Sibutramine Tied to 1.4% Bump in CVD Events

Some physicians maintain that sibutramine should still be available for select patients.

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STOCKHOLM — When European drug regulators called for a study to push the safety profile of the sympathomimetic weight-loss drug sibutramine to its limit, sibutramine failed the test.

In a randomized, placebo-controlled trial with nearly 10,000 patients, most of whom had a history of cardiovascular disease, an average of nearly 4 years of treatment with 10-15 mg sibutramine daily produced a 1.4% absolute increased rate of cardiovascular events, especially nonfatal myocardial infarction and stroke, compared with placebo patients—a 16% relative increased risk that was statistically significant, Dr. Luc van Gaal, a professor of medicine at Antwerp University Hospital, Belgium, said at the meeting. This excess risk from sibutramine seemed linked to a consistent rise in recipient's blood pressure of 1.5-2.0 mm Hg, and heart rate by 2-4 beats per minute.

Results from the Sibutramine Cardiovascular Outcome Trial (SCOUT) also showed that the drug effectively aided weight loss, producing a significant loss of at least 5% of baseline weight in 42% of treated patients, and these bigger losers had their risk for a cardiovascular event substantially blunted.

Preliminary results of SCOUT were given to the Food and Drug Administration and the European Medicines Agency (EMA) last fall, and in January both regulators took action: FDA contraindicated sibutramine in people with a history of cardiovascular disease, and EMA withdrew its marketing approval. The drug remains available in several other countries including Australia and Brazil.

This inconsistent approach to the new data appeared to rankle European physicians who treat obesity and heard the SCOUT results reported for the first time at the meeting. They seemed especially puzzled by SCOUT's design, with its enrollment largely including patients with cardiovascular disease history or risk even though these are label contraindications, and by continuing patients on chronic sibutramine even when they lacked a weight-loss response.

"Some of us feel we could use sibutramine in a responsible way to benefit patients" despite the safety problem that SCOUT revealed, said Dr. Stephen Rössner, an obesity specialist and professor of health-related behavioral science at the Karolinska Institute in Stockholm, who spoke as a discussant of SCOUT and was not involved in the study. "For many patients, on an individual basis, sibutramine would be very beneficial. We had desperate patients calling when they found out that they would not be able to get the drug anymore." Currently, The European Union gives marketing approval to just one drug for obesity treatment, orlistat (Xenical), he noted.

"Everyone agrees that sibutramine has cardiologic effects that you need to control for. But many patients without cardiology problems need weight-loss maintenance for treating sleep apnea or osteoarthritis. Sibutramine could be very helpful provided you can control the risks, but I think that can be done by a responsible physician," Dr. Rössner said in an interview.

SCOUT was sponsored by Abbott, which markets sibutramine (Meridia), to address questions about the drug's safety from the EMA. An independent steering committee formed to run the study, led by Dr. W. Philip T. James, of the London School of Hygiene and Tropical Health and president of the International Association for the Study of Obesity, the meeting organizer.

VITALS

Major Finding: Treating patients with sibutramine for an average of 4 years led to a significant, 1.4% increased rate of cardiovascular disease end points compared with patients on placebo.

Data Source: SCOUT, a multicenter study with 9,804 patients randomized; 76% of study patients had a history of cardiovascular disease.

Disclosures: Abbott sponsored the trial. Dr. W. Philip T. James, has been a consultant to and served on an advisory board for Abbott, Sanofi-Aventis, and GlaxoSmithKline and has been a speaker for Roche and Sanofi-Aventis. Dr. van Gaal and Dr. Caterson had no disclosures; Dr. Rössner has received research and travel support from numerous companies, including Abbott; and Dr. Sharma has served as a consultant to GlaxoSmithKline.

The trial ran at 297 sites in 16 countries, including Australia, Brazil, and Mexico, as well as several European countries. The first patient randomized in February 2003, the last patient in December 2005, and the follow-up database closed in November 2009.

When SCOUT began, it enrolled three types of patients in equal numbers: patients with type 2 diabetes and at least one cardiovascular risk factor—controlled hypertension, dyslipidemia, smoking, or diabetic nephropathy with microalbuminuria; patients only with diagnosed coronary artery disease or peripheral arterial disease; and patients who fulfilled both of these two criteria. Less than a year into the study, the steering committee decided to boost the event rate in the trial by narrowing enrollment to only patients with a history of cardiovascular disease, either alone or with type 2 diabetes. The consequence was that of the 9,996 patients randomized in SCOUT 76% had a history of cardiovascular disease, and 84% had type 2 diabetes; 60% had both. Their average age was 63, older than is typical in a weight-loss study, and 58% were men, more than is typical in a weight-loss trial. Their average baseline body mass index was 34 kg/m^2.

All patients began on 10 mg sibutramine daily for a 6-week run-in to screen out patients whose blood pressure rose too high. Most patients also lost weight during this phase, an average of 2.2 kg.

After 6 weeks, randomization assigned patients to either 10 mg sibutramine or placebo. Those in the active-treatment arm could have their dosage raised to 15 mg/day, which happened for a third of the sibutramine patients.

The intention-to-treat primary end–point analysis included 4,906 patients treated with sibutramine and 4,898 who received placebo followed for an average of 3.8 years on treatment. In addition to the primary end point, the combined rate of nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, and cardiovascular death (see table), the SCOUT investigators reported several other important outcomes.

In the 24% of patients with diabetes and one risk factor, the primary end–point rate ran 6.5% in both the sibutramine and placebo groups. In contrast, in patients with cardiovascular disease history and diabetes sibutramine added 2% to the placebo risk, and in those with cardiovascular disease history only sibutramine produced an added 1.8% of event rates over placebo.

The results also documented sibutramine's efficacy for weight loss. Forty-two percent of patients in the sibutramine group lost at least 5% of their baseline weight, compared with 24% of the placebo patients. The percent of patients who gained weight on the regimen was 24% on sibutramine and 38% on placebo. Patients who responded to sibutramine by losing weight also had an improved prognosis. For each 1 kg lost during the 6-week sibutramine-treatment phase for all patients, patients had a 0.8% reduction in their incidence of a primary outcome event during follow-up, said Dr. Ian Caterson, professor of human nutrition at the University of Sydney and another collaborator on the study.

In addition, patients who lost weight had a significant reduction in their blood pressure. The average blood pressure of patients who lost at least 5% of their baseline weight closely tracked with the placebo level throughout the 5 years of the study. Only patients on sibutramine who failed to lose at least 5% had significantly increased blood pressure, compared with the placebo group, reported Dr. Arya M. Sharma, professor of medicine and chairman of obesity research and management at the University of Alberta, Edmonton, and another member of the SCOUT steering committee.

Despite the positive weight-loss results, the known action of sibutramine as a serotonin-noradrenalin reuptake inhibitor, its discernable blood pressure effect, and the excess of cardiovascular events it caused in SCOUT together create a "causal train" between the drug and clinically meaningful adverse events, said Dr. Steven B. Heymsfield. "Drug companies will stay away from this," said Dr. Heymsfield, who spoke as the session's second invited discussant and is executive director of clinical sciences and head of obesity drug development at Merck in Rahway, N.J.

"The question is risk benefit, and they haven't shown the benefit of [sibutramine.] It's critical to show a medical benefit" from sibutramine, Dr. Heymsfield said.

Despite Dr. Heymsfield's skepticism about regulators accepting a future role for sibutramine in routine practice, one member of the steering committee voiced his support of countries that have kept sibutramine available.

"In Brazil sibutramine is still on the market and widely used, with a million prescriptions per year," said Dr. Walmir Coutinho, an endocrinologist at Catholic University in Rio de Janeiro, and a member of the SCOUT steering committee. "Brazilian physicians believe it should remain on the market," he said, citing a recent statement from the society of Brazilian endocrinologists. "The event rates in patients without cardiovascular disease were very low."

Aside from Dr. Coutinho's statement of support for the Brazilian approach to regulating sibutramine, the SCOUT steering committee members who presented the study's data deliberately avoided commenting on the EMA's action. The closest anyone came was when Dr. James, in response to a question, referred back to what Dr. Coutinho had said. He "said effectively that [the EMA's decision] wasn't appropriate," Dr. James said. ■