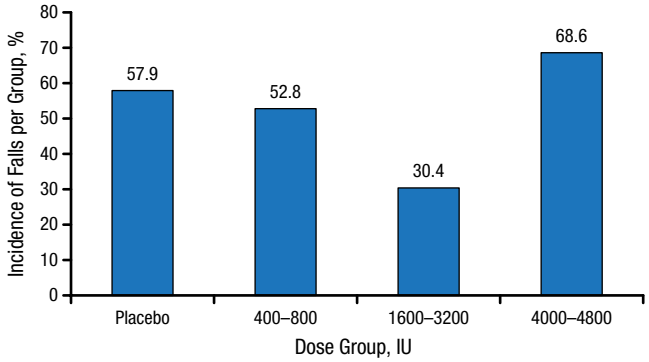
Figure 1. Incidence of Falls Stratified by Vitamin D Supplementation Dosage



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demonstrated higher levels of $1,25(OH)_2D$ compared with patients who received placebo, but there was no significant difference in $1,25(OH)_2D$ levels between patients who did or did not experience falls, regardless of the amount of supplementation. Similarly, 25(OH)D levels increased in a dose-response fashion among patients who received supplementation; however, there was no significant difference in 25(OH)D levels between patients who did or did not experience falls.

The fall rate varied among the arms of the trial. Patients in the placebo arm and those patients who received 400 to 800 IU QD of vitamin D experienced similar fall rates (Figure 1). However, the fall rate was considerably lower in patients who received 1600 to 3200 IU QD of vitamin D, whereas patients who received the largest dose of vitamin D had an even higher fall rate.

The timed up and go (TUG) value was slower at 1 year among all arms; however, patients who received 1600 to 3200 IU QD or 4000 to 4800 IU QD of vitamin D appeared to have a slower rate of increase in the TUG value. At 1 year, there was no significant difference in the chair stand test among all of the arms.

In conclusion, the results of the VIDOS study suggest that, overall, vitamin D supplementation did not appear to improve physical performance or the incidence of falls. However, Dr Yousefian pointed out that there was a U-shaped distribution for the incidence of falls among the various doses of vitamin D supplementation, suggesting that there may be an optimal dose for fall prevention at about 2000 IU QD. However, additional larger studies are needed to better assess the role of vitamin D supplementation in the incidence of falls among elderly patients.

Liraglutide Leads to Increased Weight Loss Response in Patients Without Diabetes

Written by Rita Buckley

In the phase 3, double-blind, randomized SCALE–Obesity and Prediabetes trial [NCT01272219], significantly more obese and overweight adults without diabetes mellitus were weight loss responders when treated with liraglutide, 3 mg, rather than placebo. Weight loss responders also had improvements in glycemic control, cardiometabolic outcomes, and quality of life. The SCALE–Obesity and Prediabetes trial was a subanalysis of the SCALE study, a large phase 3 clinical program investigating the safety and efficacy of liraglutide, 3 mg, for weight management in people with and without diabetes.

Patrick O'Neil, PhD, Medical University of South Carolina, Charleston, South Carolina, USA, presented the results of the subanalysis. Overweight (body mass index [BMI] ≥ 27 kg/m^2 with ≥ 1 comorbidities) or obese (BMI ≥ 30 kg/m^2) patients without diabetes mellitus were randomized to liraglutide, 3 mg (n = 2487), or placebo (n = 1244) as an adjunct to diet and exercise. Overall baseline characteristics included a mean age of 45 years, a body weight of 106 kg, and a BMI of 38 kg/m^2.

The analysis compared key efficacy and safety outcomes of responders (≥ 5% weight loss at week 56 from baseline) vs nonresponders (< 5% weight loss at week 56 from baseline). At week 56, significantly more individuals on liraglutide vs placebo were weight loss responders (63.2% vs 27.1%; $P < .0001$). Mean weight loss for responders vs nonresponders on liraglutide was –11.7% vs –1.7%. In the placebo group, the respective figures were –10.0% vs +0.1%. Liraglutide was also associated with a greater reduction in waist circumference in responders vs nonresponders (–11.0 vs –3.3 cm). Respective figures in the placebo group were –10.0 vs –1.7 cm.

Fasting plasma glucose was lower for responders in the liraglutide vs placebo group (–8.3 vs –2.8 mg/dL). For nonresponders, the figures were –5.0 vs +1.1 mg/dL. In liraglutide vs placebo responders, respective reductions in systolic blood pressure were –5.5 vs –3.4 mm Hg. Nonresponders in both groups had respective findings of –2.0 vs –0.8 mm Hg. Change in overall physical health scores on the SF-36 Health Survey Update questionnaire for liraglutide vs placebo responders was +4.3 vs +4.1; for nonresponders, the respective outcomes were +2.1 vs +1.3.

The most common adverse events (AEs) were gastrointestinal related. These were higher in liraglutide vs

placebo responders (69.2% vs 44.4%, respectively) than in liraglutide and placebo nonresponders (67.2% vs 39.6%, respectively). Responders had lower rates of AEs leading to withdrawal (liraglutide, 4.5%; placebo, 0.9%). In nonresponders, the figures were 17% for liraglutide vs 4.8% for placebo.

Liraglutide responders had greater improvements than nonresponders across a range of efficacy outcomes. Overall, weight loss ≥ 5% was achieved in a higher proportion of patients on liraglutide, 3 mg, with a stronger effect among responders. The rates of AEs were largely equivalent in responders and nonresponders.

A mean weight loss of 11.7% was achieved by patients who were overweight or obese without diabetes and responded to liraglutide. The weight loss responders in both treatment groups also had improved glycemic, cardiometabolic, and health-related quality-of-life outcomes. The SCALE–Obesity and Prediabetes trial showed that liraglutide is a safe and effective weight loss option in the study population.

Significant HbA_{1c} Reduction With Empagliflozin/ Linagliptin Combination

Written by Rita Buckley

One tablet of empagliflozin and linagliptin significantly reduced HbA_{1c} in patients with type 2 diabetes. Andrew J. Lewin, MD, National Research Institute, Los Angeles, California, USA, and colleagues conducted a randomized, double-blind, parallel-group, phase 3 study, the Safety and Efficacy of the Combination of Empagliflozin and Linagliptin Compared to Linagliptin Alone Over 24 Weeks in Patients With Type 2 Diabetes study [Lewin A et al. *Diabetes Care*. 2015].

Empagliflozin reduces renal glucose reabsorption, thereby increasing urinary glucose excretion. This leads to a decline in plasma glucose levels in an insulin-independent manner [Heise T et al. *Diabetes Obes Metab*. 2013]. Linagliptin prevents the inactivation of incretin peptides, such as glucagon-like peptide-1 (GLP-1), stimulates insulin release, and inhibits glucagon secretion [Gallwitz B. *Diabetes Metab Syndr Obes*. 2013]. Each drug is an FDA-approved treatment for patients with type 2 diabetes. As compared with the single agent treatment groups, those treated with the dual combination achieved lower A_{1c} levels.

Efficacy was evaluated in 667 patients who had not received antihyperglycemic therapy for ≥ 12 weeks. Their mean (standard deviation) age was 54.6 (10.2) years; mean weight was 87.9 (20.1) kg; average body mass index was 31.6 (5.6) kg/m^2; and mean HbA_{1c} level was 8.02% (0.96). Baseline characteristics were balanced between treatment groups.

Patients were randomized (1:1:1:1:1) to receive empagliflozin 25 mg/linagliptin 5 mg as a fixed-dose combination (FDC) tablet; empagliflozin 10 mg/linagliptin 5 mg as an FDC tablet; empagliflozin 25 mg; empagliflozin 10 mg; or linagliptin 5 mg for 52 weeks. The primary end point was the change from baseline in HbA_{1c} at week 24.

At week 24, reductions from baseline in HbA_{1c} were significantly greater for empagliflozin 25 mg/linagliptin 5 mg compared with linagliptin 5 mg ($P<.001$), but not compared with empagliflozin 25 mg ($P<.179$), and were significantly greater for empagliflozin 10 mg/linagliptin 5 mg compared with individual doses ($P<.001$ for both). At week 24, 55.4% of patients with baseline $HbA_{1c} \geq 7\%$ reached $HbA_{1c} < 7\%$ with empagliflozin 25 mg/linagliptin 5 mg; 62.3% did so with empagliflozin 10 mg/linagliptin 5 mg; 41.5% with empagliflozin 25 mg; 38.8% with empagliflozin 10 mg; and 32.3% with linagliptin 5 mg. Efficacy was maintained at week 52.

The proportion of patients with adverse events over this time was similar across groups (68.9% to 81.5%), with no confirmed hypoglycemic adverse events in either combination group. Empagliflozin/linagliptin was well-tolerated, with an overall safety profile similar to those of the individual drugs.

This was the first randomized controlled trial to evaluate the efficacy and safety of the initial combination of a sodium-glucose cotransporter 2 (SGLT2) inhibitor (empagliflozin) and a DPP-4 inhibitor (linagliptin) in patients with type 2 diabetes.

ATL1103 Effective in Reducing IGF-1 Levels in Patients With Acromegaly

Written by Jill Shuman

Acromegaly is a chronic disorder resulting from excessive secretion of growth hormone, with a resulting increase in the production of the hormone known as insulinlike growth factor 1 (IGF-1). ATL1103 is a second-generation antisense drug designed to silence growth hormone receptor expression, thereby reducing levels of IGF-1 in the blood. It is currently under investigation as a potential treatment for diseases associated with excessive growth hormone action, such as acromegaly [Störmann S, Schopohl J. *Expert Opin Emerg Drugs*. 2014].

Peter J. Trainer, MD, The Christie National Health Service Foundation Trust, Manchester, United Kingdom, reported primary efficacy results from the phase 2 clinical trial of ATL1103 in patients with acromegaly [2012-003147-30]. The ATL1103 phase 2 trial was a randomized, open-label, multicenter, parallel group study