cusi, the FIELD study included about 3,600 women and showed some differential benefit compared to males, particularly if they were younger than age 65. Total cardiovascular disease, which is not the primary endpoint, had some benefit. It is not strong data because it resulted from a secondary outcome in a subgroup analysis. In the absence of any stronger data, these data may suggest that fibrate therapy would be of benefit to female patients with type 2 diabetes.

Locator: Case Study 2/Treatment Options Beyond Statins

6. **b.** According to Dr. Robertson, bile acid sequestrants in this type of patient may be a successful treatment if LDL rises substantially with fibric acid monotherapy. If niacin were considered, it would be primarily because the patient's glycemic control was good, but their HDL did not change despite the addition of a fibric acid to therapy.

Locator: Case Study 2/Use of Bile Acid Sequestrants in Patients with Type 2 Diabetes

7. **d.** With ezetimibe, the labeling states that the combination of the drug with fibrates is not recommended until use in patients is studied. There is enough anecdotal data to suggest that bile acid sequestrants and fibrates can be used together, but long-term safety data are still being collected. While colesevelam and fenofibrate work well together, the safety of ezetimibe and fibric acids is still being determined.

Locator: Case Study 2/Use of Bile Acid Sequestrants in Patients with Type 2 Diabetes

8. **a.** The bile acid sequestrants cholestyramine and colesevelam both have a tendency to elevate triglycerides. However, this is not usually an issue when used in combination with a fibric acid. There can be a favorable synergy for LDL, HDL, and even triglycerides when these agents are used together.

Locator: Case Study 2/Use of Bile Acid Sequestrants in Patients with Type 2 Diabetes

9. **c.** According to Dr. Robertson, this particular fixed combination is likely of limited use and is perhaps more appropriate in patients without known cardiovascular disease. In this type of patient, the ability to adjust the drugs independently is important. Putting the patient on a moderate dose of statin and then adding a moderate dose of niacin is acceptable, and with demonstrated benefit the patient could be moved to that fixed combination as consolidation therapy.

Locator: Case Study 3/Statin+Niacin Combination

10. **b.** Dr. Ginsberg noted that there may not be a significant difference between an LDL of 70 and 80, therefore it might be appropriate to cut back the statin dose first and then add on fibrate therapy. Dr. Jones added that with the tendency now to use higher doses of statins, he would be quite concerned about using gemfibrozil. He commented that lower doses of statin plus gemfibrozil have been used, but the higher the dose, the more the patient is at risk. Therefore, if the higher statin dose is maintained, he would add fenofibrate, but he agreed with Dr. Ginsberg's point that it might be better to cut back on the statin dose first before adding fenofibrate.

Locator: Case Study 3/Options for Combination Therapy with Maximum-Dose Statins

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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: March 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 key findings from the FIELD study with a focus on the role of fibrate therapy for lipid management in patients with type 2 diabetes without manifest cardiovascular disease.
- Consider the impact of the FIELD study on treatment strategies for patients with type 2 diabetes who are statin intolerant.
- Discuss the implications of the FIELD study in patients with type 2 diabetes who fail to achieve lipid goals despite treatment with a maximal dose of statin monotherapy.
- Review safety considerations associated with using a fibrate or niacin in combination with statin therapy in patients with type 2 diabetes.

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 1.25 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 1.25 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 A. 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. Ginsberg** has received grant/research support from Pfizer Labs and Takeda Pharmaceuticals North America; has served as consultant for AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Merck & Co., Pfizer Labs, Sankyo Pharma, and Takeda Pharmaceuticals North America; and has been a member of the scientific advisory board of Takeda Pharmaceuticals North America.

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 Glaxo-SmithKline Pharmaceuticals.

Dr. Robertson has served as consultant for Abbott Laboratories and Eli Lilly and Co., and has served on the speakers' bureaus of Abbott Laboratories, AstraZeneca Pharmaceuticals, Eli Lilly and Co., 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 Health Products, and Taisho Pharmaceuticals; has served on the speakers' bureaus of Bristol-Myers Squibb, Merck & Co., Pfizer Labs, and sanofi-aventis; and is a member of the scientific advisory boards of Pfizer Labs and Schering-Plough Healthcare Products.

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.

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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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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, much of these data were based on angiographic studies. The recently released Fenofibrate Intervention and 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 end point significant benefits were observed in some secondary endpoints and patient subsets. In this **Medical Crossfire**, a panel of national experts discussed patient case studies that offered the opportunity to explore the potential impact of the FIELD study on future treatment and clinical decisions.

Case Study 1: Type 2 Diabetes in the Absence of CVD

Evidence-Based Approaches to Treatment

Peter H. Jones, MD, the moderator of this **Medical Crossfire**, began by describing the first patient case, a 60-year old male with type 2 diabetes without manifest cardiovascular disease. His LDL cholesterol is 90 mg/dL, he has persistently high triglycerides of around 250 mg/dL, and low HDL cholesterol of 38 mg/dL. The patient's non-HDL cholesterol is 140 mg/dL and he currently takes no lipid lowering treatment. "What are the goals of treatment from a lipid standpoint on this patient?" Dr. Jones asked.

Henry Ginsberg, MD, suggested that one issue that should be dealt with is whether this patient should be on statin therapy and have his LDL lowered. He noted that, based on data extracted from the Heart Protection Study (HPS),⁵ as well as forthcoming data from subgroup analyses of the TNT study,⁶ patients with LDL levels of approximately

90 mg/dL may receive additional benefit from further LDL lowering. Dr. Ginsberg noted that the TNT results are in patients who have had cardiovascular events, and so they might not be relevant to the patient under discussion. For the patient in this current case study, Dr. Ginsberg suggested that, with a non-HDL of 140 mg/dL, statin therapy could be used to lower LDL and consequently non-HDL, with the potential for VLDL lowering as well. Dr. Ginsberg added that some clinicians "believe that statins have other unique effects, and therefore all patients with diabetes should be on a statin regardless of LDL."

Another consideration, Dr. Ginsberg continued, would be to initiate therapy focused on lowering triglycerides and increasing HDL. Specifically, he noted that "This patient has an LDL level below the goal for a patient with diabetes, which would be less than 100 mg/dL. This is not a very high-risk patient with diabetes because there is no prior cardiovascular disease, his HDL is borderline, and he is not hypertensive. The

strategy would then be to focus on triglycerides and HDL.” He pointed out that the guidelines from the National Cholesterol Education Program (NCEP)⁷ do not provide definitive targets for these levels. However, according to guidelines from the American Diabetes Association (ADA),⁸ which recommend that in adults with type 2 diabetes, triglycerides remain below 150 mg/dL and HDL remains above 40 mg/dL, this patient’s triglyceride and HDL levels are both missing their targets. Dr. Ginsberg then reviewed three options for balancing this patient’s lipids without using statins:

- Fibrates would lower triglycerides and raise HDL with no effect on glucose control.
 - Fenofibrate could lower LDL by 5% to 6%.
 - Gemfibrozil could be an alternative choice for monotherapy.
- Niacin is an option in the well-controlled patient with diabetes, if the clinician is willing to modify the treatment if hemoglobin A1c increases.
- Omega-3 fatty acids may lower triglycerides, though with this patient’s triglyceride levels, omega-3 fatty acids would likely not affect HDL.

Dr. Ginsberg then described a third treatment strategy for this type of patient: combination therapy beginning with a statin followed by a reassessment of the patient’s need for further treatment of triglyceride and HDL levels. “If additional treatment is needed, the clinician can select any of the choices that were mentioned above,” he suggested. “There are multiple possibilities for such a patient, even though the lack of head-to-head trials with long term outcomes adds confusion as to what the best approach would be.”

Scott Grundy, MD, PhD, concurred with Dr. Ginsberg’s “thorough overview of the possible treatment approaches,” and added that “If this were my patient, I would look to see if he had other characteristics that might

put him at greater risk. Age, blood pressure, and other factors could all come into play. If I then thought the patient was at high risk, I would likely use a statin as first therapy, as the Heart Protection Study supports the use of a statin. The next question is whether to use monotherapy or combination therapy, and I would likely begin with monotherapy in this patient.” He continued, “The VA-HIT² trial tells us that monotherapy with a fibrate would be beneficial in this type of patient as well, so that would be another viable option.”

“This patient—having diabetes without known cardiovascular disease—would have fit into the population of the CARDS⁹ trial of statin use,” offered Dr. Jones. “Even with the LDL at this level, such patients appear to benefit from statin monotherapy. Still,” he contended, “the high triglycerides and low HDL are a considerable concern and issue.”

“I believe that all people with diabetes are very high-risk patients,” interjected David G. Robertson, MD. This patient’s exact situation was reflected in the FIELD study, which included patients with and without known cardiovascular disease, he noted.

FIELD Study Design and Treatment Implications

Results of the FIELD study were published in *The Lancet* and presented simultaneously at the 2005 American Heart Association Scientific Sessions in Dallas. The panelists noted that the FIELD trial was unique in its patient population, as well as the era in which it was conducted. 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 examined cardiovascular risk reduction in patients with diabetes. In addition, during the time the study was conducted the importance of statin therapy for cardiovascular risk reduction emerged, changing recommendations for lipid and cardiovascular management.¹⁰ Consequently, statin therapy was initiated during the study and may have affected the results.

The FIELD study was conducted in Australia, New Zealand, and Finland and included 9,795 patients between 50 and 75 years of age who were not on statin therapy at study entry. The primary outcome was coronary events. The majority of the patients were low risk—slightly more than 2,000 had previous cardiovascular disease, and approximately 7,600 did not. The structure of the trial allowed for observations of both short- and long-term effects with fenofibrate.¹¹ Before randomization to the fenofibrate or placebo arms, patients had a run-in phase that included a six-week single blind active run-in on 200 mg fenofibrate daily. Compared with the results after randomization, this helped gauge long- and short-term clinical benefits of the treatment's efficacy in modifying different lipid fractions.

"The reduction of both fatal and non-fatal heart attacks in the trial was limited and did not reach statistical significance," reported Dr. Robertson. "However, in patients without previous cardiovascular events, both the primary endpoint of non-fatal myocardial infarction [MI] and also cardiovascular death were reduced. Total cardiovascular endpoints were reduced, and a number of other diabetes endpoints also improved."

He continued, "Based on this evidence, is the magnitude of benefit from statin therapy necessarily greater than the magnitude of benefit from fenofibrate or fibric acid therapy?" Dr. Robertson noted that the data are not clear on this issue.

"We may need to be fairly aggressive in treating patients we consider to be at high risk," added Dr. Jones. The most-recent ATP-III update recommends that some patients may warrant lowering of their LDL to less than 70 mg/dL and their non-HDL cholesterol to less than 100 mg/dL. "Why shouldn't all patients considered at reasonable risk have those kinds of 'optional' goals? And if that is the case, would this gentleman fit as a candidate for statin treatment based on that alone?" he asked.

"Certainly," acknowledged Kenneth Cusi, MD. "Based on available evidence, any starting dose of a statin would likely lower LDL to about 70 mg/dL in someone like our patient with a baseline LDL of 90 mg/dL, which based on available evidence,⁵ would reduce cardiovascular events by about 25%. It is also likely that his triglycerides will drop 10% to 20% to about 200 mg/dL, and his HDL would increase only slightly. But after several office visits, we would still be facing a patient who has risk, and the question arises as to whether this target is sufficient."

Dr. Cusi then compared data from the VA-HIT and FIELD studies. In FIELD, the patients' baseline triglycerides were 150 mg/dL and HDL was 42 mg/dL, "which is what our patient would reach on statin therapy," he asserted. Although we do not have the analysis from FIELD specific for those patients combination therapy regarding cardiovascular events, "it is important to understand that in the FIELD study patients with no prior cardiovascular events and only five years of diabetes had a 25% reduction in coronary heart disease events, and a similar 19% reduction in total cardiovascular events. Extrapolated from this, the patient would clearly benefit," he advised.

He also noted that additional findings from FIELD were important, including reduction in retinopathy of about 30% and some prevention in progression of microalbuminuria. "Investigators could not ascribe these additional results to blood pressure differences or glycemic control differences," Dr. Cusi continued. "We are all eager to look deeper into the details of this, and if it is confirmed that the benefit is due to fibrate therapy, it would also make an additional case to consider fibrates in these types of patients."

Gauging Risk in Patients with Type 2 Diabetes

"Should all patients with diabetes be automatically classified as very high risk?" queried Dr. Jones.

“I would contend that we should give our patients a risk profile and not simply label them all as ‘very high risk;’ doing this will give us more alternatives for therapeutic approaches,” responded Dr. Ginsberg. “A point from the FIELD study that we have not mentioned is that the average patient did not really reach the very high-risk category. The age of the average patient was just over 60. They had several years of diabetes, and many were very well controlled with diet and did not need medication. However, their five-year event rates for the primary endpoint were about 6%, or 1.2% per year. Total cardiovascular disease, which included revascularization, was up at about 2.5% per year. It is important that we start to think outside of the Finnish study and the Norwegian study, which suggest that all patients with diabetes have coronary heart disease equivalency in their risk.^{12,13} We need to look at patients and try to give them a risk profile, not simply label them ‘very high risk’ or ‘high, high risk.’ Such an approach will give us more therapeutic options to choose from.”

“That is an important point,” observed Dr. Jones, adding that almost 80% of the patients in the FIELD study population had no known cardiovascular disease at baseline. “This kind of patient with diabetes may be in the 10% to 20% 10-year risk range provided they are well controlled with other medications.” However, he cautioned, “many patients with diabetes who have manifest cardiovascular disease certainly have undesirable outcomes.”

“In this patient case, I would use a modest dose of a statin to drop LDL a little further, based on findings from the HPS and TNT studies,” remarked Dr. Ginsberg. “A patient with even a moderate risk above optimal would benefit nearly 100% of the time from having their LDL lowered 35% to 40%,” he contended, adding that “Treatment with statins has evolved over time based on data and experience. The safety of statins is well proven, and their efficacy across a broad range of patients is well documented.” The question of whether to add multiple drugs to

“We need to look at patients and try to give them a risk profile, not simply label them ‘very high risk’ or ‘high, high risk.’ Such an approach will give us more therapeutic options to choose from.”

—Dr. Ginsberg

get the LDL to a certain number is “a little less certain. It is unfortunate that the FIELD trial has the confounding aspect of statin drop-in,” he lamented, reminding his colleagues that the FIELD study began before the results of the Heart Protection study indicated that statins should be considered to be a primary treatment for lipid lowering; consequently, some patients in the study began taking statins in the middle of the study.

Offering his thoughts on patient risk profiles, Dr. Cusi remarked, “The patients with diabetes in the FIELD population are not the very high-risk patients with diabetes that we saw in the Scandinavian Simvastatin Survival Study (4S).¹⁴ Compared to earlier clinical trials, patients who participated in FIELD had relatively well controlled blood pressure and an average hemoglobin A_{1c} of 6.9%—both parameters much better controlled than the average patient with diabetes in the United States. In FIELD, fenofibrate provided benefit to a substantial number of patients with more moderate cardiovascular risk, and in particular, those without a prior cardiovascular event. In the coming years I believe we are heading toward background statin therapy for patients with diabetes, and with the moderate-risk patient, possibly adding fibrate therapy for additional benefit.”

Dr. Grundy offered that “the best way to approach a patient with type 2 diabetes who might not be at as high risk as someone with coronary heart disease continues to be a matter of debate. When you have an individual patient sitting in front of you, it is hard to know a patient’s risk without knowing the complete history of the patient. Certainly some will be at high risk; some will be at somewhat lower risk. The question is whether it is prudent to treat the lower risk patient as a high risk patient.”

Beyond Statins: Choices for Balancing Remaining Lipids

Dr. Jones posed another question regarding this patient case: would statins sufficiently balance triglycerides and HDL and achieve

non-HDL cholesterol goals? Acknowledging that “therapeutic lifestyle change could really help this patient’s triglycerides and likely his HDL and his glucose control,” Dr. Jones asked the panel, “If you chose to use statins in this patient and then needed to further lower triglycerides and raise HDL, would niacin, fibrates, or fish oil be your first choice?”

Dr. Robertson noted that knowing the level of glycemic control is a very important factor for making a treatment decision, and more information is needed in this patient case. “Patients tend to benefit from fibric acid therapy whether or not their diabetes is well controlled. In terms of triglycerides, they tend not to benefit from intensification of statins if the diabetes is not well controlled.” He added that “The Helsinki Heart Study¹ and the FIELD study demonstrate that early therapy with a fibric acid offers some benefit.”

“Niacin can be a problem if the diabetes is not currently controlled due to the agent’s effects on lipid metabolism within the liver,” cautioned Dr. Robertson. Based on results from a study performed by Dr. Grundy, niacin also has negative effects on the release of free fatty acids, which are suppressed early in treatment but then rebound later, he reported.¹⁵ However, if the patient’s glucose in this case were extremely well controlled, “considering adding niacin is reasonable. We do not have much outcome data for niacin in diabetes, but the data we do have suggest that the benefits are similar in patients with diabetes to patients without diabetes. The practical issue with niacin in this patient is that the benefits are probably drawn out over several years of follow-up.”

“As for fish oils,” he concluded, “they are moderately effective in improving HDL and are of relatively limited benefit in this patient because they increase LDL while reducing triglycerides without broader benefits for the rest of the lipid profile.”¹⁶

Fibrate Safety

Dr. Jones next proposed a hypothetical situation to the panel. “If you were going to add

a fibrate to this patient's treatment, which fibrate would you choose for efficacy and safety in combination with the statin?"

"A head-to-head study comparing gemfibrozil and fenofibrate would have been ideal for answering that question," Dr. Cusi remarked. "We have only two small studies that demonstrate fenofibrate would be slightly more effective. Therefore, we need better data."

A limiting factor for the primary-care physician is fear of causing more myositis, he explained, and in that regard, "pharmacokinetic studies have shown that fenofibrate does not increase the levels of most statins with which it has been tested. It has been found that gemfibrozil does increase the level of cerivastatin," he noted. "There is also a warning in the package inserts for simvastatin,¹⁷ rosuvastatin,¹⁸ pravastatin,¹⁹ and lovastatin²⁰ and about using them concurrently with gemfibrozil. The evidence that supports the use of fenofibrate in my clinic are the data that the FDA reported for adverse events—the number of cases of rhabdomyolysis are 15-higher with gemfibrozil compared to fenofibrate per number of prescriptions.²¹ As a clinician, I was very glad to see that in the FIELD study, fenofibrate appeared to be very safe in terms of myopathy in nearly 10,000 patients. There was an increase in pancreatitis and a small increase in pulmonary emboli, below 1%. Based on these factors, I usually choose to add fenofibrate to statin therapy when combination therapy is necessary."

Dr. Jones observed that the incidence of rhabdomyolysis with fenofibrate plus statins, when compared to gemfibrozil plus statins, was about 15- to 18-fold lower with fenofibrate. "Whether that is truly an indication of safety is uncertain, but it supports the pharmacokinetic information about the lack of effect on glucuronidation metabolism with fenofibrate when combined with a statin," he explained. Conversely, inhibition of statin glucuronidation occurs when gemfibrozil is combined with statin therapy, causing an

increase in statin plasma levels. The belief that statin plasma levels may be related to myopathy risk would explain the greater incidence of myopathy seen with the gemfibrozil and statin combination.

Dr. Jones then asked Dr. Ginsberg to provide an additional safety perspective on the use of these drugs in combination by relating information from trials in progress.

Beginning with the AIM-HIGH trial, which will study niacin and simvastatin in patients both with and without diabetes, Dr. Ginsberg noted that "The information from the population without diabetes will be more critical in terms of effect on glycemic control and the potential downside of glucose levels and conversion to diabetes in that group. The ACCORD trial, in which I am intimately involved, will not report results for about three and a half years," he commented. "In ACCORD, all patients are on simvastatin, and at the present time 5,500 patients out of a total of 10,000 have been randomized to the sub-study of lipid control with either fenofibrate or placebo in combination with 20 mg or 40 mg of simvastatin. Clinicians may be wondering how gemfibrozil or fenofibrate compare to each other, or how they compare to statin therapy alone. In reality, I think they will more likely be used in combination therapy, and ACCORD will hopefully demonstrate to clinicians whether additional benefits are seen when adding fenofibrate to statin therapy," he claimed.

"But the question regarding the role for combination therapy in addition to fibric acid remains unanswered."

—Dr. Robertson

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 endpoint (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 cross-over 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.

Case Study 2: Type 2 Diabetes with Statin Intolerance

Treatment Options Beyond Statins

Dr. Jones presented the second patient case, which he noted is similar to patients he often sees in his clinical practice. The patient is a 56-year old female with type 2 diabetes, an LDL-cholesterol of 105 mg/dL, triglycerides of 200 mg/dL, and an HDL of 40 mg/dL. Her non-HDL cholesterol is 145 mg/dL, and she has no manifest cardiovascular disease. Her treatment challenge is that she cannot tolerate any of the four statins that her clinician has prescribed, primarily due to muscle ache symptoms. “Many clinicians can relate to this case, because this situation certainly occurs in clinical practice,” he noted. He then asked the panel to discuss statin intolerance, its incidence, and treatment options for this patient.

Dr. Robertson remarked that the incidence of statin intolerance can be difficult to determine in a referral practice. “The frequency is skewed in my practice, but to have a patient referred for this reason is certainly something we see often,” he reported. “In most cases like this, repeated efforts to prescribe statins are usually of little success because even if the patient’s labs look good, her adherence is affected so severely by the perception of muscle aches that statin therapy will essentially be of no help.”

He continued, noting that it would be helpful to have trial results that show the success of other therapeutic agents in this type of patient. Many of the older trials, including all of the gemfibrozil trials, consisted of mostly male patients, “so the fact that the patient in this case is female makes it harder to extrapolate from these trials. Fortunately, based on the studies that have contained both genders, there has never been any suggestion that the benefit of these agents varies based on gender.”

“This case patient,” he pointed out, “is an example of the patients in the FIELD

trial, and based on that trial there is certainly a suggestion that she could benefit from fibric acid therapy. My goal for her therapy would be to have her LDL remain well below 100 mg/dL, her non-HDL be below 100 mg/dL on active treatment, and for her HDL to approach 50 mg/dL.”

Dr. Cusi agreed, while noting that the FIELD study, which included about 3,600 women, showed some differential benefit compared to males, particularly if they were younger than age 65. “Total cardiovascular disease, which was not the primary endpoint, demonstrated some benefit. However, we must recognize that these data are not as strong as we would like them to be because they resulted from a post-hoc subgroup analysis.” Nevertheless, he acknowledged, “in the absence of stronger data, these data may suggest that fibrate therapy would be of benefit. My take-home point for the practitioner in this instance is that it is likely that adding pharmacological therapy would have benefit in this type of patient. More information, such as whether she is a smoker or if she has microalbuminuria, would further help us to evaluate her cardiovascular risk and the possibility of benefit with pharmacological intervention.”

“But the question regarding the role for combination therapy in addition to fibric acid remains unanswered,” pointed out Dr. Robertson. “To treat this patient, I would look at her initial response. If the LDL component rises substantially on fibric acid monotherapy, I have found the use of a bile acid sequestrant in this type of patient to be quite successful. If I was to consider niacin, it would be primarily because her glycemic control was good and her HDL did not increase despite the addition of a fibric acid to her therapy.” He cautioned that another concern is that a small number of patients are intolerant of both statins and fibric acids, although there is no known explanation for the cause of this treatment challenge.

Use of Bile Acid Sequestrants in Patients with Type 2 Diabetes

Dr. Jones remarked that bile acid sequestrants were studied in the Coronary Primary Prevention Trial²² 20 years ago. “We did notice the benefit of lowering LDL with an old form of a bulky bile acid sequestrant, cholestyramine.” He asked the panel, “What is your opinion about the use of bile acid sequestrants in patients with diabetes?”

Dr. Grundy described a study performed in patients with type 2 diabetes using bile acid sequestrants, in which “they got quite a good LDL reduction.²³ Bile acid sequestrants were well tolerated, in contrast to the opinion which some clinicians held that patients with diabetes might not tolerate bile acid sequestrants very well, and the pattern of response was good. Another drug, ezetimibe, could also be used; a combination of this agent and a bile acid sequestrant could lower LDL.”

“I worked with the team that studied that combination,” declared Dr. Jones.²⁴ “We followed patients who were started on one drug, the bile acid sequestrant colesevelam, and then added ezetimibe. We did observe an additive reduction in LDL cholesterol.”

“That certainly is an option,” affirmed Dr. Grundy. “Or, in line with both FIELD and VA-HIT, this patient could be treated with a fibrate only.”

“Regardless of what we do for this type of patient, we do not have a great deal of evidence,” commented Dr. Ginsberg. “In a patient like this, the data are there to support the use of statins, but as we said, she cannot tolerate a statin. We do not have evidence for bile acid binding resins in a patient who starts with an LDL of about 100 mg/dL, and we do not have evidence for the use of ezetimibe or niacin in this case. For fibrates, the Helsinki Heart Study enrolled very few patients with diabetes, and VA-HIT highlighted secondary prevention in men. The FIELD study contained about 35% women; although

we have some data for primary prevention in female patients, the data are soft. The subgroup analyses in FIELD looks at gender, incidence of cardiovascular disease, and total cardiovascular events, but we do not have a subgroup analysis for the primary endpoint of non-fatal MI. Clinicians must therefore treat based on our clinical sense rather than evidence.”

“The FIELD study might be the first to give some suggestion of fibrate monotherapy in the type of patient that has not been looked at very well in clinical trials,” suggested Dr. Jones. He then asked the panel to discuss how they might consider the data on adding a specific bile acid resin like colesevelam or ezetimibe to a fibrate such as fenofibrate, “assuming that fibrate monotherapy would not lower LDL enough.”

“There are enough anecdotal data to suggest these agents can be used together, but long-term safety data are still being collected,” answered Dr. Robertson, noting that colesevelam and fenofibrate work well together. A small published study combined colesevelam and fenofibrate and found them to be quite compatible and effective in lowering the LDL.^{25,26} “The advantage of colesevelam is that it would not interfere with the absorption of most other medications and would not necessarily complicate the treatment of diabetes or other disorders, such as hypertension,” he explained. “Cholestyramine and colesevelam both have a tendency to elevate triglycerides, but in combination with a fibric acid that is usually actually not an issue. My personal experience has been that there can be a favorable synergy for LDL, HDL, and even triglycerides when using colesevelam and fenofibrate in combination.

“The safety of ezetimibe and fibric acids is still being determined,” continued Dr. Robertson. The labeling for ezetimibe presently states that the combination of the drug with fibrates is not recommended until use in patients is studied.²⁷ “Certainly there is

a wide range of experience and a number of trials underway for that combination,” he offered. “The main concern is the issue of lithogenicity of the bile. We know that fibric acids in general do increase the risk of gallstones, particularly with the oldest fibric acids, and that was a significant problem. This is still an issue with gemfibrozil and occasionally with fenofibrate, and ezetimibe does alter the composition of the bile. We do not know how much that combination will aggravate the risk of gallstones,” he concluded.

Dr. Ginsberg pointed out that patients in the FIELD study who took fibrates were found to be at a slightly greater risk of pancreatitis as compared to those on placebo, though the numbers were very small (0.5% vs. 0.8%) “It would be important to learn whether some of those patients had gallstone-induced pancreatitis,” he noted.

“There have been case reports of pancreatitis associated with fibrate use over the past 40 years,” added Dr. Jones. “It is hard to know whether the pancreatitis was due to the drug or due to the hypertriglyceridemia that was being treated,” he speculated, adding that “It is always a very hard thing to determine.”

HDL as Target

Dr. Ginsberg interjected a question of his own into the discussion: what are the implications of HDL in FIELD and VA-HIT, and what can clinicians expect from fibrates in patients with low HDL? “If we put either of our case patients on fenofibrate and there is little change in their HDL, does that mean it is a drug failure?” he posed. “In FIELD, there was a very small change in HDL by the end of the trial—only about 2%. But in VA-HIT, the patients with diabetes demonstrated a 3% rise of 1 mg/dL in HDL, and yet the study showed a very clear benefit both in non-fatal and fatal events. All that said, how does HDL play a role in demonstrating how these drugs work?”

“That is a great point,” remarked Dr. Jones. Acknowledging that “We consider HDL an important target,” he asked his colleagues, “does HDL actually have to increase in order to be a surrogate for whatever benefit the drug has on other aspects of lipid metabolism?” He noted benefits such as changing particle composition, postprandial lipemia, or triglyceride-rich lipoproteins.

“It is difficult to look at results across different sized groups of patients,” he advised. “We started with 2,500 patients in VA-HIT, and added to that 10,000 from FIELD. Now, instead of an average of 10% to 15% increase in HDL seen with fibrates in small groups of patients over short periods of time, these percentages are spread out in large numbers of patients over longer periods of time. There is regression to the mean, and while there may be relatively small changes in HDL, the patient may still see the benefits of the overall effect on lipoprotein metabolism.”

Dr. Cusi relayed his experience in treating a group of 25 patients with fenofibrate and cited improvement in markers of vascular inflammation.²⁸ “We conducted insulin sensitivity tests using the euglycemic hyperinsulinemic clamp technique, which is a gold standard, and examined compositional changes on plasma lipoproteins by nuclear magnetic resonance (NMR) spectroscopy and measured inflammatory markers. There was a trend toward improved insulin sensitivity, but overall it was not statistically significant. However, what we did see, in addition to beneficial plasma lipoprotein compositional changes similar to those seen in the SAFARI study,²⁹ was a significant reduction in markers of vascular inflammation such as CRP, interleukin-6, and intercellular adhesion molecule (ICAM).²⁹ The question is, how much value do we give to improvements in non-traditional markers of cardiovascular disease (i.e., markers of vascular inflammation) in assisting clinical decisions? The answer is, we really do not know,” he concluded.

“Cardiologists are using one-gram doses of omega-3 fatty acids to prevent events like sudden death, and this new study from Japan strengthens the argument for that although I still consider it to be a little soft.”
—Dr. Ginsberg

Case Study 3: Type 2 Diabetes with Documented CVD

Options for Combination Therapy with Maximum-Dose Statins

Dr. Jones shifted the discussion to the third patient case, “which is a 50-year-old man with type 2 diabetes and documented myocardial ischemia.” The patient has persistently high triglycerides of about 200 mg/dL, a low HDL of 38 mg/dL, and an LDL of 72 mg/dL. He is currently taking a maximum dose of a statin, and his non-HDL cholesterol is 112 mg/dL.

Dr. Ginsberg pointed out that this type of patient (as well as the other patient types discussed by the panel) could benefit greatly from therapeutic lifestyle changes. “Let’s assume, for example, that the person has a BMI of 31 or 32, and is not exercising at all. And obviously with a myocardial ischemia he might need some supervision. But if this person could lose 20 pounds and get on an exercise program, and he lowers his triglycerides to 160 mg/dL and his HDL increases to 41 mg/dL, we might be happy with this result.”

In the absence of such improvement, “the decision boils down to what agent do we want to add—niacin or fibrate—and what is the evidence for using one drug over another,” he remarked. “This is further complicated in cases where the patient has coronary heart disease. In this patient, the fibrate versus niacin issue still stands, but if we say for the sake of argument that fibrates are preferred, then the question is which fibrate?”

“My view is that when you use a standard dose of a statin, which this patient was on, and then move up to a high dose, you have exhausted your options,” suggested Dr. Grundy. He mentioned again the three available options—high doses of statins, add a fibrate or add nicotinic acid. Noting the lack of evidenced-based data to help in this decision, including data on potential adverse effects of high dose statin therapy plus fibrate therapy, Dr. Grundy suggested that he would encourage aggressive lifestyle intervention in this patient.

Dr. Ginsberg suggested an alternative approach. “I have had patients with horrible lipid profiles and a lot of disease, and I put them on 80 mg of atorvastatin or simvastatin plus a fibrate. I was within the odds of 1 in 100 or 1 in 200 risk of myositis, but none developed. Still, since I am not sure there is a difference between an LDL of 70 mg/dL and an LDL of 80 mg/dL, I would feel much more comfortable cutting back the statin dose first. If you cut back the statin dose to 40 mg, and if this is an average patient, his LDL is only going to go up to the high 70s mg/dL. Would you feel more comfortable about adding a fibrate then?”

“I probably would,” agreed Dr. Grundy.

“With the tendency now to use higher doses of statins, I would be quite concerned about using gemfibrozil,” acknowledged Dr. Jones. Lower doses of statin plus gemfibrozil have been used, but the higher the statin dose, the greater the risk to the patient. “Therefore, with a higher dose of statin, fenofibrate may be a safer choice, but I do also agree with the strategy of cutting back on the statin dose and adding fenofibrate.”

Statin+Niacin Combination

“We have an FDA-approved combination of a statin and niacin,” offered Dr. Jones. “How does the panel feel about using such a formulation in a patient like this?”

“That particular fixed combination is probably going to be of limited use and is perhaps more appropriate in patients without known cardiovascular disease,” answered Dr. Robertson “In this type of patient, you want to be able to adjust the drugs independently. It is fine to put the patient on a moderate dose of statin and then add a moderate dose of niacin. With demonstrated benefit, if you wanted to persist, you could move the patient to that fixed combination as resolution and consolidation therapy. However, this patient is clearly on high dose statin at 80 mg, and you cannot mimic such treatment

with the fixed combination. You could have him on a more moderate dose of 40 mg of lovastatin, but that would be a marked reduction. Other fixed combinations may be more appropriate.”

Omega-3 Fatty Acids

Dr. Jones presented a final question to the panel. “Would omega-3 fatty acids added onto the maximal dose statin in this patient with documented myocardial ischemia be helpful?”

Dr. Ginsberg cited evidence from the GISSI study, which showed benefit for patients with diabetes with coronary disease with the use of omega-3 fatty acids.³⁰ “There was approximately a 14% reduction in cardiovascular mortality. There is also a Japanese primary prevention trial, JELIS, that was recently presented at the American Heart Association.³¹ In that study there was a 19% reduction in major cardiovascular events in patients on pravastatin, most of whom had not had a prior event. The JELIS results did not quite fit with the GISSI trial because it was non-fatal MIs that were reduced, not sudden death as had been the case in GISSI.” Dr. Ginsberg noted that he does not put all his patients on the standard dose of one gram of omega-3s, and tends to use it mainly to treat very high triglycerides. “It is time to reassess this issue,” he pronounced. “Cardiologists are using one-gram doses of omega-3 fatty acids to prevent events like sudden death, and this new study from Japan strengthens the argument for that although I still consider it to be a little soft and would not use it. In this patient it would have very little effect on the HDL, and I consider it to be a separate category of cardiovascular prevention, rather than lipid lowering.”

Dr. Jones agreed and added that one gram of EPA/DHA omega-3 fatty acids usually does not have much effect on triglycerides. “The JELIS study used two grams of EPA and DHA, which is getting closer to something that might have a triglyceride lowering effect.”³¹

Final Thoughts

In offering a concluding message from this *Medical Crossfire*, Dr. Robertson highlighted the importance of focusing on the patient with diabetes and their overall risk for cardiovascular disease. “In our treatments we want to impact all aspects of the disease, including hypertension, hyperglycemia, and dyslipidemia. Statins are the cornerstone of lipid lowering therapy. If there are still isolated areas of risk that do not seem to be responding to the statin, we have a much greater awareness of opportunities to consider alternative therapies. The issues of the impact on outcomes, the efficacy of the drug therapies on lipid parameters, and most importantly the safety of these treatments have been explored widely, and the FIELD study adds to our experience there.”

“For the practicing clinician, I think the message is that we are treating unique patients with unique constellations of cardiovascular risk factors, and we have guidelines that can be applied to those individual patients,” remarked Dr. Cusi. “At the moment, we do not have definitive data on what to add to statin therapy to maximize the cardiovascular risk reduction. We are waiting on head-to-head studies, but results will not be available for years. Aggressive lipid lowering is extremely important in improving the cardiovascular risk of our patients. Factors such as behavior modification, glycemic control, HDL, and blood pressure are going to make a big impact on our patients, and the key issue is to follow-up closely.”

Dr. Ginsberg agreed that statin use is the mainstay of therapy and is “likely indicated in 90% to 95% of patients who present with diabetes, and is certainly indicated for secondary prevention. For primary prevention,

the large majority of patients with LDLs over 100 mg/dL will still clearly benefit. As for what to do with the triglyceride and HDL issue, the data are much less clear.” Dr. Ginsberg continued, “Overall, fibrates have potentially demonstrated somewhere between 10% and 25% reduction in monotherapy trials. As for how much more reduction can be achieved when adding a fibrate to a statin, that will remain unknown until results of the ACCORD trial are available. If a patient has a very low HDL below 35 mg/dL and a triglyceride well over 200 mg/dL, there is a good indication that there is benefit from lowering those levels, and fibrates are somewhat ahead of niacin at this point.”

Dr. Grundy summarized his perspective by noting that although clinicians tend to focus on glucose problems in diabetes patients, “we also have to recognize that most of these patients are going to die of cardiovascular disease. Prevention of vascular disease must therefore be a very high priority in therapy, and that means treating all the risk factors. We have some recent evidence to suggest that reducing glucose levels further will prevent cardiovascular disease. That is good news if it can be confirmed, and it looks promising. Blood pressure, cholesterol, and the prothrombotic state that patients with diabetes exhibit should all be targets of treatment,” he contended. “LDL lowering with statins in combination with other lipid lowering drugs such as fibrate if appropriate, is likely a good idea. Controlling and reducing blood pressure to even lower levels is important, as is the use of aspirin therapy to reduce thrombosis. If we do all of those things and incorporate lifestyle changes, we ought to see a substantial reduction in vascular risk in these patients,” he concluded. ■

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Additional Reduction of CV Risk Beyond LDL-C

Applying the Data to Clinical Practice

CME Test

- Which of the following statements about the FIELD study is *not* accurate:
 - The study was structured to observe both short-term and long-term effects of fenofibrate.
 - Most patients were on statin therapy at the start of the study.
 - A proportion of patients who participated in the study had no prior history of cardiovascular disease.
 - The primary outcome measure for the study was coronary heart disease events.
- In the FIELD study, fenofibrate had a beneficial effect on each of the following except
 - decrease in blood pressure.
 - total CHD events in patients without a prior history of cardiovascular disease.
 - rate of retinopathy.
 - progression of microalbuminuria.
- Approximately what percentage of patients in the FIELD study did not have a history of cardiovascular disease at the start of the study?
 - 20%
 - 40%
 - 60%
 - 80%
- Which agent is known to increase the statin plasma levels in combination therapy, potentially leading to serious side effects?
 - gemfibrozil
 - niacin
 - fenofibrate
 - fish oils
- Subgroup analysis in the FIELD study revealed a differential benefit for women versus men in which endpoint?
 - fatal and non-fatal MI
 - glucose control
 - total cardiovascular disease
 - cardiovascular death
- Which agent may be a good alternative for a statin-intolerant hypercholesterolemic patient with diabetes, elevated LDL, and who does not respond to fibrates?
 - probucol
 - bile acid sequestrant
 - omega-3 fatty acids
 - low-dose statins
- What does the ezetimibe label mention regarding its use in combination with fibrates?
 - The combination is available in a formulation with gemfibrozil.
 - The combination is contraindicated in type 2 diabetes patients.
 - The combination is effective for lowering LDL.
 - The combination is not recommended until use in patients is studied.
- Cholestyramine and colestevlam both have a tendency to elevate which lipid?
 - triglycerides
 - HDL
 - LDL
 - non-HDL
- Which statement about use of a fixed formulation of statin plus niacin in patients with type 2 diabetes and a history of cardiovascular disease is most accurate?
 - It is effective only in patients that require high doses of statins.
 - It is particularly effective in patients with known cardiovascular disease.
 - It is appropriate to use as consolidation therapy after starting a patient on a moderate of dose of statin and adding a moderate dose of niacin.
 - The formulation is not effective in these patients.
- Appropriate therapy for a patient with type 2 diabetes currently on maximum dose of statin therapy with LDL of 72 mg/dL but persistently high TGs and low HDL might be to
 - switch to a lower dose of another statin.
 - add fibrate therapy and consider reducing the statin dose to minimize safety concerns.
 - switch to the maximum dose of another statin and add fibrate therapy.
 - decrease the statin dose and add ezetimibe.

University of Medicine & Dentistry of New Jersey
Center for Continuing and Outreach Education
and
Medical Crossfire/Liberty Communications Network

Additional Reduction of CV Risk Beyond LDL-C
Applying the Data to Clinical Practice

Registration Form

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/JE03] Audio CD [08MC05/JE04]

I certify that I have completed the “Additional Reduction of CV Risk Beyond LDL-C: Applying the Data to Clinical Practice” activity as designed and I am claiming [up to 1.25 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

University of Medicine & Dentistry of New Jersey
Center for Continuing and Outreach Education

Additional Reduction of CV Risk Beyond LDL-C

Applying the Data to Clinical Practice

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 key findings from the FIELD study with a focus on the role of fibrate therapy for lipid management in patients with type 2 diabetes without manifest cardiovascular disease. 5 4 3 2 1

Consider the impact of the FIELD study on treatment strategies for patients with type 2 diabetes who are statin intolerant. 5 4 3 2 1

Discuss the implications of the FIELD study in patients with type 2 diabetes who fail to achieve lipid goals despite treatment with a maximal dose of statin monotherapy. 5 4 3 2 1

Review safety considerations associated with using a fibrate or niacin in combination with statin therapy in patients with type 2 diabetes. 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.