American Diabetes Association Postgraduate Meetings—2011

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At the American Diabetes Association (ADA) Postgraduate Meetings held 25–26 February 2011 in New York, a discussion of health-care reform and diabetes was opened by Herbert Pardes, chief executive officer of New York-Presbyterian Hospital, who stated that "the focus on health care by the entire country . . . and the world has never been so great." His medical center is one of the largest hospital networks in the country, with 2,300 beds and two medical schools, and is the largest private enterprise in New York. He discussed the Naomi Berry Diabetes Center, treating >10,000 diabetic individuals, with one of the largest pediatric diabetes practices in the U.S. At the Weill Cornell Hospital, surgical treatment for diabetes is being studied. Safety programs are being developed in hand washing and in error prevention. Information technology is being expanded, with (as an example) software tools to reduce deep vein thrombosis. More online access to medical records by patients and initiatives such as health information exchanges are being studied to avoid "costly, redundant tests."

Hospitals around the country are, along with politicians and the general public, focusing on health-care reform because of increasing costs, large numbers of uninsured individuals, and increasing numbers of individuals with chronic diseases, in part because of increasing longevity. Cost-effectiveness is an issue, with the U.S. ranking first in per capita spending but far lower in health outcomes. "A lot of populations," Pardes said, "are not getting the kind of care that they should." Health-care reform efforts include measures to increase coverage, eliminate exclusions for preexisting illnesses and "lifetime caps," allow older dependent children to remain on parents' plans, and to eliminate costs to patients for annual preventive care. All these concepts are relevant to the treatment of diabetes. Quality has also become an important focus, with proposals that "the provider needs to take more responsibility for the posthospital care," to avoid preventable readmissions. Measures that have been suggested include posthospital calls to review patients' plans for follow-up visits and to go over medications and exact dosages, pointing out the importance of patient education so that patients themselves "can make their health care better" while at the same time coordinating treatment of outpatient with inpatient health-care providers. This will in part be the result of "new standards" by which "providers will have to start bearing . . . performance risks . . . bearing the costs of their mistakes." Pardes emphasized, however, that "not every readmission can be prevented" and expressed concern that payers not penalize providers for complications not in their control. "Much of the specifics [by which reimbursement will be determined] are yet to be worked out," he said; the bill proposes collaboration between health-care providers and payers with payment bundling, under which multiple providers will be "reimbursed for an entire condition over time," requiring development of approaches to sharing, with payment of portions of "savings" back to providers.

"The concept of caring for a population's health is not new," Pardes stated, and his hospital has endeavored to remain involved in such efforts for a long period of time. The New York-Presbyterian Washington Heights community is largely Hispanic and underinsured; >20% are obese, and >10% have diabetes: "all of these factors argued for a new response." The "medical home" is such a structure, which has been implemented at his institution, facilitating medication refills and appointment scheduling, targeting diabetes and childhood obesity, and working to increase adoption of electronic medical records in the community. The identification of the most ill 1,500 individuals in the community, with the highest health-care costs, may be effective in improving health outcomes and reducing health-care costs. He emphasized the need for the government to appropriately interact with the medical community, particularly in strengthening specialty as well as primary care. He noted that "these are very broad issues," with prevention being important, but suggested that promotion of the teaching hospitals in the process of improving the U.S. health-care system is important and has not been sufficiently emphasized.

GUIDELINES AND TREATMENT OPTIONS

—Patrick J. O'Connor, Minneapolis, Minnesota, discussed guidelines, noting that there has been a recent change from "standardized" to "personalized" approaches and that the coming move from "goal-based" to "risk-based" approaches represents "a big change from one size fits all." This "way that makes sense" should help in appropriately treating individual patients. The old approach recommends that all diabetic individuals strive for A1C <7%, blood pressure <130/80 mmHg, LDL cholesterol <100 or <70 mg/dL, use of aspirin, and cigarette discontinuation. Such "standardized goals have their advantages," he said, particularly in quality measurement, either in considering the individual clinical domains of A1C, blood pressure, lipids, aspirin, and tobacco separately or in constructing composite measures. However, standardized goals may be overstated/overly aggressive based on epidemiologic evidence, and increasingly complex randomized controlled trial evidence suggests that more may not necessarily be better and that different subgroups may need different goals. Presumably referring to ACCORD (Action to Control Cardiovascular Risk in Diabetes), he noted that glycemic goals might reduce retinopathy but increase mortality, although positing such a dichotomy may be simplistic in failing to distinguish between the mechanism of benefit in improving glycemia and that of treatment-related harm.

O'Connor termed existing methods for individualizing goals "primitive," as

being based on medical intuition, suggesting that better approaches would be based on randomized controlled trial subgroup analysis and on the risks in specific individuals of hypoglycemia, and of nonadherence, as well as individuals' specific risks of micro- and macrovascular complications. As an example, he reviewed evidence for personalization of lipid goals based on ACCORD. Use of statins is not controversial, but subsequent addition of a fibrate to manage HDL cholesterol/triglyceride is controversial. In ACCORD, fenofibrate addition was not associated with overall benefit, but those individuals with triglyceride >200 and HDL cholesterol >35 mg/dL may have had benefit, suggesting that this may be an additional treatment group. "When it comes to A1C it's a much trickier proposition," he said, because benefits decrease and risks increase as additional drugs are added, and it may be appropriate to have a goal of <7% for individuals requiring metformin and lifestyle change but a goal of <8% for those requiring multiple agents, particularly if they have increased mortality risk. To avoid eye and renal complications, A1C <6.5% is desirable but only modestly beneficial with a "number needed to treat" >70, but this glycemic goal was also associated with increased mortality in all patient subgroups in ACCORD in his interpretation of the study, with a "number needed to harm" of 94. He suggested that the choice of A1C goal requires ascertaining a given patient's preferences for longevity versus eye/renal complications, a very difficult conversation to have with patients, many of whom are "just not able to understand" these concepts. "As difficult it is to talk about it now . . . it's going to get more difficult," he said, describing a study of 9p21 genotype status, with the A/A and A/G genotypes not appearing to have 10-year mortality benefit of improved glycemia, whereas the G/G genotype showed worse outcome than those with an A allele with A1C in the upper tertile, though they had better outcome with glycemic control (1). With increasing understanding of the mechanisms of complications, complex algorithms may be required to determine appropriate individualized treatment approaches.

For an individualized risk-based approach, O'Connor recommended that one take into account the extent to which risk of, say, cardiovascular disease, is reversible above that based on age, sex, and genotype, allowing prioritization of goals. With use of such an approach in an analysis at his center, the total cardiovascular risk of diabetic patients was 23.3%, but only 5.7% of risk could be considered reversible. Approximately one-third of patients did have >10% reversible risk, however, so that it may be rational to treat specific patients at specific times, particularly if the electronic medical record permits entry of data in a risk calculation "engine" based on glucose, blood pressure, lipids, cigarette use, obesity, and aspirin use, allowing specific recommendations for specific patients. Of course, risk calculation must always use the most current clinical trial data. This concept of risk-based prioritization incorporating patient preferences will, O'Connor concluded, be critical to appropriate development of personalized goals along with new understanding of genetic factors contributing to risk and, in the future, will allow optimal choice of specific medications.

Sheldon Greenfield, Irvine, California, distinguished clinical practice guidelines from quality of care or performance measures, noting that the former are recommendations, or "guides," and are meant to be overridden by clinical circumstances and judgment, whereas quality of care measures should be seen as being more of a standardized test so that clinical circumstances must be part of the measure, with flexibility included in the scoring methodology for the measure to be appropriately designed (2). Patient preferences should also be taken into account, and one must avoid the scores becoming "very rigidified." Guidelines are applied by health-care practitioners and do not require specifications, while quality of care measures can be applied by nonpractitioners based on precise specifications. Quality of care measures should be based on the highest levels of evidence, while guidelines can be based on clinical recommendations. The Institute of Medicine committee on setting standards for guidelines, which he chairs, aims to "try to make sense of the chaos" (3). As an example, Greenfield pointed out that the evidence that A1C should be tested at least twice yearly is level E, which he termed "fine for providers, [but] not fine for quality." We are realizing that less stringent A1C goals are appropriate for patients with a history of severe hypoglycemia or with limited life expectancy or extensive complications, but, Greenfield asked, "how can a person abstracting data" know this for a given charted patient? Quality measures are developed by multiple organizations, then endorsed, and then adopted, and in part because of these efforts, the frequency of blood pressure measurement, A1C, and nephropathy testing and eye examination has gradually increased, whereas the prevalence of poor glycemic and blood pressure control has decreased, with individuals having Medicaid insurance lagging behind those with Medicare and commercial insurance, suggesting that further efforts will be important. He wondered whether we are quibbling about whether A1C levels should be 6, 6.5, or 7%, while "there's a lot to do at the upper end" with many individuals having levels >9%, and similarly blood pressure and lipid control are often far above desirable levels. A given person's degree of control is often "not under our control," and, rather, requires a great deal of patient adherence.

New measures that are potentially "more fair . . . to the patients [and] to the doctors" will need to be weighted, perhaps on baseline levels, so that a high A1C that has decreased from a higher level may actually represent an important clinical accomplishment. Greenfield also recommended composites of different elements, "tailored or linked" measures, such as the use of statins or angiotensin-directed blood pressure–lowering medications, and risk-adjusted measures, reviewing his analysis, which suggests that the benefit of A1C lowering depends on patient comorbidity (4). Patient reports are important, and incorporation of such measures will allow more understanding of adherence, vaccination status, cigarette smoking, foot examination, and functional status.

Carol H. Wysham, Spokane, Washington, discussed guidelines in light of recent clinical trials, suggesting that the ACCORD blood pressure study implies strongly that goal levels should not be reduced, in view of the greater likelihoods of hypotension, bradycardia, hyper- and hypokalemia, and increased creatinine seen in patients treated to a systolic blood pressure of 120 rather than 135 mmHg, although the more intensely treated group did have a reduction in stroke frequency (5). In most of the major hypertension trials, she pointed out, goals have not been reached, with the results of ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) suggesting benefit at a systolic blood pressure level of 135 mmHg (6) so that although the

ADA goal remains <130 mmHg, "based on patient characteristics and response to therapy higher or lower systolic blood pressure targets may be appropriate." Lifestyle approaches beyond weight loss include that of the Dietary Approaches to Stop Hypertension (DASH) trial (7), described on dashdiet.org, of reducing sodium and increasing potassium intake, with moderation of alcohol and greater levels of physical activity. Typically, one starts with an ACE inhibitor or angiotensin receptor blocker unless there is childbearing potential, adding a diuretic if needed to goal, but Wysham emphasized the need to monitor renal function and potassium levels. Wysham pointed out that there is little evidence pertaining to use of more than three blood pressure–lowering drugs and that there remains the question as to whether diastolic levels <60 mmHg are too low, as myocardial blood flow occurs during diastole and might be impaired below this level. The potential for hypotensive agents to cause side effects and to interact with other treatments must be kept in mind.

Addressing lipid goals, Wysham discussed the ACCORD combination lipid-lowering treatment trial in which simvastatin-treated patients received placebo versus fenofibrate (8). The LDL cholesterol goal was <70 and <100 mg/dL in those with and without evidence of cardiovascular disease, respectively. Although HDL cholesterol was slightly higher and triglyceride was substantially lower with fenofibrate, no overall benefit was seen. Post hoc analysis did suggest benefit in those who had a baseline HDL cholesterol <34 mg/dL and triglyceride >204 mg/dL, and because this is the group that clinically is given fenofibrate, such an approach is strengthened. Serum creatinine levels increased in 28% of women receiving fenofibrate but in 19% with placebo, with a similar effect in men, but microalbuminuria decreased, so it is uncertain whether there was renal harm or benefit. In the ACCORD retinopathy report, fenofibrate was associated with a 40% reduction in progression (9), suggesting a separate potential benefit of this agent. The standards of care recommendations continue to be for LDL cholesterol reduction as the first goal, and Wysham concluded that for triglyceride and HDL cholesterol "there is limited evidence that intervention with fibrate with statin reduces cardiovascular risk." Although data on the addition of niacin to other lipid-lowering agents is interesting,

Wysham suggested that the results of AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health study) would be important in determining whether this should be used in diabetic individuals; we have subsequently learned that the combination of niacin with a statin and ezitimibe is not effective in reducing event rates (10).

She concluded by noting that the evidence favoring antiplatelet therapy for all individuals with diabetes is rather weak (11,12) so that "aspirin should not be recommended for cardiovascular disease prevention for adults with diabetes at low cardiovascular disease risk (10-year cardiovascular disease risk <5%)." Most diabetic men over age 50 years and most women over age 60 years, and those with at least one additional risk factor, should, she said, receive aspirin. The take-home message: "Treatment targets . . . must be individualized."

Elizabeth R. Seaquist, Minneapolis, Minnesota, reviewed an important aspect of individualizing treatment goals for patients with diabetes: the issue of hypoglycemia. A recent ADA workgroup recommended that hypoglycemia be considered severe if the assistance of another person is required, symptomatic based on typical symptoms accompanied by glucose ≤70 mg/dL, and asymptomatic if not accompanied by typical symptoms but with measured plasma glucose ≤70 mg/dL. Subtle neurologic signs occur at glucose levels of 70–80 mg/dL, with counter-regulatory hormonal responses between 60 and 70 mg/dL and adrenergic symptoms between 50 and 60 mg/dL. Hypoglycemia is the limiting factor that prevents achievement of A1C goals, with the potential for "serious outcomes such as coma, seizure, and death"; the association of hypoglycemia with mortality is well recognized (13). In type 2 diabetes, the death rate among patients with severe hypoglycemia in the ACCORD and ADVANCE studies exceeded that among those who did not experience a severe hypoglycemic episode, although Seaquist reviewed the contention of the ACCORD investigators that "they're not dying of hypoglycemia," with only 8.1% of individuals who had severe hypoglycemia during the trial dying within 30 days of the hypoglycemic episode. The finding of a relationship between severe hypoglycemia and adverse outcome, but that the two do not "always happen in close proximity" (14), has led to the suggestion

that hypoglycemia may be a marker rather than a mediator of adverse outcome. Hypoglycemia may, however, cause abnormal cardiac repolarization, perhaps in a catecholamine-mediated fashion, as shown by an increased corrected QT interval (15), and may also activate proinflammatory factors, increase platelet activation, and decreases systemic fibrinolysis by decreasing plasminogen activator inhibitor-1.

Hypoglycemia was not associated with decline in cognitive function in the Diabetes Control and Complications Trial (DCCT) (16), but certain aspects of cognitive performance decrease during hypoglycemic episodes (17), and nocturnal hypoglycemia reduces sleep-associated consolidation of memory (18), with the potential of an impact on learning, particularly in children. A study of children of mean age 9 years showed that performance was reduced both in those with high blood glucose and in those with low blood glucose (19). Evaluation of the Kaiser managed care registry of 16,667 individuals >55 years of age found that those with hypoglycemia requiring an emergency room visit or hospitalization had increased likelihood of subsequent diagnosis of dementia (20). In animal models, hypoglycemia leads to neuronal cell death in the cortex and hippocampus (21), further buttressing this hypothesis.

Seaquist reviewed risk factors for hypoglycemia, such as excessive insulin or insulin secretagogue doses, poor timing of dosage, missed meals, alcohol reducing glucose production, exercise increasing glucose utilization, improvement in insulin sensitivity as occurs with weight loss, and reduction in insulin clearance as in renal insufficiency. She reviewed the concept of hypoglycemia-associated autonomic failure, seen in individuals with severe insulin deficiency, who have had severe hypoglycemia and/or hypoglycemic unawareness, particularly when receiving aggressive glycemic treatment. Avoidance of hypoglycemia requires reevaluation of glycemic goals, education of patients on anticipating and on recognizing hypoglycemia and on appropriate treatment, particularly in the timing and dosing of insulin.

Jack Leahy, Colchester, Vermont, noted that there has been increasing availability of new treatment options over the past decade, with "the concept that the pharmaceutical industry will bring us new tools" highly attractive, so that, to his mind, the ADA/European

Association for the Study of Diabetes consensus algorithm (22) "feels a little dated." He contrasted this with the American Association of Clinical Endocrinologists approach, which he termed "certainly much more comprehensive [although] it looks a little overwhelming," in which treatment strategy is adjusted based on the patient's A1C (23). Leahy focused on incretin therapies as the most interesting of the currently available new approaches. Incretins are, he suggested, "the connection between eating a meal and having an insulin response to that meal," a system which he suggested might be "defective in type 2 diabetes," suggesting particular benefit of the approach. Because glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic peptide exhibit rapid inactivation by DPP4, the system is "beautifully fine-tuned on a minute-to-minute basis." Infusion of GLP-1 in type 2 diabetic patients lowers glucose levels rapidly, stimulating insulin and suppressing glucagon secretion, in a fashion that wanes as the blood glucose decreases (24), suggesting that "incretins do a lot more than simply producing an insulin response." The glucose dependency introduces a measure of safety, making this particularly attractive as a treatment. With a 6-week continuous infusion of GLP-1, A1C decreased from 9.1 to 7.9% with reduction in hunger and food intake and consequent weight loss (25). Incretin receptors are expressed in most tissues, including adipocytes, bone, cardiomyocytes, and the brain, although, Leahy cautioned, "none of these have known clinical effect" at present.

There are currently two available GLP-1 receptor agonists, exenatide and liraglutide, with the latter structurally more similar to GLP-1 with >14 h duration of action, while the former has ~50% homology and duration of action 4–6 h. Exenatide lowers A1C 0.8–0.9% starting in the low 8% range, while liraglutide appears to be somewhat more potent. Side effects of both agents are hypoglycemia in patients also receiving sulfonylureas, nausea, somewhat more likely to occur with exenatide, and vomiting and diarrhea (26). The question of whether pancreatitis occurs has been raised with exenatide and with sitagliptin. The frequency of pancreatitis was no greater with these agents than that with metformin or glyburide in a large U.S. commercial health database (27). Others, however, who have analyzed the U.S. Food and Drug Administration event-reporting database,

suggest there may be as much as a sixfold increase in pancreatitis, as well as an increase in pancreatic cancer (28), though, Leahy stated, "one wonders [whether] there has been sampling bias." There also is evidence of reduction in blood pressure, LDL cholesterol, and triglycerides, leading to speculation as to potential cardiovascular benefits, but, Leahy continued, "until we get outcome studies it's all up for discussion."

A 26-week comparison of liraglutide with exenatide in patients with starting A1C 8.1–8.2% showed reductions of 1.1 and 0.8%, respectively, likely explained by the greater fasting glucose reduction with liraglutide because of its longer duration of action, offsetting the greater postprandial glucose lowering with exenatide (29). The frequency of nausea decreased more rapidly with liraglutide. Comparison of exenatide with exenatide in a once-weekly preparation appears to similarly show greater A1C and fasting glucose reduction with the latter (30). Leahy noted the great current interest in coadministration of these drugs with insulin. Exenatide and glargine have different effects on glycemia, the latter more acting on fasting, the former on postprandial glucose (31). The combination of these agents, then, may particularly improve glycemic control. Another area of interest is the use of the GLP-1 analog agents in monotherapy. The use of high doses of liraglutide in prediabetes has shown weight loss and reversal of glucose intolerance (32). Discussing the dipeptidyl peptidase-4 inhibitors, Leahy noted that they "are less potent," with the available agents rather similar, having glycemic effect equivalent to that of sulfonylureas, although causing less weight gain and less hypoglycemia. Gastrointestinal side effects do not occur with these agents, and although there may be an increase in headaches and upper respiratory symptoms, of interest is the reduction in cardiovascular events in the saxagliptin registration trials. These are, Leahy concluded, reasonable agents in the elderly, in patients with renal insufficiency, and in individuals needing initial combination treatment. Leahy termed their combination with insulin "not stunning," suggesting that this is not an area in which these agents should be used.

ANTIPSYCHOTIC MEDICATIONS AND DIABETES—David C. Henderson, Boston, Massachusetts, pointed out that because

second-generation antipsychotic (SGA) agents "are used everywhere" and to an increasing degree, "it is important to understand" their medical risks. These are in part related to weight gain, but they may also directly increase insulin resistance, increasing the likelihood of diabetes, dyslipidemia, and hypertension. Cardiovascular disease is, he noted, the primary cause of death in individuals with mental illness, and "many of the risk factors are modifiable," including lipids, diabetes, hypertension, physical inactivity, smoking, and poor access to medical care (33). Individuals with mental illness are less likely to be screened for dyslipidemia, hyperglycemia, and hypertension; less likely to receive treatment for these factors; and less likely to receive pharmacologic treatment and interventions after cardiovascular events (34).

Henderson characterized tardive dyskinesia, the major side effect of the first-generation antipsychotic agents, as being quite uncomfortable but not associated with increased mortality, while there is concern that SGA agents side effects may in fact increase mortality. The diagnosis of schizophrenia itself appears to be associated with visceral adiposity (35,36), and nearly half of schizophrenic patients have metabolic syndrome (37), making this is a high-risk group for such adverse drug effects. Similar evidence of adverse metabolic effects of SGA has been found in children and adolescents (38). There is extensive evidence that SGA agents, particularly clozapine and olanzapine, and to a lesser extent risperidone and quetiapine (39), are associated with increased likelihood of diabetes (40) and with progressive weight gain, although ziprasidone and fluphenazine appear to be weight neutral. Furthermore, clozapine and olanzapine are associated with reduced insulin sensitivity in comparison with risperidone, even in the absence of obesity (41). There has been interest in the use of medications to cause weight loss—including the antidepressants bupropion, fluoxetine, and sertraline; the antiepileptic topiramate, although its association with cognitive impairment limits its use; and zonisamide, metformin, and chromium. A study of patients with new-onset schizophrenia receiving olanzapine showed that adding metformin attenuated weight gain (42), although with some gastrointestinal side effects (43), but "the best data," Henderson stated, "has been switching the patient off the offending agent" (44,45), with diabetes sometimes resolving after discontinuation

of such drugs "even in the absence of weight loss" and even on occasion in patients whose presenting manifestation of diabetes is ketoacidosis. Ketoacidosis may particularly be an issue because schizophrenic patients fail to seek medical attention with early symptoms of illness so that some patients presenting in this fashion will be found to have markedly elevated A1C levels, suggesting long-standing disease (46). He pointed out that a rapid increase in triglyceride levels may presage the glycemic abnormality, speculating that this may be a marker of insulin resistance and that development of diabetes is progressive with continued use and is not always associated with weight gain (47). Regular monitoring of weight, waist circumference, blood pressure, and fasting glucose and lipids is important (48), but such testing is carried out in no more than one-third of patients (49), perhaps as a manifestation of "clinical inertia" (50).

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