The SCOUT study: risk-benefit profile of sibutramine in overweight high-risk cardiovascular patients

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KEYWORDS
Cardiovascular risk; Obesity; Randomized trial; SCOUT

Moderate weight loss improves metabolic and cardiovascular risk factors and prevents the progression to Type 2 diabetes. Furthermore, a healthy lifestyle is associated with lower cardiovascular mortality, whereas sustained weight loss and increased fitness are both associated with reduced cardiovascular mortality. Currently available anti-obesity drugs have been shown to deliver moderate weight loss in more patients and for longer than diet and exercise alone. In addition, these anti-obesity agents impact positively on multiple cardiovascular risk factors. The question of whether the use of weight loss agents can prevent cardiovascular morbidity and mortality has not been studied so far. The Sibutramine Cardiovascular Outcome Trial (SCOUT) has been designed to determine whether weight management in cardiovascular high-risk overweight and obese patients can impact upon cardiovascular endpoints. Patient enrolment for the SCOUT trial began in December 2002 with the first patient randomized in February 2003. The study will involve ~9000 patients in 16 countries. They will be treated with a novel lifestyle intervention programme and randomized in a double-blind fashion to receive either sibutramine or placebo.

The previous articles have highlighted the importance of cardiovascular disease as the biggest killer in the world and also demonstrated that the new epidemic of obesity is having a whole array of effects on the risk factors for cardiovascular disease. The link between obesity with its associated inappropriate diet and physical inactivity and premature cardiovascular disease and death is clear in patients <75 years of age. Furthermore, weight loss limits or corrects high total and LDL cholesterol, triglycerides, low HDL cholesterol, and hyperglycaemia and also reduces waist circumferences, with the result that fewer patients are classified as having the metabolic syndrome.

Modest, sustained weight loss also provides significant health benefits. In the Chinese, Finnish, and US Diabetes Prevention Program trials, overall weight loss of up to 5% reduced the progression to diabetes in those with glucose intolerance. A recent Cochrane analysis of five epidemiological studies also suggests that intentional, but not unintentional, weight loss in women with pre-existing associated disease reduces total cancer and cardiovascular mortality by 30%, whereas among men and women with diabetes, mortality fell by 42%. Although weight loss in obese men did not reduce cardiovascular mortality, this was suggested as being a consequence of men avoiding medical care.5

Weight loss of >15% following bariatric surgery in patients with a body mass index (BMI) exceeding 40 kg/m2 reduces Type 2 diabetes, even though at present, there are no long-term data to show a reduction in hypertension rates or mortality.6

However, the case for weight loss is undermined by observational studies that appear to suggest that weight loss over a prolonged period enhances mortality in subjects with pre-existing heart failure. Such studies may be criticized for not differentiating between intentional and unintentional weight loss. Nevertheless, there are also confusing data on the effect of obesity on the outcome of different cardiac interventions: although traditionally considered a risk factor for coronary revascularization, recent data from clinical trials and...
registry studies have shown a possible protective effect of obesity on the outcomes after percutaneous coronary intervention.8–10 This uncertainty is compounded by the fact that no formal trials documenting the impact of weight loss on cardiovascular events and mortality have yet been published.

Given the clear benefits in terms of cardiovascular risk factors but confusion relating to cardiovascular outcomes, the challenge is to assess the value of modest but sustained weight loss rather than extreme weight changes in the millions of middle aged and elderly who have obesity-related diabetes and cardiovascular disease. The validity of using pharmacotherapy to aid this approach to weight management also needs to be tested.

**Sibutramine and weight loss**

Sibutramine was first marketed in the USA in 1997. It is now registered in over 80 countries and has been prescribed to over 16 million people.

A number of randomized placebo-controlled studies have shown that sibutramine given in conjunction with lifestyle and dietary advice can induce dose-dependent weight loss of 5–10% in most patients.11–15 including those with Type 2 diabetes.16,17 Overall, sibutramine increases by three to four times the proportion of patients sustaining ≥5% weight loss.18

The Summary of Product Characteristics for sibutramine notes that a mean increase in resting systolic and diastolic blood pressures of 2–3 mmHg and a mean increase in heart rate of 3–7 b.p.m. have been observed.19 These effects have been noted in the combined analysis of dose-finding studies conducted in normotensive subjects with doses of up to 30 mg. As noted by the previous presentation,20 the effect is considerably less marked in the licensed dosages of 10 and 15 mg. Furthermore, sibutramine is not contraindicated in patients with well-controlled hypertension, and several studies have shown that treatment for periods of up to 12 months is safe and effective in these patients.21–25

However, there is a widespread belief that sibutramine should not be used in patients who have hypertension. In March 2002, the Italian regulatory authorities temporarily suspended market authorization of sibutramine following reported adverse reactions, which included two cardiovascular deaths purportedly linked to sibutramine. A subsequent independent review by the European Committee for Proprietary Medicinal Products concluded that the risk-benefit profile of the drug remained positive and that clinicians could continue using it in clinical practice. Significantly, extensive post-marketing data, collected over the last 7 years, have revealed no significant problems.26

In fact, there is reason to suggest that patients who lose weight with sibutramine may derive additional benefit in terms of cardiovascular protection. Studies suggest that the drug increases serum concentrations of HDL cholesterol independently of weight loss,13 and there is also evidence that sibutramine-induced weight loss causes regression of left ventricular mass independent of blood pressure.27 In obese hypertensive subjects, sibutramine appears to block the enhanced central adrenergic drive of the sympathetic nervous system (SNS) while stimulating the peripheral SNS.28

It is increasingly clear that patients with cardiovascular disease benefit from weight management,29 and yet losing weight is a challenge to most individuals.30 Although the possible additional effects of sibutramine suggest a wider role for the drug, doctors have an overwhelming responsibility to 'first do no harm'. Therefore, the Sibutramine Cardiovascular Outcomes Trial (SCOUT) has been designed to determine the impact of weight loss with sibutramine on cardiovascular endpoints in a large group of overweight and obese subjects at high risk for cardiovascular disease.

**The SCOUT trial**

The SCOUT trial is a multi-centre, double-blind, placebo-controlled trial designed to evaluate the potential benefits of weight management on cardiovascular outcomes in overweight and obese patients at high risk for cardiovascular events. Weight management in SCOUT includes weight loss and weight maintenance induced by a novel lifestyle intervention programme. In addition, the 9000 patients will be randomized in a double-blind fashion to receive either sibutramine (10–15 mg daily) or matching placebo.

Unlike most obesity trials, which include patients aged 18–65, SCOUT is designed to assess higher risk patients and, therefore, includes patients aged 55 years and older. The trial uses standard WHO BMI criteria for overweight and obese.31 Patients, both men and women, are eligible for inclusion in SCOUT if they have a BMI of ≥27 and ≤45 kg/m² or ≥25 and ≤27 kg/m² with a waist circumference of ≥102 cm (men) or ≥88 cm (women). In addition, patients must also have experienced a cardiovascular event or have diagnosed Type 2 diabetes and another cardiovascular risk factor.

Patients with a history of coronary artery disease, peripheral arterial occlusive disease, cerebrovascular disease (stroke or transient ischaemic attack), controlled hypertension, or New York Heart Association classes I and II heart failure are eligible for inclusion in SCOUT. The primary endpoint of the trial will include a composite of myocardial infarction, stroke, resuscitated cardiac arrest, and cardiovascular death.

SCOUT is an event-driven trial and estimated event rates have been modelled on the basis of those reported in trials recruiting subjects at similar levels of risk.32–35

**Study design**

Patients recruited to SCOUT will first undergo a 2-week screening phase before entering a 6-week single-blind lead-in period, during which all patients will receive sibutramine 10 mg daily in addition to the study’s unique diet and lifestyle programme (Figure 1).
The lead-in phase is designed to ensure the safety of study patients: it allows evaluation of study patients for safety and tolerability including blood pressure and heart rate changes. It also serves to familiarize patients with the diet and exercise programme prior to randomization and permits an assessment of compliance; patients who take <85% of study drug during this phase are not eligible for further inclusion in the trial.

It is estimated that the study will continue for 3 years after the last patient is recruited. Treatment will be continued throughout this period, and all patients will be monitored at regular intervals (trimonthly and annual visits are scheduled), together with a final analysis of every patient, including those who discontinue study drug.

The SCOUT study design.

Figure 2. The multi-national SCOUT will be the first study to report the potential benefits of weight management on cardiovascular outcomes in overweight and obese patients at high risk for cardiovascular events.

Conduct of the trial

The SCOUT trial is being conducted in over 300 centres in 16 countries. It is predominantly a European trial, with centres in Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Poland, Portugal, Romania, Slovakia, Spain, and the UK. However, the trial also includes centres in Mexico, Brazil, and Australia (Figure 2). The study does not include Asia where different criteria apply for overweight and obesity.
An Executive Steering Committee is leading SCOUT, while an independent Data Safety Monitoring Board is monitoring all data collected, and potential outcome events are adjudicated by an independent Event Adjudication Committee. Both the Executive Steering Committee and the Data Safety Monitoring Board are providing regular and detailed updates on the progress of the study to the European regulatory agencies.

Patient enrollment for SCOUT began in late December 2002 with the first patient randomized in February 2003; it is expected that randomization will be complete in mid-2005. All patients will be followed for 3 years, thus the trial will continue till 2008. The Executive Steering Committee is confident that SCOUT will then be able to provide the evidence needed to transform the clinical management of overweight and obesity in high-risk cardiovascular patients.

**Key points**

- Cardiovascular disease is the leading cause of death worldwide; obesity is associated with a number of risk factors for cardiovascular disease.
- Modest, sustained weight loss has a beneficial impact on a range of cardiovascular risk factors; in contrast, extreme weight change appears to have a detrimental impact.
- No formal clinical trials documenting the impact of modest weight loss on cardiovascular events and mortality have yet been published.
- The ongoing SCOUT trial has been designed to determine the impact of weight loss with sibutramine on cardiovascular endpoints in a large group of overweight and obese subjects at high risk for cardiovascular disease.

**Conflict of interest:** The author has consulted for Abbott and lectured at Abbott-sponsored symposia. He chairs the Executive Steering Committee of the Abbott-sponsored SCOUT trial.

**References**