

# Diabetes 2008

From the 57th Annual Scientific Sessions of the American College of Cardiology ■ Chicago, IL

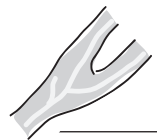
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## ENHANCing Our Understanding of LDL and CVD



Important data on diabetes presented at the 57th Annual Scientific Sessions of the American College of Cardiology come to you in **Diabetes 2008**, a newsletter CME program that is being offered to you by Yale University School of Medicine. Fax or e-mail delivery to your office of **Diabetes 2008** will be followed by a **Diabetes 2008** 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.

**Diabetes 2008** is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

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

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The importance of reducing levels of low-density lipoprotein (LDL) cholesterol in the prevention of cardiovascular (CV) disease is now well established. A number of recent studies have also suggested that high-dose statin therapy, aimed at more aggressively lowering LDL-cholesterol, may further reduce CV risk in dyslipidemic patients, including those with diabetes. However, high-dose statin therapy achieves only a modest additional reduction in LDL-cholesterol and brings with it an increased risk of adverse events (myalgias, etc.). In this context, newer compounds that act to reduce LDL-cholesterol through separate mechanisms might provide the additional cardioprotective effect without exposing individuals to limiting drug-related toxicity. One such compound that has been introduced to the market is ezetimibe. Ezetimibe binds to the Niemann-Pick C-1 like 1 (NPC1L1) protein, thereby inhibiting the transport of cholesterol and non-cholesterol sterols through the intestinal wall.

In a late-breaking clinical session this week at the American Cardiology of Cardiology conference, Dr. John Kastelein on behalf of the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression trial) investigators presented the results of a 2-year, double-blind, randomized multicenter trial of daily therapy with 80 mg of simvastatin combined with either placebo or 10 mg of ezetimibe in 720 patients

with familial hypercholesterolemia (abstract 404-12). This study was simultaneously published in the *New England Journal of Medicine* (358:1431). The primary outcome measure in this trial was carotid-artery intima-media thickness (IMT), a commonly used surrogate measure for CV risk, using B-mode ultrasonography. The patients in each group were well matched for age (~45 years) and gender (~50% male), established CV risk factors (e.g., smoking history, diabetes, hypertension), previous statin use (~80%), and baseline lipid profile. Dr. Kastelein reported that compliance rates for the study drugs were high (78-84%) and that just under 10% of each study group experienced an adverse event necessitating withdrawal from the trial.

The investigators found that after 2 years of therapy the simvastatin/ezetimibe combination was more effective than simvastatin alone in improving lipid profiles (Table 1). For instance, mean levels of LDL-cholesterol fell from 318 ± 66 to 193 ± 60 mg/dl in the simvastatin monotherapy group, while in the simvastatin/ezetimibe combination group levels fell from 319 ± 65 to 141 ± 53 mg/dl, a between-group difference of 16.5% (p < 0.01).

With these impressive changes in lipid profiles with combination therapy, it was a surprise when the investigators then revealed that no significant change was seen in the primary

**Table 1. Percent Change from Baseline in Lipid Parameters and C-reactive Protein: Simvastatin ± Ezetimibe**

Variable	Simvastatin Monotherapy (n=363)	Simvastatin + Ezetimibe (n=357)	p-value
Cholesterol*			
Total	-31.9±0.8	-45.3±0.8	<0.01
LDL	-39.1±0.9	-55.6±0.9	<0.01
HDL	7.8±0.9	10.2±1.0	0.05
Triglycerides (median)	-23.2	-29.8	<0.01
Apolipoprotein B*	-33.1±0.9	-46.7±0.9	<0.01
C-reactive protein (median)	-23.5	-49.2	<0.01

\*Least-square mean change.

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## ENHANCing Our Understanding ...

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outcome variable, namely, mean (SEM) change from baseline in IMT of the carotid artery ( $0.0058 \pm 0.0037$  mm vs.  $0.0111 \pm 0.0038$  with simvastatin vs. simvastatin/ezetimibe, respectively,  $p=0.29$ ). Neither did the study group find differences in the secondary outcome measures of new plaque formation or mean maximum IMT.

Following presentation of this data the investigators concluded that combination simvastatin and ezetimibe therapy in patients with familial hypercholesterolemia provided a significant additional reduction of LDL-cholesterol, but this for some reason was not associated with additional benefit in terms of a reduction in carotid atherosclerosis. As IMT is a surrogate measure for CV disease risk, it would suggest that the combination therapy would therefore

not reduce CV event rates. However, a large event trial with ezetimibe is currently underway.

In an accompanying editorial in the *New England Journal of Medicine* (358:14;1504-07), Drs. Brown and Taylor from Seattle and Washington D.C., respectively, commented that these findings now challenge the mantra that "lower is better." They noted that most (30 of 34) studies show a modest positive correlation between IMT and angiographic evidence of coronary atherosclerosis, although no study of 2 years or less has actually shown a reduction in CV events. However, as the progression of IMT was not slowed during this trial then no clinical benefit would be expected in this population with prolonged treatment. The authors did note that the high percentage of patients pre-treated with a statin may have limited the benefit to be gained with combination therapy, and that longer trials might show some clinical

benefit. It was concluded that, until further evidence becomes available, physicians should aim first to achieve recommended targets for LDL- and HDL-cholesterol using statin monotherapy. If combination therapy is required, then the current evidence favors addition of nicotinic acid derivatives, fibrates, or bile-acid sequestrants, as tolerated. Ezetimibe, they suggested, should be reserved for those patients not achieving recommended targets on these regimens. As they commented, it may not only be "how low you go" but also "how you get there". We would add that this specific study, conducted in patients with genetically-determined, extremely elevated LDL-cholesterol levels, may not reflect the effects of ezetimibe in those with more modest hyperlipidemia. In addition, a complete impression of the ENHANCE study data must necessarily await the conclusion of other ongoing clinical trials that are assessing actual CV events.



## Diabetes Drugs and their Cardiovascular Implications



Many patients with Type 2 diabetes are treated with sulfonylureas. Concern has been raised over the years about the possibility that these agents may be associated with an increased risk of CV events. It should be noted, however, that this notion derived mainly from rodent studies and a single trial in the 1970's (UGDP) suggesting increased CV risk from an older sulfonylurea, tolbutamide, as compared to diet or insulin therapy. The larger and more recent UKPDS, however, failed to confirm any significant CV risk with several members of this insulin secretagogue class. Cardiac ATP-sensitive potassium ( $K_{ATP}$ ) channels are ordinarily open during myocardial ischemia, a response that is generally believed to be adaptive and protective. Conversely, blockade of cardiac  $K_{ATP}$  channels, as might occur with sulfonylureas, may predispose to ischemic injury and increase the propensity for ischemic arrhythmias. Glyburide, for example, has been shown to increase myocardial infarct size in rats. Pioglitazone, a thiazolidinedione (TZD), also in the rat, may actually reduce infarct size, although the mechanism is entirely speculative, perhaps involving enhanced endothelial function, microvascular flow, or improved cardiomyocyte energy dynamics. Ye and colleagues from the University of Texas investigated whether the effect of sulfonylureas was agent-specific and whether it persisted after combination use with pioglitazone (abstract 1003-41). They compared the effects of 3-day oral treatment with pioglitazone (5mg/kg/d), pioglitazone + glyburide (10mg/kg/d), pioglitazone

+ glimepiride (4mg/kg/d), or water alone in male Sprague-Dawley rats ( $n=6$  in each group). Drugs were administered by oral gavage and 5% sugar was added to water to prevent hypoglycemia. Rats then underwent 30-minute coronary artery occlusion followed by 4-hour reperfusion. The investigators reported that infarct size was significantly smaller in the pioglitazone (5.1% left ventricular area,  $p<0.001$ ) and pioglitazone + glimepiride (4.5%,  $p<0.001$ ) groups than in the control group (12.9%). In contrast, glyburide completely blocked any protective effect of pioglitazone (14.9%,  $p<0.001$ ). They concluded that oral glyburide, but not glimepiride, blocks the infarct size limiting effects of pioglitazone, and thus the negative CV effect of sulfonylureas may be agent-specific. These data should be interpreted with caution. As is common with many of these animal studies, tested agents are administered in "industrial" doses. In this case, had the rat been an average 70 kg human, the dose would have been equivalent to 280 mg/day of glimepiride and 700 mg/day of glyburide!

Lu and colleagues from the University of Colorado took a novel approach to examining the potential cardiac effects of TZDs (abstract 1015-97). This group had found in previous studies that TZDs could also block  $K_{ATP}$  channels in non-cardiac cells *in vitro*. In the current investigation, 30 pigs were subjected to 90 minutes regional low-flow coronary ischemia under treatment with troglitazone (10 mg/kg IV) or rosiglitazone (0.1 or

1.0 mg/kg IV). Cardiac action potential was shortened in duration when compared to vehicle (to  $12 \pm 8$  and  $6 \pm 6$  msec with troglitazone and rosiglitazone, respectively, both  $p<0.01$ ). Intriguingly these findings suggest that troglitazone and rosiglitazone act as  $K_{ATP}$  blockers—a unique observation. Consistent with this, three tested TZDs (troglitazone, rosiglitazone, and pioglitazone) each reversed the effects of the potassium channel opener (levcromakalim  $1 \mu\text{g}/\text{kg}/\text{min}$ ) on cardiac action potentials during ischemia. One potential related effect is to increase arrhythmic risk. The investigators then found that following complete coronary occlusion, the median time to development of ventricular fibrillation was 6 minutes with rosiglitazone, compared to 30 minutes with vehicle ( $p=0.03$ ), consistent with a pro-fibrillatory effect in ischemia. The mechanism through which TZDs might affect the  $K_{ATP}$  channel is unknown, but its rapidity argues against this working at the level of gene transcription. This raises the possibility of non-specific drug effects and highlights the importance of continued observation for unexpected adverse events in clinical trials. As above, it is not clear how applicable these findings might be in humans, who are treated with comparatively lower doses of these agents.

TZD medications for Type 2 diabetes increase the risk of peripheral edema (5-15%), with a smaller but important increment in risk of heart failure (~1%). This area has not been extensively investigated but is an aspect of TZD therapy that

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concerns both patients and their physicians. To address this issue Stream and colleagues, University of Texas, performed an analysis of patients on rosiglitazone who developed new or worsening edema in comparison to those who did not, using measures of plasma volume status, peak oxygen consumption (VO<sub>2</sub>peak) during maximal exercise, and cardiac MRI measures (abstract 1021-213). They reported a small but significant decline in VO<sub>2</sub>peak in those patients who developed new or worsening edema. However, they could detect no significant worsening in MRI parameters of cardiac structure/function, while stroke volume actually increased (Table 2). In contrast, measures reflecting plasma volume expansion all significantly worsened. In keeping with earlier investigations, this group concluded that TZD edema is most likely attributable, at least in part, to plasma volume expansion, with no evidence of any pernicious effects on cardiac structure/function.

Mimetics of the incretin hormone, glucagon-like peptide (GLP)-1, have now entered into clinical practice as a therapeutic option for individuals with Type 2 diabetes. GLP-1 has a short-half life in circulation, being rapidly broken down by the enzyme DPP-4, a fact led to the development of anti-hyperglycemic agents that block this enzyme, namely the DPP-4 inhibitors. One of the

**Table 2. Changes Over Six Months in Cardiovascular Performance and Cardiac Function in Rosiglitazone-Treated Patients With New/Worsening Edema**

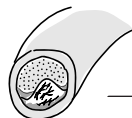
Characteristic	Baseline	6-Months	p-value*
Left ventricular end-diastolic volume (ml)	115.6 (97.7, 142.7)	126.1 (115.3, 151.2)	0.000
VO <sub>2</sub> peak (ml/kg [fat free mass]/min)	24.5 (20.5, 30.1)	24.1 (21.3, 27.9)	0.003
Ejection fraction (%)	65.9 (59.2, 70.0)	66.4 (57.0, 70.4)	0.424
Stroke volume (ml)	73.3 (62.2, 88.1)	83.3 (73.9, 89.1)	0.008
Peak flow reserve (ml/sec)	59.5 (39.5, 93.6)	77.5 (46.6, 127.3)	0.118
Left ventricular mass (g/m <sup>2</sup> )	76.9 (65.8, 89.3)	77.4 (64.2, 86.9)	0.419

Data presented as mean (95% CI).

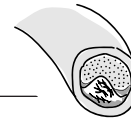
\* Non-parametric paired sample analysis.

degradation products of GLP-1 metabolism is GLP-1(9-36) amide (GLP1-dp), a peptide previously thought inert. However, in a presentation by Gundewar and colleagues, Albert Einstein College of Medicine, New York, potential cardioprotective effects of GLP1-dp were elegantly demonstrated in two *in vivo* diabetic murine models of myocardial ischemia-reperfusion injury (abstract 1036-311). They treated diabetic (db/db [leptin receptor mutant] and streptozotocin-treated) mice with 2.4 µg/day of GLP1-dp via an infusion pump for seven days and then subjected the mice to 45 minutes of left coronary artery occlusion followed by 2 hours of reperfusion. Hearts were then excised and evaluated for infarct size using 2,3,5-triphenyltetrazolium chloride staining. Interestingly, the investigators found that seven days of GLP1-

dp therapy in db/db, but not streptozotocin, mice resulted in a 48% reduction in blood glucose values. In addition, both mouse models treated with GLP1-dp exhibited a 37% and 45% reduction in infarct size and showed significantly greater benefit in terms of post-infarction left ventricular ejection fraction, as measured by echocardiography, in comparison to controls. The authors concluded that the administration of GLP1-dp peptide confers cardioprotection in diabetic mice by attenuating the extent of myocardial injury following ischemia-reperfusion, effects that appear to be independent of its glucose-lowering action. There are few cardiovascular data thus far in humans with GLP-1 mimetics (e.g., exenatide) or with DPP-4 inhibitors (e.g., sitagliptin), but this area appears clearly worthy of further study.



## Plaque Attack



The inextricable link between diabetes and coronary heart disease was the subject of numerous presentations made at this week's American College of Cardiology Scientific Sessions. Investigations to better characterize atherosclerotic plaque content and vulnerability add to our understanding of why diabetic patients have a greater likelihood of plaque rupture than non-diabetics, with consequent adverse clinical sequelae.

Plaque rupture and subsequent thrombus formation is the most important mechanism leading to acute myocardial infarction (AMI). Hong and co-workers from South Korea conducted a study to compare the intravascular ultrasound (IVUS) findings following AMI in patients with and without diabetes (abstract 1010-76). The study population included 112 patients with IVUS-evident plaque ruptures (i.e., a cavity that communicated with the lumen with an overlying residual fibrous cap fragment); 58 patients had ST segment elevation MI (STEMI). The investigators observed that diabetic AMI patients (n=47) had greater plaque vulnerability, as evidenced by more frequent multiple plaque

ruptures (60% vs. 29%, p=0.001) and thrombus formation (i.e., discrete intraluminal filling defects) (72% vs. 52%, p=0.032), which was accompanied by a higher inflammatory state (high-sensitivity C-reactive protein, 4.6 vs. 2.4 mg/dl, p=0.050). In addition, reference segment plaque burden was greater (37% vs. 31%, p=0.006), plaque cavity

was larger (2.6 vs. 2.2 mm<sup>2</sup>, p=0.046), and ruptured plaque length was longer (3.0 vs. 2.5 mm, p=0.031) in those with diabetes.

The same research group used "virtual histology" IVUS to study *de novo* coronary lesions and plaque composition in patients with acute coronary syndrome (ACS) or stable angina (abstract 2900-

**Table 3. Plaque Composition and Incidence of Culprit Lesion Thin-Cap Fibroatheroma in Diabetes vs. Non-Diabetes Patients**

	Diabetes Patients (n=61)	Non-Diabetes Patients (n=136)	p-value
Necrotic core area			
Minimum lumen sites	17.3 ± 11.8%	12.6 ± 9.8%	0.023
Largest necrotic core sites	30.2 ± 10.8%	20.9 ± 9.6%	<0.001
Necrotic core volume	16.5 ± 9.4%	13.8 ± 7.8%	0.036
Thin-cap fibroatheroma* within culprit lesions			
At least 1 overall	59%	37%	0.004
At least 1 in ACS patients	60%	42%	0.035
At least 1 in stable angina patients	55%	19%	0.026
Multiple	25%	11%	0.014

\* defined as plaque burden ≥40%.

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## Plaque Attack

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130). The percent necrotic core area and necrotic core volume were significantly greater in diabetic compared with non-diabetic patients (Table 3). Those with diabetes also had a higher frequency of thin-cap fibroatheroma lesions, the most prevalent substrate of plaque rupture, regardless of their clinical presentation (i.e., in both ACS and stable angina). In multivariate analysis, diabetes was the only independent predictor of these more vulnerable lesions (odds ratio=2.2, 95% CI 1.1-4.4;  $p=0.031$ ).

Adding to these data are the findings of Manfrini *et al.* from Italy, who used CT angiography to determine the impact of diabetes on coronary atherosclerotic plaques (abstract 905-278). The study population included 199 patients with no history of ischemic heart disease, 102 of whom had Type 2 diabetes. Coronary plaque (defined as thickening of the arterial wall  $>0.5$  mm) was more common in patients with diabetes (65.7% vs. 26.2% of controls,  $p<0.001$ ). The duration of diabetes was an independent predictor of coronary atherosclerosis (OR= 1.12,  $p=0.026$ ) and was strongly related to

plaque density ( $r=0.37$ ,  $p<0.05$ ). There was no difference in overall burden of coronary atherosclerosis, evaluated by the volume of fibro-fatty components plus calcium volume, based on diabetic status. As it relates to morphology of the coronary lesions, plaques in patients with diabetes showed impaired adaptive remodeling (56.5% vs. 35.6%,  $p<0.01$ ) and higher tissue density (58.8 vs. 47.3 HU,  $p<0.001$ ).

These studies continue to demonstrate the unique features of atherosclerosis affecting our diabetic patients, placing them at greater risk of cardiovascular morbidity.



## Diabetes and the Heart: Destined to Fail?



Heart failure is an increasingly common comorbidity in patients with diabetes and is associated with an increased risk of adverse outcomes. The age-adjusted relative risk of heart failure is at least 2-5 fold increased in diabetic patients as compared to the general population. Moreover, in a large population-based sample of nearly 50,000 diabetic patients, each 1% increase in HbA1c was associated with a 12% increased risk of heart failure hospitalization and/or mortality, after adjustments for age and gender (Iribarren *et al.*, *Circulation* 2001), although the development of heart failure may be more closely related to the duration of diabetes than to glycemic control *per se*.

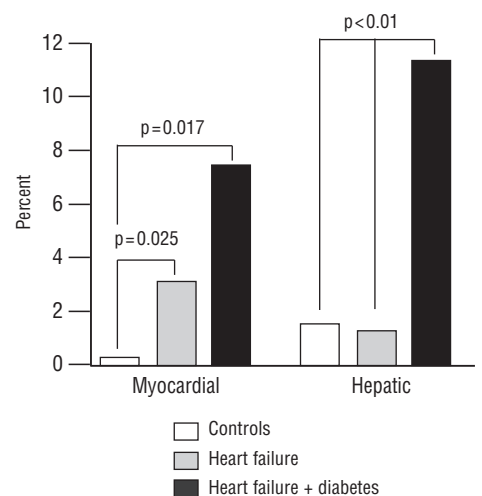
Recent observations have actually challenged the benefits of tight glycemic control in reducing long-term mortality in heart failure patients with diabetes. Jhavar *et al.* from the Cleveland Clinic and University of Missouri evaluated the impact of rate of change in serial HbA1c over time (i.e., slope of HbA1c linearly regressed over time) on long-term mortality in a cohort of 2,571 diabetes patients with heart failure (mean age 70 years, 60% male, HbA1c 7.8%, 49% treated with insulin) (abstract 1019-155). A total of 799 deaths/cardiac transplants occurred over a period of  $4.4 \pm 2$  years. Mortality rates were lower in patients with less rapid increases and less rapid decreases in HbA1c over time (i.e., a "U-shaped" mortality curve). Of particular note, patients with more rapid fall in HbA1c experienced poorer outcomes than those with more rapid rise in HbA1c ( $p=0.0038$ ). After adjustments for age, renal function, hypertension, and use of anti-hyperglycemic medications (Cox proportional hazard analysis), increase in HbA1c was actually associated with a more favorable prognosis (hazard ratio 0.465, 95% CI 0.34 - 0.64;  $p<0.001$ ). Given worse long-term prognosis with rapid fall in HbA1c seen in this single-center study, further studies are needed to clarify whether tight glycemic control might be culpable.

On the other hand, there is also data suggesting that poor glucose control has untoward effects in diabetic patients with heart failure, as suggested by Lavine and associates (abstract 1016-18). In a 6-month crossover study, 11 mongrel dogs with induced chronic left ventricular dysfunction (ejection fraction 35-40%) and diabetes were randomized to either a good glucose control group (fasting blood glucose:100-150 mg/dl) or poor glucose control group (250-350 mg/dl) for 3 months, and then to the opposite glycemic control group for 3 months. While no statistically significant changes in ventricular performance from baseline were noted with good control (mean HbA1c=4.0%), deleterious alterations were observed during the poor glucose control period (mean HbA1c=8.9%): shortened diastolic filling time (-107 msec), progressive left ventricular dysfunction (-4% in ejection fraction), and increased left ventricular end-diastolic pressure (+3 mm Hg). Afterload stress (arterial pressure +58 mm Hg) during poor glycemic control further exacerbated resting diastolic and systolic abnormalities, as compared to good control: decreased diastolic filling period (-46 msec), 40% greater increase in both end-diastolic and end-systolic volumes, and increased left ventricular end-diastolic pressure (+3 mm Hg) and isovolumic relaxation time (+16 msec). Such discordant data raise the possibility of some uncontrolled bias in the observational human study. We clearly need to learn more about the implications of tight glucose control for our patients with heart failure.

Indeed, the impact of various anti-hyperglycemic regimens on the clinical status of patients with heart failure is an area of growing interest and some controversy. In a large observational study, Al Zadjali *et al.* from Scotland used a Cox regression model to determine differences in outcomes based on oral agent therapy in diabetes patients with incident heart failure (mean age 74 years, 55% male) (abstract 1009-4).

Over a 10-year follow-up period, all-cause mortality rate was lower among patients treated with metformin alone (60%) compared to those treated with sulfonylurea monotherapy (77%,  $p<0.0001$ ). One-year mortality rates were lower with metformin monotherapy (unadjusted relative risk [RR] 0.52,  $p<0.05$ ) and combination therapy (unadjusted RR 0.71,  $p<0.05$ ) than with sulfonylurea alone. After adjustments for confounding factors (HbA1c, blood pressure, comorbidities, complications) and propensity score, the adjusted mortality risk (vs. sulfonylurea) was 0.45 for metformin and 0.66 for the combination group (each  $p<0.05$ ). Patients in the metformin group also had a lower 1-year risk of hospitalization (RR 0.74,  $p<0.05$ ). The combined endpoint (all-cause hospitalization or mortality) was significantly lower in the metformin monotherapy group as

**Figure 1. Myocardial and Hepatic Triglyceride Content in Heart Failure Patients**



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well (RR 0.74,  $p < 0.05$ ), but not in the combination group (RR 0.92), compared to sulfonylureas alone. These results are consistent with those of Eurich *et al.* (*Diabetes Care* 2005;28:2345), and Masoudi *et al.* (*Circulation* 2005;111:583), suggesting that long-held concerns about metformin use in patients with heart failure, based on the fear of lactic acidosis, may be unfounded. To the contrary, metformin use may have favorable effects based on both lower morbidity (hospitalizations) and mortality. Of note, the US Food and

Drug Administration recently lifted the contraindication for metformin in stable heart failure patients with normal renal function.

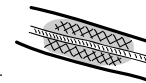
At a mechanistic level, among various factors contributing to the pathophysiology of ventricular dysfunction in patients with heart failure, intracellular and extracellular cardiac lipid deposition may be one factor according to data presented by Ruberg *et al.* from Boston (abstract 1023-5). Using ECG-gated, proton magnetic resonance spectroscopy, the researchers measured myocardial and hepatic triglyceride content in 12 heart failure patients—7 with diabetes—and 3 controls. Whereas

hepatic lipid accumulation was seen only in the diabetic patients, myocardial lipid was detected in both groups, although to a much higher degree in those with diabetes (Figure 1). The extent to which such myocardial 'lipotoxicity' plays a causative role in the heart failure associated with diabetes is not yet clear.

An improvement in our understanding of the biological underpinnings of heart failure in diabetic patients and its relationship to glucose control will hopefully lead to better prevention and treatment strategies.



## On the Fence About Stents

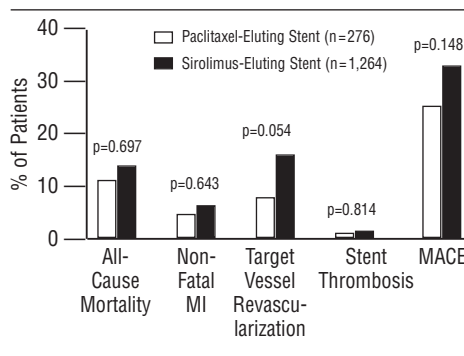


Diabetes is associated with poorer outcomes following percutaneous coronary intervention (PCI): increased risk of restenosis, stent thrombosis, and even mortality. This may result from increased intimal hyperplasia, altered coagulability, inflammatory response, endothelial dysfunction, as well as other co-morbid features that are often present in diabetic patients. Drug-eluting stents (DES) reduce restenosis rates in comparison to "bare metal" stents—likely reflective of a suppressive effect on intimal hyperplasia, but these have not entirely eliminated the disadvantage posed by diabetes in patients undergoing PCI. This observation was the focus of several presentations at this week's Scientific Sessions.

Butler *et al.* from Australia evaluated the impact of diabetes on early and late mortality as well as on major adverse cardiac events (MACE) in 5,068 patients (23% with diabetes) undergoing PCI (abstract 1033-129). DES was more frequently utilized in those with vs. without diabetes (68% vs. 47%,  $p < 0.0001$ ). At 30-day follow-up, mortality (3.2% vs. 1.6%,  $p < 0.001$ ) and MACE (7.4% vs. 5.9%,  $p < 0.05$ ) were also significantly higher in the diabetic group. Despite comparable rates of target-lesion revascularization at 12 months (6.5% vs. 5.3%,  $p = 0.29$ ), mortality (6.6% vs. 3.6%,  $p = 0.002$ ) and MACE (18.1% vs. 13.8%,  $p = 0.01$ ) at 12 months remained higher in diabetic patients. According to logistic regression, diabetes (odds ratio [OR] 1.5; 95% CI 1.2-2.0) and the absence of a DES (OR 1.6; 1.2-2.1) were the strongest predictors of MACE at 12 months.

Results of a study conducted by Chia and colleagues provide insight into potential causes of poor post-PCI outcomes in diabetes (abstract 1010-66). Single-photon emission computed tomography was used to assess infarct size and

**Figure 2. Three-Year Event Rates Following Paclitaxel- and Sirolimus-Eluting Stents In Diabetic Patients**



left ventricular ejection fraction (LVEF) five and 30 days after PCI for acute STEMI in 387 patients (69 diabetic) who had been enrolled in the double-blind, randomized EVOLVE (EValuation Of MCC-135 for Left VEntricular Salvage in Acute Myocardial Infarction) study (abstract 1010-66). Although diabetic patients had similar high rates of post-procedural TIMI flow grade 3 after primary PCI compared to non-diabetic patients (83% vs. 86%, respectively), they were more likely to have larger infarct size ( $p = 0.004$ ) as well as reduced LVEF at 30 days ( $p < 0.05$ ). Kaplan-Meier analysis revealed a trend towards increased 30-day adverse composite clinical endpoint (i.e., death, re-infarction, new/worsening heart failure, cardiogenic shock, cardiac re-hospitalization, and life-threatening ventricular arrhythmias) in the diabetic group (22% vs. 14%,  $p = 0.10$ ). In a subgroup of patients who had Tc-99m sestamibi injected prior to reperfusion (10 with and 82

without diabetes), the estimated myocardial salvage post-PCI did not differ between the groups. These data suggest that differences in infarct size and ventricular function in diabetic patients post-PCI may explain, at least in part, their worse long-term clinical outcomes.

Pfeiffer *et al.* from Springfield, Illinois conducted a study to determine if there are differences in outcomes based on type of DES (abstract 2900-55). The study included 1,540 diabetic patients (2,376 lesions) who underwent first stent placement between May 2003 and December 2006. Patients who received a sirolimus-eluting stent were similar to those who received a paclitaxel-eluting stent based on gender, age, renal function, smoking history, and STEMI presentation. Sirolimus-eluting stents were placed more often in patients who had a prior PCI (33.5% vs. 25.7%;  $p = 0.013$ ) and unstable angina at presentation (37.6% vs. 26.8%;  $p = 0.001$ ); paclitaxel-eluting stents were utilized more often (each  $p < 0.001$ ) in lesions that were high-risk (ACC defined) (46.4% vs. 37.4%), involved a bifurcation (20.5% vs. 10.0%), and had a longer length ( $21.1 \pm 13.3$  vs.  $19.2 \pm 9.7$ ). Despite paclitaxel-eluting stent use in more complex lesions, there was a trend toward lower 3-year target vessel revascularization rate with paclitaxel- as compared to sirolimus-eluting stents (Figure 2).

Whatever the specific intervention, a consistent theme emerging from PCI studies in patients with diabetes is that their clinical outcomes are not as good as in non-diabetic peers. There is an ongoing need for trials that will specifically address this issue so that the prognosis of our diabetic patients with CAD may improve.



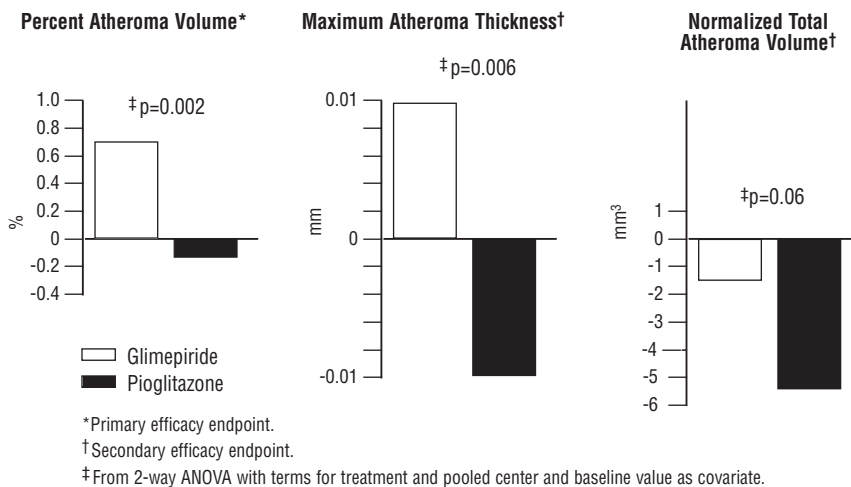
## Late-Breaking Cardiovascular News



At the American College of Cardiology conference in Chicago a series of “late-breaking” clinical trials were presented which might affect current clinical practice and therapeutic guidelines. Important findings from these sessions are summarized below.

Last spring, Dr. Steven Nissen from the Cleveland Clinic published a widely cited meta-analysis in the *New England Journal of Medicine* of 42 published and unpublished randomized clinical trials of patients taking rosiglitazone for a minimum of 24 weeks. Their analysis found an increased risk for myocardial infarction (RR=1.43) in those subjects assigned to rosiglitazone. These findings raised appropriate concern about TZD therapy for diabetes—drugs that had been purported to reduce CV risk because of their effect as insulin sensitizers. PERISCOPE looked at the effects of another TZD, pioglitazone, on a direct measure of atherosclerosis. This was a double-blind, randomized, multicenter trial conducted at 97 centers in North and South America in 543 high-risk patients with established coronary artery disease (CAD) and Type 2 diabetes (abstract 407-13). The patients all underwent IVUS and were then randomized to receive glimepiride (1-4 mg) or pioglitazone (15-45 mg) for 18 months with titration to maximum tolerated dosage. Atherosclerotic progression was measured by repeat IVUS in 360 patients upon completion of the study. The patients in each arm of the trial were well matched; around 70% were male and the average age was ~60 years. As you would predict, almost all had co-morbid conditions such as hypertension and dyslipidemia, and the majority were on additional therapy such as statins (82%), ACE inhibitor/angiotensin receptor blocker (ARB) (~80%), and aspirin (~90%). After 18 months of therapy, the subjects on pioglitazone had a significantly greater fall in mean [95% CI] HbA1c as compared to those taking glimepiride (-0.55 [-0.68 to -0.42] vs. -0.36 [-0.48 to -0.24]%;  $p<0.05$ ), fasting plasma glucose (-8.5 [-12.7 to -4.3] vs. 0.4 [-3.7 to 4.5] mg/dl;  $p<0.05$ ), and fasting insulin (-5.0 [-7.0 to -4.0] vs. 1.3 [-0.5 to 5.0]  $\mu\text{U/ml}$ ;  $p<0.001$ ). Pioglitazone also had a significant effect (each  $p<0.001$ ) on the change in: HDL-cholesterol (+5.7 [4.4 to 7.0] vs. +0.9 [-0.3 to 2.1] mg/dl); fasting triglycerides (-16.3 [-27.7 to -11.0] vs. +3.3 [-10.7 to 11.7] mg/dl); and CRP (-1.0 [-1.5 to -0.8] vs. -0.4 [-0.9 to -0.2] mg/l). There was also a statistically significant difference between the treatment groups favoring pioglitazone, based on the primary outcome measure of percent atheroma volume (PAV), as well

**Figure 3. Mean Change from Baseline in Intravascular Ultrasound Endpoints: PERISCOPE**



as for the secondary endpoint of maximum atheroma thickness (Figure 3). (PAV is essentially the difference between the vessel external elastic membrane borders and the luminal cross-sectional area, and thus provides an index of the amount of plaque within the vessel wall.)

No significant differences were found in CV event rates between the two treatment groups, although it should be noted that the trial was designed and powered only to look at changes in IVUS and not actual clinical outcomes. These data appear to buttress the findings from the PROactive study, which showed a modest 16% reduction in the secondary outcome of mortality, myocardial infarction, and stroke in high-risk Type 2 diabetic patients treated with pioglitazone on top of standard anti-hyperglycemic therapy (Dormandy JA *et al. Lancet* 2005; 366:1279). While a higher incidence of hypoglycemia (37% vs. 15%;  $p<0.001$ ) was noted in the patients on glimepiride, more patients on pioglitazone experienced peripheral edema (18% vs. 11.0%;  $p=0.02$ ) as well as bone fractures (3% vs. 0%;  $p=0.004$ ).

In a last-day late-breaker session at the ACC meeting, Dr. Olivier Bertrand presented the results of the VICTORY (VeIn-Coronary ATHerOsclerosis and Rosiglitazone after Bypass surgerY) trial, a multicenter (Canada, Spain), randomized, double-blind, placebo-controlled trial of rosiglitazone (titrated over an 8-week period up to 8 mg/day or maximum tolerated dose) for prevention of atherosclerosis progression within bypass grafts in patients with diabetes (abstract 413-4). Eligible patients had stable Type 2 diabetes (no

new treatment or change in anti-hyperglycemic agent dose in the previous 3 months) and stable CAD, 1 to 10 years after coronary bypass graft (CABG) surgery. Important exclusions were: recent MI or ACS ( $\leq 90$  days), last LVEF  $\leq 35\%$ , unstable angina (Canadian Cardiovascular Society class III and IV), acute or advanced heart failure, and chronic insulin use.

IVUS of 1 saphenous vein graft (segment length of at least 40 mm) and the anastomosed native coronary artery corresponding to the saphenous vein graft chosen (segment length of at least 20 mm) was performed at baseline and at 12 months to assess atherosclerosis.

The study population was smaller ( $n=193$ ) than the target enrollment of 280. The mean age of patients was ~65 years, 92% were male, diabetes duration ~8 years, and the mean time period since CABG surgery was ~4 years. Patients enrolled in the study had well-controlled diabetes (mean HbA1c < 7%) and CV risk factors at baseline (mean blood pressure=129/72 mmHg with ~90% of patients treated with an ACE inhibitor/ARB, 79% a calcium channel blocker, 95% a statin, and virtually all taking an anti-platelet agent).

Despite favorable changes in various metabolic (blood glucose, HbA1C), lipid (e.g., HDL-cholesterol, % small, dense LDL-cholesterol), pro-thrombotic (PAI-1), and inflammatory (CRP) markers, rosiglitazone therapy had a neutral effect on the progression of atherosclerosis. No statistically significant changes in the primary endpoint of saphenous vein graft plaque volume over 12 months was found in the rosiglitazone group (+0.9% [3 mm<sup>3</sup>] vs. +2.8% [10 mm<sup>3</sup>] with placebo,

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adjusted  $p=0.22$ ). Modest weight gain was observed in the rosiglitazone group, mainly the result of an increase in subcutaneous fat mass. There were no differences between rosiglitazone and placebo based on treatment-emergent heart failure or CV events in this relatively small study.

It is interesting to contrast the PERISCOPE findings with those of VICTORY, particularly in light of the recent suggestion of discordant clinical trial findings as far as CV events are concerned with the two TZDs.

ONTARGET was a 4-year randomized, placebo-controlled trial of the ACE inhibitor ramipril vs. the ARB telmisartan vs. a combination of ramipril and telmisartan in an international multicenter trial of ~29,000 high-risk patients (abstract 407-5). While not specifically focused on patients with diabetes, ~40% of the study cohort had Type 2 diabetes and so the outcomes of this trial are clearly relevant to our practices. The study population was mostly male (~75%), had a mean age of ~66 years, and most were on additional therapy such as statins (~62%), beta-blockers (57%), and aspirin (~75%). In this trial both ramipril and telmisartan were titrated up to 10 and 80 mg per day, respectively. The study questions were whether telmisartan was as effective as ramipril and whether the combination provided any additional benefits. The investigators reported a significant drop in blood pressure in all arms: systolic -6.0 vs. -6.9 vs. -8.4 mmHg and diastolic -4.6 vs. -5.2 vs. -6.0 mmHg at study end (ramipril vs. telmisartan vs. both, respectively). Adverse events were infrequent, with hypotensive symptoms more common with telmisartan and cough more common with ramipril. For the primary outcome measure (composite CV events), no significant differences were found between the two groups. In fact, there was almost the same number of events (~1400) in each. Thus, telmisartan proved as effective as ramipril. However, and to the surprise of the investigators, despite the increased blood pressure lowering effect, there was no significant incremental benefit from the combination of the ACE inhibitor and the ARB on individual or composite CV event rates. Moreover, there was a clear difference in tolerability with the combination having an increased relative risk of discontinuation due to hypotension (~2.8), syncope (~2.0), diarrhea (~3.3), and renal impairment (~1.6), as compared with ramipril. Dr. Yusuf did note that the renal outcomes data are not yet available and that information regarding glucose metabolism is also still being analyzed. He concluded that telmisartan was an effective and well tolerated alternative to ramipril in the treatment of hyper-

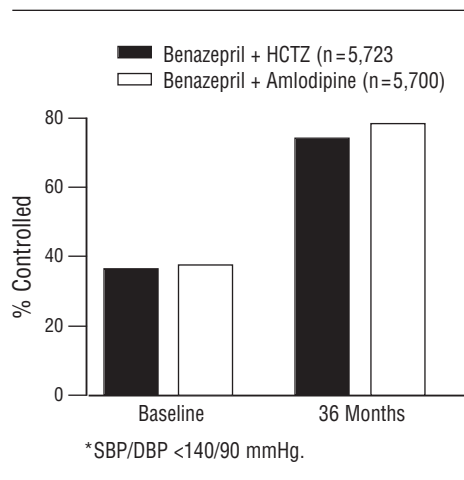
tension, but that there was no additional benefit on CV events from combination therapy.

ACCOMPLISH aimed to develop a new strategy for managing patients with hypertension. The investigators sought to specifically examine the impact of different combination therapies, given as a single tablet, in the treatment of hypertension. To this end they compared a combination of benazepril and amlodipine with benazepril and HCTZ in a large (~5700 in each group) study of high-risk patients with hypertension (systolic blood pressure >160 mmHg) (abstract 407-7). Approximately 60% of the study population had Type 2 diabetes. After screening and a wash-out period, patients were randomized into the two treatment groups and followed up regularly. Combining the two types of antihypertensive agents in the one compound proved very effective. While only 37% of patients at baseline had achieved their blood pressure goals, over 75% of patients on either combination successfully reached target (<140/90 mmHg) at 36 months (Figure 4). They found a slight difference in favor of the benazepril/amlodipine combination. Perhaps more surprisingly, given the near equivalence of the blood pressure lowering effect, there were significant differences between the groups in terms of CV risk reduction. The benazepril/amlodipine combination proved more effective (21% risk reduction; 95% CI 1.06-1.37) than the benazepril/thiazide combination and, moreover, on sub-analysis all components of CV risk lined up in favor of the ACE inhibitor/calcium channel blocker combination. This study has clear implications for clinical practice and the panelists at the ACC all agreed that hypertension management guidelines would likely reflect this in the near future.

Approximately one-third of the US population is obese (BMI >30 kg/m<sup>2</sup>). Adipose tissue secretes adipocytokines that mediate fat and glucose metabolism, and it is now recognized that these play a role in the development of insulin resistance. The endocannabinoid system clearly regulates the intake, transport, storage, and utilization of energy and is suspected to play a direct role in adipocyte biology. Overactivation of cannabinoid type 1 (CB1) receptors has also been linked to dyslipidemia, abnormal glucose homeostasis, and obesity. In the light of these discoveries, the pharmaceutical industry has explored the use of agents that can interfere with these actions, namely the still investigational CB1 antagonists.

The first compound to emerge from this research and to find its way into clinical trials is rimonabant, which recently failed to garner FDA approval as an anti-obesity drug, due to concerns about the induction of depressive symptoms. At this week's meeting, Dr. Steven Nissen, on

**Figure 4. Blood Pressure Control\* with ACE-I plus Thiazide or Calcium Channel Blocker**



behalf of the STRADIVARIUS (SStrategy to Reduce Atherosclerosis Development InvolVing Administration of Rimonabant—The Intravascular Ultrasound Study) investigators presented data from an 18-month follow-up study of the effects of rimonabant in 839 patients with obesity and CAD (abstract 412-5). Inclusion criteria for this trial included an increased waist circumference (>102 cm male; >88 cm female), two additional metabolic syndrome defining risk factors or current smoking history, and the presence of angiographically confirmed CAD. The patients were randomized to receive 18 months of either rimonabant 20 mg daily (n=422) or placebo (n=417). The primary end-point was percent atheroma volume (PAV) as measured by IVUS.

At baseline the patients were evenly distributed between groups. The mean age was 58 years, 65% were male, 95% Caucasian, mean BMI 35 kg/m<sup>2</sup>. The majority of patients had co-morbid conditions and a high-risk cardiometabolic profile and was on multiple medications, but no differences were apparent between groups. On completion of the trial rimonabant proved more effective than placebo in reducing both body weight (mean change from baseline [95% CI] -4.3 [-5.1 to -3.5] vs. -0.5 [-1.3 to 0.3] kg) and waist circumference (-4.5 [-5.4 to -3.7] vs. -1.0 [-1.9 to -0.2] cm), and this was associated with a significant rise in HDL-cholesterol (5.8 [4.9 to 6.8] vs. 1.8 [0.9-2.7] mg/dl) and fall in triglycerides (-24.8 [-35.4 to -17.3] vs. -8.9 [-14.2 to -1.8] mg/dl) (~20% vs. 6%) in comparison to the placebo group (all  $p<0.001$ ). Significant changes in favor of rimonabant were also seen in HbA1c, fasting insulin, and hsCRP. However, despite this favorable effect on the cardiometabolic parameters, no significant difference

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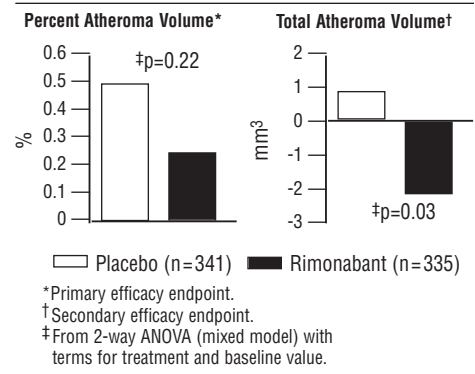
was seen between groups on the primary outcome measure of PAV (Figure 5). A significant difference was found in total atheroma volume, but this was only a secondary endpoint.

One of the other issues highlighted in earlier trials with this drug was the potential for adverse effects given that CB1 receptors are found in many brain areas not known to be involved in energy homeostasis. This also proved to be the case in STRADIVARIUS. While a significant percentage of the study cohort had baseline psychiatric co-morbidities, by the end of the trial 43% of the rimonabant group (vs. 28% of placebo) had a treatment-emergent psychiatric disorder (mostly

anxiety and depression). In addition, a significant proportion of patients on rimonabant experienced gastrointestinal side effects (34% vs. 18%) and erectile dysfunction (3 vs. 1%). No significant differences were found in the composite endpoint of CV death, non-fatal MI, non-fatal stroke, or hospitalization (10.4 vs. 11.0%;  $p=0.79$ ), although the study was not powered for these events.

So, although the investigational CB1 antagonists are effective weight loss agents, there appears to be no clear benefit—at least from rimonabant—on the progression of coronary atherosclerosis. Moreover, with persistent concerns surrounding these drugs' psychiatric effects, their future role in the treatment of obesity or metabolic syndrome remains uncertain.

**Figure 5. Mean Change from Baseline in Intravascular Ultrasound Endpoints: STRADIVARIUS**



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



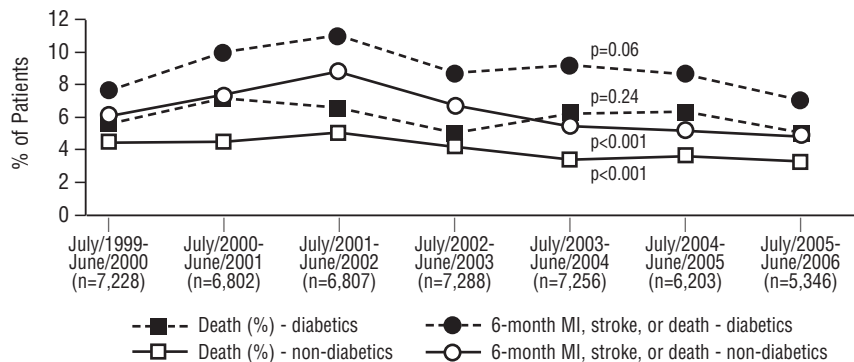
### ACS Outcomes in Diabetes

Improvements in the management of acute coronary syndrome (ACS) have led to short-term reductions in adverse CV events in non-diabetic (n=35,026), but not in diabetic patients (n=11,550). This was according to the results of a prospective, multicenter (n=113) international observational study conducted over a 7-year period (1999-2006) by the GRACE study investigators (abstract 1012-134). Diabetic patients with ACS appeared to be treated somewhat less aggressively than non-diabetic patients (i.e., lower rates of cardiac catheterization [62% vs. 68%, respectively] and PCI [36% vs. 46%]). Over the 7-year observation period, hospital mortality and the combined endpoint of myocardial infarction (MI), stroke, or death declined in non-diabetic patients with an ACS but remained unchanged in the diabetic cohort (Figure 6).

### Aspirin Therapy: A Reconsideration

Berwanger *et al.* from Brazil conducted a meta-analysis of 5 suitable randomized trials (n=5,594) to evaluate the effect of aspirin therapy in diabetic patients without atherosclerosis (abstract 1035-207). Despite the recommendation of daily aspirin intake in several diabetes management guidelines, including the 2008 Standards of Care from the American Diabetes Association, a statistically significant treatment effect was not observed from aspirin on the primary composite endpoint (CV mortality, nonfatal MI, and nonfatal stroke) (RR=0.93, 95% CI 0.82, 1.06), on any of the individual endpoints (CV mortality, RR=0.89; MI, RR=0.75; stroke, RR=1.15), or all-cause mortality (RR=0.94), confidence intervals for

**Figure 6. Inpatient Mortality and 6-Month Post-Discharge Endpoint Among Diabetic and Non-Diabetic Patients With Acute Coronary Syndrome**



which each included 1. The risk of major bleeding, however, was increased by 42%. This study challenges the widely-held impression that prophylactic aspirin therapy benefits our otherwise asymptomatic diabetic patients.

### Vagal Tone & CVD Mortality

Mortality rate following MI is higher in patients with vs. without diabetes. As cardiac autonomic neuropathy is a common finding in diabetic patients, Bauer and German coworkers conducted a study to evaluate the prognostic significance of post-infarction vagal activity on mortality (abstract 1029-115). Holter recordings were performed within the second week after infarction in 2,343 survivors of acute MI in normal sinus

rhythm, 412 of whom had diabetes. Tonic vagal activity (assessed by heart rate deceleration capacity;  $4.4 \pm 3.5$  vs.  $5.8 \pm 3.7$  in non-diabetic patients) and reflex vagal activity (assessed by heart rate turbulence slope;  $6.1 \pm 7.3$  vs.  $9.4 \pm 9.1$  ms/RR interval in non-diabetic patients) were impaired (each  $p < 0.0001$ ) in post-infarction patients who had diabetes. Each factor, if abnormal, was an independent predictor of 5-year mortality rate (i.e., 9.0% vs. 4.1% if normal). The combination of abnormal tonic and reflex vagal activity identified a subgroup of diabetic post-MI patients at extremely high risk for subsequent death (5-year rate=43.2%). These data add to a growing body of evidence that strongly indicates a relationship between cardiac autonomic neuropathy and adverse clinical outcomes.

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