Table 1. AEs Specific to SGLT2 Inhibitor Class of Agents Observed, No. (%)

		Canagliflozin	
	Placebo, n = 237	100 mg, n = 241	300 mg, n = 236
Urinary tract infection	24 (10.1)	35 (14.5)	39 (16.5)
Genital mycotic infection			
Male	2 (1.4)	7 (5.6)	14 (10.9)
Female	4 (4.3)	28 (23.9)	20 (18.7)
Osmotic diuresis-related AEs[a]	13 (5.5)	22 (9.1)	29 (12.3)

AEs, adverse events; SGLT2, sodium-glucose cotransporter 2.

[a]Includes dry mouth, dry throat, micturition disorder, micturition urgency, nocturia, pollakuria, polydipsia, thirst, and increased urine output.

Table 2. Documented Hypoglycemia Through Week 104, No. (%)

Antihyperglycemic Agent Associated With Hypoglycemia	Placebo	Canagliflozin	
		100 mg	300 mg
Patients on agent	176	181	172
Hypoglycemia[a]	86 (48.9)	98 (54.1)	105 (61.0)
< 3.1 mmol/L (< 56 mg/dL)	43 (24.4)	42 (23.2)	51 (29.7)
Severe hypoglycemia	8 (4.5)	5 (2.8)	5 (2.9)
Patients not on agent	61	60	64
Hypoglycemia[a]	4 (6.6)	11 (18.3)	7 (10.9)
< 3.1 mmol/L (< 56 mg/dL)	1 (1.6)	0	0
Severe hypoglycemia	0	1 (1.7)	0

[a]Documented hypoglycemia included episodes that were biochemically documented (≤3.9 mmol/L [<70 mg/dL]) or severe (ie, requiring the assistance of another individual or resulting in seizure or loss of consciousness).

Volume-related AEs (eg, dehydration, dizziness, and presyncope) were more common in canagliflozin patients, occurred more frequently in the first 26 weeks, but were relatively infrequent (5.4% and 5.9% in the 100-mg and 300-mg treatment groups, respectively). The majority of fungal infections were treated with topical therapy. Incidence of documented hypoglycemia was higher with both canagliflozin doses than with placebo, but there were few severe hypoglycemia episodes in any of the treatment groups (Table 2).

In summary, canagliflozin, both 100 mg and 300 mg, improved glycemic control, reduced bodyweight, and lowered BP when compared with placebo over 104 weeks in older patients with T2DM whose HbA_{1c} values were inadequately controlled by their current regimens. The incidence of documented hypoglycemia was higher with both doses of canagliflozin than with placebo, although there were few severe episodes noted. Canagliflozin was generally well tolerated, with a safety profile in this study consistent with that seen in other phase 3 canagliflozin studies.

Combined Saxagliptin and Dapagliflozin Reduce Blood Glucose Levels in T2DM Patients

Written by Nicola Parry

Julio Rosenstock, MD, Dallas Diabetes and Endocrine Center, Dallas, Texas, USA, presented results from the Safety and Efficacy of Combination Saxagliptin & Dapagliflozin Added to Metformin to Treat Subjects With Type 2 Diabetes trial [NCT01606007]. This active-controlled, double-blind, parallel-group phase 3 study demonstrated that combined saxagliptin and dapagliflozin, when added to metformin, were more effective in reducing glucose than treatment with metformin alone in adults with type 2 diabetes mellitus (T2DM).

According to Dr Rosenstock, the sequential addition of a single glycemic control agent is the recommended approach for T2DM patients who are poorly controlled on metformin monotherapy. However, this approach may be inadequate, particularly when HbA_{1c} levels are significantly elevated.

The study aimed to investigate the efficacy and safety of early triple therapy that includes metformin and the concomitant initiation of dual oral therapy with the dipeptidyl peptidase 4 inhibitor saxagliptin and the sodium-glucose cotransporter 2 inhibitor dapagliflozin.

Patients (n = 534) were randomized to saxagliptin –5 mg + dapagliflozin–10 mg + metformin (n = 179), saxagliptin–5 mg + metformin + placebo (n = 176), or dapagliflozin–10 mg + metformin + placebo (n = 179). The study enrolled adults (> 18 years) with a body mass index ≤ 45 kg/m^2, HbA_{1c} levels ≥ 8% and ≤ 12%, and an estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2. All participants were receiving ≥ 1500 mg/d of metformin before randomization.

The primary end point was the adjusted mean change in baseline HbA_{1c} levels at week 24. At 24 weeks, the reduction in mean HbA_{1c} levels was significantly greater in patients treated with saxagliptin + dapagliflozin + metformin when compared with saxagliptin + metformin (–1.5% vs –0.9%; $P < .001$) and dapagliflozin + metformin (–1.5% vs –1.2%; $P = .02$;). Additionally, more patients

in the saxagliptin + dapagliflozin + metformin group achieved a target HbA_{1c} < 7% (41% vs 18% vs 22%).

No deaths were reported in any of the groups. The incidence of serious adverse events (AEs) was similar in all 3 groups (1% vs 3% vs 1%). The incidence of AEs leading to treatment discontinuation was also similar (0.6% vs 0% vs 0%). With respect to AEs of special interest, the incidence of urinary tract infections was also similar in all 3 groups (0.6% vs 5% vs 4%), and the incidence of hypoglycemia was low (1% in all groups). Genital infections were not recorded in the saxagliptin + dapagliflozin + metformin group (0% vs 0.6% vs 6%).

In his concluding remarks, Dr Rosenstock stated that when compared with monotherapy, the addition of saxagliptin and dapagliflozin to metformin in poorly controlled TD2M patients led to greater reductions in HbA_{1c} and allowed more patients to achieve a target HbA_{1c} < 7%. Dual add-on therapy was also well tolerated and did not increase the risk of hypoglycemia in patients.

Combining Empagliflozin and Linagliptin With Metformin Reduces HbA_{1c} in Patients With T2DM

Written by Nicola Parry

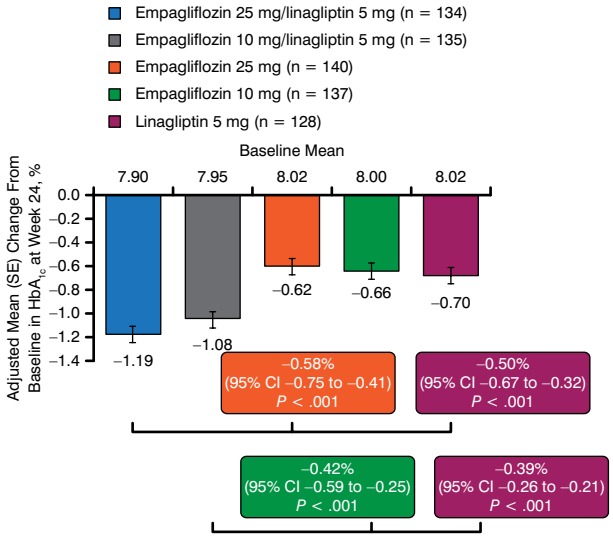
Combined empagliflozin and linagliptin as add-on therapy to metformin provided enhanced glucose-reducing efficacy when compared with either drug as monotherapy in individuals with type 2 diabetes mellitus (T2DM), stated Ralph A. DeFronzo, MD, University of Texas, San Antonio, Texas, USA, while presenting results from a phase 3 double-blind, parallel-group study.

According to Dr DeFronzo, sodium-glucose cotransporter 2 inhibitors, such as empagliflozin, are a new class of drugs for the management of T2DM. Linagliptin is a dipeptidyl peptidase 4 inhibitor and is considered to provide additional benefit in T2DM treatment when combined with empagliflozin, due to its ability to inhibit glucagon and enhance insulin secretion.

This study aimed to investigate the efficacy and safety of empagliflozin and linagliptin, individually and in combination as add-on therapy to metformin in adults with T2DM.

Patients in this study were all > 18 years of age, with a body mass index of ≤ 45 kg/m^2 and HbA_{1c} levels between 7% and 10.5%. All subjects had to have received a stable background therapy of metformin for ≥ 12 weeks before randomization. Patients were excluded who had an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 during screening or placebo run-in.

Figure 1. Change in Mean HbA_{1c} From Baseline at 24 Weeks



SE, standard error.

Source: DeFronzo R et al. *Diabetes*. 2014 (abstr 130-LB).

Dr DeFronzo and colleagues randomized 677 patients to empagliflozin–25 mg + linagliptin–5 mg (n = 137), empagliflozin–10 mg + linagliptin–5 mg (n = 136), empagliflozin–25 mg (n = 135), empagliflozin–10 mg (n = 134), and linagliptin–5 mg (n = 135). The primary end point was the change from baseline in HbA_{1c} at week 24. The study continued to week 52.

At 24 weeks, patients treated with both fixed-dose combinations of empagliflozin + linagliptin showed significant HbA_{1c} reductions as compared with the monotherapies, with a higher percentage of the combinations achieving HbA_{1c} < 7% (P < .001; Figure 1). Adjusted mean HbA_{1c} changes from baseline for those receiving the combination therapies were –1.19% for empagliflozin –25 mg + linagliptin–5 mg and –1.08% for empagliflozin –10 mg + linagliptin–5 mg. For those receiving one of the monotherapies, the changes observed were –0.62% for empaglifozin–25 mg, –0.66% for empagliflozin –10 mg, and –0.70% for linagliptin–5 mg [DeFronzo R et al. *Diabetes*. 2014 (abstr 130-LB)].

This effect continued to 52 weeks, at which point significantly higher percentages of patients treated with both fixed-dose combinations continued to show reductions in HbA_{1c} < 7% as compared with the monotherapies (P < .001). Adjusted mean HbA_{1c} changes from baseline for the combinations at 52 weeks were –1.21% for empagliflozin –25 mg + linagliptin–5 mg and –1.05% for empagliflozin