

# Diabetes 2006

From the 55th Annual Scientific Sessions of the  
American College of Cardiology ■ Atlanta, GA

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## Symposium Update: Diabetes for the Cardiologist



Important data on diabetes presented at the 55th Annual Scientific Sessions of the American College of Cardiology come to you in **Diabetes 2006**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals North America, Inc. Fax or e-mail delivery to your office of **Diabetes 2006** will be followed by a **Diabetes 2006** booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained and remitting a \$25 processing 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 2006** 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.

Yale University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education to physicians. 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 spent in the educational activity.

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The epidemic of diabetes with its associated increased cardiovascular risk has brought the condition to the attention of the cardiology community. Often the diagnosis of diabetes is first made during an admission for acute coronary syndrome, or during routine testing in the cardiology clinic. The initial steps in management may therefore fall to cardiologists. During a major symposium at the ACC meeting in Atlanta this week, cardiologists from around the world were provided an update on new developments in lipid management, new therapies for diabetes, and the interaction between diabetes and heart failure.

In the first presentation by Dr. Haffner of San Antonio, the audience was shown data from a subgroup of patients with metabolic syndrome in the Treatment to New Targets (TNT) study. TNT, reported last year in the *New England Journal of Medicine* (NEJM 2005; 352:1425), was a multicenter, prospective, randomized study comparing the effects of aggressive lowering of LDL-cholesterol with 80 mg, as opposed to 10 mg, of atorvastatin. The higher dose, which achieved an LDL-cholesterol of around 75 mg/dl, was associated with a 22% relative risk reduction in the primary composite endpoint of death from coronary artery disease (CAD), non-fatal MI, resuscitation after cardiac arrest, or fatal or non-fatal stroke. Dr. Haffner reported that 56% of the TNT cohort had metabolic syndrome as defined by the National Cholesterol Education Program (NCEP 2005) criteria. The patients in TNT with metabolic syndrome were found to be at greater cardiovascular risk (HR 1.44 [95% CI 1.26-1.64],  $p < 0.0001$ ) in comparison to patients without metabolic syndrome. Overall LDL-cholesterol reduction following atorvastatin 80 mg in the group with metabolic syndrome was similar to the group as a whole, and was associated with a 29% relative risk reduction in the primary endpoint. Dr. Haffner felt that future trials might target even more aggressive LDL targets and consider other risk factors such as triglycerides and HDL-cholesterol in patients with diabetes and/or metabolic syndrome.

This conclusion opened the way for Dr. Rosenson, Chicago, to discuss the FIELD trial (see

"Field of Dreams" *Diabetes 2005*, Volume 12, pages 23-24), which reported (*Lancet* 2005; 366:1849) the effect of triglyceride lowering with the PPAR $\alpha$  agonist, fenofibrate, on cardiovascular events in diabetic patients. Fibrates are known to reduce plasma triglycerides and increase HDL-cholesterol. This made fibrates an obvious choice of therapy for individuals with diabetes who typically show the dyslipidemic pattern of high triglycerides and low HDL. However, FIELD was disappointing in that it showed no significant reduction in the primary composite endpoint after five years of follow-up. Dr. Rosenson noted that, following the publication of several statin trials, many of the patients in FIELD had been started on statin therapy ("statin drop-ins") and there were more of these in the control arm of the trial, possibly contributing to the study's negative outcome. He also remarked that review of the earlier fibrate trials (e.g., Helsinki Heart Study, VA-HIT) suggests that most of the benefits were in individuals with a triglyceride level  $> 200$  mg/dl. As the patients in FIELD had mean triglyceride levels at baseline of 130-140 mg/dl, this may also have contributed to the study's results. Dr. Rosenson concluded by saying that fibrate therapy is probably not indicated in diabetic patients with mild hypertriglyceridemia (150-200 mg/dl). We would add that it remains unclear what the appropriate threshold for initiating pharmacological therapy should be.

Dr. Mazzone, also from Chicago, then provided a review of the newer agents for the treatment of Type 2 diabetes, including the GLP-1 agonists, DPP IV inhibitors, and inhaled insulin, each of which have been reviewed extensively in this journal. Dr. Mazzone pointed to the conflicting data surrounding the value of tight glycemic control in reducing cardiovascular risk and noted that while there is some supportive evidence of benefit, a consensus may not emerge until the ACCORD trial is reported, which will address this issue directly in over 10,000 patients, and is due for completion in four to six years.

The concluding presentation came from Dr. Fonarow, Los Angeles, who discussed the

Continued on page 2

## Symposium Update...

Continued from page 1

interesting relationship that has emerged between diabetes and heart failure. Dr. Fonarow pointed out that in the Framingham study diabetic men had a two-fold increased risk of developing heart failure, while diabetic women had a three-fold increased risk. He noted that for each 1% increase in HbA1c there was a 15% increase in incident heart failure, and that in recent studies approximately 45% of patients hospitalized with this diagnosis have diabetes. The relationship between diabetes and heart failure is likely not unidirectional. In fact, the effects of heart failure on neurohormonal release should be considered. Specifically, catecholamines, which circulate in high concentrations in heart failure, induce insulin resistance, and this may render the predisposed individual to develop overt hyperglycemia.

Interestingly, there is little clear evidence that diabetes impacts mortality in heart failure patients. In the SOLVD and BEST trials, diabetes emerged as only a modest independent risk factor, and then only in those whose heart failure was the result of CAD. Heart failure risk in diabetes can be reduced. The Micro-HOPE study showed the benefits of the ACE inhibitor, ramipril, at reducing heart failure risk (13.3% to 11%), and the UKPDS showed a 56% relative risk reduction of heart failure in diabetic patients treated with an ACE inhibitor or beta-blocker. In the treatment of diabetic patients with heart failure, the CHARM and Val-HEFT studies suggested no added benefit from combination therapy with an ACE inhibitor + angiotensin receptor blocker, but RALES and EPHEUS (in which 32% of the cohort had diabetes) showed a clear benefit from the addition of aldosterone antagonist therapy. Additionally, the COPERNICUS trial

demonstrated the benefit of beta-blocker therapy, while the COMET study suggested that, within this class, there may be some advantage to using carvedilol, which was additionally associated with a reduction in the incidence of newly diagnosed diabetes. On the other hand, and as noted above, improving glycemic control has generally *not* been shown to reduce cardiovascular endpoints, including heart failure. Indeed, more recently, from retrospective studies (which sometimes give misleading results!), it has been suggested that insulin replacement therapy may actually increase the risk of adverse cardiac outcomes in this group of patients.

The cardiology community's growing interest in diabetes is a reflection of the increasing realization of the important interplay between this condition and cardiovascular diseases. Collaborative efforts involving primary care physicians, endocrinologists, and cardiologists will promote improved outcomes for our patients.



## Urine Trouble



Recently, the relationship between diabetes, cardiovascular complications, and chronic kidney disease has received increased attention. Several presentations at this week's ACC meeting continued this trend.

Gowdak and a group of Brazilian investigators prospectively evaluated survival probability, based on the interaction between diabetes and CAD (defined by at least one coronary artery stenosis >70%), among 283 patients with end-stage renal disease (ESRD) (abstract 905-234). Patients were categorized into four distinct groups and followed for a median of nine months: (1) without diabetes or CAD; (2) diabetic but no CAD; (3) CAD but no diabetes; and (4) diabetes and CAD. A total of 78 fatal/nonfatal major adverse cardiac events (MACE) occurred during the time frame. Not surprisingly, MACE-free survival as depicted by Kaplan-Meier curves was significantly better for persons without diabetes and without CAD versus the remaining three groups ( $p < 0.001$ ). As has been reported in the general population, the incidence of MACE in patients with diabetes but no CAD versus those with CAD but no diabetes was statistically equivalent (HR 1.33 [95% CI 0.58 - 3.46],  $p = 0.51$ ). Overall,

the researchers concluded that, in the setting of ESRD, diabetes increases the incidence of MACE to a similar extent as does prevalent CAD.

In an oral contribution, Ahmed and colleagues from Boston described the combined impact of diabetes and renal impairment on non ST-segment elevation acute coronary syndrome (NSTEMI-ACS) (abstract 830-3). The presenters pooled data from five NSTEMI-ACS thrombolysis trials, characterizing 13,140 patients into various groups based on diabetes status and degree of renal

impairment. The data (Table 1) reveal that although diabetes and kidney disease each share a higher risk of death and myocardial infarction, with each acting synergistically to increase risk, moderate renal impairment alone is associated with a greater risk than diabetes alone.

Given these important implications for our patients, the nexus of diabetes, chronic kidney disease, and cardiovascular morbidity is apt to be an area of significant interest over the next several years.

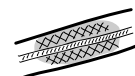
**Table 1. Independent and Combined Risks from Diabetes and Kidney Disease in Patients with Non ST-Segment Elevation Acute Coronary Syndrome**

	Death OR (p-value)	MI OR (p-value)	Death/MI OR (p-value)
DM alone	1.3 (NS)	0.7 (NS)	0.9 (NS)
Mild RI alone	1.2 (NS)	1.0 (NS)	1.1 (NS)
Moderate RI alone	2.4 (<0.001)	1.4 (0.007)	1.7 (<0.001)
DM + Mild RI	2.0 (<0.001)	1.7 (<0.001)	1.7 (<0.001)
DM + Moderate RI	3.0 (<0.001)	2.5 (<0.001)	2.4 (<0.001)

DM = diabetes mellitus; RI = renal impairment; mild RI = GFR 60-89 ml/min/m<sup>2</sup>; moderate RI = GFR 30-59 ml/min/m<sup>2</sup>



## Dollars and Stents



Significant controversy has emerged over the optimal interventional management of the diabetic patient with CAD. Early studies indicated significantly worse outcomes from coronary

angioplasty vs. coronary artery bypass graft (CABG) surgery in this population. Increased restenosis rates were documented, likely the result of more exuberant neointimal hyperplasia.

These differences were not significantly mitigated by the development of intra-coronary stents. Now, in the drug-eluting stent (DES) era, with in-stent restenosis less of a concern, outcomes in

Continued on page 3

## Dollars and Stents

Continued from page 2

diabetic subgroups have been carefully monitored. In studies performed to date involving DES, marked reductions in restenosis rates and the need for target vessel revascularization (TVR) have been demonstrated in the CAD population at large. Preliminary data suggest a similar benefit in diabetes as well.

**Moussa** and colleagues from New York, reported on the impact of diabetes on in-stent restenosis using intravascular ultrasound (IVUS) following placement of a DES for coronary stenosis (abstract 2801-8). IVUS identified 49 in-stent restenosis lesions: 22 in 17 patients with diabetes and 27 in 25 patients without diabetes. No differences were found between patient groups in terms of minimal lumen area, intimal hyperplasia, net volume obstruction, or neointima-free stent length. The authors concluded that, in this small group of patients receiving DES, there was no evidence of a more aggressive neointimal growth pattern with diabetes, suggesting that restenosis rates may be similar. However, it should be pointed out that this technique does not provide information on plaque stability, and, moreover, clinical events were not reported.

**Drug-eluting stents** are currently available in two forms, sarcolimus-eluting (SES) and paclitaxel-eluting (PES) stents, and clinical trials comparing the two are underway. **Corbett** and colleagues from Italy (abstract 2916-67), found no difference in major adverse cardiac events (MACE), TVR, or angiographic restenosis in 367 diabetic patients who had received either a PES (n = 182) or an SES (n = 185).

**Dulisse** from Boston, looked at the cost-effectiveness of PCI with or without DES vs. CABG in diabetic patients with multi-vessel coronary disease by comparing one-year results from the ARTS (Arterial Revascularization Therapy Study) trial with data from the ARTS II Registry (abstract 2916-66). ARTS was the largest, randomized, clinical trial to compare percutaneous coronary intervention (PCI) (with bare metal stents) vs. CABG in individuals with multi-vessel disease. ARTS reported that, overall, there was no significant difference between PCI and CABG, based on rates of death/stroke or AMI at one year of follow-up, but a 17% difference in favor of CABG with regard to the need for revascularization. However, there was a significant reduction in costs with PCI over CABG. The ARTS II Registry is designed to compare these same outcome measures in patients with multi-

vessel CAD who received the newer DES (in this case, sarcolimus). In this report, **Dr. Dulisse** found that, compared with CABG, SES was associated with lower rates of death/MI/stroke, while reducing initial hospital and total one-year costs in diabetic patients (Table 2). He concluded that use of PCI with SES in individuals with multi-vessel disease was an economically attractive therapeutic intervention. However, it should be remembered that there are serious limitations to using historical controls (the ARTS cohort) in an analysis such as this, so while this data supports the use of SES, the findings need to be proven in prospective, randomized clinical trials.

In ARTS (see above), those patients with multi-vessel disease and diabetes who had received bare metal stents had worse outcomes and lower event-free survival rates than diabetic patients assigned to CABG. The reason for the apparent benefit of CABG in diabetes may lie in the fact that risk of plaque rupture is related to the stability of plaque and not necessarily to the patency of the vessel, the majority of episodes of occlusion occurring in vessels with angiographically mild disease. Because diabetes is generally associated with more severe and more diffuse CAD at presentation, the inherent limitation of PCI with stents in this group may be that it has no effect on the remainder of the coronary vessel. This issue was spotlighted by **Briguari** and colleagues of Italy (abstract 2916-69), who

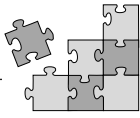
reported on the effect of microvascular disease in diabetes on coronary outcomes after successful SES insertion. A total of 214 patients with diabetes were divided into four groups based on the presence or absence of microvascular disease. Those patients with evidence of proliferative retinopathy (Group 3) or who had both proliferative retinopathy and nephropathy (Group 4) had significantly greater rates of MACE (37% and 51%, respectively) than patients with no evidence of microvascular disease (Group 1, 20%) or nephropathy alone (Group 2, 17%). The authors reported that diabetic retinopathy (HR 4.6, 95% CI 1.4 - 15.1; p = 0.005) and vessel diameter <2.75 mm (HR 4.1, 95% CI 1.2 - 13.9; p = 0.012) were independent predictors of MACE after multivariate adjustment. These findings suggest that poorer outcomes seen in diabetic patients following PCI, even with DES, may reflect more widespread and diffuse atherosclerosis.

The most appropriate interventional management of diabetic individuals with CAD remains unclear, with most evidence to date indicating a survival advantage with CABG in patients who have multi-vessel disease. The ongoing FREEDOM (Future Revascularization in Patients with Diabetes—Optimal Management of Multi-Vessel Disease) trial, which will prospectively compare DES with CABG, should shed important light on this issue.

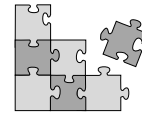
**Table 2. One-Year Risk-Adjusted Outcomes and Costs in Diabetic Patients in ARTS II**

	<i>Sirolimus-Eluting Stent</i> (n = 159)	<i>Bare Metal Stent</i> (n = 112)	<i>CABG</i> (n = 96)
<b>Index Procedure</b>			
Total procedure duration (min)	86*	116	244
No. of stents	3.7*	3.1	0.1
Glycoprotein 2b3a antagonist use	22.0%*†	3.6	0.0%
<b>One-year Outcomes</b>			
Death	2.1%	6.2%	3.3%
Death/MI/stroke	2.5%*†	14.4%	7.4%
Repeat revascularization	13.5%*†	28.4%	5.3%
<b>Costs</b>			
Index hospitalization	\$26,381*	\$22,549	\$35,321
Follow-up medical care	\$6,238	\$9,334	\$3,369
One-year total	\$32,618*	\$31,884	\$38,689

\*p < 0.05, sarcolimus-eluting stent vs. CABG; †p < 0.05, sarcolimus-eluting stent vs. bare metal stent.



## The Sum of Its Parts?



The controversial role of the metabolic syndrome as a predictor of cardiovascular events was addressed by several investigators this week. The various definitions of the syndrome were a particular focus.

Saely and Austrian colleagues evaluated the predictive value of the metabolic syndrome for vascular events as defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) versus the International Diabetes Federation (IDF) (abstract 850-7). Coronary patients (n=750) were prospectively identified and vascular events recorded over four years. Of those, 37.3% (n=280) and 45.5% (n=341) had the metabolic syndrome as defined by ATP III and IDF, respectively. Vascular events were significantly better predicted in those defined by ATP III (adjusted hazard ratio 1.72 [95% CI 1.24-2.38], p=0.001) versus those defined by IDF (adjusted hazard ratio 1.25 [95% CI 0.91-1.72], p=0.18). Correspondingly, patients as defined by ATP III had significantly lower event-free survival than those in the IDF group (p=0.012). Metabolic syndrome as defined by ATP III criteria remained significantly predictive of vascular events after adjustment for Type 2 diabetes, but not after additional adjustments for high triglycerides and low HDL cholesterol. These lipid abnormalities proved significantly predictive of vascular events even after adjustment for metabolic syndrome. From these data, the researchers determined that the ATP III definition is of greater predictive value for vascular events in comparison with the IDF definition. However, it does not provide prognostic information beyond indices of dyslipidemia.

Similarly, Moon and Korean investigators sought to determine the applicability of an Asian modification of the ATP III criteria for metabolic syndrome vs. those of the World Health Organization (WHO) (abstract 939-205). Due to lower mean BMI in Asia, the authors felt that more culturally precise and stringent cutpoints were necessary in their study population. Metabolic profiles and risk of coronary artery

disease (CAD) were compared in a group of 2,724 non-diabetic, Korean patients in whom 728 had significant CAD. A total of 522 (19.2%) met the original ATP III definition, 796 (29.2%) met the Asian-modified ATP III criteria, 361 (13.3%) met the established WHO standards, while 576 (21.1%) met the Asian modified WHO criteria. Odds ratios for CAD prediction, however, were not significantly different according to the metabolic criteria. Additionally, clinical and lipid parameters were comparable among the groups. The investigators concluded that, despite similar CAD predictive values for each group, the modified Asian criteria tend to identify greater numbers of patients and may reduce the risk for under-diagnosis of the metabolic syndrome.

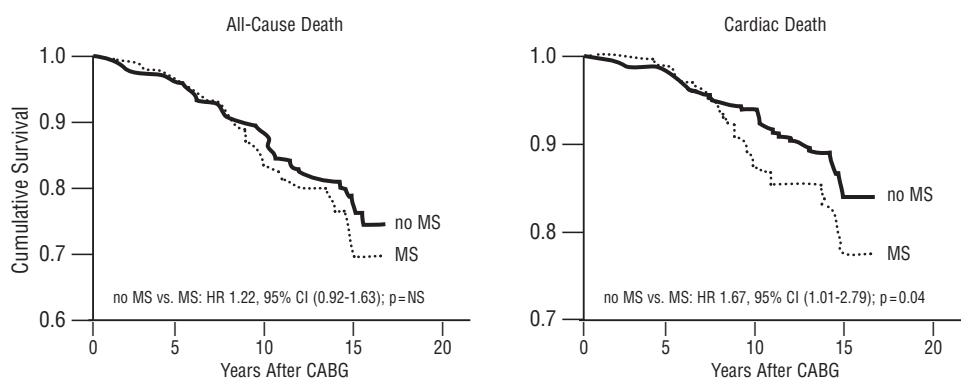
Researchers from Indiana University, Ligler *et al.* (abstract 961-200) investigated whether the metabolic syndrome is predictive of CAD beyond the traditional risk factors such as diabetes, smoking, and hypertension. Over 17 months, 1,520 consecutive patients referred for stress imaging were categorized as meeting the ATP III definition and/or having three or more coronary risk factors. Positive stress echocardiography was used to identify patients with CAD. Presence of CAD was correlated equally in those identified with three or more coronary risk factors versus those with metabolic syndrome alone (p=0.88). CAD was

also similarly prevalent in patients with three or more coronary risk factors and metabolic syndrome versus metabolic syndrome alone (p=0.62). Prevalence of CAD in patients with less than three risk factors and no metabolic syndrome was lower when compared with those patients with at least three risk factors alone (p=0.02), and those with metabolic syndrome alone (p=0.03). The researchers concluded that metabolic syndrome alone confers a similar CAD risk as three or more coronary risk factors.

Long-term data examining the cardiovascular risk of metabolic syndrome in patients undergoing CABG were presented by Kajimoto *et al.* from Japan (abstract 939-207). A total of 722 consecutive CABG patients were separated into two groups based on the ATP III definition (41% with metabolic syndrome). Mortality, cardiovascular and all-cause, was evaluated over an 11-year (±4 years) follow-up period. The presence of metabolic syndrome imposed a far greater risk of cardiac death, whereas the prevalence of all-cause mortality was similar between the two groups (Figure 1).

Despite the recent controversies about the metabolic syndrome's definition and its role as a predictor of future cardiovascular events, it appears to be, at a minimum, a useful clinical tool to identify high-risk patients.

**Figure 1. Impact of Metabolic Syndrome on Death Following CABG**



## Waist Loss



Cardiologists have long recognized that obesity plays a major role in cardiovascular diseases. This increasingly prevalent condition, which predisposes patients to myocardial infarction

and stroke, as well as diabetes, was the focus of several presentations at this week's meeting.

The impact of bariatric surgery on short-term weight loss is well described, yet long-term

cardiovascular risk reduction has not been established. Batsis *et al.* of Minneapolis (abstract 842-8) performed a population-based, longitudinal study to determine the effect of bariatric surgery

## Waist Loss

Continued from page 4

on long-term cardiovascular risk in patients with class II-III obesity. The investigators compared 197 consecutive patients treated with Roux-en-Y gastric bypass with 163 historical controls involved in a weight reduction program. Parameters such as BMI, blood pressure, lipids, fasting glucose, and smoking were used to predict cardiovascular risk. At baseline, the 10-year estimated risk for an event was similar for both groups, 37.1% in the surgical group and 30.2% in controls. After a mean follow up period of 3.3 years, risk had decreased to 18.3% in the surgical group while remaining unchanged (30.0%) for the controls. During this time period, gastric surgery resulted in a BMI reduction from  $49.4 \pm 8.9$  to  $34.0 \pm 8.1$  kg/m<sup>2</sup> whereas BMI did not change in the control group ( $43.9 \pm 5.7$  to  $43.7 \pm 7.7$  kg/m<sup>2</sup>). Extrapolated to a 10-year outcome assessment, it was estimated that 16.2 cardiovascular events and 4.1 overall deaths would be prevented per 100 patients treated by surgery. We would note that this is a very crude estimate of the risk of future cardiovascular events. While it appears to favor bariatric surgery, appropriate prospective clinical trials with hard outcomes are needed.

In an oral presentation, Pi-Sunyer and US colleagues presented data on rimonabant, an investigational weight loss agent, and its impact on metabolic parameters independent of weight loss (abstract 849-3). Previous clinical trials have suggested that rimonabant, a cannabinoid-1 receptor antagonist, may have some peripheral actions, in addition to its notable effect on appetite. For instance, the drug has been associated with increased adiponectin production and glucose

uptake, as well as decreased lipogenesis. Whether these are intrinsic effects of rimonabant or simply parphenomena of weight loss is not fully understood. The investigators pooled one-year data from four clinical trials to assess the impact of rimonabant on body weight, and its influence on HDL-cholesterol, triglycerides, HbA1c, and fasting insulin levels. By using change in weight loss from baseline as a covariate (to minimize effects attributable to weight loss) along with standard regression methodology, the impact of rimonabant on these metabolic parameters was approximated (Table 3). The authors concluded that rimonabant therapy was independently associated with other positive metabolic effects. Whether such conclusions are

valid from a statistical basis remains unclear, especially since successful weight loss may lead to other positive behaviors that might influence these parameters (e.g., increased physical activity).

Unfortunately, sustained weight loss from diet and exercise alone has been illusive for many of our patients. Yet, when they actively participate in therapeutic lifestyle change, the benefits extend beyond weight reduction—to improved insulin sensitivity, cardiovascular health, even emotional status. Bariatric surgery should generally still be reserved for the most dramatically obese, for whom the significant short-term risks are outweighed by the potential long-term benefits. The precise role of pharmacotherapy for this condition remains controversial.

**Table 3. Impact of Rimonabant 20 mg versus Placebo at One Year**

Parameter	Overall Effect (mean difference vs. placebo)	Effect <i>Not</i> Attributable to Weight Loss Alone	Percent Overall Effect <i>Not</i> Attributable to Weight Loss
HDL-cholesterol (%)	+8.0 (±0.6) p<0.001	+3.6 (±0.6) p<0.001	45%
Triglycerides (%)	-14.0 (±1.4) p<0.001	-6.5 (±1.4) p<0.001	46%
Fasting insulin (µIU/ml)	-2.74 (±0.48) p<0.001	-1.34 (±0.51) p=0.018	49%
Adiponectin (µg/ml)	+1.5 (±0.2) p<0.001	+0.85 (±0.21) p<0.001	57%
HbA1c (%)	-0.67 (±0.07) p<0.001	-0.37 (±0.07) p<0.001	55%

Results are presented as mean (SEM).



## Semi-Sweet

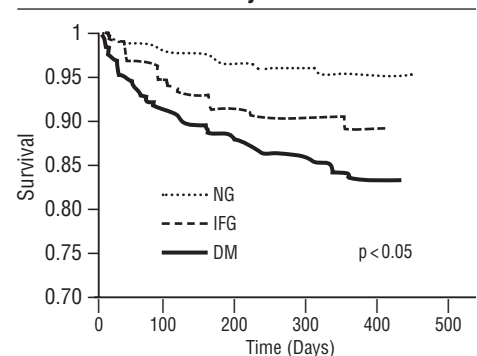


It is well known that individuals with impaired glucose tolerance (IGT), while not frankly diabetic, still have an increased risk (~2 to 3-fold) of acute myocardial infarction (AMI) in comparison to individuals with normal glucose metabolism. Beer and colleagues (abstract 996-237) from France, sought to establish whether the new criteria of impaired fasting glucose (IFG) as defined by the ADA (100-125 mg/dl) also carries with it an increased risk of mortality after AMI. 847 participants in the RICO study who had survived an AMI were grouped according to ADA criteria for fasting glucose as normal fasting glucose (NFG; n=392), IFG (n=118), or diabetes (DM; n=337). At one-year follow-up, cardiovascular mortality was 3%, 8%, and 15% for NFG, IFG,

and DM, respectively. After adjustment for confounding factors (age, sex, anterior location of MI, and LVEF), both IFG and DM were found to be independent predictors for one-year cardiovascular mortality (respectively, RR 1.67 [95% CI 1.29-2.16], p<0.0001 and RR 2.79 [95% CI 1.68-4.55], p<0.0001) (Figure 2). In patients surviving an AMI, both IFG and DM were highly prevalent and associated with an increased risk of cardiovascular death at one year.

Similarly, Suleiman and Israeli colleagues (abstract 830-5), studied the relationship between fasting glucose within 24 hours of admission for AMI and long-term (6-42 months, median 23 months) cardiovascular risk. Patients were characterized as NGT (in this study, using the

**Figure 2. Effect of Diabetic State on Cardiovascular Mortality After an Acute Myocardial Infarction**



Continued on page 6

## Semi-Sweet

Continued from page 5

older cutpoint of <110 mg/dl; n=472), IFG (110-125 mg/dl; n=151), or DM (>125 mg/dl; n=162.) Cox proportional hazards analyses were performed to look at the relationship between fasting glucose and mortality after adjusting for other parameters known to have an impact on cardiovascular mortality (e.g., age, sex, baseline creatinine, hypertension). Mortality rates were

6.2%, 17.0%, and 36.6% in patients with NGT, IFG, and DM, respectively. Compared to NGT, the adjusted RR for mortality was 2.7 (95% CI 1.5-4.6) for individuals with IGT (p<0.0005) and 4.5 (95% CI 2.8-7.3) for patients with DM (p<0.0001).

What is not clear from these data is whether the mild hyperglycemia in these patients is driving the risk. Alternatively, the glucose may simply be a marker of other underlying

metabolic defects that are pro-atherogenic or pro-thrombotic, such as dyslipidemia, insulin resistance, or hypercoagulability. Nonetheless, it now appears that the early identification of patients with mild disorders of glucose regulation in the immediate aftermath of AMI is important and may allow, at the very least, for more aggressive risk factor modification. This should help improve cardiovascular outcomes in these high-risk individuals.



## Reducing Resistance



The anti-inflammatory role of the thiazolidinediones (TZDs) in improving metabolic control and cardiovascular outcomes, independent of insulin sensitizing and lipid lowering effects, continues to be elucidated. Two poster presentations this week added to our current body of knowledge.

Nakayam and colleagues of Japan (abstract 914-207) utilized intravascular ultrasound (IVUS) to examine coronary atherosclerotic plaque in patients with Type 2 diabetes or impaired glucose tolerance undergoing PCI. Patients on insulin were excluded. Two groups were evaluated over six months: one receiving pioglitazone (15mg daily for the initial 14 days, then 30 mg daily, n = 13) and, the second, a control group (n = 13). Measures included baseline and six month volumetric analyses of selected plaques via IVUS along with lipid profiles and inflammatory markers. After six months, patients receiving pioglitazone showed a significant decrease in plasma triglyceride levels (141 ± 57 to 121 ± 61 mg/dl, p=0.039), significant increase in HDL cholesterol (49 ± 10 to 59 ±16, mg/dl, p=0.011), and no difference in LDL cholesterol concentrations. C-reactive protein levels showed a trend toward reduction in the pioglitazone group, but was not significant

(p=0.057). Plaque volumes were significantly lower in the pioglitazone group at six months as well (101.3 ± 32.1 to 94.6 ± 33.6 mm<sup>3</sup>, p = 0.0003). Based on these findings, the investigators suggest that pioglitazone may play a role in causing regression of coronary atherosclerotic plaques, without any evidence of LDL-lowering. They did not, however, identify concomitant interventions that may have influenced patient outcomes. Also, the patient numbers in this study are very small.

In a related trial conducted by Gulba (abstract 905-238), pioglitazone was compared with metformin and glibenclamide in the reduction of cardiovascular risk by measures of surrogate markers. Patients with stable CAD and Type 2 diabetes on monotherapy were evaluated in an open, controlled, multicenter, parallel cohort study. Participants received concomitant pioglitazone 30 mg day (n = 380), metformin average daily dose of 1900 mg (n = 380), or glibenclamide average dose of 6.2 mg (n = 380) over one year. Outcome measures identified similar reductions in HbA1c from baseline for each group (p < 0.001) with no differences between cohorts. Significant increases in HDL cholesterol versus baseline and decreases in high sensitivity CRP

occurred in the pioglitazone and metformin groups. As compared to the other two therapies, pioglitazone significantly decreased HOMA-IR (a calculated marker of insulin sensitivity), adiponectin (a fat-derived cytokine that correlates positively with insulin sensitivity) and MMP-9, a metalloproteinase thought to have an important role in atherosclerotic plaque rupture (all, p < 0.01). Clinical outcomes during the observation period were similar for each group for episodes of heart failure. Overall, the researchers concluded that pioglitazone had the most favorable profile on cardiovascular surrogate markers in the presence of comparable HbA1c lowering.

These encouraging data need to be placed in the context of the only clinical outcomes trial of TZD therapy, the recent PROactive study (Dormandy *et al. Lancet* 2005). This investigation, involving over 5,000 high-risk patients with Type 2 diabetes, yielded mixed and somewhat controversial results (see *Diabetes 2005*, Volume 12, pages 4-6). We look forward to ongoing investigations in this important area. The precise role of TZDs in the prevention of macrovascular disease remains incompletely defined.



## Slow Burn



Atherosclerosis as an inflammatory disease continues to garner much attention from cardiologists and vascular biologists. C-reactive protein (CRP) levels predict cardiovascular outcomes in healthy individuals and in those with acute coronary syndromes (ACS). It is less certain, however, whether CRP predicts outcomes in stable CAD, or whether the new, lower American College of Cardiology cut-points for CRP will

prove useful. To address this issue, an analysis of a subset of patients (n=3,771) from the PEACE trial was performed. PEACE is a placebo-controlled trial of the ACE inhibitor, trandolopril, in patients with CAD and stable left ventricular function. The results from this analysis were presented this week by Dr. Sabatine of Boston, on behalf of his colleagues (abstract 850-8). Patients had a high-sensitivity CRP measured at

baseline and have been followed up for a median of 4.8 years. Data on cardiovascular outcomes and incident diabetes were collected and analyzed using multivariable Cox regression adjusting for age, gender, BMI, traditional cardiovascular risk factors, renal function, and other cardiac medications. A significant predictive value of baseline CRP ≥1mg/l was found for the composite of cardiovascular disease/MI/stroke (Figure 3).

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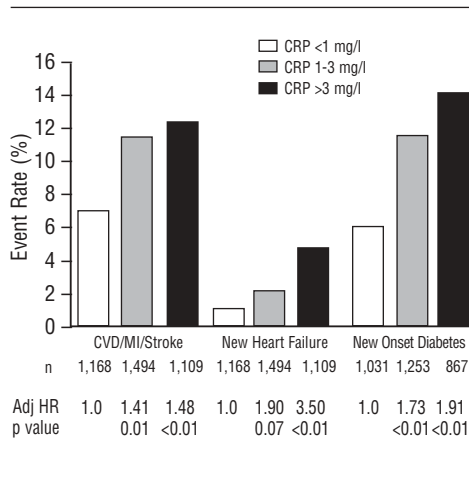
## Slow Burn

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Dr. Sabatine concluded that in patients with stable CAD an elevated CRP, even  $\geq 1$  mg/l, is a strong and independent predictor both of cardiovascular outcomes and new-onset diabetes. This report illustrates the growing prognostic utility of CRP.

Tsimis and Greek colleagues, used the novel approach of "coronary thermography" to investigate the inflammatory state of coronary plaques in CAD patients with or without diabetes undergoing PCI (abstract 1019-234). Patients were matched for age, statin and aspirin use, and percent angiographic stenosis. Coronary thermography was used to determine the temperature difference between atherosclerotic plaque in culprit lesions and proximal coronary vessel wall in 63 non-diabetic and 45 diabetic patients. Patients were also divided into those with stable CAD ( $n=65$ )

**Figure 3. Predictive Value of CRP for CVD/MI/Stroke, New Heart Failure, and New Onset Diabetes in Patients with Stable CAD**



or those with ACS ( $n=43$ ). Plaque temperatures were higher among ACS patients with diabetes ( $n=21$ ) compared to non-diabetic patients (temperature difference  $0.29 \pm 0.31$  °C vs.  $0.15 \pm 0.21$  °C;  $p=0.02$ ). Similarly, diabetic patients with stable CAD had higher relative plaque temperatures than non-diabetic patients ( $0.09 \pm 0.08$  °C vs.  $0.05 \pm 0.04$  °C;  $p=0.006$ ). These findings suggest that the inflammatory process in culprit coronary lesions in diabetic patients is more aggressive than in comparable patients without diabetes, and may, in part, explain the excess morbidity and mortality in this group.

Despite the enormous interest in the inflammatory aspects of vascular disease, we've yet to see any pharmacological interventions that specifically address this process. Therefore, while inflammation appears to be an integral component of atherosclerosis, its precise role as a therapeutic target remains undisclosed.



## So Many Posters, So Little Time...



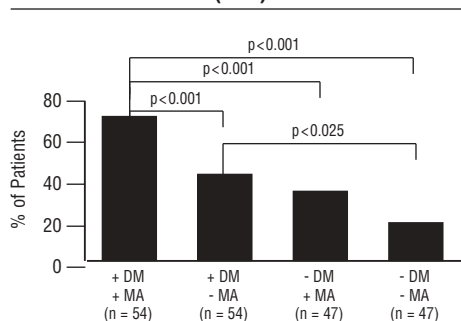
## Insulin and A-Fib

Using care management databases, Brar and co-workers from Kaiser Permanente and UCLA examined the prevalence of atrial fibrillation and flutter in 28,009 patients with heart failure. Among these, 4,754 (17% of the heart failure population) had insulin-requiring diabetes and 7,884 (28% of the heart failure population) had diabetes treated without insulin (abstract 804-7). Mean ( $\pm$  SD) ejection fraction (data available for 7,350 individuals) was nearly identical between groups ( $42\% \pm 17\%$ ,  $43\% \pm 17\%$ , and  $44\% \pm 17\%$  for non-diabetics and diabetics without and with insulin, respectively.) In a multiple logistic regression model (adjusted for age, gender, hypertension, CAD, valvular disease and surgery, thyroid disease, COPD, education, and income), the risk of atrial fibrillation/flutter in diabetic insulin users with heart failure was significantly less ( $p < 0.001$ ) as compared to diabetic non-insulin users (adjusted OR 0.81) and non-diabetics (adjusted OR = 0.77) with heart failure. Especially given the fact that patients with Type 2 diabetes on insulin tend to have more advanced vascular disease, these results suggest a possible beneficial effect of insulin on atrial electrical activity in patients with heart failure. Unfortunately, the data could not be controlled for degree of glycemic control, nor could those patients with Type 1 diabetes be identified.

## Albuminuria as a Risk Marker

Sukhija and colleagues from the University of Arkansas and NY Medical College presented data that underscore the value of microalbuminuria as a risk factor for CAD—in this case, for luminal stenosis  $\geq 50\%$  by coronary angiogram (abstract 842-5). Patients with microalbuminuria, and particularly those who were diabetic, had more severe CAD than did those without microalbuminuria (Figure 4). Thus, the presence of microalbuminuria in diabetic patients might signal the need for earlier CAD screening and more aggressive risk factor treatment.

**Figure 4. Prevalence of 3-Vessel CAD by Microalbuminuria (MA) and Type 2 Diabetes Mellitus (DM) Status**



## Silent But Deadly...

In a Sunday morning poster session, Choi *et al.* from Seoul National University Hospital, Korea, reported on clinical outcomes in patients with Type 2 diabetes and CAD who were evaluated over a five-year period (abstract 905-236). Asymptomatic patients ( $n=70$ , positive stress test and CAD by coronary angiography) were more often male and had a longer duration of diabetes and higher incidence of retinopathy, as compared to symptomatic patients (AMI = 67, unstable angina = 188, chronic stable angina = 112). While there was no difference in severity of atherosclerosis or rates of adverse cardiac events based on presence/absence of symptoms, asymptomatic patients had a higher cardiovascular mortality rate (five-year survival of 66% vs. 86% for symptomatic patients;  $p=0.001$ ). Notably, asymptomatic patients had lower revascularization rates (27% vs. 62%, respectively;  $p < 0.001$ ). Whether this could explain the poorer outcomes is not clear. However, revascularization at the time of index angiography was independently associated with improved survival in patients with silent myocardial ischemia (HR 0.052 [95% CI 0.006-0.483] after multivariate adjustment).

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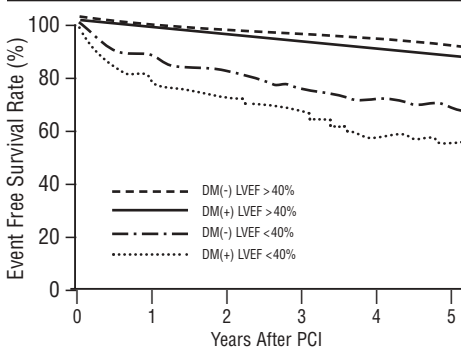
## So Many Posters...

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### DM, PCI, and LVEF

Ando and Japanese associates conducted a study of almost 10,000 consecutive patients, ~25% diabetic) who underwent PCI for stable angina between September 1981 and July 1998 (abstract 905-240). Despite a similar inpatient clinical success rate (i.e., procedural success without death/MI/CABG, 89% each), the five-year survival rate was significantly lower in patients with diabetes vs. those without diabetes (84% vs. 88,  $p < 0.0001$ ). Co-existence of low left ventricular ejection fraction (LVEF  $< 40\%$ ) had a negative impact on survival, more so in diabetics (absolute risk increase of 33% vs. 23% in patients without diabetes) (Figure 5).

**Figure 5. Event-Free Survival Following PCI by Diabetes Mellitus (DM) and LVEF Status**

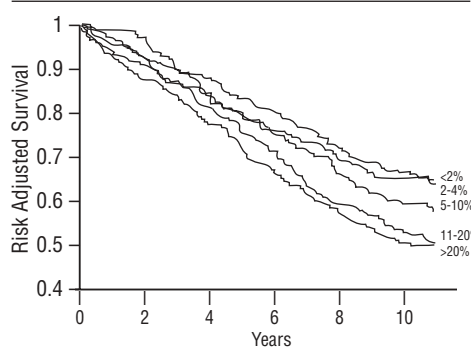


### Size Matters

Kang *et al.* reported 11-year follow-up data for 1,291 consecutive diabetic patients who underwent exercise or vasodilator stress myocardial perfusion single photon emission computed tomography (SPECT) (abstract 926-10). From their normalized summed stress score, patients were divided into groups based on % abnormal myocardium:  $< 2\%$  ( $n = 382$ ), 2-4% ( $n = 123$ ), 5-10% ( $n = 237$ ), 11-20% ( $n = 220$ ), and  $> 20\%$  ( $n = 329$ ). In the Cox hazards model, stress defect size  $> 10\%$ , age, shortness of breath, left ventricular enlargement, higher resting systolic BP, and lower heart rate ratio (stress/rest) were independent predictors of all-cause mortality (each  $p \leq 0.007$ ), as were abnormal ECG at rest, peripheral vascular disease, lower resting diastolic BP, and BMI (each,  $p < 0.05$ ). Gender, history of AMI or revas-

cularization, symptomatic angina, stress type, and stress defect  $\leq 10\%$  were not predictive. There was also a significant relationship between the size of the stress defect and risk-adjusted survival ( $p < 0.001$ ). (Figure 6)

**Figure 6. Risk-Adjusted Survival by Myocardial Perfusion SPECT Defect Size in Diabetes**



### Another Reason to Avoid the Common Cold

In a study of 51 children with Type 1 diabetes, Liuba and Swedish researchers found common carotid artery compliance was decreased ( $p = 0.06$ ) and stiffness index was increased ( $p = 0.09$ ) in those who commonly suffer from viral upper respiratory tract infections (URTI) (i.e.,  $> 4$  in the previous year) (abstract 935-181). The prevalence of viral URIs did not affect intima-media thickness or inflammatory indices (C-reactive protein, orosomucoid). Whether the apparent cumulative adverse effects of recurrent viral infections on arterial elasticity in diabetic children lead to adverse effects on arterial structure requires further study.

### Sildenafil: Benefits Beyond ED?

Twenty patients with Type 2 diabetes were enrolled in a double-blind, crossover study in which they were randomized to sildenafil 100 mg QD for three days then either 25 mg TID for four weeks, or 25 mg TID for four days followed by placebo TID for three weeks. Vitale *et al.* from Italy (abstract 957-177) measured flow mediated dilation and the following serum levels of inflammatory and endothelial markers: nitric oxide, endothelin-1, CRP, IL-6, ICAM, and VCAM, at baseline and at the end of each week thereafter during the study. After one week, a significant improvement in flow-mediated dilation was observed, with response increasing further from

weeks 2 to 4 in those in the active treatment group (84% increase vs. baseline at week four,  $p = 0.01$ ) and regressing over the same period in those in the placebo group. In addition to the improvement in endothelial function, a treatment benefit based on changes in vascular inflammation markers was also observed.

### A New Anti-Anginal on the Horizon

Rosano and associates from Italy randomized 20 diabetic patients with CAD to the fatty acid oxidation inhibitor trimetazidine vs. placebo as adjunctive therapy to their standard anti-anginal agents, for six months (abstract 999-252). They used 24-hour ambulatory ECG monitoring to assess myocardial ischemia. At study end, trimetazidine reduced (each  $p < 0.01$ ) silent episodes of myocardial ischemia ( $-39\%$  vs. placebo for number of episodes;  $-35\%$  vs. placebo for ischemia time/24 hours), symptomatic episodes of myocardial ischemia ( $-27\%$  vs. placebo for number of episodes), and total ischemic burden ( $-29\%$  vs. placebo). Reductions from baseline for the active drug were of a similar magnitude and degree of statistical significance. This investigational agent appears to work by improving the energy dynamics within the heart by decreasing fatty acid beta oxidation.

### Stress Hyperglycemia During AMI

In a prospective, observational study of all patients admitted for AMI, Schiele and French researchers evaluated the predictive value of stress hyperglycemia (cut point of 138 mg/dl 12 hours after admission) on mortality (abstract 996-238). A total of 175 (24%) had pre-existing diabetes, 154 (21%) were non-diabetic patients with stress hyperglycemia, and the balance, 395, had neither diabetes nor stress hyperglycemia. In non-diabetic patients, stress hyperglycemia increased the one-year mortality rate to that of diabetic patients (18.8%, 16.6% and 6.1%, for patients with stress hyperglycemia, diabetes, and neither, respectively). The predictive value of stress hyperglycemia on mortality remained strong after stratification by risk score (based on the Global Registry of Acute Coronary Events) and use of guideline-recommended treatment. Lowering the glucose cut point to 115 mg/dl changed the prevalence of stress hyperglycemia, but not its value in predicting mortality. These observational data echo the findings of several other groups. To what extent treating stress hyperglycemia improves outcomes remains a controversial point.

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