抗肥満薬は心血管イベントを増加させない (Abstract 2069)

CAMELLIA-TIMI 61：スタディの結果、心血管リスクの高い患者における体重管理目的でのlorcaserin使用が支持される

CAMELLIA-TIMI 61: Study supports use of lorcaserin for weight management in patients at high cardiovascular risk

抗肥満薬lorcaserinは心血管イベントを増加させないとのCAMELLIA-TIMI 61トライアルのレイトブレイキングの結果がESC Congress 2018 で発表され、*New England Journal of Medicine* に掲載された。食事療法および運動療法に追加することにより、この薬剤はプラセボに比べ軽度の体重減少をもたらし、主要心血管イベント（MACE）を増加させなかった。追跡期間中央値3.3年の時点で、MACEはlorcaserin 群の6.1% およびプラセボ群の6.2%に発現し、非劣性が示された（p<0.001）。これらの結果から、例え患者の心血管リスクが高い場合でも体重管理目的でのlorcaserin 使用は支持される、と筆者らは述べている。

Full Text

The weight loss drug lorcaserin does not increase cardiovascular events, according to late breaking results from the CAMELLIA-TIMI 61 trial presented in a Hot Line Session at ESC Congress and published in the *New England Journal of Medicine*.

Lorcaserin is an appetite suppressant, increasing the sense of fullness after a meal and reducing hunger before meals. It is not approved as a weight loss drug in Europe. The European Medicines Agency has expressed concerns about the potential risk of tumors based on animal data, psychiatric disorders including depression, and problems with heart valves.

The US Food and Drug Administration (FDA) in June 2012 approved the medication for weight loss in overweight adults with a body mass index (BMI) of 30 kg/m^2 or greater, or with a BMI of 27 kg/m^2 or greater and at least one weight-related health condition such as high blood pressure, type 2 diabetes, or high cholesterol. As with all weight loss agents, the FDA's approval was contingent on postmarketing studies assessing the risk for major adverse cardiovascular events.

The CAMELLIA-TIMI 61 trial was conducted as part of the FDA's postmarketing requirement. The trial examined the safety and efficacy of the drug with regard to major adverse cardiovascular events (MACE) and progression to diabetes in overweight or obese individuals with, or at risk for, cardiovascular disease.

The trial enrolled 12,000 adults from 473 centers in eight countries between January 2014 and November 2015. Participants had a BMI of at least 27 kg/m^2 and either 1) established cardiovascular disease (with or without diabetes) or 2) diabetes and at least one other cardiovascular risk factor. Participants were randomly allocated in a 1:1 ratio to lorcaserin (10 mg twice a day) or matching placebo. All participants were advised to exercise and eat healthily.

The primary safety endpoint was noninferiority of the drug compared to placebo for MACE (cardiovascular death, myocardial infarction, or stroke) after 460 events had occurred. If the safety endpoint was met, the trial would proceed to completion and assess the primary efficacy endpoint of superiority of the drug for MACE plus hospitalization for unstable angina, heart failure, or any coronary revascularization. Secondary endpoints included delay or prevention of conversion to type 2 diabetes in those with pre-diabetes at baseline, and the effect on weight, heart rate, blood pressure, lipids, and blood sugar.

The average age of participants was 64 years, 64% were male, and the median BMI was 35 kg/m^2. Three-quarters (8,958; 75%) had a history of at least one established cardiovascular disease: 8,153 (68%) had coronary artery disease, 1,129 (9.4%) had cerebrovascular disease, and 657 (5.5%) had peripheral artery disease. More than half (57%) had diabetes, 90% had hypertension, 94% had hyperlipidemia, and 20% had renal insufficiency.

The interim analysis after 460 events showed that the trial met its primary safety objective. At study completion with a median follow-up of 3.3 years, MACE occurred in 6.1% of those taking lorcaserin and 6.2% of those on placebo, demonstrating noninferiority (p<0.001).

The trial did not meet its superiority endpoint. The composite of MACE plus hospitalization for unstable angina, heart failure, or any coronary revascularization occurred in 11.8% of participants taking the drug and 12.1% of those on placebo (p=0.55).

On top of lifestyle counselling, those taking lorcaserin lost an average of 4.2 kg in the first year compared to 1.4 kg for those taking placebo (p<0.001). At one year, 39% of those taking the drug had lost at least 5% of their body weight compared to 17% of the placebo group (p<0.001) while 15% on the drug lost 10% of their body weight compared to 5% on placebo (p<0.001). The differences between groups remained statistically significant at 3.3-years of follow-up.

Regarding secondary endpoints, compared to placebo, the medication reduced the conversion rate to diabetes in participants with pre-diabetes at baseline. The drug also led to small improvements in levels of triglycerides, blood glucose, heart rate and blood pressure.

In the CAMELLIA-TIMI 61 study, the most common side effects possibly related to the drug and leading to drug discontinuation were dizziness, fatigue, headache and nausea – all of which are listed on the FDA-approved label. There was no difference in the occurrence of malignancy between the drug and placebo groups. In a dedicated echocardiographic substudy, there was a non-significant imbalance in the incidence of valvular disease at one year between the drug and placebo groups (1.8% versus 1.3%; p=0.24). Serious hypoglycemia was more common in patients on lorcaserin, a side effect observed in prior studies.

Lorcaserin is not approved for use in women who are pregnant, breastfeeding, or planning to become pregnant. It should be used with caution in patients with congestive heart failure. If signs or symptoms of valvular heart disease develop, such as dyspnea or a new cardiac murmur, patients should be evaluated and discontinuation of the drug considered. People taking the drug should be monitored for depression, changes in mood, and suicidal thoughts or behaviors – the drug should be discontinued if the latter are experienced.

"We have been able to show for the first time that this weight loss drug does what it is intended to do. It helps people lose weight without causing an increase in major adverse cardiovascular events in a population at higher risk for heart attacks and strokes," said Dr. Erin Bohula, an investigator with the CAMELLIA-TIMI 61 trial and TIMI Study Group investigator at Brigham and Women's Hospital, Boston, US.

"One of our hypotheses was that losing weight with this medication might also lead to a cardiovascular benefit but we did not see that," she continued. "While there were improvements in multiple cardiovascular risk factors, including weight, lipids and blood glucose, the magnitude of impact on these risk factors was relatively small."

Dr. Bohula said: "Nevertheless, the CAMELLIA-TIMI 61 study is notable as it provides the first demonstration of cardiovascular safety of any weight loss agent in a dedicated cardiovascular outcomes trial."

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Conference News