SGLT2 Inhibitors Studied for A1C Lowering & Weight Loss in Type 2 Diabetes

Several posters explored the use of SGLT2 inhibitors for glycemic control and weight loss in individuals with type 2 diabetes.

Davidson and colleagues\(^1\) reported that the SGLT2 inhibitor, canagliflozin (CANA), was superior to the DPP-4 inhibitor, sitagliptin (SITA), for reducing A1C and body weight in individuals with type 2 diabetes across two phase 3 studies. Both studies randomized subjects with type 2 diabetes whose glucose was inadequately controlled on metformin or metformin in combination with a sulfonylurea (canagliflozin 300 mg only) to canagliflozin 100 mg, canagliflozin 300 mg, or sitagliptin 100 mg over 52 weeks.

**A1C Reduction**

In the first study with 1,284 subjects (mean baseline A1C, 7.9%; baseline body weight, 87.2 kg), mean A1C change from baseline was -0.73%, -0.88%, and -0.73% for CANA 100 mg, CANA 300 mg, and SITA 100 mg. In the second study with 755 subjects (mean baseline A1C, 8.1%; baseline body weight, 88.3 kg), mean A1C change was -1.03 for CANA 300 mg and -0.66% for SITA 100 mg.

**SCALE Weighs Efficacy of Liraglutide 3.0 mg on Weight Loss & Metabolic Improvement in T2D**

Adults who are overweight or obese with prediabetes who were treated with liraglutide 3.0 mg were more than twice as likely to achieve weight loss of ≥5% compared with their counterparts who took placebo in the SCALE Obesity and Prediabetes trial. The weight loss yielded improvements in glycemic and cardiovascular/cardiometabolic risk factors.

Significantly more liraglutide-treated subjects achieved ≥5% weight loss: 63.2% vs 27.1% for placebo (P<0.0001). Weight loss among these “responders” was -11.7% for liraglutide and -1.7% for placebo vs -10% and +0.1%, respectively, for “nonresponders.” Treatment was in combination with a reduced-calorie diet and increased physical activity.

Responders in both groups enjoyed greater improvement in FPG: -8.3 mg/dL for liraglutide-

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treated subjects and -2.8 mg/dl for placebo-treated subjects—compared with nonresponders: -5.0 mg/dL vs +1.1 mg/dL, respectively. Improvements in systolic blood pressure (SBP) control were also more pronounced in responders vs nonresponders. SBP among liraglutide and placebo responders improved by 5.5 mm Hg and 3.4 mm Hg, respectively—compared with nonresponders: -2.0 mm Hg and -0.8 mm Hg.

Rates of hypoglycemia in the liraglutide and placebo groups were similar: 1.3% vs 1.0%, respectively. More liraglutide-treated subjects had reported hypoglycemia episodes during FPG visits—3.6% vs 0.8% placebo—or OGTT—8.3% vs 1.4%, respectively.

About SCALE Obesity and Prediabetes

- Randomized 3,371 subjects (mean age, 45 yrs; prediabetes, 61%) with obesity or overweight with comorbidities to liraglutide 3.0 mg (n=2,487) or placebo (n=1,244).
- Assessed weight loss over 56 weeks

FPG=fasting plasma glucose; OGTT=oral glucose tolerance test


Lau DC, Davies M, Pi-Sunyer FX, et al. Hypoglycemia reported with liraglutide 3.0 mg in overweight and obese adults with and without prediabetes: results of the randomized, double-blind, placebo-controlled 56-week SCALE Obesity and Prediabetes trial. OR07-2.

RYGB Improves Weight & Glycemic Control Over Sleeve Gastrectomy

Greater weight loss and improvements in metabolic parameters were seen among individuals who underwent Roux-en-Y gastric bypass (RYGB) compared with sleeve gastrectomy (SG) at 12 and 24 months post-surgery.

Lager and colleagues reported significantly greater weight loss for RYGB vs SG at 12 months: -68.6% vs 55% (P<0.0001); and at 24 months: -65.6% vs -52%, respectively (P<0.0001). At baseline, BMI and weight were significantly lower among RYGB participants.

A1C at 12 months was also significantly lower among RYGB subjects: -1.4% vs -0.75% for placebo. Serum creatinine, measured as an indirect marker of lean mass, was significantly lower for RYGB compared with placebo: -0.1 mg/dL vs -0.04 mg/dL (P<0.0001).

A total of 81% of participants in the RYGB group (n=392 at baseline; n=269 at 12 months; n=186 at 24 months) were female; 77% in the SG group (n=337 at baseline; n=203 at 12 months; n=89 at 24 months) were female.

Lager CJ, Esfandiari NH, Subauste AR, et al. The two obesity surgeries: are they truly comparable? OR07-1.

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Weight Loss
In Study 1, mean change in body weight was -3.8%, -4.2%, and -1.3% for CANA 100 mg, CANA 300 mg, and SITA 100 mg. In the second study, CANA 300 mg weight change was -1.03% compared with -0.3% with SITA 100 mg.

The overall incidence of adverse events was similar across treatment groups.

Patel and colleagues\(^2\) demonstrated that combination therapy with the SGLT2 inhibitor, empagliflozin (EMPA), and the DPP-4 inhibitor, linagliptin (LINA), significantly reduced A1C and weight compared with their respective monotherapies as second-line therapy for type 2 diabetes.

A total of 674 subjects with type 2 diabetes (mean age, 56 yrs; BMI, 30.9 kg/m\(^2\); A1C, 7.97%) were randomized to EMPA 25/LINA 5 mg, EMPA 10/LINA 5 mg, EMPA 25 mg, EMPA 10 mg, or EMPA 5 mg over 52 weeks. All subjects were on background metformin therapy.

A1C Reduction
Mean A1C change from baseline was -1.21%, -1.05%, -0.64%, -0.69%, and -0.48% for EMPA 25/LINA 5, EMPA 10/LINA 5, EMPA 25, EMPA 10, and LINA 5, respectively.

Compared with LINA 5, A1C was significantly reduced with:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>A1C Change (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA 25/LINA 5</td>
<td>-0.73% (-0.93, -0.53)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EMPA 10/LINA 5</td>
<td>-0.57% (-0.77, -0.37)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Compared with EMPA 10, A1C was significantly reduced with:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>A1C Change (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA 10/LINA 5</td>
<td>-0.36% (-0.56, -0.17)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Body Weight
Compared with LINA 5, body weight was significantly reduced with:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Weight Change (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA 25/LINA 5</td>
<td>-2.9 kg (-3.8, -2.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EMPA 10/LINA 5</td>
<td>-2.4 kg (-3.3, -1.5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

EMPA/LINA combinations did not significantly reduce weight vs their respective monotherapies. Adverse events were similar across treatment groups. No hyperglycemia events reported required assistance.

Lewin and colleagues\(^3\) reported similar results for A1C and weight reduction for combination therapy with empagliflozin and linagliptin—but in treatment naïve patients with type 2 diabetes.

A total of 667 treatment-naïve (≥12 wks) subjects with type 2 diabetes (mean age, 56 yrs; BMI, 31.6 kg/m\(^2\); A1C, 8%) were randomized to EMPA 25/LINA 5 mg, EMPA 10/LINA 5 mg, EMPA 25 mg, EMPA 10 mg, or EMPA 5 mg over 52 weeks.

Continued on Page 5
## Gut Microbiota May Be Associated With Various Glycemic States

Gut bacteria may change over time, suggesting a potential link to glycemic states, a new report suggests.

Ciubotaru and colleagues investigated the relationship between gut microbiota and changes in glycemic control among 16 African-American men with prediabetes (mean age, 60 years). Subjects were stratified into four groups based on changes in OGTT between baseline and 12-month study conclusion.

### Results:

<table>
<thead>
<tr>
<th>Group 1: Men whose glucose remained stable through follow-up</th>
<th>These men had more gut bacteria considered beneficial for metabolic health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2: Men whose glucose was impaired at baseline but remained stable through follow-up</td>
<td>These men had fewer beneficial and more harmful gut bacteria</td>
</tr>
<tr>
<td>Group 3: Men whose glucose worsened through follow-up</td>
<td>These men also had fewer beneficial and more harmful gut bacteria</td>
</tr>
<tr>
<td>Group 4: Men whose glucose improved through follow-up</td>
<td>These men had even more healthy bacteria than those who maintained normal glycemic control</td>
</tr>
</tbody>
</table>

Glucose that remained normal throughout the year-long study had more gut bacteria that are considered beneficial for metabolic health. Those who remained in a prediabetic state, however, had fewer beneficial bacteria. Men whose glucose improved had the highest levels of beneficial gut bacteria.

OGTT=oral glucose tolerance test


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## Reduce Fat, Not Carbs, to Lose Weight in Obesity

A diet that restricted fat intake was more effective for weight loss than a diet that restricted carbohydrate intake, Hall and colleagues reported.

They admitted 19 obese subjects without diabetes (mean age, 34 years; BMI, 36 kg/m2) to a metabolic ward for 5 days; all subjects were fed a eucaloric diet to maintain weight: 50% carbs, 35% fat, 15% protein. For the next 6 days, subjects were randomized to a 30% reduced-energy diet by having fat or carb intake restricted. After a 2- to 4-week washout period, subjects were readmitted to repeat the 5-day diet on the alternate intervention—those who were initially on reduced fat were switched to reduced carbs and vice versa.

Results showed a 67% greater weight loss in the low-fat diet group: -394 g vs -236 g (P=0.0003). Hall KD, Bemis T, Brychta RJ, et al. Is a calorie a calorie? Metabolic fat balance following selective isocaloric restriction of dietary carbohydrate vs fat in obese adults. Poster THR-553.
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A1C Reduction
Mean A1C change from baseline was -1.17%, -1.22%, -1.01%, -0.85%, and -0.51% for EMPA 25/LINA 5, EMPA 10/LINA 5, EMPA 25, EMPA 10, and LINA 5, respectively.

Compared with LINA 5, A1C was significantly reduced with:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>A1C Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA 25/LINA 5</td>
<td>-0.66%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EMPA 10/LINA 5</td>
<td>-0.71%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Compared with EMPA 10, A1C was significantly reduced with:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>A1C Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA 10/LINA 5</td>
<td>-0.37%</td>
<td>0.0017</td>
</tr>
</tbody>
</table>

Weight Reduction
Compared with LINA 5, body weight was significantly reduced with:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Weight Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA 25/LINA 5</td>
<td>-1.7 kg</td>
<td>0.0016</td>
</tr>
<tr>
<td>EMPA 10/LINA 5</td>
<td>-1.3 kg</td>
<td>0.0172</td>
</tr>
</tbody>
</table>

EMPA/LINA combinations did not significantly reduce weight compared with their respective monotherapies.

Canagliflozin, empagliflozin, and sitagliptin are not FDA approved for weight loss in the United States.


Health Nuts: Higher Nut Intake Tied to Lower Metabolic Syndrome Risk
Adolescents and teenagers (aged 12-19 yrs) who a high daily intake of nuts had a lower risk for metabolic syndrome, said a new report.

Kim and colleagues examined the association between nut intake and metabolic syndrome in 2,233 adolescents from NHANES. Overall prevalence of metabolic syndrome in the cohort was 7.4%. Nut intake of 12.9 g/day was considered significant.

A higher daily intake of nuts lowered risk for metabolic syndrome: odds ratio, 0.43 (95% CI: 0.20, 0.93).

NHANES=National Health and Nutrition Examination Survey.

LEARNING OBJECTIVES:
• Discuss the latest clinically relevant data pertaining to the use of pharmacologic and nonpharmacologic treatment options for type 2 diabetes and its comorbidities, including obesity
• Review the implications of new clinical evidence assessing treatment options and apply to clinical practice as appropriate
• Review the evidence for the potential efficacy of novel agents for reducing weight loss in individuals with obesity

TARGET AUDIENCE:
This newsletter is designed for primary care physicians, cardiologists, endocrinologists, and other healthcare professionals involved in the management of patients with type 2 diabetes and its complications and comorbidities.

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