

# Diabetes 2005

**Volume 11**

*Highlights from the*  
**54th Annual Scientific  
Sessions of the American  
College of Cardiology**

**March 6 - 9, 2005**

**Orlando, Florida**

*and*

**65th Annual Scientific  
Sessions of the American  
Diabetes Association**

**June 10 - 14, 2005**

**San Diego, CA**



*This CME program is sponsored by Yale University  
School of Medicine and supported by an unrestricted  
educational grant from Takeda Pharmaceuticals  
America, Inc. and Eli Lilly and Company.*

## **Diabetes 2005**

### **Editors:**

Silvio E. Inzucchi, M.D.  
Robert S. Sherwin, M.D.

### **Contributing Authors:**

Margo Farber, Pharm.D.  
Ripu Hundal, M.D.  
Sandra Norris, Pharm.D.  
Susan Ruffalo, Pharm.D.

### **CME Reviewer:**

Rory McCrimmon, M.D.

**T**his monograph is supported through an unrestricted educational grant from Takeda Pharmaceuticals America, Inc. and Eli Lilly and Company.

**I**n meeting the requirements of full disclosure and in compliance with the Accreditation Council for Continuing Medical Education Essentials, Standards for Commercial Support, and Guidelines, the following information has been provided by our editors regarding potential conflicts of interest: Robert S. Sherwin, M.D. is engaged in research activities supported by Bayer, Chiron, Eli Lilly and Company, Novartis Pharmaceuticals Corporation, Pfizer Inc., and Takeda Pharmaceuticals America, Inc. Silvio E. Inzucchi, M.D. is a consultant to Aventis, Eli Lilly and Company, Novartis Pharmaceuticals Corporation, GlaxoSmithKline, and Takeda Pharmaceuticals America, Inc. In accordance with the 2004 ACCME Standards for Commercial Support, a peer review process has been established for this program and all Conflict of Interest issues (if any) have been resolved.

**D**isclosure Policy: It is the policy of Yale University School of Medicine, Continuing Medical Education, to ensure balance, independence, objectivity and scientific rigor in all its educational programs. All participants in this program are required to disclose any relevant financial relationship(s) they (or spouse/partner) have with a commercial interest that benefits the individual in any financial amount that has occurred within the past 12 months; and the opportunity to affect the content of CME about the products or services of the commercial interests. The Center for Continuing Medical Education will ensure that any conflicts of interest are resolved prior to this activity.

**T**his CME Activity was planned and produced in accordance with the ACCME Essentials.

### **Published by Norris Communications**

87 Cloverly Road  
Grosse Pointe Farms, MI 48236  
313-642-4737

© 2005 Norris Communications

ISBN 1-890973-19-X  
All rights reserved.

**T**he information presented in this publication is a summary of that presented at recent meetings sponsored by the American College of Cardiology and American Diabetes Association, and does not reflect the opinions or recommendations of Yale University School of Medicine, the sponsor, Norris Communications, the publisher, or Takeda Pharmaceuticals America, Inc. and Eli Lilly and Company, the commercial supporters. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this publication should not be used by clinicians without evaluation of their patients' conditions and of possible contraindications or dangers in use, review of any applicable manufacturer's product information, and comparison with the recommendations of other authorities.

# Diabetes**2005**

**From the 54th Annual Scientific Sessions of the American College of Cardiology  
and the 65th Annual Scientific Sessions of the American Diabetes Association**

*July 2005*

**Dear Colleague:**

Time restraints prevented many of you from attending the 54th Annual Scientific Sessions of the American College of Cardiology (ACC) which was held during March in Orlando, Florida and the 65th Annual Scientific Sessions of the American Diabetes Association (ADA) which was held a few weeks ago in San Diego, CA. Therefore, we developed **Diabetes 2005** so that important information presented at the Conferences could be shared with you on a timely basis.

**Diabetes 2005**, a newsletter CME program, is being offered to you by Yale University School of Medicine with the support of an unrestricted educational grant from Takeda Pharmaceuticals America, Inc. and Eli Lilly and Company. This booklet contains five **Diabetes 2005** newsletters and a post-test. After successfully completing the test and evaluation form and remitting a \$25 processing fee to the Yale Center for Continuing Medical Education, you will qualify for a maximum of 5.5 Category 1 credits towards the AMA Physician's Recognition Award to be issued by Yale University School of Medicine.

After successfully completing the program, you will be able to:

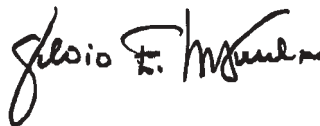
- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- Describe the evolving cellular mechanisms associated with the progression of diabetes and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the important association between insulin resistance/metabolic syndrome and atherosclerosis in patients with Type 2 diabetes.
- Compare the mechanisms of actions of the various pharmacologic agents for the treatment of diabetes, their risks and benefits, and their proper role in the management of this disease.
- Identify evolving and emerging management strategies for diabetes (e.g., combination antihyperglycemic therapy, new insulin delivery systems, new glucose monitoring techniques, novel drugs.)
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.
- Identify unique management issues among special sub-populations of patients with diabetes.
- Discuss the impact of diabetes on the healthcare system.

Given the recent explosion of information on diabetes, as well as its relationship to cardiovascular diseases, we began publishing this newsletter series five years ago. We hope the information presented in these newsletters will prove useful to you in the management of your patients.

Sincerely,



Robert S. Sherwin, M.D.  
C.N.H. Long Professor of Medicine  
Yale University  
Director, Yale Diabetes & Endocrinology  
Research Center



Silvio E. Inzucchi, M.D.  
Professor of Medicine  
Yale University  
Director, Yale Diabetes Center

## ***Educational Needs***

This program seeks to provide physicians with the latest and most important information presented at scientific meetings this year. Unfortunately, despite the valuable information that can be gained at these conferences, the majority of practicing physicians are unable to attend them. And, given the size and scope of these meetings, attendees often miss data presentations of interest to them. Therefore, programs designed to disseminate information from these meetings on a timely basis to physicians who either cannot attend the conferences or who miss some of the presentations fulfill an educational need that would otherwise not be met.

## ***Learning Objectives***

At the conclusion of this program, the participant should be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- Describe the evolving cellular mechanisms associated with the progression of diabetes and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the important association between insulin resistance/metabolic syndrome and atherosclerosis in patients with Type 2 diabetes.
- Compare the mechanisms of actions of the various pharmacologic agents for the treatment of diabetes, their risks and benefits, and their proper role in the management of this disease.
- Identify evolving and emerging management strategies for diabetes (e.g., combination antihyperglycemic therapy, new insulin delivery systems, new glucose monitoring techniques, novel drugs.)
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.
- Identify unique management issues among special sub-populations of patients with diabetes.
- Discuss the impact of diabetes on the healthcare system.

## ***Target Audience***

All endocrinologists and internal medicine and family practice physicians who have a special interest in and treat patients with diabetes.

## ***Educational Methods***

At the end of each conference day, a newsletter will be faxed or sent by e-mail to the office of participating physicians. Shortly after the ADA conference concludes, participants will receive a ***Diabetes 2005*** booklet containing all of the newsletters, a program highlights summary from the program co-editors, a course evaluation form, and a post-test.

## ***Evaluation***

A course evaluation form will provide participants with the opportunity to review the program content and method of delivery and to identify future educational needs and possible bias in the presentation.

## ***Accreditation***

This program has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of Yale University School of Medicine. Yale University School of Medicine is accredited by the ACCME to sponsor continuing medical education for physicians and takes responsibility for the content, quality, and scientific integrity of this CME program.

## ***Designation***

Yale University School of Medicine designates this continuing medical education activity for a maximum of 5.5 Category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spends in the educational activity.

# Table of Contents

|                        |   |
|------------------------|---|
| Editors' Summary ..... | 2 |
|------------------------|---|

## **2005 Scientific Sessions of the American College of Cardiology**

### **Issue One**

|   |    |
|---|----|
| <i>The Failing Diabetic Heart</i> .....                               | 3  |
| <i>Hey... Who Keeps Moving My Target?</i> .....                       | 4  |
| <i>Acute Myocardial Infarction in Diabetes: The Rule of Two</i> ..... | 5  |
| <i>PPARs and the Cardiologist</i> .....                               | 6  |
| <i>Makes Stents to Us!</i> .....                                      | 8  |
| <i>Identifying Pre-Diabetes: A New Imperative?</i> .....              | 9  |
| <i>Perils of the Protuberant Paunch</i> .....                         | 10 |

## **2005 Scientific Sessions of the American Diabetes Association**

### **Issue Two**

|   |    |
|---|----|
| <i>Intensive Insulin Infusion in Acute Myocardial Infarction?</i> ..... | 11 |
| <i>Diabetic Dyslipidemia: The Troublesome Triad</i> .....               | 13 |
| <i>Farewell to Fingersticks?</i> .....                                  | 14 |
| <i>Diabetes Prevention: Drugs vs. Lifestyle</i> .....                   | 15 |
| <i>So Many Posters, So Little Time</i> .....                            | 15 |

### **Issue Three**

|  |    |
|--|----|
| <i>Metabolic Syndrome: Treating the Parts, Not the Sum</i> ..... | 16 |
| <i>Insulin Administration: New Routes (Even Snouts)</i> .....    | 18 |
| <i>On the Horizon</i> .....                                      | 20 |
| <i>So Many Posters, So Little Time</i> .....                     | 20 |

### **Issue Four**

|  |    |
|--|----|
| <i>New Paths to Glycemic Control</i> ..... | 21 |
| <i>MOMMY and ME-tformin</i> .....          | 23 |
| <i>Feeling Low?</i> .....                  | 24 |
| <i>Late Breaking Clinical Trials</i> ..... | 25 |

### **Issue Five**

|   |    |
|---|----|
| <i>Not Your Traditional Risk Factors</i> .....    | 26 |
| <i>Activating PPARs – TZDs &amp; Beyond</i> ..... | 27 |
| <i>Diabetic Nephropathy</i> .....                 | 29 |
| <i>The Politics of Food</i> .....                 | 30 |
| <i>So Many Posters, So Little Time</i> .....      | 30 |

|  |    |
|--|----|
| <i>Diabetes 2005 Test</i> .....        | 31 |
| <i>Diabetes 2005 Evaluation</i> .....  | 32 |
| <i>Diabetes 2005 Answer Form</i> ..... | 33 |

# Diabetes2005

## Editors' Summary

In this issue of the *Diabetes 2005* monograph, we summarize important new scientific information that was presented at the 54th Annual Scientific Sessions of the American College of Cardiology (ACC) and the 65th Annual Scientific Sessions of the American Diabetes Association (ADA). Noteworthy among the many scientific presentations made at the ACC meeting (all patients) and ADA meeting (diabetes patients) were the results of the Treating to New Targets (TNT) study. During a “standing-room only,” Late-Breaking Clinical Trials session at the ADA meeting, Dr. James Shepherd from Glasgow shared the results for the diabetes subset of TNT. A total of 1,501 such patients were randomized to receive atorvastatin 10 mg or 80 mg daily and followed for 4.9 years. The average LDL-cholesterol at the completion of the trial was 100 mg/dl and 77 mg/dl in the 10 mg and 80 mg atorvastatin groups, respectively. Diabetic patients receiving 80 mg had a 25% relative risk reduction in the time to first major cardiovascular event ( $p=0.026$ ) and a 31% reduction in cerebrovascular events ( $p=0.037$ ). In the total patient population of over 10,000 patients, atorvastatin 80 mg reduced the relative risk of vascular events by 22% ( $p<0.001$ ). The results of this trial confirm that aggressive lipid lowering therapy, as is now recommended by the ADA (*Diabetes Care* 2005), should become standard for all patients with diabetes.

During the opening session of the ADA meeting, the value of intensive insulin therapy in acute myocardial infarction (AMI) was discussed. After a healthy debate and lively Q & A session, it was agreed that moderate-severe hyperglycemia must be avoided in AMI patients, that IV insulin by itself has no benefit unless glucose levels are also targeted, and that more data are needed to better understand the benefits of euglycemia during AMI. In a related abstract by Zeller *et al.*, almost a quarter of their diabetes patients developed heart failure after an AMI, with fasting glucose abnormality ( $>110$  mg/dl or “pre-diabetes”) an independent predictor of heart failure after controlling for multiple covariates (OR 2.58,  $p<0.0001$ ) (ACC abstract 1033-216). Plasma N-terminal Pro-B-type natriuretic peptide (N-BNP) may prove to be as a useful prognostic marker for patients with diabetes presenting with AMI (ACC abstract 1088-207).

Evidence for the important consequences of metabolic syndrome was underscored by Saely *et al.*, who noted that cardiovascular risk increases directly with the number of metabolic syndrome risk factors (e.g., central obesity, dyslipidemia, hyperglycemia, hyperinsulinemia, hypertension, endothelial dysfunction). The syndrome is an independent predictor of vascular events (hazard ratio 2.4 among men with known or suspected coronary artery disease), including in those who have already progressed to Type 2 diabetes (hazard ratio 3.9) (ACC abstract 803-6). In a study of over 5,000 Type 2 diabetes patients, Wong *et al.* from Australia found that patients with metabolic syndrome had cardiovascular disease prevalence rates that were similar to those observed in non-metabolic syndrome patients who were 10 years older (ADA abstract 255-OR), suggesting the need to initiate treatment a decade earlier in affected patients to mitigate risk. Another important observation was the presence of metabolic syndrome in 89% of children and adolescents with Type 2 diabetes (262-OR).

We anticipate exciting changes in the treatment of Type 2 diabetes based on the results of numerous presentations made at this year's ADA meeting. Studies of inhaled insulin\* (abstracts 355-OR, 356-OR, 357-OR, 359-OR, 361-OR), oral insulin\* (418-P), intra-nasal insulin\* (430-P), and transdermal insulin\* (362-OR) suggest a potential for these newer routes of delivery. Agents that decrease glucagon secretion, slow gastric emptying, and modulate appetite are the subjects of ongoing investigations. These include pramlintide (recently approved in the U.S., Symlylin<sup>®</sup>), a synthetic analogue of amylin (48-OR, 478-P); exenatide (recently approved in the U.S., Byetta<sup>®</sup>), a Glucagon-Like Peptide-1 (GLP-1) agonist (9-OR, 477-P); CJC-1131\*, a GLP-1 analogue (10-OR); and MK-0431\*, a dipeptidyl peptidase IV inhibitor (11-OR, 41-OR). In addition, results of preliminary studies were presented for: pinitol\*, an agent that acts downstream of the insulin signaling pathway to mimic insulin's effect (385-P); SGL0010\*, an orally active inhibitor of the renal sodium-dependent glucose transporter to increase urinary glucose losses (473-P); Gpi688\*, a glycogen phosphorylase inhibitor (492-P); MB06322\*, an oral selective fructose 1,6-biphosphatase inhibitor that attenuates gluconeogenesis (503-P); PSN101\* and PSN010\*, glucokinase activators that decrease hepatic glucose production and increase glucose-dependent pancreatic insulin secretion (522-P); gene therapy\* (i.e., GLP-1 chimeric expression vectors (589-P); and, an orally active modified fragment of the human growth hormone (hGH)\* to enhance lipolysis (1835-P). It remains to be seen which of these agents become a meaningful part of our armamentarium for diabetes and/or obesity over the coming years.

The results of two recently conducted studies—the first to compare pioglitazone and rosiglitazone—help to differentiate the currently available TZDs. In a multicenter, double-blind, randomized study of Type 2 diabetes patients who did not receive other lipid-lowering therapies, statistically significant differences favoring pioglitazone over rosiglitazone were observed based on improvements in triglycerides, HDL-cholesterol, and LDL-cholesterol particle concentration and size (ADA abstract 874-4). These results were echoed in an open-label study (COMPLEMENT) of patients with Type 2 diabetes and fasting triglyceride between 200 – 1000 mg/dl who had received stable ( $>90$  days) statin and rosiglitazone therapy and were switched at baseline from rosiglitazone to pioglitazone (30 mg/day titrated to 45 mg/day, at the discretion of the investigator) (ADA abstract 553-P). Lipid-lowering agents were maintained at stable, pre-study doses throughout the 17-week study. Statistically significant mean decreases in triglyceride and total cholesterol levels were observed, as was a significant mean increase in apolipoprotein A-1 (+9.7 mg/dl,  $p<0.001$ ) and a significant mean decrease in apolipoprotein B (-2.6 mg/dl,  $p<0.05$ ). These lipid changes were apparently independent of glycemic control, which was comparable for the two TZDs. In a follow-up study to TRIPOD, Dr. Tom Buchanan reported results from the PIPOD study in which 89 women with a previous history of gestational diabetes were treated with pioglitazone (157-OR). The results of both studies suggest that unloading the  $\beta$ -cell from insulin resistance is closely associated with diabetes prevention during TZD treatment. Together, the data continue to suggest that TZDs have possible beneficial effects on the  $\beta$ -cell and on the vasculature, although true outcomes studies are still ongoing. Results from the first TZD cardiovascular endpoint study, PROACTIVE, will be announced later this year at the annual congress of the European Association for the Study of Diabetes (EASD) in Athens, Greece.

More details on these and other topics are found in this volume of *Diabetes 2005*.

\* The product is not labeled for the use under discussion or the product is still investigational.

# Diabetes 2005

From the 54th Annual Scientific Sessions of the  
American College of Cardiology ■ Orlando, FL

2001 2002 2003 2004 **2005** 2006 2007

Sponsored by **Yale University School of Medicine**,  
Department of Internal Medicine, Section of Endocrinology

Volume **11** ■ March 9, 2005 ■ Issue **1**



## The Failing Diabetic Heart



Heart failure is an under-appreciated major contributor to cardiovascular deaths in patients with diabetes. It is frequently the consequence of systolic dysfunction from myocardial injury from both epicardial coronary atherosclerosis as well as microvascular disease. In addition, diastolic dysfunction is the consequence of diabetic cardiomyopathy and left ventricular hypertrophy due to frequently coexisting hypertension. Several research groups presented data at the ACC Scientific Sessions that add to our understanding of the prevalence and morbidity of heart failure in diabetic patients.

Investigators from the Mayo Clinic found left ventricular systolic dysfunction to be highly prevalent and associated with a poor prognosis in asymptomatic diabetics. Left ventricular dysfunction (defined as LVEF <50% by stress single photon emission computed tomography [SPECT]) was observed in 16.7% (n=175; mean LVEF =  $40.0 \pm 7.7\%$ ) of 1046 patients with diabetes (83% with Type 2 diabetes, mean HbA1c 9.0%, BMI 30 kg/m<sup>2</sup>) without cardiovascular symptoms and with no known coronary artery disease (abstract 809-7). This group was older (63 vs. 59 yrs; p=0.005), had more peripheral arterial disease (45% vs. 29%; p<0.001), a higher proportion with Q waves on ECG (21% vs. 9%; p<0.001), and more intermediate/high-risk "Summed Stress Scores," an objective measure of ischemia on scintigraphy (74% vs. 38%; p<0.001) than the group with normal LV function. Importantly, survival was markedly reduced in patients with LV dysfunction (p<0.0001 vs. LVEF  $\geq 50\%$ ), with an annual mortality rate of 7%.

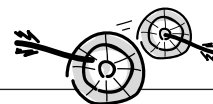
Zeller and French co-workers investigated the influence of abnormal fasting glycemia on the occurrence of heart failure after acute myocardial infarction (abstract 1033-216). Among 894 such patients, 22% developed heart failure. Patients with heart failure were significantly older (median age 75 vs. 63 years; p<0.0001) and had higher admission blood glucose (149 vs. 125 mg/dl; p<0.001), fasting blood glucose (118 vs. 104 mg/dl; p<0.001), and HbA1c (6.1 vs. 5.7%;

p<0.01) values as compared to those without heart failure. Not surprisingly, patients with heart failure also had a higher incidence of LVEF  $\leq 40\%$  (28% vs. 10%; p<0.05) and in-hospital mortality (12% vs. 3%; p<0.001). By logistic regression analysis, heart failure was a strong independent predictor of in-hospital death (OR 4.53; p<0.0001). Fasting glucose abnormality (>110 mg/dl; "pre-diabetes") was an independent predictor of heart failure, even after adjustment for covariates (age, gender, hypertension, prior myocardial infarction, ST elevation myocardial infarction [STEMI], LVEF, and creatinine level) (OR 2.58; p<0.0001). (See more on outcomes in patients with pre-diabetes on page 7).

Therapy for heart failure in the diabetic patient should be initiated early in the course of disease, with aggressive targeting of all modifiable risk factors, specifically with ACE-inhibitors,  $\beta$ -blockers, aspirin, and antihyperglycemic and lipid therapies. Lifestyle changes (e.g., reducing body weight and sodium intake, smoking cessation, exercise) should also be recommended. The UKPDS showed an 8%-13% increased risk of heart failure for every 1% rise in HbA1c. In the STENO-2 study, a multi-pronged approach targeting HbA1c <6.5%, total cholesterol <175 mg/dl, triglycerides <150 mg/dl, and systolic/diastolic blood pressure <130/80 mm Hg was shown to reduce risk of heart failure in individuals with diabetes (Gaede *et al.*, *N Engl J Med* 2003). However, the effect of glucose lowering therapies in heart failure patients with diabetes has not been extensively studied. Moreover, no large trial has specifically evaluated the various therapeutic interventions (ACE inhibitors,  $\beta$ -blockers) to reduce risk in diabetic heart failure patients. Sub-group analyses of numerous multicenter, randomized studies, however, suggest a similar, if not greater, benefit in patients with diabetes as compared to the non-diabetic population. Clearly, we need more data to best prevent and treat this important cardiovascular complication in our patients with diabetes.



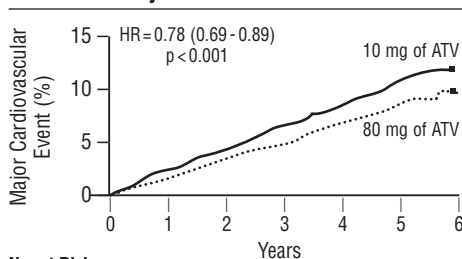
## Hey... Who Keeps Moving My Target?



Great emphasis continues to be placed on LDL-cholesterol lowering to reduce risk of cardiovascular events. It is now established that lowering LDL-cholesterol to a target level of 100 mg/dl is beneficial in patients with acute coronary syndromes. During a Late-Breaking Clinical Trials session at this week's ACC meeting, Dr. John LaRosa presented what many consider "landmark" findings of the Treating to New Targets (TNT) trial. The TNT investigators prospectively assessed over a median of 4.9 years the effect of lowering LDL-cholesterol to a target of 75 mg/dl in patients with stable coronary heart disease (also just published in this week's *New England Journal of Medicine*). A total of 10,001 patients with established coronary heart disease and LDL-cholesterol levels of less than 130 mg/dl were randomized to two groups (15% of patients in both groups had diabetes;  $n \approx 750$ ) in the double-blind, prospective trial. One group ( $n = 5006$ ) received atorvastatin 10 mg daily with a target LDL-cholesterol of 100 mg/dl, the other ( $n = 4995$ ) received atorvastatin 80 mg daily with a target LDL-cholesterol of 75 mg/dl. Treatment with the higher dose of atorvastatin resulted in a lower mean LDL-cholesterol level (77 mg/dl vs. 101 mg/dl) and greater decreases in total cholesterol and triglycerides, as compared to the lower dose, but with no additional effect on HDL-cholesterol. A primary event (defined as a first major cardiovascular event) occurred in 434 patients (8.7%) receiving atorvastatin 80 mg and 548 patients (10.9%) receiving atorvastatin 10 mg, which represents an absolute reduction in the rate of major cardiovascular events of 2.2%, and a relative risk reduction of 22% (hazard ratio [HR] 0.78, 95% CI 0.69-0.89) (Figure 1). Patients in the higher-dose atorvastatin group showed additional reductions in the risk of: any coronary event (HR 0.79, 95% CI 0.73-0.86;  $p < 0.001$ ), a cerebrovascular event (HR 0.77, 95% CI 0.64-0.93;  $p < 0.01$ ), and hospitalization with heart failure (HR 0.74, 95% CI 0.59-0.94;  $p = 0.01$ ). The investigators also noted that there were no significant differences between groups in the rates of hemorrhagic stroke or cancer, two concerns that had emerged from previous statin trials. It was, however, noted that 1.2% of the high-dose atorvastatin group showed a persistent three-fold elevation in liver ALT/AST levels, in comparison with 0.2% in the low-dose atorvastatin group ( $p < 0.001$ ), although there were no significant differences in statin-related myalgia or rhabdomyolysis.

The Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment

**Figure 1. Cumulative Incidence of a First Major Cardiovascular Event**



| No. at Risk | 0    | 1    | 2    | 3    | 4    | 5    | 6 |
|-------------|------|------|------|------|------|------|---|
| ATV 10 mg   | 5006 | 4866 | 4738 | 4596 | 4456 | 2304 | 0 |
| ATV 80 mg   | 4995 | 4889 | 4774 | 4654 | 4521 | 2344 | 0 |

HR denotes hazard ratio for the group given atorvastatin (ATV) 80 mg as compared with the group given ATV 10 mg

Panel has recommended an LDL-cholesterol level of less than 100 mg/dl as the goal for therapy for patients at high risk of coronary heart disease, with an optional target of 70 mg/dl for those at very high risk. These were based on the findings of the Heart Protection Study (HPS) and the Pravastatin or Atorvastatin Evaluation and Infection Trial (PROVE IT). We feel the TNT results confirm that these recommendations are not only sound, but actually may need to be strengthened—so that the LDL-cholesterol goal for most coronary artery disease (CAD) patients would now be in the 70-75 mg/dl range. Also, since diabetes is considered to be a CAD risk-equivalent, the question will now be: should all diabetic patients have their LDL lowered to this range? Stay tuned for potential new recommendations from the NCEP and the American Diabetes Association...

At least three major recent statin trials therefore tell us that there is a direct and linear relationship between LDL-lowering within the normal range and clinical outcomes—with seemingly no lower threshold. Having said that, the majority of our patients with diabetes will find it difficult to achieve all lipid targets (LDL-C  $< 100$  mg/dl [ $? < 70$  mg/dl], triglycerides  $< 150$  mg/dl, HDL-C  $> 40$  mg/dl in men and  $> 50$  mg/dl in women) with statin monotherapy. Furthermore, the dyslipidemia of diabetes is characterized by hypertriglyceridemia, low HDL-cholesterol, and only a modestly elevated LDL-cholesterol. With this in mind, there were several interesting presentations made this week on effects of various agents on the often forgotten "other" lipoproteins.

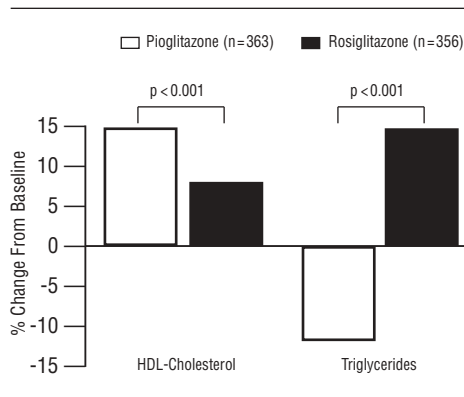
Taylor *et al.* from Walter Reed Army Medical Center randomized patients with known coronary heart disease, mean LDL-cholesterol of 89 mg/dl, and low levels of HDL-cholesterol

( $< 45$  mg/dl) to placebo or extended-release niacin (1000 mg) once daily, each added to background statin therapy (ARBITER 2) (abstract 1001-114). These investigators previously reported that niacin slowed the progression of carotid atherosclerosis when added to statin monotherapy. Additional analyses presented this week examined the relationship between glucose intolerance and the effects of niacin on common carotid artery intima-media thickness (CIMT). Among 149 that completed the study, 88 had diabetes or the metabolic syndrome. Niacin increased HDL-cholesterol to a similar degree ( $\approx 20\%$ ) in those with normal glucose levels, metabolic syndrome, and diabetes. The lowest progression rate was observed in niacin-treated patients with normal glucose levels and the highest with placebo, irrespective of glycemic status. In multivariable linear regression, a greater increase in HDL-cholesterol was independently associated with superior effects on CIMT.\* These benefits of niacin must be weighed against the real-world challenges of flushing, the small risk of LFT abnormalities, and increases in insulin resistance, with the potential for hyperglycemia, the latter of which may require adjustment of the antidiabetic regimen.

Goldberg and coworkers presented the results of the first large, prospective, multicenter, double-blind study comparing thiazolidinediones (TZDs) based on changes in cardiovascular risk determinants (abstract 874-4). After a four-week placebo washout period, 802 patients with Type 2 diabetes and associated dyslipidemia were randomized to pioglitazone 30 mg daily or rosiglitazone 4 mg daily for 12 weeks, with the dosages then increased to 45 mg daily and 4 mg twice daily for 12 weeks, respectively. Study patients did not receive other lipid-lowering therapies during the study. Despite similar glycemic control, statistically significantly different lipid effects favoring pioglitazone were observed at the study endpoint, including improvements in triglycerides and HDL-cholesterol (Figure 2), perhaps based on differential activation of PPAR- $\alpha$ . Both drugs increased LDL-cholesterol, with greater effects in the rosiglitazone group. However, this was felt to be secondary to a mean increase in the size of LDL particles and not an increase in LDL particle number. Such changes suggest a less atherogenic LDL. The cardiovascular implications of these TZD-induced lipid changes remain unclear. The results of the first TZD cardiovascular outcomes trial (PROactive) is expected to be announced later this year (pioglitazone vs. placebo in diabetic patients with stable coronary artery disease.)

Davidson and co-workers from Rush-Presbyterian-St. Lukes in Chicago presented the results of two phase 2 trials involving torcetrapib,\* an inhibitor of cholesteryl ester transferase protein—a drug that has been shown to prominently raise HDL-cholesterol levels (abstract 802-3). These were multi-center, double-blind, randomized trials in which patients (not exclusively diabetics) with low HDL-cholesterol (men <44 mg/dl; women <54 mg/dl) were randomized to receive torcetrapib 10, 30, 60, or 90 mg once daily or placebo. One study enrolled patients taking no other lipid-modifying therapy (n=162), and the other enrolled patients who required such therapy (n=174). These patients received

**Figure 2. Differential Effects of TZDs on Cardiovascular Risk Factors**



**Table 1. Lipid Lowering Medications for Patients With Diabetes**

| Class                             | Agents  | LDL-C | HDL-C | Triglycerides |
|-----------------------------------|---|-------|-------|---------------|
| Statins                           | Rosuvastatin, atorvastatin, simvastatin, pravastatin, fluvastatin, lovastatin | ↓↓↓   | ↔ - ↑ | ↓ - ↓↓        |
| Fibrates                          | fenofibrate, gemfibrozil  | ↔ - ↓ | ↑     | ↓↓↓           |
| Niacin*                           |   | ↓↓↓   | ↑↑↑   | ↓↓↓           |
| Binding resins†                   | cholestevam, colestipol, cholestyramine                                       | ↓↓↓   | ↔     | ↑             |
| Cholesterol absorption inhibitors | ezetimibe   | ↓↓↓   | ↔     | ↓             |

\* May increase insulin resistance; monitor glucose levels closely.  
 † May increase triglyceride levels.

atorvastatin 20 mg/day during an eight-week run-in period and during the eight-week treatment period with study drug. When torcetrapib was used as monotherapy, least squares mean changes from baseline (relative to placebo) at week 8 ranged from +3.6 to +21.5 mg/dl (+9 to +55%) (p=0.0001 for the 30 mg and higher doses) for HDL-cholesterol and from +2.1 to -19.9 mg/dl (+3 to -17%) (p<0.001 for the 90 mg dose) for LDL-cholesterol. When combined with a statin, least squares mean changes from the statin-established baseline (relative to placebo) ranged from +3.7 to +16.5 mg/dl (+8 to +40%) (p=0.0001 for 30 mg and higher doses) for HDL-cholesterol and from +2.3 to -16.4 mg/dl (+3% to -19%) (p<0.01 for 60 mg and 90 mg doses) for LDL-cholesterol. Particle size for both HDL and LDL increased with active drug. No significant drug-related adverse events were observed. However, in some treatment groups, small increases in systolic and diastolic blood pressures were noted.

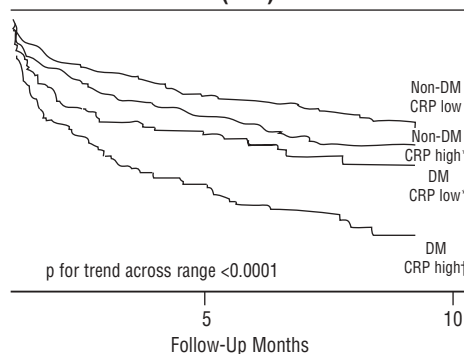
Understanding the unique effects and indications of each class of lipid-lowering drugs is important for optimal patient management (see Table 1). With more stringent lipid targets, combination therapies are likely to play a greater role in the management of dyslipidemia in our patients with diabetes. Caution is advised when combining certain classes, such as statins with fibrates and/or niacin due to a modestly increased risk of myositis and/or LFT abnormalities.

## Acute Myocardial Infarction in Diabetes: The Rule of Two

Coronary heart disease (CHD) is the leading cause of death in patients with diabetes. Based on a comparable 10-year risk for a CHD event (>20%) between patients with diabetes who do not have recognized CHD and patients with prior myocardial infarction but no diabetes, diabetes is now considered a CHD risk equivalent in the NCEP ATP III guidelines. Dr. Burton Stobel of the University of Vermont described in a symposium on "Diabetes and Coronary Artery Disease" at this week's meeting that patients with diabetes followed the 'Rule of Two'. They have twice the risk of having an acute myocardial infarction (AMI), twice the amount of myocardial necrosis as a result of these infarcts, and twice the risk of developing subsequent complications, such as congestive cardiac failure or sudden death.

Faced with the higher in-hospital mortality of diabetic patients with acute coronary syndromes, many investigators are currently searching for

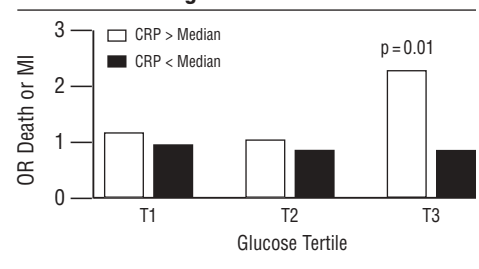
**Figure 3. Kaplan–Meier Estimate of Event-Free Survival (Death/MI) by Diabetes (DM) and CRP Status**



\* DM/CRP low vs. non-DM/CRP high p=0.3  
 † DM/CRP high vs. all other groups p<0.0001

ways to identify those patients at increased risk. Zeller and colleagues (abstract 1088-207) from

**Figure 4. Interaction Between Glucose and CRP on Death or MI Among Diabetic Patients**

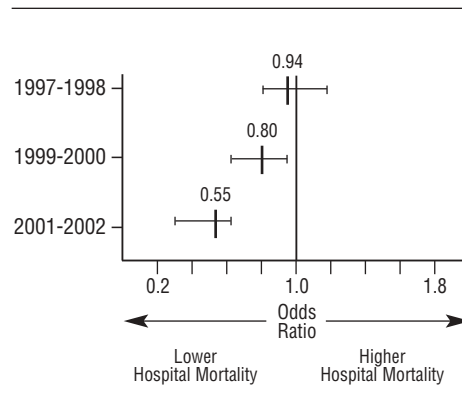


the French RICO survey examined whether plasma N-terminal Pro-B-type natriuretic peptide (N-BNP) obtained on admission for AMI might yield any prognostic information. N-BNP is secreted in response to changes in diastolic intra-ventricular pressure that results from myocardial ischemia, and has been shown in non-diabetic individuals to identify

those at a higher short- and long-term risk from cardiac complications. Of the 560 patients with AMI in this survey, 199 patients had diabetes, defined by the investigators as a documented history of the disease or the mean of two fasting glucoses on days 4 and 5 post-AMI >126 mg/dl. Median (25th-75th percentiles) N-BNP levels were significantly higher in diabetic (245 [81-777] pmol/l) than non-diabetic (130 [49-299] pmol/l) individuals, a difference that remained significant even after adjustment for age, creatinine clearance, and left ventricular ejection fraction (LVEF). Diabetes patients showed a significantly higher in-hospital mortality (17% vs. 6%) and rate of cardiogenic shock (16% vs. 7%). Multivariate analysis within the diabetic population showed a direct and highly significant association between in-hospital mortality, cardiogenic shock, and plasma N-BNP, and an inverse relationship with LVEF. These findings indicate that N-BNP may also prove a useful prognostic marker for individuals with diabetes presenting with AMI, as has already been demonstrated in the general CHD population.

Ray and colleagues from Harvard Medical School looked at the impact of hyperglycemia and inflammation on outcomes in patients with acute coronary syndrome enrolled in the OPUS-TIMI 16 and TACTICS-TIMI 18 trials (abstract 832-4). They noted higher median C-reactive protein (CRP) on admission in diabetic than non-diabetic patients in both trials. When the diabetic patients were stratified by median CRP, the inflammatory marker was found to be predictive of poorer outcomes (death/MI) (Figure 3). Interestingly, this was not the case in the non-diabetic patients. Moreover, in the diabetic population, high glucose on admission

**Figure 5. Effect of Adherence to Guidelines on In-Hospital Mortality of STEMI in Patients with Diabetes**



was found to heighten the cardiovascular risk associated with high CRP (Figure 4). A Cox-regression model revealed a significant interaction between death/MI and admission glucose and CRP ( $p < 0.05$ ). These findings would suggest that therapies designed to reduce both hyperglycemia and inflammation during acute coronary syndrome may reduce the high risk faced by diabetic patients. We would note, however, that recent trials (MIRACL, A-to-Z) have yielded mixed results on the benefits of acute, aggressive lipid lowering therapy with statins in acute coronary syndrome, a treatment which is known to reduce CRP levels (obviously, among other things.)

An interesting paradox of obesity is that while it increases an individual's risk of AMI, it reduces the risk of that individual dying as a result of their infarct. This relationship is all the

more striking because of the known association of obesity with other CHD risk factors, including diabetes. The obesity paradox received some confirmation this week in the report from the National Registry for Myocardial Infarction (NRM1)-4 database (abstract 1033-218). Of 172,061 patients in the database with ST-elevation myocardial infarction (STEMI), obese individuals (BMI >30 kg/m<sup>2</sup>) showed a *decreased* mortality across all age groups. This may be because obese individuals generally had lower "TIMI risk scores" at presentation. (The TIMI score is a simple arithmetic sum of independent predictors of mortality weighted according to the adjusted odds ratios from logistic regression analysis of patients in the Thrombolysis in Myocardial Infarction study.) However, it was also noted that obese individuals were significantly more likely to have received reperfusion and adjunctive medical therapy, and were less likely to have suffered an asymptomatic AMI.

Strict adherence to guidelines was shown to improve outcomes from STEMI by the MITRA PLUS investigators (Gitt *et al.*, abstract 1004-226). From 1994 to 2002 patients presenting to a group of 319 regional hospitals in Germany have been registered in a database. In-hospital mortality at these institutions has fallen from 20.5% in 1994/96 to 13.2% in 2001/2002 ( $p < 0.001$  for trend). This was associated with an increase in acute reperfusion therapy (mainly through the increased use of primary percutaneous intervention [PCI]) as well as the increased use of adjunctive therapy (especially  $\beta$ -blockers and statins). The influence of adherence to guidelines was especially valuable in reducing in-hospital mortality of STEMI in diabetic patients (Figure 5).



## PPARs and the Cardiologist



Over the past several years, we've observed increasing attention to diabetes, particularly vis-à-vis the use of insulin sensitizing drugs, at national cardiology meetings. This newfound interest has emerged from decades of research linking insulin resistance to vascular disease (see page 8), and, more recently, the availability of pharmacological agents that enhance insulin-mediated glucose uptake—namely the insulin sensitizing thiazolidinediones (TZDs). These drugs, sometimes referred to as "PPAR agonists" have a unique mechanism of anti-hyperglycemic action: activation of the nuclear transcription factor known as peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ). Such activation enhances the transcription of a variety of genes related not only to glucose

regulation, but also to lipoprotein metabolism and vascular biology. TZDs are purported to have anti-atherosclerotic effects—but, importantly, no cardiovascular outcomes studies are yet available. Dozens of abstracts were presented at this week's ACC Scientific Sessions on this drug class in both diabetic and non-diabetic patients.

### Reduction in Restenosis

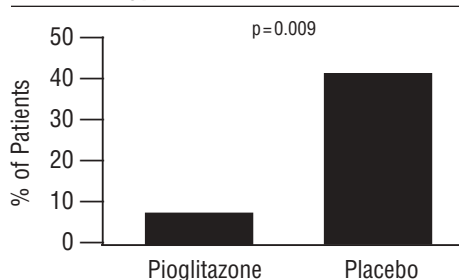
The incidence of in-stent restenosis has been dramatically reduced by the use of drug-eluting stents (page 6). In humans, TZDs improve several cardiovascular risk factors, including HDL-cholesterol (see page 2). In animal models, they appear to reduce atherosclerosis. In *in vitro* sys-

tems, these agents attenuate some of the molecular events associated with atheroma development, including smooth muscle cell proliferation. Interest in this drug class in the cardiology community was stimulated several years ago when they were shown to reduce neointimal proliferation in coronary stents and, therefore, the risk of in-stent restenosis.\* Although this specific effect may be less exciting these days with restenosis a less common event due to drug-eluting stents, research in this area continues to grow. The hypothesis of TZD benefit following percutaneous coronary intervention was examined by Yokoyama and Japanese co-workers who compared the in-stent restenosis rate following successful coronary angioplasty with a bare metal

stent in 40 Type 2 diabetes patients. Sixteen patients (24 lesions) were treated with pioglitazone 15 mg daily added to previous anti-hyperglycemic therapy for six months and 24 patients (26 lesions) were treated with conventional antihyperglycemic therapy without pioglitazone (control group) (abstract 1038-4). The treatment groups were comparable based on baseline prevalences of hyperlipidemia and hypertension, type of lesion, reference vessel diameter, and lesion length. Six months after the procedure, angiographically-confirmed restenosis (defined as >50%) was significantly lower in the pioglitazone group than in the control group (Figure 6). Of note, the rate of in-stent restenosis in pioglitazone-treated patients was comparable to that observed after use of drug-eluting stents.

The impact of pioglitazone on in-stent restenosis was also evaluated in two studies of patients without diabetes. Katayama and Japanese co-workers randomized non-diabetic patients (based on glucose tolerance testing) with stable angina to six months treatment with pioglitazone 30 mg daily (16 patients with 18 lesions) or placebo (18 patients with 20 lesions) after coronary stenting (abstract 1065-21). After six months, intimal area (1.2 vs. 1.8 mm<sup>2</sup>) and intimal index (0.13 vs. 0.2) measured using intravascular ultrasound (IVUS) were significantly smaller (*i.e.*, better) in the pioglitazone group than controls (each  $p < 0.05$ ). Diameter restenosis evaluated by quantitative angiography was also significantly smaller in the pioglitazone group (22.9% vs. 39.5%,  $p < 0.01$ ). Three control patients (15%) and none treated with pioglitazone required target lesion revascularization. In a late-breaking clinical trials session, Marx and German investigators presented their findings from a double-blind trial of non-diabetic patients randomized to pioglitazone 30 mg (20 evaluable patients, 29 lesions) or placebo (22 evaluable patients, 31 lesions) for six months after coronary stent implantation. In line with the findings of Katayama *et al.*, a treatment effect favoring the TZD was observed based on mean percent diameter restenosis and neointimal volume index. Taken together, these findings suggest that pioglitazone reduces neointimal hyperplasia and re-stenosis after coronary stent implantation, regardless of patients' glycemic status. Such a beneficial effect of TZDs observed among individuals without diabetes may result from anti-inflammatory activity, decreased trophic effects from lower insulin levels, regulation of smooth muscle cell proliferation, and/or promotion of re-endothelialization after PTCA.

**Figure 6. Effect of Pioglitazone on In-stent Restenosis Rate in Type 2 Diabetes Patients**



### Improvement in Cardiac Metabolism and Endothelial Function

Preserving myocardial glucose uptake is important for the viability of jeopardized myocardium in patients with ischemic coronary artery disease. Lautamäki and Finnish co-workers conducted a double-blind study in which 54 patients with Type 2 diabetes and coronary disease were randomized to receive rosiglitazone or placebo, with PET scans using [18F]fluorodeoxyglucose (FDG) performed during a hyperinsulinemic euglycemic clamp before and after 16 weeks of treatment (abstract 1006-222). Myocardial glucose uptake increased by 6.12  $\mu\text{mol}/100\text{g}/\text{min}$  in ischemic regions ( $p = 0.023$ , ANCOVA adjusted for gender and baseline), localized by the combination of rest-stress 99m Tc-SPECT imaging and coronary angiography, and by 8.40  $\mu\text{mol}/100\text{g}/\text{min}$  in non-ischemic regions ( $p = 0.003$ ) on rosiglitazone as compared to placebo. Significant improvements in whole body insulin sensitivity and glycemic control were also observed with rosiglitazone. TZD therapy may therefore improve myocardial glucose utilization in the ischemic, diabetic myocardium.\* How this would translate to a clinically meaningful effect is not clear, but worthy of further study.

Watanabe and Japanese colleagues randomized 40 patients with CAD and metabolic syndrome to receive pioglitazone and fenofibrate (a PPAR- $\alpha$  agonist) or no PPAR agonist (control group) (abstract 1116-213). Insulin resistance was evaluated by HOMA-IR. Endothelial function was assessed by measuring flow-mediated dilation by brachial artery ultrasound. Aortic stiffness was determined using aortic pulse wave velocity by an oscillometric technique. Finally, exercise tolerance was assessed by time to ST segment depression ( $\geq 0.10$  mV) during a treadmill exercise test. Flow-mediated dilation and exercise tolerance were significantly increased, and pulse wave velocity was significantly

**Table 2. Changes in Edema Status From Baseline to Endpoint**

|                 | Pioglitazone | Rosiglitazone |
|-----------------|--------------|---------------|
| No Change       | 295 (81%)    | 287 (80%)     |
| Improving Edema | 21 (6%)      | 25 (7%)       |
| Worsening Edema | 49 (13%)     | 46 (13%)      |

decreased at six months in the combined (*i.e.*  $\alpha/\gamma$ ) PPAR-agonist group. These results are provocative in light of the recent pursuit by several pharmaceutical companies of single drugs that have both PPAR- $\alpha$  and PPAR- $\gamma$  activity (so-called "dual-PPARs"). These agents, in early trials, appear to have additive beneficial lipid effects as compared to conventional TZDs.\* Whether they come to market soon is less clear, as several high-profile drugs of the dual-PPAR category have been dropped in late-stage clinical trials due to toxicities. However, the data from Watanabe *et al.* may suggest significant benefit of such agents in vascular disease patients.

### Heart Failure

TZDs may contribute to fluid retention, which in some patients with established heart failure may precipitate or exacerbate symptoms. Several studies examining the prevalence of TZD-induced fluid retention and its impact on patients with heart failure were presented this week.

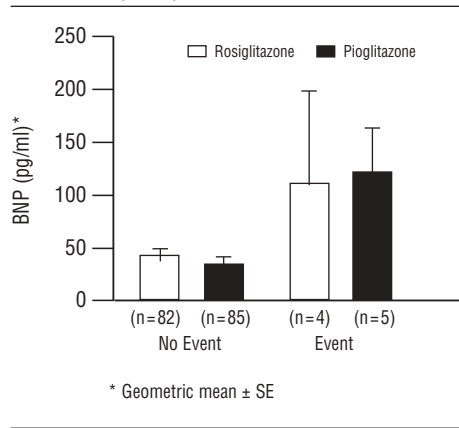
In a prospective, multicenter, randomized, double-blind study, Kendall *et al.* compared the TZDs, pioglitazone (30/45 mg once daily) and rosiglitazone (4 mg/8 mg once daily), based on incidence of edema and weight gain (abstract 874-4). While most patients experienced either no change or an improvement in edema status (Table 2), worsening edema and weight gain (mean,  $3.0 \pm 0.2$  kg vs.  $2.7 \pm 0.2$  kg,  $p = 0.157$ ) occurred at a similar rate for both TZDs after 24 weeks of therapy. Only one episode of heart failure was reported (in a rosiglitazone-treated patient).

To determine the value of B-type natriuretic peptide (BNP) to identify diabetes patients at risk of developing TZD-related fluid retention, Dargie and Scottish associates conducted a multicenter, double-blind study in which 224 patients with Type 2 diabetes and New York Heart Association (NYHA) class I/II heart failure were randomized to rosiglitazone 4-8 mg daily or placebo in addition to background anti-hyperglycemic agents (titrated as required to achieve fasting plasma glucose  $< 126$  mg/dl) for 52 weeks (abstract 1048-173). Heart failure medications including diuretics were changed as appropriate. Irrespective of the

treatment received, patients who subsequently developed heart failure (Figure 7), edema, or dyspnea during the 52-week study had a higher baseline BNP compared to those who remained stable. These findings suggest that BNP may be a useful tool for identifying patients at risk of clinically important fluid retention when treated with a TZD.

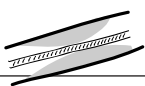
To explore the mechanism by which TZDs cause fluid retention, Dargie and his co-investigators from Scotland randomized 224 Type 2 diabetes patients with NYHA class I/II heart failure to rosiglitazone (4-8 mg daily) or placebo in addition to background anti-hyperglycemic agents for 52 weeks (abstract 874-3). Background anti-hyperglycemic medications were uptitrated as required to achieve the glycemic goal of fasting glucose <126 mg/dl, and heart failure medications

**Figure 7. Heart Failure by Baseline B-Type Natriuretic Peptide (BNP) Level**

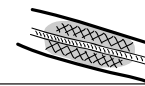


were changed as necessary. The investigators found no differences between the TZD and placebo groups based on cardiac structure or ejection fraction (37.8% vs. 36.8%) at the end of the study year, confirming the results of prior studies, that TZDs do not adversely affect cardiac structure or function in diabetes patients with heart failure.

We anxiously await the results of the first TZD endpoint study, PROactive, anticipated later this year. Until then, the prescription of an antihyperglycemic agent for a patient with Type 2 diabetes should primarily take into account its glucose lowering effect. However, careful consideration of any "non-glycemic benefits" as well as the side effect profile will allow the practitioner to optimize individual regimens for each patient.



## Makes Stents to Us!



Percutaneous intervention (PCI) therapy is increasingly used in the management of acute coronary syndromes, and has been associated with improved outcomes in non-diabetic subjects. However, in patients with diabetes there are concerns that PCI is less effective, and that it may even have a negative impact on outcomes. Many cardiologists suspect that the poor performance of PCI in diabetic patients may relate to the more diffuse and extensive nature of their coronary disease, as well as the use of bare-metal stents, which tend to undergo in-stent restenosis, especially in diabetes. The use of drug-eluting stents in non-diabetic patients is having a remarkable effect in reducing restenosis rates and improving outcomes from PCI. However, what about their efficacy in diabetic patients?

Eikouf and colleagues from Connecticut reported on 660 diabetic patients admitted to the Hartford Hospital for elective or emergency PCI (abstract 1093-19). Increasing use of sirolimus-eluting stents (55%), as well as adjunctive medical therapy, was associated with no measurable differences in clinical outcomes in diabetic patients with stable or unstable angina as well as non-ST-elevation myocardial infarction (STEMI) when compared with non-diabetic patients during the same time period. However, diabetic patients with STEMI continued to show poorer outcomes than non-diabetic subjects. In contrast, Kuchulakanti and colleagues from Washington Hospital Center compared outcomes of PCI with sirolimus-eluting stents in 1407 patients with Type 1 diabetes (n=160), Type 2 diabetes (n=332), and those

without diabetes (n=915) (abstract 1150-33). In the inpatient setting, Type 1 diabetes patients suffered a higher incidence of in-hospital complications including death (1.3% vs. 0.0% vs. 0.0%, Type 1 vs. Type 2 vs. no diabetes; p<0.001) and conversion to CABG (1.3% vs. 0.3% vs. 0.1%; p=0.04). At six-months, the groups differed in terms of a higher incidence of major adverse cardiovascular events (5.4% vs. 6.3% vs. 2.7%; p=0.03).

It has been difficult to make definitive conclusions on the use of drug-eluting stents in patients with diabetes because the number of patients included in most trials has been small. To address this, Abizaid and colleagues from Brazil and Columbia University Medical Center performed an integrated analysis of the diabetic patients included in six prospective trials (RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, DIRECT, and SVELTE) who had received sirolimus-eluting stents (n=292) or bare-metal stents (n=233), looking at six to eight month angiographic follow-up data and clinical outcomes (abstract 807-7). Rates of in-stent and in-lesion re-stenosis, non-Q wave MI, and major adverse cardiac events were significantly lower in the drug-eluting vs. bare metal stent groups (Table 3).

Jimenez-Quevedo and colleagues from Spain, reported preliminary findings from the Diabetes and Sirolimus-Eluting Stent Trial (abstract 839-7). From January to November 2003, 160 diabetic patients presenting with acute coronary syndrome were enrolled in a study to compare sirolimus-eluting with bare metal stents. In addition to PCI, the use of abciximab and dual

**Table 3. Impact of Stent Type on Outcomes in Diabetic Patients**

|                      | Sirolimus-Eluting Stents (n = 292) | Bare Metal Stents (n = 233) | p-value |
|----------------------|------------------------------------|-----------------------------|---------|
| In-stent restenosis  | 5.7%                               | 50.6%                       | <0.0001 |
| In-lesion restenosis | 11.8%                              | 52.5%                       | <0.0001 |
| Death                | 2.1%                               | 0.9%                        | 1.00    |
| Q-wave MI            | 0.7%                               | 0.4%                        | 1.0     |
| Non-Q-wave MI        | 1.0%                               | 4.7%                        | 0.0123  |
| MACE                 | 8.9%                               | 24.0%                       | <0.0001 |

MACE = major adverse cardiac events

anti-platelet therapy (aspirin and clopidogrel) was routinely recommended for all patients. The investigators reported that the use of sirolimus-eluting stents was associated with a significant reduction in the rate of target lesion revascularization (11.1% vs. 41.3% at one-year follow-up; p<0.0001), but no difference in mortality (1.9% with sirolimus-eluting stents vs. 3.2% with bare metal stents; p=NS) or myocardial infarction rates (3.8 vs. 6.5%; p=NS).

Although by no means definitive, the findings from these preliminary studies indicate that diabetic patients may derive benefit from the use of drug-eluting stents with PCI. We are therefore encouraged by these short-term results. Further studies are needed, however, so that we may better understand their effects on long-term outcomes.

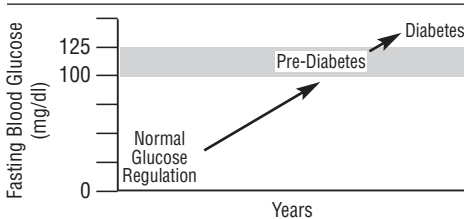


## Identifying Pre-Diabetes: A New Imperative?



Defects in glucose homeostasis evolve over a continuum, from normal to “impaired glucose regulation” (which includes both impaired fasting glucose [IFG] and impaired glucose tolerance [IGT]) to overt diabetes (Figure 8). Patients with IFG and/or IGT are also referred to as having “pre-diabetes” because of their high risk of progressing to frank hyperglycemia. The ADA recently redefined the cut-point for normal fasting plasma glucose levels from 110 mg/dl to 100 mg/dl. Based on this new criterion, the Department of Health and Human Services estimates that 40% (41 million) of U.S. adults between 40 and 74 years old are pre-diabetic. In two presentations made this week at the ACC Scientific Sessions, the new ADA criteria for IFG were shown to identify patients at risk for not only diabetes but also both cardiovascular disease and adverse clinical outcomes.

**Figure 8. Typical Progression of Impaired Glucose Regulation**



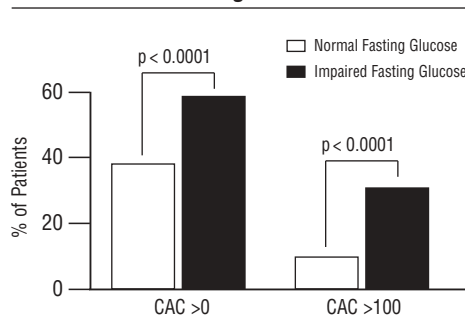
Nasir and coworkers from Johns Hopkins and Brazil evaluated 539 asymptomatic men without diabetes (479 with fasting glucose < 100 mg/dl and 60 with fasting glucose 110-125 mg/dl; on no antihyperglycemic medication) who presented for cardiac electron-beam computed tomography (EBCT) (abstract 1155-106). Individuals with IFG had higher systolic blood pressure, BMI, and triglycerides and lower HDL-cholesterol as compared to those with normal fasting glucose. The prevalence of any coronary artery calcification (CAC) as well as an elevated CAC score ( $\geq 100$ ) was significantly higher among men with IFG (Figure 9). According to multivariate regression analyses adjusting for coronary heart disease risk factors, patients with IFG were significantly more likely to have any CAC (OR 1.9, 95% CI 1.2-3.6;  $p=0.02$ ) and CAC  $\geq 100$  (OR 2.6, 1.4-5.3;  $p=0.01$ ), as compared to those with normal fasting glucose. These data suggest fasting glucose in the pre-diabetes range is independently associated with presence and severity of coronary artery calcification, a marker of coronary atherosclerosis, in otherwise apparently healthy men.

**Table 4. Diabetes Prevention with RAS Blockade**

| Study  | N      | Mean Follow-up (years) | ACE-I/ARB | RR (95% CI)*     |
|--------|--------|------------------------|-----------|------------------|
| CAPP   | 10,985 | 6.1                    | ACE-I     | 0.79 (0.67-0.94) |
| STOP-2 | 6,614  | 5.0                    | ACE-I     | 0.96 (0.72-1.27) |
| HOPE   | 9,297  | 5.0                    | ACE-I     | 0.66 (0.51-0.85) |
| LIFE   | 9,193  | 4.8                    | ARB       | 0.75 (0.63-0.88) |
| ALLHAT | 24,309 | 4.9                    | ACE-I     | 0.70 (0.56-0.86) |
| ANBP2  | 5,626  | 4.1†                   | ACE-I     | 0.66 (0.54-0.85) |
| SCOPE  | 4,937  | 3.7                    | ARB       | 0.81 (0.61-1.02) |
| ALPINE | 392    | 1                      | ARB       | 0.13 (0.03-0.99) |
| CHARM  | 7,601  | 3.2                    | ARB       | 0.78 (0.64-0.96) |
| INVEST | 22,576 | 2.7                    | ACE-I     | 0.98 (0.82-1.18) |
| SOLVD  | 291    | 3.4                    | ACE-I     | 0.26 (0.13-0.53) |
| VALUE  | 15,245 | 4.2                    | ARB       | 0.77 (0.69-0.86) |
| PEACE  | 8,290  | 4.8†                   | ACE-I     | 0.83 (0.72-0.96) |

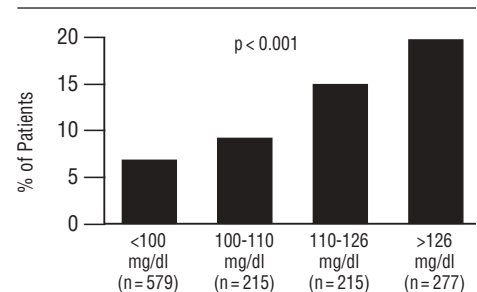
\* Development of diabetes. † Median

**Figure 9. Coronary Artery Calcium (CAC) and Fasting Blood Glucose**



Otten and coworkers from the University of Michigan assessed the impact of the pre-diabetic state on inpatient clinical outcomes in 1763 patients presenting with acute coronary syndrome (abstract 1033-215). Adverse clinical events, including death ( $p<0.001$ ), stroke ( $p=0.033$ ), pulmonary edema ( $p<0.001$ ), and major cardiac adverse events (MACE,  $p<0.001$ ; Figure 10), were significantly higher in pre-diabetic and diabetic patients compared to those with normal fasting glucose. Multivariate risk adjustment demonstrated a gradient of adverse clinical outcome risk (composite) that was proportional to fasting glucose: 1.3 ( $p=0.369$ ) for levels between 100-110 mg/dl; 1.9 ( $p=0.023$ ) for levels between 110-126 mg/dl; and 3.0 ( $p<0.001$ ) for levels  $>126$  mg/dl. This study suggests that the pre-diabetic state is at least a marker for worse prognosis in patients with acute coronary syndrome. What cannot be known from these data is whether more aggressive

**Figure 10. Major Adverse Cardiac Events in Patients with Acute Coronary Syndrome by Fasting Blood Glucose**



treatment strategies for prediabetic patients prior to or immediately following acute cardiovascular events would improve their outcomes.

Accumulating evidence now shows it is possible to prevent progression from pre-diabetes to Type 2 diabetes. Many risk factors, including the metabolic syndrome (see article on page 8), have been implicated in disease progression, and several lines of research are in progress to identify diabetes prevention strategies, among them diet and exercise, and treatment with thiazolidinediones,\* metformin,\* alpha-glucosidase inhibitors,\* meglitinides,\* and anti-obesity agents.\* Interestingly, modulation of the renin-angiotensin axis by either angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) has also been suggested as a novel approach in Type 2 diabetes prevention.\* Abuissa and colleagues from the University of Alabama

conducted a meta-analysis, using a random effects model, of 13 clinical trials of an ACE-I or ARB involving a total of 125,356 patients to assess if one can prevent the onset of diabetes by blocking the renin-angiotensin system (RAS) (abstract 1058-117). These investigators found the incidence of newly diagnosed diabetes was

reduced by 24% with an ACE-I and 23% with an ARB (23% reduction in the combined pooled analysis) (Table 4). The authors suggested that the use of an ACE-I or ARB be considered in patients with metabolic syndrome, hypertension, IFG, family history of diabetes, obesity, heart failure, or other risk factors for the development of

Type 2 diabetes. We would point out that to date no primary endpoint study has demonstrated this effect in a prospective, randomized, double-blind fashion. However, two such investigations—DREAM (rosiglitazone and/or ramipril in IFG/IGT patients) and NAVIGATOR (nateglinide and/or valsartan in IFG/IGT patients)—are currently underway.



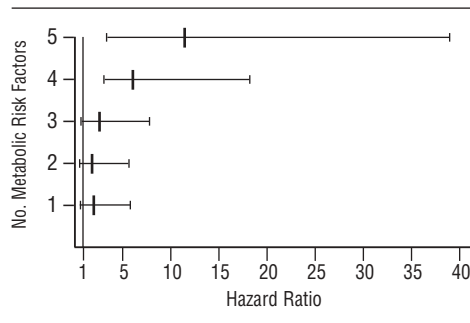
## Perils of the Protuberant Paunch



The metabolic syndrome, increasingly recognized as a major risk factor for cardiovascular disease, affects approximately one-quarter of the US adult population. According to the most recent NHANES III data, about 47 million people in the US have this constellation of clinical and biochemical features of insulin resistance. The metabolic syndrome encompasses numerous conditions including central (primarily visceral) obesity, dyslipidemia, hyperglycemia, hyperinsulinemia, hypertension, endothelial dysfunction, hypercoagulability, and vascular inflammation. The two pivotal components of the syndrome, obesity and reduced insulin sensitivity, have driven the alarming increase in the prevalence of this condition across all demographic groups. The criteria used to diagnose the metabolic syndrome are likely to be revised in the near future (perhaps to include C-reactive protein), but presently the National Cholesterol Education Program (NCEP) advises that the diagnosis be made when an individual has three or more of the five major risk determinants: increased waist circumference (males >40 inches, females >35 inches), hypertriglyceridemia ( $\geq 150$  mg/dl), low HDL-cholesterol (male <40 mg/dl, female <50 mg/dl), hypertension ( $\geq 130/\geq 85$  mm Hg), or high fasting glucose ( $\geq 110$  mg/dl).

Given the risk of coronary heart disease associated with the metabolic syndrome, it is not surprising that it has come to the attention of cardiologists, as evidenced by several presentations made this week. Lopes and colleagues from Brazil reported on the association between the metabolic syndrome and its components and the incidence of cardiovascular end-points in a group of individuals with multi-vessel coronary artery disease followed in the MASS II study (abstract 1035-230). The presence of the metabolic syndrome ( $p = 0.05$ ) and glucose intol-

**Figure 11. Cardiovascular Risk Associated With Metabolic Risk Factors**



erance ( $p = 0.04$ ) were both associated with an increased risk of mortality over the two-year follow-up period. Saely *et al.* from Austria followed 750 consecutive men undergoing coronary angiography for known or suspected coronary artery disease (abstract 803-6). During the two-year follow-up period, the metabolic syndrome was shown to be an independent predictor of vascular events (hazard ratio 2.4; 95% CI 1.5-3.8). The investigators also noted that cardiovascular risk increases gradually with increasing number of metabolic syndrome risk factors, even when adjusted for age, sex, and smoking history (Figure 11). Interestingly, the metabolic syndrome was also shown to be an independent predictor of vascular events within a group of patients who had already progressed to Type 2 diabetes ( $n = 164$ ; HR 3.9, 95% CI 1.1-3.5). Moreover, after adjustments for metabolic syndrome, they found that HOMA-IR, a calculated measure of insulin resistance based on fasting glucose and insulin levels, was still predictive of future vascular events. These data confirm the findings of many other investigators that insulin resistance and the metabolic syndrome are inde-

pendent risk factors for cardiovascular morbidity.

Nakajima and Japanese colleagues also reported on possible adverse outcomes associated with hyperinsulinemia, a marker of insulin resistance (abstract 1065-20). They performed standard 75 gm oral glucose tolerance tests (OGTTs) on 166 non-diabetic patients who had undergone coronary artery stenting. Patients who suffered from restenosis had significantly higher insulin responses during the OGTT, despite having normal glucose profiles (OR = 4.41, 95% CI 2.1-9.2;  $p < 0.001$ ). These findings suggest that restenosis may result from smooth muscle cell proliferation and hypercoagulability associated with insulin resistance. Whether such effects are actually induced by hyperinsulinemia remains less clear.

Rupture of vulnerable plaques with subsequent local thrombosis formation is thought to be the primary cause of acute coronary syndrome. Kunimasa and Japanese colleagues used multi-slice computed tomography to examine 63 patients with known or suspected coronary artery disease, and took measurements of known metabolic syndrome risk factors (abstract 1060-195). Half of the patients had "soft" coronary plaques, which are more prone to rupture. Among the many features associated with the metabolic syndrome, logistic regression analysis revealed that a HOMA-IR score of  $\geq 1.7$  (indicating lower insulin sensitivity) was the most powerful associated risk factor (OR = 3.2, 95% CI 1.08-9.66;  $p = 0.04$ ) for the presence of such plaques.

Clinical and epidemiological investigations such as these have stimulated the vascular biology community to explore the molecular events that link insulin resistance and atherosclerosis—a fundamental question that spans the disciplines of internal medicine, endocrinology, and cardiology.

\* The product is not labeled for the use under discussion or the product is still investigational.

# Diabetes 2005

From the 65th Annual Scientific Sessions of the American Diabetes Association ■ San Diego, CA

2001 2002 2003 2004 **2005** 2006 2007

Sponsored by Yale University School of Medicine, Department of Internal Medicine, Section of Endocrinology

Volume 11 ■ June 11, 2005 ■ Issue 2



## Intensive Insulin Infusion in Acute Myocardial Infarction?



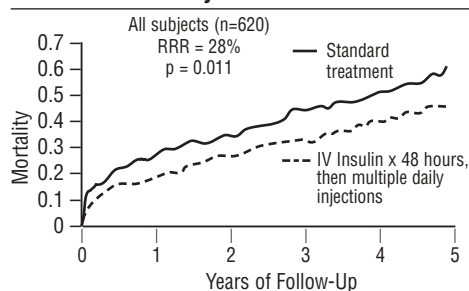
In a debate during the opening session of this week's American Diabetes Association's (ADA) Scientific Sessions, Drs. Hertzell Gerstein from McMaster University and Silvio Inzucchi from Yale University squared off on opposite sides of this contentious issue. First, Dr. Inzucchi, taking the "con" position, pointed out that the best randomized data that adequately demonstrate a benefit from insulin infusion in critically ill patients come mainly from surgical intensive care units. There is extensive observational evidence that admission plasma glucose concentrations are closely associated with patient outcomes following not only acute myocardial infarction (AMI), but a variety of other cardiovascular events. However, a "cause and effect" association cannot be proven from such investigations. Stress hyperglycemia is known to result from the counter-regulatory factors (catecholamines, cortisol) that surge during acute illness. As a result, the plasma glucose is likely to be a parphenomenon, merely a reflection of the sickest (or the "most diabetic") patients. The answer as to whether hyperglycemia during acute cardiovascular events is worthy of treatment must come from randomized clinical trials.

The DIGAMI study (Malmberg, *BMJ* 1997) did show a mortality benefit in those AMI patients with diabetes who were treated with a two-component insulin program (Figure 1). The first involved IV insulin (with dextrose), targeting a plasma glucose of 126-196 mg/dl, relatively conservative by

some of the standards currently being proposed. The second involved an intensive insulin regimen of at least three injections per day upon discharge and extending at least three months. An approximate 30% all-cause mortality benefit was demonstrated at one year and persisted to the study's conclusion at five years. This landmark study set the stage for future investigations in this field. Dr. Inzucchi noted, however, that firm conclusions could not be made from the DIGAMI study because it is impossible to know whether the mortality benefit was attributable to one or the other treatment component. In the DIGAMI-2 study, which was recently published (Malmberg, *Europ Heart J* 2005), the same group of Swedish investigators tackled this specific issue. By randomizing diabetic AMI patients into three groups—intensive IV insulin + intensive outpatient insulin (Group 1) vs. intensive IV insulin only and conventional outpatient care (Group 2) vs. conventional inpatient and outpatient diabetes care (Group 3)—they attempted to tease out the individual effects of the various treatment regimens. (The glucose target in the intensive groups was 126-180 mg/dl.) Unfortunately, as reported in *Diabetes 2004* from Munich, Germany (Volume 10, pg 4), the DIGAMI-2 steering committee stopped the study due to poor patient recruitment and less than anticipated glycemic differences between the three groups of patients. In addition, the overall event rate was much lower than had been predicted, due to implementation of evidence-based cardiovascular risk factor reduction strategies in all groups (aspirin, statins, beta-blockers, ACE inhibitors). In the end there were no statistical differences in cardiovascular and all-cause mortality (Figure 2). In fact, there appeared to be some trends toward fewer events in the conventionally treated group. Based on DIGAMI-2, the use of IV insulin cannot be supported in and of itself, since it had no demonstrable effects on patient outcomes.

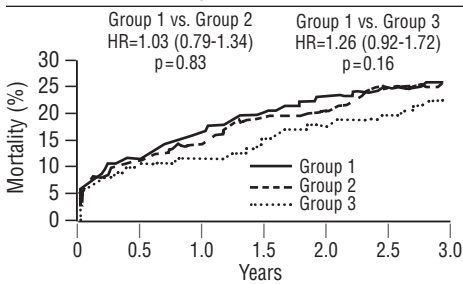
Glucose-Insulin-Potassium (GIK) infusion has been proposed for decades as important adjunctive therapy in AMI patients, with multiple theoretical benefits including increasing intracellular potassium to stabilize cardiac membranes,

**Figure 1. DIGAMI Study: All-Cause Mortality After AMI**



Source: Malmberg et al., *BMJ* 1997.

**Figure 2. DIGAMI-2: All-Cause Mortality After AMI**



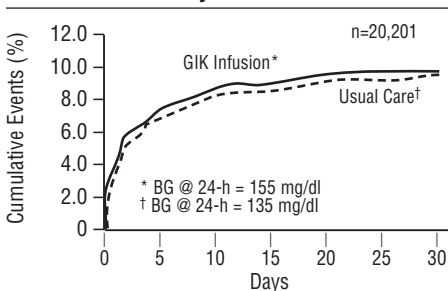
Group 1: Intensive IV insulin + intensive outpatient insulin  
 Group 2: Intensive IV insulin only  
 Group 3: Conventional diabetes care

Source: Malmberg et al., *Europ Heart J* 2005.

augmenting intracellular glycolytic flux, decreasing fatty acid availability and oxidation to lower myocardial oxygen demands, and directly reducing cardiac myocyte apoptosis, ultimately decreasing myocardial damage and the chance of arrhythmia. Small randomized GIK studies have previously suggested benefit, but with large confidence intervals. A meta-analysis (Fath-Ordoubadi and Beatt, *Lancet* 1999) was inconclusive, indicating a possible small benefit, but with only a statistical trend ( $p = 0.06$ ). Accordingly, a large international GIK study involving over 20,000 AMI patients was conducted and recently published (CREATE-ECLA Study Group, *JAMA* 2005). Patients were randomized to high-dose GIK vs. conventional care. No benefit on mortality after 30 days was demonstrated in the GIK group (Figure 3).

Administration of IV insulin is not without risk, most notably hypoglycemia, which is considered “the cost of doing business” for intensive glucose control in the inpatient setting. However, the implications of hypoglycemia for the ischemic myocardium are not well known. Several studies have clearly shown a marked increase in circulating epinephrine levels even with mild hypoglycemia (<50-60 mg/dl). Insulin also stimulates the sympathetic nervous system by itself, augments

**Figure 3. CREATE-ECLA Study: Mortality Results**



Source: CREATE-ECLA Study Group, *JAMA* 2005.

ventricular stroke volume, thereby increasing myocardial oxygen demands, leads to important potassium and phosphate shifts, and may have under-appreciated mitogenic effects. A small observational study recently published from Sweden actually suggested that *both* admission hyperglycemia and any hypoglycemia occurring during hospitalization for acute coronary syndrome significantly increases mortality.

The issue of competing clinical priorities was next reviewed. The cardiovascular field is replete with extensive guidelines concerning the acute and chronic management of AMI patients. The question was posed as to whether the recently published inpatient guidelines from the American Association of Clinical Endocrinologists (AACE) and the ADA are evidence based enough to be added to the “table.” Finally, patient groups in the various intensive care units were compared, and the issue that a surgical ICU or medical ICU patient is different from a Coronary Care Unit (CCU) patient was raised. These groups have distinct diagnoses, lengths of stays, and complication and mortality rates. Therefore, the benefit of tight glucose control demonstrated in some of these other settings may not necessarily extend to AMI patients.

Dr. Gerstein next provided an excellent overview of the relationship between glucose and cardiovascular disease. He pointed out that the vast majority of acute coronary syndrome patients has either diabetes or prediabetes. Some studies have shown that only about one-third to one-quarter of patients with acute coronary syndromes or being invasively assessed for coronary artery disease actually has normal glucose metabolism. Also, the degree of hyperglycemia in these patients, whether assessed by admission plasma glucose, average in-hospital glucose control, or oral glucose tolerance testing after cardiac events, was closely aligned with outcomes. In fact, the prognostic implications of hyperglycemia in these settings are very strong and not well appreciated by physicians. Hyperglycemia also has many well-recognized deleterious effects on the vasculature. Moreover, since any degree of hyperglycemia in any setting indicates at least relative insulin deficiency, it is logical to focus on providing adequate insulin to reduced glucose levels to normal or near-normal in these patients.

The biochemical and cellular benefits of insulin on the ischemic myocardium were described, with a focus on glycolytic pathways and mitochondrial fatty acid metabolism. Essentially, insulin improves coronary blood flow while at the same time decreasing myocardial oxygen demands by enhancing metabolic efficiencies of energy generation.

Dr. Gerstein emphasized the important findings of DIGAMI-1, pointing out that the negative

results of DIGAMI-2 do not nullify those of the earlier study. DIGAMI-2 was ultimately underpowered to show benefit, particularly since the treatment groups were not, in the end, distinct enough to make any conclusive statements about the effect of glucose control in the acute setting. Dr. Gerstein pointed out that the glucose differences between the intensive and conventional groups in DIGAMI-1 were marked, whereas those in the follow-up study were minimal, and only at earlier time points. Also, DIGAMI-2’s event rates were too low to easily detect any superimposed effects of glucose control. Next, Dr. Gerstein addressed the CREATE-ECLA study results, emphasizing that the GIK group actually had higher, not lower, glucose levels than did conventionally treated patients. Therefore, all that could be concluded was that if insulin is given in AMI but not in a manner that normalizes glucose, it will be ineffective. He underscored the need for a new GIK study with adequate methodology—to provide enough insulin to substantially lower glucose. Only then can the benefits of GIK be really known. Other methodological flaws of the study were also proposed, including lower than ideal primary reperfusion rates and the likelihood that the GIK infusions were not started early enough upon patient presentation.

Dr. Gerstein then reviewed data from the literature showing widespread benefits of tight glucose control in a number of critical care settings. He highlighted the landmark Leuven Study (van den Berghe, *N Engl J Med* 2001), conducted in the surgical ICU. This investigation showed a 42% reduction in ICU mortality in mechanically ventilated patients placed on an aggressive IV insulin infusion that targeted a blood glucose of 80-110 mg/dl. Other important benefits of tight glucose control in the Leuven study included a reduced need for dialysis, blood transfusion, and prolonged mechanical ventilation. Dr. Gerstein believes that such benefits would be extended to other critically ill patients, but only if the same glucose targets are achieved.

In the Q & A session that followed, audience members underscored the reticence on the part of the cardiology community to readily embrace the notion of tight glucose control in their AMI patients. Some remarked that hyperglycemia remains a major problem in their CCU patients. Others pointed out the recognized vasodilatory and anti-inflammatory effects of insulin and their potential benefits in the acute coronary syndrome setting.

In the end, it was agreed that moderate-severe hyperglycemia must be avoided in AMI patients, that IV insulin by itself has no benefit unless glucose levels are also targeted, and that more data are needed to better understand the benefits of euglycemia during AMI.



## Diabetic Dyslipidemia: The Troublesome Triad

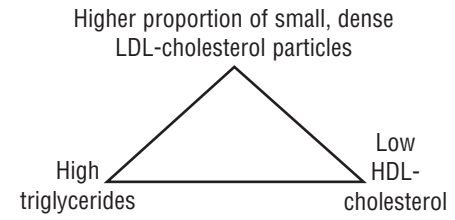


**Dyslipidemia**—characterized by low HDL-cholesterol, high triglycerides, and a higher proportion of small, dense LDL-cholesterol (LDL-C) particles—is highly prevalent among patients with Type 2 diabetes (Figure 4). LDL-C is a long-established risk factor for coronary heart disease. In a symposium on “Lipid Targets for Cardiovascular Disease in Diabetes,” Dr. Neil Stone from Northwestern University reviewed the benefits of LDL-C reduction as observed in both the general population and in those with diabetes from randomized, controlled clinical trials. He pointed out that reduction in coronary heart disease risk (~25%) has been confirmed through the spectrum of baseline LDL-C levels. Based on results of the Heart Protection Study (*Lancet* 2003) and CARDS (*Lancet* 2004), the ADA recently revised their LDL-C goals to <100 mg/dl (<70 mg/dl in high-risk patients, e.g., those with overt cardiovascular disease) (*Diabetes Care* 2005). Parenthetically, the results of a recent study suggest that 25% of diabetics will require more than two lipid-lowering drugs to decrease their LDL-C below 70 mg/dl (*Diabetes Care* 2005), underscoring how difficult this goal will be for many of our patients.

**Drs. John Brunzell** from the University of Washington School of Medicine and Henry Ginsberg from Columbia College of Physicians and Surgeons next discussed low HDL-cholesterol (HDL-C) and high triglycerides as secondary therapeutic targets. Each has been demonstrated to be independent risk factors for coronary disease. Both speakers emphasized the physiologic inter-relatedness of the lipoproteins, as well as the atherogenic properties each has beyond its association in the dyslipidemic triad. Aside from the VA-HIT study, however, there are few data that indicate a benefit on cardiovascular disease endpoints from targeted lowering of triglycerides or attention to low HDL-C. Moreover, there are essentially no data in diabetic patients. Yet, both of these lipoprotein abnormalities remain highly predictive of vascular risk and both are intimately linked to the metabolic syndrome. Several studies are underway to further explore the potential benefit of modulating the levels of lipoproteins other than LDL-C.

**In the Q & A session**, the speakers were asked what triglyceride and HDL-C targets should be used after the guideline LDL-C level has been achieved. The discussants emphasized that for both HDL-C and triglyceride-targeted therapeutics, drugs will need to be evaluated for their *incremental* benefits on top of guideline-based LDL-C lowering. For instance, in the ACCORD trial, fenofibrate is being added to simvastatin to determine the

**Figure 4. Dyslipidemic Triad of Diabetes**



effects of the fibrate therapy to the LDL-C lowering of the statin. Some of the thiazolidinedione (TZDs) end-point studies, including PROACTIVE (due later this year), may allow us to better understand the impact of reducing triglycerides and raising HDL-C in diabetic patients. Of course, these effects of the TZDs (see below) will be difficult to sort out from the well-known effects of these drugs on insulin resistance itself as well as glucose concentrations. It is anticipated that the results of these types of studies, and others, will guide the future comprehensive approach to the treatment of dyslipidemia in patients with diabetes and/or metabolic syndrome.

**In a related abstract**, a double-blind, multicenter, randomized trial of 1902 diabetic patients with hypercholesterolemia was presented by Ballantyne *et al.* (962-P). Those patients randomized to combination ezetimibe/simvastatin vs. atorvastatin (at mg-equivalent statin doses between 10 mg and 80 mg for six weeks) showed greater improvements in LDL-C, total cholesterol, and HDL-C (-10.6%, -6.4%, and +2.5% treatment differences, respectively) with similar improvement in triglyceride (~ -26% each).

**The effects of the TZDs on lipid metabolism** have been a point of some controversy. Moreover, their impact in patients already aggressively treated

with statins is largely unknown. Khan *et al.* conducted an open-label study (COMPLEMENT) in which 305 patients with Type 2 diabetes and fasting triglyceride between 200 - 1000 mg/dl who had received stable (>90 days) statin and rosiglitazone therapy were switched at baseline from rosiglitazone to pioglitazone (30 mg/day titrated to 45 mg/day, at the discretion of the investigator) (553-P). Lipid-lowering agents were maintained at stable, pre-study doses throughout the 17-week study. Statistically significant mean decreases in triglyceride and total cholesterol levels were observed (Table 1), as was a significant mean increase in apolipoprotein A-1 (+9.7 mg/dl,  $p < 0.001$ ) and a significant mean decrease in apolipoprotein B (-2.6 mg/dl,  $p < 0.05$ ). These lipid changes were apparently independent of glycemic control. Furthermore, lipid fractionation showed a shift in LDL-C composition toward larger, more buoyant, less atherogenic particles (555-P). The impact of such changes on cardiovascular risk remains debatable. We would also point out that the methodology of this study (open-label design) was suboptimal, although it did echo results from a recent randomized, controlled trial in patients not taking statins (*Diabetes* 2004, Volume 10, pg 26).

**Finally**, La Choice and Canadian coworkers studied the contribution of visceral adiposity to postprandial lipemia in patients with Type 2 diabetes (5-OR). Postprandial triglyceride (TG)-rich lipoprotein levels (chylomicron, chylomicron remnants, and very low density lipoprotein [VLDL]) were measured following a standardized breakfast of high fat content (60 g fat/m<sup>2</sup> body surface area) among 65 men with normal glucose tolerance and 14 males with newly diagnosed but yet untreated Type 2 diabetes. The diabetic patients had significantly higher postprandial TG-rich lipoprotein levels at all timepoints (0, 2, 4, 6, and 8 hours;  $p < 0.03$ ) as well as increased visceral adipose tissue mass (287.2 vs. 125.1 cm<sup>2</sup> in those with normal glucose tolerance;  $p < 0.0001$ ). However, after adjustment for visceral adiposity, there was no significant difference in post-prandial TG response between the groups. These data underscore the important role of abdominal adiposity in deranged lipoprotein metabolism in our patients with Type 2 diabetes. Since most lipid trials have assessed the less dynamic fasting lipoprotein profile, this has become the standard way to measure lipids in clinical practice. The optimal ways to assess and treat post-prandial hyperlipemia and its clinical import remain largely unknown.

**Table 1. Incremental Lipid Effects of Switching From Rosiglitazone to Pioglitazone in Patients Taking Statins**

|                   | Baseline Mean (n=303) | Week 17 Mean Change (n=280) | % Mean Change      |
|-------------------|-----------------------|-----------------------------|--------------------|
| Triglyceride      | 303 mg/dl             | -64.9 mg/dl                 | -15.2 <sup>†</sup> |
| Total cholesterol | 199 mg/dl             | -20.6 mg/dl                 | -9.0 <sup>†</sup>  |
| LDL-cholesterol   | 104 mg/dl             | -2.6 mg/dl                  | 2.2                |
| HDL-cholesterol   | 42 mg/dl              | 0.0                         | 1.8*               |

\*  $p < 0.05$ ; <sup>†</sup>  $p < 0.0001$ .



## Farewell to Fingersticks?



Strict control of glycemia decreases the risk of microvascular complications, but when such a treatment strategy involves insulin, the risk of hypoglycemia is increased. Periodic monitoring of blood glucose with fingerstick meters has enabled patients to better assess their day-to-day control, but often misses hypoglycemic periods and post-prandial hyperglycemic excursions. Optimally, the measurement of blood glucose should be accurate, precise, reliable, and continuous. Various sensors that provide the patient minute-to-minute blood or interstitial glucose information are being evaluated to address this need. Several studies were described at this week's ADA Scientific Sessions, highlighting the utility of various glucose monitoring technologies.

Miller *et al.* reported on a total of over 20+ patient-years of experience in 26 Type 1 diabetes patients with a long-term sensor system,\* which is comprised of an intravascular glucose sensor electronically connected to an implanted insulin pump that is refilled every 90 days (Medtronic) (404-P). Although these components are operating independently during the ongoing multicenter feasibility study, a link can be made through software, resulting in a fully implanted "artificial pancreas." Calculated glucose sensor output was determined using a prospective calibration routine based on previously measured home glucose meter data. The sensor's accuracy is determined by comparing its output to home glucose meter data and computing the mean absolute difference (MAD). When MAD exceeds 25% for more than 21 days, the sensor is replaced. Based on this procedure, the mean sensor life is currently 259 days (operational range 90-431 days). After 11 months of use, the implanted sensors had a MAD of 16.4% with over 6000 paired sensor and measured blood glucose values—fairly good by current industry standards. Over 95% of all data points were in the A + B zones of the "Clarke Error Grid." (In these grid zones on a conventional x-y axis graph, proper clinical decisions would have been made by the patient as a result of the sensor reading as compared to the meter reading).

Jovannovic *et al.* prospectively evaluated the accuracy and reproducibility of a transcutaneous glucose sensor\* (DexCom, Inc.) in 15 patients with Type 1 diabetes (398-P). Two of the enzyme-electrode sensors were inserted under the skin of each study patient, with one sensor providing real-time continuous glucose data to

the patient and the other used in comparisons to fingerstick values. During the first 12 hours of the study, comparative blood glucose values were measured every 20 minutes in a clinic setting; home use data (seven values per day) were collected over the subsequent 60 hours. Of 1139 matched blood/sensor glucose values, 97.5% were in the A + B region of the Clarke Error Grid. Mean absolute relative difference (MARD) was 21.1%. Sensitivity/specificity at established high (200 mg/dl) and low (80 mg/dl) thresholds were 84.8%/88.5% and 84.0%/83.1%, respectively. Reproducibility between the sensors in each patient was assessed using Mean Relative Difference (MRD), which was -1.7% and MARD, which was 16.2%. Patients did not report any adverse events related to the sensors. We feel these results are noteworthy, but such a system may not yet be accurate enough for clinical use.

Interstitial continuous glucose monitoring technology was the subject of several investigations. For example, Deiss and European co-workers described the findings of a pilot study of the Guardian® RT (Real Time)\* (Medtronic MiniMed) used at home for 10 days by 12 children and 12 adults with Type 1 diabetes (393-P). The Guardian is an adaptation of MiniMed's Continuous Glucose Monitoring System (CGMS®) that has been available for several years mainly for physician use. It is a telemetered glucose monitoring system with continuous display of glucose values and low/high alerts for preset glucose values. Patients changed their own sensor every three days. Based on alarm settings for hypoglycemia (mean 63 mg/dl, range 50-81 mg/dl) and hyperglycemia (mean 200 mg/dl, range 162-234 mg/dl), patients experienced a mean of 0.6 hypoglycemia and 0.8 hyperglycemia alarms overnight and 1.4 hypoglycemia and

2.4 hyperglycemia alarms during daytime hours. As compared to the first day, there was a 38% decrease ( $p < 0.05$ ) in the number of excursions over 200 mg/dl. Fourteen patients reported greater satisfaction with their glycemic management. Four patients reported six mild adverse events, four related to sensor insertion.

Farhy *et al.* from Charlottesville, VA compared the accuracy of two continuous glucose sensors, the FreeStyle Navigator™ (Abbott Diabetes Care) and CGMS® (Minimed), which were concurrently placed on 16 Type 1 diabetes patients (394-P). Patients underwent two hyperinsulinemic clamp studies, each consisting of 70-210 minutes of euglycemia (goal 110 mg/dl) followed by a 1 mg/dl/minute decrease in blood glucose to hypoglycemia (goal 40 mg/dl). Arterial blood glucose was measured every five minutes. While the performance of both sensors was similar in the euglycemic range, the FreeStyle Navigator appeared more accurate in the setting of hypoglycemia (82.4% vs. 61.6% with CGMS,  $p < 0.0005$ ) (Table 2).

In late-breaking posters, a feasibility study of continuous glucose monitoring using near-infrared spectroscopy\* (1-LB) was described, as were preliminary findings of a biodegradable glucose sensor measuring transcutaneous fluorescence lifetime\* (3-LB).

Such glucose sensor devices, while interesting, are not ready for widespread use in all diabetes patients. There remain concerns about reliability and cost. It is our hope that research efforts, such as those presented this week, will culminate in one or more of these emerging technologies eventually replacing fingerstick glucose monitoring. This will be a benefit to our patients not only for convenience. With more data, as long as properly interpreted and acted upon, better control should follow.

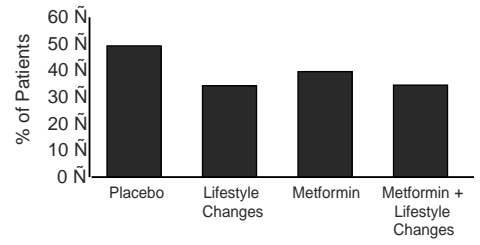
**Table 2. Accuracy of Continuous Glucose Sensors in Euglycemia vs. Hypoglycemia**

|                            | Hypoglycemia (BG ≤ 70 mg/dl)<br>(n = 250) |       | Euglycemia (70 mg/dl<br>< BG < 180 mg/dl) (n = 1104) |       |
|----------------------------|---|-------|--|-------|
|                            | Navigator                                 | CGMS  | Navigator  | CGMS  |
| Accurate readings (A zone) | 82.4%                                     | 61.6% | 88.8%  | 89.3% |
| Benign errors (B zone)     | 5.6%                                      | 1.2%  | 10.2%  | 9.0%  |
| A + B zone                 | 88.0%                                     | 62.8% | 99.0%  | 98.3% |
| Erroneous readings         | 12.0%                                     | 37.2% | 1.0%   | 1.7%  |

BG = blood glucose; CGMS = continuous glucose monitoring system



Figure 5. Incidence of Diabetes Over 30 Months in the Indian Diabetes Prevention Program



\* The product is not labeled for the use under discussion or the product is still investigational.