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,

University of Texas Southwestern Medical School, Dallas, Texas, USA, presented findings from the study.

The primary outcome for the 24-week, randomized, multicenter trial was efficacy of specific doses of ITCA 650. Eligibility criteria included males or females aged 18 to 70 years with type 2 diabetes mellitus for ≥6 months prior to Screening Visit 1; a stable (>3 months prior to Screening Visit 1) treatment regimen of metformin monotherapy; fasting plasma glucose <240 mg/dL at Screening Visit 1; and HbA1C ≥7% and ≤10% at Screening Visit 1.

Exclusion criteria included prior treatment with exenatide, TZDs, sulfonylureas, DPP IV inhibitors, acarbose, or insulin (injected or inhaled); history of type 1 diabetes and/or diabetic ketoacidosis; body mass index ≥40 kg/m^2; and history of organ transplantation.

Subjects (n=155) were randomized to receive ITCA 650, implanted every 3 months at 20, 40, 60, or 80 mcg/day following 12 weeks of either ITCA 650 (20 or 40 mcg/day) or exenatide injections (10 mcg BID). At Week 12, the completion rate for ITCA 650 was 93% versus 89% for exenatide injections; respective withdrawals due to nausea were 3.9% versus 5.7%.

At Week 24, subjects were offered the option to continue treatment at their current dose for an additional 24 weeks; 85% of eligible subjects elected to continue treatment. During the 6-month extension, HbA1C and body weight reductions were sustained. No subjects withdrew for any reason. One patient reported nausea; none reported vomiting. No cases of hypoglycemia occurred.

Significant reductions in HbA1C ($p<0.0001$ for all does groups) and weight ($p<0.001$ for the 40 mcg/day dose and $p<0.05$ for all other doses) at Week 48 were maintained from those that were initially observed at Week 24. Desirable trends in lipids and blood pressure were also noted. Changes that were seen at 60 mcg/day, the long-term dose that was selected for future studies, were -3.1% for total cholesterol, -9.9% for triglycerides, -5.2% for low-density lipoprotein cholesterol, -1.7 mm Hg for systolic blood pressure, and -7.8 mm Hg for diastolic blood pressure. High-density lipoprotein cholesterol increased by 0.5%. Continuing treatment with ITCA 650 was very well tolerated, with minimal side effects and a completion rate of 85%.

Study delivery technology consisted of sterile, nonbiodegradable, single-use devices for continuous, subcutaneous administration of therapeutic molecules at steady rates. It is capable of delivering a wide range of therapeutic molecules for durations that range from 3 to 12 months [Rohloff CM et al. *J Diabetes Sci Technol* 2008].

This extension study shows that long-term treatment with ITCA 650 is effective in controlling glycemic parameters and weight and can also lead to potentially positive cardiovascular benefits through beneficial changes in lipids and blood pressure. In addition, tolerability is excellent, with minimal gastrointestinal side effects. Phase 3 studies will evaluate chronic treatment with ITCA 650 using devices of 6 to 12 months in duration.

Novel Agent Found to Reduce HbA1C in Type 2 Diabetes

Written by Lori Alexander

A randomized, double-blind, multicenter study demonstrated that a G-protein-coupled receptor 40 (GPR40) agonist had glucose-lowering efficacy for the treatment of type 2 diabetes. The novel agent significantly reduced HbA1C compared with placebo, with efficacy that was comparable with glimepiride but with a significantly lower rate of hypoglycemia.

Prabhakar Viswanathan, MD, PhD, State University of New York, Buffalo, New York, USA, reported the findings of the study. He first explained that the agent, TAK-875, is a highly selective and potent GPR40 agonist with glucose-dependent insulinotropic action.

The study was designed to evaluate the efficacy, safety, and tolerability of TAK-875 at 5 doses—6.25, 25, 50, 100, and 200 mg—given once daily for 12 weeks. The 426 study subjects were randomly assigned a different dose of TAK-875, glimepiride (4 mg), or placebo, with 60 to 62 subjects in each group. About 75% of the 426 patients were taking metformin at baseline.

The primary efficacy endpoint was change in HbA1C from baseline to Week 12. Several other efficacy and safety endpoints were also evaluated, including changes in HbA1C over time, fasting plasma glucose (FPG) level, 2-hour glucose level during oral glucose tolerance testing (OGTT), and incidence of hypoglycemia.

Dr. Viswanathan reported that all doses of the drug led to greater reductions in HbA1C at 12 weeks than placebo, with the efficacy of the drug reaching a plateau at the 50-mg dose. Doses ≥50 mg of TAK-875 led to reductions that were comparable with those found with glimepiride. The mean reduction in HbA1C was significantly different by the time of the first testing (4 weeks), and the difference remained significant at all time points. Nearly