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

and again at 18 months (p<0.001). There was a significant decline in median stimulated C-peptide concentrations for both groups from baseline to Month 12 (0.88 to 0.73 nmol/l for atorvastatin and 0.89 to 0.71 nmol/l for placebo; p<0.01 for both). This decline continued in the placebo group at Month 18 (p=0.047) but did not occur in the atorvastatin group.

The course of metabolic control was similar between the two groups. However, at 12 months, insulin doses varied between the two groups (p=0.007). An increase in HbA1C levels was observed in the placebo group from 12 to 18 months, but this was not the case in the atorvastatin group. Those who were treated with atorvastatin demonstrated decreases in systemic levels of C-reactive protein, total and low-density lipoprotein cholesterol, and triglycerides (p<0.001 for all). Additionally, the course of the chemokine MCP-1 differed between the two groups, as a decrease was observed in the placebo group but not in the atorvastatin group (p=0.009). The course of the other 14 immune mediators appeared to be similar for atorvastatin and placebo. There did not appear to be covariates that were associated with atorvastatin and C-peptide secretion such as age, body mass index, or baseline serum C-peptide concentrations.

Atorvastatin may delay the loss of residual beta-cell function in patients with newly diagnosed T1DM and merits further investigation in a larger clinical trial.

Caffeine Supplementation for the Prevention of Exercise-Induced Hypoglycemia

Caffeine ingestion prior to exercise may reduce hypoglycemic episodes and slow the decline in blood glucose during exercise in patients with type 1 diabetes mellitus (T1DM). Ian W. Gallen, MD, Wycombe Hospital, Buckinghamshire, United Kingdom, presented findings from a small study that investigated the physiological impact of caffeine ingestion prior to exercise.

This study evaluated 5 patients with T1DM (4 males and 1 female) who were on multiple daily injection therapy. The mean age was 38.2 years, and the mean body mass index was 27.32. Study Day 1 consisted of workload assessment, as determined by maximum oxygen consumption (VO_2 max). Patients were randomized to receive either caffeine 5 mg/kg or placebo 2 hours postprandially/after glargine-aspart injection with rest for 30 minutes prior to exercise. Subjects exercised on a cycle ergometer for 10 minutes at 50% VO_2 max, increasing to 70% VO_2 max for 30 minutes. After a total of 40 minutes of exercise, patients rested for 30 minutes. Arterialized blood glucose and lactate were measured every 10 minutes, gas exchange was measured continuously, and respiratory exchange rate (RER) was calculated. At least 1 week later, an identical exercise protocol was administered, but the patients received the opposite treatment regimen (those who previously received caffeine were given placebo and vice versa).

Blood glucose remained similar to baseline levels throughout the duration of the exercise and into the resting phase of the program in those who received caffeine. None of the subjects in the caffeine group required oral glucose. Subjects who were taking caffeine demonstrated significantly higher blood glucose levels compared with placebo after exercising at 70% VO_2 max for 10 minutes (p=0.014), after exercising at 70% for 30 minutes (p=0.032), and after 30 minutes of postexercise rest (p=0.01). Blood glucose levels began to fall at the start of exercise in those who received placebo, and this rapid decline continued throughout the exercise program. Oral glucose (20 g) was administered to 2 of the patients in the placebo group in order to avoid a hypoglycemic event.

Lactate and RER measurements remained relatively consistent throughout the exercise program in those who received caffeine. Caffeine did not appear to alter RER or increase lactate levels, which suggests that caffeine does not alter substrate oxidation. These findings also suggest that caffeine may augment endogenous glucose production and oxidation when coupled with exercise.

Caffeine may be a useful tool in the prevention of hypoglycemic events during exercise in patients with T1DM. However, larger studies are needed to establish the safety and efficacy of such an approach.