Empagliflozin–25 mg produced slightly lower 24-hour systolic BP than empagliflozin–10 mg.

Similar results were found for diastolic BP. On average, systolic and diastolic BP among subjects who received the 25 mg of empagliflozin decreased by 4.2 mm Hg ($p < .001$) and 1.7 mm Hg ($p < .01$), respectively, compared with placebo. The average decrease in systolic and diastolic BP among patients who received the 10 mg of empagliflozin was 3.4 mm Hg ($p < .001$) and 1.4 mm Hg ($p < .01$), respectively, compared with placebo.

From baseline to Week 12, the average HbA_{1c} level dropped by 0.62% and 0.65% with 10 and 25 mg of empagliflozin, respectively, compared with placebo. Subjects tolerated empagliflozin well, with no increased rate of side effects compared with placebo. Most adverse events that occurred in all 3 groups were mild.

The authors speculate that the improved blood sugar levels evident in subjects receiving empagliflozin reflect reduced glucose reabsorption in the kidneys, which leads to glucose elimination in the urine. The findings suggest the potential of empagliflozin to reduce the risk of cardiovascular events with longer-term treatment. This possibility is being addressed in the long-term EMPA-REG OUTCOME trial [Zinman B et al. *Cardiovasc Diabetol* 2014], which is expected to finish in 2015. The primary end point of the latter trial is the time to first occurrence of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Table 1. Patient Demographics and Characteristics

	Placebo (n = 207)	Empagliflozin 10 mg (n = 217)	Empagliflozin 25 mg (n = 213)
Male	116 (56.0)	125 (57.6)	120 (56.3)
Age, y	56.0 ± 9.7	55.5 ± 9.9	55.6 ± 10.2
Race			
Asian	92 (44.4)	99 (45.6)	98 (46.0)
White	113 (54.6)	112 (51.6)	113 (53.1)
Other	2 (1.0)	6 (2.8)	2 (0.9)
Time since T2DM diagnosis, years			
≤1	19 (9.2)	20 (9.2)	19 (8.9)
> 1-5	83 (40.1)	78 (35.9)	69 (32.4)
> 5-10	65 (31.4)	68 (31.3)	74 (34.7)
> 10	40 (19.3)	51 (23.5)	51 (23.9)
HbA_{1c}, %	7.90 ± 0.88	7.94 ± 0.79	7.86 ± 0.87
Body weight, kg	79.7 ± 18.6	81.6 ± 18.5	82.2 ± 19.3
Blood pressure, mm Hg			
Systolic	128.6 ± 14.7	129.6 ± 14.1	130.0 ± 15.1
Diastolic	78.1 ± 7.9	79.6 ± 8.0	78.4 ± 8.4

Data are expressed as number (%) or mean±standard deviation.
T2DM=type 2 diabetes mellitus.

Reductions in HbA_{1c} and Weight in Type 2 Diabetics With the Empagliflozin Add-On Regimen

Written by Brian Hoyle

Empagliflozin, 10 or 25 mg, used as an add-on to metformin therapy for ≥ 76 weeks among patients with type 2 diabetes mellitus (T2DM) produces significant and sustained decreases in glycated hemoglobin (HbA_{1c}), body weight, and systolic blood pressure (SBP), compared with placebo. The results of the extension portion of a randomized Phase 3 trial involving 637 patients were reported by Ludwig Merker, MD, Diabetes- und Nierenzentrum, Dormagen, Germany.

Empagliflozin is a potent and selective inhibitor of sodium glucose cotransporter 2 [Grempler R et al. *Diabetes Obes Metab* 2012]. A prior Phase 3 trial [EMPA-REG MET; Häring H-U et al. *Diabetes Care* 2014] showed improved glycemic control as measured by HbA_{1c} and fasting plasma glucose, as well as body weight and blood pressure, among T2DM patients who received empagliflozin, 10 or 25 mg, as an add-on to metformin therapy over 24 weeks of treatment, compared with placebo. The present extension study, the Safety and Efficacy of Empagliflozin (BI 10773) and Sitagliptin Versus Placebo Over 76 Weeks in Patients With Type 2 Diabetes study [EMPA-REG EXTEND MET; NCT01289990], assessed the long-term safety, tolerability, and efficacy of the empagliflozin add-on regimen.

The full analysis population included 637 patients with HbA_{1c} between 7.0% and 10% despite a diet and exercise regimen. All patients received metformin (≥ 1500 mg daily) and were randomly assigned to receive a daily add-on of placebo (n = 207); empagliflozin, 10 mg (n = 217); or empagliflozin, 25 mg (n = 213). The main outcomes were changes from baseline to Week 76 of treatment in HbA_{1c}, body weight, and SBP. Safety was assessed among 463

Table 2. Lipid Parameters

	Placebo (n = 206)	Empagliflozin, 10 mg (n = 217)	Empagliflozin, 25 mg (n = 214)
Total cholesterol, mg/dL[a]			
Baseline	175.7 ± 2.7	173.8 ± 2.3	177.2 ± 2.7
Change from baseline at Week 76	3.5 ± 1.9	10.0 ± 1.9	8.9 ± 1.9
Difference versus placebo (95% CI)		6.6 (1.5 to 12.0)[c]	5.4 (0.0 to 10.8)[d]
Low-density lipoprotein cholesterol, mg/dL[b]			
Baseline	95.0 ± 2.3	92.7 ± 2.3	95.8 ± 2.3
Change from baseline at Week 76	1.5 ± 1.5	6.2 ± 1.5	6.2 ± 1.5
Difference versus placebo (95% CI)		4.3 (0.0 to 8.9)	4.3 (0.0 to 8.9)
High-density lipoprotein cholesterol, mg/dL[a]			
Baseline	47.1 ± 0.8	49.4 ± 0.8	49.4 ± 0.8
Change from baseline at Week 76	0.0 ± 0.4	3.1 ± 0.4	2.3 ± 0.4
Difference versus placebo (95% CI)		3.1 (1.5 to 4.6)[e]	2.3 (0.8 to 3.9)[f]
Triglycerides, mg/dL[a]			
Baseline	173.5 ± 8.0	172.6 ± 8.0	162.8 ± 7.1
Change from baseline at Week 76	6.2 ± 7.1	8.9 ± 6.2	5.3 ± 6.2
Difference versus placebo (95% CI)		2.7 (–15.9 to 21.2)	–0.9 (–19.5 to 16.8)

Data are expressed as mean±standard error unless indicated otherwise.

[a]Placebo (n = 203); empagliflozin, 10 mg (n = 211); empagliflozin, 25 mg (n = 213).

[b]Placebo (n = 196); empagliflozin, 10 mg (n = 200); empagliflozin, 25 mg (n = 203).

[c]p = .013.

[d]p = .043.

[e]p < .001.

[f]p = .002.

patients (72.7% of total) who were treated at least once with empagliflozin. Patient demographics and characteristics for the full analysis population (N = 637) were similar among groups (Table 1).

Comparison of baseline and Week 76 values of HbA_{1c} revealed changes from baseline of –0.01% for the placebo group. The difference to placebo was –0.61% (95% CI, –0.75 to –0.48) for the empagliflozin–10 mg group and –0.73% (95% CI, –0.88 to –0.58) for the empagliflozin–25 mg group. Both treatment groups differed significantly from the placebo group (both, p < .001). The greatest declines in HbA_{1c} with 10 or 25 mg of empagliflozin occurred between Weeks 0 and 12. The use of rescue medication was 34.3% with placebo, 15.2% with empagliflozin–10 mg (OR versus placebo, 0.31; 95% CI, 0.19 to 0.50; p < .001), and 8.9% with empagliflozin–25 mg (OR versus placebo, 0.17; 95% CI, 0.09 to 0.30; p < .001).

Baseline and Week 76 comparison of body weight revealed changes from baseline of –0.5 kg for the placebo group. The difference to placebo was –1.9 kg (95% CI, –2.5 to –1.3) for the empagliflozin–10 mg group and –2.2 kg (95% CI, –2.8 to –1.6) for the empagliflozin–25 mg group. Both treatment groups differed significantly from the placebo group (both, p < .001).

Comparison of baseline and Week 76 SBP revealed changes from baseline of –0.8 for the placebo group. The difference to placebo was –4.4 (95% CI, –6.6 to –2.3) for the empagliflozin–10 mg group and –3.7 (95% CI, –5.9 to

–1.5) for the empagliflozin–25 mg group. Both treatment groups differed significantly from the placebo group (both, $p < .001$).

There was a small but statistically significant increase in high-density lipoprotein cholesterol for the empagliflozin treatment groups, as well as total cholesterol, compared to placebo. Lipid parameters are summarized in Table 2.

The proportion of patients reporting ≥ 1 adverse events was similar in the treatment groups. The researchers concluded that the use of 10 or 25 mg of empagliflozin as an add-on to metformin therapy for 76 weeks is well tolerated and produces significant and sustained reductions of $HbA_{1c,}$ body weight, and systolic blood pressure compared with placebo in patients with T2DM.

Liraglutide Improves Body Weight, Prediabetes in Overweight and Obese Patients Without T2DM

Written by Emma Hitt Nichols, PhD

Overweight and obese patients without type 2 diabetes mellitus (T2DM) who were treated with liraglutide experienced a greater reduction in body weight and were more likely to revert to normoglycemia compared to those treated with placebo. Xavier Pi-Sunyer, MD, MPH, Columbia University, New York, New York, USA, presented data from a poster on the Effect of Liraglutide on Body Weight in Nondiabetic Obese Subjects or Overweight Subjects With Comorbidities—Obesity and Prediabetes trial [SCALE; NCT01272219].

Obesity is associated with prediabetes, which substantially increases the risk of developing T2DM and related complications [Kasuga M. *J Clin Invest* 2006]. The SCALE trial was designed to evaluate the safety and efficacy of liraglutide on weight management. The purpose of this analysis was to evaluate the effect of liraglutide on weight loss and measurements of diabetes, including fasting and postload glucose, as well as the prevalence of prediabetes and the onset of T2DM.

In the double-blind multicenter Phase 3 SCALE trial, 3731 patients without T2DM who were overweight or obese and had a body mass index (BMI) ≥ 27 kg/m² and ≥ 1 comorbidity were randomly assigned to receive 3.0 mg of subcutaneous liraglutide or placebo for 56 weeks. Patients who received liraglutide were again randomly assigned to liraglutide or placebo for an additional 12 weeks, while patients receiving placebo remained on it. All patients were followed for an additional 2 weeks.

Patients aged ≥ 18 years were eligible for the SCALE trial if they had a BMI ≥ 30 kg/m² or ≥ 27 kg/m² plus dyslipidemia or hypertension (treated or untreated) and stable body weight with a history of failed dietary effort to reduce it. Exclusion criteria were $HbA_{1c} \geq 6.5\%$, fasting plasma glucose ≥ 126 mg/dL, or a 2-hour postchallenge plasma glucose ≥ 200 mg/dL at baseline. All patients were counseled to reduce their caloric consumption by 500 kcal/day and to start an exercise program.

Patients who had received liraglutide experienced a decrease in body weight of 8.0% (8.4 kg) over 56 weeks, compared with 2.6% (2.8 kg) in patients who received placebo, with an estimated treatment difference of –5.4% (–5.6 kg; 95% CI, –5.8% to –5.0%; $p < .0001$). In addition, a greater number of patients in the liraglutide arm experienced a weight loss over 56 weeks of ≥ 5% (estimated OR [EOR], 4.8; 95% CI, 4.1 to 5.6; $p < .0001$) and > 10% (EOR, 4.3; 95% CI, 3.5 to 5.3; $p < .0001$) compared with patients in the placebo arm.

Patients who had received liraglutide and were then randomly reassigned to placebo during the additional 12 weeks experienced weight gain compared with those who remained on liraglutide (estimated treatment difference, 2.2%; $p < .0001$). Liraglutide treatment improved fasting and postload glycemia compared with placebo, as measured by an oral glucose tolerance test, with patients with prediabetes experiencing a greater improvement than those without it.

At 56 weeks, 20.7% of patients in the placebo arm had progressed from normoglycemia to prediabetes compared with 7.2% of patients in the liraglutide arm (EOR, 3.3; logistic regression, $p < .0001$). Furthermore, 69.2% of patients in the liraglutide arm with prediabetes at baseline reverted to normoglycemia at 56 weeks, compared with 32.7% of the placebo arm (EOR, 4.85; $p < .0001$).

More patients in the placebo arm developed T2DM compared with patients in the liraglutide arm (14 vs 4, respectively; EOR, 8.06; $p = .0003$). During the additional 12 weeks, patients randomly reassigned to placebo developed prediabetes more frequently compared with patients who remained on liraglutide.

Dr. Pi-Sunyer indicated that, in his opinion, the data from this analysis of the SCALE trial suggest that the addition of liraglutide to diet and exercise resulted in superior improvements in the prevalence of prediabetes, T2DM, and body weight compared with placebo.