HEALTHCARE GROUP

CENTRE FOR DIABETES & ENDOCRINOLOGY

CDE Academy - Diabetes Literature Review

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Academy

T2D: tirzepatide vs semaglutide as an add-on to metformin

@merican Diabetes Association (ADA) 81st Scientific Sessions, 2021

Takeaway

Tirzepatide (TZP) at all doses was associated with significant and superior improvements in glycaemic control and weight loss compared with semaglutide (SEMA) as an adjunct to metformin in people with type 2 diabetes (T2D).

Why this matters

TZP is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist under development for treating T2D.

Study design

In the phase 3 SURPASS-2 trial, people with T2D (n=1879; mean age, 56.6 years; baseline mean glycated haemoglobin [HbA1c], 8.28%; body mass index, 34.2 kg/m^2) were randomly assigned (1:1:1:1) to TZP (5, 10, 15 mg) or SEMA (1 mg) once weekly for 40 weeks.

The primary outcome in this study funded by Eli Lilly, was change in HbA1c level at 40 weeks.

Key results

The estimated mean change in HbA1c at 40 weeks from baseline was -2.01, -2.24, and -2.30 percentage points with TZP 5, 10, and 15 mg, respectively, vs -1.86 percentage points with SEMA 1 mg. Estimated differences in HbA1c for TZP 5, 10, and 15 mg groups vs SEMA were -0.15 (P=.02), -0.39 (P<.001), and -0.45 percentage points (P<.001), respectively.

Significant reductions in body weight were observed with TZP 5, 10, and 15 mg vs SEMA (least-squares mean estimated treatment differences, -1.9, -3.6, and -5.5 kg, respectively; P<.001 for all).

The most common treatment-emergent adverse events in the TZP and SEMA groups were gastrointestinal, with primarily mild to moderate severity.

The incidence of clinically significant hypoglycaemia (blood glucose, < 3.0 mmol/l / 54 mg/dL) was low in the TZP groups (0.2%-1.7%) as well as SEMA group (0.4%).

Limitations of this study

- Open-label.
- Short treatment duration.
- Low representation of Black participants.
- Unavailability of higher doses of SEMA for comparison.

Frías JP et al. Efficacy and Safety of Tirzepatide vs. Semaglutide Once-Weekly as Add-On Therapy to Metformin in People with Type 2 Diabetes (SURPASS-2). Late-breaking Poster 84. Presented at the *American Diabetes Association (ADA) 81st Scientific Sessions* on 25 June 2021.

Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, Cui X, Brown K; SURPASS-2 Investigators. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med*. 2021 Jun 25 [Epub ahead of print]. doi: 10.1056/NEJMoa2107519. PMID: 34170647

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Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2

BACKGROUND

Four glucagon-like peptide-1 (GLP-1) receptor agonists that are structurally similar to human GLP-1 have been shown to reduce the risk of adverse cardiovascular events among persons with type 2 diabetes. The effect of an exendin-based GLP-1 receptor agonist, efpeglenatide, on cardiovascular and renal outcomes in patients with type 2 diabetes who are also at high risk for adverse cardiovascular events is uncertain.

METHODS

In this randomised, placebo-controlled trial conducted at 344 sites across 28 countries, we evaluated efpeglenatide in participants with type 2 diabetes and either a history of cardiovascular disease or current kidney disease (defined as an estimated glomerular filtration rate of 25.0 to 59.9 ml per minute per 1.73 m^2 of body-surface area) plus at least one other cardiovascular risk factor. Participants were randomly assigned in a 1:1:1 ratio to receive weekly subcutaneous injections of efpeglenatide at a dose of 4 or 6 mg or placebo. Randomisation was stratified according to use of sodium–glucose cotransporter 2 inhibitors. The primary outcome was the first major adverse cardiovascular event (MACE; a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular or undetermined causes).

RESULTS

A total of 4076 participants were enrolled; 2717 were assigned to receive efpeglenatide and 1359 to receive placebo. During a median follow-up of 1.81 years, an incident MACE occurred in 189 participants (7.0%) assigned to receive efpeglenatide (3.9 events per 100 person-years) and 125 participants (9.2%) assigned to receive placebo (5.3 events per 100 person-years) (hazard ratio, 0.73; 95% confidence interval [CI], 0.58 to 0.92; P<0.001 for noninferiority; P=0.007 for superiority). A composite renal outcome event (a decrease in kidney function or macroalbuminuria) occurred in 353 participants (13.0%) assigned to receive efpeglenatide and in 250 participants (18.4%) assigned to receive placebo (hazard ratio, 0.68; 95% CI, 0.57 to 0.79; P<0.001). Diarrhoea, constipation, nausea, vomiting, or bloating occurred more frequently with efpeglenatide than with placebo.

CONCLUSIONS

In this trial involving participants with type 2 diabetes who had either a history of cardiovascular disease or current kidney disease plus at least one other cardiovascular risk factor, the risk of cardiovascular events was lower among those who received weekly subcutaneous injections of efpeglenatide at a dose of 4 or 6 mg than among those who received placebo.

Funded by Sanofi; AMPLITUDE-O ClinicalTrials.gov number, NCT03496298

Hertzel C. Gerstein, Naveed Sattar, Julio Rosenstock, et al for the AMPLITUDE-O Trial Investigators

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"Trial evaluated efpeglenatide in participants with type 2 diabetes and either a history of cardiovascular disease or current kidney disease plus at least one other cardiovascular risk factor."

EMPEROR-Preserved: Positive Top-Line Results for Empagliflozin in HFpEF

Treatment with the sodium-glucose cotransporter 2 (SGLT2 inhibitor empagliflozin (Jardiance, Boehringer Ingelheim/Eli Lilly) significantly reduces the risk of cardiovascular death or hospitalisation for heart failure in adults with heart failure and preserved ejection fraction (HFpEF), according to top-line results of the EMPEROR-Preserved phase 3 study.

EMPEROR-Preserved investigated the safety and efficacy of empagliflozin 10 mg compared with placebo in 5988 patients with HFpEF with or without diabetes.

The primary endpoint was time to first event of adjudicated CV death or HF hospitalisation over the course of up to 38 months.

"HFpEF has long been the most challenging form of heart failure to treat," principal investigator Stefan Anker, MD, PhD, Charité Berlin, Germany, said in a statement from the company announcing the top-line results today.

"The EMPEROR-Preserved findings demonstrate that empagliflozin reduces cardiovascular death or hospitalisation for heart failure and has the potential to transform the care of people living with heart failure"

"The EMPEROR-Preserved findings demonstrate that empagliflozin reduces cardiovascular death or hospitalisation for heart failure and has the potential to transform the care of people living with heart failure," said Anker. The results are in line with the EMPEROR-Reduced trial, which showed that empagliflozin significantly reduced the combined relative risk of CV death or HF hospitalisation by 25% compared with placebo in adults with HF and reduced ejection fraction (HFrEF).

The EMPEROR-Reduced results formed the basis of the recent approval of a new indication for empagliflozin for the treatment of adults with HFrEF by the European Commission.

Empagliflozin is not approved for HF in the United States. Boehringer Ingelheim and Lilly have submitted a supplemental new drug application for empagliflozin to reduce the risk of CV death or HF hospitalisation in adults with HFrEF to the US Food and Drug Administration, with a decision expected later this year.

The companies plan regulatory submissions for empagliflozin for HFpEF this year.

"No approved therapies have been clinically proven to improve outcomes specifically for people with HFpEF, leaving a significant unmet medical need in this already prevalent and increasingly common form of heart failure," Mohamed Eid, MD, Boehringer Ingelheim vice president, clinical development and medical affairs, cardio-metabolism & respiratory medicine, said in the news release.

"The totality of the data from the EMPEROR-Preserved trial marks a possible new chapter in heart failure, supporting the potential of Jardiance to become the first SGLT2 inhibitor to treat a defined population of adults with heart failure with either preserved or reduced ejection fraction," Eid said.

EMPEROR-Preserved: Positive Top-Line Results for Empagliflozin in HFpEF - *Medscape* - July 06, 2021

Low-Density Lipoprotein Cholesterol Is Associated With Insulin Secretion

Abstract

Context

Pharmacological lowering of low-density lipoprotein (LDL) cholesterol potently reduces cardiovascular risk while concurrently increasing type 2 diabetes risk.

Objective

The aim of this study was to investigate the relationship between LDL cholesterol concentrations and insulin secretion and glucagon levels.

Methods

A total of 3039 individuals without cholesterol-lowering therapy, but with increased risk for diabetes, underwent routine blood tests and a 5-point oral glucose tolerance test (OGTT). Glucagon concentrations, insulin secretion, and insulin clearance indices were derived from the OGTT.

Results

There was no association between LDL cholesterol and fasting glucagon (P = .7, β = –.01) or post-glucose load glucagon levels (P = .7, β = –.07), but we detected significant positive associations of LDL cholesterol and C-peptide-based indices of insulin secretion (area under the curve $[AUC]_{C\text{-}Peptide(0–30min)}/AUC_{Glucose(0–30min)}$: P < .001, β = .06; $AUC_{C\text{-}Peptide(0–120min)}/AUC_{Glucose(0–120min)}$: P < .001, β = –.08).

In contrast, we found a negative association of insulin-based insulin secretion indices with LDL concentrations (insulinogenic index: P = .01, β = –.04; disposition index: P < .001, β = –.06).

LDL cholesterol levels, however, were positively associated with insulin clearance assessed from C-peptide and insulin concentrations, both in the fasting state and post–glucose load (P < .001, β = .09 and P < .001, β = .06, respectively).

Conclusion

As C-peptide based indices reflect insulin secretion independent of hepatic clearance, our results indicate lower insulin secretion in case of lesser LDL cholesterol. This could explain deteriorating glycaemic control in response to cholesterol-lowering drugs.

"...results indicate lower insulin secretion in case of lesser LDL cholesterol. This could explain deteriorating glycaemic control in response to cholesterol-lowering drugs..."

Corinna Dannecker; Robert Wagner; Andreas Peter; Julia Hummel; Andreas Vosseler; Hans-Ulrich Häring; Andreas Fritsche; Andreas L. Birkenfeld; Norbert Stefan; Martin Heni

***J Clin Endocrinol Metab*. 2021;106(6):1576-1584.**