Rosiglitazone and New Insights in the BARI 2D Trial

According to post hoc analyses of the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D; NCT00006305) data, rosiglitazone is not associated with an increased risk of major adverse cardiovascular events, including myocardial infarction (MI) and death, in patients with type 2 diabetes mellitus (T2DM) and established coronary artery disease (CAD). The thiazolidinedione (TZD) rosiglitazone has received a great deal of attention over the past few years based on meta-analysis data that were published in the *New England Journal of Medicine* in 2007, concluding that "rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance" [Nissen SE et al. *New Engl J Med* 2007]. However, previous data have not focused on patients with T2DM with established CAD. The risk of inadequate glycemic control and adverse cardiac events in this group is fundamentally higher than would be present in diabetic patients without a prior history of CAD. Therefore, the current BARI 2D analyses evaluate the long-term effect of rosiglitazone in a high-risk cohort with CAD (angiographically documented with ≥1 significant lesion, suitable for elective revascularization).

BARI 2D included 2368 patients with T2DM and CAD who were randomized in a 2x2 factorial design to undergo either prompt revascularization with intensive medical therapy or medical therapy with delayed or no revascularization and received either insulin sensitization (n=1183) or insulin provision (n=1185) therapy with a target glycated hemoglobin <7.0%. TZDs or metformin were used in patients who received insulin sensitization therapy, and the option of rosiglitazone treatment was left to the discretion of the treating investigator. Additionally, patients in the insulin provision group received TZDs or metformin if glycated hemoglobin could not be maintained below 8.0%.

Richard D. Bach, MD, Washington University School of Medicine, St. Louis, MO, presented data that focused on a comparison of patients who were treated with rosiglitazone versus those who did not receive a TZD in BARI 2D. The primary endpoint was all-cause mortality. The secondary endpoints included a composite outcome of death, MI, or stroke (major cardiovascular events), congestive heart failure (CHF), and fracture. The mean follow-up was 5.3 years for mortality and 4.5 years for all other endpoints. The groups were similar at baseline, with the exception of glycated hemoglobin values (mean HbA1C 7.8±1.6% in the rosiglitazone group vs 7.5±1.6% in the no-TZD group; p<0.0001). Post hoc analyses included a comparison of endpoint frequencies, expressed as number per 100 patient-years for patients while on rosiglitazone treatment versus those who did not receive TZD treatment. In a separate secondary analysis, potential legacy effects 3 months post-treatment were also examined, based on events that occurred during that time period.

Treatment with rosiglitazone was not associated with an increase in adverse ischemic cardiovascular events, including death and MI. The on-treatment composite rate of death, MI, and stroke was significantly 28% lower in the rosiglitazone group than in the no-TZD group (adjusted relative risk [RR]) 0.72; p=0.01). When factoring in 3-month post-treatment events, rosiglitazone treatment was associated with a lower rate of stroke compared with no TZD (RR, 0.40; 95% CI, 0.18 to 0.87; p=0.02) and a trend toward a lower rate of death, MI, and stroke (RR, 0.80; p=0.08). The incidence of CHF was higher in the rosiglitazone group than in the no-TZD group, but this did not reach statistical significance. A significantly higher rate of fractures was observed in the rosiglitazone group compared with no TZD (RR, 1.62; p=0.03). No significant interactions resulting in increased cardiovascular risk were found with regard to rosiglitazone and other treatments, such as insulin, metformin, nitrates, and angiotensin-converting enzyme inhibitors although an interaction between rosiglitazone and metformin was observed that suggested that concurrent metformin treatment appeared to mitigate an increased risk of CHF with rosiglitazone.

There were two potential limitations of BARI 2D. First, the rosiglitazone cohort was not part of the randomization. Second, many patients received more than one antidiabetic agent over the course of the study, which may limit the ability to differentiate between agents and determine effects accurately.

Saul Genuth, MD, Case Western Reserve University, Cleveland, OH, elaborated on the insulin strategy findings in relation to the revascularization data from BARI 2D. Of the 2368 patients who were selected for revascularization, 1605 underwent percutaneous coronary intervention (PCI) and 763 underwent coronary artery bypass grafting (CABG). No difference was found between prompt revascularization plus aggressive medical therapy and aggressive medical therapy alone in the outcomes of total

mortality or the composite of cardiovascular death, MI, and stroke.

Dr. Genuth pointed out that while BARI 2D does not provide evidence of superiority for insulin sensitization over insulin provision, insulin sensitization may be more beneficial in those who undergo CABG or PCI, depending upon the severity of disease. Furthermore, the difference in baseline glycated hemoglobin levels between the two insulin therapy groups does not appear to account for this beneficial effect. There were baseline differences among the CABG and PCI groups that were related to CAD severity that should be considered. At baseline, 20% had 3-vessel disease in the PCI group versus 52% in the CABG group. When categorizing by baseline CAD subgroup of less advanced CAD (1-vessel disease and/or myocardial jeopardy index 0-35) or more advanced CAD (≥2-vessel disease and/or myocardial jeopardy index >35), the effect of insulin sensitivity appeared to benefit patients with more advanced CAD in the CABG group and those with less advanced CAD in the PCI group (Table 1).

Table 1. IS vs IP on Composite Outcome in Prompt Revascularization Stratum According to Degree of CAD.

Baseline characteristics	IS/IP Hazard Ratio
CABG	
More CAD	0.62 (0.38-1.01)
Less CAD	0.83 (0.26-2.63)
PCI	
More CAD	0.67 (0.45-0.99)
Less CAD	1.13 (0.74-1.73)

IS = Insulin-Sensitivity; IP = Insulin-Provision.

Severe hypoglycemia (defined as hypoglycemia that required assistance with treatment and either a blood glucose level of <50 mg/dL or confusion, irrational or uncontrollable behavior, convulsions, or coma reversed by blood glucose-raising treatment) was more frequent in the insulin provision group than in the insulin sensitization group (9.2% vs 5.9%, respectively; p=0.003). Peripheral pitting edema was more frequent in the insulin sensitization group than in the insulin provision group (p=0.02). Other adverse event rates were similar between the groups [The BARI 2D Study Group. *New Engl J Med* 2009].

Rosiglitazone is not associated with an increased risk of major adverse cardiovascular events in diabetic patients with established CAD. However, it is associated with an increased risk of fractures. When considering rosiglitazone in the setting of revascularization strategies, it is important to note that the benefit of rosiglitazone may be dependent upon the severity of disease and type of intervention. These new insights into the BARI 2D trial may help clarify the effect of rosiglitazone in a specific subset of diabetic patients and may assist clinicians in the decision-making process when this treatment is being considered.

The Effect of Atorvastatin on Beta-Cell Function

Atorvastatin therapy may delay the loss of beta-cell function in patients with recent-onset type 1 diabetes mellitus (T1DM). In rheumatoid arthritis patients, atorvastatin diminishes immune-mediated disease activity, but little is known about the systemic immune response that is associated with atorvastatin in patients with newly diagnosed T1DM. Hubert Kolb, PhD, Heinrich-Heine University, Dusseldorf, Germany, presented a study that investigated this issue.

The multicenter, randomized, placebo-controlled Diabetes and Atorvastatin (DIATOR) trial included 89 patients aged 18 to 39 years with newly diagnosed T1DM and islet autoantibodies. Patients were randomized to receive either atorvastatin (40 mg daily for 4 weeks followed by 80 mg daily; n=46) or placebo (n=43) for a total of 18 months. At 12 months, 33 patients in the atorvastatin group and 35 patients in the placebo group were included in the analysis. The final analysis at 18 months included 29 patients from the atorvastatin group and 34 patients from the placebo group. The groups were well matched at baseline. The primary endpoint was change in serum C-peptide levels from baseline to 12 and 18 months. C-peptide levels were assessed before and 90 minutes after patients received a standardized liquid mixed meal (Boost HP).

At 18 months, the median stimulated C-peptide and fasting C-peptide concentrations were higher in the atorvastatin group than in the placebo group (48% and 50%, respectively). Due to the high interindividual variation, this difference was not significant. Secondary analyses indicated partial preservation of beta-cell function in the atorvastatin but not the placebo group. Median fasting C-peptide levels within the atorvastatin group remained stable throughout the duration of the study. However, median fasting C-peptide levels in the placebo group decreased from baseline to 12 months