# American College of Endocrinology Pre-Diabetes Consensus Conference: Part Two

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The American College of Endocrinology held a Consensus Conference in Washington, DC, on 21–22 July 2008 on the topic of pre-diabetes, organized around a series of interrelated questions. This is the second of a three-part series summarizing presentations at the conference.

**What goals and treatment modalities should be the focus of the management of pre-diabetes? Does early intervention make a difference?**

Scott Grundy (Dallas, TX) and Christie Ballantyne (Houston, TX) discussed aspects of the nonglycemic goals of pre-diabetes treatment, addressing obesity, blood pressure, and lipid management, as well as goals of thrombus prevention. Ballantyne discussed the concept of the metabolic syndrome, pointing out that a number of commonly measured clinical variables may be used in predicting diabetes (such as waist circumference, hypertension, family history of diabetes, ethnicity, age, fasting glucose, and lipids [1]) and suggesting that the metabolic syndrome thus offers a practical means of allowing physicians to integrate many of these factors rather than itself adding to risk. For cardiovascular disease prediction, Ballantyne suggested, blood glucose is less important than blood pressure and HDL cholesterol, which are particularly important, as metabolic syndrome components (2); and, of course, LDL cholesterol and cigarette use are additional factors that must be taken into account. Other measures, such as microalbuminuria, retinal abnormalities, A1C, C-reactive protein, lipoprotein-associated phospholipase A2, carotid ultrasound, and coronary calcium score, may be useful as well. Recognizing that 98% of women have a Framingham risk score below 10%, Ballantyne proposed redefining intermediate risk as between 5 and 20% per decade.

Grundy described metabolic syndrome as a subtype of obesity, caused by environmental (increased dietary calories and lack of exercise) and genetic factors, resulting in atherogenic dyslipidemia, hypertension, a prothrombotic state, and many other conditions, as well as pre-diabetes. The National Health and Nutrition Evaluation Survey II, carried out from 1988 to 1994, showed substantial overlap between pre-diabetes and metabolic syndrome (3), which Grudy termed the cardiovascular disease–centric and glucose-centric views, suggesting the need to address the combined syndrome. Both metabolic syndrome without impaired fasting glucose (IFG) and IFG without metabolic syndrome are associated with fivefold increases in diabetes, while the combination of both is associated with a >20-fold increase; thus, the metabolic syndrome, with or without IFG, may be considered a form of pre-diabetes (4). Meta-analysis shows metabolic syndrome to be associated with a 1.6- to 2.0-fold increase in a variety of forms of cardiovascular disease (5). Eight-year follow-up data from the Framingham Offspring Study similarly showed metabolic syndrome without diabetes to be associated with high cardiovascular disease risk for both women and men, with women having metabolic syndrome alone at somewhat greater risk than women having type 2 diabetes alone.

Weight loss is an effective approach to treatment of metabolic syndrome (6), as is regular physical activity (7). Reasonable lifestyle goals are for a 7–10% weight loss and 30–60 min/day of regular moderate-intensity physical activity. Antihypertensive treatment with an average reduction of 12–13 mmHg in systolic blood pressure over 4 years of follow-up was associated with a 21% reduction in coronary heart disease, 37% reduction in stroke, 25% reduction in total cardiovascular mortality, and 13% reduction in all-cause mortality in a pooled analysis of randomized controlled trials (8). A reasonable goal, if diabetes is present, is to achieve blood pressure <130/80 mmHg (9) with approaches including lifestyle, alcohol moderation, sodium restriction, and pharmacotherapy (renin-angiotensin system agents primarily, as well as thiazides in low doses; it should be noted that β-blockers may worsen insulin resistance).

Ballantyne reviewed benefits of administration of statins in metabolic syndrome (10), pointing out that with the compelling evidence of statin benefit, an argument may be made favoring the more intensive statin treatment goals of LDL and non-HDL cholesterol 70 and 100 mg/dl, respectively, and apolipoprotein B 80 mg/dl. Grundy reviewed a prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins showing that for every 1 mmol/l lowering of LDL cholesterol coronary disease mortality decreased by 19% (11). The long-term safety of statins has been confirmed, and statins are the first-line agents for lipid treatment. Grundy pointed out their cost-effective benefit, now that these agents are available as generics, for individuals with a 5% 10-year risk, characterizing their use as "like taking aspirin, more or less." The bile acid sequestrant cholestyramine lowered LDL cholesterol by 20% and reduced coronary heart disease death and/or definite nonfatal myocardial infarction by 19% in the Lipid Research Clinic trials (12). The agent also lowered glucose levels, now confirmed in studies of colesevelam (13), which "wouldn't be a bad idea for a patient with pre-diabetes." Given bile acid sequestrants' action to increase triglycerides, however, Ballantyne observed that combination treatment using resins with niacin may offer complimentary benefits and offset each other's side effects, as nicotinic

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DOI: 10.2337/dc08-zb11

## NEWS FROM THE FOOD AND DRUG ADMINISTRATION

*From time to time, new announcements by the FDA pertaining to aspects of diabetes treatment will be highlighted in this section.*

The FDA reported that patients who use icodextrin (Extraneal) for peritoneal dialysis and glucose-monitoring devices and do not use a glucose-specific test strip (including the Accu-Chek [Roche] and FreeStyle [Abbott]) will, because maltose is a metabolic product of icodextrin, have elevated blood maltose levels resulting in falsely elevated blood glucose readings. This may lead to inappropriate insulin administration, which has caused hypoglycemia, coma, and death and may cause cases of true hypoglycemia to go untreated.

acid (which had a favorable cardiovascular effect in several large trials [14]) raises glucose (15). However, studies suggest that diabetic patients have stable glucose levels despite using this agent.

Fibric acids are particularly effective with a high triglyceride/metabolic syndrome pattern, as was shown in the Veterans Administration HDL Intervention Trial, the Fenofibrate Intervention and Event Lowering in Diabetes Study, the Bezafibrate Infarction Prevention trial, and the Helsinki trials. Fibrates lower triglycerides and raise HDL cholesterol, with evidence of reduction in albuminuria and retinopathy (16), although increases in creatinine and homocysteine may be issues; particularly, patients with hyperinsulinemia may benefit from fibrates (17). n-3 fatty acids reduce triglycerides and non-HDL cholesterol, and some (18) but not all (19) studies show reduction in end points with this treatment. The cholesterol absorption inhibitor ezetimibe still requires a clinical trial to demonstrate safety and efficacy. Goals for individuals with established cardiovascular disease are <70 mg/dl for LDL cholesterol and <100 mg/dl for non-HDL cholesterol and are 30 mg/dl higher without established cardiovascular disease. Although the Adult Treatment Panel III guidelines would allow an LDL cholesterol of 130 mg/dl as a goal for metabolic syndrome and, by extension, prediabetes, Grundy proposed that "most people think that if you have metabolic syndrome you ought to get the LDL to <100."

Antiplatelet therapy reduces vascular risk by 23%, with cost not a factor for aspirin, and although there may be safety issues with gastrointestinal and cerebral hemorrhage, such agents should certainly be administered with 10-year major cardiovascular disease event risk ≥10% (20). Grundy summarized that from a therapeutic view point, rather than considering metabolic syndrome and prediabetes to be separate entities, "they really should be combined into one, in my view."

Ralph DeFronzo (San Antonio, TX) discussed approaches to early treatment of diabetes, with focus on the role of thiazolidinediones (TZDs). He presented an analysis of the development of diabetes using the disposition index, calculated as the ratio of insulin secretion to insulin resistance. The data can be interpreted to show that "pathophysiologically [people with pre-diabetes] really have type 2 diabetes," having an 80% or greater reduction in this index. The relationship between 2-h glucose disposition index, DeFronzo said, "really [has] no cut point. . . . This is a physiologic continuum." He reviewed evidence that β-cell volume on autopsy studies is inversely proportional to fasting glucose, decreasing by half at the stage of impaired glucose tolerance (IGT), with further progression in individuals with type 2 diabetes (21). Given the evidence of retinopathy and neuropathy in IGT in the Diabetes Prevention Program (DPP) reviewed by Ratner (see part one of this series [22]), DeFronzo suggested, "We need to intervene early. . . . It would be ideal to begin . . . long before we have IGT."

Of therapeutic options, both metformin and TZDs are effective in the liver, with TZDs to a greater extent than metformin having effect in muscle. When both agents are administered in submaximal doses, weight gain and fluid retention from the TZD are reduced, as are gastrointestinal side effects of metformin. A number of drugs appear to have β-cell benefits, including TZDs and perhaps glucagon-like peptide (GLP)-1 receptor activators. There is, DeFronzo said, no definite evidence that dipeptidyl peptidase-4 inhibitors benefit β-cell function. Neither sulfonylureas nor metformin has such an effect; both had an initial benefit and a subsequent rise in A1C in the UK Prospective Diabetes Study and, particularly for sulfonylureas, in many additional studies. In a large study, β-cell function decreased 6% per year with glyburide versus 2% per year with rosiglitazone (23). In individuals with pre-diabetes, TZDs reduced conversion to type 2 diabetes by 52–81%.

DeFronzo described the Actos Now for Prevention of Diabetes (ACT-NOW) study of 602 individuals with IGT, fasting glucose >95 mg/dl, and one additional risk factor. Subjects were randomized to pioglitazone versus placebo, with annual rates of diabetes development 1.5 vs. 6.8%, respectively, as well as a twofold greater rate of conversion to normal glucose tolerance (NGT) and improvement in the disposition index. TZDs may directly affect β-cells via action on peroxisome proliferator–activated receptor-γ or may act indirectly by improving insulin resistance, reducing free fatty acids, or reducing glucose toxicity.

David Marrero (Indianapolis, IN) reviewed the lifestyle intervention of the DPP. Each patient was assigned a personal trainer, with supervised exercise sessions, group classes, and motivational campaigns using strategies including free exercise sneakers and even payments for achieving behavioral goals: "a very well-funded and resource-rich environment." In nine studies that have used a "reduced" DPP curriculum, weight loss has averaged 2–5%, although one version of the DPP curriculum offered in community settings achieved a 6% weight loss that was maintained 12–14 months after the intervention. "Until we do a little bit more research," he concluded, "we should stay with the core curriculum." He reviewed the basic components of this curriculum.

**Self-monitoring of food, drink, and exercise.** "Everybody underestimates what they eat," Marrero said. We need to increase patients' awareness of behavior, measure their progress, improve compliance with behavior change, and identify sources of excess calories.

**Goal setting.** In an analysis of the weight loss goals of 60 obese women, most felt that loss of 25% of body weight would be the lowest degree acceptable and that they would be disappointed with a weight loss of 17% (24). We need, then, to help patients establish realistic antecedent goals by limiting eating places; reducing the rate of food consumption; setting goals

for calorie, fat, and activity levels; and establishing consequence goals for relapse prevention and rewards. Goals need to be specific, manageable, and attainable.

**Stimulus control.** It is important to increase cues for healthy eating and exercise and to decrease cues for overeating and inactivity.

**Cognitive strategies.** An important aspect of the curriculum is the restructuring of maladaptive thought patterns to eliminate the idea of "failing."

**Social support.** Perception of support correlates with weight loss, and including spouses in a program modestly improves success, with successful supporters particularly helpful in participants' achieving goals.

**Reinforcement of success.** It is important to reward behavior as soon after the accomplishment as possible. Even if without weight loss, what was done correctly should be identified and the patient should be congratulated.

A summary analysis of nine trials has shown 7–10% weight loss with such an approach, although there is subsequent weight gain (30% of patients regaining quickly, but the remaining participants also showing slow increase in body weight). This is, of course, not just true of the DPP protocol. In an analysis of outcome of a number of programs, by 5 years, 50% or more of weight loss participants have regained all or most of the weight lost (25). "It's the maintenance that's critical," Marrero commented. "That's what we as a society have to consider."

The target population of pre-diabetic adults can be linked with health plan/employer physician reimbursement. In addition, community institutions are often able to provide structured lifestyle interventions to achieve 5–7% weight loss and then ongoing behavior support at least monthly. In the DPP, the intervention cost was $1,476/ per patient-year, but group-format interventions with a lay instructor have been carried out for $243 per patient-year and it may be possible to extend the approach to commercial and internet-based weight loss programs.

Mary Parks of the Food and Drug Administration (FDA) discussed regulatory issues in approving pharmacotherapy of pre-diabetes and reviewing new requirements for drug development in diabetes. There are currently no drugs approved for diabetes prevention, but the FDA draft guidance statement for diabetes therapies has issued a description of potential end points supporting approval of such agents relative to placebo, including a delay in type 2 diabetes diagnosis by, for example, American Diabetes Association (ADA) criteria, with comparison needed to assess whether the proposed agent causes a durable benefit (26). When such an analysis is undertaken with regard to acarbose in STOP-type 2 diabetes, a 25% reduction in diabetes development was seen; metformin in the DPP, 31%; orlistat in the XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study, 37%; TZDs (as discussed by DeFronzo), 50–80%; and lifestyle in the Da Qing study, 42%, and in both the DPP and Finnish DPS, 58%. She considered the diagnosis of diabetes based on a glucose tolerance test (GTT), confirmed with repeat testing, to be a clinically meaningful end point but stated that a question exists as to whether pharmacological intervention with antidiabetes agents merely treats disease in advance of its diagnosis, thereby masking its detection. In STOP-type 2 diabetes, after a 3-month washout, 15% of those who had received acarbose versus 10.5% of the placebo subjects developed diabetes, and in the Troglitazone in Prevention of Diabetes (TRIPOD) study, at 3-year follow-up there was similar incidence of type 2 diabetes in patients formerly treated with troglitazone versus those who had received placebo. "Whether or not this is evidence that these drugs are not delaying progression to diabetes" is uncertain, Parks noted, observing that "if you stop therapies then the benefit may no longer be evident."

What, she asked, constitute other suitable end points? Safety end point analysis is required to address drug risk. Surrogate end points rather than clinical benefit end points include measures such as weight loss, lipids, blood pressure, and quality of life, but clinical outcome is clearly more meaningful. In STOP-type 2 diabetes, cardiovascular disease outcomes decreased, with hypertension also developing less frequently, although Parks observed that before accepting this as an effect of α-glucosidase inhibitors "we do need some confirmatory data." To appropriately determine whether a drug treatment is appropriate for pre-diabetes, we therefore must be able to address its risk-benefit ratio. As all drugs have some risk, targeting an otherwise healthy population in which some individuals at risk never develop diabetes requires special caution and assessment of costs to the individual, to industry, and to society. A drug may be only useful in particular subsets of at-risk patients, with the DPP, as an example, showing a particularly great effect of metformin in patients who were younger and had higher BMI or fasting glucose levels at baseline.

A special FDA public advisory committee held 1–2 July 2008 was asked whether antidiabetes therapy without a concerning cardiovascular safety signal during phase 2–3 of development will be required to conduct a long-term cardiovascular trial or to provide other equivalent evidence to exclude unacceptable cardiovascular risk; 14 committee members voted in favor of, and two voted against, requiring such tests. Based on other discussions at the advisory committee meeting, Parks stated that A1C is still considered a valid efficacy end point for antidiabetes drug approval, that type 2 diabetes is a chronic disease requiring lifelong therapy, that long-term safety profile is important for informed use, and that while demonstration of cardiovascular benefit is not required, it is critical to ensure no cardiovascular harm. Presumably, these preliminary considerations could be applied to a trial of a drug for diabetes prevention. Currently, "none of the drugs are labeled for prevention of microvascular or macrovascular outcomes" but, rather, are labeled for reduction of hyperglycemia. In discussion of Parks' presentation, it was noted that Ratner's power calculations about the trial size needed to show cardiovascular benefit would be likely to apply to a trial designed to show lack of cardiovascular harm, such that a 3-year study of a pre-diabetic population with a 0.5–1% annual cardiovascular disease rate would require tens of thousands of subjects to prove lack of a 40% increase in adverse events.

George Bray (Batton Rouge, LA) discussed the effect of weight loss drugs and bariatric surgery in pre-diabetic and diabetic patients, reminding the audience that "[in which fat depot] we put . . . the fat makes a great difference." The norepinephrine, serotonin, and dopamine reuptake inhibitor sibutramine is effective (27). Although weight loss is not maintained after placebo washout, it is with ongoing treatment (28), and triglycerides and LDL and HDL cholesterol all improved over 18 months. Diabetic patients also show weight loss with sibutramine (29), but most studies show an increase in blood pressure (30) and, using meta-analysis, glycemic improvement cannot be demonstrated (31). Side effects in-

clude dry mouth, asthenia, insomnia, constipation, tachycardia, and increase in blood pressure.

Orlistat, an intestinal lipase inhibitor, leads to loss of ~30% of ingested fat and appears to have additional glucose- and cholesterol-lowering effects that last over 2 years (32), with loss of efficacy if placebo is given. The 4-year XENDOS study showed reduction in conversion to diabetes (33) (as did other studies [34]) with a meta-analysis showing 61% reduction in diabetes development and 72% reversion of IGT to NGT, whereas this only occurred in 49% of placebo-treated patients (35). In diabetic patients, HDL and glucose levels are consistently found to improve (36); the drug was submitted to the FDA as an antidiabetes drug but was not approved for this indication. An interesting study not cited by Bray, appearing after the conference, indicated that orlistat may reduce endogenous GLP-1 levels and accelerate gastric emptying (37), suggesting a mechanism by which its efficacy may be limited or, alternatively, that the combination of orlistat with a drug increasing GLP-1 levels or GLP-1 receptor activation might be particularly effective.

A number of additional pharmacologic approaches may be used for weight loss (38). Topiramate, a carbonic anhydrase inhibitor, appears to produce ongoing weight loss over 12–15 months: a study of diabetic patients showed improvement in glucose and blood pressure, although HDL cholesterol was reduced and the agent causes sedation and is no longer being developed (39). Rimonabant is a cannabinoid receptor antagonist that reduces food intake (40) and improves waist circumference, weight, triglyceride, HDL cholesterol, and blood pressure, with the effect lost when the agent is discontinued. The ADAGIO lipids study of 803 individuals with atherogenic dyslipidemia showed increased HDL, decreased triglycerides, decreased weight, and increased adiponectin—all to greater extent than placebo—with decreased ALT and, as ascertained with a computed tomography scan, improvement in visceral adipose tissue and liver fat. Diabetic patients show these effects and show improvement in A1C, "so it has a broader metabolic effect" with both newly diagnosed (41) and established (42) diabetes. In a study of 839 individuals undergoing intravascular ultrasound, weight and total (but not percent) atheroma volume decreased but discontinuation for anxiety and depression was seen (a significant caution) and nausea rates tripled (43). "Exenatide is complex," Bray stated, because of its requirement for parenteral administration. He predicted that "combinations will be eventually the way we treat."

There has been tremendous growth in the use of bariatric surgery (44). These procedures improve glycemia in diabetic and pre-diabetic patients (45). Gastric banding, gastroplasty, and, to a greater extent, gastric bypass procedures lead to weight loss sustained over a 15-year follow-up, with nonrandomized controlled trial evidence that surgical treatment reduces development of diabetes to a degree proportional to the weight loss, lengthening life and reducing mortality (46). New studies are assessing the benefit of these procedures at lower levels of obesity beginning at BMI 30 kg/m$^2$, with evidence of benefits for nondiabetic individuals with BMI 30–35 kg/m$^2$ (47) and for individuals with BMI 30–40 kg/m$^2$ and diabetes duration ≤2 years (48).

Bray pointed out that pharmacologic and surgical treatments of obesity tend to equally affect visceral and subcutaneous fat, although the latter is more relevant metabolically. Liposuction removing on average 9 kg of subcutaneous fat has been studied, with no change in glucose and insulin levels, blood pressure, HDL cholesterol, triglycerides, adiponectin, tumor necrosis factor-α, or interleukin-6, although leptin decreased (49). In contrast, with TZD use, despite increases in weight and total body fat, visceral fat does not increase and there is improvement in cardiometabolic risk factors (50).

Jean-Louis Chiasson (Montreal, Canada) reminded the audience that "at the present time there are no hard data for the pharmacological treatment of pre-diabetes." Metformin reduces the rate of diabetes development (51). In the DPP, metformin was associated with weight loss and reduced insulin resistance rather than improving insulin secretion (52). Benefits were seen particularly in those aged <25–44 years with BMI ≥35 kg/m$^2$ (reduced metabolic syndrome). Chiasson discussed a Chinese multicenter study of 325 pre-diabetic sbjects randomized to control, diet/exercise, acarbose, and metformin groups, with baseline BMI 25 kg/m$^2$ (53). Diabetes developed in 11.6% of control subjects but in 4.1% of those receiving metformin. The Indian Diabetes Prevention Programme of 531 pre-diabetic subjects with mean BMI 25 kg/m$^2$ found a reduction in diabetes incidence from 55% after 4 years without intervention to 39% after lifestyle intervention, metformin, or both; all interventions reduced diabetes by 28–29%. (54).

Studies with acarbose suggest an overall benefit similar to that with metformin. In the Chinese study, the risk of diabetes development was reduced 83% with acarbose (53). These findings were confirmed by the STOP-type 2 diabetes study, in which there was 36% reduction in likelihood of conversion from pre-diabetes to diabetes occurring across all ages, in both sexes, and those with BMI <30 or ≥30 kg/m$^2$ (55). Conversion from IGT to NGT increased 1.42-fold, insulin sensitivity improved by 16%, and there was a smaller but significant improvement in insulin secretion. Chiasson reviewed the evidence of prevention of cardiovascular disease outcomes in the study (56), characterizing it "at best [as] hypothesis-generating data, at worst . . . a fluke, so let's not over-interpret." A three-cardiologist blinded adjudication committee confirmed that 32 cardiovascular disease events occurred in placebo subjects but 15 in acarbose-treated trial participants, with favorable trends for angina and revascularization and significant reduction of myocardial infarction—after a 2-year lag period, suggesting a biologically relevant mechanism. If silent myocardial infarctions were added, acarbose showed additional benefits over placebo, contrary to the findings with regard to pioglitazone in the PROactive study, in which inclusion of silent myocardial infarction would have made the "principal secondary end point" benefit nonsignificant. Acarbose increases flow-mediated brachial artery vasodilatation in the postprandial period (57), a potential mechanism of beneficial effect, and also reduces markers of oxidative stress, inflammation, and coagulation. "The evidence is overwhelming," Chiasson concluded, that "type 2 diabetes can be prevented or delayed through lifestyle modifications or pharmacological interventions. The beneficial effect is lost if the intervention is discontinued whether it be lifestyle or pharmacological." The ongoing Acarbose Cardiovascular Evaluation (ACE) trial will randomize 7,500 patients with IGT and acute cardiovascular disease to acarbose versus placebo (58) to more fully address whether this is an agent that should be administered in the treatment of pre-diabetes.

Carl Pepine (Miami, FL) discussed the diabetes risk associated with hyper-

tension and the glycemic implications of blood pressure treatments, noting in particular that thiazide diuretics have long been recognized to have unfavorable metabolic effects. Hypertension is, he stated, the main cardiovascular risk factor in the U.S. Diabetes is a cardiovascular disease risk equivalent (59) and is associated with increased mortality following acute coronary syndrome (60). Glucose levels are associated with greater risk of hospitalization for individuals with congestive heart failure, with a trend suggesting adverse effect of IFG (61). The fasting glucose level also is associated with risk of atrial fibrillation. Few studies have carried out a GTT, so there is little information about the risk of IGT. Glucose intolerance may influence left ventricular mass and wall thickness, worsen atherosclerosis, increase inflammation, interfere with nitric oxide metabolism, and worsen endothelial apoptosis and may simply be a marker of insulin resistance rather than directly causing adverse outcome.

In a study of 795 individuals with uncomplicated, initially untreated hypertension, followed for 15 years, new diabetes was associated with a three- to fourfold increase in cardiovascular events (similar to the effect of established diabetes), after a 3–5 year lag period. Left ventricular hypertrophy was a particularly important cardiovascular risk marker in this study, and thiazide diuretic use was a significant diabetes risk factor (62). A meta-analysis showed β-blockers and thiazides to be worse than placebo, calcium channel blockers similar, and renin-angiotensin system antagonists protective against diabetes (63). In a study of hypertensive individuals not having overt coronary artery disease randomized to amlodipine with or without perindopril versus atenolol with or without thiazide, new-onset diabetes was more likely to occur in the latter group, independent of other diabetes risks such as fasting glucose, obesity, triglycerides, and systolic blood pressure levels (64). Higher HDL cholesterol, alcohol intake, and age >55 years reduced likelihood of diabetes. In a study comparing verapamil and trandolapril with atenolol and a thiazide in patients with established coronary disease, new-onset diabetes was more common in the latter group after a lag of several years (65). Younger age and higher on-treatment systolic blood pressure were associated with greater risk of new-onset diabetes. Cardiovascular benefits were equivalent, with or without prior myocardial infarction, in the primary analysis, but in multivariate analysis the verapamil-based strategy was less beneficial than that using atenolol (66); therefore, determining which drugs are most appropriate should not be based solely on diabetes risk. Pepine discussed a number of relatively new drugs to be considered: the vasodilating β-blockers nebivolol, dilevalol, celiprolol, and carvedilol; moxonidine, a selective imidazole II–receptor agonist that lowers blood pressure with glycemic and insulin-sensitizing benefits; and ranolazine, an antianginal agent with antiarrhythmic effect on cellular sodium and calcium transport, which may reduce new diabetes. He suggested that patients' risk profile be considered and that thiazides be avoided or used at the lowest possible doses, and he suggested using either ACE inhibitors or angiotensin receptor blockers "but not both of them given the results of ONTARGET" (67).

Edwin Gale (Bristol, U.K.) asked, "What advice should we give to people with pre-diabetes?" He addressed the relationship between pre-diabetes, diabetes, and cardiovascular disease, pointing out that the term "prediction" should not be used as a synonym for "association." Pre-diabetes was first mentioned, he said, in the 1930s in association with obesity and family history. Conn and Fajans discussed the pre-diabetes state some 30 years later as an approach to prevention, suggesting that parameters of study other than carbohydrate metabolism would be of interest (68).

In type 1 diabetes, screening for high risk based on family history, antibody positivity, and glycemic abnormalities allows high predictive power, offering a rational scheme of genetic risk, then etiologic status, then target organ dysfunction, and finally system failure to offer a 750-fold increase in risk prediction. For type 2 diabetes, however, genetic testing is much more modest in its ability to predict risk. Over the range in BMI from <20 to >40 kg/m$^2$, there is a 100-fold increase in diabetes risk, but there is progressive increase in weight with age, and individuals developing diabetes have considerable overlap with the nondiabetic population. Obesity and obesity-related states such as metabolic syndrome and its individual components are, again, only modestly associated with diabetes. Gale asked, then, how cutoff points can be drawn, distinguishing statistical, clinical, prognostic, and operational approaches (69). The first Wold Health Organization (WHO) expert committee, in 1965, suggested establishing two levels: fasting glucose >130 mg/dl as diagnostic of diabetes and <110 mg/dl of nondiabetes, with the intermediate levels considered borderline. A second WHO committee, in 1981, used evidence that there is an inflection point for microvascular risk at a 2-h postload glucose of 200 mg/dl. The ADA 1997 statement suggested the use of clinical information based on association of fasting glucose microvascular risk. Although there appears to be a point of inflection in microvascular risk at fasting and 2-h postload glucose levels of 126 and 200 mg/dl, macrovascular risk appears to increase linearly with increase in glucose, and the 2003 ADA statement appears to take a statistical approach to the diagnosis of diabetes—which he suggested to be less desirable than the other approaches.

Certainly, raised glucose is a marker of cardiovascular risk, but Gale asserted that there is no evidence that treatment of pre-diabetes reduces risk and, hence, no evidence base with which to justify specific glucose-lowering treatment for pre-diabetes. The question, then, is one of defining pre-diabetes, given that the GTT is admittedly less feasible in large populations while fasting glucose alone is clearly less useful. Analysis from the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) dataset only showed a 29% overlap between the 1997 ADA definition and WHO criteria, suggesting that the two approaches identify different populations (70). DECODE found more cases with the 1997 definition, with Gale noting that the ADA definition eliminates younger and heavier individuals. Gale cautioned the audience to avoid definitions resembling Lewis Carroll's Cheshire Cat, which "fade away when you try to define them," and pointed out that, currently, "hyperglycemia defines pre-diabetes and pre-diabetes defines hyperglycemia," citing the German psychiatrist Carl Wunderlich's statement: "A view which takes abstract concepts as things, implying their actual existence and at once treating them as entities, is a logical blunder that has frequently crept into medicine and flourished there."

Gale suggested, then, that pre-diabetes is not a real disease and that we may "impoverish ourselves by going back to IFG and IGT," such that it may be more appropriate to tell patients that their blood glucose is raised, explain that this is

a risk factor, and identify and treat other risk factors aggressively with treatments that do not raise glucose but not, at this point, more "pseudo-precisely" characterize glucose or offer treatment for some but not all glucose levels not reaching the criterion of diabetes. "There are so many other things we can do," he went on to state, such as aggressively treating blood pressure and lipids and administering aspirin, that we should be very cautious about treating blood glucose at levels where it is not clear that intervention is beneficial. "Clinical medicine needs individualizing," Gale continued, stating that it is appropriate to closely follow blood glucose and A1C levels and to recognize that the best overall approach is lifestyle modification, with pharmacological treatment only if that cannot be accomplished. His personal preference is to add metformin if these parameters increase progressively.

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