

# Diabetes 2005

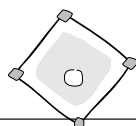
From the 2005 Scientific Sessions of the  
American Heart Association ■ Dallas, TX

2001 2002 2003 2004 **2005** 2006 2007

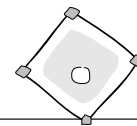
Sponsored by **Yale University School of Medicine**,  
Department of Internal Medicine, Section of Endocrinology

Volume **12**

November 16, 2005



## FIELD of Dreams?



Important data on diabetes presented at the 2005 Scientific Sessions of the American Heart Association 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 (EASD and AHA 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 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.

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.

*Supported through an unrestricted educational grant from Takeda Pharmaceuticals America, Inc. and Eli Lilly and Company.*

Diabetic patients have a three-to-four fold increased risk of cardiovascular disease, resulting in a five to 10 year decreased life expectancy as compared to the general population. Much of this increased risk has been attributed to the classic diabetic dyslipidemic triad: high triglycerides, low HDL-cholesterol, and small, dense LDL particles. In this context, statin trials have shown no clear lower threshold of benefit, leading many to believe that essentially all patients with diabetes should be treated with a statin at a dose sufficient to reduce LDL cholesterol to <100 mg/dl, or by at least 30% from baseline. Less clear, however, is the role of fibrates, either alone or, more likely, as an addition to statins. These agents are agonists of the nuclear receptor, PPAR- $\alpha$ . They reduce plasma triglycerides and increase HDL cholesterol and, as a result, reverse cholesterol transport. They may also have beneficial effects on LDL particle size, vascular inflammation, and atherosclerosis. The results of post-hoc analyses from the Helsinki Heart Study, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), and the Bezafibrate Infarct Prevention (BIP) trial suggest that fibrates reduce cardiovascular endpoints in patients with diabetes/metabolic syndrome. The results of the first large clinical-endpoint study of fibrate therapy in diabetic patients were presented this week by Dr. Anthony Keech from the University of Sydney during the Late-Breaking Clinical Trials session and published in *Lancet*.

The Fenofibrate Intervention & Event Lowering in Diabetes (FIELD) study was a double-blind, multicenter study (63 sites in Australia, New Zealand, and Finland) into which 9,795 patients aged 50-75 years with Type 2 diabetes were randomized to fenofibrate 200 mg or matching placebo once daily. Eligible patients had a baseline total cholesterol between 116-251 mg/dl, plus either a total to HDL cholesterol ratio of  $\geq 4$  or a plasma triglyceride level of between 89-443 mg/dl. Patients taking lipid-modifying therapy were excluded, as were those with renal impairment, known chronic liver disease, symptomatic gall bladder disease, and a cardiovascular event within the three months prior to recruitment into the study.

The median follow-up period was five years.

At baseline, the two treatment groups were similar to one another, based on demographic characteristics (37% females, mean age 62.2 years; median BMI 29.8 kg/m<sup>2</sup>), lipid profile (mean total cholesterol 196 mg/dl; mean LDL-cholesterol 120 mg/dl; mean HDL-cholesterol 43 mg/dl; median triglycerides 154 mg/dl), duration of diabetes (median 5 years), and history of cardiovascular disease (CVD) (22%). After four months of treatment, changes in lipid values with fenofibrate relative to placebo were -11% for total cholesterol, -12% for LDL, -29% for triglycerides, and +5% for HDL, although some decline in efficacy was observed by study close. Importantly, more patients allocated to placebo (17%) than to fenofibrate (8%) began lipid-lowering drugs, especially statins, during the course of the trial.

In the intent-to-treat analyses, mixed results were observed in clinical endpoints (Table 1). An 11% relative reduction in the primary endpoint—i.e., time to first occurrence of either non-fatal myocardial infarction (MI) or death from coronary heart disease (CHD)—occurred with fenofibrate, which did not reach statistical significance ( $p=0.16$ ). This corresponded to a significant 24% relative reduction in non-fatal MI ( $p=0.01$ ) and a non-significant 19% increase in CHD mortality ( $p=0.22$ ). Statistically significant treatment group differences favoring fibrate were observed for the secondary endpoints of total CVD events, coronary revascularization, and all revascularizations; however, non-significant increases in CVD and total mortality were also found. Favorable and statistically significant effects on microalbuminuria progression and retinopathy requiring laser treatment were seen with fenofibrate.

According to pre-specified sub-group analyses of total CVD events, treatment effects were greater in patients without pre-existing CVD (HR 0.81,  $p=0.004$  vs. HR 1.02 in patients with CVD,  $p=0.85$ ) and in the patients <65 years old (HR = 0.80,  $p=0.003$ ).

The study drug was generally well tolerated. There were no treatment group differences based on adverse events, with the exception of increased incidence of pancreatitis (0.8% vs. 0.5% with

*Continued on page 2*

## FIELD of Dreams?

Continued from page 1

placebo,  $p=0.031$ ) and pulmonary embolism (1.1% vs. 0.7% with placebo,  $p=0.02$ ) in the fibrates-treated patients.

We find the FIELD study results somewhat difficult to interpret, especially since the study was purposefully conducted in the vacuum of minimal statin exposure. While there appears to be a modest benefit on total CVD events with fenofibrate, there is no effect whatsoever on mortality—in fact, non-significant—though still concerning—increases in all-cause and CHD mortality were found in the active therapy group. While it is true that the higher rate of starting statin therapy in placebo patients may have masked a larger treatment effect from fenofibrate, it is unlikely that equal statin use between treatment groups would have significantly altered these results. Based on this study, the benefit of fibrates in diabetic patients with normal to mildly elevated triglycerides is questionable. These drugs still have

**Table 1. Treatment Effect on Primary and Secondary Clinical Endpoints**

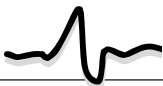
	Placebo (n = 4,900)	Fenofibrate (n = 4,895)			
	(Rate/1000 person-years at risk)		HR	95% CI	Log-rank p
<b>Primary Outcome*</b>					
Coronary events	11.7	10.4	0.89	0.75-1.05	0.16
CHD mortality	3.7	4.4	1.19	0.90-1.57	0.22
Non-fatal MI	8.4	6.4	0.76	0.62-0.94	0.01
<b>Secondary Outcomes</b>					
Total CVD events†	29.0	25.8	0.89	0.80-0.99	0.035
CVD mortality	5.1	5.6	1.11	0.87-1.41	0.41
Total mortality	12.9	14.2	1.11	0.95-1.29	0.18
Total stroke	7.1	6.4	0.90	0.73-1.12	0.36
Coronary revascularization	15.0	11.9	0.79	0.68-0.93	0.003

\* Time to first occurrence of either non-fatal MI or death from CHD.

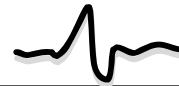
† CHD events, total stroke, other cardiovascular death combined, and coronary and carotid revascularization.

a major role, however, in the therapy of the markedly hypertriglyceridemic patient with or without diabetes. We also await the results of the ACCORD trial which should shed light on the role of fibrates

on a background of aggressive statin therapy in Type 2 diabetes. For now, based on FIELD, treatment of normal to mildly elevated triglyceride levels in Type 2 diabetic patients with fibrates appears unwarranted.



## STEMI-ng the Tide of AMI in Diabetes



Diabetic patients are at increased risk of acute myocardial infarction (AMI), and suffer increased morbidity (reinfarction, heart failure) and mortality following these events. The frequently advanced vasculopathy in these patients has been to blame, along with evidence of abnormal ventricular remodeling in the setting of ischemic injury. Several abstracts this week highlighted the differences between diabetic and non-diabetic patients experiencing acute coronary syndromes (ACS).

### (Infarct) Size Matters

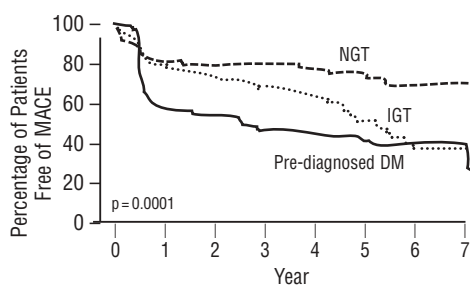
Patients with diabetes are at increased risk of death following AMI, as compared to those without diabetes. In the EMERALD trial of 501 patients who underwent emergent percutaneous coronary intervention (PCI) following AMI, cumulative six-month mortality was 13.2% in diabetics and 2.3% in those without diabetes ( $p<0.001$ ) (abstract 1830). Larger infarct size as well as reduced myocardial perfusion (by angiography) and less complete ST-segment resolution (43% vs. 64% in non-diabetics,  $p=0.003$ ) following PCI may contribute to this observation. Median infarct size in patients with and without diabetes was 14% and 10% of the left ventricle ( $p=0.013$  after adjustment for infarct location, initial TIMI-grade flow, prior AMI, and time to reperfusion). In patients with both infarct size measurement

and six-month follow-up data, only infarct size was an independent predictor of late mortality.

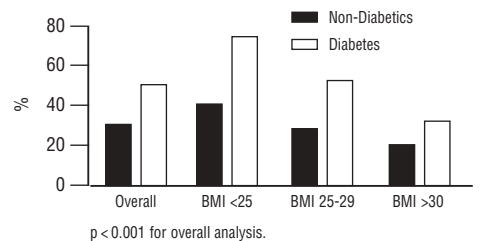
### The Intolerant Patient

Even patients with mild glucose dysregulation appear to be at increased risk in the setting of AMI. Tamita and Japanese associates evaluated the association between newly diagnosed impaired glucose tolerance (IGT) and long-term major adverse cardiovascular events (MACE) in 275 patients with AMI (abstract 2503). Over a median follow-up period of 4.6 years, MACE in patients with IGT were higher than in those with normal glucose tolerance (NGT)—actually comparable to those with diabetes (DM) (Figure 1). Glucometabolic status was a strong predictor for future cardiovascular events (HR vs. NGT: 2.1 for IGT,  $p=0.003$ ; 2.9 for DM,  $p=0.001$ ).

**Figure 1. Kaplan-Meier Curves for MACE**



**Figure 2. 8-Year Mortality Risk by BMI**



### The Obesity Paradox

It has been reported by many groups that patients with diabetes do more poorly following AMI, but that obesity may actually protect against at least early mortality. The actual explanation for this “obesity paradox” has proven elusive. In a study of 3096 AMI patients conducted by faculty of the Mayo Clinic, in-hospital mortality (12.1% vs. 7.0%,  $p<0.0001$ ) and eight-year post-discharge mortality ( $p<0.001$ , Figure 2) were significantly higher in patients with vs. without diabetes (abstract 1831). After adjustment for age and BMI, diabetes increased by about two-fold the risk of in-hospital mortality (OR 1.8,  $p<0.0001$ ) and eight-year mortality (HR 1.9,  $p<0.0001$ ). Mortality was lowest in those with the highest BMI, in both diabetic and non-diabetic cohorts. The test of interaction between BMI and diabetes was non-significant, suggesting they act

Continued on page 3

## STEMI-*ng* the Tide of AMI in Diabetes

Continued from page 2

independently (and in different directions) with regard to post-AMI outcomes.

## The Rise and Fall of Admission Glucose

The acute effect of hyperglycemia has garnered much recent attention after the publication of a series of articles indicating an independent adverse association between mortality and the degree of blood glucose elevation at presentation with AMI, especially in patients without a previous history of diabetes. Whether hyperglycemia is simply a marker of degree of illness or whether a mediator of adverse outcomes remains controversial. If the latter, prompt and aggressive therapy with insulin would certainly be warranted. Intravenous insulin therapy studies in AMI, however, have yielded mixed results.

In a study of ~1,000 patients (16% with diabetes; mean glucose 164 mg/dl) presenting with ST-segment elevation myocardial infarction (STEMI) and treated with PCI, Worthley and Canadian coworkers confirmed the impact of admission blood glucose on 30-day mortality (abstract 1833). The group assessed many additional factors, including age, sex, established diabetes, heart rate, systolic blood pressure, left ventricular end diastolic blood pressure, peak CK levels, WBC count, and baseline creatinine. Mortality rate in patients by quartile of admission glucose are presented in Table 2. Based on multiple logistic regression analysis, admission glucose (OR 1.7,  $p=0.005$ ) and baseline creatinine (OR 1.7,  $p=0.001$ ) were the most influential factors on short-term mortality.

Goyal and colleagues from the US (abstract 3627) reported data from a substudy of the CARDINAL trial, which is assessing the effect of complement inhibition in 1,903 AMI patients

**Table 2. Short-Term Mortality (%) After AMI by Admission Blood Glucose**

	<119 mg/dl (n = 258)	120-140 mg/dl (n = 244)	141-180 mg/dl (n = 246)	≥181 mg/dl (n = 232)	p-value
In-Hospital Mortality	0.4	2	2	10	<0.001
30-Day Mortality	0.4	2	2	14	<0.001

undergoing primary reperfusion. The authors analyzed 1,469 patients with blood glucose data on admission and after 24 hours to determine their relationship to 30-day mortality, after adjustment for baseline clinical covariates. The mean admission glucose was 143 mg/dl, falling to 120 mg/dl at 24 hours. After 30 days, 45 patients had died. In the 250 diabetic patients in this cohort, neither admission glucose nor its fall at 24 hours predicted outcomes. However, in the non-diabetic group ( $n=1,219$ ), both baseline glucose ( $p=0.005$ ) and the 24-hour glucose drop ( $p<0.0001$ ) independently predicted mortality. Moreover, in non-diabetics, a more significant fall in glucose over the first 24 hours of admission predicted improved survival, regardless of the baseline glucose level.

Further insights into the acute effects of glucose in AMI patients was provided by a French group, led by Cochet (abstract 2269). Admission glucose was measured in 164 patients with STEMI treated with successful primary PCI. Magnetic resonance imaging (MRI) was performed between two and seven days following PCI, using paramagnetic contrast agents to allow for the assessment of microvascular flow and the extent of infarction. MRI data were then compared according to quartiles of admission glucose levels. MRI measures of microvascular obstruction and the extent of transmural damage were significantly higher in the groups with the highest glucose levels. The authors felt that their data confirm the impact of admission glycemia on the consequences of AMI and response to PCI. An alternative explanation from these unadjusted

observations is that the actual success of the PCI may have been determined in part by the severity and/or duration of the coronary occlusion at admission—which itself may have influenced the degree of stress hyperglycemia.

Another physiological study in this area came from an Italian group led by Battista (abstract 3627). These collaborators were interested in the effects of hyperglycemia on cerebral perfusion, since stroke outcomes appear to be worse in the most hyperglycemic patients. They measured cerebral perfusion by single positron emission computed tomography (SPECT) in 24 patients with Type 1 diabetes (mean age  $44 \pm 2.5$  years). The patients were first studied in the setting of poor control (mean BG  $221 \pm 18$  mg/dl). 42% of the patients had at least three perfusion defects. Univariate analysis showed an association between perfusion defects and fasting glucose and HbA1c, but not age, gender, BMI, and diabetes duration. After restoration of euglycemia, perfusion imaging was repeated. Regional perfusion defects were significantly reduced (from  $4.4 \pm 0.7$  to  $1.3 \pm 0.4$ ,  $p<0.001$ ). Markers of endothelial dysfunction were also significantly reduced. It was concluded that functional changes in regional cerebral perfusion are linked to glycemic control and that hyperglycemia-induced endothelial dysfunction likely plays a major role. This specific study is more convincing of an acute and reversible effect of glucose on vascular function, supporting the recent move toward aggressively treating hyperglycemia in patients admitted with acute vascular events.



## Diabetes & CVD: A Not-So-Sweet Future



To lead off the opening day of this year's AHA Scientific Sessions, a crowded room heard the symposium entitled *Diabetes and Cardiovascular Disease: The Future is Not So Sweet*. This session was chaired by Dr. Scott Grundy of the University of Texas, Southwestern and Dr. Kathy Berra from Stanford.

Dr. Steve Haffner, of the University of Texas, San Antonio, led off the discussions with a lecture entitled "Preventing Diabetes and Preventing CVD: What Do We Need to Do?" Dr. Haffner reminded the audience that diabetes is a CVD risk equivalent,

based on his own work with Finnish collaborators in the East-West Study. This longitudinal investigation equated the risk of MI in the patient with Type 2 diabetes but no overt CHD to that of a non-diabetic patient with a prior history of MI. Importantly—but often overlooked when this study is quoted—nearly one in two patients who had both diabetes and previous MI suffered another infarct within the follow-up period of seven years. Rates of undiagnosed diabetes and IGT in CHD patients were then reviewed. Norhammer and Swedish colleagues (*Lancet* 2002) have previously

reported an impressive 35% prevalence of newly recognized diabetes and a 31% prevalence of IGT in 181 patients hospitalized for AMI. Three months after discharge, the percentages (25% and 40%, respectively) remained high. Notably, relying on fasting glucose or even HbA1c in this population did not find nearly as many cases as did oral glucose tolerance testing (OGTT).

Nonetheless, the relationship between glucose and CVD risk is a complex one. By Cox proportional hazards models in the United Kingdom Prospective Diabetes Study (UKPDS), baseline

Continued on page 4

## Diabetes & CVD...

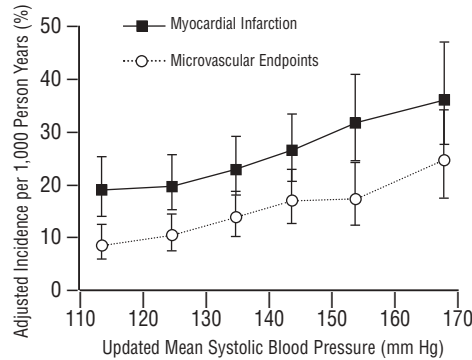
Continued from page 3

LDL-cholesterol, followed, in order, by HDL-cholesterol, HbA1c, systolic blood pressure, and smoking proved to be the most important predictors of MI risk (Figure 3). However, epidemiological analysis from the treatment component of this prospective investigation demonstrated a much weaker effect of HbA1c on macrovascular than on microvascular risk. This is contrasted with the relationship between these risks and blood pressure, which is essentially identical. In light of these data, Dr. Haffner raised the possibility that HbA1c was not the best measure of glycemic derangement, alluding to the much stronger relationship between cardiovascular risk and post-prandial glucose. Alternatively, the accumulated CVD risk in the prediabetic phase may attenuate the influence of glucose control once frank hyperglycemia becomes established.

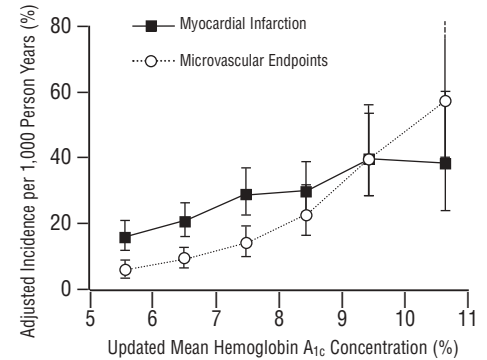
The link between diabetes and CVD is felt by many authorities to involve insulin resistance. In the San Antonio Heart Study (Hanley *et al.*, *Diabetes Care* 2002), insulin resistance, as measured by the HOMA equation, was closely associated with CVD risk. Those patients in the lowest quintile of insulin sensitivity had 2.6-fold the number of coronary events than those in the highest quintile. After adjustments for age, gender, ethnicity, fasting glucose, HDL-cholesterol, LDL-cholesterol, and triglycerides, the relationship was attenuated only partially, but remained significant ( $p < 0.008$ ). The only treatment trial to assess the effect of the insulin sensitizing thiazolidinediones, the PROactive study (Dormandy *et al.*, *Lancet* 2005) was reviewed. In PROactive, the addition of pioglitazone to established antihyperglycemic therapy in patients with Type 2 diabetes and macrovascular disease resulted in a 16% reduction ( $p = 0.027$ ) in the composite of all-cause mortality, myocardial infarction, and stroke. The study has raised some controversy, since a larger treatment effect had been anticipated. In addition, the broader primary composite endpoint (which included physician-determined "events" such as angioplasty and leg revascularization) did not achieve statistical significance. Dr. Haffner reminded the audience that several important recent cardiovascular trials, including PROVE-IT (lipids), CHARM, and Val-HeFT (heart failure) and several clopidogrel studies had endpoint reductions of a similar degree.

Finally, Type 2 diabetes prevention strategies were reviewed. Lifestyle interventions (diet and exercise) in the Da Qing, Finnish Diabetes Prevention, and Diabetes Prevention Program (DPP) studies have resulted in major risk reductions (42-58%) in patients with IGT.

**Figure 3. Incidence Rates for Myocardial Infarction and Microvascular Complications Based on Blood Pressure and Glucose Control in the UKPDS**



Source: Stratton *BMJ* 2000.



Source: Adler, *BMJ* 2000.

Pharmacological therapy using insulin sensitizers or blockers of intestinal carbohydrate absorption also appear to reduce risk, including metformin (DPP, -31%), troglitazone (TRIPOD, -56%), and acarbose (STOP-NIDDM, -25%). Other diabetes prevention studies currently underway include DREAM (rosiglitazone and/or ramipril), ACT-NOW (pioglitazone), and NAVIGATOR (nateglinide and/or valsartan).

Dr. Salim Yusuf from McMaster University in Canada next presented "The Continuum of Risk: MS to IR to T2DM or Not?" Dr. Yusuf made several important points concerning the epidemiology of cardiovascular disease. From a series of studies from his group and others, it has been suggested that just nine risk determinants account for >90% of the global risk for CVD (see Table 3). Dr. Yusuf also underscored a point that is often lost in an era seemingly obsessed with numerical risk factors and strict cutpoints: the risk imparted by essentially every CVD risk factor is a *continuum* and, in most cases, linear. Moreover, the effect of these risk factors tends to be underestimated in studies that dichotomize a certain biochemical value, clinical feature, or habit as being "present" or "absent." This error is compounded when analyzing risks that are themselves correlated with each other, as is the case with the currently defined "metabolic syndrome," which Dr. Yusuf referred to as a "fundamentally flawed concept."

Most epidemiological studies in this area have an additional major flaw—they are typically restricted to one ethnic group or geographic region of the world. In westernized societies, for example, LDL-cholesterol levels are all generally elevated. Analyzing the effect of LDL on CVD risk within this population is condemned to underes-

**Table 3. Nine Major Global Determinants of CVD Risk (per Yusuf)**

<ul style="list-style-type: none"> <li>■ Lipid abnormalities (Apo B/Apo A1 ratio)</li> <li>■ Current smoking</li> <li>■ Diabetes</li> <li>■ Hypertension</li> <li>■ Abdominal obesity</li> <li>■ Psychosocial stress</li> </ul>	}	↑'s risk
<ul style="list-style-type: none"> <li>■ Exercise</li> <li>■ Intake of fruits and vegetables</li> <li>■ Alcohol intake</li> </ul>	}	↓'s risk

timating its importance. The amusing analogy offered was the futile circumstance of trying to determine the deleterious effect of smoking in a room full of smokers!

William McClellan from Emory University next addressed "Renal Dysfunction and Cardiovascular Risk", an issue that is becoming increasingly important in our diabetic patients. The point was made that the measurement of serum creatinine does not adequately reflect renal function, as measured by glomerular filtration rate (GFR) and creatinine clearance. For example, a 70-year old Caucasian woman weighing 60 kg and a 25 year old black man weighing 70 kg may both have a serum creatinine concentration of 1.2 mg/dl—yet this reflects a GFR in the man of 95.0 ml/min/1.73 m<sup>2</sup> body surface area, but a GFR of only 47.2 in the woman (as measured by the Modification of Diet in Renal Disease [MDRD] equation.) Web-based calculators for GFR are now available at <http://kidney.org> and <http://nephron.com/cgi-bin/MDRD.cgi>.

## Diabetes & CVD...

Continued from page 4

The new designations of chronic kidney disease (CKD) stages were reviewed, as shown in Table 4. CKD stage 3 or higher is now a well-recognized risk factor for cardiovascular disease, including coronary artery disease (CAD) and heart failure. Due to their increased CVD and renal risk, the blood pressure goal in patients with CKD Stage 3 or above is now <130/80 mmHg, not <140/90 mmHg as for the general hypertensive population. Agents that block the renin-angiotensin system are preferred. Clinical trial data support the use of ACE inhibitors in CKD patients with Type 1 diabetes and ARBs for Type 2 patients. These drugs not only slow the progression of renal disease, but also appear to reduce cardiovascular events as well. It was pointed out that these modulators of the renin-angiotensin axis reduce intraglomerular pressures, and, as a result, reduce GFR. This should not be viewed as a side effect but as an expected, even desired outcome. Permanent changes in serum creatinine are not seen, since GFR rebounds promptly upon discontinuation of the ACE inhibitor or ARB. Hyperkalemia is not a significant concern unless the patient has progressive renal disease or also takes a potassium-sparing diuretic.

Dr. Silvio Inzucchi from Yale University presented his thoughts on "The Role of Insulin Sensitizing Agents in Non-Diabetic Patients." Insulin sensitizers are drugs that improve insulin action. Currently, they include metformin and the thiazolidinediones (TZDs) (rosiglitazone and pioglitazone), with the former exerting its effect primarily in liver, and the latter primarily in fat and skeletal muscle. Because of the association between insulin resistance and CVD, it has been long proposed that insulin sensitizer therapy may reduce cardiovascular events. Metformin had previously been shown in the UKPDS to reduce MI rates in newly diagnosed, overweight patients with Type 2 diabetes. The TZDs had been expected to have even greater effects. The PROactive study, as mentioned above, demonstrated a modest effect (RRR = 0.84) on mortality, MI, and stroke in high-risk diabetic patients. This study also found a slight increase in non-adjudicated heart failure hospitalization with pioglitazone, albeit without any difference in heart failure mortality. Studies are underway to further characterize both the benefit and risk of these agents in patients with diabetes.

As far as non-diabetic patients are concerned, there is a paucity of data in the literature. The vast majority of clinical trials thus far reported have been conducted in patients with established Type 2 diabetes. Most of the other studies involve small, short-term investigations in a variety of

**Table 4. CKD Definitions Based on GFR**

CKD Stage	ICD-9 code	Definitions
1	585.1	Kidney damage with normal or high GFR (>90)
2	585.2	GFR 60-89
3	585.3	GFR 30-59
4	585.4	GFR 15-29
5	585.5	GFR<15 or on dialysis

GFR in ml/min/1.73 m<sup>2</sup>.

insulin resistant patients, including women with polycystic ovary syndrome (PCOS), or patients with non-alcoholic fatty liver disease, HIV-associated lipodystrophy, or prediabetes. Only a handful of studies, mainly assessing surrogate metabolic and vascular markers, could be found with insulin sensitizers in non-diabetic CVD patients. These suggest a potential benefit on markers of insulin resistance and atherosclerosis, but randomized clinical trials will be needed. Dr. Inzucchi concluded that, presently, the role of insulin sensitizing drugs in non-diabetic patients is very limited—perhaps to metformin to improve ovulatory capacity and fertility in PCOS patients, an off-label use, but one that has gained widespread acceptance in the gynecology community.

Dr. Larry Young, also from Yale, closed the symposium by reviewing CAD screening in asymptomatic diabetic patients. In 1998, a combined AHA-ADA consensus statement delineated the indications for screening the asymptomatic patient with diabetes (see Table 5.) More recently the American College of Cardiology has evaluated the appropriateness of SPECT myocardial perfusion imaging (MPI) in asymptomatic patients (*J Amer Coll Cardiol* 2005). According to this document, it would be appropriate to screen any patient with a high Framingham risk score and/or with a high coronary artery calcium (CAC) score (>400 Agatston units) if screened by electron beam

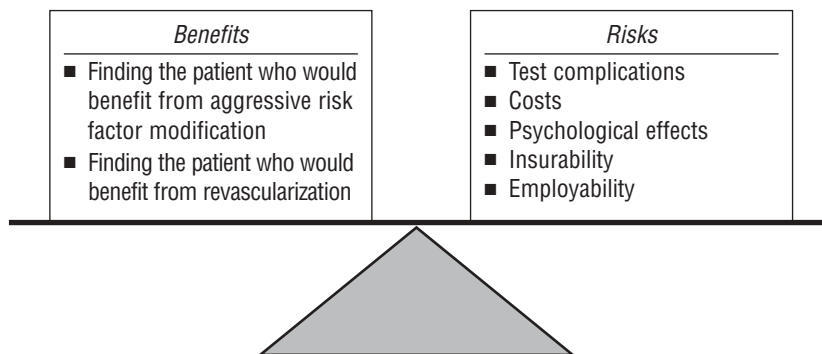
**Table 5. AHA/ADA Criteria for Screening Asymptomatic Diabetics for CAD**

- Resting ECG showing ischemia or infarction
- Peripheral arterial disease or carotid disease
- Sedentary lifestyle, age < 35, prior to beginning a vigorous exercise program
- ≥2 of the following risk factors (in addition to diabetes):
  - Total cholesterol >240 mg/dl, LDL >160 mg/dl, or HDL <35 mg/dl
  - Blood pressure >140/90 mmHg
  - Current smoking
  - Family history of premature CAD
  - Microalbuminuria

computed tomography (EBCT). Additionally, it would be appropriate to screen someone with very low exercise capacity (<4 METS), as part of a preoperative assessment. It was deemed of uncertain benefit to screen asymptomatic patients with only moderate Framingham scores, unless the patient had a high-risk occupation (e.g., pilot). Interestingly, these guidelines did not specifically address the diabetic patient—who is most commonly affected by silent CAD!

Dr. Young pointed out that before evidence-based screening strategies are revised, several pieces of information would be necessary. These would include: the prevalence of abnormal studies in diabetic patients; clinical risk factors that might predict abnormal tests; how severe the ischemia one might expect to find; the optimal screening modality (e.g., ECG vs. stress echo vs. MPI vs. EBCT); whether the identification of ischemia actually predicts event rates; and how best to treat the patient once found to have asymptomatic ischemia. In general, the answers to most of these questions are not available. The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study (Wackers *et al. Diabetes Care* 2004) has recently given insights into the first query.

**Figure 4. Weighing the Risks & Benefits of Silent CAD Screening in Diabetic Patients**



## Diabetes & CVD...

Continued from page 5

This study, previously reviewed in earlier editions of this newsletter, screened 561 asymptomatic patients with Type 2 diabetes, age 50-75, with adenosine SPECT sestamibi MPI. (In addition 562 patients were enrolled into DIAD but not screened—this group constitutes the “natural history” group. Event rates in the two groups will ultimately be compared after five years of follow-up to ascertain the benefit of screening.)

In all, 22% of DIAD patients had an abnormal study. Slightly more than a third of all perfusion

abnormalities were moderate to large in extent, representing about one out of every 16 scans. In multivariate analysis, the predictors of abnormal MPI included male gender, duration of diabetes, and abnormal cardiac autonomic testing. Interestingly, in this cohort, conventional and emerging risk factors, including lipids, HbA1c, and CRP, were not predictive of ischemia. Of note, had the ADA-AHA criteria for screening been employed in this population, 41% of all abnormal tests would have been missed.

Without detailed knowledge of subsequent therapeutic interventions and event rates in a

screened population, it is impossible to assess the actual value of screening for CAD in diabetic patients. These are being tracked in DIAD, with final results available in approximately two years. The risks and benefits of screening must clearly be weighed in each patient, as shown in Figure 4.

This session covered a myriad of topics on the intersection between diabetes and cardiovascular disease. This is an area of significant clinical and research interest, as the population of patients with obesity, insulin resistance, and abnormal glucose regulation continues to grow.



## Should Metformin's Contraindications Be Contraindicated?



Recently, several studies have called into question the contraindication for metformin therapy in Type 2 diabetic patients requiring pharmacological therapy for heart failure (Masoudi *et al.*, *Circulation* 2005; Eurich *et al.*, *Diabetes Care* 2005.) Because metformin has various cardiovascular benefits and since there is new evidence that insulin resistance may be an independent risk factor for heart failure (Ingelsson *et al.*, *Arch Intern Med* 2005), it is reasonable to consider the potential role of this antihyperglycemic drug in the failing ventricle. Horwich and colleagues from Los Angeles (abstract 3163) assessed the effect of metformin therapy on cardiac function and outcomes in 244

diabetic patients with advanced systolic heart failure. Patients were divided into those treated with metformin and those on other antihyperglycemic medications and/or insulin. The groups were evenly matched for baseline left ventricular ejection fraction (LVEF), B-type natriuretic peptide levels, NYHA class, the presence of CAD, BMI, and HbA1c. During follow-up, an increase in LVEF was observed in 63% of metformin-treated patients but in only 40% of those not treated with metformin ( $p=0.04$ ). After adjustments for gender, LVEF, and renal function, metformin therapy was associated with a decreased risk of death or urgent heart transplant at one year (HR 0.43,

95% CI 0.20-0.92). Based on their data, the authors felt that prospective studies assessing the safety and efficacy of metformin in heart failure patients are warranted. This issue is becoming increasingly important as the coexistence of diabetes and heart failure grows because of an aging population, rising prevalence of diabetes, and improved survival following AMI. Greenberg *et al.* from the US (abstract 3826), for example, this week reported results from the OPTIMIZE-HF registry on the prevalence of diabetes in patients hospitalized with heart failure. 48,612 patients in 259 hospitals were assessed. Of these, a striking 20,162 (42%) had diabetes.



## Common Stents



The world of percutaneous coronary angioplasty has been revolutionized over the past several years with the new availability of drug-eluting stents (DES). These products provide local concentrations of potent pharmacological agents (e.g. sirolimus, paclitaxel) that suppress the neointimal proliferation that has been blamed for restenosis in up to 30% of older bare metal stents. Generally, restenosis rates have dropped to 5% or less with DES. Our diabetic patients are at significantly increased risk for restenosis. Whether this can also be reduced by DES has been an important clinical question. Dozens of stent-related abstracts were presented this week, with several specifically focusing on the diabetic patient. In general, it appears that restenosis rates in patients with diabetes are reduced markedly by DES—nearly to the same degree as seen in non-diabetic patients. Whether this will translate to a reduction in subsequent cardiac events is less clear. In a representative meta-analysis of 10

individual studies, Kumbhani *et al.* from the US compared the outcomes from a combined group of 1,497 diabetic patients undergoing drug-eluting ( $n=713$ ) vs. bare metal ( $n=784$ ) stent placement (abstract 3081). Follow-up ranged from 6 to 12 months. In all, major adverse cardiac outcomes were reduced by 61% by DES (RR=0.39, 95% CI 0.29-0.53,  $p<0.0001$ .) This was primarily driven by a 66% reduction in target vessel revascularization—not a surprising finding, since restenosis will frequently lead to the requirement for such a repeat procedure or even bypass surgery. There was, however, also a strong trend toward less MIs in DES patients (RR=0.50, 0.22-1.14,  $p=0.099$ ). The risk reductions were similar in Type 1 vs. Type 2 diabetic patients and also between sirolimus and paclitaxel stents. However, a non-significant increase in in-segment restenosis was observed in paclitaxel patients at nine to 12 months (RR=1.72, 95% CI 0.97-3.04,  $p=0.065$ .)

In a related study, in a group of patients with IGT, not diabetes, a Japanese group led by Nakajima assessed the effect of TZD therapy on restenosis. A total of 33 patients with IGT who had undergone bare metal stenting of coronary atherosclerosis were randomized to pioglitazone (at a low dose of 15 mg QD) vs. placebo. After six months, quantitative CT was performed. Pioglitazone reduced the occurrence of in-stent restenosis (11% vs. 45%,  $p=0.01$ ) and target vessel revascularization (6% vs. 40%,  $p<0.01$ ). Although there was no change in glucose values between groups, pioglitazone therapy did lead to reductions in triglycerides, insulin levels, and C-reactive protein (CRP). This suggests either a direct vascular effect of pioglitazone, or perhaps one mediated through its insulin sensitizing activities. These studies will need to be replicated in DES patients.

## PROactive Update: MI Subgroup

The primary results from the PROspective pioglitazone Clinical Trial In macroVascular Events (PROactive) were presented at the 2005 EASD Annual Meeting in September (*Diabetes 2005*, Volume 12, Issue 1) and later published in *Lancet* (Dormandy *et al.*, October 2005). In brief, PROactive was a randomized, double-blind, placebo-controlled clinical outcomes study that assessed the incremental benefit of pioglitazone added to antihyperglycemic and other agents in over 5000 high-risk Type 2 diabetics. Eligible patients had established macrovascular disease, defined by one or more of: myocardial infarction or stroke at least six months before study entry, acute coronary syndrome at least three months before entry, PCI or coronary bypass surgery at least six months before recruitment, CAD defined by objective evidence, or obstructive lower extremity arterial disease.

During a Late-Breaking Clinical Trials session conducted this week, Dr. Erdmann of Germany presented a subgroup analysis from PROactive involving those patients with a history of MI (n=1230, pioglitazone; n=1215, placebo). Their mean age 62 years, three-quarters were male, median duration of diabetes was eight years, and about 42% had previous PCI/CABG. Over a mean follow-up period of three years, there was a 28% reduction in the risk of recurrent fatal or non-fatal MI (HR 0.72, p=0.045), a pre-specified analysis for the MI subgroup. The hazard ratios for two other pre-specified composite CVD endpoints (CV death or non-fatal MI; CV death, non-fatal MI, or stroke) were both 0.84, but were not statistically significant. Other findings included a 37% reduction in ACS (HR 0.63, p=0.035), although this was not a pre-specified analysis and was based on small

numbers. Rates of heart failure hospitalization were 7.5% and 5.2% and all-cause death in heart failure patients were 1.8% and 1.7% for patients in the TZD and placebo groups, respectively. Based on the findings of this study, adding pioglitazone to existing, near-optimal therapy of 1,000 high-risk patients would prevent 22 recurrent MI and 23 ACS events over three years. While these data are provocative, it should be realized that subgroup analyses from large clinical trials can sometimes be misleading. Therefore, these findings need to be interpreted in light of the overall study results (see page 4). Moreover, it remains unclear whether any treatment benefit from pioglitazone was simply the result of improved glucose control (HbA1c difference between groups, 0.5%) or related to the specific mechanism of action of the drug (i.e., insulin sensitization).



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



#### CAC Facts

Radford and coworkers from Dallas examined the association between coronary artery calcium (CAC) score (CAC quantified from electron beam tomography with the Agatston score), prevalent CVD risk factors, and CVD events (i.e., death from CHD, non-fatal MI, coronary revascularization, or stroke) in a cohort of 745 diabetics without known CVD (abstract 2033). The mean follow-up period was 3.6 years. After controlling for conventional risk factors (age > 55, current smoker, hypertension, hypercholesterolemia, and hypertriglyceridemia), the risk of having a CVD event was two-fold higher (HR 2.0) for those with higher vs. lower CAC scores (defined as <250 and ≥250, respectively). CAC scores appeared to increase CVD prediction beyond that from conventional risk factors (Table 6).

**Table 6. CVD Events (per 1000 person-years) in Diabetics, by CAC Score and Number of Risk Factors**

Number of Risk Factors	CAC Score	
	<250	≥250
0-1	8.0	24.8
> 2	13.8	28.0

#### Are All Sensitizers Created Equally?

The established antihyperglycemic effects of insulin sensitizers have set the stage for numerous investigations of their non-glycemic effects, and specifically on the vasculature. In one such study Stocker and associates, of the Walter Reed Army Hospital, compared the effects of two insulin sensitizers on CRP, a marker of inflammation, and carotid intimal medial thickness (CIMT), which reflects sub-clinical atherosclerosis (abstract 3825). A total of 92 patients with poorly controlled Type 2 diabetes were randomized to metformin 850 mg twice daily or the TZD rosiglitazone 4 mg once daily for 24 weeks. Despite a similar change in HbA1c (-1.18% and -1.08%, respectively), a significant decrease from baseline CRP was observed among patients treated with the TZD, but not with metformin (-68% vs. -4%). Similarly, maximal CIMT and mean CIMT progressed in the metformin group and regressed in the rosiglitazone group. While this study appears to suggest a potential cardiovascular benefit of TZDs over metformin, there have been no clinical trials that have yet adequately tested this hypothesis.

#### Against the Grain

Saely *et al.* from Australia presented results challenging the paradigm that diabetes is a CAD risk equivalent. Over a follow-up period of four years in a population of 750 consecutive patients, the investigators noted the incidence of vascular events to be strongly affected by coronary angiography status, more so than by diabetes status (Table 7) (abstract 3861). After adjustment for multiple variables in Cox regression analyses, Type 2 diabetes increased vascular risk in patients with CAD (adjusted HR 1.82, p=0.004), but not in patients without CAD at baseline (adjusted HR=0.87, p=0.812). In contrast, CAD increased vascular risk in both patients with (adjusted HR=4.4, p=0.007) and without diabetes (adjusted HR=2.5, p=0.001).

**Table 7. Incidence of Vascular Events by Diabetes and CAD Status**

	DM	No DM
CAD	(n=114) 40.2%*	(n=342) 23.8%*†
No CAD	(n=50) 10.0%†‡	(n=244) 8.9%

\* p < 0.001 vs. no DM/no CVD.

† p < 0.001 vs. DM/CVD.

‡ p < 0.05 vs. no DM/CVD.

**Silvio E. Inzucchi, MD**  
**Robert S. Sherwin, MD**

Editors, Yale University,  
New Haven, Connecticut