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M E D I C A L

# CROSSFIRE®

DEBATES, PEER EXCHANGE, AND INSIGHTS IN MEDICINE®

**SPECIAL EDITION**

## **Emerging Evidence in Cardiovascular Outcomes** Optimal Management of Diabetes and Insulin Resistance

CME-Certified Activity

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1. **b.** The impact of insulin sensitization on nontraditional markers of cardiovascular disease in patients with diabetes was demonstrated in the PROactive study, which showed that thiazolidinedione reduced serum levels of MMP-9 and CRP.

**Locator:** The Role of Metabolic Syndrome, Insulin Resistance, and Diabetes in CVD/Presenting the Data

2. **a.** The NCEP ATP III did not include insulin resistance in its five-component definition of metabolic syndrome, whereas both the World Health Organization and the European Group for the Study of Insulin Resistance consider insulin resistance as being a central element of metabolic syndrome. Until the controversy is settled, Dr. Ginsberg recommended the following clinical approach: “When a patient meets three of the five ATP III criteria for metabolic syndrome, ...take a second look at whether or not that patient is insulin resistant.”

**Locator:** The Role of Metabolic Syndrome, Insulin Resistance, and Diabetes in CVD/Presenting the Data

3. **c.** “The vast majority of people with cardiovascular disease have either diabetes or pre-diabetes,” asserted Dr. Buse, who offered supporting data from a study of 1,200 patients with acute coronary syndrome. Of those individuals with recorded fasting glucose measurements, about 75% had known diabetes, undiagnosed diabetes, or pre-diabetes.

**Locator:** Assessing the Metabolic Syndrome and Cardiovascular Risk/Presenting the Data

4. **b.** Although lowering LDL-C levels “is a mainstay of reducing the risk for cardiovascular disease in diabetic patients,” said Dr. Ginsberg, “patients with diabetes start with greater risk and remain at greater risk, even after we lower LDL-C.” One analysis of data from the 4S and CARE trials, for example, shows that despite similar reductions in LDL-C with statin therapy, patients with diabetes had a higher risk of sustaining a major coronary event than did patients without diabetes.

**Locator:** Lipid Markers and CVD Risk in Insulin Resistance/Presenting the Data

5. **c.** Among the many potential risk factors that could explain the excess cardiovascular risk among diabetic patients, stated Dr. Ginsberg, is a characteristic dyslipidemia triad. “This lipid triad of high TG, low HDL-C, and abnormal LDL-C (e.g., small dense LDL-C, etc.) is driven, to a great degree, by abnormalities in the periphery fat cells and liver related to insulin resistance,” he said.

**Locator:** Lipid Markers and CVD Risk in Insulin Resistance/Presenting the Data

6. **d.** Because diabetes has been classified as a cardiovascular risk equivalent, observed Dr. Fonseca, “Many practitioners take that to mean that the goal in diabetes, as in acute coronary syndrome, should be an LDL-C under 70 mg/dL.” This strategy, however, is not promulgated in existing guidelines.

**Locator:** Lipid Markers and CVD Risk in Insulin Resistance/Presenting the Data

7. **c.** Statin therapy conferred a 25% reduction in vascular events among diabetics enrolled in the Heart Protection Study and a 37% reduction in primary cardiovascular endpoints among diabetics enrolled in the CARDS study. As a result, stated Dr. Fonseca, “we have come to the recommendation that most people with diabetes—at least those over the age of 40—should be on a statin.”

**Locator:** The Metabolic Syndrome and Cardiovascular Risk: the Spectrum of Interventions/Presenting the Data

8. **d.** Studies show that PPAR activation lowers blood pressure by 3 or 4 mm Hg and decreases carotid intima-media thickness. “PPAR-gamma agonists hold great potential,” remarked Dr. Ginsberg, especially if “the dose can really be pushed to drive down blood pressure, reduce TG, raise HDL, and have vessel-wall effects.”

**Locator:** The Metabolic Syndrome and Cardiovascular Risk: the Spectrum of Interventions/Discussing the Issues

9. **d.** In addition to a significant 16% reduction in all-cause mortality, MI, and stroke, the PPAR-gamma agonist pioglitazone conferred significant improvements in four metabolic parameters—A1c, LDL-C, TG, and HDL-C—among high-risk patients with diabetes enrolled in the PROactive trial.

**Locator:** Treatment Considerations for Improving CVD Risk and Mortality in Diabetes/Presenting the Data

10. **c.** The FIELD study of fenofibrate versus placebo showed no significant reduction in the primary outcome (coronary heart disease death or nonfatal myocardial infarction) whereas it did show a significant reduction in the secondary outcome (total cardiovascular events—i.e., the composite of cardiovascular death, myocardial infarction, stroke, and coronary and carotid revascularization).

**Locator:** Treatment Considerations for Improving CVD Risk and Mortality in Diabetes/Presenting the Data

# Emerging Evidence in Cardiovascular Outcomes

## Optimal Management of Diabetes and Insulin Resistance

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: January 2006 • Expiration Date: March 31, 2007

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

### Educational Overview

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 cardiovascular disease (CVD) risk. Lowering of LDL cholesterol (LDL-C) is clearly beneficial and has been stressed in clinical guidelines. Increasingly, data suggest that elevated triglyceride levels and low levels of HDL cholesterol (HDL-C) play a critical role in the development of CVD. In addition to hyperlipidemia, emerging evidence suggests an ever-increasing role for inflammatory markers and endothelial dysfunction in diabetic atherosclerosis.

This *Medical Crossfire*<sup>®</sup> panel of national experts, combining didactic presentation with authoritative peer exchange, will discuss the clinical relevance of managing complex dyslipidemia and vascular inflammation which contribute to cardiovascular risk in patients with type 2 diabetes and insulin resistance.

### Target Audience

This educational activity is designed for cardiologists and other healthcare professionals interested in or involved with the management of patients at increased risk of developing CVD.

### Learning Objectives

- Describe the role of type 2 diabetes and insulin resistance in CVD.
- Discuss methods for identifying patients at risk for CVD.
- Appraise how multiple parameters including abnormal lipids, vascular inflammation, coagulation factors, and glycemic control contribute to atherosclerosis in patients with type 2 diabetes and insulin resistance.
- Explore prevention and treatment options for improving cardiovascular risk and mortality.

### 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 2.5 hours.

### Accreditation

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

UMDNJ—Center for Continuing and Outreach Education designates this educational activity for a maximum of 2.5 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

This activity was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by John B Kostis, MD; Syed Atif Hussain, MD; and Anthony Messina, MD.

### CME Academic Advisor

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## Disclosure Declarations

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## Faculty Disclosure Declarations

**Dr. Buse** has received grant/research support from Bristol-Myers Squibb, Novartis Pharmaceuticals Corp., and Pfizer Labs; and has been a consultant for Amylin Pharmaceuticals, BMS/Merck, Eli Lilly and Co., and Novartis Pharmaceuticals Corp.

**Dr. Edelman** has received grant/research support from Amylin Pharmaceuticals, Eli Lilly and Co., Novo Nordisk, and Takeda Pharmaceuticals North America; and has been a consultant for and has served on the speakers' bureaus of Amylin Pharmaceuticals, Aventis Pharmaceuticals, Eli Lilly and Co., GlaxoSmithKline Pharmaceuticals, Novo Nordisk, and Takeda Pharmaceuticals North America.

**Dr. Fonseca** has received grant/research support from Aventis Pharmaceuticals, GlaxoSmithKline Pharmaceuticals, Novartis Pharmaceuticals Corp., Pfizer Labs, and Takeda Pharmaceuticals North America; has been a consultant for GlaxoSmithKline Pharmaceuticals and Novartis Pharmaceuticals Corp.; has served on the speakers' bureaus of AstraZeneca Pharmaceuticals, GlaxoSmithKline Pharmaceuticals, and Novartis Pharmaceuticals Corp.; and has served on the scientific advisory board of Eli Lilly and Co.

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

**Dr. Masoudi** has served on the speakers' bureaus of AstraZeneca Pharmaceuticals, Pfizer Labs, and Takeda Pharmaceuticals North America; and has served on the scientific advisory board of Takeda Pharmaceuticals North America.

**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., Novo Nordisk, and Takeda Pharmaceuticals North America; and has served on the speakers' bureaus of AstraZeneca Pharmaceuticals, GlaxoSmithKline Pharmaceuticals, Merck & Co., 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 Corp., and Taisho Pharmaceuticals Co.; has served on the speakers' bureaus of Bristol-Myers Squibb, Sanofi, Merck & Co., and Pfizer Labs; and is a member of the scientific advisory boards of Schering-Plough Corp. and Pfizer Labs.

**Dr. Hussain** and **Dr. Messina** have no financial arrangements or affiliations to disclose.

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# Emerging Evidence in Cardiovascular Outcomes

## Optimal Management of Diabetes and Insulin Resistance

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**T**he leading cause of death in diabetes is cardiovascular disease, but, paradoxically, diabetes mortality has increased precipitously while cardiovascular mortality has declined sharply over the past two decades.<sup>1</sup> How can this phenomenon be explained? Precursors to diabetes—impaired glucose tolerance, insulin resistance, and metabolic syndrome—may be implicated. Possibly, a unique dyslipidemia characteristic of this population may play a role. Or, an ever-expanding constellation of established and emerging metabolic, vascular, and inflammatory risk factors may be involved. To address the complex issues at stake in managing the patient at risk of cardiovascular and diabetic sequelae, a panel of national experts convened in this **Medical Crossfire**. Moderator Steven V. Edelman, MD began by explaining, “each panelist will make a short presentation, at the conclusion of which I will open the floor for an interactive exchange among the panel on related clinical issues.”

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## **The Role of Metabolic Syndrome, Insulin Resistance, and Diabetes in CVD**

### *Presenting the Data*

“We have come to learn a great deal about the transition from the normal arterial wall to the atherosclerotic state,” observed Jorge Plutzky, MD, in beginning the first presentation of this **Medical Crossfire**. “Many lines of evidence point to the important role that inflammation plays in driving the various stages in development that ultimately culminate in the complicated atherosclerotic plaque.

“If we think about this disease process through the lens of diabetes, insulin resistance, and the metabolic syndrome, there are some insights to be gained about mechanisms that may be at work,” he continued. “Of course, hyperglycemia, as part of insulin resistance and the diabetic state, certainly contributes to a host of molecular mechanisms that have been implicated in many studies by many laboratories around the world. Interestingly, tumor necrosis factor alpha [TNF- $\alpha$ ] itself has been implicated in

insulin resistance. We know that these states contribute to activation of NF-kappa B.

“There is a lot of exciting work into how advanced glycation of end products can signal through specific receptors,” pointed out Dr. Plutzky. There are data from in vitro studies, animal models, and even human surrogate studies implicating CD40 and CD40-ligand interactions. In addition, various cytokines have been implicated in this process. “All of these factors, to varying extents, may account for some of the issues related to atherosclerosis in patients with insulin resistance and diabetes,” he explained.

“We have to overlay those mechanisms onto what we know about atherosclerosis itself,” continued Dr. Plutzky, “and the current dogma holds that the maintenance of the fibrous cap is a critical element in determining the development of the complicated scenario of plaque rupture and acute myocardial infarction [MI].” This appears to be a balance of forces between the synthesis of the materials that make up the fibrous cap—collagen and elastin—as well as the breakdown of that fibrous cap, which can occur

through enzymes such as matrix metalloproteinases (MMP). Interestingly, both limbs of that process of synthesis and breakdown seem to be controlled by inflammatory stimuli as regulated through lymphocytes and macrophages.

“Ultimately, we have to ask, What is the clinical relevance of these issues of inflammation?” noted Dr. Plutzky. While there is considerable evidence to implicate markers of inflammation as indicators of cardiovascular risk, there is also growing evidence to support that markers of inflammation such as high sensitivity C-reactive protein (CRP) may predict cardiovascular risk independently of other known risk factors such as the total cholesterol (TC) to high-density lipoprotein (HDL) ratio. Ridker and colleagues have shown that CRP adds to the predictive value of the TC:HDL ratio in determining the risk of first MI in apparently healthy men.<sup>2</sup>

Data supporting the hypothesis that chronic subclinical inflammation is part of the insulin resistance syndrome come from the Insulin Resistance Atherosclerosis Study.<sup>3</sup> “This study examined the number of metabolic disorders that are associated with the metabolic syndrome and the relationship of that number to levels of CRP” in 1,008 nondiabetic persons without clinical coronary artery disease (CAD), explained Dr. Plutzky. “As obesity, hypertension, increased triglycerides [TG], low HDL-C, and hyperinsulinemia are added to the evaluation, one sees an impressive stepwise increase in CRP. This is suggestive that perhaps these are all proinflammatory drivers that may contribute to risk.”

Further and more recent support for the possibility of an interaction between CRP and the metabolic syndrome can be found in data from a study of 14,719 initially healthy women conducted by Ridker and colleagues; 24% of participants had metabolic syndrome at study entry.<sup>4</sup> The CRP, total cholesterol, and HDL-C levels of patients who suffered a first myocardial infarction were compared with those who remained free of cardiovas-

cular disease (CVD) over an eight-year follow-up. As shown in **Figure 1**, pointed out Dr. Plutzky, “The authors took a stepwise stochastic approach to CRP and the metabolic syndrome, asking what was the CVD event-free survival probability in four patient groups: those subjects who had CRP less than 3 or greater than 3, and then whether or not they had the metabolic syndrome.”

**Figure 1** shows the stepwise predictive value of CRP level and metabolic syndrome status across the four patient groups, with the presence of both CRP greater than 3 and metabolic syndrome “being the most suggestive of a chance of a cardiovascular event,” reviewed Dr. Plutzky. “These data suggest that there may be mechanistic issues at work here in terms of inflammation.” Further support for this hypothesis is demonstrated with the Ridker et al data “by simply segregating risk according to the ATP III definition<sup>5</sup> of the metabolic syndrome across this gradient of CRP,” stated Dr. Plutzky, with the probability of CVD event-free survival dropping with increasing CRP levels.

Taking a mechanistic look at some of the various components that contribute to atherosclerosis in individuals with diabetes or insulin resistance,<sup>6</sup> Dr. Plutzky explained, “One really has to begin with a recognition that the process extends beyond glucose and involves

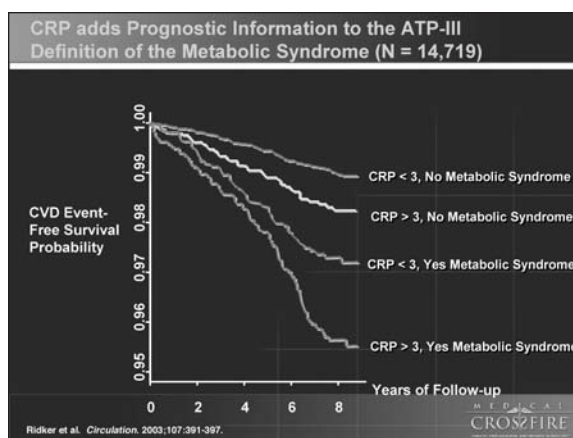


Figure 1. Support for the possibility of an atherosclerotic interaction between CRP and the metabolic syndrome is seen in these data from Ridker and associates. From: Ridker et al. *Circulation*. 2003;107:391-397.

a whole constellation of various metabolic abnormalities that all converge on the arterial wall. Whether they are classic risk factors such as hypertension and low-density-lipoprotein cholesterol [LDL-C] or emerging issues such as inflammation, there are a variety of forces directed towards the arterial wall that may contribute to this process.

“Some of these can involve critical elements of insulin resistance itself, the organ basis in the skeletal muscles, the liver, the pancreatic response, and, ultimately, the fat tissue itself,” continued Dr. Plutzky. “And these, to varying degrees, contribute to mechanisms of atherosclerosis that may, for example, drive issues such as the increased coagulability seen in such patients with diabetes, increases in fibrinogen, and a shift towards a more procoagulant state with an increase in plasminogen activator inhibitor 1 [PAI-1] and a decrease in tissue plasminogen activator [tPA].”

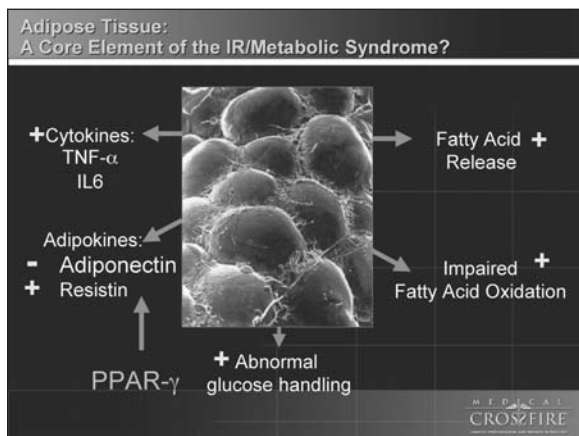
Adipose tissue has become a particularly intriguing avenue for further insight into the process of insulin resistance and metabolic syndrome, observed Dr. Plutzky, because many inflammatory stimuli appear to occur through fat tissue, as shown in **Figure 2**. In particular, he pointed out, “Adiponectin—one of the fat-specific hormones adipokines—has been associated with a decrease in inflammation, raising many intriguing issues

about its relationship with atherosclerosis in patients with diabetes. This has focused interest on PPAR-gamma—the nuclear receptor peroxisome proliferator-activated receptor gamma—which has been shown in both animal and human studies to direct adiponectin, as well as to increase levels of adiponectin.” This mechanism has led to interest in “the possibility that PPAR activation—either through PPAR-alpha activation by fibrates, which lower triglycerides and raise HDL; or by PPAR-gamma activation by thiazolidinediones [TZDs], which are insulin sensitizers used to treat diabetes—may ultimately have an impact on atherosclerosis,” said Dr. Plutzky.

The impact of insulin sensitization on nontraditional markers of cardiovascular disease in patients with diabetes was demonstrated in a study showing that treatment with the thiazolidinedione rosiglitazone reduced serum levels of MMP-9 and CRP.<sup>8</sup> “This field has evolved rapidly, and we now have results from PROactive,<sup>9</sup> the first of several cardiovascular endpoint trials to come,” remarked Dr. Plutzky, noting that this trial will be reviewed in more detail in Dr. Masoudi’s presentation. Among patients with diabetes and macrovascular disease randomized to the thiazolidinedione pioglitazone or placebo, he reviewed, “a significant 16% reduction in the secondary endpoint of death, myocardial infarction, or stroke was demonstrated in the treatment arm. This has contributed to the ongoing discussion of the potential impact of thiazolidinediones on cardiovascular disease and diabetes. In addition, the possibility that fat itself may be a target for therapeutic intervention continues to receive attention.”

### Discussing the Issues

“What is the clinical relevance of the indicators of these vascular inflammatory markers that Dr. Plutzky has described?” asked Dr. Edelman to begin the panel discussion. “And does it assist us in further risk stratifying patients with diabetes?”



**Figure 2.** Adipose tissue has become a particularly intriguing avenue for further insight into the process of insulin resistance and metabolic syndrome because many inflammatory stimuli appear to occur through fat tissue.

“First, we need to draw a distinction between diabetes and the metabolic syndrome,” replied Vivian Fonseca, MD. “When patients have diabetes, because of high glucose, glycosylation, and other factors, they are at greatly increased risk of cardiovascular disease. The average patient with diabetes has a very high risk of MI within the next five to 10 years. Measuring markers of inflammation really does not help in the situation of existing diabetes.” The true benefit, suggested Dr. Fonseca, may lie in the ability to utilize these markers “earlier in the natural history of the disease, before the onset of diabetes. The patient with metabolic syndrome may derive benefit from measuring a marker of inflammation such as CRP.”

“Why do so many cardiologists order measurements of CRP and other inflammatory markers?” challenged Dr. Edelman.

“There is an important role for these markers in patients who are in intermediate-risk groups, but not in patients with diabetes who are already known to be at a substantially increased risk,” opined Frederick A. Masoudi, MD, MSPH, FACC. Inflammatory markers such as CRP, he said, “can be useful in clarifying risk in patients who are at intermediate risk and potentially in patients with metabolic syndrome.”

“Is the mechanism of atherosclerosis different in patients with diabetes versus those without diabetes?” inquired Dr. Edelman.

“It is surprising to me that we do not know the answer to such a basic question as whether or not atherosclerosis and its complications are different in individuals with and without diabetes,” noted Dr. Plutzky. “Our attention is drawn to glucose, but there are no data indicating that hyperglycemia plays a role. Other than hyperglycemia, there is a suggestion that many of the mechanisms may be amplified, but quite similar, between individuals with diabetes and individuals who have nondiabetic atherosclerosis.”

“Dr. Plutzky, do you think we should change our definition of diabetes?” asked Dr.

Fonseca. Currently, diabetes is defined as fasting glucose levels greater than 126 mg/dL, based on an association with retinopathy above that level, he pointed out. “But cardiovascular risk goes up with fasting glucose levels of more than 100 mg/dL. Should we come down lower than 126 mg/dL on the definition of diabetes because of the cardiovascular complications?”

“The disease, presumably, is not changing, but our insight into the disease is,” remarked Dr. Plutzky. “There may be value in at least recognizing those intermediate zones, and I believe endocrinology is evolving towards that.”

Henry Ginsberg, MD, cautioned against adopting a new definition of diabetes based on a lower fasting glucose level. “The risk would be the use of glucose-lowering agents in individuals with lower and lower glucose levels, without evidence of benefit for either micro- or macrovascular disease,” he explained. He recommended maintaining the current definition while “understanding that patients with glucose levels between 100 and 126 mg/dL are in a range at which they are likely to have insulin resistance and be at increased risk for atherosclerosis.”

“The real reason we have had a hard time sorting out what is special about the diabetes phenotype with regard to the pathophysiology of cardiovascular disease is that the vast majority of patients with clinical cardiovascular disease probably have either diabetes or pre-diabetes,” proposed John B. Buse, MD, PhD, who noted that he would review data supporting this contention in his own presentation. “We have had a hard time finding a segment of this population that has no contribution from insulin resistance.”

“Are there core metabolic abnormalities in the metabolic syndrome that deserve more attention than others?” queried Dr. Edelman.

Dr. Ginsberg began his response by questioning the definition of metabolic syndrome as promulgated by the NCEP ATP III guidelines,<sup>5</sup> which hold that metabolic syndrome is

identified in the patient with three of the following five risk factors: abdominal obesity, elevated TG, reduced HDL-C, elevated blood pressure, and elevated fasting glucose. “For a number of reasons, the ATP III expert panel decided not to put insulin resistance in a central position as regards metabolic syndrome, whereas the European Group for the Study of Insulin Resistance [EGIR] and the World Health Organization [WHO]<sup>10</sup> consider insulin resistance to be the focus,” he explained. “When we see a patient who meets three of the five ATP III criteria for metabolic syndrome, we should take a second look at whether that patient is insulin resistant. I do not have evidence to support my opinion, and there are no data in the literature yet, but I believe there is increased cardiovascular risk in a patient who has three of the five criteria plus insulin resistance as compared with a patient who has three of five criteria without insulin resistance.”

“How would the average physician decide whether a patient has insulin resistance?” asked Dr. Edelman.

Dr. Ginsberg listed several factors that may indicate insulin resistance, including a family history of diabetes, obesity, hypertension, and a cholesterol profile that comprises high TG and low HDL-C levels. The likelihood of insulin resistance rises with the accumulation of these risk factors, he stated. When the practicing physician is in doubt, he offered, “I would err on the side of assuming the patient is insulin resistant.”

“Dr. Ginsberg, it appears you are aligned with the EGIR and WHO definitions of the metabolic syndrome, which specify some features of insulin resistance,” commented Dr. Fonseca. “Let me ask you, then, should we be measuring insulin levels in nondiabetics?”

“There are two assays that critically need to be standardized on the national and international level: one is insulin, and one is apolipoprotein B,” responded Dr. Ginsberg. “If these assays existed and were standardized, that would be very helpful.”

“Can the link between the components of the metabolic syndrome and the risk for cardiovascular risk mortality be simplified?” proposed Dr. Edelman.

Dr. Masoudi expressed resistance to this idea, asserting, “In many respects, the situation is already oversimplified. Trying to incorporate several different risk parameters into a dichotomous outcome—yes, metabolic syndrome or, no, not metabolic syndrome—is an oversimplification that does not take into account the complex relationship between these individual factors and the risk for cardiovascular disease.” Providing an example, he explained, “With HDL-C and hypertension there is a clear linear relationship between the level of the risk factor and the outcome, whereas with triglycerides the relationship is much less clear.”

“In some ways, a lot of the risk in metabolic syndrome is subsumed in patients who have diabetes, prediabetes, or clinical cardiovascular disease,” suggested Dr. Buse. “The complicated issue is how to assign risk and devise a therapeutic approach for those patients who do not have an abnormality of glucose or clinical cardiovascular disease. I am not sure whether metabolic syndrome gives all the answers in that regard.”

## Assessing the Metabolic Syndrome and Cardiovascular Risk

### *Presenting the Data*

“Although we have done better at reducing mortality, particularly in cardiovascular disease, over the past few decades, in the area of diabetes we have not done nearly as good a job of reducing cardiovascular risk,” stated Dr. Buse to set the stage for his presentation. Since 1979, he said, the rate of diabetes mortality has risen by approximately 35%, whereas the rates of cancer, all-cause, and major CVD mortality have all declined.<sup>1</sup> The clinical importance of this point is underscored when one considers that “the vast majority of patients with cardiovascular disease have either diabetes or pre-diabetes,” he noted.

This statement is supported by data among 1,200 patients with acute coronary syndrome who were evaluated for diabetes status.<sup>11</sup> Of those individuals with recorded fasting glucose measurements, approximately 75% had known diabetes, undiagnosed diabetes, or impaired fasting glucose (i.e., pre-diabetes). This finding lends credence to the belief that “metabolic underpinnings contribute to cardiovascular risk,” asserted Dr. Buse. Various metabolic risk factors are among “the large number of established and emerging markers of cardiovascular risk that have been identified over the past several decades,” he added.

Some of these markers—such as age, blood pressure, and family history of early vascular disease—are simple ones easily obtained in clinical practice; others—such as proinsulin levels and cystatin C—are more complex and unlikely to be measured in clinical practice. “There are various cardiovascular risk markers, and the literature is full of studies exploring the relative risk of this marker or that combination of markers. Trying to parse this long list of potential cardiovascular risk markers for a set that provides increased efficiency of clinical practice to reduce cardiovascular disease is really a daunting task,” he asserted.

The metabolic syndrome has recently provoked a great deal of interest as regards its potential for streamlining the process of identifying at-risk individuals. However, stated Dr. Buse, “My feeling is that metabolic syndrome has become a distraction with respect to caring for patients with diabetes. And that is why I joined the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) in a process that resulted in the recent publication of a paper critically appraising metabolic syndrome.<sup>12</sup>” In this analysis of the literature to date, Dr. Buse and his co-authors question whether metabolic syndrome as currently defined is ideally suited for clinical use.

“We believe that patients with diabetes are at very high risk of cardiovascular dis-

ease, whether or not they meet criteria for metabolic syndrome,” he stated, adding that there is insufficient evidence for the supposition that those diabetics who do not have metabolic syndrome do not require as aggressive an intervention strategy as those who do. The current ADA guidelines, which Dr. Buse helped to develop, provide evidence-based recommendations for the management of patients with diabetes as well as for those with impaired fasting glucose or impaired glucose tolerance (i.e., pre-diabetes).<sup>13</sup> These recommendations are reviewed in **Figure 3**.

Returning to the joint ADA/EASD paper on metabolic syndrome, Dr. Buse explained that he and his co-authors focused “on issues in metabolic syndrome and how they apply to cardiovascular risk management. Therefore, we did not include papers that focused on the ability of metabolic syndrome to predict diabetes,” an ability for which there is ample evidence. Explaining that the practical use of diagnosing metabolic syndrome is not as a predictor of diabetes but rather as a multivariate risk factor for CVD, Dr. Buse questioned whether metabolic syndrome adds predictive power beyond that of fasting plasma glucose levels. He cited data from the San Antonio Heart Study,<sup>14</sup> in which “fasting plasma glucose as a single marker had similar positive and negative predictive value for cardiovascular disease as the NCEP ATP III definition for metabolic syndrome.”

Rationale
<ul style="list-style-type: none"> <li>• Arguably, metabolic syndrome is a distraction with respect to caring for people with diabetes.</li> <li>• Current ADA guidelines for patients with diabetes recommend:               <ul style="list-style-type: none"> <li>– Lifestyle intervention (Medical Nutrition Therapy MNT and Physical Activity PA)</li> <li>– Aggressive CVD risk management</li> </ul> </li> <li>• Current ADA guidelines for patients with IFG/IGT recommend:               <ul style="list-style-type: none"> <li>– Lifestyle intervention (MNT and PA)</li> <li>– Monitoring for the development of diabetes should be performed every 1–2 years</li> <li>– Close attention should be given to, and appropriate treatment given for, other CVD risk factors (e.g., tobacco use, hypertension, dyslipidemia)</li> <li>– Drug therapy should not be routinely used to prevent diabetes until more information is known about its cost-effectiveness</li> </ul> </li> </ul>
<p>ADA. <i>Diabetes Care</i>. 2005;28:S4-S36.</p> <p>MEDICAL CROSSFIRE</p>

Figure 3. Current guidelines from the ADA recommend intervention for cardiovascular protection in both diabetes and prediabetes—metabolic syndrome aside. Adapted from: ADA. *Diabetes Care*. 2005;28:S4-S36.

“It should be understood that my co-authors and I felt very strongly that cardiovascular risk factors do occur together more often than would be expected by chance alone, and that the concept of metabolic syndrome has been very useful in driving numerous research studies that have increased our awareness of cardiovascular risk factors and their importance in primary prevention of cardiovascular disease,” emphasized Dr. Buse. “But we are concerned that the particular risk factors that were identified as defining metabolic syndrome may not be the optimal risk factors.” Until some of the imprecision and uncertainty surrounding metabolic syndrome has been clarified, the ADA/EASD joint paper made several clinical recommendations, outlined in Figure 4.

### Discussing the Issues

“The joint ADA/EASD statement is an important article that is making many diabetes and cardiovascular organizations look critically at the importance of defining the metabolic syndrome,” commented Dr. Edelman, who then turned to Dr. Plutzky to begin the discussion.

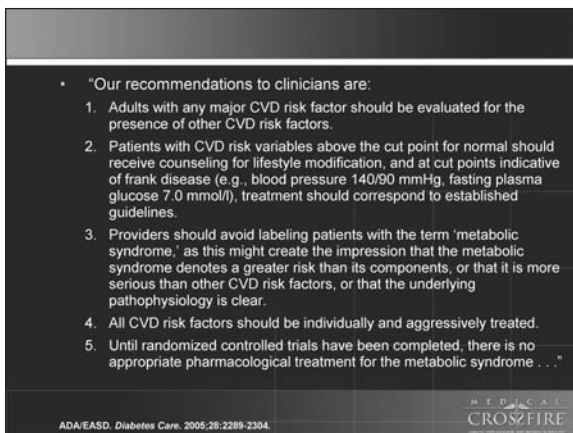


Figure 4. The American Diabetes Association and the European Association for the Study of Diabetes critically appraised the literature on metabolic syndrome and cardiovascular risk and concluded with several clinical recommendations. From: ADA/EASD, *Diabetes Care*.2005;28:2289-2304.

“Given the ADA/EASD position statement, what, if any, clinical utility is there in better defining the metabolic syndrome? Is metabolic syndrome even a clinically useful tool?”

“I find clinical utility in the notion of metabolic syndrome,” declared Dr. Plutzky, commending the joint ADA/EASD position statement for being “a wonderful, thoughtful document that critically looks at these issues and lays out a lot for us to think about.” Still, he explained, “In my practice, the metabolic syndrome has real meaning as a framework for both myself and my patients in terms of recognizing a constellation of issues that contribute to cardiovascular risk.” Furthermore, he stated, the idea of metabolic syndrome provides a framework for patients to understand “the interactions between their diet and their weight and their lipids and their glucose. In practice, the goal of avoiding diabetes is a real motivator for patients.

“But I do see that, in some sense, the notion of metabolic syndrome reflects our ignorance,” continued Dr. Plutzky. He likened the current concept of metabolic syndrome to “a runway for where we are headed, which is toward a better understanding of the interactions between all these underlying causes.”

“I agree 100% with your comments, Dr. Plutzky,” stated Dr. Buse. “We all agree that metabolic syndrome is a useful concept. The devil is in the details, however, as to whether we have arrived at the optimal definition.”

Having spoken with several members of the NCEP ATP III, Dr. Ginsberg posited, “I believe that perhaps there was a sense among the panel that LDL-C had been the primary focus of cardiovascular prevention, but interventions such as medical nutrition therapy and physical activity were being ignored in favor of the effective drug therapies. There was also an epidemic—or at least a marked increase—in obesity with new-onset of diabetes as well as a cluster of defined abnormalities that seemed to be exacerbated by weight gain and inactivity that were probably linked through insulin resistance.” Dr. Ginsberg

speculated that the NCEP ATP III pushed the concept of metabolic syndrome as a means to motivate physicians to promote diet and exercise in their obese patients. “I believe that intention was lost,” he proposed, “and the concept of metabolic syndrome has jumped ahead of where it should be.”

“Let me disagree with Dr. Buse on one issue,” requested Dr. Fonseca, who objected to Dr. Buse’s suggestion that the presence of metabolic syndrome is irrelevant in patients with known risk factors for CVD. “What about the patient who is obese but does not yet have diabetes?” he proposed. “Not all of the patients in this population are at equal risk for getting diabetes or cardiovascular disease. Clinicians are overwhelmed in practice and need to focus on the patients who have the greatest risk. Couldn’t metabolic syndrome be used to identify these patients?”

“There is a point to what you say,” conceded Dr. Buse, stating, “I agree with you, Dr. Fonseca, that having ways to stratify a patient’s risk—whether the patient is identified through obesity or insulin resistance or some other entrance pathway—could be very useful.” The problem, however, explained Dr. Buse, is that different organizations use different parameters to define metabolic syndrome “and some of these parameters are associated with increased cardiovascular risk and some are not.”

“Well, then, do the current definitions of metabolic syndrome appropriately identify patients at risk for cardiovascular disease?” challenged Dr. Edelman.

“One of the problems I have with the current definition of metabolic syndrome, particularly the NCEP ATP III definition, is that it ignores insulin resistance, as Dr. Ginsberg mentioned,” answered Dr. Fonseca. “Only about 50% of individuals who meet NCEP ATP III criteria for metabolic syndrome have insulin resistance; therefore, if you believe that insulin resistance is driving some cardiovascular abnormalities, then you are wrong 50% of the time.” To overcome this problem,

he proposed, “We may need to refine our definition of metabolic syndrome for better alignment with insulin resistance as well as better risk prediction for cardiovascular events.”

“Do the current ATP III guidelines identify too many or too few patients with the metabolic syndrome?” asked Dr. Edelman.

“The current guidelines identify the number of patients with metabolic syndrome as defined by the cut points set by committees,” stated Dr. Ginsberg. “I do not mean to be glib, but we need to remember that the proportion of the population that has been classified as having the metabolic syndrome is totally determined by the cut points.” The cut point for triglyceride levels—150 mg/dL—translates to about the 70th percentile for middle-aged men and women, for example, whereas the cut point for glucose level—110 mg/dL—is at about the 90th percentile. “The cut points were reasoned based on epidemiologic data on risk, sustainable costs, and the clinical capability of physicians,” he explained. “It is a very artificial situation that deals with a very real problem.”

“I completely agree with you, Dr. Ginsberg, that this is a very large group and also too much of a heterogeneous group,” noted Dr. Masoudi, pointing out that in the population of persons with metabolic syndrome as currently defined “some have very high cardiovascular risk and others have relatively low cardiovascular risk. The benefit of a concept like the metabolic syndrome is, in large part, its usefulness in identifying individuals at risk, and its usefulness suffers from this heterogeneity in the spectrum of cardiovascular risk within the syndrome.”

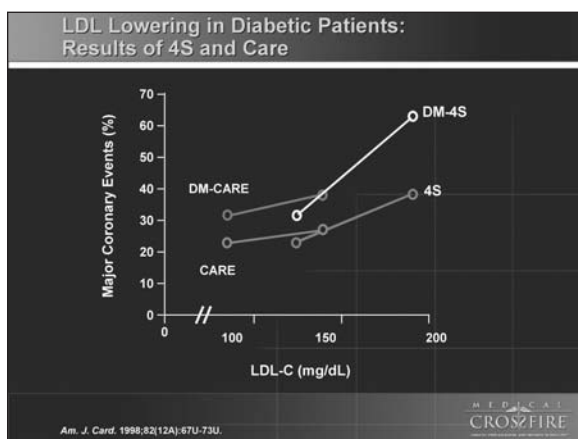
“That is because of the dichotomous nature of each of the component parts,” added Dr. Buse. “A person with a waist measurement of 37 1/2 inches and a glucose of 99 mg/dL would theoretically have a low risk based on metabolic syndrome criteria. But let us say this person also had three other risk factors—with the waist and glucose measurements so close to the cut points, they would

actually be at reasonably high risk.” Succinctly summarizing the problem with the metabolic syndrome, Dr. Buse posited, “It captures too many patients and too few patients at the same time.”

Dr. Ginsberg offered a counterpoint: “I believe it is okay to capture a lot of patients when the therapy is a natural, relatively inexpensive, and certainly safe therapy, that is, exercise and diet.”

Turning to the therapeutic outcome trials, Dr. Edelman asked, “Do trials such as VA-HIT, PROactive, and the statin trials support the need for comprehensive versus targeted treatment of the components of metabolic syndrome?”

Pointing out that in both the VA-HIT study<sup>15-17</sup> and the PROactive study,<sup>9</sup> patients who had clinical cardiovascular disease and were at high risk remained at high risk even after drug treatment, Dr. Buse proposed, “This suggests that we need to do something more comprehensive, but treating each of the component parts is really where we have the data. So it is a difficult question, but I believe that we need to treat cardiovascular risk factors broadly in patients with diabetes, clinical cardiovascular disease, and metabolic syndrome.”



**Figure 5.** Patients with diabetes retain a greater CVD risk than persons without diabetes even when similar reductions in LDL-C levels are achieved. Reprinted from *The American Journal of Cardiology*, Vol. 82, Kreisberg, 67U-73U, 1998, with permission from Excerpta Medica Inc.

## Lipid Markers and CVD Risk in Insulin Resistance

### Presenting the Data

“We know that patients with diabetes have increased risk for cardiovascular death,” stated Dr. Ginsberg, citing data from the very large cohort of patients in the Multiple Risk Factor Intervention Trial (MR-FIT).<sup>18</sup> “Five thousand patients with diabetes and 360,000 patients without diabetes were screened in this trial. In both groups, and in parallel fashion, the risk of death increased with the number of typical risk factors—high cholesterol, smoking, and high blood pressure. But the risk was far greater in the diabetics, who were at more risk than the controls for having one, two, or three risk factors.

“We also know that lowering LDL-C levels—for patients with or without diabetes, whether it be by statin or by any other means—reduces risk, no matter the baseline level of LDL-C,” continued Dr. Ginsberg. “And lowering LDL-C levels further will significantly reduce the number of cardiovascular events. These outcomes are essentially the same, in a relative way, in diabetics and non-diabetics.” In the recent CARDS study, for example, atorvastatin was compared with placebo for primary prevention in patients with diabetes.<sup>19</sup> “This study showed a very nice reduction of over 30% in CVD events in diabetic patients with lowered LDL-C levels,” reviewed Dr. Ginsberg. “There is no doubt that lowering LDL is a mainstay of reducing the risk for cardiovascular disease in diabetic patients.

“But importantly,” noted Dr. Ginsberg, “we know that our patients with diabetes start with greater risk and remain at greater risk, even after we lower LDL-C,” as depicted in **Figure 5**. This analysis of data from the 4S and CARE trials shows that despite similar reductions in LDL-C with statin therapy, patients with diabetes had a higher risk of sustaining a major coronary event than did patients without diabetes.<sup>20</sup> The question,

then, becomes, “Where is that excess risk coming from?” posited Dr. Ginsberg.

Among the many potential risk factors that could explain this excess risk, he said, “are other lipid factors that are well characterized.” Hypertriglyceridemia, driven by increased production and secretion of very-low-density lipoproteins [VLDL], is an important part of the rest of the lipid risk in our patients with diabetes, insulin resistance, and metabolic syndrome. Hypertriglyceridemia is followed by reductions in the level of protective HDL-C. This lipid triad of high TG, low HDL-C, and abnormal LDL-C is driven, to a great degree, by abnormalities in the periphery fat cells and liver related to insulin resistance.

“But what are the data showing us that a high TG and/or a low HDL have an impact on risk?” asked Dr. Ginsberg rhetorically. Confirmatory data come from several studies, including PROCAM, a population-based study conducted in Germany by Assmann and colleagues.<sup>21</sup> “These authors have followed patients for a few decades now, and, as you can see in **Figure 6**, at each LDL-C range, individuals with TG levels above 200 mg/dL had a greater CHD risk than did those individuals with TG levels below 200 mg/dL, and this risk increased with increasing levels of TG and LDL-C.” Similar patterns are demonstrated in the Copenhagen study<sup>22</sup> as well as in data from Brown and associates.<sup>23</sup> In fact, stated Dr. Ginsberg, “Patients with lower LDL-C levels but a combination of high TG and low HDL-C levels have significantly more risk than do those with higher LDL-C levels but better TG and HDL-C levels.”

Finally, Dr. Ginsberg pointed to data from VA-HIT, in which men who had had a cardiovascular event were randomized to placebo or to gemfibrozil, which lowers TG and raises HDL-C levels.<sup>17</sup> In both the diabetic and nondiabetic groups, treatment with gemfibrozil conferred a 24% reduction in the risk of subsequent vascular events. However, pointed out Dr. Ginsberg, “The diabetic group had more events than did the nondia-

betic group. From these data, it is clear that diabetic patients have more risk, and this risk is related to a more complicated lipid disorder. In addition, these data provide evidence that changing TG and HDL can have beneficial outcomes.”

### Discussing the Issues

“Given that mixed lipid disorders are so common in patients with diabetes and the metabolic syndrome, why has LDL-C been the primary marker for CVD?” asked Dr. Edelman to launch the discussion of Dr. Ginsberg’s presentation.

“The strength of both the epidemiological association and the treatment data has driven this specific interest in LDL-C,” replied Dr. Masoudi. “But as more data become available on, first, the relationship between other lipid abnormalities and cardiovascular risk and, second, outcome data on treatments directed at HDL-C, triglycerides, and other components of dyslipidemia, this may change.”

“Has the focus on LDL-C been effective in reducing cardiovascular disease?” inquired Dr. Edelman.

“The obvious answer to that question is, yes; statin therapy in particular has saved tens of thousands if not hundreds of thou-

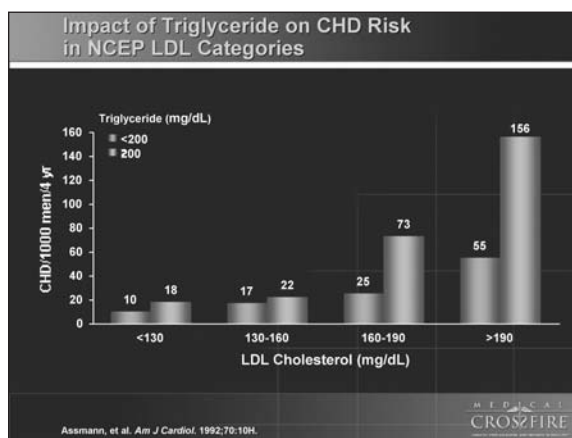


Figure 6. Elevated triglyceride levels are associated with increased risk of coronary heart disease at each category of LDL-C in the PROCAM study. Reprinted from *The American Journal of Cardiology*, Vol. 70, Assman G, Schulte H. Role of triglycerides in coronary artery disease: lessons from the Prospective Cardiovascular Munster Study, 10H-13H, 1992, with permission from Excerpta Medica Inc.

sands of lives already and has played a big part in the reduction in cardiovascular mortality,” answered Dr. Buse. The obvious success of statin therapy, however, “may distract us a bit from dealing with other, more-difficult-to-treat risk factors like blood pressure, dyslipidemia, and diabetes. This last major risk factor, I would argue, is the most difficult to attend to.”

“At the moment and, I believe, for the foreseeable future, TG and HDL-C will be addressed after LDL-C has been treated with a statin or another LDL-C-lowering agent,” speculated Dr. Ginsberg. “Addressing TG and HDL-C is important; it will lower residual risk after LDL-C is lowered.”

“The discussion in the diabetes community has evolved to the point where the question is no longer, ‘Should this patient be on a statin?’ but rather ‘How low should we go with statin therapy?’” posited Dr. Buse, explaining that “a rapidly evolving notion” among diabetes practitioners holds that all patients with diabetes “should go on a statin at diagnosis, and the more you lower LDL-C the better.”

Pointing out that diabetes has been classified as a cardiovascular risk equivalent, Dr. Fonseca observed, “Many practitioners take that to mean that the goal in diabetes, as in acute coronary syndrome, should be an LDL-C under 70 mg/dL.” Seeking the opinion of his colleague, he asked, “Dr. Plutzky, what is your view?”

“Whether to equate a patient with diabetes to a patient with acute coronary syndrome remains questionable,” opined Dr. Plutzky. “At the same time, relative risk does come down as LDL-C is lowered further; the drugs that can reduce levels dramatically do so in the vast majority of cases safely and effectively; and, in my opinion, there is nothing pathologic about an LDL-C under 70 mg/dL in most cases.”

“Dr. Ginsberg, in your presentation you showed us that the relative risk reduction after LDL-C-lowering therapy is as good or

better in diabetics than in nondiabetics, but their absolute risk stays much higher,” recalled Dr. Edelman. “What evidence supports the role of residual cardiovascular risk factors despite statin therapy in patients with diabetes?”

“Yes, we have seen this phenomenon in all the statin trials and now we have seen it in the VA-HIT trial of gemfibrozil<sup>17</sup>,” confirmed Dr. Ginsberg, adding that Dr. Edelman’s question cannot be answered without further clinical evidence. “Can we get more ‘bang for our buck’ by attacking all of the other risk factors—targeting TG and HDL-C, more aggressively lowering blood pressure, and more aggressively using anti-inflammatory therapy? The ongoing ACCORD trial—which several of us on this panel are involved in—will give some of those answers.”

“When you think of all the factors that we can attack—blood pressure, LDL-C, triglycerides, HDL-C, smoking, inflammation, glucose—each of those could confer a 20% to 40% benefit,” remarked Dr. Buse, who mused, “Add them all together, and could we wipe out coronary disease?”

“Well, then, Dr. Buse, what is your view on targeting therapy more directly at HDL-C and TG lipid abnormalities?” queried Dr. Edelman.

“Personally, I do that clinically,” offered Dr. Buse. “There are different pathways by which you can alter lipid metabolism. To me, it makes sense to address LDL-C as well as triglycerides and HDL-C.”

## **The Metabolic Syndrome and Cardiovascular Risk: the Spectrum of Interventions**

### *Presenting the Data*

“This discussion leads directly into my presentation, in which I want to address multifactorial intervention,” remarked Dr. Fonseca. As background, he reviewed data from the UKPDS: 23 diabetes trial, in which the researchers ranked the significance of five

established modifiable cardiovascular risk factors.<sup>24</sup> The rankings were, in declining order of value, LDL-C, HDL-C, hemoglobin A1C, systolic blood pressure, and smoking. “This leads to the dilemma, how do we treat the combination of high LDL-C levels and low HDL-C levels?” observed Dr. Fonseca. “Especially when, on top of that, we need to address hemoglobin A1C, systolic blood pressure, and cigarette smoking.

“The first possibility that I want to address is the ACE inhibitors, which may have effects beyond lowering blood pressure,” stated Dr. Fonseca. In the HOPE study and MICRO-HOPE substudy of the ACE inhibitor ramipril,<sup>25</sup> he reviewed, “The patients with diabetes did extremely well, with reductions in total mortality (25%), stroke (33%), myocardial infarction (22%), and cardiovascular mortality (37%) that were greater than those seen in patients without diabetes.

“One important post-hoc analysis of the HOPE data revealed the interesting fact that treatment with an ACE inhibitor prevented new-onset diabetes in the nondiabetic group,” noted Dr. Fonseca. “It is interesting to speculate that when treating the patient with metabolic syndrome or prediabetes for cardiovascular prevention, it may be useful to choose an agent that would prevent diabetes at the same time.” Cautioning that this use is not an approved indication, Dr. Fonseca remarked that the DREAM trial is currently underway to investigate the use of ramipril, rosiglitazone, or the two in combination for diabetes prevention and cardiovascular endpoints. “ACE inhibitors have become established as one of the primary ways to reduce cardiovascular disease in patients with diabetes, whether or not they have hypertension, and clearly if they have microalbuminuria,” he noted.

As for lipid lowering, “the Heart Protection Study, with its large number of participants with diabetes, really changed the way we manage our diabetic patients,” commented Dr. Fonseca, due to its finding that lowering LDL-C levels by 40% in diabetics was asso-

ciated with a 25% reduction in vascular events.<sup>26</sup> Likewise, the CARDS study found a 37% risk reduction for primary endpoints in patients with diabetes on lipid-lowering therapy.<sup>19</sup> “As a result of HPS and CARDS,” observed Dr. Fonseca, “we have come to the recommendation that most patients with diabetes—at least those over the age of 40—should be on a statin.”

Summarizing the ADA<sup>13</sup> and NCEP ATP III<sup>5</sup> recommendations for lipid management in patients with diabetes, Dr. Fonseca stated, “The first priority is to bring the LDL-C below 100 mg/dL and to initiate statin therapy in most patients, particularly those aged over 40 years. The second priority should be to raise HDL-C above 40 mg/dL and get the triglycerides below 150 mg/dL via therapy that may include aggressive statin therapy, improving glycemic control, and adding fibrates or nicotinic acid. And, of course, consider weight loss, exercise, and smoking cessation.

“And now I want to turn our attention to glycemic control, which often seems to be the ‘neglected stepsister’ of cardiovascular risk factors,” observed Dr. Fonseca. Part of this neglect, he surmised, arose from disappointing results in trials like UKPDS in which “a significant reduction in myocardial infarction and cardiovascular mortality was not seen with good glycemic control, except in a small subgroup of obese individuals who were treated with metformin.<sup>27</sup> And although there was a significant reduction in cardiovascular events with metformin, the event rate remained very high.” This problem may be attributable in part to the fact that “most patients on metformin did not maintain adequate glycemic control over the duration of the study, so we need to think beyond surface appearances,” asserted Dr. Fonseca.

“A more recent study shows that patients with diabetes who were treated with metformin at the time of discharge from hospital had better outcomes in regard to cardiovascular morbidity and mortality than those treated with sulfonylurea,<sup>28</sup>” he contin-

ued. “In addition, patients treated with the combination of a thiazolidinedione and metformin had better outcomes than those treated with traditional combinations like sulfonylureas and metformin. Why is this? Does it go back to the issue of other risk factors, both established ones and these so-called nontraditional risk factors,<sup>29</sup> as shown in Figure 7?”

Dr. Fonseca then reviewed several potential avenues for treatment. “Reducing insulin resistance with a sensitizer may decrease

those risk factors and may decrease cardiovascular events. We have seen a reduction in CRP with PPAR-gamma agonists,<sup>30</sup> and these drugs also may lower blood pressure by 3 or 4 mm Hg.<sup>31</sup> This small effect may make a difference in outcomes when taken together with, say, an improvement in glycemic control and an elevation in HDL-C.”

An emerging concept is the combined use of sensitizers to achieve additive effects on CRP, PAI-1, and MMP-9. One group achieved this goal by combining two classes of sensitizers, metformin and a thiazolidinedione,<sup>32</sup> as shown in Figure 8. In addition, a number of studies have established the efficacy of PPAR activation in decreasing carotid intima-media thickness,<sup>33-36</sup> which, Dr. Fonseca pointed out, is an important early marker of atherosclerosis and a predictor of cardiovascular events.

“I wish to end my presentation by emphasizing the potential of the multiple risk factor reduction approach,” announced Dr. Fonseca. In the STENO-2 trial, reported in 2003, 80 patients with diabetes were randomized to conservative treatment or to intensive treatment that targeted hyperglycemia (A1c < 6.5%), hypertension (BP < 130/80 mm Hg), dyslipidemia (TC < 175 mg/dL; TG < 150 mg/dL), microalbuminuria, and secondary prevention of cardiovascular disease with aspirin.<sup>37</sup> “Even though the study group did not quite meet their targets—they were a little lax in their interventions—the reduction in the primary endpoint of combined cardiovascular disease was still 53%,” noted Dr. Fonseca.

“We are now moving toward even lower goals,” he continued, citing the parameters of the ongoing ACCORD trial in 10,000 patients with diabetes. “The targets in the intensive-treatment group are less than 6% for A1c and less than 120 mm Hg for systolic blood pressure. In addition, in the lipid arm of the trial, we are comparing statin versus

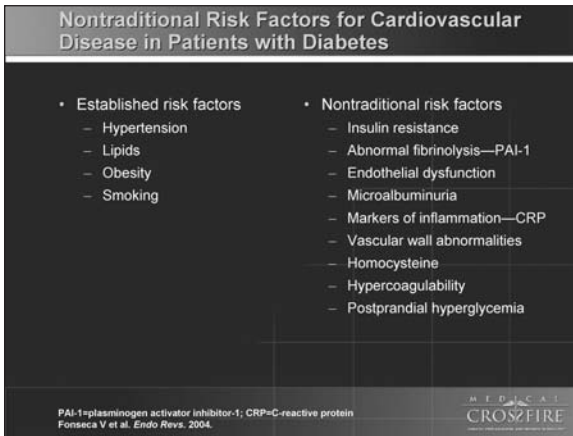


Figure 7. The strategy of targeting multiple risk factors can be optimized by utilizing therapies that have effects on more than one of the established and nontraditional risk factors. From: Fonseca et al. *Endo Revs.* 2004.

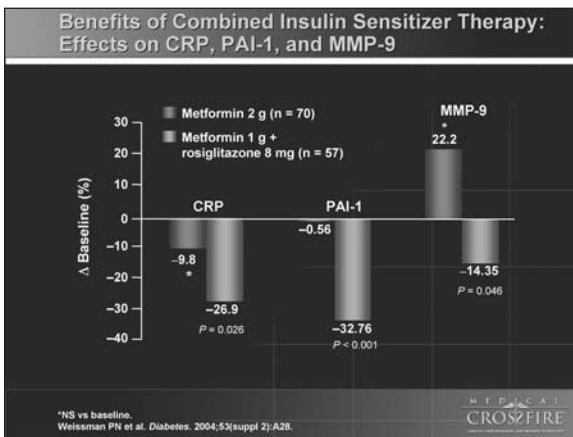


Figure 8. Combining metformin and a thiazolidinedione provides an additive benefit in modifying these nontraditional risk factors. From: Weissman et al. *Diabetes.* 2004;53(suppl 2):A28.

the combination of fenofibrate and statin.” If the results of ACCORD do show a significant reduction in cardiovascular events, asserted Dr. Fonseca, “It is going to change the way we practice medicine in the next decade.”

### *Discussing the Issues*

To initiate discussion of Dr. Fonseca’s presentation, Dr. Edelman asked, “What preventative measures are recommended for each of the components of metabolic syndrome?”

“Certainly, we should focus on medical nutrition therapy and exercise to prevent diabetes in patients with metabolic syndrome, especially in the approximately one-half who have impaired glucose tolerance,” recommended Dr. Ginsberg. Patients with metabolic syndrome and impaired glucose tolerance, he noted, “have very high rates of conversion to diabetes. We know that diet and exercise can markedly reduce conversion to diabetes, confer beneficial effects on triglycerides and HDL-C, and reduce blood pressure.”

“One value of the metabolic syndrome is increased surveillance for the patient,” suggested Dr. Plutzky, noting that such surveillance leads to prompt recognition when blood pressure levels cross the threshold for intervention. “An appealing intervention is drug therapy targeted for blood pressure—ACE inhibitors, certainly, and there are intriguing data for ARBs—that also have an impact on the development of diabetes.”

“How should the clinician focus on the glucose aspect of metabolic syndrome?” inquired Dr. Edelman.

“Glucose is the area in which we have the most data about prevention of diabetes, whereas we do not have much information on preventing cardiovascular disease in patients with prediabetes or impaired fasting glucose,” answered Dr. Buse, speculating that new data will be forthcoming from ongoing trials of available drugs such as metformin and glitazones, as well as from the development of new drugs.

Dr. Edelman agreed that the question is complicated and pointed out, “The Diabetes Prevention Program showed that metformin resulted in a 30% reduction in patients who were heavier and younger.<sup>38</sup> We do need more data. Many prevention trials are going on now, and the results should be exciting.”

“Dr. Ginsberg, what agents specifically target metabolic syndrome in relation to lipids?” queried Dr. Edelman.

“Pioglitazone has been shown to lower triglycerides, raise HDL-C, and have variable effects on LDL-C,” replied Dr. Ginsberg. “Clearly, the triglyceride/HDL-C axis is affected by that PPAR-gamma agonist. Rosiglitazone raises HDL-C, perhaps not as well as pioglitazone, but it is clearly differentiated in terms of triglycerides; it raises HDL-C without changing triglycerides. Fibrates raise HDL-C and lower triglycerides.” Current debate focuses on whether these various therapies are equally cardioprotective, noted Dr. Ginsberg, who called for more trials to provide insight.

“Dr. Fonseca, can you comment on obesity?” requested Dr. Edelman. “We have so many new pharmacologic agents that may be important in that arena.”

“Obesity is a big challenge, Dr. Edelman, because we know lifestyle change—diet and exercise—works, but no one wants to do it; everyone wants exercise in a pill,” lamented Dr. Fonseca. Although several agents are approved for the treatment of obesity, inadequate outcome data and troublesome side effects may limit their usefulness, he suggested. “An exciting new drug called rimonabant for the management of obesity is under review by the FDA, with metabolic syndrome as an indication,” observed Dr. Fonseca. “This is an interesting concept, because rimonabant affects a range of risk factors while reducing weight.” Lastly, he pointed out that the NIH-sponsored Look AHEAD trial is being conducted to examine the long-term effects of weight loss and weight-loss interventions on the prevention of cardiovascular disease in obese persons with diabetes.

“Do any of the medications we have discussed during this *Medical Crossfire* have any unique mechanisms of action?” inquired Dr. Edelman.

“The ACE inhibitors have some important effects on insulin signaling,” replied Dr. Fonseca. “Bradykinin has an effect. There is a direct negative effect of angiotensin on insulin signaling. They are weak insulin sensitizers. They are not like the TZDs, but they have some insulin-sensitizing effect that may play a role beyond reducing blood pressure. We have interesting data with statins indicating that they have pleiotropic effects on inflammation, endothelial function, and other processes. We are seeing these effects with the TZDs as well.”

“PPAR-gamma agonists hold great potential,” remarked Dr. Ginsberg. If restrictions on dose necessitated by salt and water retention can be overcome, he proposed, then “the dose can really be pushed to drive down blood pressure, reduce TG, raise HDL, and have vessel-wall effects. Right now, however, PPAR-gamma agonists fall short because of the limitation on potency.”

## Treatment Considerations for Improving CVD Risk and Mortality in Diabetes

### Presenting the Data

“I would like to discuss recent and emerging trials that address this issue of residual cardiovascular risk in patients with diabetes,” said Dr. Masoudi to introduce the topic of his presentation. “The PPAR—or peroxisome proliferator-activated receptor—agonists, as we have discussed already in this *Medical Crossfire*, are of interest in this issue because of their effects on metabolic parameters.”

The PPAR agonists include the PPAR-gamma agonists (the TZDs, namely, rosiglitazone or pioglitazone) and the PPAR-alpha agonists (the fibrates), reviewed Dr. Masoudi. “In this presentation, I will focus on three important trials of PPAR agonists for cardiovascular risk reduction in patients with type 2 diabetes,” he explained. These three trials are PROactive,<sup>9</sup> with pioglitazone; FIELD,<sup>39</sup> with fenofibrate; and the ongoing ACCORD trial of fenofibrate.

“The PROactive trial is a randomized controlled trial comparing the TZD pioglitazone, titrated to 45 mg, with placebo,” observed Dr. Masoudi. “This multicenter study was conducted in Europe and included almost entirely Caucasian patients. Of the 5,240 patients, all had type 2 diabetes and were defined as high risk in having established macrovascular disease before study enrollment. Patients were followed for a mean of two and a half years. The goals of the study were, one, to determine if pioglitazone would reduce mortality and cardiovascular morbidity in these high-risk patients with type 2 diabetes and a previous macrovascular event and, two, to further assess the safety profile of pioglitazone.”

The primary endpoint was a composite of all-cause mortality, myocardial infarction (including silent MI), stroke, limb amputation, coronary revascularization, and peripheral revascularization. The main secondary end-

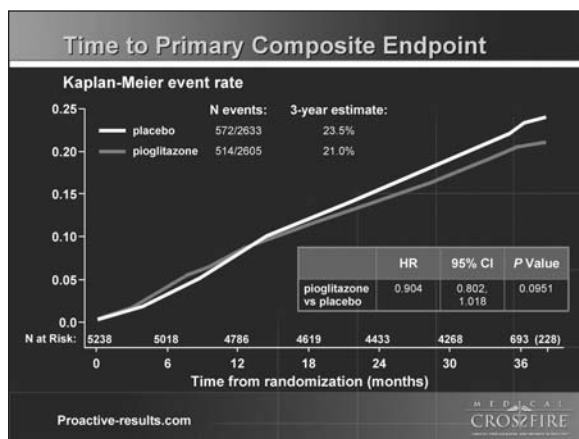


Figure 9. The PROactive trial results for time to primary composite endpoint. From: *proactive-results.com*. Accessed December 8, 2005.

point was a composite of the following hard endpoints: all-cause mortality, myocardial infarction (not including silent MI), and stroke. “In terms of the primary composite endpoint,” stated Dr. Masoudi, reviewing the study results, “there was a relative reduction of 10% in favor of pioglitazone; however, this reduction was not statistically significant, as demonstrated in Figure 9. In terms of the secondary endpoint—which, again, includes all-cause mortality, MI, or stroke and does not include procedural endpoints—there was a statistically significant 16% reduction in favor of pioglitazone, as shown in Figure 10.

“In addition, there were a number of metabolic effects seen in the pioglitazone group that were different than those seen in placebo-treated patients,” continued Dr. Masoudi; these effects are illustrated in Figure 11. Each of the differences in four metabolic parameters—A1c, TG, HDL-C, and LDL-C—were statistically significant and favored pioglitazone. “And, I would add, the PROactive protocol mandated that all patients be managed according to existing European guidelines,” pointed out Dr. Masoudi, “which meant that substantial numbers of patients were treated with aspirin, ACE inhibitors, and statins. Therefore, the metabolic changes seen with pioglitazone were above and beyond the baseline treatment provided with guideline-recommended medications.”

Turning to the issue of safety, Dr. Masoudi stated, “There was, not surprisingly, a higher rate of edema, 21% versus 13%, in patients treated with pioglitazone as compared with those treated with placebo.” In both the treatment and placebo groups, he continued, “very few patients discontinued treatment as a result of weight gain,” the rates being 0.8% and 0.2% in the pioglitazone and placebo groups, respectively.

With respect to heart failure, the reported, but not adjudicated, rate of heart failure was 10.8% and 7.5% in the pioglitazone and

placebo groups, respectively; the rate of unadjudicated heart failure hospitalization was 5.7% and 4.1%, respectively; and the rate of adjudicated heart failure death was 0.96% and 0.84%, respectively. Dr. Masoudi commented on the heart failure data, “There was a 1.6% absolute difference in the risk of heart failure hospitalization between the groups. Importantly, there was no difference in the risk of death due to heart failure, and these deaths were all adjudicated, with small numbers of patients in both arms who died because of heart failure.”

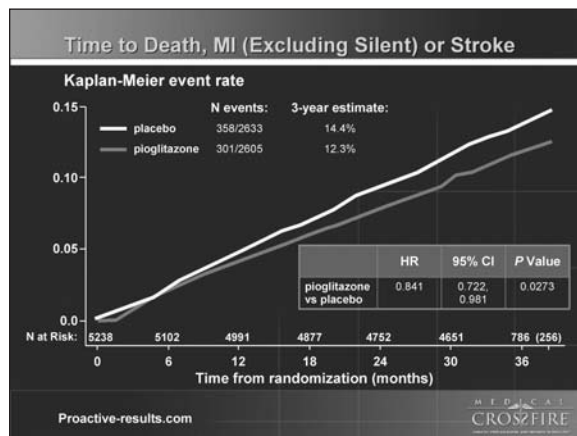


Figure 10. The PROactive trial demonstrated a 16% reduction in the secondary endpoint—which included all-cause mortality, MI, and stroke and excluded procedural endpoints—with pioglitazone versus placebo. From: *proactive-results.com*. Accessed December 8, 2005.

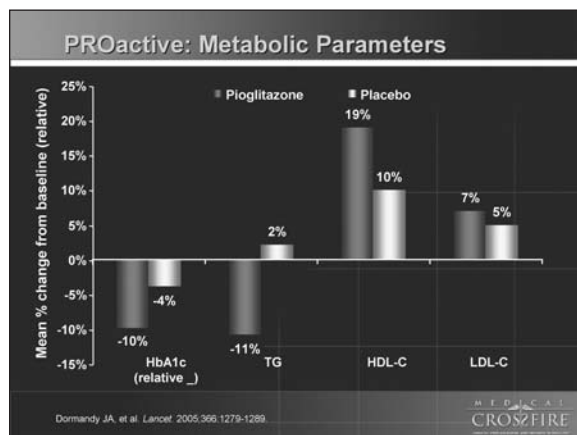


Figure 11. More data from the PROactive trial. Pioglitazone demonstrated statistically significant differences in four metabolic parameters above and beyond the changes achieved with baseline medications. From: Dormandy et al. *Lancet*. 2005;366:1279-1289.

Dr. Masoudi then turned his attention to the FIELD trial. “This is a multicenter, randomized, controlled trial of fenofibrate versus placebo conducted in almost 10,000 subjects with type 2 diabetes,” he reviewed. “This is both a primary and a secondary prevention study, with about 25% of patients having had a prior macrovascular event and about 40% of patients having a five-year cardiovascular risk greater than 15%. The follow-up was five years.” At the 2005 American Heart Association Scientific Sessions, the investigators reported the results of FIELD. The study demonstrated that fenofibrate did not significantly reduce the risk of the primary outcome (coronary heart disease death or nonfatal myocardial infarction), but it did significantly reduce total cardiovascular events, mainly by reducing nonfatal MI by 24% and revascularization by 21%. A large number of patients in the placebo arm initiated (or “dropped in” to) statin therapy during the follow-up period. It is possible that this differential drop-in obscured the effects of fenofibrate in the study.<sup>39</sup>

The third trial, ACCORD, is designed to assess the impact of tight glycemic and blood pressure control on cardiovascular prevention in diabetes, observed Dr. Masoudi. “This very large, ongoing clinical trial is testing three complementary treatment strategies that are intended to reduce cardiovascular morbidity in type 2 diabetes. The treatment strategies are: one, intensive glycemic control to obtain A<sub>1c</sub> levels below 6%; two, modification of HDL-C and TG via combination fenofibrate-plus-statin therapy; and, three, intensive blood pressure control with a target of less than 120 mm Hg.” These strategies are to be tested against standard regimens in a randomized fashion. “ACCORD is a multicenter trial in 71 North American centers that will enroll 10,000 patients who will be followed for an anticipated mean of 5.6 years, with results available in 2010,” concluded Dr. Masoudi, “and will provide evidence of the effects of fenofibrate in patients with diabetes already treated with a statin.”

### *Discussing the Data*

Observing that the patient with diabetes and cardiovascular disease “is a common patient to see in our practices,” Dr. Edelman asked, “What are the implications of the PROactive study for the care of these patients?”

“I believe PROactive will be viewed as a landmark study,” declared Dr. Buse. “It is the first cardiovascular outcomes study designed to test whether glycemic intervention can reduce cardiovascular disease. As with UKPDS, technically, it is a negative study for the primary endpoint, but it reflects a biological process in that using insulin sensitization is associated with a reduction in cardiovascular events.

“To me, the most interesting part of PROactive is that there was a 0.5% reduction in A<sub>1c</sub>, a 3 mm Hg reduction in blood pressure, a reduction in triglycerides, and an increase in HDL, and these changes may account for the majority of the benefit with regard to cardiovascular event reduction that was observed with pioglitazone,” continued Dr. Buse. In addition, he asserted his belief that “by the nature of its design, this study probably underestimates the benefit and overestimates the risk of pioglitazone, because it enrolled patients with advanced disease and was a very-short-duration study in which benefits did not have much time to emerge.”

Noting that, “50% of the PROactive patients had already had a myocardial infarction,” Dr. Edelman commented, “This study took patients who were already far along in the natural history of heart disease and in 2.5 years produced a significant reduction in cardiovascular events.”

“Yes, 50% had a prior MI, and 52% had two of the criteria for a cardiovascular event,” confirmed Dr. Plutzky, who then suggested another reason that the effect of pioglitazone may have been underestimated in this trial. The primary endpoint, he pointed out, “included peripheral vascular disease and revascularization, and that was a component of the primary endpoint that really went in the wrong direction.” In fact, in the authors’ discussion of their study, they stated

“their assumption that peripheral vascular disease would behave, in terms of atherosclerosis, like coronary vascular disease,” noted Dr. Plutzky. “Many vascular biologists and cardiologists would be quick to point out this is not a fair assumption, because we have had a difficult time showing any therapeutic intervention that changes lower-extremity revascularization. So this false assumption may have contributed to a real issue with underestimating.”

Picking up on this line of debate, Dr. Edelman pointed out that there were seven components to the primary endpoint, with the three most important components—all-cause mortality, MI, and stroke—comprising the secondary endpoint. “Dr. Masoudi, I want to ask you, not being a statistician myself, for your view on this issue. To me, the secondary endpoint provides a pretty impressive result, especially since it was statistically significant and included all three of the important primary endpoint components.”

“I agree that the procedural endpoints could, to some degree, certainly obscure some of the differences in some of these other hard endpoints,” affirmed Dr. Masoudi. He elaborated, explaining that patients who underwent a revascularization that was part of the primary endpoint and who subsequently did not die or experience a myocardial infarction or stroke would contribute to the primary endpoint, but not the principal secondary endpoint.

“Dr. Fonseca, does the PROactive trial tell us anything about patients with cardiovascular disease, whether they have diabetes or not?” inquired Dr. Edelman.

“Since PROactive was performed in patients with diabetes, it is very difficult to extrapolate the data to patients without diabetes,” suggested Dr. Fonseca. “But a number of the studies on cardiovascular risk factors and surrogate markers have been done in obese patients without diabetes. The effects of PPAR-gamma agonism will affect the vasculature whether patients have diabetes or not, but we have to wait for studies in nondi-

abetic patients—studies like DREAM, with rosiglitazone; ACT NOW, with pioglitazone; and the continuation of TRIPOD, with troglitazone—for definitive answers. We will wait for those results before drawing conclusions about managing patients without diabetes.”

“What effect do PPARs have on specific cardiovascular risk factors? And what might account for the benefit of TZDs for patients with diabetes and/or the metabolic syndrome?” inquired Dr. Edelman.

“As I mentioned earlier in this discussion, there are reductions in A1C and blood pressure as well as improvements in triglycerides and HDL-C,” answered Dr. Buse. “The other important thing to remember is that in these drugs that work in nuclear receptors, the details of the structure of the drug and how it interacts with the receptor may have a lot to do with the effects. We have had three marketed glitazones—troglitazone, rosiglitazone, and pioglitazone—and they each seem to have slightly different lipid parameters. As Dr. Ginsberg mentioned, pioglitazone and rosiglitazone seem to have differential effects on triglycerides and also on LDL-C particle number. Therefore, they have broad-based effects on parameters that we measure in clinical practice.”

“The possibility is there that a PPAR-gamma agonist given to patients with metabolic syndrome without diabetes might effect changes in glucose that are less than those seen in PROactive, although the TG, HDL-C, and blood pressure effects would still be there,” speculated Dr. Ginsberg. “Is that the way PROactive benefit was achieved? Or were there other effects? We have to do the trials to get the answers.” After all, he reasoned, “When a trial shows a difference in outcome, all we can state definitively is that one group received the medication and one group did not. When we try to tease out how the outcome occurred, the statistics get very complex and relatively soft.”

“Dr. Masoudi, could you provide some clinical advice on managing the safety con-

siderations that were seen in the PROactive study in its high-risk population?” requested Dr. Edelman.

“One of the keys issues is awareness among both patients and practitioners, whether they be physicians or nurses, that fluid retention and edema is a side effect of these medications, that it is dose related, and that it may be worse in patients treated with insulin,” advised Dr. Masoudi. A second key issue, he continued, is that “not all of the potential mechanisms whereby TZDs cause edema are clearly related to heart failure.” He explained that the TZDs may cause increases in plasma volume, but that these changes are modest. Also, TZDs may up-regulate specific sodium channels in the renal collecting duct, which may be amenable to treatment with specific types of diuretics. TZDs may also up-regulate vascular endothelial growth factor (VEGF), which may cause edema.

“Recognizing that not all edema is heart failure, that not all of the mechanisms are heart failure, is, I believe, also important,” continued Dr. Masoudi. “The current recommendations for use are very sensible in patients with heart failure—specifically, the recommendations that, one, use of these medications be restricted to patients with class I or class II heart failure and, two, that these medications should be used at relatively low doses that are increased only gradually.” Finally, Dr. Masoudi reiterated his initial injunction that both patients and practitioners “must be aware of this side effect and be vigilant in recognizing it.”

Pointing out that a joint statement from the ADA and AHA on this issue is available, Dr. Fonseca elaborated on Dr. Masoudi’s recommendations. “Assess your patient clinically; make sure that they are suitable candidates in that they do not have class III or class IV heart failure. Remember that not every patient with edema is a heart failure patient; look for other causes of edema, such as venous insufficiency, nephrotic syndrome, or

nonsteroidal anti-inflammatory drug use, for example. And finally, remember that these patients are at great risk for heart failure for other reasons; consider that progressive coronary artery disease, asymptomatic coronary artery disease, or a cardiomyopathy may have developed. Appropriate investigation is indicated, because you cannot always blame the medication.”

“This is not an official recommendation, but brain natriuretic peptide [BNP] levels might be useful,” observed Dr. Edelman. “Dr. Plutzky, do you see any utility in measuring BNP levels in patients in whom you want to use a TZD but may be at high risk?”

“I am not sure that BNP levels are clinically useful at this juncture,” responded Dr. Plutzky. “We certainly have evidence, in scenarios in which there was already left ventricular dysfunction, that BNP levels will rise in response to a TZD. Furthermore, this response did not occur when there was not existing left ventricular dysfunction.”

Dr. Plutzky then commented on “a salient issue that bears underscoring,” namely, the onset of left-sided classic congestive heart failure in patients with diabetes and cardiovascular disease. “As shown in the PROactive trial,” he noted, “the onset of left-sided classic congestive heart failure in these patients is associated with quite untoward outcomes over the course of the ensuing several years. And the fact that there was no mortality difference in PROactive would cause cardiologists to question the assumption of left-sided heart failure being the explanation for the observed fluid retention and edema. That is because we would have expected patient mortality to have been much worse if, in fact, the TZDs were inducing some kind of myocardial effect.”

“But, just to be clear, there was no difference in heart failure mortality between the pioglitazone and placebo groups?” asked Dr. Buse, seeking clarification.

“That is correct,” confirmed Dr. Plutzky.

## Final Thoughts

“There is significant evidence that the atherosclerotic process begins when patients are in their 20s and 30s, and by the time an MI or diabetes comes along, that is a late event,” stated Dr. Plutzky, who offered the first take-away message from this *Medical Crossfire*. This knowledge, he declared, combined with a growing understanding of disease processes, will lead “to a mandate for earlier treatment. There is an opportunity in both diabetes and cardiovascular disease for us to assess risk earlier, to intervene with diet and exercise earlier, and, ultimately, to treat with drug therapy earlier. Where these two diseases converge in the early stages is in a condition called metabolic syndrome, and I believe we need to continue to chase it.”

Although there may be continued debate about the definition of metabolic syndrome, stated Dr. Buse, more important is the “across-the-board agreement that metabolic syndrome is a very useful concept for helping clinicians to think about the need for broad-based therapies. In patients with diabetes, we now have tools with the potential to get virtually every A1C to target, virtually every blood pressure to target, and virtually every lipid abnormality tucked away. We just need to accomplish that clinically by developing disease management programs that can help us to fulfill this potential for all of our patients.”

“From the physician’s standpoint,” commented Dr. Ginsberg, “we need to think of metabolic syndrome as a trigger that makes us think, ‘Let me look at this patient’s blood

pressure, lipids, glucose, family history of diabetes, and body habitus. Let me look at all the individual risk factors that may affect my management strategy in this patient.’ And, when each of these individual risk factors cross guideline thresholds and require pharmacological intervention, just remember how important medical nutrition therapy, exercise, and weight loss are in attacking all these risk factors together.”

“I want to emphasize that we need to take a multiple-risk-factor approach to treatment of diabetes,” advised Dr. Fonseca, “otherwise, we will be left with small relative risk reductions that are not quite what we achieve in nondiabetics. Secondly, we need to recognize the benefit of modifying the non-traditional risk factors, and many of the drugs we use actually do so through their pleiotropic effects. We are in an exciting time, with a full toolbox that we can use to treat our patients.”

“There really needs to be a greater emphasis on treating earlier and treating more aggressively, because, despite the fact that we have the tools to achieve targets in blood pressure, glucose control, lipid levels, and other goals, in general we are failing to do so,” observed Dr. Masoudi. “We also need to focus on these mediators of the excess risk for cardiovascular events that are seen in patients with diabetes and insulin resistance, and, for this reason, I am excited about upcoming trials that will help us address this incremental risk in this patient population.” ■

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# Emerging Evidence in Cardiovascular Outcomes

## Optimal Management of Diabetes and Insulin Resistance

### CME Test

1. In the PROactive study, the impact of insulin sensitization via thiazolidinediones on cardiovascular risk is mediated through

- a. increased levels of MMP-9 and CRP.
- b. decreased levels of MMP-9 and CRP.
- c. increased levels of PAI-1 and tPA.
- d. decreased levels of PAI-1 and tPA.

2. Which of the following characteristics is *not* included in the NCEP ATP III definition of metabolic syndrome?

- a. insulin resistance
- b. elevated TG
- c. reduced HDL-C
- d. elevated blood pressure

3. Approximately, what proportion of the population with cardiovascular disease also has diabetes or pre-diabetes (i.e., insulin resistance)?

- a. a minority
- b. about half
- c. a majority
- d. Data are inconclusive.

4. LDL-C levels are lowered equally in a patient with diabetes and a patient without diabetes; given this, which of the following statements about cardiovascular risk is *not* true?

- a. The patients' risk has been equalized.
- b. The diabetic patient remains at higher risk compared to similarly-treated nondiabetics.
- c. The nondiabetic patient is now at higher risk.
- d. The nondiabetic patient's risk has dropped dramatically, while the diabetic patient's risk is virtually unchanged.

5. The dyslipidemia characteristic of diabetes is a triad comprising abnormal LDL-C and which of the following?

- a. high TG and low VLDL
- b. low TG and high VLDL
- c. high TG and low HDL-C
- d. low TG and high HDL-C

6. The practice of targeting LDL-C levels at lower than 70 mg/dL in patients with diabetes is based on which of the following?

- a. substantial clinical evidence
- b. inconclusive clinical evidence
- c. the recommendation of guidelines
- d. the categorization of diabetes as a cardiovascular risk equivalent

7. According to the panel, which of the following is true regarding statin therapy in patients with diabetes?

- a. Statin therapy should be initiated in all diabetics.
- b. Statin therapy should be initiated in those diabetics with the characteristic dyslipidemia of diabetes.
- c. Statin therapy should be initiated in most diabetics, especially those aged over 40.
- d. Statin therapy should be initiated in most diabetics, especially those aged over 60.

8. Using insulin sensitizers to reduce insulin resistance may confer which of the following additional benefits?

- a. small reduction in blood pressure
- b. reduction in vessel-wall thickness
- c. reduction in weight
- d. both a and b

9. Treatment with a PPAR-gamma agonist in high-risk patients with diabetes confers significant improvements in which metabolic parameter(s)?

- a. A1c
- b. A1c and LDL-C
- c. TG and HDL-C
- d. A1c, LDL-C, TG, and HDL-C

10. In the FIELD study, fenofibrate treatment in patients with diabetes was shown to reduce which of the following?

- a. all-cause mortality
- b. cardiovascular mortality
- c. total cardiovascular events
- d. amputation

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Optimal Management of Diabetes and Insulin Resistance

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Degree \_\_\_\_\_

Specialty \_\_\_\_\_

Day Phone \_\_\_\_\_ Evening Phone \_\_\_\_\_

Fax \_\_\_\_\_ E-Mail \_\_\_\_\_

Preferred Mailing Address:  Home  Business \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Zip \_\_\_\_\_

I certify that I have completed the “Emerging Evidence in Cardiovascular Outcomes: Optimal Management of Diabetes and Insulin Resistance” activity as designed and I am claiming [up to 2.5 credits] \_\_\_\_\_ AMA/PRA category 1 credit(s).

Signature \_\_\_\_\_

Date \_\_\_\_\_

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

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

UMDNJ—Center for Continuing and Outreach Education, PO Box 1709, Newark, NJ 07101-1709

Phone: (973) 972-4267 or (800) 227-4852 CE Activity Code: 06MC38/JE02

**Emerging Evidence in Cardiovascular Outcomes**  
Optimal Management of Diabetes and Insulin Resistance

**Activity Evaluation Form**

The planning and execution of self 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:					
Describe the role of type 2 diabetes and insulin resistance in CVD.	5	4	3	2	1
Discuss methods for identifying patients at risk for CVD.	5	4	3	2	1
Appraise how to help patients including abnormal lipids, insulin resistance, inflammation, coagulation factors, and glycemic control contribute to atherosclerosis in patients with type 2 diabetes and insulin resistance.	5	4	3	2	1
Explore prevention and treatment options for improving cardiovascular risk and mortality.	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 their knowledge of the subject.	5	4	3	2	1
The activity was educationally sound and scientifically balanced.	5	4	3	2	1
The activity was free of commercial bias/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 have identified any gaps 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.

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

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

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