Of 668 and 745 glucose observations in the exenatide and MOD groups, respectively, there were numerically fewer overall hypoglycemic episodes in the exenatide group (0.9% vs 1.2%; p=0.57), including severe events (0% vs 0.3%; p=0.18). BG in exenatide-treated patients was more frequently within the target range (100 to 140 mg/dL; 37% vs 29%; p<0.001) and within 71 to 140 mg/dL (48% vs 39%; p<0.001) compared with MOD. No serious adverse events were observed in the exenatide group.

The study objective was to determine the feasibility, efficacy, and safety of glucose-lowering with IV exenatide monotherapy in hyperglycemic patients who were admitted to the CICU. The findings suggest that fixed-dose IV exenatide is feasible in hyperglycemic ICU patients, achieves similar efficacy compared with IV insulin, and does not cause severe hypoglycemia.

Risk of Mortality Increased with Divergence from Glycemic Target

Written by Lori Alexander

Glucose levels that deviated from established glycemic targets were found to be associated with an increased risk of mortality in an analysis of self-monitoring blood glucose (SMBG) data from a subset of patients in the ACCORD trial.

"The more you diverge from what you're trying to achieve, the higher [the] risk of mortality," said Richard Bergenstal, MD, International Diabetes Center at Park Nicollet, Minneapolis, Minnesota, USA, who reported the findings.

The subanalysis was done in an effort to better understand the excess mortality that was found with intensive therapy (target HbA1C <6%) compared with standard therapy (target HbA1C <7% to 7.9%) in the ACCORD trial. Increased mortality in the study was found to be associated with severe hypoglycemia, but the risk was similar in both groups and could not account for the difference between the groups. The hypothesis was that mild/moderate hypoglycemia may be the cause, leading the investigators to study SMBG data.

Approximately half (52%) of the patients in ACCORD had downloaded any SMBG data; most had downloaded data for at least 2 years. The patients who downloaded SMBG data were representative of the entire study population, as their characteristics were similar to those of the patients who had not downloaded SMBG data.

Subjects in the intensive group tested their glucose levels more frequently (2.7 vs 2 times per day in the standard group). There was a significant correlation between drop in HbA1C and increasing frequency of SMBG tests for both groups (11% reduction in the intensive group and 6% reduction in the standard group; p<0.001 by rank correlation). This finding suggests that more frequent self-monitoring may be worthwhile.

The frequency of hypoglycemia (glucose level <70 mg/dL) was 3 times greater in the intensive group than in the standard group, and the frequency of hyperglycemia (glucose level >200 mg/dL) was 2 times greater in the standard group than in the intensive group. However, patients in the intensive group who died were not more likely to have had hypoglycemia than those who remained alive. Instead, the proportion of patients with glucose levels >140 mg/dL was higher among the patients who died.

In evaluating mortality according to the frequency of hypoglycemia, the highest mortality (more than 5%) was found among patients in the intensive group who had fewer than 1% of low glucose levels; the rate was 5 times greater than that for patients in the standard group with few low levels. In the standard group, the highest mortality was associated with the greatest frequency of hypoglycemia; the rate was nearly twice as high as that for patients in the intensive group with the same percentage of low levels.

In terms of hyperglycemia, mortality was highest in both groups when the frequency of high glucose level was greatest; the rate for the intensive treatment group was more than twice that for the standard group.

Dr. Bergenstal recommended setting a glucose goal in addition to an HbA1C goal. "Evaluate the [glucose] profiles, and if you're not achieving the target you set, then be careful and think about whether you want to intensify treatment further if the levels diverge from [the target]." Clinicians should be careful about even mild to moderate hypoglycemia, particularly in people for whom goals have been relaxed, such as frail older patients.

High HbA1C levels are dangerous, not only because of the risk for hyperglycemia but also because patients with high HbA1C levels had the worst frequency of hypoglycemia.

Depression Increases Risk for Mortality in People with T2DM

Written by Lori Alexander

The ACCORD Health-Related Quality of Life (HRQL) study demonstrated that depression is a strong predictor of increased mortality and may increase the risk of

cardiovascular (CV) events in people with type 2 diabetes mellitus (T2DM). The findings of the study were reported by Patrick J. O'Connor, MD, MPH, HealthPartners, Minneapolis, Minnesota, USA.

Approximately 20% to 25% of people with diabetes have depression, and the condition has been shown to predict all-cause mortality in older patients with diabetes. However, the ACCORD HRQL trial is one of few studies designed to investigate the effects of depression on composite CV disease outcomes, macrovascular complications, or microvascular complications in people with T2DM.

The trial included 2053 participants who completed the depression measure from the Patient Health Questionnaire (PHQ-9) at baseline and at 1, 3, and 4 years. The depression measure consists of nine items, each of which is scored 0 to 3 points. Participants were classified as having depression in three different ways: (a) a score of 10 or more on the PHQ-9 (which has been shown to have 77% sensitivity and 94% specificity for the diagnosis of major depression); (b) major depression, defined as five PHQ symptoms scored at least 2, one of which was depressed mood or lack of pleasure; or (c) minor depression, defined as three or four PHQ symptoms scored at least 2, one of which was depressed mood or lack of pleasure.

Nearly one-third of the participants had depression at baseline. Depression at baseline was associated with female gender, higher rate of tobacco use, higher body-mass index (BMI), higher median triglyceride level, and higher mean HbA1C level ($p<0.0001$ for all). Because of the potentially confounding effects of such differences on subsequent mortality risk, Cox proportional-hazards regression models were used to adjust for several variables, including age, gender, race/ethnicity, HbA1C level, blood pressure, lipid levels, tobacco use, and coronary heart disease status.

Analysis of the data showed that major depression was a significant independent predictor of increased mortality, with a greater risk for all-cause mortality among participants with a PHQ score of 10 or more (HR=1.84) or with major depression (HR=2.24; p=0.008 for both; Table 1). This excess mortality risk was not accounted for by worse HbA1C level, lipid levels, aspirin use, BMI, tobacco use, or other baseline characteristics.

Major depression had a borderline impact on the ACCORD combined macrovascular endpoint, which included major coronary artery disease events, specifically fatal events, nonfatal myocardial infarction (MI), and unstable angina (HR=1.42; p=0.055; Table 1). Major depression was not significantly related to the ACCORD microvascular composite outcome, defined as fatal or nonfatal renal failure, retinal photocoagulation, or vitrectomy (HR=0.93; p=0.79), or to the ACCORD primary composite outcome, defined as CV death, nonfatal MI, or stroke (HR=1.53; p=0.153; Table 1). Minor depression had no significant impact on any outcome.

Table 1. Outcomes According to Depression Status.

Outcome	Hazard Ratio	95% CI	p value
All-cause mortality			
PHQ score ≥10	1.84	1.17, 2.89	0.008
Major depression	2.24	1.24, 4.06	0.008
Minor depression	1.14	0.59, 2.21	0.69
Composite macrovascular endpoint			
PHQ score ≥10	1.14	0.88, 1.49	0.33
Major depression	1.42	0.99, 2.04	0.055
Minor depression	1.23	0.85, 1.78	0.28
Composite microvascular endpoint			
PHQ score ≥10	1.27	0.9, 1.79	0.18
Major depression	0.93	0.53, 1.62	0.79
Minor depression	1.14	0.7, 1.85	0.60
ACCORD primary composite endpoint			
PHQ score ≥10	1.13	0.73, 1.75	0.584
Major depression	1.53	0.85, 2.73	0.153
Minor depression	1.03	0.56, 1.92	0.917

These findings underscore the importance of early identification and effective treatment of depression in patients with T2DM.

Long-Term Injection-Free Subcutaneous Delivery of Exenatide via ITCA 650 Improves Compliance and Controls Glycemic Parameters and Weight

Written by Rita Buckely

Exenatide therapy in patients with type 2 diabetes who take metformin requires twice-daily self-injections and is associated with significant nausea and vomiting [Pinelli NR, Hurren KM. *Ann Pharmacother 2011*]. Continuous delivery of exenatide was evaluated in a Phase 2, randomized study with ITCA 650, a subcutaneous osmotic delivery system that provides constant delivery of exenatide at specified doses [ITCA 650; NCT00943917]. Julio Rosenstock, MD,