

sure was relatively short. It may be that a longer follow-up period would be needed to show either a protective effect of blood-pressure lowering at the levels achieved in the ACCORD study or an increase to significance of the nonsignificant deleterious effect of intensive blood-pressure control that was found in the study. It is also possible that there is little effect of blood-pressure control in persons of the age and with the risk factors of the ACCORD Eye participants.

Although change in visual acuity was not a primary outcome of the ACCORD Eye study, data on this important functional result are provided. No significant beneficial effect on moderate vision loss was shown for any of the interventions.

There are many differences among studies of risk factors for the progression of retinopathy that might lead to the observed variation in their results. The means of ascertainment of retinopathy severity has not been uniform across studies. Even when photographs are taken, the protocols for photography may vary, as may the grading techniques and severity scales used. In addition, comparing findings between patients with type 1 diabetes and those with type 2 diabetes is not always appropriate. Finally, the inadequacy of some sample sizes and the use of repeated testing may also color our interpretation of study findings.

Overall, the ACCORD Eye trial has added substantially to our knowledge and confidence about

the importance of glycemic control in the progression of diabetic retinopathy. The findings also strongly suggest the need for further evaluation of the potential importance of fenofibrate in our armamentarium of treatments for this condition.

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## Drug Management of Obesity — Efficacy versus Safety

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The history of pharmacologic treatment of obesity is characterized by repetition: most drugs that have achieved regulatory approval and reached the markets have subsequently been withdrawn owing to postmarketing discovery of serious adverse effects. In 2007, the cannabinoid-receptor antagonist rimonabant was not approved by the Food and Drug Administration (FDA) and was withdrawn from the market in Europe because of an increased risk of depression, anxiety, and suicidal ideation<sup>1</sup>; the development program for several compounds of the same class that were in phase 3 studies had to be terminated. In January of this year, the European Medicine Agency's Committee for Medicinal Products for Human

Use<sup>2</sup> recommended that use of another weight-loss compound, the serotonin and norepinephrine reuptake inhibitor sibutramine, be suspended; it was removed from the European market. That decision was prompted by the preliminary report from the 10,000-patient, 6-year Sibutramine Cardiovascular Outcome Trial (SCOUT; ClinicalTrials.gov number, NCT00234832) in patients with cardiovascular disease and type 2 diabetes, which showed an increased risk of serious, nonfatal cardiovascular events, such as stroke or heart attack with sibutramine as compared with placebo.<sup>2,3</sup> The FDA requested that the manufacturer add new contraindications to the sibutramine label, stating that the drug should not be

used in patients with a history of cardiovascular disease.<sup>3</sup> Later this year, the FDA will complete a review of the potential benefits and risks of sibutramine; the fate of sibutramine in the U.S. market remains undecided until then.

Drugs targeting the serotonergic system also have a long history in the management of obesity. Fenfluramine, a racemic mixture of the two isomers, levofenfluramine and dexfenfluramine, causes the release of endogenous serotonin from neurons and platelets and was approved by the FDA in 1973 as an adjunct for the treatment of obesity. Dexfenfluramine, which was thought to have fewer adverse effects than fenfluramine, was approved for use in the United States in 1996. These weight-loss drugs became extremely popular as used in combination with phentermine, which provided additional weight-loss efficacy. However, both fenfluramine compounds were withdrawn from the market in 1997, following reports of a serious adverse event: valvular heart disease causing regurgitation. The first reports of cardiac valvular disease in association with fenfluramine noted that an unusual form of the disease developed in 24 women receiving fenfluramine.<sup>4</sup> The echocardiographic and histologic features of the valve specimens resembled those in carcinoid heart disease and ergot alkaloid-induced heart disease. Fenfluramine use has also been associated with an increased risk of pulmonary arterial hypertension.<sup>5</sup>

The effects of nonselective serotonergic agents on valvulopathy and pulmonary arterial hypertension are thought to occur through agonism of the 5-hydroxytryptamine (5-HT, or serotonin) receptor 5-HT<sub>2B</sub>, expressed on cardiac valvular interstitial cells and pulmonary-artery smooth-muscle cells, whereas the suppression of appetite is predominantly mediated by the 5-HT<sub>1B</sub> and 5-HT<sub>2C</sub> receptors.<sup>6</sup>

Given the specific subtypes of 5-HT receptor involved in appetite suppression, it makes good sense to develop more selective agents that work on the 5-HT<sub>2C</sub> receptors with little or no effects on the 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors. Lorcaserin is a new compound designed to work selectively on the central 5-HT<sub>2C</sub> receptors, with a functional selectivity of approximately 15 and 100 times over that for 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors, respectively. A recent, 12-week, phase 2 trial (NCT00116740) showed promising weight-loss potential of lorcaserin, without any effects on heart

valves or pulmonary arterial pressure.<sup>7</sup> Smith and colleagues (the same group) now report, in this issue of the *Journal*, the results of a larger phase 3 study of lorcaserin (NCT00395135).<sup>8</sup>

The authors randomly assigned 3182 overweight or obese patients to receive lorcaserin (10 mg) or placebo twice daily, in combination with a diet and exercise program. After 1 year, weight loss was approximately 4 kg greater in the lorcaserin group than in the placebo group. After 1 year, patients receiving lorcaserin were randomly assigned again, in a 2:1 ratio, to either continue to receive lorcaserin or to switch to placebo for the second year. The patients who were switched from lorcaserin to placebo gained back the lost weight and at 2 years had approximately the same body weight as those who had received placebo for both years. In contrast, patients who received lorcaserin for both years gained back less weight and had lost approximately 2 kg more after 2 years than those who had received placebo. Although the statistical analyses of the drug's effect on weight loss are complicated by the fact that only about 50% and 36% of the randomly assigned patients completed the first and second years of the study, respectively, the various statistical approaches were used to deal with the high dropout rate, and the efficacy results therefore seem robust.

The weight-loss efficacy of lorcaserin is slightly less than or equivalent to that of the lipase inhibitor orlistat, and slightly less than that of sibutramine, the two other weight-loss compounds on the market. The justification for putting lorcaserin on the market, therefore, needs to be considered. However, safety and adverse-event profiles seem to be better with lorcaserin than with orlistat or sibutramine. Lorcaserin use does not seem to increase the risk of valvulopathy, pulmonary hypertension, depression, or suicidal thought, but phase 3 studies will be required to confirm these initial findings in larger populations of patients.

Lorcaserin therapy also resulted in slight, but clinically relevant, improvements in almost all reported surrogate measures of diabetes and cardiovascular risk. These findings are important in light of the problems with drugs such as rimonabant and sibutramine, which do not produce similar reductions in blood pressure, heart rate, and levels of low-density lipoprotein cholesterol that would be expected with the weight loss

achieved. The most common adverse events in the lorcaserin group were upper respiratory infections, headache, dizziness, and nausea; these led to an only slightly higher rate of discontinuation in the lorcaserin group than in the placebo group (7.1 and 6.7%, respectively).

The justification for using lorcaserin to manage obesity is not greater efficacy than currently available drugs, but rather an apparently much better safety and adverse-event profile and very clear-cut beneficial effects on risk factors for type 2 diabetes and cardiovascular disease. Where lorcaserin will fit into the management of obesity remains to be seen. Future studies could investigate the potential for improved weight-loss efficacy by combining lorcaserin with other receptor-selective weight-loss compounds such as analogues of glucagon-like peptide 1. Given the history, we will need to be doubly sure about the safety of lorcaserin, used either alone or in combination with other weight-loss drugs.

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