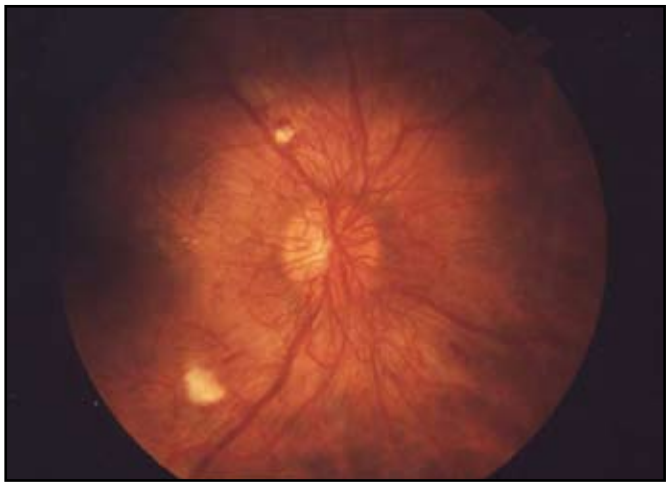
Diabetic Retinopathy and the ACCORD Trial

According to substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD; NCT00000620) trial, intensive glycemic control and combination fenofibrate + simvastatin therapy reduce the rate of diabetic retinopathy progression. Emily Y. Chew, MD, National Eye Institute, Bethesda, MD, presented findings from a substudy of ACCORD.

The ACCORD eye study included a comprehensive eye evaluation that included visual acuity measurement, fundus photography of 7 standard stereoscopic fields (Figure 1), and central grading of the fundus photography using the Early Treatment Diabetic Retinopathy Study (ETDRS) classification scale of diabetic retinopathy. These exams were administered at baseline and at Year 4. The objective of this study was to determine whether intensive glycemic control, intensive blood pressure control, or combination (fenofibrate + simvastatin) therapy for dyslipidemia would affect the progression of diabetic retinopathy in patients with type 2 diabetes mellitus (T2DM). ACCORD participants were excluded from participation in this substudy if they had previous laser photocoagulation, vitrectomy, or inability to progress 3 steps on the ETDRS scale of diabetic retinopathy severity.

Figure 1. Diabetic Retinopathy.



Reproduced with permission from E. Chew, MD.

The primary outcome was progression of retinopathy, defined as the progression of diabetic retinopathy of ≥3 levels on the EDTRS scale, assessed on fundus photographs at 4 years compared with baseline; photocoagulation; or vitrectomy during follow-up. Patients who participated in the ACCORD eye study who had both baseline and follow-up visits (n=2856) were included in the final data analysis. Of the 3472 patients who were seen for baseline visits, 616 were missing at follow-up. The mean HbA1C was 8.2%, the mean high-density lipoprotein cholesterol was 41.9 mg/dL, the mean low-density lipoprotein cholesterol was 100.7 mg/dL, and mean triglyceride level was 195.1 mg/dL. The mean systolic blood pressure (BP) in this group was 134.5 mm Hg, and the mean diastolic BP was 74.9 mm Hg.

A total of 253 patients had progression of retinopathy (8.9%) at 4 years, of which 7.3% was in the intensive therapy group (n=104/1429) and 10.4% was in the standard therapy group (n=149/1427). Progression of retinopathy was more frequent among patients who received standard glycemic therapy versus intensive therapy (OR, 0.67; 95% CI, 0.51 to 0.87; p=0.003). Patients who received combination lipid therapy also had less incidence of retinopathy progression compared with placebo (OR, 0.60; 95% CI, 0.42 to 0.87; p=0.006).

Intensive glycemic and combination lipid therapy significantly reduced the incidence of progressive retinopathy at 4 years. These effects were consistent across subgroups. Intensive BP control to 120 mm Hg did not appear to influence the progression of retinopathy. No significant interactions were found with regard to any of the prespecified subgroups.

STAR 3 Study

The use of sensor-augmented pump (SAP) therapy resulted in significant decreases in HbA1C compared with multiple daily injection (MDI) therapy across age groups. Richard M. Bergenstal, MD, International Diabetes Center at Park Nicollet, Minneapolis, MN, presented findings from the Sensor-Augmented Pump Therapy for A1C Reduction 3 (STAR 3; NCT00406133).

STAR 3 was a 1-year, multicenter, randomized, controlled trial that included 485 patients aged 7 to 70 years (329 adults and 156 children) with inadequately controlled type 1 diabetes mellitus (T1DM) on MDI (≥3 injections, including a long-acting analog, for at least 3 months). Patients were randomized to receive either SAP (n=244) or MDI (n=241), and all patients utilized diabetes management software (CareLink Therapy Management Systems for Diabetes-Clinical, Medtronic)

Continued on page 23

Continued from page 19

throughout the duration of the study. The groups were well matched at baseline with the exception of weight and student status among adult patients in both treatment groups. The baseline mean glycated hemoglobin for all treatment groups, regardless of age, was 8.3%. The glycated hemoglobin target throughout the duration of STAR 3 was <7.0%.

Follow-up visits took place at 3, 6, 9, and 12 months. The primary endpoint was the difference in HbA1C from baseline to 1 year. The secondary endpoints included the frequency of severe hypoglycemia (defined as an episode that required assistance and documented blood glucose value <50 mg/dL or recovery with restoration of plasma glucose), percentage of patients with A1C ≤7%, and area under the curve (AUC) from continuous glucose monitoring >180 mg/dL and <70 mg/dL.

The baseline mean glycated hemoglobin in the SAP group had decreased to 7.5% at 1 year compared with 8.1% in the MDI group (absolute reduction of 0.8±0.8% for SAP vs 0.2±0.9% for MDI; p<0.001). When stratified according to age group, the between-group differences favored SAP among children (aged 7 to 18 years) and adults (aged ≥19 years; p<0.001 for both). At 1 year, 27% of patients in the SAP group (n=67) achieved the target glycated hemoglobin of ≤7% versus 10% in the MDI group (n=23; p<0.001). Of those who reached glycated hemoglobin of ≤7%, children accounted for 13% in the SAP group and 5% in the MDI group. Of note, increased frequency of sensor use in the SAP group was associated with greater reductions in glycated hemoglobin levels at 1 year (p=0.003 after adjustment for baseline levels).

Rates of severe hypoglycemia and diabetic ketoacidosis were similar among the two treatment groups at 1 year (Table 1). Three serious adverse events occurred during the study. One death from sudden cardiac arrest occurred in a patient with a history of cardiovascular disease in the MDI group, and there were 2 hospitalizations due to cellulites that resulted from insertion-site infections in the SAP group. At 1 year, no severe hypoglycemic events were observed among children with glycated hemoglobin ≤7%, regardless of the treatment regimen.

SAP significantly decreased HbA1C concentrations regardless of age. This decrease was observed within the first 3 months of treatment and was sustained through the first year. This benefit was not associated with increased incidence of severe hypoglycemia, diabetic ketoacidosis, or weight gain. Patients who were treated with SAP are more likely to reach the target HbA1C (≤7%) than those on MDI therapy, and age does not appear to be a factor. An integrated approach that includes sensors, pumps, and diabetes management software may be appropriate for patients with inadequately controlled T1DM.

Table 1. Severe Hypoglycemia and Ketoacidosis.

All Patients			
Variables	**SAP (n=247)**	**MDI (n=248)**	**p value**
Severe hypoglycemia			
No. of events	32	27	0.58
No. of patients	21	17	
Rate per 100 person/year	13.31	13.48	0.84
Diabetic ketoacidosis			
No. of events	3	2	0.38
No. of patients	3	1	
Rate per 100 person/year	0.01	<0.01	0.60
Adults			
Variables	**SAP (n=169)**	**MDI (n=167)**	**p value**
Severe hypoglycemia			
No. of events	25	23	0.53
No. of patients	17	13	
Rate per 100 person/year	15.31	17.62	0.66
Diabetic ketoacidosis			
No. of events	2	0	NA
No. of patients	2	0	
Rate per 100 person/year	0.01	0	NA
Children			
Variables	**SAP (n=78)**	**MDI (n=81)**	**p value**
Severe hypoglycemia			
No. of events	7	4	0.53
No. of patients	4	4	
Rate per 100 person/year	8.98	4.95	0.35
Diabetic ketoacidosis			
No. of events	1	2	0.49
No. of patients	1	1	
Rate per 100 person/year	0.02	0.02	0.20

Additional Reading

Published online ahead of print June 29, 2010 and appearing in print July 22, 2010 Bergenstal RM et al. Effectiveness of Sensor-Augmented Insulin-Pump Therapy in Type 1 Diabetes. *New Engl J Med* 2010.