

# Diabetes 2005

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Important data on diabetes presented at the 54th Annual Scientific Sessions of the American College of Cardiology come to you in **Diabetes 2005**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals America, Inc. and Eli Lilly and Company. Fax or e-mail delivery to your office of **Diabetes 2005** will be followed by a **Diabetes 2005** booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained and remitting a \$10 certificate fee to the Yale Office of Continuing Education, you will qualify for up to 5.5 Category 1 credits towards the Physician's Recognition Award of the American Medical Association to be issued by Yale University School of Medicine.

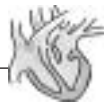
**Diabetes 2005** is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- 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.
- 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.

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## 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±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 ≥50%), with an annual mortality rate of 7%.

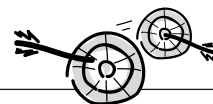
Zeller and French co-workers investigated the influence of abnormal fasting glycemia on the occurrence of heart failure after acute myocardial infarction (abstract 1033-216). Among 894 such patients, 22% developed heart failure. Patients with heart failure were significantly older (median age 75 vs. 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 ≤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, β-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, β-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.



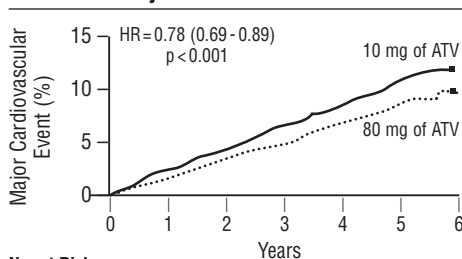
## Hey... Who Keeps Moving My Target?



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=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 (~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.

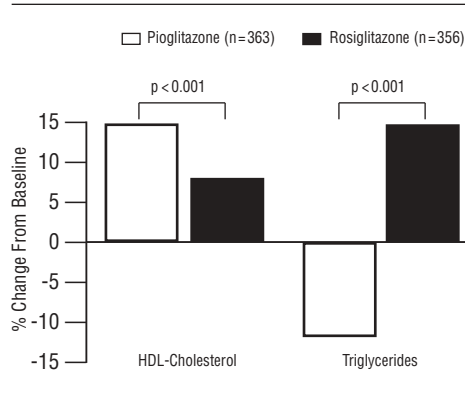
Goldberg and coworkers presented the results of the first large, prospective, multicenter, double-blind study comparing thiazolidinediones (TZDs) based on changes in cardiovascular risk determinants (abstract 874-4). After a four-week placebo washout period, 802 patients with Type 2 diabetes and associated 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.)

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## Hey... Who Keeps Moving My Target? Continued from page 2

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

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



such therapy (n=174). These patients received 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.

**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.

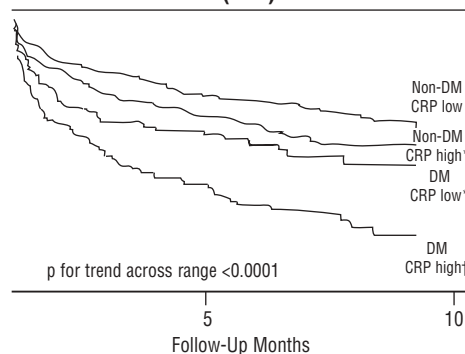
† May increase triglyceride levels.

## 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**

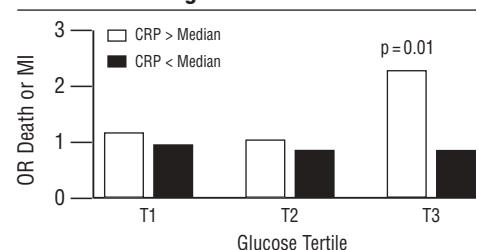


\* DM/CRP low vs. non-DM/CRP high p=0.3

† 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

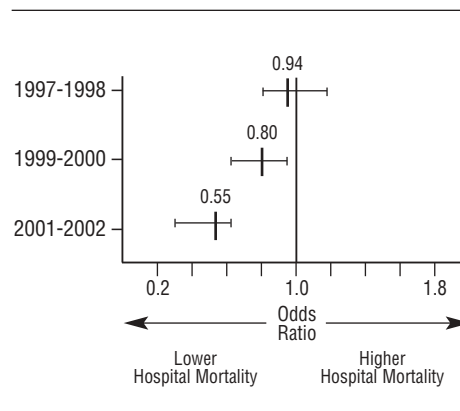
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## Acute Myocardial Infarction in Diabetes... Continued from page 3

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

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

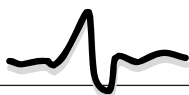


not the case in the non-diabetic patients. Moreover, in the diabetic population, high glucose on admission was found to heighten the cardiovascular risk associated with high CRP (Figure 4). A Cox-regression model revealed a significant interaction between death/MI and admission glucose and CRP ( $p < 0.05$ ). 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 (NRFMI)-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* systems, these agents attenuate some of the molec-

ular 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

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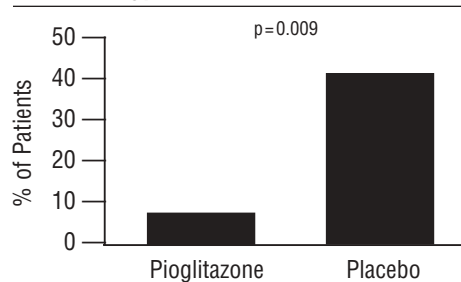
## PPARs and the Cardiologist

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(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 decreased at six months in the combined (*i.e.*  $\alpha/\gamma$ )

**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%)

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

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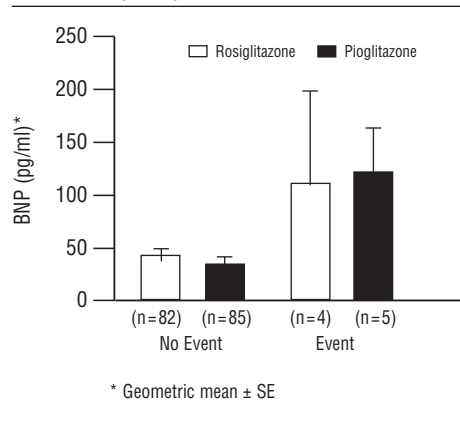
## PPARs and the Cardiologist

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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.

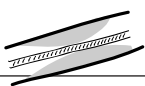
To explore the mechanism by which TZDs cause fluid retention, Dargie and his co-investigators from Scotland randomized 224 Type 2 diabetes patients with NYHA class I/II heart failure to rosiglitazone (4-8 mg daily) or placebo in addition to background anti-hyperglycemic agents for 52 weeks (abstract 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**

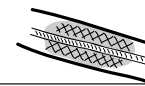


were changed as necessary. The investigators found no differences between the TZD and placebo groups based on cardiac structure or ejection fraction (37.8% vs. 36.8%) at the end of the study year, confirming the results of prior studies, that TZDs do not adversely affect cardiac structure or function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

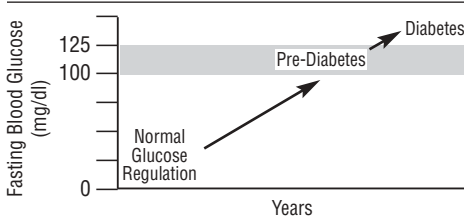


## Identifying Pre-Diabetes: A New Imperative?



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**



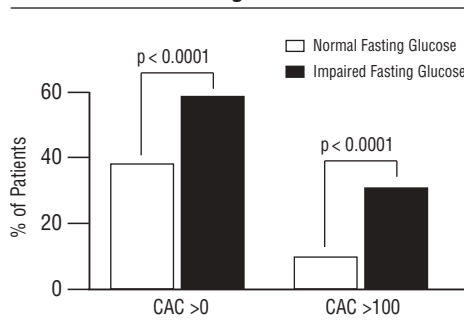
Nasir and coworkers from Johns Hopkins and Brazil evaluated 539 asymptomatic men without diabetes (479 with fasting glucose < 100 mg/dl and 60 with fasting glucose 110-125 mg/dl; on no antihyperglycemic medication) who presented for cardiac electron-beam computed tomography (EBCT) (abstract 1155-106). 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)

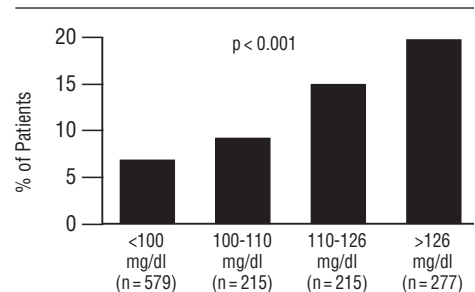
\* Development of diabetes. † Median

**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

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



whether more aggressive 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

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## Identifying Pre-Diabetes...

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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 fail-

ure, 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.



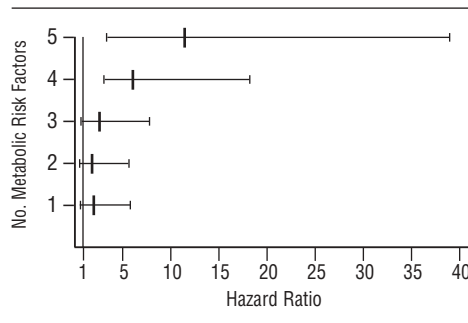
## Perils of the Protuberant Paunch



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 intoler-

**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.