Important data on diabetes presented at the 2010 Scientific Sessions of the American Heart Association come to you in Diabetes 2010, 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 2010 will be followed by a Diabetes 2010 booklet (EASD and AHA 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 2010 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 Amylin Pharmaceuticals, Inc. and Lilly USA, LLC, Bayer Healthcare Diabetes Care; Boehringer Ingelheim Pharmaceuticals, Inc., Medtronic MiniMed, Inc. d/b/a Medtronic Diabetes, Merck & Co., Inc., Novo-Nordisk Inc., and Takeda Pharmaceuticals of North America, Inc. It is understood that supporters will in no way control the content of this program.

Owing to recent controversies regarding the impact of antihyperglycemic agents on cardiac risk, substantial interest was demonstrated at this week’s Scientific Sessions on the cardiovascular (CV) effect of both established and emerging diabetes medications.

In a well-attended symposium on Monday afternoon, diabetes experts from around the world convened to discuss Glucose Lowering: Is It Safe for the Heart? Dr. Hertz Gerstein from McMaster University in Canada first addressed the question, “Insulin: Cardiovascular Friend or Foe?” Dr. Gerstein defined Type 2 diabetes as a disease of insulin deficiency, irrespective of earlier pathophysiological defects, such as insulin resistance. He presented data from the UKPDS follow-up study, which revealed a 15% reduction in myocardial infarction (MI) in the group of patients initially randomized to more intensive therapy with sulfonylureas or insulin. This was despite nearly equal HbA1c levels between the two groups during most of the post-randomized study follow-up period. He then presented the results from a meta-analysis that incorporated data from the largest diabetes/CV clinical trials focusing on overall glycemic targets (UKPDS, ACCORD, ADVANCE, and VADT), not any specific drug regimen. This study found a 9% relative risk reduction in major CV events and a 15% reduction in MI as compared to the standard therapy arms of the trials. No overall benefit on all-cause mortality was demonstrated, and in one study, ACCORD, the hazard ratio (HR) for mortality was actually increased (1.22) in the intensive group. Dr. Gerstein next listed the benefits (universal effectiveness, titratable, no recognized drug toxicities, and extensive experience dating back nearly 9 decades) and risks (hypoglycemia, weight gain, new concerns about cancer) of insulin. He concluded his comments by reviewing the design of the ORIGIN trial, now underway. In this clinical trial, persons with pre-diabetes or early Type 2 diabetes at high CV risk are being randomized to a single injection of glargine insulin vs. no insulin, with a variety of outcomes being tracked, including CV endpoints.

Dr. Rury Holman from Oxford, England next tackled “Metformin and Sulfonylureas: Good or Bad for CVD Risk?” First, the benefits of metformin were extolled. Dr. Holman reviewed the CV effects of metformin from the UKPDS, a study for which he served as principal investigator. 753 overweight patients were randomized to metformin (342) vs. conventional diet therapy (411). Over a 10-year median follow-up, with an average HbA1c difference of just 0.6%, the metformin group experienced a relative 39% reduction in MI (p=0.01) and a 36% reduction in all-cause mortality (p=0.01) vs. standard (diet) therapy. In the non-randomized follow-up to this landmark study, benefits persisted with the HR for MI being 0.67 (p=0.005) after nearly 20 years. Dr. Holman also observed that even in a group of patients in whom it was previously felt that metformin was contraindicated, namely those with heart failure, a mortality benefit has been suggested by several observational studies.

In shifting his discussion to sulfonylureas, Dr. Holman remarked that these older agents appear to be neutral with regard to CV outcomes. Their relative safety has been confirmed in the UKPDS as well as the ADVANCE trials. He did note that in a substudy within the UKPDS, the addition of metformin to failing sulfonylurea therapy was associated with a 96% relative increase in diabetes related deaths (p=0.039) and a 60% increase in all-cause mortality (p=0.041) vs. continued sulfonylurea monotherapy. Dr. Holman suggested that these were chance findings, since the expected mortality in the sulfonylurea group was predicted to be nearly two-fold higher than that observed. The Oxford group is now coordinating a large metformin CV trial in prediabetic patients.

Dr. Curt Furberg from Wake Forest University next took the stage to discuss the safety of thiazolidinediones (TZDs). He reviewed the history of this controversial drug class, beginning in 1997 with the approval of the ill-fated troglitazone. The currently available drugs of this class, pioglitazone and rosiglitazone, were associated with an increased risk of edema and heart failure soon after they became available. Observational studies suggest that the risk of heart failure may be greater with...
Cardiovascular Impact of Diabetes Therapies
Continued from page 1

The latter compound. A now famous meta-analysis of rosiglitazone clinical trials (n = 42) was published by Cleveland Clinic investigators in 2007, reporting a relative 43% increase in MI events in patients randomized to the drug vs. placebo or other diabetic agent. This finding was later supported by a separate meta-analysis conducted by the Wake Forest group. Very recently, rosiglitazone was removed from the market in Europe and now has significant restrictions in the US. Such a CV risk has not been ascribed to pioglitazone, however. (Indeed, a pioglitazone meta-analysis and a secondary outcome from a large randomized clinical trial [PROActive] actually suggested a potential CV protective effect.) Nonetheless, Dr. Furberg felt that a cloud has been cast over the entire drug class. He suggested that the TZD experience should encourage drug regulatory authorities to be more selective in the drugs they approve and to shy away from approval based on surrogate endpoints, such as inflammatory markers, markers of insulin resistance, etc.

Dr. Silvio Inzucchi from Yale next presented on “New Kids on the Block: DPP-4 Inhibitors and GLP-1 Analogs.” The relative lack of clinical trial data on CV endpoints with these relatively newer incretin-based therapies was acknowledged. The speaker reviewed incretin physiology and the metabolic effects of these related drug classes. The injectable GLP-1 receptor agonists have been associated with improvement in several CV risk factors, including (in addition to glucose) weight, blood pressure, and lipids. Moreover, preliminary data from both animal models and small human trials have suggested a potential direct effect on cardiac tissue (reduction in infarct size, improvement in left ventricular function). The oral DPP-4 inhibitors, which raise endogenous GLP-1 levels, are weight neutral and, to date, appear to be generally well tolerated. The ultimate effects on CV outcomes from incretin-based therapies is completely unknown however. To address this knowledge void, several large clinical trials, such as TECOS (sitagliptin) and LEADER (liraglutide), are now underway, as recently encouraged by the US Food & Drug Administration (FDA).

Previously, the ADA and the AHA jointly recommended that diabetes patients at increased cardiovascular disease (CVD) risk take daily aspirin (75-162 mg) for primary prevention. Recently, however, questions about efficacy were raised from two randomized, controlled clinical trials—the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial (RR, 95% CI for CVD events in aspirin treated subjects = 0.87, 0.40-1.87) and the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial (1.09, 0.82-1.44). The ADA, AHA, and the American

Aspirin as Primary Prevention

Continued on page 3
Aspirin as Primary Prevention
Continued from page 2

College of Cardiology Foundation (ACCF) recently considered all the available evidence and issued an updated and more conservative recommendation (Table 1).

The results of subgroup analyses of the JPAD study were presented this week, shedding some light on which subgroups of diabetic patients might derive the most benefit from aspirin prophylaxis. The JPAD trial was a randomized, controlled, open-label blinded-endpoint study that was conducted to examine the efficacy of low-dose aspirin therapy for primary prevention of atherosclerotic events. A total of 2,539 Japanese patients with Type 2 diabetes were enrolled and followed for a median 4.4 years.

In one post-hoc analysis, Okada et al. analyzed risk of atherosclerotic events (HR, 95% CI) by therapeutic regimen for diabetes, as a surrogate for diabetes severity (abstract 12166). The regimens used at baseline included insulin (n=326), oral hypoglycemic agent (OHA) (n=1750), and diet (n=463). The insulin group had the longest duration of diabetes, the highest level of HbA1c and fasting plasma glucose, and the highest prevalence of diabetic microvascular disease; in contrast, the diet group had characteristics consistent with the lowest disease severity. The incidence of atherosclerotic events was 26.6, 14.6, and 10.4 cases per 1,000 person-years in the insulin, OHA, and diet groups, respectively. Aspirin therapy significantly reduced events in the sub-group of patients with early-stage illness being treated with diet, despite them having the lowest event rates (Figure 3; p = 0.21, 0.05-0.64; p < 0.01), but did not affect outcomes in patients on insulin (1.19, 0.60-2.40) or OHAs (0.84, 0.57-1.24).

In a second post-hoc analysis of JPAD, Soejima et al. analyzed risk of stroke events (HR, 95% CI) by level of blood pressure control (uncontrolled defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg in one analysis and systolic BP ≥130 mmHg and/or diastolic BP ≥80 mmHg in another analysis) (abstract 12906). At a cutpoint of ≥140/≥90 mmHg, the incidence of stroke events was significantly higher in the uncontrolled versus controlled blood pressure group (2.18, 1.37-3.50; p = 0.0008), whereas there was no between-group difference for incidence of coronary events (p = 0.9751). There was a difference in the incidence of stroke events between the uncontrolled and controlled blood pressure groups in those not assigned to aspirin prophylaxis (2.84, 1.52-5.51; p = 0.0008). In contrast, in those taking aspirin, patients with either controlled or uncontrolled blood pressure had similar (and relatively low) stroke rates (Figure 4). When the blood pressure cutpoint was made more stringent, however (uncontrolled defined as ≥130/≥80 mmHg), there was no significant difference between the uncontrolled and controlled blood pressure groups, regardless of aspirin use status.

In summary, these post-hoc analyses of JPAD identified potential benefit from low-dose aspirin in reducing the risk of: 1) atherosclerotic events in patients with early stage (vs. more advanced) diabetes, and 2) cerebrovascular events in diabetes patients with poorly controlled blood pressure. We find these results a bit perplexing. In the hypertension analysis, it would appear that aspirin may provide a benefit in the more ‘diseased’ patients—those individuals substantially not at target. Yet, in the diabetes treatment analysis, it was the more mildly affected patients that appeared to benefit from aspirin prophylaxis. Perhaps more advanced diabetes nullifies the effect of anti-platelet therapy—it is difficult to say. Subgroup analyses, we would point out, are sometimes not entirely consistent and should be considered merely hypothesis generating.

### Table 1. Low-Dose Aspirin* for Primary Prevention of Cardiovascular Events In Patients with Diabetes

<table>
<thead>
<tr>
<th>Event Rate (%)</th>
<th>No aspirin</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Microvascular Disease</td>
<td>0.21 (0.05-0.64)</td>
<td>0.02 (0.01-0.06)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.05 (0.01-0.21)</td>
<td>0.00 (0.00-0.03)</td>
</tr>
<tr>
<td>Family history of premature CVD</td>
<td>0.01 (0.00-0.04)</td>
<td>0.00 (0.00-0.01)</td>
</tr>
</tbody>
</table>

*75-162 mg per day

†Refer to ADA Risk Assessment Tool, Diabetes PPHD: http://www.diabetes.org/phd

patients (mean age 52 years, 47% male) with impaired glucose tolerance (IGT), reported all-cause mortality rates (at a minimum), recruited at least 100 patients, and had a follow-up period of at least 1 year (abstract 15435). Over a mean study period of ~3 years, the investigators determined that drug and/or lifestyle interventions delayed or prevented progression to diabetes quite significantly (risk ratio [RR] 0.66, 95% CI 0.55-0.80 vs. control), with drug-based (n=20,872) superior to lifestyle interventions (n=3,495). There was no difference, however, between the intervention group versus control group in risks of all-cause mortality (0.96, 0.84-1.10), CV death (1.04, 0.61-1.78), or MI (0.59, 0.23-1.50), whereas stroke death was reduced by 24% (0.76, 0.58-0.99). However, the latter data came from only three of the trials and was heavily influenced by results in one of them. The presenter concluded that the focus of treatment for IGT patients should be on CV risk factor reduction beyond blood glucose. During Q&A, one of the attendees remarked that the follow-up period might have been too short to see benefit in IGT patients who are at low CV risk. Further, the point was made that favorable CV findings have been observed for at least one drug (i.e., acarbose in STOP-NIDDM; Chiasson et al., JAMA 2003; 290:486-94), although that signal was lost when combined with other drugs in this meta-analysis.

**Fenofibrate and Peripheral Neuropathy**

The results of a post-hoc analysis of FIELD (Fenofibrate Intervention and Event Lowering in Diabetes), a 5-year randomized trial of fenofibrate 200 mg/day or matching placebo in patients with Type 2 diabetes (Lancet 2005;366:1849-61), were presented this week at the AHA Scientific Sessions. Rajamani and Australian collaborators assessed peripheral neuropathy progression, as determined by presence of neuropathy symptoms and sensation tested by a standard monofilament technique at baseline, 2 years, and study end (abstract 18987). At baseline, 5.8% of participants (564/9795) had documented monofilament neuropathy. According to logistic regression, neuropathy was increased with female sex, history of prior CVD, diabetes duration (per 10 years), insulin use, and height (all p<0.01). Additional factors associated with incident neuropathy included prior retinopathy, age, glycemia (elevated HbA1c), and hypertriglyceridemia (all p<0.03). By study close, neuropathy was present in 8.0% of placebo patients, compared with 6.6% of fenofibrate-treated patients (between-group difference, adjusted for baseline neuropathy; p=0.003). This difference was based on an 18% reduction in new neuropathy (OR 0.82, 95% CI 0.67-1.01; p=0.06) and a greater reversal of baseline neuropathy with treatment (OR 1.67, 95% CI 1.14-2.38; p=0.009). Neuropathy was one of the strongest predictors of amputation, increasing the risk of a first amputation by ~3-fold (HR 2.7, 95% CI 1.8-4.1; p<0.001). We find these data to be provocative, in the context of previously disclosed benefits of this fibrate derivative on both retinopathy and albuminuria endpoints from FIELD. All these data obviously need to be interpreted cautiously given that the trial was neither initially designed nor powered to investigate microvascular outcomes. (FIELD was primarily designed to assess the effect of fenofibrate, and, by inference, triglyceride lowering and HDL raising, on macrovascular outcomes. No overall benefit was found from the treatment strategy on the composite CV primary outcome.) In addition, there have been few biologically plausible explanations for these findings. Clearly, more study is needed on the potential effect of this lipid-lowering medication on microvascular disease.

**CVD Risk Factors are Poorly Controlled in Type 2 Diabetes**

Using the cross-sectional National Health and Nutrition Examination Survey (NHANES 2003-2006) database, Glovaci et al. from California and New Jersey found that insulin-treated patients were more likely than otherwise-treated Type 2 diabetes patients to be obese, have poorly controlled glycemia and triglycerides, and have pre-existing CVD, chronic kidney disease, or macroalbuminuria (abstract 18450). Only a minority (10%) of all patients was at goal for HbA1c (<7%), blood pressure (<130/80 mmHg), and LDL-C (<100 mg/dl), with a lower proportion of insulin-treated versus non-insulin-treated patients at this composite target. The differences might reflect the impact of comorbidities and the complexities of polypharmacy in a population with more advanced diabetes. These data underscore the need for increased efforts targeting risk-factor control in Type 2 diabetes patients, in particular insulin users, to prevent CVD-related complications.