

Diabetes 2009

From the 58th Annual Scientific Sessions of the
American College of Cardiology ■ Orlando, FL

2005 2006 2007 2008 **2009** 2010 2011

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

Volume **19** ■ April 1, 2009 ■ Issue **1**

Important data on diabetes presented at the 58th Annual Scientific Sessions of the American College of Cardiology come to you in **Diabetes 2009**, 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 2009** will be followed by a **Diabetes 2009** 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 AMA PRA Category 1 Credits™ to be issued by Yale University School of Medicine.

Diabetes 2009 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Describe the mechanisms of β-cell failure, the progression of diabetes, and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapies.
- Understand the interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Compare the mechanisms of action of diabetes therapies, their risks, benefits, and proper roles in disease management.
- Identify evolving and emerging therapeutic strategies in diabetes care.
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.

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

Yale University School of Medicine designates this continuing medical education activity for a maximum of 11 AMA PRA Category 1 Credits™ (5.5 credit hours per test). Physicians should only claim credit commensurate with the extent of their participation in the activity.

Supported in part through educational grants from Takeda Pharmaceuticals North America, Inc., Merck & Co., Inc., and Amylin Pharmaceuticals, Inc./Eli Lilly and Company. It is understood that supporters will in no way control the content of this program.



Silence is not Golden



In a symposium on Sunday, Dr J. Bax from the Netherlands discussed asymptomatic cardiac disease in diabetes. Dr. Bax reminded the audience that cardiovascular complications, including coronary artery disease (CAD), are the leading cause of morbidity and mortality in Type 2 diabetes; the 10-year mortality in those with CAD and diabetes exceeds 70%. Moreover, in patients with diabetes, CAD frequently progresses to an advanced state, including heart failure, before it becomes clinically manifest.

In addressing the issue of silent CAD, Dr. Bax presented some data from a recent study (*Heart* 2008;94:290) where multi-slice computed tomography (MSCT) was used to measure the coronary artery calcium burden (calcium scoring), an index of coronary atherosclerosis, and by performing non-invasive angiography. 80% (56/70) of the Type 2 diabetes patients were found to have some degree of CAD on the angio component of the test. In these 56, there were 322 coronary segments with plaque, of which 132 (41%) were non-calcified, 125 (39%) calcified, and 65 (20%) mixed. The percentage of patients with obstructive CAD was associated with increasing calcium score.

Dr. Bax then went on to state that significant CAD could be present without coronary calcium and illustrated this with a case history of a 43-year old male with diabetes. At initial assessment, this individual had no symptoms of CAD, a normal ECG, a left ventricular ejection fraction (LVEF) of 68%, and no evidence of coronary calcium on MSCT. One year later on re-evaluation, he remained asymptomatic, but now had an abnormal ECG, a LVEF that had reduced to 43%, and defects in ventricular wall motion at rest and following stress. An MRI confirmed he had suffered a silent MI at some point in the past year. Expanding on this further, Dr. Bax referred also to those asymptomatic diabetic patients with perfusion defects by nuclear stress testing. In the *Detection of Ischemia in Asymptomatic*

Diabetics (DIAD) study, investigators found that 22% of asymptomatic patients with Type 2 diabetes, age 50-75 years, had evidence of silent myocardial ischemia, with 16% showing abnormal perfusion on sestmibi single photon emission computed tomography (SPECT).

Finally, Dr. Bax briefly commented on the potential pathogenesis of cardiac failure in diabetes. Using data obtained from NMR-spectroscopy, his group observed that the triglyceride (TG) content of heart muscle was significantly increased in asymptomatic diabetic patients—so-called ‘cardiac steatosis’. Cardiac muscle TG correlates with diastolic dysfunction, and might be responsible for lipotoxic myocardial injury. They found that a 16-week very low calorie diet in diabetic patients reduced heart muscle TG content and improved diastolic function. Moreover, therapy with the thiazolidinedione (TZD) pioglitazone, but not metformin, was also found to reduce heart muscle TG content using this technique.

Dr. Bax concluded that much remains unknown about asymptomatic CAD in diabetes. It is clearly very prevalent and multi-factorial in etiology. These studies remind us how important it is to treat all patients with diabetes aggressively with risk factor reduction strategies. We would point out that many of the tools described by the speaker to investigate CAD in asymptomatic diabetic patients remain in large part investigational, until a clear advantage from invasive interventions over medical therapy is established. Indeed, at last year’s ADA Scientific Sessions (see *Diabetes 2008* 17:30), the 5-year follow-up of the DIAD cohort was announced, showing no definitive advantage in cardiovascular outcomes from routine CAD screening as compared to conventional follow-up alone. One of the conclusions from this study is that routine, but aggressive, control of CAD risk factors likely attenuates any benefit from early screening for silent heart disease.



How Low to Go? Which Road to Hoe?



Over the past year, a number of clinical trials have cast some doubt on the value of intensive anti-hyperglycemic therapy in patients with established diabetes. The DCCT, UKPDS, and DIGAMI trials all seemed to point to a new era of aggressive glucose lowering to minimize both micro- and macro-vascular complications. However, along came ACCORD, ADVANCE, and VADT, which appeared to indicate no overall cardiovascular (CV) benefit—and perhaps even some risk—from normalizing glucose in diabetic individuals. Given that a major target of these trials was CAD prevention, ether primary or secondary, it was no surprise to find a number of symposia at this week's ACC meeting reviewing this emerging literature. In addition, the relative benefits and risks of an increasingly complex array of anti-hyperglycemic medications (Table 1) for patients with Type 2 diabetes remains highly controversial.

The importance of glucose control in diabetic patients with cardiovascular disease (CVD) was the topic of a talk given by Dr. Darren McGuire,

on Monday evening. He reminded the audience of the rapidly increasing prevalence of diabetes and particularly Type 2 diabetes in the US, and the increased morbidity and mortality associated with this disease. Trials such as the DCCT in Type 1 diabetes and the UKPDS in Type 2 had convincingly shown that lowering average blood glucose levels significantly reduce both the incidence of new, and the progression of established, microvascular complications such as retinopathy and albuminuria. In contrast, the impact of glucose control on macrovascular disease was until recently uncertain. This is important because, as Dr. McGuire noted, CVD is the major cause of morbidity and mortality in diabetes. As an example, less than 10% of the Type 2 diabetic patients in the UKPDS developed any microvascular complication after 10 years of follow up, whereas >20% developed CAD and >25% developed any macrovascular disease. One of the problems faced in many of the current trials looking at the impact of glucose-lowering therapy on macrovascular disease in

diabetes is that they are of relatively short duration and are often not large enough to produce a sufficient number of end-points, especially in the context of modern risk factor reduction strategies. As such, the data is inconsistent and not strongly supportive of any specific aggressive glucose-lowering therapy or strategy in Type 2 diabetes. The main exceptions include the small metformin sub-study of the UKPDS, which showed a 39% reduction in MI in the more aggressively treated patients as compared to diet therapy, and PROactive, which revealed a trend toward benefit with pioglitazone therapy over placebo on a broad CVD composite (HR 0.90 [95% CI, 0.80-1.02; p=0.095]), when added to existing anti-hyperglycemic therapy.

In another session on Tuesday, Dr. William Cushman, Memphis, TN, highlighted these issues in his review of the ACCORD trial. The ACCORD trial is a multicenter US study of 10,251 patients with Type 2 diabetes at high risk of CAD. The mean age was 62 years, duration of diabetes ~10 years, BMI 32 kg/m², and baseline HbA1c 8.3%.

Table 1. Anti-Hyperglycemic Drugs in Type 2 Diabetes Mellitus

Agent	Mechanism of action	HbA1c Effect	Adverse Effects	CV Concerns
Sulfonylureas • Glyburide • Glipizide • Glimepiride	Stimulate insulin release	-1 to -2%	• hypoglycemia • weight gain	• Hypoglycemia may precipitate ischemia, arrhythmia • K _{ATP} channel closure may impair ischemic preconditioning
Meglitinides • Repaglinide • Nateglinide	Stimulate insulin release	-1 to -1.5%	• hypoglycemia • weight gain	• Hypoglycemia may precipitate ischemia, arrhythmia • K _{ATP} channel closure may impair ischemic preconditioning
Biguanides • Metformin	Decrease hepatic glucose production	-1 to -2%	• diarrhea, nausea • lactic acidosis • ↓ B12 levels	• May improve CVD outcomes (UKPDS) • Should not be used in acute or unstable HF due to lactic acidosis risk
α-Glucosidase Inhibitors • Acarbose • Miglitol	Slow GI carbohydrate absorption	-0.5%	• flatulence • GI distress	• Improves post-prandial glucose excursions, which are more tightly associated with CVD than fasting glucose • May reduce MI risk (STOP-NIDDM trial)
Thiazolidinediones • Rosiglitazone • Pioglitazone	Increase insulin sensitivity	-1 to -1.5%	• weight gain • edema • fractures in women	• Contraindicated in HF (due to fluid retention) • May precipitate clinical HF in predisposed individuals • Pioglitazone may reduce MI & stroke risk (PROactive trial) • Rosiglitazone may increase MI risk (several meta-analyses)
Incretin Modulators - GLP-1 Mimetics • Exenatide* - DPP-IV inhibitors • Sitagliptin	Augment insulin secretion, decrease glucagon secretion, delay gastric emptying, enhance satiety	-1%	• nausea, vomiting • ? pancreatitis	• Very preliminary data suggest possible benefit in patients with cardiomyopathy
Bile acid sequestrants • Colesevelam	Unknown	-0.5%	• constipation	• Added benefit on LDL cholesterol • May increase triglycerides
Amylinomimetics • Pramlintide*	Decrease glucagon secretion, delay gastric emptying, enhance satiety	-0.5%	• hypoglycemia (with insulin) • nausea/vomiting	—
Insulin*	Increases insulin supply	Limitless	• hypoglycemia • weight gain	• Retrospective data in HF suggests worse clinical outcomes in patients treated with insulin

CVD, cardiovascular disease; GLP-1, Glucagon-like peptide 1; HF, heart failure; MI, myocardial infarction. * injectable

How Low to Go? Which Road to Hoe?

Continued from page 2

In its original multifactorial design, the impact of intensive glucose control (HbA1c 7.0-7.9 vs. <6.0%), blood pressure control (systolic BP <140 vs. <120 mmHg), and lipid control (statin vs. statin + fibrate) were to be examined. The study's data safety monitoring board decided in early 2008, however, to discontinue the intensive glucose-control aspect of the trial, because of a 22% increase in total mortality risk, and a 35% increased risk of CVD mortality. Further analysis demonstrated that most subgroups showed a similar effect. Interestingly, however, those with the lowest HbA1c at entry and those with no prior CVD history did not. Given that three recent randomized intervention trials of tight glucose control (ACCORD achieving a mean HbA1c of 6.4%, ADVANCE 6.5%, and VADT 6.9%) have all failed to show clear benefits in terms of total and CVD-related mortality, Dr. Cushman concluded that in high-risk Type 2 diabetic patients it would be safer to target a HbA1c of 7.0-7.9%, until new data emerge. The full analysis of ACCORD, including the blood pressure and lipid sub-studies, is expected in 2010.

The next speaker in this symposium, Dr. McGuire from Texas, discussed which therapies might be most suitable for individuals with Type 2 diabetes. Dr. McGuire noted a previous analysis performed of the SYMPHONY (*Sibrafiban versus aspirin to Yield Maximum Protection from ischemic Heart events post-acute cOroNary sYndromes*) and 2nd SYMPHONY studies' datasets. These two large-scale, randomized, international trials have now been examined to further explore the rela-

tionship between glycemic control strategies and CV outcomes in patients with Type 2 diabetes. Of the 15,800 patients enrolled, 3,101 (19.6%) had diabetes. The diabetic cohort had higher 90-day unadjusted risk of the composites of death/myocardial infarction (MI)/severe recurrent ischemia (SRI), death/MI, and death alone, as well as a near doubling of 1-year mortality rates. Importantly, glucose-lowering therapy, which included only insulin and/or sulfonylurea (insulin-providing; n=1,473) was associated with higher 90-day death/MI/SRI compared with therapy that included only biguanide and/or TZD therapy (insulin-sensitizing; n=100) (12.0% vs 5.0%); (adjusted OR, 2.1 [1.2, 3.7]). Dr. McGuire commented that this was consistent with both the UKPDS-Metformin sub-study and PROactive and suggested that insulin-sensitizing therapy might be the most appropriate place to start in diabetes patients with CAD. However, it is important to note that this analysis of non-randomized data set was exploratory, and the insulin-sensitizing group was small. Clearly, further trials are needed to confirm the benefit of an insulin-sensitizer strategy for patients with diabetes and CAD. In this light, the BARI 2D trial is expected to announce its results later this year. Among other things, this study will be comparing outcomes in diabetic patients with CAD treated with two anti-hyperglycemic strategies, once focusing on insulin-provision and the other on insulin-sensitization.

A poster presentation explored one aspect of anti-hyperglycemic therapy for Type 2 diabetes, namely the effects of TZDs on CVD outcomes. Naderi and colleagues (abstract 1019-16), from Utah, reported on the effects of rosiglitazone and

pioglitazone therapy in 2,096 patients with Type 2 diabetes and CAD (stenosis >70%) enrolled in the Intermountain Heart registry (average age 63.7±11.4 years). Using Cox regression models, death and MI event rates were compared between patients discharged on rosiglitazone (n=209), pioglitazone (n=121), or other diabetic medications (n=1,766). Over 4.3±3.2 years, death occurred in 30.2% (rosiglitazone 17.7%, pioglitazone 16.5%, other 32.6%, p<0.0001) and MI in 16.3% (rosiglitazone 10.5%, pioglitazone 9.9%, other 17.4%, p=0.006) of the patients. After adjustments for baseline features, neither rosiglitazone (HR 0.78, p=0.15) nor pioglitazone (HR 0.85, p=0.48) was associated with an increased risk of death when compared to other anti-hyperglycemic medications. No beneficial effect of pioglitazone over rosiglitazone was seen in this study (death, HR=0.86, p=0.59; MI, HR=0.75, p=0.43). The investigators concluded that neither rosiglitazone nor pioglitazone was associated with an increase in the risk of CV events compared to other diabetic medications or compared to each other in patients with pre-existing CAD.

What we've learned over the past year is that a 'cookie-cutter' approach to glucose lowering, especially in older, high-risk patients, is likely not an optimal therapeutic strategy. Both glycemic targets and specific drug regimens must be individualized to optimize patient outcomes. The best regimens for various patient types will remain a fertile field of clinical investigation over the next few years. Until then, we must employ sound clinical judgement, taking into consideration the capacities and tolerances of each patient.



Sticky Platelets

The current recommendation from the American Diabetes Association (ADA) is to prescribe aspirin 75-162 mg/day as a primary prevention strategy in patients with Type 1 or 2 diabetes who are older than 40 years of age or have additional CV risk factors. Clopidrogel 75 mg/day is advised for those with documented aspirin allergy. Combination therapy is endorsed for up to a year after an acute coronary syndrome (*Diabetes Care*, 2009, Suppl 1). Evidence is mounting, however, that anti-platelet therapy may not be as effective in this disease as previously thought. For example, it is now well recognized that there is an increased tendency for platelet aggregation and thrombotic events in diabetes. This has led some investigators to question whether the ADA recommendations provide sufficient anti-platelet

effect for our patients, especially in the context of secondary CAD prevention strategies. A number of posters at the ACC conference in Orlando addressed this very issue.

In an interesting presentation, Dr. Singla and colleagues from Baltimore retrospectively examined platelet reactivity in 71 patients with established CAD undergoing elective stenting while taking daily aspirin (81 mg) and clopidrogel (75 mg) (abstract 1031-99). They were divided into diabetic (n=36; age 62±8.9 years) and non-diabetic groups (n=35; age 62±13.0 years). Platelet aggregation was measured by 'light transmittance aggregometry' (LTA), and thromboelastography (a measure of the quantitative and qualitative properties of a clot) was also performed. The investigators found no difference in thrombin-induced

platelet-fibrin clot strength between diabetic and non-diabetic patients (70.2±5.2 vs. 68±4.1, p=0.79). However, platelet reactivity was increased in the diabetic patients despite equivalent anti-platelet drug therapy. Furthermore, when the diabetic patients were divided on the basis of HbA1c into well-controlled (HbA1c <7%, n=16) and poorly-controlled (HbA1c >7%; n=20), the investigators also noted a significant effect of glycemic control (Figure 1).

Although the numbers are too small to draw firm conclusions, a significant correlation was also seen between 5- and 20µM ADP-induced percent aggregation and HbA1c (both correlation coefficients ~0.6, p<0.0001). These findings suggest that poorly controlled diabetic patients may have significantly higher on-treat-

Continued on page 4



Sticky Platelets

Continued from page 3

ment platelet reactivity than non-diabetic patients even while on dual anti-platelet therapy.

Platelet reactivity was measured by Italian investigators using the VerifyNow™ assay. This uses ADP to induce platelet activation. ADP activation of platelets is blocked at the P2Y12 ADP binding site by clopidogrel, and so this assay provides a measure of the degree of platelet function inhibited by clopidogrel. A level of ≥ 240 P2Y12 reaction units (PRU) after clopidogrel loading, indicating a low level of platelet inhibition, is associated with a significantly higher risk of peri-procedural MI in patients undergoing PCI. Mangiacapra and colleagues prospectively evaluated the influence of diabetes on residual platelet reactivity and peri-procedural outcomes after PCI in a cohort of 254 patients (n=96 [38%] with diabetes) (abstract 2505-659). They reported that diabetic patients had higher platelet reactivity (210 ± 82 vs. 190 ± 70 PRU; $p=0.04$). A PRU value ≥ 240 was also more frequently observed in diabetic than in non-

Table 2. Clinical Outcomes at 7 Days in Diabetic AMI Patients Undergoing PCI

Outcome	Dual Anti-platelet Therapy (n=1,220)	Triple Anti-platelet Therapy (n=854)	p-value
Total Death	69 (5.7%)	16 (1.9%)	<0.001
Re-infarction	3 (0.2%)	1 (0.1%)	0.6
Re-vascularization	12 (1.0%)	6 (0.7%)	0.5
Total MACE	84 (6.9%)	23 (2.7%)	<0.001
Major bleeding episodes	8 (0.7%)	4 (0.5%)	0.8

MACE=major adverse cardiovascular events.

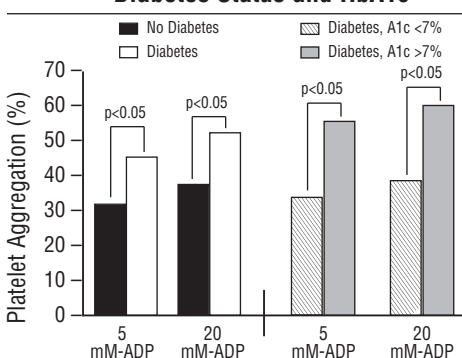
diabetic patients (34% vs. 21%; $p=0.017$). Among patients with diabetes, a PRU value ≥ 240 was associated with higher incidence of peri-procedural MI (15% vs. 2% in those with PRU <240; $p=0.017$), while this association was not observed in the non-diabetic group ($p=0.159$). The investigators concluded that diabetes is associated with an impaired platelet response to clopidogrel and poorer peri-procedural outcomes when undergoing PCI.

Both of these studies indicate that in diabetic patients more aggressive antithrombotic strategies may be needed to reduce complications in the setting of PCI, a topic addressed by Chen and colleagues as part of the Korean KAMIR investigators (abstract 2505-661). This group tested the hypothesis that triple antiplatelet therapy would be superior to a dual antiplatelet strategy in diabetic patients with AMI undergoing PCI with drug-eluting stents (DES). A total of 2,074 diabetic patients with AMI underwent PCI with DES and received either dual (aspirin + clopidogrel, n=1,220) or triple antiplatelet therapy (aspirin + clopidogrel + cilostazol, n=854). Bleeding

complications and clinical outcomes at 7 days, 1 month, and 8 months were compared between these groups, and total major adverse cardiac events (MACE) were recorded. The researchers reported significant improvements in both short (7-day and 1-month) and long-term (8-month) outcomes with triple therapy. Total mortality and MACE were reduced at 7 days following triple vs. dual therapy (Table 2). No differences were found between the incidence of myocardial re-infarction, revascularization, and major bleeding. They concluded that triple antiplatelet therapy appears to be superior to the more conventional dual antiplatelet approach in reducing early mortality and MACE, without increasing major bleeding in diabetic AMI patients undergoing PCI with DES. This approach warrants further study in different patient populations.

Along with the recent POPADAD study, which called into question the utility of routine anti-platelet prophylaxis in diabetes (Belch *et al. BMJ* 2008;337:1840), this week's investigations suggest that a more aggressive stance against the hyperactive platelet in diabetes may be warranted.

Figure 1. Platelet Aggregation (%) by Diabetes Status and HbA1c



Hospital Hyperglycemia

There were several presentations made this week at the ACC Scientific Sessions that further our understanding of the link between glucose, diabetes, and heart disease.

Glucose & Post-MI Mortality

Goyal and North American collaborators combined the data from 2 large glucose-insulin-potassium (GIK) trials in patients with ST-segment elevation MI (STEMI) (CREATE-ECLA and OASIS-6) and presented their findings on clinical outcomes associated with in-hospital glucose abnormalities (abstract 405-7). Admission and post-admission glucose values were recorded in 30,297 and 25,513 patients, respectively. The investigators

constructed adjusted Cox models to compare the prognostic value of hypoglycemia (defined as glucose ≤ 70 mg/dl) and hyperglycemia (≥ 140 mg/dl), as compared to normoglycemia, at and following admission, on 30-day mortality. Across the study patients, admission hyperglycemia (HR 1.43, 95% CI 1.32-1.56) and post-admission hyperglycemia (HR 1.47, 1.31-1.66) predicted 30-day death. The association appeared to be greater in non-diabetic as opposed to diabetic patients. There was no association, however, between hypoglycemia, either at (HR 1.16, 0.84-1.62) or after (HR 0.96, 0.72-1.26) admission and mortality. These findings lie in some contrast to data from other groups, which have found an association of *both* inpatient hyperglycemia and hypoglycemia and adverse

outcomes following AMI. It bears mentioning that insulin was not dosed to specifically decrease glucose levels in the GIK studies.

Glucose & Post-Cath Renal Injury

Block and US colleagues evaluated the risk of acute kidney injury (AKI) following coronary angiography, with or without intervention (catheterization \pm PCI), as a function of pre-procedural blood glucose levels in 6,358 patients hospitalized for AMI (abstract 1028-07). Acute kidney injury was defined as ≥ 0.3 mg/dl absolute or $\geq 50\%$ relative serum creatinine increase during the 48 hours post-procedure. The investigators found a clear association ($p<0.001$) between hyper-



Continued on page 5

Hospital Hyperglycemia

Continued from page 4

glycemia and risk of contrast-induced AKI: 9.8%, 11.0%, 13.6%, 14.8%, and 20.5% in patients with a pre-procedure blood glucose level of <110, 110-<140, 140-<170, 170-<200, and ≥200 mg/dl, respectively. Interestingly, these investigators found the nature of this relationship to be very different in patients with diabetes vs. without diabetes. In logistic regression models, after adjustments for multiple, potentially confounding variables (including baseline GFR), higher blood glucose was associated with a steep post-procedural

Table 3. Risk (OR) of Contrast-Induced Acute Kidney Injury by Diabetes Status

Blood Glucose (mg/dl)	No Diabetes	Diabetes
110- <140	1.27	0.71
140 - <170	1.50	0.82
170 - <200	1.56	0.73
≥200	2.35	0.94

Reference is blood glucose <110 mg/dl.

increase in AKI among the patients without, but not in those with, diabetes (Table 3). In contrast,

while patients with diabetes did experience high rates of AKI, pre-procedural blood glucose did not provide additional information in predicting this risk. The investigators recommended that further study is needed to determine whether hyperglycemia might be a treatable mediator, and not just a marker, of post-contrast AKI.

There obviously continues to be intense interest in the relationship between hyperglycemia and adverse outcomes in the setting of AMI. The issue of hospital management of hyperglycemia has recently become highly controversial since last week's publication of the NICE-SUGAR trial results (*N Engl J Med* 2009;360:1283.)



A Pooped Pump



Approximately 1-4% of the population, depending on age, has heart failure (HF), whereas this proportion is increased to ~12% in diabetes, rising impressively to 22% in diabetic patients >64 years of age (*Diabetes Care* 2005;28:612). This is perhaps not surprising, given that the two major risk factors for HF are CAD and hypertension, both of which are themselves more widely prevalent in diabetes. HF in a diabetic patient is associated with a markedly worsened prognosis. For example, diabetic patients in the DIABHYCAR (*type 2 DIABetes Hypertension Cardiovascular events And Ramipril study*) study with incident HF had a 12-fold increase in annual mortality over those patients who did not develop HF (*Diabetes Care* 2003;26:855).

The increased mortality in this population was further illustrated in a poster presentation by Kamalesh and French colleagues who performed a meta-analysis of observational and randomized trials reporting on HF and mortality in diabetes since 2001 (abstract 1037-02). The investigators only included studies with a minimum follow-up of at least 6 months, and outcome measures extracted from published results. They included data from 15 trials involving 30,197 eligible patients. A total of 8,260 deaths occurred in this cohort, 2,351 in the diabetic population. The relative risk (RR) of death was increased by 28% (95% CI 1.22-1.34; $p < 0.0001$) in those with diabetes. Similarly, their pooled RR for hospitalization was also significantly higher by 36% (95% CI 1.26-1.48; $p < 0.0001$).

The diagnosis of diabetes is based on the glucose level at which the risk of microvascular complications begins to increase significantly. The increased risk of macrovascular disease, however, appears to evolve earlier, in the pre-diabetic stage, and may show a more linear relationship to fasting glucose. Exploring this further in an elderly

Table 4. Measures of Glycemic Status at Baseline and Incident Heart Failure Risk (n=2,386)

Variable	Mean ± SD	Cox Model*	
		HR (95% CI)	p-value
Fasting glucose, mg/dl	96 ± 18	1.19 (1.04-1.35)	0.009
HbA1c, %	6.1 ± 0.7	1.19 (1.03-1.38)	0.002
2-hour OGTT glucose, mg/dl	133 ± 53	1.15 (0.97-1.36)	0.11
Fasting insulin, μIU/dl	8.2 ± 5.5	0.92 (0.77-1.10)	0.36
Insulin resistance, HOMA-IR units	2.0 ± 1.6	0.99 (0.84-1.17)	0.92
β-cell function, HOMA-β units	1.0 ± 0.6	0.85 (0.72-1.03)	0.09

*Adjusted for age, history of coronary artery disease and smoking, systolic blood pressure and heart rate, left ventricular hypertrophy on ECG, and creatinine and albumin levels. Hazard ratio (HR) was calculated per standard deviation (SD) of increase.

population, Kalogeropoulos and colleagues, Atlanta, GA, studied 2,386 elderly participants without established diabetes who were enrolled in the Health ABC Study (median age 73 years, 47.6% men, 62.5% white, 37.5% black) (abstract 1028-13). They evaluated, using Cox models, the association of incident HF (defined as hospitalization for new-onset HF) with measures of glycemic status at baseline, including fasting glucose, oral glucose tolerance testing (OGTT), fasting insulin, HbA1c, and homeostasis model assessment (HOMA) of insulin resistance and insulin secretion. The results are shown in Table 4.

The investigators reported that fasting glucose was the strongest predictor of incident HF when adjusted for variables such as age and history of CAD. Results were similar across races and genders. The adjusted HR per 10 mg/dl increase in fasting glucose was 1.10 (95% CI, 1.02-1.18), a highly significant increase ($p < 0.001$). In elderly subjects, the development of HF is therefore strongly linked to hyperglycemia, even into the non-diabetic range.

The limitations of a commonly used test in diabetic patients with HF were illustrated by data presented by Shah and colleagues, Boston, MA (abstract 1051-179). This group reported on results from a cardiac echo sub-study of VALIANT (*Valsartan in Acute Myocardial Infarction Trial*) that enrolled 603 post-MI patients with left ventricular systolic dysfunction or HF. Baseline parameters of left ventricular deformation (strain and strain rate) among diabetics (n=138) and non-diabetics with preserved (EF ≥40%, n=299; mean EF 43.9%) and reduced (EF <40%, n=304; mean EF 34.7%) systolic function were analyzed. Patients were then followed for a mean of 24.7 months. Left ventricular strain and strain rate are believed to be measures of the actual pumping work of the heart, reflecting both the amount of blood ejected from the ventricle and the rate at which it is ejected. A number of studies have shown that reduced left ventricular strain predicts HF in non-diabetic patients with CAD. The investigators found that among patients with EF ≥40%, diabetic patients had a more than 2-fold greater risk of death or HF

Continued on page 6

A Pooped Pump

Continued from page 5

hospitalization compared to non-diabetic individuals (33.8% vs. 14.7%, adjusted OR 2.91, 95% CI 1.31-6.46). They also noted that those with diabetes and an EF $\geq 40\%$ showed significantly

lower global left ventricular strain compared to non-diabetics, indicating that their left ventricular function was far from normal. The investigators concluded that diabetes was associated with a higher rate of death and hospitalization post-MI, even with left ventricular EF $>40\%$. They postu-

lated that altered cardiac strain may partly account for this finding.

These abstracts underscore the significant burden and diagnostic challenges of heart failure in the diabetic and pre-diabetic populations.



Debates in Lipidology



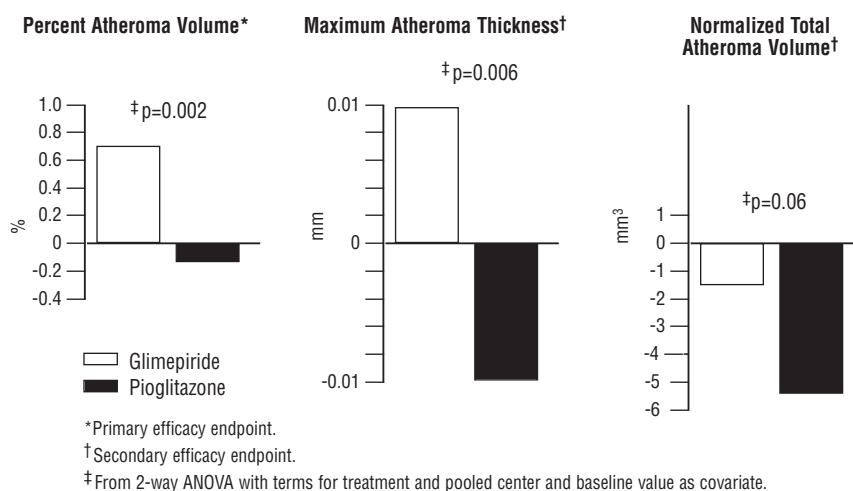
A symposium entitled, "Great Debates in Prevention" was conducted at this week's sessions. Treatments to increase HDL-cholesterol were reviewed by Dr. Steve Nissen from Cleveland, OH, and the role of maximizing statins for LDL-cholesterol reduction was discussed by Dr. Antonio Goto from New York City. Dr. Michael Davidson of Chicago, IL, then addressed combination therapy to reduce LDL.

HDL, the smallest of the lipoproteins, serves to enhance 'reverse cholesterol transport', thereby removing cholesterol from atheromata for ultimate metabolism in the liver. The inverse relationship between HDL-cholesterol (C) levels and coronary heart disease (CHD) risk has been long appreciated. Yet, HDL-C remains an elusive therapeutic target in cardiovascular medicine.

Dr. Nissen began the session by reviewing several agents that increase HDL-C levels, including niacin, statins, PPAR-agonists, and several investigational agents. Over 3 decades ago, in the Coronary Drug Project, niacin was reported to decrease the risk of coronary events by 16%, as compared to placebo. In ARBITER II (*ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol*), niacin ER 1000 mg once daily significantly increased HDL-cholesterol (21%, $p < 0.001$) while slowing atherosclerotic progression by 68%, as measured by carotid intimal-medial thickness (CIMT), an ultrasound CV risk surrogate, at 12 months vs. placebo ($p = 0.08$) (Taylor *et al.*, *Circulation* 2004;110:3512). Notably, niacin has additional benefits on LDL-C and triglyceride levels as well. Recently, clinical trials have also confirmed the lipid benefits of combined niacin ER and laropiprant, an investigational prostaglandin inhibitor that reduces flushing—the most common complaint from patients using niacin compounds. This combination, if FDA approved, may broaden both the tolerance for and the appeal of niacin therapy in dyslipidemic patients. We would add that niacin therapy may worsen insulin resistance, which may limit its use in at least some patients with Type 2 diabetes. Moreover, we are not aware of any study examining the effects of niacin on long-term clinical CV events in diabetic patients.

Statins, often considered to be primarily

Figure 2. Mean Change from Baseline in Intravascular Ultrasound Endpoints: PERISCOPE



directed at LDL-C, also raise HDL-C, although to a much lesser degree than niacin (3-15%). For example, Nicholls *et al.* conducted post-hoc analyses of 4 studies of patients with CAD who underwent serial intracoronary vascular ultrasound (IVUS) while receiving statin therapy for 18-24 months (*JAMA* 2007;297:499). The investigators determined that both increasing HDL-C and lowering LDL-C were independent predictors of disease regression (percent atheroma volume [PAV]). In ASTEROID (*A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden*), 507 CHD patients were treated with rosuvastatin 40 mg/day for 24 months. Their mean LDL-C levels were reduced by 53% (to 61 mg/dl), accompanied by a significant mean increase of 14% (to 48 mg/dl) in HDL-C; these changes were associated with regression of atherosclerosis (i.e., decreased percent diameter stenosis and improved minimum lumen diameter). Statistically, it was determined that ~60% of the disease regression appeared to be driven by changes in HDL-C (Ballantyne *et al.*, *Circulation* 2008;117:2458).

Dr. Nissen next mentioned the TZDs, or PPAR- γ agonists, specifically, pioglitazone, currently used as antihyperglycemic agents in Type 2 diabetes (T2DM). In the PERISCOPE (*Pioglitazone*

Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) study, 543 high-risk patients with established CAD and T2DM were randomized to 18 months of daily treatment with glimepiride or pioglitazone (Nissen *et al.*, *JAMA* 2008;299:1561). Atherosclerotic progression was measured by IVUS in 360 patients at baseline and study completion. Pioglitazone significantly increased HDL from baseline, as compared to the sulfonylurea (16% vs. 4% with glimepiride group; $p < 0.001$). There was also a significant (-0.73 mm³) decrease in PAV with pioglitazone (Figure 2), although it was unclear if this change was driven by the lipid changes or by other pleiotropic effects of the TZD (insulin sensitization, CRP reduction, etc.)

Several investigational agents were then discussed. HDL and HDL-mimetic infusions have led to rapid regression of aortic lesions in rabbits, prompting experiments in humans. In one such study, Nissen's group observed significant regression of atherosclerosis (-15.1 mm³ total atheroma volume) after administration of a synthetic HDL mimetic for 5 weeks to 57 patients with a history of acute coronary syndrome (ACS) (*JAMA* 2003; 290:2292). While this study's findings appeared prematurely in a provocative NY Times article

Continued on page 7

Debates in Lipidology

Continued from page 6

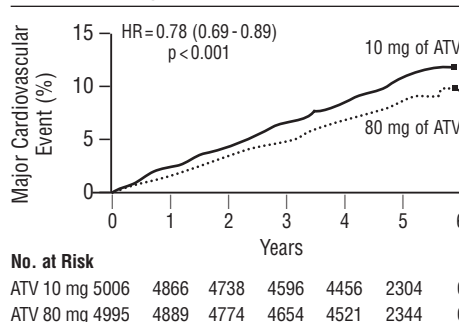
entitled “Drano for the Heart”, it has added to our understanding of the effects of modifying HDL metabolism on coronary atherosclerosis.

The combination of torcetrapib, a cholesterol ester transfer protein (CETP) inhibitor, with atorvastatin was found to significantly increase HDL-C, as compared with the statin alone in RADIANCE I (*Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor*) (Kastelein *et al.*, *N Engl J Med* 2007;356:1620). Surprisingly, however, there was no further reduction in atherosclerosis progression (as assessed by CIMT), and an actual increase in CV events was observed with torcetrapib. These findings may have subsequently been explained when increased blood pressure was noted in the active therapy group, an effect now ascribed to the CETP inhibitor’s aldosterone-like properties. In post-hoc analyses, Nicholls *et al.* determined that atheroma regression actually did occur among patients in the lowest quartile of baseline HDL-C, in whom, it was conjectured, that increased HDL overcame the drugs’ effect on blood pressure (*Circulation* 2008;118:2506). Other CETP inhibitors (dalcetrapid, anacetrapid) are under investigation, but the future of this drug class remains uncertain.

The next speaker, Dr. Gotto, began his presentation by highlighting the direct relationship between LDL-C level and CHD risk. He then summarized results from the PROVE-IT and TNT studies in which intensive LDL-reduction led to more favorable clinical outcomes vs. standard therapy. In PROVE-IT (*Pravastatin or Atorvastatin Evaluation and Infection Therapy*), the effects of standard (pravastatin 40 mg) and intensive (atorvastatin 80 mg) statin therapy were compared in patients treated in the early post-ACS period (Ahmed *et al.*, *Eur Heart J* 2006;27:2323). The investigators compared outcomes between patients with diabetes (n=978) to those without diabetes (n=3,184). The rate of acute cardiac events (death, MI, and unstable angina requiring rehospitalization) was significantly reduced with intensive therapy—to a similar degree in diabetic (21.1 vs. 26.6%, HR=0.75, p=0.03) and non-diabetic patients (14.0 vs. 18.0%, HR=0.76, p=0.002).

TNT (*Treat to New Targets*) was a multicenter, prospective, randomized study comparing the effects of aggressive lowering of LDL-C with 80 mg vs. 10 mg of atorvastatin in ~10,000 patients with clinically evident CHD and LDL-C levels <130 mg/dl (LaRosa *et al.*, *N Engl J Med* 2005;352:1452). The higher statin dose, which achieved an LDL-C level of ~75 mg/dl, was associated with a 22% relative risk reduction in the

Figure 3. Cumulative Incidence of a First Major Cardiovascular Event



HR denotes hazard ratio for the group given atorvastatin (ATV) 80 mg as compared with the group given ATV 10 mg.

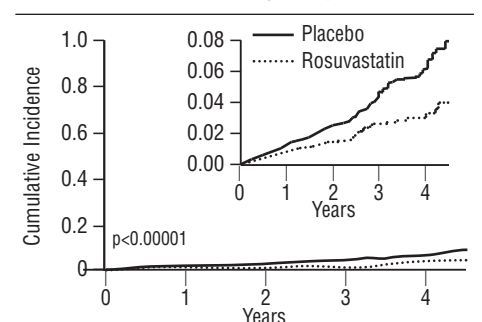
Source: LaRosa *et al.* *NEJM* 2005;352:1452.

primary composite CV endpoint (HR, 0.78; p<0.001; Figure 3). This study, in combination with PROVE-IT, were important in driving down the national LDL treatment targets in very high-risk patients with pre-existing CAD.

In the more recent JUPITER (*Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin*), therapy with an even more potent statin was evaluated in a large, double-blind, multinational study of 17,802 apparently healthy individuals (≥50 years of age for men; ≥60 years of age for women). Each had low or normal LDL-C levels (<130 mg/dl), but elevated levels of the inflammation marker, C-reactive protein (hsCRP ≥2 mg/l). They were randomized to rosuvastatin 20 mg/day or placebo (Ridker *et al.*, *N Engl J Med* 2008;359:2195). This study design was based on the observations that CV risk reduction from statins appears to be greater than that predicted by LDL-lowering alone and highest in those patients with elevated CRP levels. At 12 months, median LDL-C and CRP levels were, respectively, 50% and 37% lower in the statin group, as compared to placebo. The study was stopped after only 1.9 (of the 5 intended) years of follow-up, when the study’s Data and Safety Monitoring Committee noted a significant treatment effect for the primary endpoint of occurrence of first CV event (hazard ratio for rosuvastatin, 0.56) (Figure 4). Statistically significant reductions in all secondary endpoints were also observed.

In the final presentation of the session, Dr. Davidson commented that while the use of a statin at maximum tolerated doses provides the general foundation for LDL-lowering, there remain patients who simply cannot achieve a target with a statin alone. With the newer LDL-C goals now at <70 mg/dl for some patients, this issue has become even more prominent. In addition, some individuals cannot tolerate the statin dose that is necessary to

Figure 4. Cumulative Incidence of the Primary Endpoint



Primary endpoint: non-fatal MI, non-fatal stroke, arterial revascularization procedure, hospitalization for unstable angina, or death from confirmed cardiovascular causes.

Source: Ridker *et al.*, *NEJM* 2008;359:2202.

achieve full benefit. In this case, many clinicians combined the statin with other drugs, including ezetimibe, a cholesterol absorption inhibitor; niacin; or, rarely, a bile acid sequestrant, such as colestevlam. The statin-ezetimibe combination had become extremely popular until publication of the ENHANCE trial (Kastelein *et al.*, *N Engl J Med* 2008;358:1431), which rendered this undertaking somewhat controversial. ENHANCE (*Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression trial*) was a 2-year, double-blind, randomized multicenter trial of daily therapy with simvastatin 80 mg combined with either placebo or ezetimibe 10 mg in 720 patients with familial hypercholesterolemia. The investigators found that 2 years of therapy with simvastatin/ezetimibe was more effective than the statin alone in improving LDL-C (e.g., -56% in the combination group vs. -39% in the simvastatin alone group; p<0.01), yet there was no between-groups difference in the primary outcome measure, mean change from baseline CIMT. These findings called into question the value of this specific combination to reduce CV events, although several concerns about the study’s methodology have been raised. A much-needed outcomes study is currently underway to assess the effect of this approach on actual clinical outcomes.

In concluding comments, Dr. Davidson reminded the audience that statins have a high compliance drop-off rate, based in part on perceived side effects. So, while he agreed that statins should be initiated and titrated to the highest tolerated dose, additional therapy may need to be considered at some point in a substantial percentage of patients to achieve modern targets.



So Many Posters, So Little Time....



NHANES Update

Using the National Health and Nutrition Examination Survey (NHANES) database (1996-2006), Sumner *et al.* from Allentown, PA, determined the prevalence of metabolic syndrome (by ATP III criteria) and its components in 41,474 participants, 18 years of age and older, with no prior CVD history (abstract 1048-85). The prevalence of the metabolic syndrome among these asymptomatic adults was 16.6%, and remained stable for the total population over the 4 survey periods over 10 years. However, the prevalence increased with age: 4.9% in young adults (age 18-29 years) and 26.7% in older adults (age >70 years). There was also a difference by age in the prevalence of metabolic syndrome component risk factors (Table 5). Compared to the elderly, young adults had lower HDL-C, less glucose intolerance, and less hypertension, a finding that has important implications in the clinical management of these patients.

Casual Cluster or Solemn Syndrome?

Panagiotakos and Greek collaborators conducted the ATTICA study to determine whether the metabolic syndrome as a cluster of risk factors had any additional value in predicting future CVD events. The investigators enrolled 1,514 men and 1,528 women (>18 years of age) without any clinical evidence of CVD into the study (abstract 1028-09). Baseline prevalence of the metabolic syndrome, according to the NCEP ATP III definition (2005), was 25% in male patients and 15% in female patients. After adjusting for age, sex, physical activity, smoking, and dietary habits, presence of the metabolic syndrome was associated with 2.1-times higher risk of developing a CVD event during the 5-year follow-up period (95% CI 1.44-3.04). The explanatory ability in predicting 5-year CVD events was very similar, however, between the metabolic syndrome (23.8%) and the individual components of the syndrome (24.7%)

New-Onset DM and Stroke

Another study from Greece, led by Tsiachris, involved 1,446 non-diabetic, hypertensive patients (mean age 54.2 years, BMI 28.4 kg/m², blood pressure 146/93 mmHg, duration of hypertension 6.1 years) over a 6-year period to determine the incidence of new-onset diabetes (defined as fasting

Table 5. Prevalence of Metabolic Syndrome Components by Age

Age (yr)	Hypertension	Low HDL-cholesterol	High Triglycerides	Obesity	Glucose Intolerance
18-29	53.9%	93.5%	83.5%	92.2%	15.5%
>70	87.2%	59.7%	81.8%	92.7%	62.7%
p-value	0.001	0.001	0.329	0.057	0.001

plasma glucose ≥ 126 mg/dl) and its effect on major cardiovascular events (MACE) (abstract 1039-68). The incidence of new-onset diabetes was 11.5%, CAD 7.3%, and stroke 6.2%. The independent predictors for new-onset diabetes were, understandably, plasma glucose (OR 1.033, $p < 0.001$), but also waist circumference (OR 1.035, $p < 0.001$), family history of diabetes (OR 2.189, $p = 0.001$), and baseline use of beta-blockers (OR 1.626, $p = 0.046$). Hypertensive subjects with new-onset diabetes had a higher incidence of stroke, especially ischemic stroke, but, interestingly, not CAD, as compared to those who did not develop diabetes (Table 6). These findings suggest a synergistic effect between blood pressure and recent diabetes on cerebrovascular events.

Table 6. Incidence of Stroke and CAD in Hypertensive Patients by Diabetes Status

	New-Onset Diabetes	No Diabetes	p-value
Stroke	10.2%	4.4%	0.001
Ischemic stroke	7.2%	1.6%	<0.001
CAD	6.6%	5.2%	0.46

The BARI-2D Cohort: A Global Glimpse

Taylor and other investigators from the multicenter, international Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study examined the geographic distribution and prevalence of traditional CV risk factors in the 2,321 diabetics with angiographically documented, stable CAD enrolled in the trial (abstract 1039-82). Mean age at enrollment was 62 ± 9 years, with diabetes duration of 10 years; 70% were male; mean HbA1C 7.8%; and an average of 6.6 medications were being taken for achieving treatment goals. The majority (>90%) of study participants were

overweight/obese, with the greatest proportion of obese men (61%) and women (72%) from the US, and the lowest proportion from Mexico City (16% and 14%, respectively; $p < 0.0001$). Smoking varied significantly by region with fewer current smokers in Sao Paolo (7%) as compared with the US (13%, $p = 0.005$) and Europe (19%, $p = 0.006$). Sedentary lifestyle was more common among patients enrolled in Mexico City (65%) relative to Sao Paolo (32%), US (19%), Canada (18%), and Europe (4%). Over half (53%) of all patients had a blood pressure >130/80 mmHg, with the highest mean systolic blood pressure in Sao Paolo (141 mmHg) and the lowest in Mexico City (119 mmHg, $p < 0.0001$). Similarly, mean LDL-C varied by region with the lowest values in Canada (94 mg/dl) and highest in Sao Paolo (113 mg/dl, $p < 0.0001$). In summary, despite an average of ~7 medications for achieving treatment goals in diabetes patients with CAD, the co-existence of sub-optimally controlled CAD risk factors was generally high, with important differences among geographic regions. These data suggest the need for global strategies to assist patients in achieving their treatment targets.

Mais oui!

In a prospective, observational study, Sicard and colleagues from Burgundy, France assessed the impact of moderate wine consumption on post-MI glycemia, a determinant of prognosis, in 210 consecutive patients with diabetes (abstract 1031-116). At 1-year follow-up, almost half (48%) of patients reported moderate wine consumption (1-3 glasses/day). Mean HbA1c was lower in the moderate wine drinkers, as compared to non-drinkers and high-drinkers combined (6.8% vs. 7.3%, respectively; $p = 0.021$). In multivariate analyses, insulin therapy (OR 0.22, 95% CI 0.07-0.67) and moderate wine intake (OR 0.37, 0.13-0.87) were independently associated with lower HbA1c.