

Diabetes 2007

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HDL: The Higher the Better...Right?



Important data on diabetes presented at the 56th Annual Scientific Sessions of the American College of Cardiology come to you in **Diabetes 2007**, 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 2007** will be followed by a **Diabetes 2007** booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained, 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.

After successfully completing this program, participants will be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the important association between insulin resistance/metabolic syndrome and atherosclerosis in patients with Type 2 diabetes.
- Identify evolving and emerging management strategies for diabetes (e.g., combination antihyperglycemic therapy, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.

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Each year, the American College of Cardiology hosts a symposium on late-breaking clinical trials. These are large randomized, placebo-controlled studies that are likely to have a major impact on clinical practice and are usually quite well attended. This year's symposium on lipids, which took place on Monday in New Orleans, was particularly interesting for clinicians with an interest in diabetes.

The predominant characteristic of diabetic dyslipidemia is a raised plasma triglyceride concentration (≥ 150 mg/dl), low plasma HDL-cholesterol (< 40 mg/dl), and increased numbers of small, dense LDL particles - the latter of which are more easily oxidized and therefore highly atherogenic. Statin therapy, while overwhelmingly the drug of choice for lowering LDL-cholesterol, has only a small effect on HDL-cholesterol and triglycerides. Fibrates lower triglycerides by 20-50% and raise HDL-cholesterol by 16-35%; however they carry a small risk of myopathy when used in combination with statins, especially gemfibrozil. Also, in FIELD, a recent, large intervention trial involving diabetic patients with mild hypertriglyceridemia and low HDL-cholesterol, fenofibrate therapy showed little effect on cardiovascular outcomes. Since HDL-cholesterol is cardioprotective, the development of compounds designed specifically to raise its concentration has been eagerly awaited.

The first presentation of the symposium was by Dr. Jean-Claude Tardif (Canada), on behalf of the Effect of rHDL on Atherosclerosis—Safety and Efficacy (ERASE) Trial investigators. ERASE was a randomized, placebo-controlled trial conducted in 17 centers, where intravascular ultrasound scanning (IVUS) was used to assess coronary atheroma at

baseline and after four weekly infusions of either placebo (saline, $n=60$), or two doses of CSL-111 (40 mg/kg, $n=111$; 80 mg/kg, $n=12$), which is reconstituted HDL (rHDL) consisting of apolipoprotein A-1 from human plasma combined with soybean phosphatidylcholine. This product resembles native HDL both chemically and biologically. The study cohort had a mean (\pm SD) age of 57.7 (± 8.8) years; 83% were male. At baseline, 99% had dyslipidemia, 57% were hypertensive, 20% diabetic, and 20% had a prior history of myocardial infarction (MI). Mean (\pm SD) baseline LDL-cholesterol was 81.9 (± 32.0) mg/dl and HDL-cholesterol, 42.1 (± 10.8) mg/dl.

An interim analysis of the data led to the safety committee prematurely ending the high-dose 80 mg/kg infusion arm of the trial due to significant increases in liver function tests. However, there was no significant increase in adverse event reports in the low-dose group; this arm of the trial was therefore completed. The effects of CSL-111 on plaque volume are shown in Table 1. Overall, no significant differences between the intervention and placebo groups were found, although the investigators did suggest that the CSL-111 group showed a greater *percent* change from baseline in atheroma volume, albeit not the primary end-point of the trial. The proportion of patients reporting adverse events did not differ between groups, although 13.8% (vs. 7.1%) of subjects receiving active therapy developed hypotension during the infusion. In addition, more subjects receiving CSL-111 showed liver function abnormalities, a difference that did not achieve statistical significance. The investigators concluded that short-term infusions of rHDL resulted in no significant reduction in atheroma burden as compared to placebo.

Table 1. Baseline and Follow-Up Plaque Volume (mm^3) for CSL-111 vs. Placebo

	Placebo (n=47)	CSL-111 (n=89)
Baseline, Mean (SD)	158.3 (66.3)	151.0 (64.1)
Follow-up, Mean (SD)	154.6 (65.7)	147.1 (62.5)
p-value vs. baseline	0.04	<0.001
p-value vs. placebo		0.39

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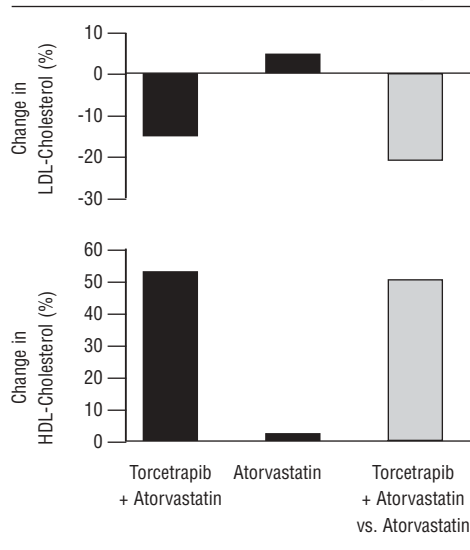
An earlier presentation of the RADIANCE 1 (Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor) trial by Dr. J. Kastelein (Netherlands) also revealed some interesting and slightly counter-intuitive results. Cholesteryl ester transfer protein (CETP) facilitates the transfer of cholesteryl esters from HDL to LDL and VLDL particles. Inhibition of CETP with the investigational agent, torcetrapib, has been shown to increase plasma HDL-cholesterol by a striking 50%. However, the effectiveness of CETP inhibition as a strategy against atherosclerosis remains unknown, as torcetrapib was recently shown to *increase* and not decrease cardiovascular events in a randomized clinical trial. In RADIANCE 1, 850 subjects with heterozygous familial hypercholesterolemia (age ~45 years, BMI 27 kg/m², ~50% males) underwent B-mode ultrasonography at baseline and at follow-up to measure changes in carotid intima-media thickness (CIMT). Patients completed an atorvastatin run-in period before being randomized to receive either atorvastatin monotherapy or atorvastatin combined with 60 mg torcetrapib for two years. After 24 months, mean (±SD) HDL-cholesterol was 52.4 (±13.5) mg/dl and mean LDL-cholesterol was 143.2 (±42.2) mg/dl in the atorvastatin group, as compared with 81.5 (±22.6) mg/dl and 115.1 (±48.5) mg/dl respectively, in the group on combination therapy (both $p < 0.001$ vs. atorvastatin alone). In addition, combination therapy resulted in a significantly greater reduction in plasma triglycerides (to median levels of 97.4 vs. 88.5 mg/dl, respectively; $p = 0.001$) Despite these impressive effects on lipid profiles (Figure 1), the change in maximum CIMT did not differ between groups: +0.0053 (0.0028) mm per year with atorvastatin and +0.0047 (0.0028) mm per year with combined statin-CETP inhibitor ($p = 0.87$). Moreover, a secondary efficacy measure, annualized change in mean CIMT at the common carotid artery, indicated a decrease of 0.0014 mm per year with atorvastatin, as compared with an *increase* of 0.0038 mm per year with combination

Table 2. Biochemical and Vascular Endpoints After 12 months of Therapy

	Placebo	ER Niacin
HDL-cholesterol (mg/dl)	38±5	47±6*
Triglycerides (mg/dl)	189±23	123±24*
hsCRP (mg/l)	2.17±0.21	1.61±0.17*
Vascular Function		
FMD (% change)	4.4±0.8	5.8±0.4*
CIMT (mm)	0.79±0.09*	0.71±0.08

* $p < 0.05$ vs. baseline measure

Figure 1. Change from Baseline in LDL- and HDL-Cholesterol with Atorvastatin ± Torcetrapib



therapy ($p = 0.005$). The investigators concluded that, despite a large increase in HDL-cholesterol and a substantial decrease in LDL-cholesterol and triglycerides, the addition of torcetrapib to baseline statin therapy did not result in any further reduction in atherosclerosis progression.

In contrast, a report by Thoenes and colleagues (abstract 1026-125) from Atlanta described clear beneficial effects of extended-release (ER) niacin on CIMT and endothelial function

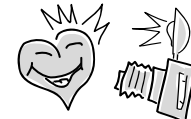
in patients with metabolic syndrome. 45 subjects that met the ATP III criteria for metabolic syndrome were randomized in a double-blind manner and at a 1:2 ratio to either placebo or ER niacin (1,000 mg/day) for 12 months. Flow mediated dilation (FMD), CIMT, and serum levels of high sensitivity C-reactive protein (hsCRP) were measured. The investigators reported that, in comparison to placebo, treatment with niacin for 12 months increased HDL-C, decreased triglycerides, and decreased the inflammatory marker (Table 2).

In conjunction with these lipid changes, the investigators found a significant increase in FMD with niacin but not with placebo. There was also a small increase in CIMT in placebo, but no change in the niacin group. Importantly, given the concerns about niacin therapy decreasing insulin sensitivity, no change in fasting glucose in either group was detected. The investigators concluded that ER niacin was effective in improving components of dyslipidemia, endothelial function, and markers of inflammation in the metabolic syndrome.

On the basis of these presentations, it is apparent that our understanding of HDL physiology and its role in reverse cholesterol transport is still very limited. Simply increasing HDL concentrations should not necessarily be a goal in and of itself. Until more information becomes available about these emerging strategies, our high-risk patients should stick to conventional approaches: diet, exercise, and standard lipid medications.



Smile, Please: Imaging the Heart



It's a clinical scenario frequently encountered by physicians in their practices: what to do with a 48-year-old African-American woman with Type 2 diabetes and a body mass index (BMI) of 32 kg/m² who complains of dyspnea and atypical chest pain? This clinical vignette was the focus of a symposium entitled, "Integrated Multimodality Imaging: Diabetic Heart Disease" conducted on Sunday at the ACC

Scientific Sessions. An international panel of speakers discussed the various approaches available to further investigate such a patient.

Dr. Marwick (Australia) pointed out that, particularly in women, atypical chest pain and dyspnea are associated with increased cardiovascular mortality. Dyspnea, when documented during stress testing, has specific prognostic significance. Dr.

Marwick used this symptom to highlight the important issue of heart failure, 'the forgotten complication' of diabetes. Chronic heart failure affects nearly 5 million people in the US and is a major contributor to mortality, hospitalization, and medical costs. Approximately 40% of patients with heart failure have normal left ventricular systolic function, but evidence of diastolic dysfunction. This is more

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common in women and in the elderly. It is also associated with diabetes, hypertension, and coronary artery disease (CAD). Diastolic dysfunction is an abnormality in left ventricular (LV) relaxation and/or compliance that effectively creates an abnormal relationship between LV pressure and volume. Higher filling pressures are needed to maintain normal cardiac output. Exercise-induced dyspnea and fatigue are common signs of this disorder.

Diastolic dysfunction is thought to arise through a combination of factors, including impaired myocardial perfusion and structural changes, such as myocyte hypertrophy, increased matrix collagen, and interstitial fibrosis. In diabetes, this is further complicated by autonomic dysfunction, disordered glucose and fatty acid metabolism, the deposition of advanced glycated end-products (AGEs), and increased generation of free radicals. Glycemic control appears to be an independent risk factor, as data from the Strong Heart Study have estimated an 8% increase in the risk of heart failure for every 1% rise in HbA1c.

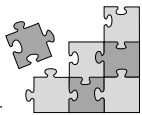
The presence of atypical chest pain in the clinical vignette was used by Dr. Lahiri (UK) to highlight some of the issues surrounding the investigation of silent ischemia in diabetes. Individuals with

diabetes have a relatively high prevalence of unrecognized CAD, and, when present, it is associated with increased cardiovascular morbidity. For the clinician, the early identification of silent ischemia is thought to be important in that there is some, albeit limited, evidence that outcomes can be improved with aggressive intervention such as coronary artery bypass grafting (CABG). A recent development in this arena has been the use of electron beam computed tomography (EBCT) in screening for CAD. Coronary plaques in diabetes tend to be bigger and more extensive, with larger necrotic cores. These findings correlate well with the presence of coronary artery calcification. EBCT studies have shown a direct relationship between coronary artery calcium (CAC) and cardiovascular mortality. Moreover, EBCT scanning can be followed by myocardial perfusion imaging to provide a more detailed and dynamic assessment of the significance of CAD if initially detected on the basis of an elevated CAC score. The use of the vasodilator adenosine is particularly useful during perfusion imaging because it permits the clinician to assess the functional impact of stenosis in a given coronary artery, something not allowed by conventional angiography.

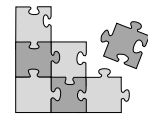
Other options for the non-invasive assessment of silent ischemia described by the speakers

include PET imaging and cardiac magnetic resonance imaging (CMRI). It was pointed out that CMRI is particularly good at identifying previous MI—even if small and not clinically apparent. For instance, CMRI recently showed that 36-44% of CABG patients had suffered a small MI during or immediately after surgery. Dr. Reichek (USA) also described recent advances in this technique that allow for assessment of the coronary arteries. When combination with MR angiography, CMRI would permit the non-invasive assessment of plaque volume as well as percent stenosis of the coronary arteries. At present, however, CMRI is not widely available and appears too time consuming and costly for widespread use.

Unfortunately, there is no good direct evidence that any of these non-invasive techniques are cost-effective tools to address the important question of early CAD screening in our diabetic patients. In prospective trials, the yield from screening has been much lower than in retrospective analyses. Moreover, the accuracy of screening to detect significant coronary stenoses remains uncertain. Finally, there is no proof yet that identification of CAD improves these patients' outcomes. Clearly, more research is needed in this area before evidence-based guidelines can be developed.



Metabolic Syndrome: Continued Controversy



The metabolic syndrome continues to attract a lot of interest in the cardiology community despite ongoing debate on its underlying role in atherosclerosis. Recently, investigators have become aware that adipokines—peptides secreted by the adipocyte—may also play a role in the development of the syndrome. Examining this issue, Kim *et al.* (abstract 1020-129) from South Korea, performed a cross-sectional, cohort study of 1,437 men and 2,071 women (age >40 years) without history of cardiovascular disease. The metabolic syndrome was defined according to the Asian-modified criteria of the NCEP Adult Treatment Panel (ATP) III report. The investigators found that mean adiponectin levels for men exhibiting 0, 1, 2, 3, 4, or 5 components of metabolic syndrome were 11.19, 10.08, 8.09, 7.14, 6.21, and 5.11 $\mu\text{g/l}$, respectively (p for trend <0.001), while those in women were 15.65, 14.03, 12.38, 11.04, 9.75, and 9.32 $\mu\text{g/l}$, respectively (p for trend <0.001). Adiponectin concentration was correlated negatively with waist circumference, triglyceride, hsCRP, fasting glucose, and insulin, and correlated positively with high-density lipoprotein and age in both sexes (p <0.001).

Multiple logistic regression analyses demonstrated that circulating adiponectin had a strong protective effect against metabolic syndrome (Odds Ratio, 0.34 [95% confidence interval 0.26 to 0.43] in males, 0.35 [0.28 to 0.44] in females). The investigators concluded that, in this Asian population, serum adiponectin levels were strongly associated with both the phenotype and individual components of metabolic syndrome. Of course, causality cannot be inferred from these data.

Genetic susceptibility is considered an important mediator of the impact of cardiovascular risk factors on coronary heart disease (CHD). Chen *et al.* (abstract 1026-38) examined whether parental CHD, a surrogate measure of genetic susceptibility, increased the vulnerability of arteries to the adverse effects of the metabolic syndrome in healthy young adults. The study cohort consisted of 1,073 subjects (31% black, 43% male), aged 25-44 years, enrolled in the Bogalusa Heart Study. Arterial structure-function dynamics were assessed by CIMT measured by B-mode ultrasound and aorta-femoral pulse wave velocity (af-PWV) by echo-Doppler. Metabolic syndrome was defined by the NCEP

guidelines. The investigators found that subjects with positive parental history of CHD had thicker CIMT (0.839 vs. 0.802 mm, $p=0.017$), higher af-PWV (5.4 vs. 5.2 m/sec, $p=0.097$), and higher prevalence of metabolic syndrome (12.1% vs. 7.6%, $p=0.019$), compared to those without such a family history. CIMT and af-PWV were significantly increased with an increasing number of metabolic syndrome components (p <0.001). The investigators concluded that genetic factors may increase the early susceptibility of arterial structure-function dynamics to metabolic derangements. The implications on long-term vascular health are considerable.

One controversial question is whether or not the metabolic syndrome provides information that is independent and additive to its individual risk components. Wael *et al.* (abstract 1020-120) from North Carolina sought to determine cardiovascular outcomes in patients with a new diagnosis of CAD, who also had diabetes or metabolic syndrome. A Duke database was used to identify patients who had a new diagnosis of CAD between 1998 and 2001. Diabetes was defined by prior clinical diagnosis, use of medications, or fasting

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glucose ≥ 126 mg/dl. Metabolic syndrome was defined by having ≥ 3 of the following: fasting glucose ≥ 100 mg/dl and < 126 mg/dl; low HDL cholesterol (< 35 mg/dl for men, < 40 mg/dl for women); triglycerides > 150 mg/dl; BMI ≥ 27 kg/m²; and hypertension. Follow-up for death, MI, and stroke was obtained every six months for a median of 5.1 years. The investigators identified 5,994 patients: diabetes (n = 1,952), metabolic syndrome (n = 2,356), and no metabolic syndrome or diabetes (n = 1,686). Cox proportional hazards models were generated to determine predictors of cardiovascular outcomes. The models accounted for the individual features of metabolic syndrome, age, gender, Charlson index, NYHA heart failure class, valvular disease, ejection fraction, revascularization, peripheral and cerebrovascular disease, smoking, and statin use. Compared with control

patients, patients with diabetes—but, notably, not those with metabolic syndrome—had a higher adjusted odds ratio for death, death/MI, and death/MI/stroke. These data suggest no additional cardiovascular risk from the composite metabolic syndrome diagnosis over that imparted by its component parts.

In contrast, Akosah *et al.* (abstract 1020-163) from Virginia concluded that metabolic syndrome does independently predict future cardiovascular events. They prospectively assessed 253 individuals with no previous history of CAD (mean [±SD] age 53 [±8] years; 55% female) scheduled for elective coronary angiography. All subjects had clinical risk scores calculated and fasting blood drawn. 28% of subjects met criteria for metabolic syndrome. Subjects were further categorized into four risk groups. Group 1 (n = 50) had metabolic syndrome without diabetes, Group 2 (n = 34) had diabetes, Group 3 (n = 136) was at low cardiovascular risk

(10-year risk $< 10\%$), and Group 4 (n = 6) was at high risk ($\geq 20\%$). After a median follow-up of 32 months, 10 subjects suffered 12 major events (death = 3, MI = 5, and stroke = 4). The rate of diagnosis of severe CAD was not different between Group 1 compared to Group 2 or Group 4, but was significantly higher when compared to Group 3 (p = 0.001). Event rates were 8% for Group 1 and 8.8% for Group 2 (p = 0.999) versus 1.5% for Group 3 (p = 0.046). A full 90% of subjects suffering major events had either frank diabetes or metabolic syndrome. The investigators concluded that, in this small prospective study, metabolic syndrome was associated with increased risk for severe CAD and this might even be as high as that for Type 2 diabetes. We would point out that this study's small numbers, the use of fasting glucose alone to diagnose diabetes, and incomplete adjustments for prevalent cardiovascular risk factors limit a full interpretation.

Venting about Stenting

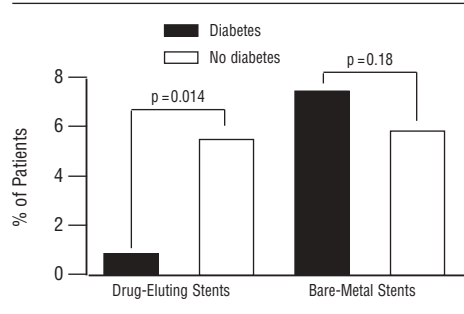
Coronary stents have had a major impact in the management of patients with CAD. When used during percutaneous coronary intervention (PCI) in patients with acute coronary syndromes, emergent revascularization with stents clearly improves clinical outcomes. They have also decreased the need for CABG. Their role, however, in patients with more stable CAD remains controversial. Debate was recently heightened after reports emerged of late thrombosis in patients who had received drug-eluting stents. These devices had been used almost exclusively over the past several years after they were demonstrated to decrease restenosis rates experienced by bare-metal stents. These discussions are further amplified in diabetic patients who have heretofore behaved differently in clinical PCI trials, with even greater restenosis rates and poorer clinical outcomes.

Andron and English co-workers conducted a study to determine the impact of diabetes on inpatient major adverse cardiac/cerebrovascular events (MACCEs) and other one-year clinical outcomes following coronary stent placement between 2000 and 2004 (abstract 1007-178). The years spanned both bare-metal and drug-eluting stent eras. A total of 4,891 consecutive patients were enrolled, 674 (13.8%) being diabetic. To account for the differences in case-mix between diabetic and non-diabetic patients, propensity-matching and multivariate adjustments were performed. Inpatient MACCE rates (1.4% and 1.0% in diabetics vs. non-diabetics, respectively), one-year event rates for death (2.8% vs. 3.0%, respectively), and overall

target lesion revascularization (TLR) (6.5% vs. 5.8%, respectively) were similar between the two groups. However, there were differences in TLR between diabetic and non-diabetic patients, but based on type of stent. The TLR rate was slightly higher (p = ns) with bare-metal stents but significantly lower (p = 0.014) with drug-eluting stents in those with diabetes (Figure 2). After logistical regression, vessel size < 2.5 mm (OR 2.3, p < 0.001), left main lesions (OR 2.9, p = 0.009), and restenotic lesions (OR 1.8, p = 0.011) were associated with increased TLR rates, while the use of drug-eluting stents had the opposite trend (OR 0.48, p = 0.005). These data confirm a specific benefit of drug-eluting stents to decrease the need for subsequent revascularization of the target vessel in diabetic patients.

In a "Late-Breaker" session, Dr. William Boden, on behalf of his COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) study co-investigators, assessed the value of PCI added to optimal medical therapy in patients with stable CAD. Eligible patients had stenosis of $\geq 70\%$ in at least one proximal epicardial coronary artery with objective evidence of myocardial ischemia (ST-segment depression or T-wave inversion on the resting ECG or inducible ischemia with either exercise or pharmacologic stress) or at least one coronary stenosis of $\geq 80\%$ with clinical angina. 2,287 patients were enrolled between 1999 and 2004; 1,149 were randomized to PCI plus optimal medical therapy (PCI group) and 1,138 to optimal medical therapy alone. Notably, no statistically significant differences

Figure 2. Target Lesion Revascularization by Diabetes Status and Type of Stent



were found in either primary or secondary endpoints. The 4.6-year cumulative primary-event rates (defined as all-cause mortality and non-fatal MI) were 19.0% in the PCI group and 18.5% in the medical-therapy group (p = 0.62). In sub-group analysis, the cumulative primary-event rates in the 766 diabetic patients were 25.0% with PCI and 24.0% with medical-therapy only. PCI did not reduce the risk of the composite of death, MI, and stroke (20.0% vs. 19.5%); hospitalization for acute coronary syndrome (12.4% vs. 11.8%); or MI (13.2% vs. 12.3%) (p = ns for all comparisons).

The COURAGE data calls into question the widespread use of PCI as initial therapy in patients with coronary stenoses that can be addressed medically. How these new data will be incorporated into clinical guidelines published by professional organizations in the cardiology community will be interesting to follow.



Cardiovascular Effects of TZDs — Two Edges to the Sword?



In diabetic patients, the high prevalence of cardiovascular disease often predates major derangements in glucose metabolism. Some authorities have ascribed this increased risk to insulin resistance, which is an early defect in patients destined to develop hyperglycemia. The insulin-sensitizing thiazolidinediones (TZDs) have been purported to reduce cardiovascular risk through metabolic and direct vascular and anti-inflammatory effects. Their use is tempered by the realization that, because of fluid retention, these agents may increase the clinical diagnosis of heart failure. TZD research in this area has major implications for primary care physicians, endocrinologists, and cardiologists alike. Several presentations at this week's conference highlighted the widespread interest in the cardiac effects of these insulin sensitizers.

Anti-Atherosclerotic Effects

Evidence of potential cardiovascular benefits of TZDs are now emerging from large clinical trials. The first was PROactive (PROspective pioglitazone Clinical Trial in macroVascular Events) in which patients with Type 2 diabetes and established macrovascular disease were randomized to pioglitazone or placebo in addition to their existing glucose-lowering and cardiovascular medications. Over a mean follow-up period of 34.5 months, there were statistically significant differences between pioglitazone and placebo for several secondary endpoints including the composite of death, MI, or stroke (relative risk reduction of 16%), but not for the primary endpoint, a broader composite of all-cause mortality, non-fatal MI, acute coronary syndrome, major amputation, coronary or leg revascularization (*Lancet* 2005;366:1279).

At the EASD meeting in Copenhagen, Denmark last year, as reported in this newsletter, Dr. Theodore Mazzone presented results from the CHICAGO trial (Carotid Intimal-Media Thickness in Atherosclerosis Using Pioglitazone) (*JAMA* 2006;296:2572). This double-blind, multi-center study compared the effects on subclinical atherosclerosis of pioglitazone vs. glimepiride for 18 months in patients with Type 2 diabetes. At the final visit, there was a treatment-group difference favoring the TZD, based on the primary endpoint of CIMT as measured by ultrasound (-0.013 mm, $p=0.02$).

Adding to this body of work is the STARR study, the results presented by Dr. Eva Lonn from Canada during a "Late-Breaker" session this week. STARR (STudy of Atherosclerosis with Ramipril and Rosiglitazone) was a sub-study of DREAM

(Diabetes REduction Assessment with ramipril and rosiglitazone Medication) (*Lancet* 2006;368:1096). As a reminder, DREAM, a double-blind, placebo-controlled study, showed that rosiglitazone had a marked benefit on progression to diabetes (RR 0.38, $p<0.0001$) in patients with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG), which was not the case with ramipril (RR 0.91, $p=0.15$). Neither drug was shown to improve cardiovascular outcomes, however, in this relatively healthy group of patients.

The selection criteria for STARR included age ≥ 30 years old, IGT and/or IFG but not diabetes, and left ventricular ejection fraction $\geq 40\%$, with the additional requirement of a baseline and at least two post-baseline carotid ultrasound examinations. 1,256 patients met these selection criteria (mean age = 54.5 years, 55% female, BMI=30 kg/m²); the mean follow-up duration was three years. Consistent with the clinical cardiovascular outcome measures of the DREAM trial, the investigators found no significant impact of rosiglitazone on CIMT progression for the primary aggregate measure (difference between groups = -0.002 mm, $p = 0.17$), although some changes in CIMT secondary end-points did achieve statistical significance (Table 3). No statistically significant differences were noted with ramipril. Taken together with the other clinical trials reported above, current data in support of an anti-atherosclerotic effect of TZDs remains mixed. Clearly, more studies are needed before we fully understand their proposed role in this regard.

In an uncontrolled trial, Mailloux and investigators from New York City treated 17 non-diabetic CAD patients with pioglitazone for three months (abstract 1002-125). Statistically significant increases from baseline in adiponectin levels (10.6 $\mu\text{g/ml}$ to 21.1 $\mu\text{g/ml}$; $p=0.001$) and endothelial-dependent flow mediated dilation (4.45% to 8.43%; $p=0.001$) were observed. They reported a moderate correlation between increases in adiponectin levels and decreases in HbA1C

($r=0.472$, $p=0.057$). Since adiponectin is associated with decreased cardiovascular risk, the implications of this group's findings are provocative.

Kelly and co-workers from the University of Minnesota randomized 36 Type 2 diabetic patients to rosiglitazone ($n=20$) or glyburide ($n=16$) in addition to metformin for six months to compare the drugs' effects on endothelial function and oxidative stress (abstract 1026-10). The rosiglitazone-metformin combination resulted in significant improvements in flow-mediated dilation by ultrasound assessment of the brachial artery (rosiglitazone: $4.8 \pm 0.8\%$ to $6.8 \pm 0.8\%$ vs. glyburide: $6.5 \pm 1.0\%$ to $5.5 \pm 0.8\%$, $p<0.05$) while also reducing C-reactive protein compared to glyburide ($p<0.01$). Trends toward improvements in carotid artery distension ($p=0.099$) and distensibility ($p=0.078$) were also observed. Despite these apparently beneficial cardiovascular effects, however, rosiglitazone did not reduce markers of systemic or vascular oxidative stress.

Heart Failure Implications

Several groups of investigators presented results of studies that evaluated the impact of TZDs on heart failure in diabetic patients. This line of research is important to refining the appropriate patient population for TZDs. Observations that therapy with these agents is associated with dose-related fluid retention in certain individuals have led experts to recommend caution when using them in patients with heart failure. Specifically, the drugs are not to be used in the setting of NYHA class 3 or 4 symptoms.

In a study by Nagai and Japanese associates, 120 Type 2 diabetic patients with coronary heart disease or cardiomyopathy underwent echodoppler study before and after pioglitazone treatment (mean 16 months, range: 1-76) (abstract 1010-99). Mean NYHA Class was 1.3 before the initiation of the TZD and unchanged at study end. No patient was hospitalized due to worsening heart failure

Table 3. CIMT Progression (mm/yr) in Rosiglitazone-Treated Patients in STARR

	Rosiglitazone (n = 621)	Placebo (n = 635)	p-value
Primary Endpoint			
Aggregate IMT ₁ *	0.0069	0.0091	0.17
Secondary Endpoints			
CCF IMT†	0.0018	0.0060	0.02
Single Maximum IMT‡	0.0002	0.0061	0.28
Aggregate IMT ₂ §	0.0042	0.0079	0.03

*sum of segment maximum IMT/number of visualized segments.

†sum of mean common carotid IMT.

‡single segment maximum IMT.

§sum of segment maximum IMT CCA + BIF/number visualized segments.

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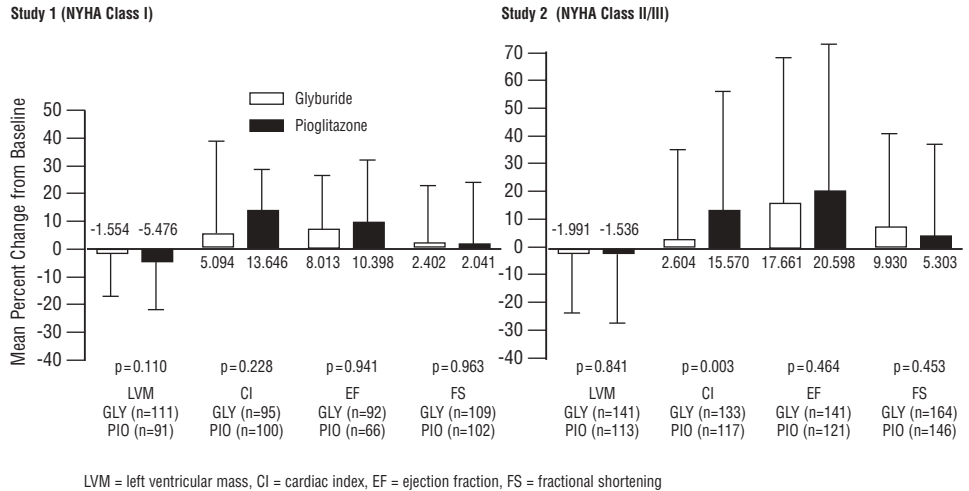
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during study participation. Furthermore, there were no changes from baseline in left ventricular filling pressure or left ventricular diastolic performance in these individuals with known structural heart disease.

Giles and American co-workers presented results of exercise stress-testing in heart failure patients treated with pioglitazone or glyburide in two randomized, double-blind studies (abstract 1016-64). There were 300 patients at NYHA class I with preserved ejection fraction in one study and 518 patients at NYHA class II or early class III and depressed ejection fraction (<30%) in the other. The presenters reported no change from baseline in distance covered during a 6-minute walk test in either study, indicating no deterioration in exercise tolerance. In addition, no changes from baseline in cardiac function or remodeling were observed based on echocardiographic findings (Figure 3). In the second study, the TZD was associated with an earlier time to onset and higher rate of the composite endpoint of first occurrence of death due to a cardiovascular cause or emergency room visit/overnight hospitalization for worsening heart failure, as compared to glyburide ($p < 0.05$). The significant difference between treatment groups for the composite endpoint was primarily based on a difference in overnight hospitalization (26 pioglitazone vs. 12 glyburide patients) and not cardiovascular mortality (5 and 6 patients, respectively). Most affected patients were successfully treated without the need for discontinuing study drug. Of interest, a higher incidence of the composite endpoint with pioglitazone was observed among the patients using insulin at study enrollment, in those ≥ 65 years of age, and among men. As was the case for the entire population, the differences for these sub-groups was apparent early on, at approximately six weeks, with subsequent stabilization. On echocardiograms, cardiac index appeared

Figure 3. Change from Baseline in Echocardiographic Measures at the Final Visit

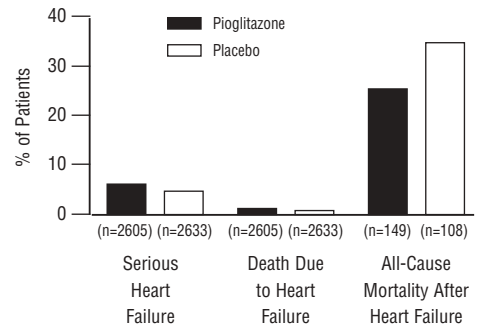


improved with pioglitazone vs. glyburide, but overall ejection fraction was the same (Figure 3).

Erdmann and co-workers conducted post-hoc analyses of data from the PROactive study to assess complications after investigator-reported serious heart failure (abstract 1016-65). The proportion of patients with these non-adjudicated events was higher in the pioglitazone group than the placebo group. Heart failure in this study was not associated with a higher rate of either all-cause- or heart-failure-related death (Figure 4). The relative risk of all-cause mortality, obtained from Cox proportional hazards modeling, was 29% lower for these pioglitazone-treated patients ($HR = 0.71$, $p = 0.13$). The investigators concluded that the overall modest benefit on macrovascular events with pioglitazone was not offset by worsened heart failure sequelae in these high-risk patients.

After being on the market for almost 10 years, we continue to learn more about these interesting

Figure 4. Serious Heart Failure and Death Following Heart Failure



insulin sensitizing drugs. As with any antihyperglycemic agent, optimal use of TZDs in our diabetic patients must take into consideration both their benefits and their risks. Heart failure in at-risk patients remains a concern.

Glucose & the Heart

Disorders of glucose homeostasis are categorized into three groups (normal, impaired, and diabetes) based on fasting plasma glucose (FPG). However, as the relationship between micro- and macrovascular complications and FPG is probably linear, using categorical variables to estimate risk has its limitations. This issue was addressed by Desai and colleagues (abstract 1,026-166) of Michigan who evaluated the prevalence of atherosclerotic cardiovascular disease (ASCVD) relative to fasting glucose levels in a cross-section of patients at high cardiovascular risk. 556 randomly selected patient charts were retrospectively reviewed from their Preventive Cardiology Clinic. The authors

reported that ASCVD prevalence climbed significantly with increasing fasting glucose levels ($p < 0.005$). Importantly, despite no significant differences in age, presence of hypertension, BMI, or family history, a significantly higher prevalence of ASCVD was observed among patients with normal fasting glucose levels between 90 and 99 mg/dl vs. lower levels (29.0% versus 9.8%, $p < 0.0005$). As glucose levels increased to 126 mg/dl, the prevalence of ASCVD continued to rise in parallel. These findings suggest that cardiovascular risk has a linear relationship with glucose and may even increase within ranges of FPG thought to be 'normal.' Ultimately, the use of linear models to cal-

culate risk based on FPG may assist in the primary prevention of cardiovascular diseases, very much as cardiac risk engines use lipid profiles.

Using categorical data, Aronson and Israeli colleagues (abstract 843-5) prospectively studied the relationship between FPG and long-term mortality in non-diabetic patients ($n = 1101$) with AMI. FPG was determined after ≥ 8 hours of fasting within 24 hours of admission. The median duration of follow-up was 24 months (range, 6 to 48). FPG was categorized into four groups: normal (< 110 mg/dl) and tertiles of elevation (110-119 mg/dl, 120-136 mg/dl, and ≥ 137 mg/dl). LVEF was classified as normal ($\geq 55\%$), mildly (45-54%), moderately

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Glucose & the Heart

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(30-44%), and severely reduced (<30%) by echocardiography. The investigators reported that for each LVEF group, mortality was lowest among patients in the lowest FPG category, and mortality was highest at the upper extremes of FPG. In a multivariate Cox model, adjusting for clinical variables and LVEF, the hazard ratio for mortality by tertile of elevated FPG compared to normal FPG were as follows: 1st tertile 1.8 (95% CI 1.0 to 3.3; $p=0.05$); 2nd tertile 2.9 (95% CI 1.8 to 4.7; $p<0.0001$); and 3rd tertile 4.2 (95% CI 2.7 to 6.5; $p<0.0001$). The authors concluded that FPG, obtained within 24 hours of AMI, was a strong predictor of long-term mortality in non-diabetic patients.

Yohannes *et al.* (abstract 1022-65) from New York looked at the impact of glycemic control during hospitalizations for heart failure on length of stay. In their prospective cohort study, patients admitted for acute heart failure were followed over a period of 12 weeks. Demographic, clinical, and laboratory data were prospectively collected, including data on glycemic control among diabetic and non-diabetic patients. Of the 212 patients with acute heart failure exacerbation, 119 (56%) also had the diagnosis of diabetes. Mean age of the entire cohort was 63 ± 0.87 years, BMI 29.3 kg/m^2 , and 92% had hypertension. Heart failure patients with

diabetes had significantly longer hospital stay, compared to the non-diabetic cohort (5.0 ± 0.29 vs 3.4 ± 0.19 days, $p<0.001$). For diabetic patients, the mean HbA1c was 8.3%, admission blood glucose (BG) 169 ± 7.7 mg/dl, and average inpatient BG was 196 ± 8.1 mg/dl. After adjusting for age, sex, weight, and presence of hypertension, hospital stay significantly correlated with admission BG ($r=0.31$, $p<0.001$) and average inpatient BG ($r=0.34$, $p=0.001$). The authors concluded that in hospitalized patients with acute heart failure, diabetes significantly prolonged hospital stay. Whether sicker patients, who required longer hospitalizations, had higher glucoses as a stress response, or whether glycemic control was driving greater morbidity is not clear from this data set. This question has plagued these types of retrospective studies for years.

In spite of this uncertainty, the prevailing view is that poor glucose control during hospitalization for AMI adversely affects clinical outcomes. As a result, guidelines have emerged from professional organizations (American Diabetes Association and the American College of Cardiology/American Heart Association) concerning the management of glucose in the peri- and post-infarct period. There is concern, however, that these guidelines are not being widely implemented. This was evident in two poster presentations in New Orleans this week. Kosiborod *et al.* (abstract 1018-183) from

the US used data from the Cerner Corporation's Health Facts™, a national database derived from the medical records at 39 medical centers, to analyze patterns of glucose control and documented insulin therapy among 16,534 patients hospitalized with AMI from 2000 through 2005. Of the 4,940 patients with diabetes (30% of total population), 2,412 (49%) had a mean BG of >200 mg/dl during the first 24 hours after admission. For the entire hospitalization, 34% had a mean BG >200 mg/dl, while 61% had a mean BG between 110-200 mg/dl, and only 5% maintained a BG <110 mg/dl. Moreover, among diabetic patients with mean hospital BG >200 mg/dl, only 138 patients (8%) received an intravenous (IV) insulin infusion, and nearly one third received no insulin therapy at all! In a related poster presentation (abstract 1,018-186) this same group also showed marked variability between hospitals in the Cerner database regarding the frequency of insulin use. Rates of use of any type of insulin varied from 0-100%, while rates of IV insulin use varied from 0-26%. The authors concluded that in patients hospitalized for AMI, average BG control is suboptimal, both during the immediate peri-infarct period and throughout the hospitalization. Moreover, hospitals vary considerably in their implementation of insulin therapy, and in most hospitals implementation rates appear inappropriately low.



Incretins: Effects Beyond the Pancreas



Incretins are gut-derived peptides, secreted in response to meals. They appear to have several tissue targets, most notably the endocrine pancreas. Here, incretins stimulate insulin secretion from the beta-cells in a glucose-dependent fashion. Some incretins also decrease glucagon secretion from pancreatic alpha-cells and slow gastric emptying as well. The major incretin hormones are glucagon-like peptide (GLP) 1 and glucose-dependent insulinotropic peptide (GIP), both metabolized and rendered inactive through the enzyme dipeptidyl peptidase (DPP) IV. Drugs that modulate the incretin system, such as exenatide (a GLP-1 agonist) and sitagliptin (a DPP-IV inhibitor) have recently been introduced into the therapeutic armamentarium for Type 2 diabetes. Research presented this week added to our emerging understanding of an additional role for these peptides—that involving cardiac function.

Boerrigter and associates from the US and Germany evaluated the impact of DPP-IV inhibition on the cardiorenal activity of two B-type natriuretic peptides (BNPs), BNP 1-32 and BNP 3-32, in a crossover study in eight anesthetized dogs (abstract

1008-118). BNP is a cardiac neurohormone secreted by the ventricles in response to volume expansion and pressure overload. Of note, DPP-IV cleaves BNP 1-32 *in vitro* to BNP 3-32. The investigators determined that BNP 1-32 reduced mean arterial pressure (-7 ± 2 vs. 0 ± 1 mmHg, $p<0.05$) and increased renal blood flow ($+51\pm 10$ vs. $+11\pm 10$ ml/min, $p<0.05$), urine sodium excretion ($+338\pm 40$ vs. $+128\pm 18$ $\mu\text{Eq/min}$, $p<0.05$), and total urine flow ($+2.8\pm 0.4$ vs. $+1.1\pm 0.2$ ml/min, $p<0.05$), reflecting increased renal vasodilating, natriuretic, and diuretic actions, as compared to BNP 3-32. These results suggest that DPP-IV may have an important role in the regulation of BNP physiology. If so, DPP-IV inhibition could confer beneficial effects in CV disease based on increasing the relative activity of circulating BNP.

Bhashyam and researchers from Pittsburgh evaluated the mechanism by which GLP-1 affects myocardial contractility and myocardial glucose uptake (abstract 1016-55). Using three-month old Sprague Dawley rats, isolated, isovolumic heart preparations were perfused with potassium, glucose, and insulin in solution. At 30 minutes, GLP-1[7-36]

or its metabolite GLP-1[9-36] was added. Myocardial contractility and glucose uptake were measured in the presence and absence of a GLP-1 antagonist (exenatide 9-39) and the sulfonylurea glibenclamide, which blocks K^+ -ATP channels. GLP-1[7-36] decreased left ventricular contractility by 29%, but increased myocardial glucose uptake by 56%. The effect on contractility, but not on glucose uptake, was blocked by exenatide. The metabolite (GLP-1[9-36]) had no effect on contractility, but increased glucose uptake, with this latter effect also abolished by glibenclamide and unchanged by exenatide. Taken together, these findings indicate that GLP-1 acts directly on the myocardium, with effects on contractility mediated through the GLP-1 receptor, and those on glucose uptake mediated through potassium channels. While very preliminary, these data suggest that GLP-1 agonists may confer a beneficial cardiac effect by addressing the known decrease in myocardial glucose uptake in insulin-resistant, Type 2 diabetic patients. More data regarding the implications on ventricular performance are needed, however.



So Many Posters, So Little Time....



In another Late-Breaker Session, Dr. Paul Erne from Switzerland reported results from the Swiss Interventional Study on Silent Ischemia Type 1 (SWISS I). Selection criteria included age between 40 and 75 years, absence of symptomatic CAD, at least one CHD risk factor, no cardiac drugs, and ST depression of ≥ 0.1 mv on exercise ECG. Of 522 individuals who were screened for participation, 54 met the selection criteria (mean age=59 years old, 61% male, LVEF=62% at rest) and were randomized to risk-factor control only vs. risk-factor control plus medical therapy (aspirin 100 mg/day \pm beta-blockers \pm calcium channel antagonists \pm long-acting nitrates). Over a mean period of 11.2 years (483 patient-years), a statistically significant benefit was observed with medical therapy based on higher survival rate without MI or hospitalization for acute coronary syndrome (HR=0.12, $p=0.001$), the primary endpoint of the study. Left ventricular ejection fraction remained stable in the medical therapy group, and decreased in the risk factor control group ($p=0.04$ at five years, $p=0.02$ at 10 years). While the study is limited by small population size and lack of a placebo group, Dr. Erne suggested that patients with silent myocardial ischemia should receive prophylactic medical therapy upon verification of ST depression on cardiac stress testing. Such a recommendation has important implications for patients with diabetes, since they frequently may have silent myocardial ischemia. Our major criticism of this study is that the "medical therapy" component was neither rigorously nor equally applied to all patients in that group. Therefore, while we find these study results interesting, they need to be confirmed in a large, placebo-controlled study before they impact care.

Tamita and associates from Japan used 64-row multidetector computed tomography (MDCT) to non-invasively investigate the coronary arteries of 21 asymptomatic Type 2 diabetes patients with no known CAD and no evidence of ischemia on resting ECG, but who had either documented peripheral vascular disease and/or at least two CHD factors (abstract 913-229). In this population, CAD prevalence by MDCT was 40%. Of 12 patients who proceeded to coronary angiography, 11 were correctly detected by MDCT (sensitivity of 92%). Segment-based analysis showed a sensitivity of 82% each for the detection of stenosis $\geq 50\%$ and stenosis $\geq 75\%$; specificity was 98%. This study provides some preliminary data regarding the diagnostic accuracy of MDCT as a non-invasive

alternative to coronary angiography in asymptomatic diabetes patients.

Dr. Aronne of Cornell University, on behalf of the Rimonabant in Obesity (RIO) investigators, conducted a post-hoc analysis of data from the recent RIO clinical studies. Four double-blind, placebo-controlled, randomized trials compared a lifestyle management program (600 kcal/day deficit) vs. either placebo or rimonabant 5 mg or 20 mg for one year. This abstract sought to specifically determine the effects in the subset of patients 60 years of age or older ($n=626$) (abstract 1002-124). In a comparison with placebo, elderly patients in the high-dose rimonabant group experienced significantly greater weight loss (-6.7 vs. -2.1 kg; $p<0.001$), reduction in waist circumference (-6.8 vs. -2.5 cm; $p<0.001$), and improvement of various cardiometabolic risk factors such as HDL-cholesterol, triglycerides, and blood pressure. These changes were comparable to those observed in younger patients (e.g., -6.2 kg for rimonabant 20 mg vs. -1.5 kg for placebo in patients <60 years). In contrast, elderly patients showed no consistent differences between the lower dose of rimonabant and placebo.

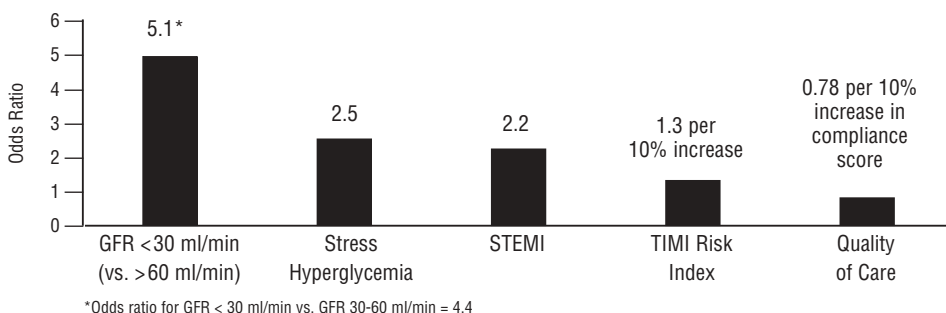
Schiele and French researchers evaluated risk factors for mortality at one-month in diabetic patients hospitalized for AMI ($n=1,388$) (abstract 1020-128). Multivariate analysis identified the following as independent predictors of early death: stress hyperglycemia (defined as admission glucose >140 mg/dl in the absence of diabetes); glomerular filtration rate <30 ml/min; TIMI risk index (a score of MI severity); ST-elevation MI (STEMI); and quality of care (based on compliance with five guidelines-recommended treatments) (Figure 5).

Given the relationship between diabetes and left ventricular (LV) dysfunction, Lavine and Prcevski from Florida and Michigan studied the

influence of glucose control on LV performance (abstract 807-6). LV dysfunction (ejection fraction 35-40%) and then diabetes were induced in 11 dogs. The animals were randomized to good glucose control using insulin for three months (fasting blood glucose: 100-150 mg/dl) or poor control (250-350 mg/dl), and then crossed over to the opposite glycemic control group for an additional three months. LV pressures, echocardiography, and Doppler were assessed after induction of ventricular dysfunction but prior to diabetes induction (baseline) and then again following the good and poor glucose control periods. Statistically significant decreases in ejection fraction and septal and posterior wall thickness were observed during periods of poor glucose control, when compared to baseline. End diastolic pressure was increased and diastolic filling period was shortened as well. During the good glycemic control period, in contrast, these parameters were similar to baseline. These results suggest that glycemic control may modulate the adverse effects of diabetes on cardiac performance.

In a report from the the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial, Chareonthaitawee *et al.* (abstract 909-235) performed an assessment of insulin-mediated whole body and regional myocardial glucose uptake with a hyperinsulinemic euglycemic clamp and positron emission tomography (F-18 fluorodeoxyglucose) at 35 ± 15 days after study enrollment. In comparison to control subjects, the patients in BARI-2D had significant reductions in whole body glucose uptake (M value 41.4 ± 15.7 vs. 13.7 ± 6.1 $\mu\text{mol}/\text{min}/\text{kg}$, respectively) as well as regional myocardial glucose uptake (rMGU 61 ± 8 vs. 30 ± 11 $\mu\text{mol}/\text{min}/100$ g, respectively). Thus, these patients with diabetes and stable CAD have severe insulin resistance detected *both* at the whole-body and the myocardial levels.

Figure 5. Risk Factors of One-Month Mortality in Diabetes Patients Hospitalized for AMI



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