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SPECIAL EDITION

Managing Dyslipidemia and Global Risk in Patients with Type 2 Diabetes and Insulin Resistance

The Role of Triglycerides and HDL Cholesterol

CME-Certified Activity

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Jointly Sponsored by



Release Date: May 2005 • **Expiration Date:** June 30, 2006

This activity is supported by an educational grant from Takeda Pharmaceuticals North America.



VOL 6 • NO 7 • MAY 2005



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Managing Dyslipidemia and Global Risk in Patients with Type 2 Diabetes and Insulin Resistance

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Educational Overview

Cardiovascular disease (CVD) is the major cause of both morbidity and mortality in patients with diabetes. Increasingly, clinicians have become aware of a similar link between pre-diabetes, insulin resistance, and CVD. Patients with type 2 diabetes and insulin resistance are at risk for a characteristic dyslipidemia and other metabolic and vascular abnormalities that contribute to the substantial increase in CVD risk.

Treatment of dyslipidemia has an established benefit—both for patients with diabetes and those at significant risk for CVD (as in patients with the metabolic syndrome, pre-diabetes and insulin resistance). Lowering of LDL cholesterol has a clear benefit and has been stressed in clinical guidelines. Additionally, data suggest that elevated triglyceride levels and low levels of HDL-cholesterol play a critical role in the development of CVD. Furthermore, managing these aspects of the dyslipidemia of diabetes and insulin resistance has emerged as a critical component of care.

Through debate and authoritative peer exchange, this activity, conducted in conjunction with the University of Medicine & Dentistry of New Jersey, will confront issues associated with the management of complex dyslipidemia and global risk of CVD in patients with type 2 diabetes and insulin resistance.

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 randomized clinical trials, current guidelines, and the clinical practice experience of the participating panelists.

Target Audience

This educational activity is designed for cardiologists, endocrinologists/diabetologists, primary-care physicians and other health care professionals interested in or involved with the management of patients with type 2 diabetes and insulin resistance.

Learning Objectives

- Review current evidence supporting the role of high triglycerides and low HDL cholesterol levels in CVD risk for patients with diabetes and insulin resistance.
- Discuss the cluster of metabolic and vascular abnormalities that contribute to cardiovascular disease in patients with insulin resistance.
- Recognize the role of therapies that target HDL-C, triglycerides, and the complex dyslipidemia of diabetes in managing the high-risk patient.
- Describe the treatment options available for the management of HDL-C and triglycerides, including both nonpharmacologic and pharmacologic approaches.
- Discuss the potential mechanisms of action of specific pharmacologic agents used to alter HDL-C and triglycerides, safety considerations, appropriate role of combination therapy, and the ongoing clinical trials evaluating such treatments.

Method of Instruction

Participants should read the learning objectives and review the activity 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 1.75 hours.

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This activity was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by John B. Kostis, MD; Adam L. Palance, MD; and Apurva Shah, MD.

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Dr. Kendall has received grant/research support from Abbott Laboratories, Aventis Pharmaceuticals, Amylin Pharmaceuticals, Eli Lilly and Co., GlaxoSmithKline Pharmaceuticals, Lifescan, Medtronic-Minimed, Merck & Co., Inc., Novartis Pharmaceuticals Corp., Novo Nordisk, Pfizer Labs, Ross, Takeda Pharmaceuticals North America, and Therasense; has served on the advisory boards of Aventis Pharmaceuticals, Amylin Pharmaceuticals, Eli Lilly and Co., Pfizer Labs, and Takeda Pharmaceuticals North America; has been a consultant for Amylin Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Co., Lifescan, Pfizer Labs, Ross, and Takeda Pharmaceuticals North America; and has served on the speakers' bureaus of Amylin Pharmaceuticals, Aventis Pharmaceuticals, Eli Lilly and Co., GlaxoSmithKline Pharmaceuticals, Merck & Co., Inc., Novo Nordisk, Pfizer Labs, and Takeda Pharmaceuticals North America.

Dr. Kostis has received grant/research support from Pfizer Labs; has been a consultant for Berlex Laboratories, Forest Laboratories, Pfizer Labs, Sankyo Pharma, Schering-Plough Corp., and Taisho Pharmaceuticals Co.; and has served on the speakers' bureaus of AstraZeneca Pharmaceuticals, Aventis Pharmaceutical, Bristol-Myers Squibb, Merck & Co., Inc. Pfizer Labs, and Sankyo Pharma.

Dr. Masoudi has been a consultant for Takeda Pharmaceuticals North America; and has served on the speakers' bureaus of AstraZeneca Pharmaceuticals, Pfizer Labs, and Takeda Pharmaceuticals North America.

Dr. Palance and **Dr. Shah** have no financial arrangements or affiliations to disclose.

Dr. Plutzky has received grant/research support from GlaxoSmithKline Pharmaceuticals and Takeda Pharmaceuticals North America; has been a consultant for Abbott Laboratories, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, GlaxoSmithKline Pharmaceuticals, Laboratories Fournier, Merck & Co., Inc., Novo Nordisk, and Takeda Pharmaceuticals North America; and has served on the speakers' bureaus of AstraZeneca Pharmaceuticals, GlaxoSmithKline Pharmaceuticals, Merck & Co., Inc., and Takeda Pharmaceuticals North America.

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Managing Dyslipidemia and Global Risk in Patients with Type 2 Diabetes and Insulin Resistance

The Role of Triglycerides and HDL Cholesterol

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Patients with type 2 diabetes mellitus have a high risk of developing cardiovascular disease,¹ with abnormal lipid profiles placing them at even greater risk.² Dyslipidemia, markers of atherosclerosis and inflammation, and a procoagulant state may also precede the onset of hyperglycemia. Overall, these patients have a 2- to 3-fold increased risk of cardiovascular disease as compared with normoglycemic patients.³ In particular, triglycerides have been identified as an independent risk factor for coronary artery disease, and it is now increasingly recognized that hypertriglyceridemia should be treated aggressively. “Managing dyslipidemia and global risk in patients with type 2 diabetes and insulin resistance is one of the principal challenges faced by cardiologists, endocrinologists, and diabetologists,” noted David M. Kendall, MD. To shed light on this important clinical challenge, Dr. Kendall moderated the following exchange among a multidisciplinary panel of experts.

The Relationship Between Insulin Resistance and Cardiovascular Disease

The importance of controlling LDL, especially in high-risk patients such as those with diabetes, is well established. However, evidence demonstrates that other factors, such as HDL and triglyceride levels, may play a profound role in getting these patients to goal and reducing the risk of cardiovascular disease.^{4,5}

To begin this *Medical Crossfire* exchange, Dr. Kendall asked his colleagues how the role of triglycerides and the relationship between lipid disorders, central obesity, insulin resistance and diabetes might be best described.

Henry Ginsberg, MD attempted to offer a concise explanation to this complicated relationship by noting that, “It all starts with insulin resistance. Although we do not really know the underlying molecular basis of insulin resistance in terms of genetics, we do know that it is associated with what I would call ‘a disorder of energy balance and an inability to store energy in an effective way.’

This inability to store fat properly in subcutaneous adipose tissue then leads to the storage of fat elsewhere—in the muscle, liver, plasma as triglyceride, and central fat.” He continued, “Together, these factors lead to insulin resistance in those tissues and organs. When the liver has excess fat in it, it tries to unload that fat by putting out very low density lipoprotein carrying that fat, the triglyceride, into the bloodstream. So you see, there is obesity, the hepatic steatosis, and high plasma triglycerides. The latter is followed by low HDL and abnormal LDL.” Seeking to clarify the role of diabetes in this context, Dr. Ginsberg noted, “certainly diabetes is the next step from the insulin resistance syndrome, with a concomitant and somehow interrelated failure of the beta cells, lack of insulin and then hyperglycemia.”

Requesting that the panel further elucidate this point, Dr. Kendall asked, “Is there a relationship between glucose control and cardiovascular outcomes in patients with diabetes?”

“We do not have an outcome study that defines the cardiovascular risk in diabetes as mitigated by changes in glycemic control,” reported John B. Buse, MD, PhD. He noted, however, that major studies such as the Diabetes Control and Complications Trial Research Group (DCCT) study,⁶ as well as the UK Prospective Diabetes Study (UKPDS), suggest there is a trend towards improvement in cardiovascular outcomes when blood glucose is well controlled. He added that results from the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) study “will robustly address this issue by comparing patients whose blood glycated hemoglobin (HbA_{1c}) were less than 6.0 versus patients with an HbA_{1c} of between 7.0 and 7.9.”

Data from the ACCORD study include 10,000 patients with type 2 diabetes, and are expected to be reported in 2010. Researchers anticipate the study will break new ground with risk-reduction therapy in diabetes, and shed light on outcomes versus safety.

Frederick A. Masoudi, MD, MSPH agreed with his colleague, and emphasized the importance of glucose control in terms of reducing risk of microvascular events, “which are essential to control in diabetic patients.”

“UKPDS also suggests that technique may depend as much as target on cardiovascular outcomes and how far to lower glucose,” remarked Dr. Buse. Referring again to UKPDS, which examined more than 4,000 subjects, he cited evidence showing that metformin was associated with greater improvement in cardiovascular risk than sulfonylureas in a subgroup of overweight diabetic patients.⁷

Confirming that “epidemiologic data in diabetes support that glucose plays a role,” Dr. Kendall asked the panel to discuss data that suggest cardiovascular risk is associated with abnormalities of glucose metabolism in patients with prediabetes. “Is cardiovascular risk associated with hyperglycemia in patients with impaired fasting glucose, or impaired glucose tolerance?” he queried.

Jorge Plutzky, MD, responded that there are some studies that suggest a very strong relationship between glucose levels themselves and cardiovascular events. “The DECODE study [Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe],” he offered, “suggests that a two-hour glucose tolerance test after a challenge is a more sensitive predictor of future cardiovascular events.”⁸ He also cited the Norfolk cohort of European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk) study, which shows evidence of HbA_{1c} being predictive of future cardiovascular risk.⁹ “These data may translate into also predicting risk in patients with impaired fasting glucose, impaired glucose tolerance and abnormal responses,” he concluded.

The DECODE study developed 5- and 10-year risk scores for cardiovascular mortality that include glucose concentrations as well as known diabetes status. The study found that, in men, for both 5- and 10-year cardiovascular mortality, fasting and two-hour glucose and fasting glucose alone, among other risk factors, were significantly associated with cardiovascular mortality. EPIC-Norfolk examined the value of HbA_{1c} concentration as a predictor of death from cardiovascular and all causes in men. The study found that HbA_{1c} seems to explain most of the excess mortality risk of diabetes in men and to be a continuous risk factor through the population distribution.

Dr. Ginsberg discussed the evolution of the theory that insulin resistance was linked to CVD by stating that “evidence of a relationship stems back from the 1970s and 1980s. Several population studies showed that the level of insulin was an independent predictor of cardiovascular outcomes, although each study missed major risk factors in their measurements.”¹⁰⁻¹² He added, “the best data that we have now comes from the Insulin Resistance Atherosclerosis Study (IRAS).”¹³ This study found that established diabetes and fasting glucose level were each

independently associated with intimal-medial wall thickening of the common carotid artery, suggesting that chronic hyperglycemia may lead to increased risk of atherosclerosis.

Dr. Ginsberg further noted that insulin resistance is associated with high triglycerides, low HDL cholesterol, hypertension, hypercoagulability, and inflammation. Because of this, he concluded, “to identify the role of insulin resistance itself as a unique predictor becomes nearly impossible.”

Some of the more sensitive markers of atherosclerosis, such as carotid intimal-medial thickness, may be associated with the metabolic syndrome. Blood pressure also has a significant amplifying effect on intimal-medial thickness. “I wonder whether we are not limited to some extent by the sensitivity of the measures that we are using, whether they are for insulin resistance or for atherosclerosis,” pondered Dr. Plutzky.

“In the setting of diabetes, there is very little evidence to demonstrate that insulin resistance adds to the risk associated with diabetes itself,” offered Dr. Buse. “Virtually all patients with diabetes are insulin resistant, so they cannot be compared to the less-insulin-resistant patients very well. Some of the data suggest that the risk associated with diabetes is higher than the risk associated with metabolic syndrome. One such example is the WISE study.” The Women’s Ischemia Syndrome Evaluation (WISE) found that in women with suspected myocardial ischemia, the prevalence of angiographically significant coronary artery disease increases in a gradient manner across the continuum of metabolic status from normal, to the metabolic syndrome, to diabetes.¹⁴

Diabetic Dyslipidemia

Having discussed the overarching relationship between insulin resistance and cardiovascular disease, Dr. Kendall asked, “What are the characteristics of lipid disorders in patients with diabetes and with insulin resistance?”

Dr. Plutzky began by describing levels typically seen in those patients who “present with LDL levels that are not particularly high and who often will have elevated triglycerides and lower HDL levels.” He added that one intriguing aspect of the typical lipid profile is that “LDL may be more atherogenic or more prone to oxidation or uptake.” The impact of LDL cholesterol was seen in the Heart Protection Study, a large trial that showed that lowering LDL cholesterol has an impact on outcome.¹⁵

Dr. Ginsberg continued Dr. Plutzky’s description of these patients’ LDL cholesterol particles. “It is important to remember that these patients have small LDL, which means they have more LDL particles for any cholesterol concentration.” LDL particles become small and dense in the dyslipidemic patient. This increases the likelihood that the LDL particles will adhere to and invade the arterial wall, and also makes them more liable to oxidation,¹⁶ “which suggests that LDL cholesterol should be reduced more aggressively in those patients in order to reduce the number of particles,” he stated.

“Cardiovascular risk associated with LDL is obviously clear, but the dyslipidemia seems more complex than that,” posed Dr. Kendall. “What potential impact may we have in going beyond targeting LDL and addressing HDL cholesterol and triglycerides?”

“By reducing the number of triglyceride-carrying lipoproteins, there will be fewer particles to penetrate the arterial wall,” explained Dr. Ginsberg. He added that several human and animal models have shown that “very low density lipoproteins (VLDL) penetrate the artery wall and are atherogenic.” In addition, “lowering fasting triglycerides reduces postprandial triglycerides, because chylomicrons and VLDL compete for the same removal pathways.” This is important, he noted, because “postprandial hypertriglyceridemia has been shown to be a predictor of outcomes in a number of studies.”¹⁷ Dr. Ginsberg further described the

impact of lowering triglycerides, which almost always raises HDL, “and we know that raising HDL is an important predictor of good outcomes. The mechanism behind this is predictably less clear, but the potential impact is broad and multifaceted. We think HDL moves cholesterol out of the artery wall and macrophages and takes it back to the liver. HDL also has antioxidant properties and affects smooth muscle cell proliferation.”

“Let’s focus on triglycerides for a moment,” requested Dr. Kendall, in noting the importance of Dr. Ginsberg’s points. “What is the role of triglycerides in global cardiovascular risk in patients both with diabetes and insulin resistance?”

“Some studies have suggested that triglycerides may be an independent risk factor,” stated Dr. Plutzky. He pointed out The Copenhagen City Heart Study¹⁸ as well as a meta-analysis by Austin that found that increased triglycerides are associated with a 14% and 34% increase in cardiovascular disease risk in men and women, respectively.¹⁹

“It has always been very hard to pinpoint the impact of triglycerides because in research analyses, we are always controlling for multivariate risk,” he admitted. “Triglyceride levels themselves are quite predictive in essentially every study. In the Framingham Heart Study, triglycerides were more predictive than LDL in postmenopausal women.”²⁰

Dr. Plutzky noted, however, that when controlling for other risk factors, “that relationship weakens or disappears, and the relationship with HDL may be part of that. At the same time, every risk factor seems to change triglycerides.” He concluded by suggesting that the contrary viewpoint “may be that one of the issues with those other risk factors is that they raise triglycerides.”

Dr. Buse agreed with Dr. Plutzky’s point that “it is clearly true that triglyceride levels in diabetes patients are an independent risk factor, more so than in the general population.” From a clinical perspective, he acknowledged “it is another area we can address in trying to improve cardiovascular risk.”

“It is clearly true that triglyceride levels in diabetes patients are an independent risk factor, more so than in the general population.”

—Dr. Buse

Managing Dyslipidemia in Insulin Resistant Patients

Nonpharmacologic Therapies

Moving ahead to treatment approaches in this high-risk patient group, Dr. Kendall remarked, “We can control dyslipidemia with both nonpharmacologic and pharmacologic therapies. What can we hope to achieve with nonpharmacologic therapies, specifically with regard to HDL and triglycerides?”

Dr. Buse verbalized strategies for controlling dyslipidemia through lifestyle modification, which “certainly has been shown to have an effect on the lipid profiles.”²¹ He noted that controlling diet has been associated with reductions in triglycerides, “specifically when patients convert from processed carbohydrates to more whole grains and eliminate foods with high fructose corn syrup. Alcohol certainly has an effect on increasing triglycerides, but also HDL. Substituting mono-unsaturated fats for saturated fats has been shown to improve the dyslipidemia in diabetes.” Exercise and resistance training have effects on HDL, he reported, as well as “smoking cessation, which has an effect on HDL and perhaps triglycerides. Weight loss is probably the most impactful lifestyle intervention.”²²

Seconding this point, Dr. Ginsberg offered, “Caloric intake is the centerpiece of any physiologic nonpharmacologic approach for elevated triglycerides. When patients take in fewer calories than they burn, triglycerides begin to fall and HDL begins to rise. Clinicians and dietitians should focus more on caloric intake and less on the composition of the diet in this population,” he suggested.

Dr. Masoudi agreed with his colleagues, but added a caveat that is familiar to practicing physicians. “We would all recommend that our patients adhere to a relatively low caloric diet, increase their exercise, and stop smoking,” he said. “But it is much more difficult to attain targets in clinical practice than in the context of clinical trials that have

shown these effects on lipids. This again brings up the issue of addressing the risk through other mechanisms.”

Dr. Buse agreed. “Historically we have put an emphasis on lifestyle changes to manage LDL, but often, we never achieve those targets. However, there is a greater potential to do this with triglycerides and HDL.”

“Eating less and exercising more is certainly background therapy, and is definitely important,” summarized Dr. Kendall.

Niacin

During the next section, the panel focused on agents for treating HDL and triglycerides. “We will assume that statin therapy will be used in a majority of these high-risk patients,” stated Dr. Kendall. “With this in mind, I would like to focus on agents that can be used in combination with a statin. What effects might niacin have on the lipid profile, and how does it work?”

“If you look across the board at niacin’s effect, it is probably the most efficacious of lipid-altering agents,” remarked Dr. Ginsberg. He then detailed niacin’s beneficial effects on lipids, noting that “it decreases triglycerides and LDL cholesterol, and it raises HDL.” While niacin’s exact mechanism of action may not be known, “niacin may reduce triglyceride synthesis in the liver or it may reduce the liver’s ability to remove APO-A1, the very important structural protein on an HDL from the circulation.”

Dr. Plutzky supported this view by mentioning data from the Coronary Drug Project, where “patients in the niacin arm exhibited a statistically significant lower incidence of definite, non-fatal myocardial infarction (MI) than the placebo group.”²³ In the 15-year follow up, a statistically significant mortality benefit was demonstrated that still exists. “This supports the use of it,” he concluded. In the patient group randomized to niacin, there were 69 (11%) fewer deaths as compared to the placebo group.²⁴

“What do the data or clinical experiences tell us about using niacin in combination with statin therapy to improve outcomes in such patient populations?” asked Dr. Kendall.

“The data with combination therapy are quite limited,” lamented Dr. Plutzky. “There are issues in real-world use that we encounter quite often, especially in patients with diabetes.” Offering experience from his own lipid clinic, where he emphasized that there are support systems in place, Dr. Plutzky noted, “we often have very good success with using niacin.” However, he specified that patients are preselected before embarking upon a trial of this agent, and “only patients who are willing to be careful, remain compliant, tolerate some initial symptoms, and report any issues are most likely to succeed. Outside of such an experienced environment, there are real challenges with the use of niacin in everyday practice.”

Commenting on potential adverse effects associated with niacin, Dr. Buse pointed out that “with all patients, there is a concern about flushing as well as liver function test abnormalities or uric acid.” He added that “there has been a lot of concern about the effects of niacin on glucose,” an issue of concern to the physician treating patients with diabetes. In fact, he related that up until approximately three years ago, “most clinicians would have believed that niacin was contraindicated in diabetes patients. Since that time, clinicians have gained substantial experience in managing lipids in patients with diabetes, and now use it at modest doses. Instead of the 3 g doses of niacin that had been used previously,” he explained, “clinicians prescribe 500 mg or 1,000 mg, which provides clinical benefit by modifying HDL and triglycerides without much change in glucose.” He stated that results from two clinical trials—ADMIT with immediate release niacin and ADVENT with extended release niacin—“suggest that moderate doses of niacin caused only minimal changes in glucose.”

“In my practice, we more often use niacin as third-line therapy because it does have more symptomatology attached with it,” offered Dr. Buse, acknowledging that although niacin has more monitoring issues and less outcomes data, “it is a very useful lipid-modifying agent.”

Agreeing with his colleagues, Dr. Ginsberg stated that, if it was not for the adverse effects of niacin, “it would be an extremely potent and widely used drug.” Adding to the comments of Dr. Buse and Dr. Plutzky, Dr. Ginsberg offered two distinct scenarios. “It is problematic to use niacin in some patients with metabolic syndrome.” This difficulty is demonstrated in a situation where, “if niacin were used in a patient with diabetes whose glucose control then worsened, the glycemic agents could be modulated to aid in management. However, if a patient with a fasting blood sugar of 110 were to go to 150, while there is improvement to the lipid profile, the addition of new agents and possibility of new diagnosis and insurance issues is a major consideration. While the latter of these situations may not offer a complete contraindication for the use of niacin, the possibility of these complications should be kept in mind, and if they occur, the patient should be taken off the drug.”

Fibrates

“How do fibrates affect lipid metabolism, and what effects are seen both on a cellular level and clinically?” asked Dr. Kendall.

“Fibrates are PPAR-alpha agents, and lipid effects occur via the pathway that turns on genes which affect the synthesis of APO-A1,” explained Dr. Ginsberg. He clarified the

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—Dr. Ginsberg

mechanism of action further by reporting that, “in vivo, fibrates are associated with a rise in APO-A1 levels in the plasma along with HDL cholesterol because the liver is putting out more APO-A1. They are very effective in lowering triglycerides, and this is associated with an increase of oxidation of fat in the liver. The liver unloads its fat by putting out LDL and triglycerides, but it can also burn the fat and oxidize it. Although this does not typically occur, in the presence of a fibrate that pathway might be improved and lower levels of triglycerides would be released.”

“Which effect predominates physiologically with fibrates?” queried Dr. Kendall.

“The data indicate that they occur simultaneously, and whenever triglycerides fall there is an increase in HDL from separate reactions in the plasma,” answered Dr. Ginsberg. “It is important to note that fenofibrate has a beneficial effect in general on LDL, whereas the effects of gemfibrozil are much more variable.”²⁵ Explaining that this is the primary difference between the two agents, he added, “the triglyceride and HDL effects are probably similar.”

“We often see pleiotropic effects—other effects that may not be directly related to the effects on lipid metabolism,” observed Dr. Kendall. “What data are there on the pleiotropic effects of fibrates?”

Dr. Plutzky addressed this issue by explaining the agents’ genetic pathway through binding to PPARs, “which are nuclear receptors and members of the steroid hormone nuclear receptor family.” He went on to describe that when the receptors are activated, “they become transcription factors, which raises the possibility of regulation of an en-

tire cassette of genes through PPARs.” Evidence from many research groups shows PPAR-alpha is expressed in various cell types throughout the vasculature and inflammatory cells like endothelial cells, smooth muscle cells, macrophages and lymphocytes, and regulates pathways that are involved in atherosclerosis as well as inflammation. This establishes the strong possibility of “fibrate effects on inflammation and on atherosclerosis, and forms a basis for impact outside of its effects on the liver and skeletal muscle.” He noted that there may also be effects beyond the lipids that could alter factors such as cholesterol efflux, cytokine production, or C-reactive protein (CRP) production. “Effects have also been shown on coagulation proteins like tissue factor adhesion molecules,” he explained, concluding that “there is a whole host of effects that may be part of the benefits of fibrates.”

Dr. Ginsberg directed the panel’s attention to data from the Veteran Administration HDL Intervention Trial (VA-HIT), “where multivariate analyses to predict the importance of lipid changes did not produce much impact.” In VA-HIT, which studied gemfibrozil’s benefits in reducing cardiovascular risk in men, about 25% of the benefit came from lipid changes. Dr. Ginsberg added that in a later subgroup analysis, which showed that the patients with diabetes had the greatest benefit in VA-HIT, “there was no rise in HDL in those patients, therefore, other non-lipid effects of fibrates may be much more potent.”²⁶

“VA-HIT suggested a significant decrease in cardiovascular events with gemfibrozil treatment, stated Dr. Masoudi. “It demonstrated a 22% reduction in events and was associated with a 6% increase in HDL cholesterol levels. In addition, the Diabetes Atherosclerosis Intervention Study (DAIS) studied fenofibrate therapy in addition to statins in patients with diabetes and demonstrated that fenofibrate decreases progression of coronary atherosclerosis.”²⁷

“What data support that glucose lowering, in and of itself, will improve the lipid profile in patients with diabetes?”

—Dr. Kendall

Dr. Ginsberg forecasted the importance of the upcoming results from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study, which will be presented in 2006. He discussed the trial, which includes nearly 10,000 patients with diabetes randomized to either fenofibrate or placebo. “The results of this trial could make or break the fibrates,” he declared. “The trial is expected to have the power needed to “address the questions and vagaries from prior studies regarding patients with LDL elevations only, and not patients with the metabolic syndrome.” The FIELD Study is expected to show benefit from fibrates and also to provide primary prevention data, “which is something that VA-HIT did not address,” he added.

“What are the safety concerns when using statin-fibrate combinations?” asked Dr. Kendall.

“One issue with both fibrates and statins is muscle aches, myositis, and myopathy,” replied Dr. Buse. “There has also been great concern about the issue of rhabdomyolysis, particularly since cerivastatin was withdrawn from the market because as many as 1 in 200 patients exposed to that combination could develop serious muscle injury.”²⁸

“More recent analyses have suggested that the risk in combining fibrates with statins is quite low,” Dr. Buse reported. “The risk is lower with fenofibrate than with gemfibrozil probably due to differences in the way that the two agents are metabolized.”²⁸

Dr. Ginsberg presented his experience as an investigator in the ongoing ACCORD trial, and stated, “one of the reasons we chose fenofibrate was that this agent does not interfere with the metabolism of the statins. It does not raise blood levels as gemfibrozil does, and we hypothesize that the statin blood level is linked mechanistically to risk of myositis.”

“With the separate data sets that support LDL lowering and fibrate use and its potential impact on outcomes, clinicians are going to have to face this question head on,”

stated Dr. Kendall. He asked the panel for their views regarding glucose elevations and lowering, and the potential impact on cardiovascular risk. He asked, “What data support that glucose lowering, in and of itself, will improve the lipid profile in patients with diabetes?”

Dr. Ginsberg began by debunking the myth that “hypertriglyceridemia in patients with diabetes is just an outcome of hyperglycemia.” With the knowledge that has been gained about insulin resistance, he contended, “we know that the metabolic syndrome precedes diabetes and that triglyceride levels are already elevated, so we can put that myth to rest.”

Commenting on the relationship between glucose control and triglycerides, he stated, “there is definitely a link. If a patient has very high triglycerides, for example over 500 or 600 mg/dL, and very high HbA_{1C}, there will be an improvement when the glucose is treated. The typical patient may have an HbA_{1C} of 7 to 8 or 8 to 9 with a triglyceride of 300. If the glucose is kept below 7, the maximum reduction in triglycerides will fall between 10% to 15%. This is a significant reduction, but it will not fall much lower than that. HDL, on the other hand, tends not to be altered in any significant manner as glucose control improves.”

“Will simply targeting insulin resistance specifically improve the dyslipidemia in this population?” asked Dr. Kendall.

“No,” responded Dr. Buse. “It is much more complicated than that. Targeting insulin resistance will not improve lipids any better than if you did not target insulin resistance. This also specifically relates to the lipid effects of particular drugs.” He developed this point by describing varying effects from the available insulin-sensitizing agents. “Sulfonylureas are very effective glucose lowering drugs, but have virtually no effect on any lipid parameter,” he noted. “Metformin, an equivalently effective glucose lowering agent that has effects on insulin

sensitivity in the liver, at least has some minimal effects on LDL, HDL and triglycerides, though these are all very, very small benefits on average. The thiazolidinediones (i.e., pioglitazone and rosiglitazone), he continued, “both improve HDL and LDL particle size, but have differential effects on triglycerides and LDL particle number.”

Thiazolidinediones

Picking up on Dr. Buse’s comments regarding the thiazolidinediones (TZDs), or glitazones, Dr. Kendall noted that, “Pioglitazone and rosiglitazone, which are commonly utilized agents for insulin resistance, are PPAR-gamma agonists. What might PPAR-gamma activation do to HDL and triglycerides?”

Dr. Ginsberg explained that it was previously believed that “all TZDs worked by sensitizing fat cells, which causes the cells to retain their fat and produce less fatty acids for the liver to process, thereby decreasing the level of triglycerides the liver produces to unload those fats. The liver would also become more sensitive to insulin, causing APO-B, the protein on VLDL, to be degraded, and less VLDL to be produced. This would in turn lead to increasing HDL levels.”

“Although it was once thought that both TZDs affected lipids the same way, this is no longer the case,” continued Dr. Ginsberg. In a head-to-head study, pioglitazone showed a more favorable effect on triglyceride and LDL levels in patients with type 2 diabetes than rosiglitazone.²⁹ Though both agents exert their effects on PPAR-gamma, “there are obviously other mechanisms involved with the regulation of lipid levels.”

He added that the different TZD effects led him to do a study on pioglitazone’s effects on triglycerides, which has recently concluded and is pending publication. “As expected, triglycerides dropped about 25% with pioglitazone in a small group of patients selected for hypertriglyceridemia with diabetes,” he stated. “However, and to our surprise, pioglitazone’s effects were not related to less

VLDL coming out of the liver, but rather, better clearance from the plasma, or better lipolysis.” He reiterated that “The fact that with rosiglitazone, triglycerides do not fall but HDL goes up fairly significantly indicates that, there definitely appear to be other mechanisms at work. The direct effects of insulin resistance on the regulation of HDL levels may also be the reason behind why HDL is low in many diabetics whose triglycerides are not high.”

“What about pleiotropic effects of PPAR-gamma, independent of PPAR-alpha?” asked Dr. Kendall.

“It is possible that the ways molecules interact with these nuclear receptors may dictate different transcriptional responses,” offered Dr. Plutzky. “As with PPAR-alpha, PPAR-gamma is expressed throughout the vasculature or inflammatory cells, which sets the stage for pleiotropic effects on atherosclerosis.”

Dr. Ginsberg proposed that the data on how glitazones raise HDL demonstrate a possible independence from the changes in triglycerides, and “suggest the HDL effect may be additive to a fibrate, which would not be competing for the same pathway.”

Dr. Plutzky emphasized that “the studies so far on patients given TZDs and fibrates in combination have been very limited, and results may be dictated by which fibrate and/or which TZD is used.”

Dr. Buse remarked that results from the PROactive Study will provide “some much-needed cardiovascular outcome data with a glitazone.” A design paper for the study was published in *Diabetes Care*, and the study will be presented in at the European Association for the Study of Diabetes (EASD) meeting in Greece.³⁰ “There are a number of small studies that have looked at intermediate outcomes,” he continued, “such as rate of progression of atherosclerotic lesions after stent placement. These kinds of things suggest the glitazones have had some benefit. Also more studies showing differences in

lipids between pioglitazone and rosiglitazone are coming out.”

Dr. Kendall turned the conversation to safety considerations. “As with statins and fibrates, we are often asked by our colleagues about the safety issues surrounding these newer classes of medications,” he said. “Are there safety considerations that clinicians need to be mindful of with TZDs as well?”

Dr. Masoudi pointed out that weight gain is one such issue, but added that this is an issue that is “perhaps misunderstood by many clinicians. Weight gain may represent a redistribution of fat from visceral to subcutaneous storage, which may actually be beneficial,” he explained.

“Fluid retention is another issue, and it relates to weight gain as well,” continued Dr. Masoudi. “The fluid retention with TZD therapy is multifactorial, and when it does occur it is dose-dependent.” He maintained that the degree to which TZDs cause an increase in plasma volume is modest, amounting to “less than 2 cc’s per kilogram of body weight.” There are many other potential mechanisms whereby this might occur, he suggested, “such as increased vascular permeability with increased VEG-F expression or increased interstitial ion transport. It is mechanistically complicated and is not related to heart failure. Fluid retention also tends to occur relatively early in treatment and is clearly synergistic with insulin.”

“My personal practice is to always discuss these issues up front with the patient,” remarked Dr. Buse. “I will even show them how to check for pretibial edema and ask them to do that every evening so they can catch it early before anasarca develops.” Starting patients with the lowest dose and adding calcium as well as advising that they avoid heavy salt intake is also suggested, he advised. “If edema evolves, it is important the patients understand how important the glitazones are to managing their diabetes, so that they adhere to treatment.”

Citing data from his Medicare analysis, Dr. Masoudi remarked that “TZDs are widely used in patients with heart failure.³¹ TZDs are not contraindicated in patients with New York Heart Association class I or II symptoms³² and are not contraindicated in patients with left ventricular systolic dysfunction.” He noted that an observational study found a relationship between the use of TZDs and lower mortality in patients with heart failure and diabetes.³³ “Although this is an observational study, it suggests that concerns about heart failure and TZD use may be somewhat exaggerated.”

Insulin Sensitizers in Prediabetes. Turning the discussion to patients with pre-diabetes, Dr. Kendall asked, “What about using insulin sensitizing therapies in this patient population?”

Explaining that there are no data outside of animal data showing that TZDs reduce the rate of disease progression, Dr. Buse cautioned that “it is premature to do this kind of therapy in pre-diabetes.” Some effects with the no longer available troglitazone were demonstrated, he acknowledged, but “we will need to wait for the outcome studies that are underway on preventing diabetes with glitazones.”

“We have to stick with accepted indications for now,” concurred Dr. Plutzky, speculating that “some of the best promise of the class may be in these earlier stages.” He maintained that cardiologists are often “getting into the game very late in a process that takes years or even decades,” and therefore emphasized that cardiologists must remain focused on getting data in patients with pre-diabetes, especially “given some of the suggestions we have had, such as TZDs in women with gestational diabetes. Changing rates of conversion to diabetes may be quite important, particularly before a cardiovascular event has occurred.”

Dr. Ginsberg interjected the point that what is called the metabolic syndrome or the

insulin resistance syndrome “does not equate to impaired glucose tolerance. The data for pioglitazone and rosiglitazone that will come out in the future will be for impaired glucose tolerance, and although we know the conversion risk for that population to full diabetes, we do not have the conversion rates for metabolic syndrome to impaired glucose tolerance or diabetes.” Dr. Ginsberg noted that if the studies with pioglitazone and rosiglitazone were to indicate positive results for the prevention of diabetes, such an outcome may result in new indications. He cautioned, however, that “to move beyond that and take in as many or more people who qualify under criteria set by a panel for the metabolic syndrome would be dangerous.”

“The next step back would not be to jump to the metabolic syndrome but instead, to go after impaired glucose tolerance,” agreed Dr. Plutzky. “From there we will need better predictors of who is headed for diabetes or cardiovascular events.”

“The advantage of doing a glucose tolerance test in this population is that roughly half of the patients who are tested are likely to have diabetes,” suggested Dr. Buse. “So aggressive treatment with a glitazone is a legitimate strategy.”

Weighing the Issues and Devising a Comprehensive Strategy

Asking the panel to consider all the individual factors in diabetes patients with cardiovascular disease or significant cardiovascular risk—glucose, lipids, insulin resistance, and hypertension, Dr. Kendall queried, “How do we address the comprehensive or global risk? Where do we begin and what are the goals?”

“The first step should be achieving the right LDL level,” declared Dr. Plutzky. “There are many agents available, including combination therapy, that can get patients to goal. Step two would be to get triglycerides and HDL to their targets.” He reiterated the importance of identifying other components

that may be contributing factors to the triglycerides, such as excluding secondary factors that increase triglycerides, such as hypothyroidism, undiagnosed or untreated diabetes, drug effects, alcohol intake, and watching the diet. “Then, in patients whose triglycerides are high and HDL is low, combination therapy can be applied where appropriate in high-risk patients.”

“Sometimes cardiologists do not focus quite as much on the details of the diabetes management,” observed Dr. Buse, noting that, “insulin is a very effective triglyceride-lowering drug.^{34,35} Using insulin and pioglitazone may help meet the treatment goals with triglycerides and HDL and eliminate the need to go to additional lipid lowering drugs to achieve the targets.”

“That brings up the interesting question about patients controlled on statins,” stated Dr. Ginsberg. Patients with diabetes often need more lipid control, as their triglycerides remain elevated and HDL remains too low after statin therapy. “The question then becomes, do you add fibrate or do you add a TZD, considering the triglyceride effect of the some agents within the latter class?” he posed. It will be interesting to see results from the PROactive study as to the type of HDL increase achieved with pioglitazone in a large population. If pioglitazone is shown to be more efficacious than a fibrate, I would certainly start to lean towards it rather than fibrates in that setting.”

“Therapy obviously needs to be individualized, but it is important to emphasize the high risk of patients with diabetes who are treated to LDL goals with statins and the high residual risk,” cautioned Dr. Masoudi. “Obviously, we need to address issues of diabetes control but we also need to manage lipids in this very high-risk population.”

“Do those issues that we discussed in managing lipids in patients with diabetes apply to those with prediabetes as well?” asked Dr. Kendall.

“I would say no,” answered Dr. Buse. “We do not have the same kind of data in pa-

tients with prediabetes, who are a somewhat lower risk population. The guidelines would suggest that clinicians should be using the Framingham risk calculator to make decisions about what the LDL targets actually were. As clinicians, we do not deal with them in the same way we do in patients with diabetes, but it should be recognized that prediabetes patients are at higher risk than if they did not have prediabetes.”

Returning to the strategy of combination therapy, Dr. Kendall asked the panel to discuss how to decide which combination to use for their patients. “How do you decide to use combination therapies for glucose lowering that may also have lipid effects?” he asked.

“It is best to decide that on a case-by-case basis,” replied Dr. Ginsberg, who recommended that clinicians “focus on secondary prevention by lowering LDL levels and then treating other components of dyslipidemia plus or minus glucose.” He added that in the insulin-resistant nondiabetic with triglycerides over 150 and HDL below 40 in males or below 50 in females, “one should consider another agent. Clinicians typically go to fibrates but, as we discussed, there is the potential to use niacin or a TZD in the patient with diabetes.”

“Given the numerous medications required for these patients, what drug-drug interactions should we be concerned about?” asked Dr. Kendall.

“Drug-drug interactions pose a substantial issue,” confirmed Dr. Masoudi. A study of the Medicare population³⁶ found that “patients with diabetes and cardiovascular disease are being treated with huge numbers of medications.” The inappropriate use of some agents should be discontinued, “such as nonsteroidal agents and non-dihydropyridine calcium channel blockers,” he noted. “The other issue is that practitioners generally do a poor job of calibrating treatment with risk. A recent study found that patients with the highest risk were ironically least likely to be treated with a statin. This was seen more often in the elderly population.”³⁷

“Practitioners generally do a poor job of calibrating treatment with risk. A recent study found that patients with the highest risk were ironically least likely to be treated with a statin.”

—Dr. Masoudi

Future Directions

“What can we expect to see in the future regarding the best treatment strategies for these patients?” asked Dr. Kendall.

“One area in which we really need more information is on LDL particle number versus LDL concentration,” noted Dr. Buse. “Clinicians routinely underestimate the atherogenicity of LDL in the setting of diabetes and metabolic syndrome. The question is, do we treat to lower LDL in all patients as much as it can be reduced, or can we determine a better technique of measuring LDL-associated risk?”

Dr. Ginsberg added to this point by mentioning the NCEP’s attempt to introduce non-HDL cholesterol. “It is not exactly to-the-point, but it does take into account that when triglyceride levels rise above 200, a lot of cholesterol is being carried to those atherogenic particles. Indirectly, it takes into account that when triglycerides are above 200, LDL is smaller and cholesterol-depleted. The non-HDL target takes some of that into account. There is also a movement to raise awareness of APO-B levels and encourage more physicians to measure it.”

“That would actually be simpler than measuring non-HDL,” confirmed Dr. Buse.

Dr. Plutzky noted that “it is one of the markers that better stratify risk. Those markers would help identify which patients out of the prediabetes population would need more aggressive intervention.”

“Results from the PROactive study, which is in a high-risk population, will be available later in 2005 and may have a great influence on how we approach cardiovascular risk and diabetes,” continued Dr. Plutzky. “The CRP lowering we see with the TZDs rivals, if not exceeds, what we have seen with statins. Within that trial we will also see the tolerability in terms of edema and weight gain, which may help us better understand the settings in which we can use TZDs in patients with increased cardiovascular risk.”

Final Thoughts

In offering his final thoughts for this *Medical Crossfire*, Dr. Ginsberg stated that “Statin therapy should be the first step, and will significantly reduce relative risk and absolute risk in these patients,” adding that diabetic patients have much higher absolute risk and that “they will continue to have more events than nondiabetics receiving similar statin therapy. Although this occurs for many reasons, certainly low HDL levels, high triglycerides, and other lipoprotein abnormalities play an important role. We have to consider that, look at those patients, and be more aggressive with the other lipids and lipoproteins.”

Dr. Plutzky reiterated the importance of future data from ongoing clinical trials that will further address the possibility of treating diabetes earlier in its natural history. “It is exciting that the PPARs give us a way to aggressively chase risk in patients with diabetes or with early forms of it,” asserted Dr. Plutzky.

Dr. Buse emphasized that lipids, blood pressure, and the pro-thrombotic state of diabetes should absolutely be controlled in patients with clinical cardiovascular risk or multiple risk markers. “It’s tougher to reach the goal of HbA_{1C} less than 7 in many patients. But if that is artfully done, it can actually improve other parameters as well.”

“Clinicians need to realize that treating LDL levels is not enough in terms of reducing the global risk of cardiovascular events,” asserted Dr. Masoudi. “This brings our attention to assessing other markers of risk and potentially treating those other markers of risk. I am looking forward to the evidence that will support that treatment. Lastly,” he concluded, “calibrating treatment to risk, identifying the highest risk patients, and treating the highest-risk patients aggressively needs to be reflected more frequently in current practice.” ■

REFERENCES

1. Garber AJ. Attenuating cardiovascular risk factors in patients with type 2 diabetes. *Am Fam Physician*. 2000;62:2633-2642, 2645-2646.
2. Garber AJ. Implications of cardiovascular risk in patients with type 2 diabetes who have abnormal lipid profiles: is lower enough? *Diabetes Obes Metab*. 2000;2:263-270.
3. Goldberg RB. Hyperlipidemia and cardiovascular risk factors in patients with type 2 diabetes. *Am J Manag Care*. 2000;6:5682-5691.
4. Brewer HB Jr. Hypertriglyceridemia: changes in the plasma lipoproteins associated with an increased risk of cardiovascular disease. *Am J Cardiol*. 1999;83:3F-12F.
5. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;105:3143-3421.
6. The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *NEJM*. 1993;329:977-986.
7. UKPDS 34. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. UKPDS Study Group. *Lancet* 1998;352:854-865.
8. Balkau B, Hu G, Qiao Q, et al. Prediction of the risk of cardiovascular mortality using a score that includes glucose as a risk factor. The DECODE Study. *Diabetologia*. 2004;47(12):2118-2128.
9. Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). *BMJ*. 2001;322(7277):15-18.
10. Welborn TA, Wearne K. Coronary heart disease incidence and cardiovascular mortality in Busseton with reference to glucose and insulin concentrations. *Diabetes Care* 1979;2:154-160.
11. Pyorala K. Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: results from two population studies in Finland. *Diabetes Care*. 1979;2(2):131-141.
12. Duimetiere P, Eschwege E, Papoz G, et al. Relationship of plasma insulin to the incidence of myocardial infarction and coronary heart disease mortality in a middle-aged population. *Diabetologia*. 1980;19:205-210.
13. Wagenknecht LE, D'Agostino R Jr, Savage PJ, et al. Duration of diabetes and carotid wall thickness. The Insulin Resistance Atherosclerosis Study (IRAS). *Stroke*. 1997;28(5):999-1005.
14. Marroquin OC, Kip KE, Kelley DE, et al. Metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women: a report from the Women's Ischemia Syndrome Evaluation. *Circulation*. 2004;109(6):714-721.
15. Collins R, Armitage J, Parish S, et al, for the Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomized placebo-controlled trial. *Lancet*. 2003;361(9374):2005-2016.
16. Krentz AJ. Lipoprotein abnormalities and their consequences for patients with type 2 diabetes. *Diabetes Obes Metab*. 2003;5 Suppl 1:S19-S27.
17. Ginsberg HN, Illingworth DR. Postprandial dyslipidemia: an atherogenic disorder common in patients with diabetes mellitus. *Am J Cardiol*. 2001;88(6A):9H-15H.
18. Friberg J, Scharling H, Gadsboll N, et al. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (The Copenhagen City Heart Study). *Am J Cardiol*. 2004;94(7):889-894.
19. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol*. 1998;81:7B-12B.
20. Murabito JM, Yang Q, Fox C, et al. Heritability of age at natural menopause in the Framingham Heart Study. *J Clin Endocrinol Metab*. 2005;10:1210.
21. Scheen AJ. Management of the metabolic syndrome. *Minerva Endocrinol*. 2004;29:31-45.
22. Mobley CC. Lifestyle interventions for "diabesity": the state of the science. *Compend Contin Educ Dent*. 2004;25:207-8, 211-2, 214-8; quiz 220.
23. Berge KG, Canner PL. Coronary drug project: experience with niacin. Coronary Drug Project Research Group. *Eur J Clin Pharmacol*. 1991;40 Suppl 1:S49-S51.
24. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986; 8(6):1245-1255.
25. Packard KA, Backes JM, Lenz TL, et al. Comparison of gemfibrozil and fenofibrate in patients with dyslipidemic coronary heart disease. *Pharmacotherapy*. 2002;22(12):1527-1532.
26. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med*. 1999;341:410-418.
27. Effect of fenofibrate on progression of coronary-artery disease in Type 2 diabetes: The Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet* 2001;357(9260):905-910.
28. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate plus statin versus gemfibrozil plus any statin. *Am J Cardiol*. 2005;95(1):120-122.
29. Peters Harmel AL, Kendall DM, Buse JB, et al. Impact of adjunctive thiazolidinedione therapy on blood lipid levels and glycemic control in patients with type 2 diabetes. *Curr Med Res Opin*. 2004;20:215-223.
30. Charbonnel B, Dormandy J, Erdmann E, et al. The prospective pioglitazone clinical trial in macrovascular events (PROactive): can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5238 patients. *Diabetes Care*. 2004;27:1647-1653.
31. Masoudi FA, Wang Y, Inzucchi SE et al. Metformin and thiazolidinedione use in Medicare patients with heart failure. *JAMA*. 2003;290:81-85.
32. The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co;1994:253-256.
33. Masoudi FA, Inzucchi SE, Wang Y et al. Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation* 2005;111:583-590.
34. Mesotten D, Swinnen JV, Vanderhoydonc F, et al. Contribution of circulating lipids to the improved outcome of critical illness by glycemic control with intensive insulin therapy. *J Clin Endocrinol Metab*. 2004;89(1):219-226.
35. Henry RR, Gumbiner B, Ditzler T, et al. Intensive conventional insulin therapy for type II diabetes. Metabolic effects during a 6-mo outpatient trial. *Diabetes Care*. 1993;16(1):21-31.
36. Abstract presented at AHA in 2004: Masoudi FA, Baillie C, Wang Y, et al. The burden of polypharmacy in older persons hospitalized with heart failure. *Circulation*. 2004;III-817.
37. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. *JAMA*. 2004;291:1864-1870.

Managing Dyslipidemia and Global Risk in Patients with Type 2 Diabetes and Insulin Resistance

The Role of Triglycerides and HDL Cholesterol

CME TEST

1. Which of the following best describes the relationship between glucose control and cardiovascular risk in patients with diabetes, as demonstrated by current evidence?
 - a. Some studies, such as the DCCT and UKPDS, suggest a risk in diabetes as mitigated by changes in glycemic control, but future studies will be needed to provide greater clarification.
 - b. The relationship between glucose control and cardiovascular outcomes has been well defined through a number of studies, including UKPDS and DCCT.
 - c. The relationship between glucose control and cardiovascular outcomes is well defined only in patients with an HbA_{1c} of 7.0 to 7.9.
 - d. No trials have as yet confirmed that there is a relationship between glucose control and cardiovascular outcomes.
2. LDL cholesterol particles in the typical insulin resistant patient who is also dyslipidemic are typically characterized as
 - a. being large and buoyant.
 - b. being small and dense.
 - c. having fewer LDL particles for any cholesterol concentration.
 - d. having fewer triglyceride-carrying lipoproteins.
3. Which of the following best describes the role of triglycerides in the global risk of patients with both diabetes and dyslipidemia?
 - a. Triglyceride levels are more of an independent risk factor of cardiovascular disease in diabetes patients than in the general population.
 - b. There is no evidence to suggest that triglycerides are an independent risk factor.
 - a. Triglycerides have been proven to be an independent risk factor only in postmenopausal women.
 - d. Triglycerides levels are a risk factor only when concurrent with low LDL levels.
4. Which nonpharmacologic intervention exerts the greatest impact on triglyceride levels?
 - a. Eliminating processed foods from the diet
 - b. Smoking cessation
 - c. Increasing exercise
 - d. Weight loss
5. In combination with a statin, the use of niacin in the diabetic dyslipidemic patient is characterized by which of the following statements?
 - a. Niacin's effects on glucose make it contraindicated in diabetes patients.
 - b. Niacin effectively regulates lipids in dyslipidemic diabetes patients at moderate doses that do not significantly affect glucose levels.
 - c. Niacin should only be used in patients with the metabolic syndrome.
 - d. Niacin is not efficacious in regulating lipids in patients with diabetes and insulin resistance.
6. Which of the following is a pleiotropic effect seen with fibrates?
 - a. No pleiotropic effects have been positively determined.
 - b. Decrease of oxidation of fat from the liver
 - c. A rise in APO-A1 levels
 - d. Decrease in HDL cholesterol
7. Which of the following describes the appropriate use of insulin sensitizing agents in prediabetes patients?
 - a. There is no role for insulin sensitizing agents in this patient group.
 - b. Clinical trials now in progress will define the place of insulin sensitizing agents in prediabetes.
 - c. Insulin sensitizing agents should be given to all patients with prediabetes.
 - d. Patients with prediabetes are not at high risk for cardiovascular events.
8. According to the panel, which should be the first step in addressing the global risk of cardiovascular disease in insulin-resistant patients?
 - a. Increase HDL first if <40 in males or <50 in females.
 - b. Begin reducing triglycerides and HDL first, then pursue LDL targets.
 - c. First achieve target LDL levels, then pursue triglycerides and HDL.
 - d. Focus only on glucose targets.
9. According to the panel, what is the best way to decide which combination therapies to use for glucose lowering that may also have lipid effects?
 - a. Use any combination except those containing niacin in diabetes patients.
 - b. Continue to use fibrates, which is the therapy clinicians use most often.
 - c. Start with a fibrate and statin combination and then switch to a TZD.
 - d. Decide on a case-by-case basis.
10. Which of the following most accurately describes the issue of drug-drug interactions when treating diabetes patients with dyslipidemia?
 - a. Drug-drug interactions do not pose a significant problem.
 - b. Drug-drug interactions pose a significant problem, and practitioners need to better calibrate treatment with risk.
 - c. Drug-drug interactions only pose a problem in patients also taking ACE inhibitors.
 - d. Patients taking statins are at the lowest risk for developing drug-drug problems.

University of Medicine & Dentistry of New Jersey
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**Managing Dyslipidemia and Global Risk in Patients
with Type 2 Diabetes and Insulin Resistance**

The Role of Triglycerides and HDL Cholesterol

Registration Form

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

1. Read the learning objectives, review the activity, and print out 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 video 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 _____

I certify that I have completed the “Managing Dyslipidemia and Global Risk in Patients with Type 2 Diabetes and Insulin Resistance: The Role of Triglycerides and HDL Cholesterol” activity as designed and I am claiming [up to 1.75 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 June 30, 2006.

UMDNJ–Center for Continuing and Outreach Education, PO Box 1709, Newark, NJ 07101-1709
Phone: (973) 972-4267 or (800) 227-4852 CE Activity Code: 05MR40/JE01(B)

Managing Dyslipidemia and Global Risk in Patients with Type 2 Diabetes and Insulin Resistance

The Role of Triglycerides and HDL Cholesterol

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

Having completed this activity, are you better able to:

	Strongly Agree			Strongly Disagree		
Review current evidence supporting the role of high triglycerides and low HDL cholesterol levels in CVD risk for patients with diabetes and insulin resistance.	5	4	3	2	1	
Discuss the cluster of metabolic and vascular abnormalities that contribute to cardiovascular disease in patients with insulin resistance.	5	4	3	2	1	
Recognize the role of therapies that target HDL-C, triglycerides, and the complex dyslipidemia of diabetes in managing the high-risk patient.	5	4	3	2	1	
Describe the treatment options available for the management of HDL-C and triglycerides, including both nonpharmacologic and pharmacologic approaches.	5	4	3	2	1	
Discuss the potential mechanisms of action of specific pharmacologic agents used to alter HDL-C and triglycerides, safety considerations, appropriate role of combination therapy, and the ongoing clinical trials evaluating such treatments.	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	

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.

1. a. According to Dr. Buse, “We do not have an outcome study that defines the cardiovascular risk in diabetes as mitigated by changes in glycemic control.” He noted, however, that major studies such as the Diabetes Control and Complications Trial Research Group (DCCT) study, as well as the UK Prospective Diabetes Study (UKPDS), suggest there is a trend towards improvement in cardiovascular outcomes when blood glucose is well controlled. He added that results from the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) study “will robustly address this issue by comparing patients whose blood glycated hemoglobin (HbA_{1C}) were less than 6.0 versus patients with an HbA_{1C} of between 7.0 and 7.9.”

Locator: The Relationship Between Insulin Resistance and Cardiovascular Disease

2. b. According to Dr. Ginsberg, “These patients have small LDL, which means they have more LDL particles for any cholesterol concentration. LDL particles are less atherogenic when they are large and buoyant, but become small and dense in the dyslipidemic patient. This increases the likelihood that the LDL particles will adhere to and invade the arterial wall, and also makes them more liable to oxidation, which suggests that LDL cholesterol should be reduced more aggressively in those patients in order to reduce the number of particles.” By reducing the number of triglyceride-carrying lipoproteins, there will be fewer particles to penetrate the arterial wall.

Locator: The Relationship Between Insulin Resistance and Cardiovascular Disease/Diabetic Dyslipidemia

3. a. According to Dr. Buse, “it is clearly true that triglyceride levels in diabetes patients are an independent risk factor, more so than in the general population.” From a clinical perspective, he acknowledged “it is another area we can address in trying to improve cardiovascular risk.”

Locator: The Relationship Between Insulin Resistance and Cardiovascular Disease/Diabetic Dyslipidemia

4. d. According to Dr. Buse and Dr. Ginsberg, weight loss and control of caloric intake make the greatest impact on triglyceride levels. Dr. Ginsberg noted that caloric intake is the centerpiece of any physiologic nonpharmacologic approach for elevated triglycerides. When patients take in fewer calories than they burn, triglycerides begin to fall and HDL begins to rise. Other factors, such as the composition of the diet, exercise, smoking cessation, and elimination of alcoholic beverages can also affect lipid levels to some degree.

Locator: Managing Dyslipidemia in Insulin Resistant Patients/Nonpharmacologic Therapies

5. b. Although niacin can affect glucose levels in diabetes patients at high doses, at moderate doses, niacin provides clinical benefit by modifying HDL and triglycerides without much change in glucose. Clinical trials show that moderate doses have only minimal effects on glucose. In diabetes patients, glycemic agents can be modulated to control any affect on glucose levels. However, in metabolic syndrome patients, this is not possible.

Locator: Managing Dyslipidemia in Insulin Resistant Patients/Niacin

6. c. Fibrate’s genetic pathway through binding to PPAR-alpha is expressed in cells responsible for atherogenesis and inflammation. In vivo, fibrates are associated with a rise in APO-A1 levels in the plasma along with HDL cholesterol because the liver is putting out more APO-A1. This is associated with an increase of oxidation of fat in the liver. Effects beyond lipid regulation could include alteration of factors such as cholesterol efflux, cytokine production, or CRP production. Effects have also been shown on coagulation proteins, such as tissue factor adhesion molecules.

Locator: Managing Dyslipidemia in Insulin Resistant Patients/Fibrates

7. b. Noting that what is called the metabolic syndrome or the insulin resistance syndrome “does not equate to impaired glucose tolerance,” Dr. Ginsberg maintained that forthcoming data for pioglitazone and rosiglitazone will provide more information on their use in glucose tolerance. Although the risk for the conversion of this population to full diabetes is known, there are no established conversion rates for metabolic syndrome to impaired glucose tolerance or diabetes. If the studies with pioglitazone and rosiglitazone were to indicate positive results for the prevention of diabetes, such an outcome may result in new indications. He cautioned, however, that treating patients with the metabolic syndrome before the data is established would be dangerous.

Locator: Managing Dyslipidemia in Insulin Resistant Patients/Thiazolidinediones/Insulin Sensitizers in Prediabetes

8. c. Dr. Plutzky suggested that the first step should be achieving the right LDL level. There are many agents available, including combination therapy, that can get patients to goal. Then, physicians should focus on reading the goals for triglycerides and HDL.

Locator: Weighing the Issues and Devising a Comprehensive Strategy

9. d. Dr. Ginsberg maintains that, it is best to decide that on a case-by-case basis. “Clinicians typically go to fibrates but, as we discussed, there is the potential to use niacin or a TZD in the patient with diabetes.” Combination therapy with insulin and a TZD may help meet treatment goals without the need for additional agents.

Locator: Weighing the Issues and Devising a Comprehensive Strategy

10. b. According to Dr. Masoudi, drug-drug interactions pose a substantial issue. His study of patients in the Medicare population found that patients with diabetes and cardiovascular disease are being treated with huge numbers of medications. The inappropriate use of some agents should be discontinued, such as nonsteroidal agents and dihydropyridine calcium channel blockers. The other issue is that practitioners generally do a poor job of calibrating treatment with risk. A recent study found that patients with the highest risk were ironically least likely to be treated with a statin. This was seen more often in the elderly population.

Locator: Weighing the Issues and Devising a Comprehensive Strategy