Sibutramine in cardiovascular disease: is SCOUT the new STORM on the horizon?

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This editorial refers to 'Cardiovascular responses to weight management and sibutramine in high-risk subjects: an analysis from the SCOUT trial' by C. Torp-Pedersen et al., on page 2915

Imagine your favourite pizza, and, after half of it is gone, your desire to eat the rest is gone as well. Sibutramine seems to have just this effect—at least for some. Doesn’t this appear like the ideal scenario for losing weight? We and other authors are not so sure about that.1 Sibutramine, a centrally acting monoamine (noradrenaline and serotonin) reuptake inhibitor, was originally developed as an antidepressant. Due to its ‘side effect’ of moderate weight loss mainly achieved via increased satiety, the drug was approved and introduced into the US market in 1997, and is today licensed worldwide for the treatment of obesity.

The World Health Organization (WHO) estimates that currently there are >1 billion overweight adults worldwide, and that 300 million of them are clinically obese.2 Indeed, it can be said that obesity has reached epidemic proportions. Some people have approached this problem from a philosophical point of view. The American psychiatrist Thomas Szasz (born 1920) has stated that ‘obesity condenses and expresses a contest between the individual and some other person or persons in his environment over the control of the individual’s body’.3 However, a wealth of data buttresses the view that obesity is a lot more than that, and that the perturbation is related to the development of diet-related chronic diseases including type 2 diabetes mellitus, cardiovascular diseases, hypertension, and stroke. The sheer volume of data all point in the same direction: it is time to act. More importantly, it is time to fight obesity before chronic diseases develop. Once chronic illnesses become manifest, the situation changes completely,4 and a higher body mass index (BMI) may have survival benefits, for example in patients with chronic heart failure.5

A number of randomized, double-blind, placebo-controlled trials have demonstrated the efficacy of sibutramine in losing weight, especially when combined with lifestyle modification and intensive follow-up.6 Those effects were reproducible in primary care conditions7 and would therefore be attributable to most individuals with obesity. The results of the Sibutramine Trial of Obesity Reduction and Maintenance (STORM) should also be kept in mind.8 Of the individuals in this study, 77% lost weight after 6 months of treatment. This effect was sustained in most patients who continued with sibutramine for another 2 years. Nonetheless, sibutramine was associated with several adverse effects, which has given rise to a debate that still endures today. Indeed, the Italian regulatory authority suspended its approval in March 2002 following a publication by British health authorities who suspected an association of sibutramine with two cardiovascular deaths and 212 reports of adverse reactions in sibutramine-treated patients. Moreover, French drug regulators reported 99 instances of sibutramine side effects, 10 of them being serious. Indeed, the drug may account for a small increase in blood pressure and heart rate, which raises suspicion for cardiovascular toxicity. The use of sibutramine is therefore not recommended in patients with uncontrolled hypertension, pre-existing cardiovascular disease, or tachycardia.6

To date, we do not have any properly designed large-scale clinical trials assessing the effects of sibutramine and its safety profile in patients with established cardiovascular diseases. The Sibutramine Cardiovascular OUTcomes (SCOUT) trial was a double-blind, randomized, placebo-controlled, parallel-group study into the effects of sibutramine 10 mg once daily on mortality in overweight (defined as a BMI ≥25 and <27 kg m−2 plus waist circumference ≥102 cm in men or ≥88 cm in women) and obese subjects (BMI ≥27 and ≤45 kg m−2) at high risk of a cardiovascular event. All subjects were older than 55 years and had a history of manifest cardiovascular disease or type 2 diabetes mellitus. Torp-Pedersen et al.9 report on the effects of sibutramine during the 6-week run-in period of the trial during which all 10 742 patients received treatment with sibutramine. SCOUT has several long-term end-points. However, the present analysis primarily tackles the cardiovascular safety debate.

Based on previous reports of increases in blood pressure and heart rate, the investigators predicted a drop-out rate...
of 25% during the single-blind lead-in period. Eventually, two consecutive increases of >10 mmHg over initial systolic or diastolic blood pressure measurements and a sustained increase in pulse rate of >10 b.p.m were experienced by 791/10 463 patients (7.6%), ranging from 10.3% in diabetics to 6.2% in those with cardiovascular disease and diabetes. Specifically, individual increases were experienced by 4.7 and 3.5% of patients, respectively. The overall drop-out rate reached 6.8%, and 329 patients (3.1%) discontinued the drug due to adverse events. Cardiac disorders (0.6%) and blood pressure increase (0.2%) caused a minority of discontinuations, whereas others were due to previously reported and well-known side effects of sibutramine. All numbers are much lower than anticipated and support the notion of the cardiovascular safety of sibutramine. This indeed has an important clinical impact as large proportions of patients with manifest cardiovascular disease and in particular those at high risk (i.e. diabetics, patients with metabolic syndrome) actually have the problem of obesity.

In conjunction with cardiovascular safety, the authors report the results from the analysis of several subgroups. These include gender analysis, and the potential interaction of concomitant treatment with β-blockers. Sibutramine had comparable effects in men and women, as well as in those treated with β-blockers or the β-blocker naïve. Nonetheless, the authors highlight the potential of β-blockers to be protective against disadvantageous changes of blood pressure and heart rate. Unfortunately, we do not have any ambulatory blood pressure data which would be supportive of the statement made by the authors. A protective effect of β-blockers would be clinically important as 61% of patients were receiving β-blockers, and this proportion would presumably increase over time. It would also be interesting to see whether this was only due to β-blocker treatment or whether the effect was type and/or dose dependent. Additionally, the authors could have presented some data on possible interactions and/or side effects with drugs other than β-blockers. Whilst blood pressure changes in hypertensive patient subgroups are reported, we do not have any insight into possible differences between patients in the three cardiovascular risk categories as defined by the authors. We feel that these analyses could identify subgroups that would particularly benefit from the treatment with sibutramine. When the complete results of the trial are available, this information will be extremely valuable for the clinician in everyday practice.

The concomitant use of sibutramine and β-blockers raises at least two conflicting issues, which we like to highlight. Recently, a 16-week randomized double-blind placebo-controlled study, the Hypertension–Obesity–Sibutramine (HOS) study, with sibutramine in addition to different antihypertensive treatment modalities in obesity-related hypertension, was published.10 Overall, sibutramine (n = 87) significantly decreased body weight, waist circumference, BMI, and diastolic blood pressure when compared with placebo (n = 84). Looking at the different antihypertensive treatment regimens (felodipine/ramipril vs. trandolapril/verapamil vs. metoprolol/hydrochlorothiazide), the antihypertensive effects were not significantly different, although the greatest decrease was obtained in the metoprolol/hydrochlorothiazide group. Far more important are the metabolic aspects of the different approaches. Treatment with metoprolol/hydrochlorothiazide markedly attenuated the effects of sibutramine on weight loss and waist circumference. Simultaneously, this treatment regimen abrogated the improvement in glucose tolerance, as assessed by an oral glucose tolerance test. One can question the validity of an oral glucose tolerance test (which is a crude measure and cannot detect subtle changes) for the assessment of insulin sensitivity, but it seems that metoprolol/hydrochlorothiazide treatment was associated with worsening of several constituents of the metabolic syndrome.

Additionally, β-blockers are traditionally associated with weight gain, which seems to be mostly due to an increase in body fat.11 Therefore, caution might be warranted regarding the concomitant use of sibutramine and β-blockers in patients with the metabolic syndrome, cardiovascular diseases, and, specifically, coronary artery disease.

So, is the SCOUT trial an important STORM in the prognostic weather charts of cardiovascular disease? The work by Torp-Pedersen et al. is a significant contribution to our knowledge of the safety of sibutramine in patients with cardiovascular diseases. A number of questions remain to be addressed. Whether there is a prognostic benefit of a combined treatment with sibutramine and a β-blocker is yet to be resolved. It is still too early to recommend the use of sibutramine, but the drug appears to be helpful in patients suffering from the metabolic syndrome and/or in patients who do not have an indication for a β-blocker. The final results of the SCOUT trial would add important information and are awaited with great expectations.

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References