

Sibutramine should be excluded from use in obese patients with preexisting cardiovascular disease

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Sibutramine, an agent that blocks the reuptake of serotonin and norepinephrine by presynaptic nerve terminals and thereby induces satiety, was approved by the FDA in 1997 for weight management in patients who are unable to lose weight by means of diet and exercise alone. In some patients sibutramine increases blood pressure, heart rate or both, owing to its sympathomimetic effects.

The SCOUT (Sibutramine Cardiovascular Outcomes) trial was a randomized, double-blind, placebo-controlled, multicenter trial in which approximately 10,000 patients who were overweight or obese and had preexisting cardiovascular disease, diabetes mellitus, or both, were randomly assigned to receive sibutramine or placebo, in addition to participating in individualized diet and exercise programs, for an average of 3.4 years.

Eligible patients included men and women, of at least 55 years old, with a body-mass index of at least 27 but less than 45, with history of cardiovascular disease, type 2 diabetes mellitus with at least one other cardiovascular risk factor, or both. They were organized into three cardiovascular-risk groups: diabetes only (DM-only group), cardiovascular disease only (CV-only group) or both (CV-DM group).

Exclusion criteria were: symptoms of heart failure greater than NYHA functional class II,

blood pressure higher than 160/100 mm Hg, a heart rate higher than 100 beats/minute, scheduled cardiac surgery or coronary angioplasty, or a weight loss of more than 3 kg within the previous 3 months.

All the subjects (10,744) underwent a lead-in period of 6 weeks, during which they received sibutramine 10 mg daily. The subjects with early and persistent increases in blood pressure or/and heart rate were excluded. After this lead-in period, eligible subjects (9804) were randomly assigned to receive 10 mg sibutramine per day, or placebo and participated in individualized cardioprotective diet and exercise programs. It was permitted an increase in the dose of sibutramine to 15 mg daily, according to the investigator's judgment.

The primary outcome was the time from randomization to the first occurrence of a primary outcome event. The primary outcome events were nonfatal myocardial infarction, nonfatal stroke, and resuscitation after cardiac arrest, and cardiovascular death. The secondary outcome was death from any cause.

The risk of a primary outcome event was 11.4% in the sibutramine group as compared with 10.0% in the placebo group ($P = 0.02$). The rates of nonfatal myocardial infarction and nonfatal stroke were 4.1% and 2.6% in the sibutramine group and 3.2% and 1.9% in the placebo group, respectively (for nonfatal myo-

cardial infarction, $P = 0.02$; for nonfatal stroke, $P = 0.03$). The rates of cardiovascular death and death from any cause were not increased. The mean weight loss during the lead-in period was 2.6 kg; after randomization, the subjects in the sibutramine group achieved and maintained further weight reduction (mean, 1.7 kg). The mean blood pressure decreased in both groups, with greater reductions in the placebo group than in the sibutramine group (mean difference, 1.2/1.4 mm Hg).

The authors discuss that in the SCOUT trial, despite that the sibutramine group lost more weight than the placebo group and maintained the weight loss, the risk of a primary outcome event was higher with 16% in the sibutramine group as compared with the placebo group, due to a higher incidence of nonfatal events among sibutramine-treated subjects who had

preexisting cardiovascular disease. The subgroup with diabetes but no evidence of preexisting cardiovascular disease had no increase in the risk of cardiovascular events, though diabetic subjects with cardiovascular disease did have an increase in risk.

The increase in the risk of cardiovascular events in the SCOUT trial could be directly related to the higher blood pressure and heart rate observed in the sibutramine-treated subjects, as compared with those receiving placebo. Alternatively, blood pressure and heart rate could simply be markers of other adverse mechanisms resulting in cardiovascular events.

The authors conclude that on the basis of these results, sibutramine should continue to be excluded from use in patients with preexisting cardiovascular disease. □



Comment on a paper:

WPT James, ID Catterson, W Coutinho et al, for the SCOUT investigators – Effect of Sibutramine on Cardiovascular Outcomes in Overweight and Obese Subjects. *N Engl J Med* 2010; 363:905-917