Treatment of Type 2 Diabetes: The American Association of Clinical Endocrinologists Meeting, May 2002

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This is the second of two articles covering the American Association of Clinical Endocrinologists Meeting in Chicago, 1–5 May 2002. Topics include the new diabetes management guidelines of the ACE.

Macrovacular risk factor treatment of persons with type 2 diabetes

Brian Hoogwerf (Cleveland, OH) discussed the use of angiotensin-converting enzyme inhibitors (ACEIs). Physiologically, the renal effect of the agents appears to involve lowering of intrarenal pressures. Early studies showed the importance of blood pressure treatment in protecting against loss of renal function (1,2). With growing evidence that captopril preserves renal function in patients with type 1 diabetes and established nephropathy (3), this treatment has gradually gained prominence. Further study showed a long-term effect of ACEIs on the development of nephropathy in persons with type 2 diabetes, showing stabilization of albuminuria and creatinine clearance with enalapril with both hypertension (4) and normal blood pressure (5). Finally, the Heart Outcomes Prevention Evaluation (HOPE) study of >3,500 subjects with diabetes who had a previous cardiovascular disease (CVD) event or at least one other CVD risk factor treated with ramipril 10 mg vs. placebo produced a 25% decrease in primary outcome of myocardial infarction, stroke, or CVD death over 4.5 years, which appeared to progressively improve with longer duration of ACEI treatment (6). Albuminuria progression also decreased. Hoogwerf concluded by pointing out that albuminuria has a continuous and graded relationship to CVD risk (7) and that risk reduction is seen regardless of renal insufficiency, diabetes, or hypertension (8).

A metaregression analysis has shown that the decrease in proteinuria with ACEIs is independent of change in blood pressure, duration of treatment, type of diabetes, or stage of nephropathy, in contrast with other antihypertensive treatments, with which the degree of benefit is related to blood pressure reduction (9). Furthermore, there is evidence from analysis of 698 patients with type 1 diabetes in 12 trials of ACEI that the benefit of ACEI increases with increasing levels of albuminuria (10). Many other studies show that ACEIs have favorable effects in diabetic patients independent of both change in blood pressure and the extent of renal disease and CVD, leading Hoogwerf to conclude that ACEIs are “probably” good for everyone with diabetes. Asked whether angiotensin receptor blockers have the same beneficial effects, he replied that the data are “fairly compelling,” particularly with new evidence of improved outcome in comparison to treatment with atenolol (11). The HOPE sequel will assess telmisartan and ramipril in combination in more than 20,000 patients.

Rury Holman (Oxford, U.K.) discussed lipid-lowering treatment for patients with diabetes. He reminded the audience of the important adverse consequences of diabetes, particularly in macrovascular disease. The U.K Prospective Diabetes Study (UKPDS) primarily used single therapies for diabetes and, thus, only achieved a 0.9% lowering of HbA1c. Holman stated, however, that “even if we were to get the HbA1c completely normal we would not abolish” the increase in risk. He noted that there were greater differences in myocardial infarction in patients treated with metformin than with other agents, despite the similar glycemic benefits, suggesting a pleiotropic effect of this agent. In the UKPDS, LDL cholesterol, HDL cholesterol, HbA1c, systolic blood pressure, and cigarette use, as well as age and gender, were significant risk factors for CVD (12). Interestingly, LDL and HDL cholesterol showed stronger effects than HbA1c and blood pressure as risk factors. Holman recalled data showing that the increase in risk with increasing cholesterol is much greater for persons with than for those without diabetes (13). Similarly, both LDL and HDL cholesterol levels of patients followed in the UKPDS show a linear relationship to myocardial infarction, with a 29% decrease in risk for each 40 mg/dl decrease in LDL and a 9% decrease for each 4 mg/dl increase in HDL. The effects of diet on entry to the UKPDS were modest, with LDL cholesterol falling 8 mg/dl and triglyceride falling 27 mg/dl. Both chlorpropamide and metformin had a mild triglyceride-lowering effect. Holman discussed the not yet published Heart Protection Study, which included administration of simvastatin 40 mg for 6 years, producing an average 40 mg/dl decrease in LDL, with a decrease in vascular events by 66 per 1,000 patients, and a 27% decrease in risk among patients with diabetes. Holman wondered whether this implies that lipid lowering should be a primary treatment in patients with type 2 diabetes. He noted that statins substantially decrease coronary heart disease (CHD) risk, that fibrates may also be useful although further clinical trials are required, and that the question of combination statin-fibrate treatment needs to be addressed as well. “To minimize the risk of diabetic complications to the greatest extent possible,” he suggested using blood pressure, glycemc, and lipid-lowering treatment for all.

**Abbreviations:** ACE, American College of Endocrinology; ACEI, angiotensin-converting enzyme inhibitor; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; EASD, European Association for the Study of Diabetes; HGP, hepatic glucose production; HOPE, Heart Outcomes Prevention Evaluation; IGT, impaired glucose tolerance; SU, sulfonylureas; TZD, thiazolidinedione; UKPDS, U.K Prospective Diabetes Study.
patients, as well as cigarette discontinuation, and perhaps other targets such as homocysteine lowering. He was reluctant to recommend this for young patients, and recommended that the decision to use multiple risk factor reductions should be reserved for patients at high risk.

At a subsequent symposium, he further discussed prediction of CVD risk for persons with diabetes. In the UKPDS, CVD risk increased by 14% per 1% increase in HbA1c, and there was a 14% increase in risk per 10 mmHg increase in systolic blood pressure “right down to the normal range” of 110 mmHg. A total of 5,063 individuals with 736 CVD events in the UKPDS who were followed from the time of diabetes diagnosis were used to derive a “UKPDS Risk Engine” (14). Using age, duration, sex, ethnicity, cigarettes, HbA1c, systolic blood pressure, and total/HDL cholesterol, one can then derive an accurate risk prediction for coronary heart disease and stroke for individuals with diabetes. A PC version can be downloaded at www.dtu.ox.ac.uk/riskengine. The model has been tested against the data set from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) population. Holman noted that persons with type 2 diabetes cannot have risk measures accurately estimated from studies based on data from persons without diabetes. Using the observed data from UKPDS, the Framingham predictor approach underestimated risk by two-thirds, whereas the UKPDS approach gave a risk essentially identical to that actually observed. A coming version of the program will also estimate risks for heart failure and retinal photoocoagulation.

Glycemic treatment of subjects with type 2 diabetes
A number of symposia at the meeting addressed aspects of glycemic treatment of type 2 diabetes. Lawrence Blonde (New Orleans, LA) mentioned that data just made available from the Centers for Disease Control (http://www.cdc.gov/diabetes) shows that the number of individuals in the U.S. with diabetes has now reached 17 million, 6.2% of the population. Having diabetes is associated with a fourfold increase in mortality rates with substantial morbidity and mortality, averaging ~25 years of life lost for individuals younger than age 35 years at the time of diagnosis, 12 years lost for individuals aged 45–54 years at diagnosis, and 5 years lost for those age 65–74 years at diagnosis.

Although some authorities (and pharmacy benefit plans) recommend not performing home glucose monitoring in patients with type 2 diabetes, Blonde noted that patients regularly using home glucose monitoring have better glycemic control (15). He also discussed the importance of apparently milder degrees of abnormality of glycemia. More than one-quarter of persons with fasting glucose between 110 and 125 mg/dl actually have diabetes according to glucose tolerance testing, and 50% of the population over age 60 years shows evidence of the metabolic syndrome. As the Diabetes Prevention Project (16) has shown that there is benefit of both lifestyle and pharmacologic treatment in this group, Blonde suggested that we need to focus on the condition. He noted the association of diabetes with both insulin resistance and impaired insulin secretion, so that even at very mild levels of fasting hyperglycemia there is attenuation and dysregulation of the insulin response to glucose (17,18).

In monotherapy, sulfonylureas (SU) and metformin produce the greatest improvements in HbA1c. SU are the most frequently prescribed initial treatment for diabetes. These agents cause modest weight gain, with 4- to 5-lb increases reported with glyburide in the UKPDS (19,20), although less evidence for weight gain with glipizide GITS or with glimepiride. Hypoglycemia may be less frequent with the latter agents, perhaps in part explaining the better weight profile. Glimepiride also increases both first- and second-phase insulin secretion and may modestly improve insulin sensitivity, perhaps only as a function of improving glucose toxicity.

Blonde discussed treatment of patients failing to respond to oral agents with addition of either NPH or insulin glargine at bedtime, allowing HbA1c <7% in the majority of patients (21). Insulin glargine has the advantage of giving more stable baseline insulin levels than that seen with NPH or ultralente (22). Further evidence for this approach are studies of the use of insulin sensitizers with insulin, with efficacy both for metformin (23,24) and for TZDs (25). Furthermore, new UKPDS data show benefit of combination treatment of insulin with SU. More than half of SU-treated patients in the study required addition of insulin to achieve glycemic control, with combination SU-insulin leading to lower HbA1c levels with lower frequency of hypoglycemia than in patients receiving insulin monotherapy (26).

Harold Lebovitz (Brooklyn, NY) addressed the question of “how low is low and how many people have to get there?” He suggested that a “goal” need not be what is generally attained, but simply the most desirable level. He reviewed the Norfolk study showing the linear increase in relative risk within what is considered the normal range. The UKPDS similarly appears to show an increase in risk beginning at HbA1c levels of 5.5%. Thus, Lebovitz concluded, “our goal ought to be to get the HbA1c down to the mid-range of the normal if possible . . . without side effects.” Using this approach, >8% is “unacceptable,” and <6% is the goal. No major trials, it should be noted, have been able to achieve a mean HbA1c <7%. Problems in attaining normal glucose are the uncoupling of normal glucose-insulin feedback leading to hypoglycemia and weight gain, the progressive deterioration of β-cell function, the failure of persons with diabetes to be able to achieve long-term lifestyle modification, and the side effects of medication.

In both the Diabetes Control and Complications Trial (DCCT) and the UKPDS studies, the risk of hypoglycemia increased with lower HbA1c. In the DCCT there was 5.1 vs. 2.4 kg weight gain during the first year with intensive versus conventional treatment. Analyzing quartiles of weight gain, the top quartile of weight gain of the intensively treated group gained 7 BMI units and a 29% increase in body weight, which has the potential to cause the development of metabolic syndrome, as shown by increase in triglyceride and HDL and LDL cholesterol (27). The use of more physiologic insulin secretagogues and insulin analogs as well as of medications to preserve β-cell function, perhaps including TZDs and glucagon-like peptide (GLP)-1, may be important. Lebovitz particularly noted the findings of the TROglitazone in Prevention of Diabetes (TRIPOD) Study that troglitazone appeared to have long-lasting benefits in this regard.

Mary Ann Banerji (Brooklyn, NY) discussed β-cell dysfunction as the “foundation of type 2 diabetes,” and addressed three questions as part of her discussion: 1) does intensive glycemic control prevent micro- and macrovascular complica-
tions? 2) how can one restore normal physiology? and 3) what is the relationship between treatment of glycemia and β-cell preservation? For micro- and macrovascular disease, epidemiologic analysis of the UKPDS showed that there is a linear relationship between HbA1c and the complications of diabetes (28). Similarly, the updated mean systolic blood pressure is related to both groups of complications (29). These data are similar to that in the DCCT and Kumamoto studies. Banerji pointed to the lower rate of retinopathy progression for the same level of HbA1c in the intervention group than the control group of DCCT, suggesting that factors other than HbA1c must play important roles (30). Indeed, not all persons with type 2 diabetes who are not obese are insulin resistant, with the determining factor appearing to be the quantity of visceral fat, the major predictor of insulin action (32).

As one progresses from normal glucose tolerance to impaired glucose tolerance (IGT) to diabetes, the 2-h insulin rises and then falls, but the 30-min insulin increase falls progressively, showing rises and then falls, but the 30-min insulin increase falls progressively, showing that even the individual with IGT has in-
studied in patients whose fasting glucose exceeded 140 mg/dl while being treated with metformin 850 mg twice daily. The subjects showed a decrease in HbA1c from 10 to 7.5%, and there was no weight gain or increase in subcutaneous or abdominal fat in the combination therapy group. Combination of oral agents with insulin has also been studied. Metformin with insulin may be more desirable in terms of weight gain, but this approach leads to a high dropout rate because of gastrointestinal side effects, and all approaches with insulin plus oral agents cause similar improvement in HbA1c (43).

Derek Le Roith (Bethesda, MD) discussed insulin strategies to achieve tight glycemic control based on the pathophysiology of type 2 diabetes, recognizing that the majority of these patients have both insulin resistance and insulin deficiency. There is a relationship between insulin sensitivity and insulin resistance in individuals who do not develop diabetes, but for those who develop diabetes, “insulin is not keeping up,” and the insulin-secretory increase that should accompany worsening insulin resistance is not seen.

Why is there B-cell dysfunction? The normal function of the B-cell is to “see” not only glucose, but also fatty acids, GLP-1, and a number of other substances. Glucose enters the B-cell via GLUT2 and is metabolized by glucokinase to glucose-6-phosphate, with the resulting increase in intracellular ATP binding to and closing the potassium channel of the SU receptor complex, which is involved in first-phase insulin release. When glucose and lipid levels increase, glucotoxicity and lipotoxicity occur, affecting B-cell insulin secretion, increasing B-cell apoptosis, and affecting insulin action in the liver, muscle, and gut. In muscle, hyperglycemia and elevated free fatty acids interfere with the metabolism or each other, and long-chain fatty acids increase protein kinase C (PKC), which stimulates serine phosphorylation of insulin receptor substrate (IRS)-1 and -2, thereby blocking tyrosine phosphorylation and causing resistance to insulin action. Given these considerations, the use of long-acting basal insulin as well as addition of preprandial bolus insulin appear to be rational approaches for persons who fail to respond to oral agent treatment.

New diabetes management guidelines of the American College of Endocrinology
Jaime Davidson (Dallas, TX) introduced a symposium on the new diabetes treatment guidelines of the American College of Endocrinology (ACE), which recommend the achievement of fasting and preprandial glucose levels <110 mg/dl and of postprandial glucose levels <140 mg/dl. The ACE recommended that HbA1c should be standardized to the DCCT test, that the term for this be changed to “A1C,” and that the goal should be levels <6.5%. Furthermore, frequent screening in high-risk populations as well as in all adults aged ≥30 years was recommended. Davidson noted that the International Diabetes Federation and European Association for the Study of Diabetes (EASD) suggest a postprandial glucose goal <135 mg/dl and that they have the same goals for preprandial glucose and HbA1c as the ACE.

Ralph DeFronzo (San Antonio, TX) discussed an approach to treatment of type 2 diabetes based on current understanding of pathophysiology. Type 2 diabetes is characterized by both insulin deficiency and resistance of the liver and skeletal muscle to insulin action. The mean plasma insulin response during a glucose tolerance test increases as fasting plasma glucose reaches ~120 mg/dl, with subsequent decreases to levels similar to those seen in persons without diabetes at fasting glucose levels around 160 mg/dl (although to levels well below those of persons without diabetes whose fasting glucose levels are elevated by glucose infusion). Normal hepatic glucose production (HGP) is 1.5–2 mg·kg⁻¹·min⁻¹. As the fasting glucose increases, HGP increases to 2.5 mg·kg⁻¹·min⁻¹ at fasting glucose around 200 mg/dl and to 3 mg·kg⁻¹·min⁻¹ at fasting glucose 300 mg/dl.

Decreased peripheral glucose uptake, DeFronzo stated, primarily plays a role in postprandial hyperglycemia. Because fasting glucose contributes approximately three-quarters and postprandial glucose approximately one-quarter of mean glycemia (44), he suggested that increased HGP is the primary factor driving hyperglycemia in type 2 diabetes.

Current ACE guidelines suggest an HbA1c goal of 6.5%, and the EASD may recommend a goal of 6.0%; the suggested goal of 7.0% for American Diabetes Association (ADA), DeFronzo suggested, is too high. He recommended exercise and, particularly, weight loss in lifestyle modification. Reviewing various oral agents, he noted that to compare different studies one must make sure that there are similar baseline levels of HbA1c. Using this approach, he stated that thiazolidinediones (TZDs) lower fasting glucose 45–55 mg/dl and HbA1c 1.3–1.4%; thus, monotherapy would control only 15–20% of patients whose baseline HbA1c level is 9%, whereas both metformin and SU lower fasting glucose 60–70 mg/dl and HbA1c 1.5–2.0% and control ~25–30% of patients whose baseline HbA1c is 9%.

The α-glucosidase inhibitors, he pointed out, are the least effective agents, reducing fasting glucose 20–30 mg/dl and HbA1c 0.6–0.8%. Based on this analysis, he recommended using the combination of metformin and SU as a primary treatment modality, which would allow normalization of HbA1c in approximately two-thirds of persons with diabetes and a baseline HbA1c of 9% in a relatively rapid fashion. He also advocated the use of metformin/glyburide combination tablets. For those patients not controlled with metformin plus SU, or for those who respond initially and subsequently show worsening glycemia, he suggested that a TZD be added, mentioning that bedtime insulin or multiple doses of insulin can be used as additional potential approaches. DeFronzo showed that TZDS lower HbA1c by 1.5% when added to SU plus metformin, suggesting that “the improvement in control seems to persist” for the period of up to several years thus far studied. In review of the effect of changing from troglitazone to pioglitazone or to rosiglitazone, he suggested that there is an increase in LDL cholesterol with rosiglitazone; thus, he prefers pioglitazone.

Helena W. Rodbard (Rockville, MD) discussed the issues of diagnosing and establishing treatment goals for type 2 diabetes, addressing the rationale of the new ACE guidelines. Worldwide, the number of persons with diabetes will increase from currently >150 million to 300 million by the year 2025. Rodbard mentioned that diabetes is present now in >7% of the U.S. population, primarily because of the 60% increase in adult obesity (45), and accounts for costs of approximately $100 billion annually in the U.S. At the time of diagnosis, half of patients with diabetes have complications. The increase in diabetes among adolescents is of particular concern. In
The goal of diabetes management is the prevention of acute and chronic complications of diabetes, both microvascular and—ever more because of their greater morbidity—macrovascular complications. CVD mortality rates increase with worsening glucose tolerance, and the frequency of CVD in persons with diabetes in the Finnish East-West study is similar to that in persons without diabetes who have already had a myocardial infarction (46). The efficacy of glycemic control in prevention of complications has been shown in type 1 diabetes in the DCCT and in type 2 diabetes in the UKPDS, in which the epidemiologic analysis mentioned by Banerji suggests that a 1% decrease in HbA1c is associated with a 14% drop in macrovascular complications, with no safe threshold for HbA1c, and evidence that macrovascular complications begin at HbA1c >6.5%. In the DCCT, the Kumamoto study, and the UKPDS, there were 40, 25, and 16% decreases, respectively, in heart disease per 1% decrease in HbA1c; 33, 28, and 19% decreases in eye disease; and 25, 50, and 26% decreases in kidney disease. Rodbard referred to the EPIC-Norfolk study described above to show a linear relationship between CVD and HbA1c at levels falling below 5%. The UKPDS showed a fourfold increase in retinopathy when comparing the lowest and middle tertiles of HbA1c (47). Another factor is postprandial glyemia. The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) Study (48) showed the importance of post–glucose load glyemia as a predictor of mortality, suggesting a goal of 140 mg/dl 2-h after glucose load. The ACE Diabetes Consensus Conference produced a new set of guidelines, addressing 1) the goal of diabetes management, 2) to what extent does glycemic control achieve diabetes management, 3) what factors should be used to assess glycemic control, 4) what are the guidelines for attaining glycemic control, and 5) what further recommendations are needed (http://www.aace.com/pub/dcc/dccwhitepaper.pdf).

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**Diabetes Care** 25:330–336, 2002
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