Approaches to Treatment of Type 2 Diabetes

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This article is based on presentations at the Metropolitan Diabetes Society on 11 December 2007 in New York, New York, and at the American Diabetes Association's 55th Annual Advanced Postgraduate Course, held 1–3 February 2008 in San Francisco, California (these lectures are available online at http://professional.diabetes.org), summarizing a number of somewhat divergent views recently expressed by different speakers on aspects type 2 diabetes treatment.

Mechanistically based treatment considerations

At the American Diabetes Association (ADA) Postgraduate Course, Ralph DeFronzo (San Antonio, TX) reviewed the mechanisms of action and utility of various antidiabetic drugs, suggesting that sulfonylureas "are very unlikely to create a durable decline in A1C," based on understanding of the physiology. Studies with glimepiride (1) and glipizide (2) show falls in fasting glucose of 40–50 mg/dl and in A1C by 1.5%—with monotherapy controlling 25–30% of patients—which he characterized as "a very good effect, initially." However, DeFronzo said that "after the first 6–12 months the A1C starts to rise progressively." Sulfonylurea-induced insulin secretion increases portal insulin levels, suppressing hepatic glucose production and lowering fasting glucose to a greater extent than postprandial glucose. In the UK Prospective Diabetes Study (UKPDS), sulfonylureas and insulin reduced microvascular risk by 37%, but myocardial infarction, stroke, and congestive health failure decreased by 14, 12, and 16% (none of the latter decreases reaching statistical significance) (3), leading DeFronzo to contend that "there is no evidence that treatment with insulin-based therapy" reduces macrovascular disease.

Insulin resistance is basic to type 2 diabetes, and β-cell failure begins prior to actual development of diabetes with imbalance between insulin resistance and insulin secretion. DeFronzo asserted that β-cell function decreases by approximately 20% by the time glucose intolerance is present, so appropriate treatment approaches must both reverse insulin resistance and improve β-cell function. The ideal antidiabetic agent would correct hyperglycemia, prevent microvascular complications, improve known cardiovascular disease risk factors, prevent macrovascular complications, and correct the pathophysiological disturbances responsible for type 2 diabetes.

At the level of the liver, metformin and thiazolidinediones (TZDs) are similarly effective in improving insulin action, although TZDs are considerably more potent in their peripheral action. DeFronzo stated that TZDs "unequivocally" are β-cell protective, citing the findings of the Diabetes Prevention Program (4) and TRoglitazone In the Prevention Of Diabetes (TRIPOD) (5) studies with troglitazone, the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study findings with rosiglitazone (6), and the Pioglitazone In the Prevention Of Diabetes (PIPOD) (7) and the Actos Now for Prevention of Diabetes (ACT NOW) studies (clinicaltrials.gov, reg. no. NCT00220961) with prioglitazone. During the first 6 months of the A Diabetes Outcome Progression Trial (ADOPT) of individuals with newly diagnosed diabetes comparing glyburide, metformin, and rosiglitazone, glyburide led to particular improvement, but over time "the best drug in this study was rosiglitazone" (8). DeFronzo commented that in addition to the liver, muscle, and the β-cell, "the fourth bad actor is the fat cell," which is also insulin resistant, leading to overproduction of fatty acids, which further worsen insulin resistance in liver and in muscle and impair β-cell function.

DeFronzo characterized TZDs as the only agents effective in inhibiting lipolysis and reducing levels of inflammatory cytokines. He noted their potential benefits in nonalcoholic steatohepatitis (9). TZDs lower fasting glucose by 40–50 mg/dl, reduce A1C by ~1.5%, and control diabetes in 25–30% of patients in clinical trials. In studies of both drug-naive and sulfonylurea-treated diabetic patients receiving placebo or one of the TZDs, A1C decreased from 8.5 to 7%, leptin decreased, and adiponectin increased. Although the TZDs are associated with weight gain, given the improved metabolic outcome, DeFronzo described this as a merely "cosmetic" consequence. The ratio of change in insulin divided by change in glucose (a measure of insulin secretion) and measures of insulin resistance both improved with TZD treatment, which DeFronzo considered "definitive" evidence of improvement in β-cell function. Both pioglitazone (10) and rosiglitazone (11) improve nonoxidative glucose disposal, and these drugs reduce multiple components of the insulin receptor substrate. Although rosiglitazone tends to raise LDL and apolipoprotein (apo)B levels while pioglitazone is LDL neutral and decreases apoB and triglycerides, other than the lipid-lowering effect there is little difference. In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study of 5,238 high-risk type 2 diabetic individuals, pioglitazone nonsignificantly decreased total events by 10% (12). DeFronzo opined that leg revascularization was an unfortunate component ("a major mistake")

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DOI: 10.2337/dc08-zb08

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.

A number of agents used or having potential to be used in diabetes treatment have come under scrutiny by the FDA for potential adverse effects related to malignancy. A concern about Regranex (becaplermin) gel, used for the treatment of lower-extremity ulcers, was recently updated with a boxed warning addition to the prescribing information for the agent, based on a study suggesting increased risk of death from cancer in patients treated with three or more tubes of Regranex compared with those who did not use the product. The FDA makes a particular point of recommending that the potential risks of using this agent be discussed with patients and only be used when benefits can be expected to outweigh the risks. This recommendation is in certain ways similar to the boxed warning made for erythropoiesis-stimulating agents several months ago, although there the caution was that people with existing malignancy may have increased mortality and more rapid tumor progression. There has been interest in the role of tumor necrosis factor (TNF)-α in mediating aspects of insulin resistance, with animal models of decreased TNF-α showing improvement in aspects of pre-diabetes and diabetes. It is therefore noteworthy that a number of TNF-α blockers (marketed as Remicade, Enbrel, Humira, and Cimzia), used in conditions such as juvenile idiopathic arthritis and Crohn's disease, are now the subject of an FDA safety review regarding the possibility that these agents may be causally related to development of lymphoma and other cancers in children and young adults. Potential applications to treatment of insulin-resistant states will undoubtedly need to be considered possibly dangerous.

Antiepileptic drugs, which are extensively used in the treatment of painful diabetic neuropathy, have been shown to have approximately twice the risk of suicidal behavior or ideation (0.43%) as seen in patients receiving placebo (0.22%). Such symptoms have been observed from 1 to 24 weeks after starting the antiepileptic drugs, including carbamazepine (marketed as Carbatrol, Equetro, Tegretol, and Tegretol XR), felbamate (marketed as Felbatol), gabapentin (marketed as Neurontin), lamotrigine (marketed as Lamictal), levetiracetam (marketed as Keppra) oxcarbazepine (marketed as Trileptal), pregabalin (marketed as Lyrica), tiagabine (marketed as Gabitril), topiramate (marketed as Topamax), valproate (marketed as Depakote, Depakote ER, Depakene, Depacon), and zonisamide (marketed as Zonegran).

added to the composite primary end point, as it occurred more often with pioglitazone. The "principal secondary end point" of death, myocardial infarction, or stroke did show significant decrease. He suggested, then, that the TZDs "have a particular benefit" (13) and that "if fat stays in fat cells it cannot hurt you," while elevated levels in intramuscular, intrahepatic, visceral, arterial, and β-cell deposition of fat all have adverse consequences. TZDs increase fat oxidation, perhaps a major explanation of this therapeutic effect.

Metformin appears to act, at least in part, by activating AMP kinase in a fashion similar to its activation by exercise. The agent decreases hepatic acetyl CoA carboxylase and sterol response element–binding protein 1c expression, both effects reducing hepatic gluconeogenesis. Metformin also exhibits a weak stimulatory effect on muscle glucose uptake, possibly involving AMP kinase and potentially further contributing to the glycemic effect of metformin. In the UKPDS, there was a 29% reduction in microvascular disease, and there were 39, 41, and 42% decreases in myocardial infarction, stroke, and death, respectively, leading DeFronzo to suggest that metformin is preferable to sulfonylureas as initial therapy. He did not discuss the troublesome increase in diabetes-related mortality seen in the UKPDS with the combination of sulfonylureas plus metformin vs. sulfonylureas alone (14). The progressive rise in A1C in the UKPDS also occurred with metformin, leading DeFronzo to conclude that the drug does not stabilize β-cell function.

Exenatide and liraglutide are incretin analogs, representing the use of "a very, very old concept," described nearly 80 years ago by La Barre (15), that oral glucose elicits a greater insulin response than intravenous glucose in response to an equivalent hyperglycemic stimulus. The effect is mediated by glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide, produced by the L-cells of the ileum and the K-cells of the duodenum, respectively, in response to neuronal signals to the presence of carbohydrate in the gastrointestinal tract, with GLP-1 also having effects on appetite and gastric emptying. Both GLP-1 and glucose-dependent insulinotropic polypeptide are rapidly degraded by dipeptidyl peptidase (DPP)-4, so GLP-1–based therapy can involve either prolongation of half-life by DPP-4 inhibition or administration of a GLP-1 receptor agonist. DeFronzo suggested that GLP-1 receptor analogs also may preserve β-cell function, though he expressed reservations about whether DPP-4 inhibitors will be demonstrated to produce this effect. In initial studies, exenatide increased insulin secretion in type 2 diabetic patients in a dose-related and glucose-sensitive fashion (16). Metformin-treated type 2 diabetic patients receiving 5 and 10 μg exenatide twice daily showed a reduction in A1C by 1.0 and 1.2%, respectively, from baseline levels of ~8.3%, with evidence of persistence of the effect over 3.5 years in an open-label extension study (although one must realize that this fails to reach the level of evidence of a randomized controlled trial such as ADOPT and the UKPDS). Even in the absence of weight loss, a 0.7–0.8% reduction in A1C was seen, while patients also exhibiting weight loss showed a 1.7% decrease in A1C at 82 weeks in the open-label study.

Liraglutide, DeFronzo said, "works in a different way," primarily lowering fasting glucose, with improvement in A1C similar to that seen with exenatide. Analysis of response to the DPP-4 inhibitor sitagliptin showed 0.6, 0.7, and 0.9% reductions in A1C in monotherapy and in combination with metformin and pioglitazone, respectively, with better effect in newly diagnosed patients (17–20). Sitagliptin does not delay gastric emptying or increase splanchnic glucose uptake and is weight neutral. A meta-analysis of studies of GLP-1 receptor agonists and of the DPP-4 inhibitors reported a 0.2% greater A1C response with the former, which were also associated with weight loss, leading DeFronzo to suggest that these

benefits outweigh the patient preference issue of pill vs. injection; however, the majority of the exenatide studies in the meta-analysis had baseline A1C 8.5%, while most of the DPP-4 inhibitor studies had baseline 8%, potentially explaining, in part, the greater reduction in A1C with the former agent. DeFronzo concluded by recommending that type 2 diabetic patients receive "triple agent therapy from the beginning" with pioglitazone, metformin, and exenatide, speculating that it might even be reasonable to begin pharmacologic treatment when patients develop impaired glucose tolerance or, perhaps, even at the time of development of insulin resistance, to prevent the progressive loss of β-cells that has typically occurred by the time of presentation of type 2 diabetes.

Clinically based treatment considerations

Mary Ann Banerji (New York, NY) discussed clinical benefits and side effects of glucose-lowering medications at the ADA Postgraduate Course. Diabetes is one of the most common noncommunicable diseases worldwide, with prevalence predicted to increase to 370 million by the year 2030, driven in part by the increasing prevalence of obesity. Epidemiologic evidence does not suggest a threshold A1C for adverse macro- and microvascular outcomes (21). The ADA recommendations are, then, to target "the lowest A1C possible without unacceptable hypoglycemia, with action recommended for A1C 7%." Given these concepts, the intensiveness of pharmacologic treatment of diabetes in the U.S. has increased, but it is not clear that glycemia is improving. Rather, with conventional approaches, A1C typically remains elevated (22). The current recommendation is that metformin be given to all patients (23) and that addition of basal insulin, a sulfonylurea, or a TZD be considered, although Banerji recommended, "just be careful about glitazones." The Agency for Healthcare Research and Quality (www.ahrq.gov), has posed the following question: "Do oral diabetes medications for the treatment of adults with type 2 diabetes differ in their ability to affect the following proximal clinical outcomes: A1C, blood pressure, lipids, w[eigh]t, [and] 2 hour postprandial glucose?" Banerji reviewed some of the available information that can be used to address these basic points.

The UKPDS showed that use of sulfonylureas, metformin, or insulin did not maintain patients at goal (24,25). In the ADOPT study, after 2 years, as DeFronzo discussed, rosiglitazone was best at maintaining glycemia. Meta-analysis of a large number of placebo-controlled studies showed mean A1C lowering of 1% with pioglitazone, 1.2% with rosiglitazone, 1.1% with metformin, 1.5% with sulfonylureas, 0.5% with nateglinide, and 0.8% with acarbose (26), leading to the suggestion that the newer agents are not as potent, although this analysis does not control for baseline levels, with Banerji noting that studies beginning at higher baseline A1C levels report greater falls (27), making it likely that the seeming differences between agents are largely explicable by studies carried out from different starting points. "Combination therapy does work," she noted, in particular citing benefits of administration of metformin with sulfonylureas and with TZDs. There is evidence that triple therapy is similarly effective when either rosiglitazone or insulin glargine is added to a metformin-sulfonylurea combination, although with greater benefit of insulin seen at high basline A1C levels (28). There is a 2–3 mmHg drop in blood pressure with TZDs, a further potential benefit of these agents. The meta-analysis showed, however, that both TZDs increased LDL cholesterol, although they also increased HDL cholesterol; pioglitazone decreased while rosiglitazone increased triglyceride levels. In comparison with metformin, weight increased both with sulfonylureas and with TZDs, without a significant difference between the effect of these two classes in the meta-analysis. Acarbose was weight neutral, and this has been Banerji's clinical experience with metformin as well. In the ADOPT study, weight decreased with metformin and at 5 years was 6.9 and 2.5 kg more with rosiglitazone and with glyburide, respectively. The meglitinides are also useful agents. Continuous glucose monitoring of type 2 diabetic patients shows glycemic variation to lead to increased oxidative stress (29), which may be related to a greater regression of carotid intima-media thickness reported in association with repaglinide than with glyburide (30). Similarly, nateglinide's particular effect on postprandial glycemia leads it to cause less hypoglycemia than glyburide (31).

Banerji characterized congestive heart failure with TZDs as "a real problem," such that patients with strong risk factors for heart failure, including having previously had heart failure, should not be considered good candidates for these agents (32). In contrast, stable heart failure is no longer considered a contraindication to use of metformin. If a patient with edema is receiving drugs associated with fluid retention such as nonsteroidal anti-inflammatory agents or has a local cause such as venous insufficiency, the excess fluid retention caused by the TZD, although not representing heart failure, may still be an issue. Fracture and macular edema are additional concerns with TZDs. Lactic acidosis in patients treated with metformin and low cardiac output and gastrointestinal symptoms in patients treated with metformin, as well as acarbose and exenatide, are additional drug-related adverse effects that may be relevant to the choice of treatment for a given individual. Other patient-specific factors for deciding on a treatment approach include the individual's risk of hypoglycemia and of weight gain, their degree of hyperglycemia, and whether there is evidence of renal or hepatic disease. Given these considerations, Banerji suggested that all the oral agents may be appropriate, in different patients, for "first-line" use.

For an individual with diabetes, treatment with insulin requires a complex set of behaviors. Banerji cited a survey reporting that patients consider the requirement for insulin to be as disadvantageous as having a major complication (33). Although this is likely to depend on the skill of the health care provider in encouraging insulin use, one should certainly be cognizant of quality-of-life factors when considering whether to recommend insulin. Banerji also pointed out that decision making strictly on the basis of A1C fails to take into account the variability of its relationship to glycemia, such that a person with a mean glucose of 150 mg/dl might have an A1C level ranging from 6.5 to 7.4%—a concept recently addressed in some detail elsewhere (34).

The second question asked by the Agency for Healthcare Research and Quality is whether treatment of type 2 diabetes decreased micro- and macrovascular complications. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications, there was decreased cardiovascular risk after many years of follow-up (35). Macrovascular outcome benefit was not shown with insulin and sulfonylureas in the UKPDS, and although diabetes-related mortality was lower with metformin monotherapy, it was significantly

increased by metformin in combination with sulfonylureas in this study. Banerji extended DeFronzo's ideas on PROactive, pointing out that in addition to there being no significant benefit of pioglitazone in primary outcome, the significant reduction in death, myocardial infarction (other than silent), and stroke appeared to be accounted for by decreased A1C, triglyceride, and blood pressure and increased HDL levels and could well be said to have been offset by increased heart failure and peripheral arterial disease events. Overall, she concluded, evidence of differences in outcome between different oral antidiabetic agents is weak.

Considerations related to ADA treatment guidelines

Robert Ratner (Washington, DC) spoke at the Metropolitan Diabetes Society meeting on the ADA/European Association for the Study of Diabetes guidelines, giving his alternative approach to the treatment of type 2 diabetes. He noted that the guidelines recommend initiation of treatment with lifestyle interventions plus metformin upon diagnosis of diabetes, while the strategy adopted in the UKPDS involved a 3-month lifestyle intervention, during which A1C fell from 9% to 7%. Might lifestyle intervention alone, then, be a useful strategy for some diabetic patients? The newest version of the guidelines suggests that TZDs may not be as safe as other approaches to second-line treatment because of issues with heart failure and bone loss; Ratner asked whether this constitutes an appropriate rejection of the use of these agents. Furthermore, he questioned the use of 7% as the A1C target for therapeutic decision making advocated by the guidelines, pointing out that only a minority of diabetic patients achieve A1C <7%. In an analysis of some 300,000 A1C tests performed at a clinical laboratory, just 45% of levels were <7%, and many of these were <6%, suggesting that these tests might have been performed for diagnosis rather than part of following treatment. In the ADA physician-recognition program describing the "best patients" in the "best centers," Ratner noted, only 25% of patients had A1C <7% in 1997, 37% in 2001, and 46% in 2003. An algorithm-driven treatment protocol implemented in Boston led to only half of patients achieving A1C <7% (36). Ratner concluded, "There's got to be something more to get the A1C down." The problem, he pointed out, is the progressive loss of glycemic control over time characteristic of type 2 diabetes. In the UKPDS, as discussed by Banerji, at 3, 6, and 9 years, ~45, 30, and 20% of treated patients, respectively, maintained A1C <7%. In ADOPT, one-third of individuals receiving glyburide, one-quarter of those receiving metformin, and one-fifth of those receiving rosiglitazone failed at 5 years with regard to the much more readily achieved goal of reaching fasting blood glucose ≤180 mg/dl. "Is the problem with our patients and our doctors," Ratner asked, "or is it with our interventions?"

Ratner suggested that although all diabetic individuals can in principle achieve A1C <7% with insulin, large doses are required, and the patient and physician must accept high levels of hypoglycemia—and weight gain. In the Treating to Target in Type 2 Diabetes study of 708 individuals with sulfonylurea and metformin failure, randomized to aspart 70/30 twice daily, detemir daily, or aspart three times daily and using a carefully followed algorithm, 9, 18, and 4%, respectively, required the addition of another insulin dose, with final treatment dose 0.52, 0.49, and 0.61 units $\cdot$ kg^{-1} $\cdot$ day^{-1} and with A1C decreasing to 7.3, 7.6, and 7.2% from a baseline level of 8.4% (37). Why, he asked, did not every patient achieve an A1C level <7%? This goal was in fact attained in the study in only 42, 28, and 49% of treated individuals. A conclusion may be that "we do not have the systems . . . to deliver optimum diabetes care to the masses" and that we need newer and better treatment approaches. Further, Ratner commented, "we are being naive if we believe that . . . the only goal" is to achieve an A1C level <7% or, according to the more aggressive American Association of Clinical Endocrinologists guidelines, <6.5%. Weight-neutral, or, better, weight loss–inducing treatment approaches with lower risk of significant hypoglycemia are required to maximize patient adherence, as well as to reduce cardiovascular disease risk and cardiovascular disease outcomes. New drugs must be safe and must also be effective, with physicians recognizing that "diabetes is a serious disease" with a complex risk-benefit equation. Weight gain is seen with TZDs, sulfonylureas, and insulin, and hypoglycemia is seen with sulfonylureas and particularly with insulin, with 20% of prandial insulin patients in the Treating to Target in Type 2 Diabetes study experiencing it. New agents such as the DPP-4 inhibitors and incretin mimetics fulfill some of these needs, although neither allows the majority of patients to achieve goal, with Ratner suggesting that "these drugs seem to work better the earlier you give them." Initial sitagliptin plus metformin does appear to potentially be a very effective approach, while only approximately 45% of persons taking sitagliptin as add on to metformin or to pioglitazone attain A1C <7%. It will be crucial to develop durability data, such as the 5-year data from ADOPT and the 10-year data from UKPDS. "We need new therapies," Ratner said, "because we're not doing well with what we've got . . . . . Even in our clinical trials," he continued, "[only] 45-50% are achieving target."

An unmet need is to alter the natural history of insulin secretory failure, recognizing that at present we have no real way of measuring β-cell preservation. Even more, we need to develop agents such as AGE blockers and protein kinase C inhibitors, which reduce the adverse effect of hyperglycemia. Ratner acknowledged the need for long-term safety and efficacy data but suggested that there is a "need to go beyond the cost of the drugs," as pharmaceutical treatments comprise only 11% of health care costs. Cost, he pointed out, is much more strongly associated with complications than with medications (38). Furthermore, although blood pressure treatment is highly cost-effective, other interventions considered reasonable, such as mammography in older women and lipid-lowering treatment, have costs per quality-adjusted life-year roughly comparable with those of glycemic control (39).

Perspectives on TZDs and cardiovascular disease

Ratner also spoke at the ADA Postgraduate Course, discussing the risk-to-benefit ratio of the TZDs, using material given at the Food and Drug Administration (FDA) hearing in July 2007, available from www.FDA.gov/ohrms/dockets/ac/07/slides/2007–4308s1–00-index.htm. He gave a set of disclosures of his research support, advisory boards, and stock ownership, as well as his "intellectual disclosure" that he is examining the effect of rosiglitazone on coronary atherosclerosis, as measured by intravascular ultrasound. The TZDs, he said, target insulin resistance, improve glycemic control, do not cause hypoglycemia, improve lipids (in different ways with different agents), and appear to benefit β-cell function. The troglitazone experience, with the idiosyncratic side effect

of liver damage considered along with the multiple potential benefits of this class, is important to note "because we've come full circle" to realizing the TZD class effect of reducing liver fat, with preliminary evidence of improvement in nonalcoholic steatohepatitis. Ratner suggested that, similarly, we should not rush to decide that there is cardiac toxicity associated with any currently used TZD. The TZDs do have side effects. Weight gain is typical, although correlating with the degree of improvement in A1C. The greatest weight gain is seen in patients receiving sulfonylureas and with insulin treatment, and this can be attenuated with caloric restriction. TZDs are associated with edema, particularly when used in combination with insulin, although with no evidence of decrease in cardiac performance. Left ventricular contractility, stroke volume, cardiac index, systemic vascular resistance, and blood pressure all improve, as documented initially with troglitazone (40). The edema and heart failure associated with TZD use, then, are related to volume overload and preload rather than to intrinsic adverse cardiac effect; this was addressed in the ADA/American Heart Association consensus statement on TZD use and fluid retention (32).

As discussed by DeFronzo, both the Diabetes Prevention Program and TRIPOD studies suggested that administration of the troglitazone led to β-cell rest, reducing progression of pre-diabetes to diabetes by 75% during 1.5 years and by 55% over 2.5 years, respectively, with similar reductions in development of diabetes by approximately 60% in the ACT NOW and DREAM studies. The ADOPT trial showed that in newly diagnosed type 2 diabetic patients, glycemic control was more durable with rosiglitazone than with metformin or glyburide. Ratner pointed out that TZDs, then, reduce development of diabetes and lower A1C, while improving insulin sensitivity, lowering free fatty acids, improving blood pressure, decreasing albuminuria, lowering C-reactive protein, and increasing adiponectin. Reduction of carotid intima-media thickness has been shown with troglitazone (41), pioglitazone (42–44), and rosiglitazone (45). TZDs have also been shown to markedly reduce rates of restenosis following coronary angioplasty and stent procedures (46), to decrease hepatic steatosis and improve steatitis (47), and to reduce waist-to-hip ratio. Lipid effects differ somewhat between rosiglitazone and pioglitazone, with both lowering free fatty acids but with the latter having greater effect in reducing triglycerides and not changing LDL, which increases with rosiglitazone, whereas HDL cholesterol increases 2.4 and 5.2 mg/dl, respectively, with the two agents (48). Although TZDs increase heart failure rates, following hospitalization, individuals who have received TZDs have better clinical outcome (49), further suggesting a benefit of the approach. In the PROactive trial, there was a 10% reduction in the primary outcome (from 23.5 to 21%) among individuals receiving placebo vs. pioglitazone over 36 months (12). As event rates only began to separate around 24 months, Ratner commented, it is entirely possible that a longer trial would have shown stronger evidence of benefit.

Reports of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D), the Action to Control CV Risks in diabetes (ACCORD), and the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trials will soon be available, although Ratner cautioned that power calculations suggest that patients already receiving aspirin, converting enzyme inhibitors, and statins have relatively low event rates, such that larger numbers are needed than was recognized when these trials began. The DREAM trial suggested that cardiovascular outcomes increased with rosiglitazone, although only the increase in heart failure was significant. In a controversial meta-analysis purporting to show an adverse cardiovascular effect of rosiglitazone (50), myocardial ischemia events were post hoc, nonadjudicated end points; there was no access to the actual data; and of the 42 studies used, only 11 were peer reviewed, with 26 never published. There were small numbers of events, and the trials were of short duration. It has been said, Ratner commented, that "meta-analysis is to analysis as metaphysics is to physics" (51), with the reported increase in risk belied by the identical incidence of myocardial ischemia events in the rosiglitazone and control groups: 0.6 and 0.62%, respectively. The meta-analysis must, then, give greater weight to some than to other studies. A reanalysis of these data by the FDA using patient-level data found no increase in what was termed "serious ischemia" and found a nonsignificant difference between the 0.73 and 0.67% respective risks of the combination of diagnosed myocardial infarction, cardiovascular disease, and stroke, although the combination of serious plus non-serious ischemia risk was 2 vs. 1.5%, a significant increase. The increased risk of myocardial ischemia was particularly seen when rosiglitazone was administered to individuals taking insulin or nitrates, findings which were incorporated into revised product labeling. Further criticism of the original meta-analysis includes its failure to perform a continuity correction, with such analyses demonstrating no significant adverse effect of rosiglitazone (52). Ratner acknowledged that "the trends [with rosiglitazone vs. pioglitazone] are in opposite directions" but questioned the suggestion that the former agent has caused more than 100,000 deaths. The Veterans Health Administration study of the relationship between all-cause mortality and oral antidiabetic drugs showed that with adjustment for age, diabetes duration, A1C, creatinine, cardiovascular history, lipid and blood pressure treatment, and diabetes-related physician visits, there was no significant difference in mortality among 39,721 diabetic patients treated with sulfonylureas, metformin, TZDs, combinations, or no drugs (53). Analysis of a managed-care medication dataset from WellPoint, Inc., in the FDA presentation compared 22,050 individuals receiving rosiglitazone, 23,768 receiving pioglitazone, and 120,771 receiving other agents. Those receiving TZDs were older and had more hospitalizations and higher rates of complications than individuals using other oral hypoglycemic agents, but the comparison failed to reveal differences between the two with regard to myocardial infarction or other complications. The Data Safety Monitoring Boards of the BARI 2D and ACCORD trials, both using rosiglitazone, failed to show an adverse cardiovascular effect of the agent.

The risk-benefit calculation for TZDs must, then, take into account their glycemic benefit in monotherapy and as adjuvants. They have added benefit in preventing diabetes development and in maintaining glycemic control; may have beneficial β-cell effects, reduce liver fat, and reduce progression of nonalcoholic steatohepatitis; and have pleiotropic that may decrease cardiovascular risk. They do increase weight and cause fluid retention and, now, have been shown to increase fractures. Furthermore, pioglitazone and rosiglitazone have different characteristics. "The available evidence," Ratner concluded, "is insufficient to de-

finitively determine if TZDs increase, reduce, or have a neutral effect on ischemic CVD or death."

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