

The Avandia Debate

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This is the first in a series of articles based on presentations at the American Diabetes Association's (ADA's) 67th Scientific Sessions in June 2007, in Chicago, reviewing aspects of thiazolidinediones (TZDs) treatment, with focus on the controversy over possible adverse effects of rosiglitazone.

On 21 May 2007, an article appeared on the *New England Journal of Medicine* Web site giving a meta-analysis of 42 trials comparing rosiglitazone with placebo or other agents. Steven Nissen and Kathy Wolski reported a significant 43% increase in myocardial infarction and a trend almost achieving statistical significance of a 64% increase in cardiovascular mortality (1). In an accompanying editorial, Bruce Psaty and Carl Furberg strongly questioned the wisdom of choosing treatments for diabetes based on "the single dimension of glycemic control," suggesting that although "high levels of glycated hemoglobin increase risk," one must "require proof of health benefits" before accepting that an agent lowering blood glucose benefits individuals with diabetes (2).

These articles were accompanied by tremendous publicity. On 22 May 2007, an article in the *New York Times* entitled "Heart Attack Risk Seen in Drug for Diabetes" summarized the public concern. The article questioned whether Glaxo-

SmithKline (GSK), the manufacturer of rosiglitazone, and the Food and Drug Administration (FDA) should have released similar data earlier, mentioned investigations being started in Congress, and quoted Nissen to have stated, "It's a huge risk," with "tens of thousands of people" having had myocardial infarction caused by the treatment (3). Patients with diabetes were understandably worried, and their physicians were faced, as often is the case with such media events, with the dilemma of determining what should be the correct advice at a time of limited data availability. Hundreds of such news articles have appeared, the GSK share price dropped by nearly one-tenth, and lawsuits are already being filed against GSK on behalf of individuals with diabetes who have cardiovascular disease (CVD) developing or worsening while receiving the drug. There is, however, uncertainty as to whether the analysis was correctly performed. Two large studies are being carried out with rosiglitazone under the aegis of the National Institutes of Health: the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials, including 2,368 and 10,251 individuals with type 2 diabetes, respectively. Both have Data Safety and Monitoring Boards, which have met and reported no increase in risk to patients in the trials and recommended that the studies proceed unchanged (4). The Endocrine Society similarly expressed concern that the Nissen study might be appropriately regarded as preliminary, given its "substantial limitations" (5).

Debate: Should TZDs be primary agents in the treatment of type 2 diabetes?

At a debate held on 10 April 2007 by the New York Metropolitan Diabetes Society,

the topic of whether TZDs should be used was addressed, Silvio Inzucchi (New Haven, CT) agreeing with their use, while Jay Skyler (Miami, FL) spoke in opposition.

Inzucchi began with a discussion of the importance of insulin resistance and of the concept that TZDs treat the root cause of type 2 diabetes, while sulfonylureas and agents acting at the glucagon-like peptide 1 receptor act on the β -cell, the latter also with glucagon-suppressing effects, and metformin acts principally in reducing hepatic glucose production. The only approach available to directly increase peripheral glucose uptake in skeletal muscle and in adipose tissue is by increasing insulin action with TZDs. Inzucchi reviewed his study comparing metformin, which decreased hepatic glucose production by 19%, with troglitazone, which increased peripheral glucose uptake, primarily in skeletal muscle, by 54% (6). This, he suggested, reverses the primary defect in early diabetes. A further argument for the TZDs comes from the important interplay between insulin resistance and CVD, which may involve glycemia, hyperinsulinemia, dyslipidemia, hypertension, hypercoagulability, and inflammation. TZDs have been shown to improve all of these abnormalities. TZDs decrease vascular smooth muscle cell and neointimal proliferation. A meta-analysis of seven clinical trials including 608 individuals has shown a reduction in the rate of restenosis with TZD treatment (7). Furthermore, recent evidence suggests reduction in carotid intima-medial thickness (IMT) with TZDs (8–11). Although Inzucchi acknowledged that IMT is a surrogate measure, he suggested that there may then be a direct anti-atherosclerotic benefit with these agents. In his study of 24,953 diabetic individuals with acute myocardial infarction and diabetes in a Medicare hospitalization database, 2,231 were discharged receiving either metformin or a TZD and 6,641 received neither agent. There was a nonsignificant 8% decrease in mortality and readmission in the sensitizer group and a significant 48% reduction in mortality among those receiving both agents (12).

In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), 5,238 diabetic individuals with CVD randomized to pioglitazone versus conventional hypoglycemic therapy

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Abbreviations: ADA, American Diabetes Association; CVD, cardiovascular disease; DREAM, Diabetes REduction Assessment with ramipril and rosiglitazone Medication; FDA, Food and Drug Administration; FFA, free fatty acid; GSK, GlaxoSmithKline; IMT, intima-medial thickness; TZD, thiazolidinedione.

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showed a 16% relative and 2% absolute reduction in the “principal secondary end point” of nonfatal myocardial infarction, nonfatal stroke, or CVD death (13), which Inzucchi suggested would be the typical end point chosen for a study of cardiovascular end points. Given this overall benefit, he suggested that subgroup analysis was appropriate, with the striking findings of a 28% reduction in recurrent myocardial infarction among the 2,445 individuals who had prior myocardial infarction (14) and a 48% reduction in recurrent stroke among 984 with prior stroke (15). He pointed out that the duration of the PROactive Study was only 3 years, while that of most other important clinical trials of strategies for prevention of atherosclerotic events, such as the Heart Protection Study, CARE, and MICRO-HOPE studies, was 5–6 years. He compared Kaplan-Meier cumulative survival plots of these studies with PROactive, suggesting that over a longer time even more favorable outcome would be seen. Despite the higher rate of hospitalization for congestive heart failure of 5.7% with pioglitazone compared with 4.1% in individuals allocated placebo, Inzucchi suggested that the prevention of events justifies the use of this treatment.

Furthermore, he presented a population analysis showing that among 16,417 Medicare beneficiaries with diabetes discharged after hospitalization with principal discharge diagnosis of heart failure, those receiving TZDs, like those receiving metformin, had a 13% lower multivariate-adjusted 1-year CVD mortality than those not receiving insulin sensitizer treatment (16).

There is a β -cell protective effect of TZD treatment, with evidence that these agents prevent diabetes, including the 58% reduction in the Troglitazone in Prevention of Diabetes (TRIPOD) Study (17), the 75% 1-year reduction in the Diabetes Prevention Program (DPP) (18), and the 62% reduction in the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial (19). The ADOPT Study of individuals with type 2 diabetes receiving glyburide, metformin, and rosiglitazone showed reduction in monotherapy failure at 5 years with the latter agent (20), further evidence of benefit.

Inzucchi concluded by citing the extensive evidence that individuals with diabetes show progressively worsening glycemia over time, as particularly shown in the UK Prospective Diabetes Study (21). Given the evidence of benefit of

TZDs, and given the 20–30% of diabetic individuals intolerant of metformin, he suggested that TZDs and inhibitors of dipeptidyl peptidase-4 should be favored over sulfonylureas and that, recognizing that all pharmaceutical agents have contraindications and adverse effects, TZDs should be considered excellent agents for the treatment of type 2 diabetes.

Jay Skyler took the opposing position, reviewing many of the same studies but suggesting they implied that TZDs should rarely be used.

He proposed that in the PROactive Study, the primary end point represents a reasonable collection of macrovascular complications of diabetes. This end point failed to show a statistically significant improvement, leading Skyler to conclude that “none of the secondary end points count.” He noted that the principal secondary end point cited by Inzucchi was not included in the original methods paper. Furthermore, he noted that subgroup analysis of this study showed benefit only for individuals not treated with statins, which he considered might be an important potential reason to consider pioglitazone not actually to be effective in an optimal treatment approach. Another weakness of the study was, he stated, the improved level of glycemic control among individuals randomized to pioglitazone, as well as the lower blood pressure and triglyceride and higher HDL cholesterol in this group, suggesting indirect mechanisms of benefit. Furthermore, he contrasted the 58 fewer primary end points with the 115 more heart failure events, suggesting that the latter should be taken into account, and he commented unfavorably about the association of pioglitazone with weight gain.

Analyzing the DREAM Trial, he suggested that, at best, rosiglitazone led to a 1-year delay in progression to diabetes, predictable from the 10 and 20 mg/dl reductions in fasting and 2-h glucose in treated individuals, so that rather than preventing diabetes, he suggested that there was merely masking of its development. Furthermore, the washout study showed identical progression after rosiglitazone discontinuation, similar to what was seen in the DPP after discontinuation of troglitazone, leading to his conclusion that the effect was simply one of pharmacologic glucose lowering. He contrasted this with the effect of lifestyle, with follow-up of the Finnish Diabetes Prevention Study showing increasing separation

over time between the control and intervention groups (22).

The concept of the DREAM Trial was based on the premise that rosiglitazone would offer benefit to individuals with impaired glucose tolerance, but in fact, Skyler suggested that the sevenfold increase in heart failure and trend to overall increase in CVD was worrisome. He also commented unfavorably on the 8-lb weight gain over the study period for rosiglitazone-treated patients.

In analyzing the ADOPT Study, although he acknowledged that rosiglitazone was better than both glyburide and metformin in reducing fasting glucose, he pointed out that metformin maintained the glucose target for 45 months, not much different from the 57 months with rosiglitazone, and with weight loss rather than weight gain. He further suggested that “glyburide is the worst of the sulfonylureas” but that despite this, the mean A1C during the first 3 years of treatment was actually lower with this agent than with either metformin or TZDs, so, perhaps, “starting with metformin and a sulfonylurea is not necessarily a bad thing.” Furthermore, he noted that adverse events occurred more frequently with rosiglitazone, with evidence of CVD in 3.4% of those receiving this agent, in 3% of those receiving metformin, and in 1.8% of those treated with glyburide; edema in 14, 7, and 8%; and with doubling of fracture rates, confirmed by subsequent analyses of the GSK and Takeda databases, for rosiglitazone and pioglitazone.

He commented that the improvement in carotid IMT with pioglitazone in the Chicago study appeared to be transient, with levels returning to baseline at 18 months, and further suggested that rosiglitazone appears to adversely affect LDL cholesterol levels, leading him to conclude that the TZDs give no better glycemic control and no better β -cell function than other agents, while, he suggested, being associated with substantial weight gain, edema, and increase in LDL cholesterol, with increased risk of congestive heart failure and of fractures, bolstering his contention that use of the agents should be avoided.

Debate: Is rosiglitazone particularly associated with adverse outcome?

Steven Nissen (Cleveland, OH) debated Philip Home (Newcastle, U.K.) on the specific question of adverse cardiac effects of rosiglitazone. Nissen began his presentation 25 June 2007 at the ADA meeting

on the issue of possible adverse effects of rosiglitazone by acknowledging, “I know I’ve made life more difficult for a lot of you and I’d like to tell you why.” In response to questions at the conclusion of the session, he said further, “We didn’t call for the withdrawal of the drug, and we didn’t call for regulatory action. We simply said that we want you and others who treat these patients to be aware of the findings. There was a lot of criticism—should this have been published or shouldn’t it—but let me say to you the alternative to us was unacceptable. The alternative would be to keep the scientific community in the dark, to not tell you that a pooled analysis of all these data showed a pretty substantial increase in the risk of the most serious complication of diabetes.”

In May 1999, he recalled that there were major concerns about the hepatic toxicity of troglitazone. In that context, as both rosiglitazone and pioglitazone appeared free of this life-threatening side effect, he stated that the FDA agreed to put aside initial studies of rosiglitazone, showing 1.2% ischemic heart disease rates in individuals treated with this agent compared with rates of 0.5% with placebo, 0.6% with sulfonylureas, and 1.3% with metformin. (Home subsequently remarked on this rate with the agent we currently recommend as first choice for treatment of diabetes.) Overall, Nissen stated that there was a 1.8-fold increase in cardiovascular risk with rosiglitazone in its registration trials. The approval letter for this agent was issued on 25 May 1999, Nissen stated, and requested that a long-term study be performed, including assessment of cardiovascular safety. The initial studies showed that rosiglitazone increased LDL cholesterol by 18.6%, a further concern, with Nissen recognizing John Buse, the ADA’s President-Elect, as having been vocal in discussing this at scientific meetings and in writing to the company and to the FDA. Despite this, he said that no major CVD outcome trials have yet been completed. Many small short-term studies have been conducted. The large DREAM (19) and ADOPT (20) studies were conducted, but Nissen stated that they did not adjudicate cardiovascular events. (This may be an erroneous statement; such adjudication was actually performed in a blinded fashion, as discussed in Appendix A of the Dream Trial online supplementary appendix [23].) Only the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) Study (24)

gives relevant information, but Nissen disparaged this as an open-label study, although following 4,400 patients for 6 years. Furthermore, he said that the study was performed at the request of the European regulatory agency to address the CVD issue, implying that it should have been performed earlier.

In the DREAM Trial, 2,635 individuals treated with rosiglitazone had 15 myocardial infarctions compared with 9 of 2,634 individuals receiving placebo. Twelve vs. 10 cardiovascular deaths occurred; there were 24 vs. 20 new cases of angina, 35 vs. 27 revascularizations, and 14 vs. 2 individuals developed congestive heart failure—a composite 75 vs. 55 cardiovascular events. Nissen recalled that he began to worry about the agent at that time, writing a letter to *Lancet* suggesting that there might be harm (25). “In ADOPT,” he said, “the same thing happened.” There were 2 fatal and 25 nonfatal myocardial infarctions with rosiglitazone but 2 and 21 with metformin and 3 and 15 with glyburide, respectively. Nissen termed this a “consistent pattern of excess myocardial infarctions,” which he found “very worrisome.” He stated that an out of court settlement of a lawsuit by New York Attorney General Elliot Spitzer required GSK to publicly disclose all clinical trial results. From this, Nissen found 42 randomized studies of at least 24 weeks’ duration, the majority of which were unpublished, comparing rosiglitazone with other agents or placebo, which he used for the meta-analysis (1). In the small trials combined there was, he said, a 1.45-fold increase, for the DREAM Trial a 1.65-fold increase, and for the ADOPT Study a 1.33-fold increase in myocardial infarction rate. Nissen performed a meta-analysis to combine the different studies, finding overall a 1.43-fold increase in myocardial infarctions. He noted, “Much has been said, pro and con, about meta-analysis, and I think we did a good job of outlining strengths and weaknesses.”

Myocardial infarctions occurred 14% more often with rosiglitazone compared with metformin, 24% more often than with sulfonylureas, 80% more often than with placebo, and 178% more often than with insulin, leading Nissen to remark, “When you see this kind of consistency in data, it makes you feel there’s something going on.” He continued, “One strength is that there was a large group of trials [and that] we used hard end points . . . [of] myocardial infarction and cardiovascular death We included every appropri-

ate randomized clinical trial and . . . the data on the company’s Web site constituted the data we used . . . we avoided . . . publication bias . . . because we had everything.” He acknowledged a number of weaknesses, that there were “no patient-level data; [that] time-to-event data [were] not available, precluding Kaplan-Meier curves; [that] cardiovascular end points were not the primary end point in any of the trials; . . . [that] events were not adjudicated; . . . [and that] small numbers of events were observed, resulting in wide confidence intervals.”

He concluded that rosiglitazone is associated with a significant increase in risk of myocardial infarction and of death, commenting, “Patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.” Furthermore, he stated that in 2005 and 2006, “we learned that GSK had performed a similar study . . . which showed statistically significant 31% greater rate of myocardial ischemic events . . . FDA announced that they had conducted their own independent meta-analysis, which showed a 40% increase in events.” He asserted that GSK subsequently commissioned “a retrospective observational study . . . using an insurance claims database of myocardial infarction and revascularization with incomplete assessment of covariates such as smoking or aspirin, showing no increased CVD.” He criticized this study, however, stating that few events were observed, that there were wide CIs and short follow-up, and that no comparison was made with pioglitazone.

“What,” he asked, “about the RECORD trial?” He maintained that “major errors in design have largely rendered this study futile.” He criticized the primary end point of death plus cardiovascular hospitalization. He observed that the study was designed based on a postulated 11% annual event rate but has had a rate of just 2.5%, terming this “a major miscalculation . . . [which] results in a huge problem . . . only about 45% power for the primary end point Bottom line, RECORD will not give us an answer.” The primary end point was 11% more likely and myocardial infarction 23% more likely, both with wide confidence limits including unity, with only heart failure being significantly more likely with rosiglitazone, occurring 115% more often than in the comparator group.

Rosiglitazone “is not,” Nissen continued, “the first agent to show a hazard in

the PPAR [peroxisome proliferator-activated receptor] class,” recalling his report that muriglitazar showed mortality plus nonfatal myocardial infarction plus stroke rates significantly increased by 123% (26), leading him to suspect a class effect. He stated that more than 50 investigational new drug applications for peroxisome proliferator-activated receptor ligands have been filed over the past 7 years and that most of these agents were rejected because of toxicity. He did state, however, that the PROactive Study with pioglitazone showed that the likelihood of the primary end point was reduced nonsignificantly by 10% and cited favorably that the combined principal secondary end point of death, myocardial infarction, and stroke decreased significantly by 16% (13), leading Nissen to conclude, “we must interpret this trial as neutral rather than favorable, but it was trending . . . [to suggest that] pioglitazone is a very different drug . . . [with] more favorable effect on lipids . . . the jury is still out but so far the trends are going in a favorable direction.” It may be relevant to Nissen’s enthusiasm for this agent, also expressed in the meta-analysis article (1), that Nissen is the principal investigator of the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation Study (27).

Nissen concluded that the FDA “rushed” to approve new TZDs in 1999 because of concern about troglitazone toxicity, stating, “In my view, that was a regulatory mistake You don’t know from a limited exposure what’s going to happen later on A strong safety signal of excess ischemic cardiovascular events was ignored.” Furthermore, he termed blood glucose a “surrogate end point . . . [which is] not acceptable given the adverse cardiovascular signal.” He characterized the postmarketing clinical trial program as including few studies that examined important health outcomes. Finally, he reiterated his thought that the limitations of RECORD are such that when completed, in 2009, 10 years after rosiglitazone was launched, we may still not know whether this agent benefits or harms individuals with type 2 diabetes, so that “each physician must decide for himself.”

Phillip Home (Newcastle, U.K.) presented what he termed “a balanced perspective” on the relationship between rosiglitazone and CVD, giving a rather different historical perspective from that

of Nissen, pointing out that by 2000, these agents were shown effective in glucose lowering, complementing existing treatment approaches, and improving insulin sensitivity—although fluid retention and occasional cardiac failure were known, as well as the mixed effects on lipid profile. European regulators required cardiovascular outcomes studies, leading to the performance of the PROactive and RECORD studies. Concerns were related to heart failure rather than to classic cardiovascular outcomes. Subsequent evidence accumulated on improvement in cardiovascular risk markers, in blood pressure, and in surrogate cardiovascular outcomes, such as carotid IMT. The ADA and European Association for the Study of Diabetes published a consensus algorithm for initiation and adjustment of treatment, including TZDs alongside insulin and sulfonylureas largely because of the safety basis of the agents not causing hypoglycemia (28).

Home pointed out that rather than there being an effort to obscure the 31% increase in CVD seen in the retrospective analysis, this was included in the revision to the European rosiglitazone labeling in September 2006, along with results of a large observational study to which Nissen referred unfavorably. Home reviewed this study in more detail. It gave 39,132 person-years of follow-up of 33,363 type 2 diabetic patients receiving rosiglitazone or comparator agents (29). The study showed a trend to lower risk of hospitalization for myocardial infarction and coronary revascularization in individuals receiving rosiglitazone than in those treated with sulfonylureas, with still lower risk among individuals receiving metformin. Contradicting Nissen’s statement that few events were observed, Home stated that annual event rates were 1.6%, 1.9%, and 2.4% among individuals receiving monotherapy, oral combination therapy, and combination therapy with insulin, respectively. One-hundred twenty myocardial infarctions occurred in the 14,975 patient-years of follow-up of individuals receiving rosiglitazone, while 203 myocardial infarctions occurred in the 24,522 patient-years of follow-up of individuals receiving metformin and/or sulfonylureas, for 0.8% annual rates in each group. Observation times were up to 36 months, with the lack of comparison with pioglitazone due to low prescription rates for this agent in the Ingenix Research Database, a proprietary research database of commercial enrollees who have both

medical and prescription benefit coverage in a large U.S. managed care organization. Home also cited a study of 200 individuals with metabolic syndrome randomized to rosiglitazone or placebo after undergoing revascularization, extending the meta-analysis cited by Inzucchi (7) with a postintervention myocardial infarction rate trending to favor rosiglitazone (30).

Home remarked that the Nissen meta-analysis failed to give a study hypothesis, leading to what he considered “data snooping on quite a large scale.” If, in fact, the study hypothesis was that myocardial infarction was increased by rosiglitazone and if this hypothesis was based on Nissen’s observations in his letter to *Lancet* about the DREAM Trial, then the inclusion of the DREAM Trial data in the meta-analysis actually would represent a flawed approach, in essence using the same information twice. Home pointed out further that many of the studies in Nissen’s meta-analysis included zero or only one report and that events were not end points but were rather based on nonadjudicated investigator reports, that there was no time-to-event analysis, and that in the fashion reported “cardiovascular death is not a hard end point either,” as deaths may be said to be of cardiac origin without actual documentation.

Given Nissen’s reservations about RECORD, Home went into some detail in describing the study. It was primarily designed as a cardiovascular safety study. Expectations in 1999–2000 were of a higher event rate than actually seen, perhaps reflecting improvements in outcome due to the widespread current use of statins and other risk-modifying agents. The primary end point is a composite of cardiac and vascular events, and the study was designed with an active comparator group, with rosiglitazone used in combination therapy and assessed for noninferiority, “mak[ing] it more relevant to your practice.” He explained that the interim analysis was necessitated by the immense publicity generated by the Nissen/Wolski meta-analysis, leading many study participants to withdraw after “members of Congress leaked data to the *New York Times*.” Home characterized the interim analysis as the “lesser of the evils.” A “fire-walled” approach was used, however, to maintain data integrity.

The RECORD Study enrolled individuals receiving either a sulfonylurea or metformin, randomized to open-label addition of either rosiglitazone or the

other agent, leading to comparison of 2,220 type 2 diabetic individuals receiving rosiglitazone in combination with either metformin or a sulfonylurea, with 2,227 receiving metformin and a sulfonylurea in combination. The approach used and the level of glycemic control achieved through 18 months in the first 1,122 participants has been reported (31). One weakness is loss to follow-up of 218 and 223 of the participants with and without rosiglitazone, respectively. In addition, 140 and 224 transferred to insulin (rescue with insulin was required by study design for A1C >8.5%), and 74 and 80 died, respectively. The interim comparison was of all individuals receiving rosiglitazone compared with all in the comparator group. Their baseline age was 59 years, 51% were male, diabetes duration was 7 years, and A1C averaged 7.9%.

Home presented the results of the interim analysis of adjudicated events at 3.75 years (24). The primary end point of CVD hospitalization (for acute myocardial infarction, congestive heart failure, stroke, unstable angina pectoris, transient ischemic attack, unplanned cardiovascular revascularization, amputation of extremities, or any other definite cardiovascular reason) or death from cardiovascular causes (including heart failure, acute myocardial infarction, sudden death, and death caused by acute vascular events including stroke) occurred in 217 individuals receiving rosiglitazone and 202 control subjects—not an unexpected finding given the inclusion of a number of heart failure end points. Cardiovascular death occurred in 29 vs. 35 individuals, and total mortality rates were 74 vs. 80. The combined end point of cardiovascular death, myocardial infarction, and stroke, a standard approach used in many trials, occurred in 93 vs. 96 individuals; there were 43 vs. 37 myocardial infarctions; and heart failure occurred significantly more frequently in 38 vs. 17 individuals. “Those are the findings,” Home said, pointing out that “rosiglitazone appears to behave similarly for cardiovascular death, all-cause death, and cardiovascular composite . . . [This] suggests that rosiglitazone should still have a role . . . [although] increase in myocardial infarction not causing death cannot be ruled out.” The strengths of RECORD are its specific design for ascertainment of cardiovascular outcomes, with a long-term trial in a large cohort, using active comparators. Home acknowledged that the lower than predicted event rate low-

ered the statistical power of the study, as did the 10% loss to follow-up. The comparator agents may have had differing efficacy, but no confounding was found differing effects of sulfonylureas from those of metformin.

Home concluded that the Nissen study is “a poor basis for making decisions, . . . [that] TZDs have a continuing role to play in glucose-lowering therapy, [and] that their role needs to be redefined in the guidelines [as] individual physicians should not be relied upon to make these assessments.” He ended by noting an observation that “worried me and still worries me.” FDA licensing files show cardiovascular events with metformin vs. comparators occurring at rates of 1.3 vs. 0.8%, with rosiglitazone at rates of 2.0 vs. 1.5%, with sitagliptin at rates of 0.8 vs. 0.3%, and in glimepiride registration studies there were five vs. no deaths; “so there does appear to be something we don’t understand from the early short-term studies.”

At the conclusion of the debate, a panel comprised of John Buse (Chapel Hill, NC), Barry Goldstein (Philadelphia, PA), and David Nathan (Boston, MA) agreed that for individuals treated with rosiglitazone in good control of diabetes and lipids that “there would be more risk in switching.” Although Buse suggested discontinuing for individuals not in good control, Goldstein expressed a “reluctance to abandon these agents . . . [which are] related to the pathogenesis of diabetes with inflammation and cytokines and increased FFA [free fatty acid] levels,” commenting that “a signal of cardiovascular damage . . . is surprising.” Nathan suggested that “there are insufficient data to come to any conclusion that would convince us all.”

Further considerations

A number of additional considerations appear relevant to the question of whether the Nissen meta-analysis was properly performed. It appears from the presentation and from review of the article that there was no literature search for all relevant studies. The Cochrane meta-analysis protocols require such a literature search to establish the base for an analysis, and a literature search readily shows randomized controlled trials of rosiglitazone treatment in which myocardial infarctions were ascertained in the treatment and control groups (32,33), including one such trial carried out in Nissen’s institution (30).

The use of a fixed effects rather than a random effects method in the meta-analysis, although described by Nissen in the article as being appropriate, is controversial. The use of fixed effects calculations does not consider the variability among studies. A classic methodological article with authors including the late Thomas Chalmers, a founder of the use of meta-analysis for quantitative comparison of multiple randomized controlled trials, showed the fixed effect model to lead to more errors in analyses including both larger and smaller studies (34). The Cochrane Collaboration “open learning material” states that “fixed effect meta-analysis are based on the mathematical assumption that a single common (or ‘fixed’) effect underlies every study in the meta-analysis A random effects analysis makes the assumption that individual studies are estimating different treatment effects The debate is not about whether the underlying assumption of a fixed effect is likely (clearly it isn’t)” (35). The random effect approach, then, is considered the more conservative approach. If as suggested in the Cochrane document, one analyzes the data in Table 3 of Nissen’s study with both fixed and random effect approaches, the fixed effect analysis relative risk is 1.42 with 95% CI 1.03–1.96 ($P = 0.033$), agreeing with the article, while the random effect relative risk is 1.30 with 95% CI 0.94–1.79 ($P = 0.110$) (36).

Nissen’s analysis used the number of events rather than time to first event. He justified this approach based on the lack of what he acknowledged would be the more accurate time-in-study data. This approach, however, biases against longer trials and weights toward the short-term studies. Furthermore, it appears that rosiglitazone, as a particularly effective glycemic treatment, is associated with greater adherence. This would lead to shorter length of follow-up among individuals taking comparators, who would nevertheless be included in study results using the “last observation carried forward” approach, allowing clinical trials to use all enrolled individuals in analyzing efficacy of various treatments. Such an approach, while being conservative in only comparing individuals responding to treatment, leads to a shorter period of observation for individuals taking the less effective treatment.

As noted by Nissen, it is not possible to ascertain the duration of follow-up for all the studies. The largest study, ADOPT,

does give interesting information along these lines. Figure 2 of this study shows the number of individuals still receiving rosiglitazone, metformin, and glyburide at 1–5 years. Summing the numbers of individuals enrolled at these time points suggests that there were 4,410 person-years of observation with rosiglitazone but 3,688 person-years of observation with glyburide—a 16% lower adherence. Even only using the 1-year ADOPT follow-up data, there were 1,207 individuals receiving rosiglitazone but 1,114 receiving glyburide—an 8% lower rate. From Nissen's Table 1, it appears that 10 of the smaller studies (excluding ADOPT and DREAM) were placebo controlled and that in 16 the control group received a sulfonylurea. This observation alone might lead one to question the assumption of the fixed-effect analysis. Furthermore, if study adherence is lower by an appreciable amount in the rosiglitazone comparator groups and if the time for observation of serious adverse events is reduced, the increase in observed myocardial infarctions with rosiglitazone might simply reflect longer follow-up with this agent.

Apparently, Nissen excluded either four or six studies not reporting events; it is difficult to ascertain this from the article. There are standard ways of dealing with a zero event rate, and inclusion of these studies would, of course, have lowered the overall event rate. Finally, Nissen's failure to define the hypothesis to be tested, as discussed by Home, leads to an analysis that is not prespecified and violates Cochrane protocol. One can imagine that multiple end points could have been considered, such as myocardial infarction, stroke, cardiovascular death, procedures, hospitalizations, etc., so that without an a priori hypothesis the statistical significance of an association becomes unknown.

FDA advisory panel recommendations

A 23-member advisory panel met 30 July 2007 to review this information (37). Although at the time of publication no formal statement had been issued, their recommendations were widely reported. The panel voted 20 to 3 that there was sufficient evidence of increased myocardial infarction risk for concern but at the same time did not consider the evidence sufficient to withdraw the agent from clinical use, voting 22 to 1 that the drug continue to be marketed (38). It is anticipated

that a warning label will be required, and it is uncertain whether this will apply only to a putative myocardial infarction risk of rosiglitazone or whether the well-established heart failure risks for both rosiglitazone and pioglitazone will lead to such a label for both of these agents.

Additional TZD presentations

As always at the ADA meetings with every topic, there were numerous fascinating studies on aspects of TZD treatment. Several studies addressed mechanism of action. Basu et al. (abstract 250) studied the insulin resistance produced in 31 type 2 diabetic individuals after infusion of a fat emulsion with heparin to increase FFA levels during a hyperinsulinemic-euglycemic clamp, showing a reduction in insulin-induced stimulation of glucose utilization (abstract numbers refer to the American Diabetes Association Scientific Sessions, *Diabetes* 56 [Suppl. 1], 2007). After 4 months of treatment, the effect of FFA on peripheral glucose utilization appeared particularly lessened by metformin, while pioglitazone both increased glucose utilization and decreased hepatic glucose production. Busui et al. (abstract 600) administered 8 mg rosiglitazone daily or 10 mg glyburide daily for 6 months to 27 type 2 diabetic individuals, finding that only the former agent reduced plasma nitrotyrosine (by 82%), as well as decreased C-reactive protein and von Willenbrad antigen; glyburide was associated with a reduction in myocardial blood flow both at rest and following stress testing. Aso et al. (abstract 333) compared effects of pioglitazone with those of voglibose administered for 12 weeks to 34 patients with type 2 diabetes, with comparable improvements in glycemia. The high molecular weight-to-total adiponectin ratio increased only with pioglitazone, and in the pioglitazone-treated patients, adiponectin showed a negative correlation with the change in A1C.

Kutoh and Wajs (abstract 609) compared effects of 3 months of treatment with pioglitazone in 26 individuals with baseline fasting insulin >15 vs. 27 with levels <7 μ U/ml. The two groups differed in baseline A1C (9.1 vs. 10.0%), triglyceride (224 vs. 166 mg/dl), and HDL cholesterol (50 vs. 61 mg/dl). In the high insulin group, A1C decreased to 7.5%, with improvement in triglyceride and HDL cholesterol and with a 41% reduction in fasting insulin, while the low insulin group showed a fall in A1C to 8.5% and a 126% increase in fasting insulin,

suggesting that pioglitazone might improve β -cell function either directly or by reducing lipo- or glucotoxicity, potentially changing the natural history of the disease. In 40 women with polycystic ovary syndrome, Jude et al. (abstract 584) compared the effects of 500 mg metformin twice daily with those receiving 4 mg rosiglitazone daily, finding a 2-kg weight loss vs. 1-kg weight gain after 3 months but with greater falls in gonadotropins, fasting glucose, and insulin levels with the latter agent. Fetuin-A is an inflammation-related glycoprotein secreted by the liver, acting to inhibit soft-tissue calcification, appearing to reduce insulin receptor tyrosine kinase activity and, hence, associated with insulin resistance. Mori et al. (abstract 611), however, reported increased serum fetuin-A levels in 10 type 2 diabetic patients receiving pioglitazone for 6 months, while neither metformin (given to nine individuals) nor an exercise program (eight participants) changed fetuin-A levels, despite similar falls in A1C. Fetuin-A may be mechanistically relevant to TZD action, both on glycemia and, as recently reported, on bone loss with these agents.

Cardiovascular effects of TZDs were addressed in a number of studies. Dietlein et al. (abstract 2,125) and Bierwirth et al. (abstract 494) reported findings in a 26-week, open, multicenter observational trial of 1,426 type 2 diabetic individuals treated with 30 or 45 mg pioglitazone daily, finding that carotid IMT decreased 57% more with the higher dose. There was a 1% reduction in A1C both in 627 individuals receiving statins and in 752 not on such treatment; the former had twice as great a reduction in mean carotid IMT, certainly suggesting that there may be benefits to the combined treatment approach, contradicting Skyler's assertion from the PROactive subset analysis. In a study of the effects of pioglitazone, simvastatin, and the combination in 125 nondiabetic individuals (109 with insulin resistance by the homeostasis model), Schöndorf et al. (abstract 613) reported that insulin sensitivity improved 43% with pioglitazone, while not changing with simvastatin, with parallel changes in adiponectin, while C-reactive protein decreased with both agents, and retinol binding protein 4 failed to change with either.

Spanheimer et al. (abstract 553) reported a significantly greater rate of hospitalizations for cardiac ischemia in placebo- than in pioglitazone-treated par-

ticipants in the PROactive Study of 5,238 type 2 diabetic individuals with macrovascular disease, with 14.2 vs. 11.9% requiring such hospitalization. Borchert et al. (abstract 251) reported observations from a randomized controlled trial of 45 mg pioglitazone vs. glimepiride (mean dose 2.7 mg) daily in 180 type 2 diabetic individuals, finding that 7 of the pioglitazone-treated individuals developed evidence of heart failure, all with elevated baseline brain natriuretic peptide and 5 with baseline levels >100 pg/ml. Edema, in contrast, although occurring threefold more often in individuals treated with pioglitazone, was not associated with the baseline brain natriuretic peptide level. This may offer a useful approach to the determination of individuals for whom TZD treatment is not appropriate. Balas et al. (abstract 617) measured whole-body fat and total body water with dual-energy X-ray absorptiometry, a tritiated water dilution technique, and bioimpedance in 35 individuals with nonalcoholic steatohepatitis and type 2 diabetes or impaired glucose tolerance receiving pioglitazone versus placebo, showing a 2.5-kg weight gain over 6 months with pioglitazone, without change in patients receiving placebo. Neither total body nor extracellular water changed, suggesting an increase in fat mass, with this population not showing evidence of fluid retention. Evangelista et al. (abstract 2,286) randomized 50 type 2 diabetic individuals to a 16-week period of treatment with pioglitazone versus metformin—the former associated with greater falls in C-reactive protein, hepatic transaminase levels, fasting plasma glucose, A1C, serum insulin, and E-selectin but with a significant increase in total cholesterol levels.

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