European Society of Hypertension Working Group on Obesity: obesity drugs and cardiovascular outcomes

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Obesity is a common comorbidity in patients with arterial hypertension. Indeed, approximately 75% of the hypertensive patients seen by general practitioners or internists are overweight or obese [1]. Even though obese hypertensive patients are often prescribed more antihypertensive medications, their blood pressure tends to be less well controlled. Given the worldwide epidemic increase in obesity, the number of obese hypertensive patients is likely to increase further. Given that obesity also increases the risk for type 2 diabetes mellitus, dyslipidemia, and other metabolic and cardiovascular ailments, obese hypertensive patients require comprehensive interdisciplinary care. Lifestyle interventions are indispensable and provide the first line of treatment. Indeed, moderate weight loss through caloric restriction and physical exercise induces a massive and sustained reduction in type 2 diabetes mellitus incidence [2,3]. Unfortunately, many patients do not respond sufficiently to lifestyle interventions or relapse after temporary improvements. Pharmacological or surgical treatments could improve weight loss in these patients. However, until recently, studies testing influences on weight loss achieved through medications or bariatric surgery on hard endpoints were scarce. The nonrandomized Swedish Obese Subjects (SOS) study compared individuals undergoing bariatric surgery to a well matched conventionally treated control group. After almost 11 years of follow-up, patients in the bariatric surgery group showed sustained reductions in body weight ranging between 14 and 25% depending on the operative procedure [4]. In the surgery group, the hazard ratio for overall mortality was 0.76 without and 0.71 with adjustment for sex, age, and risk factors. The most common causes of death were myocardial infarction and cancer. Remarkably, bariatric surgery dramatically reduced the risk for type 2 diabetes mellitus, whereas arterial hypertension risk was unaffected [5]. A retrospective cohort study showed similar reductions in cardiovascular and cancer mortalities with bariatric surgery in severely obese patients [6]. These findings created hope that weight loss through medications could have a similar positive influence on cardiovascular morbidity and mortality, particularly in high-risk populations. The recently published results from the Sibutramine Cardiovascular Outcomes (SCOUT) trial and Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) do not support this idea. We will briefly review the background, findings, and implications of these important outcome trials. Furthermore, we will discuss whether drug treatment of obesity is, indeed, a dead end in terms of cardiovascular risk reduction.

Weight-reducing effects of agents acting as laxatives and diuretics, of thyroxin, and of chemicals such as dinitrophenol have long been employed by obese individuals, often without medical advice. In the 1950s, monoamine-releasing agents, such as dexamphetamine, were developed and marketed as appetite suppressants. Due to their high abuse potential, these were replaced by phentermine and fenfluramine among others [7]. In response to the increased risk of valvulopathies and pulmonal hypertension observed by fenfluramine/dexfenfluramine treatment, all monoamine-releasing agents were officially withdrawn from the market in Europe in the early 2000s as a result of several benefit-risk assessments by the European Medicines Agency (EMA). In the United States, however, several of these older drugs, including phendimetrazine, phentermine, and diethylpropion are still available. Moreover, a large internet-based gray market has developed over the years allowing obese patients worldwide to order useless and in many cases potentially hazardous 'medications'.

Sibutramine is a serotonin and norepinephrine uptake inhibitor. Unlike earlier weight loss drugs, such as fenfluramine and dexfenfluramine, sibutramine does not induce serotonin release [8]. The pharmacological profile likely explains why cardiovascular complications typical for serotonin-releasing drugs, such as pulmonary

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hypertension and cardiac valve disease, have not been observed with sibutramine [9]. Sibutramine reduces caloric intake by increasing satiety presumably through serotoninergic and adrenergic actions in the brain [10]. Some but not all studies suggest that sibutramine may also attenuate reductions in metabolic rate that normally occur during weight loss [11,12]. Both mechanisms contribute to weight loss. In a meta-analysis, sibutramine was shown to induce approximately 4.2 kg additional weight loss compared with placebo [13]. However, combination of sibutramine with an intense lifestyle intervention over 1 year decreased body weight by 12 kg [14]. In the same study, body weight decreased by 6.7 kg with the intense lifestyle intervention alone, 7.5 kg with sibutramine combined with a less intense lifestyle intervention, and 5 kg with sibutramine alone. Sibutramine-induced weight loss is associated with improvements in high-density cholesterol, triglycerides, glucose metabolism, and various other cardiovascular and metabolic risk markers [15,16]. The main side effects of sibutramine are related to inhibition of norepinephrine uptake in peripheral tissues. Sibutramine increases heart rate, particularly in the upright position [17,18]. In some but not all patients, sibutramine increases blood pressure [19,20]. The variable response may be explained by the combination of peripheral norepinephrine uptake inhibition, which tends to raise blood pressure and heart rate, and norepinephrine uptake inhibition in the brain, which reduces centrally generated sympathetic activity through a 'clonidine-like' mechanism [21,22]. Sibutramine was approved for the treatment of obesity in patients without a history of cardiovascular disease in conjunction with lifestyle interventions for up to 2 years.

The SCOUT trial evaluated long-term effects of sibutramine on hard cardiovascular endpoints in patients with high cardiovascular risk in a randomized, double-blind, and placebo-controlled fashion [23]. Women and men aged at least 55 years with a BMI at least 27 kg/m^2 and of 45 kg/m^2 or less were eligible. Patients with a BMI between 25 and 27 kg/m^2 and a waist circumference of at least 88 cm in women and at least 102 cm in men were also eligible. Patients had to have a history of cardiovascular disease and/or type 2 diabetes mellitus with at least one additional cardiovascular risk factor. Exclusion criteria were blood pressure above 160/100 mmHg and a pulse rate more than 100 bpm among others.

All patients included in the SCOUT trial were submitted to a 6-week lead-in-period [23]. Data from the lead-in-phase have been previously published [18,24]. During this period, patients were treated with 10 mg sibutramine per day. Patients showing excessive increases in heart rate or blood pressure or not tolerating sibutramine for other reasons were excluded during this period. Then, patients were randomized in a 1 : 1 fashion to treatment with sibutramine or placebo. Sibutramine treatment was begun with a dose of 10 mg/day and increased to 15 mg/day if needed. The primary endpoint was occurrence of nonfatal myocardial infarction, nonfatal stroke, resuscitation after cardiac arrest, or cardiac death. The observed event rate was much lower than expected. Therefore, after 15 months, recruitment was restricted to patients with cardiovascular disease and diabetes mellitus. Furthermore, follow-up was extended from the initially planned 5–6 years.

Of 10 744 patients included in SCOUT, 8.7% dropped out during the lead-in-phase. Of the remaining patients, 4902 were randomized to sibutramine and 4898 were randomized to placebo. A large proportion of patients received antihypertensive agents, platelet inhibitors, and lipid-lowering drugs. After mean follow-up of 3.4 years, more than 40% of the patients in each group had dropped out of the double-blind treatment. The relative risk to experience the primary outcome was significantly increased by 16% in the sibutramine group. The absolute risk increased 1.4%. Accordingly, the number needed to harm was 71. Sibutramine treatment increased the number of nonfatal strokes and myocardial infarctions. The investigators conducted a subgroup analysis. None of the subgroups showed a beneficial response to sibutramine in terms of cardiovascular endpoints. Cardiovascular death and death from any cause did not differ between groups. Patients in the sibutramine group showed a moderate 2.4 kg body weight decrease compared with placebo-treated patients. Sibutramine increased pulse rate approximately 4 bpm. With nonpharmacological weight loss, blood pressure tends to decrease [25,26]. In contrast, sibutramine-induced weight loss was associated with an approximately 1–2 mmHg increase in mean systolic and mean diastolic blood pressure. The increase in heart rate and blood pressure may have contributed to the adverse outcome. The manufacturer has voluntarily withdrawn sibutramine in the United States, Australia, and Canada in line with an earlier cessation in Europe (www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm228830.htm).

The endocannabinoid system consists of endogenous arachidonic acid derivates activating cannabinoid receptors 1 (CB1) and 2 (CB2). The CB1 receptor is the most abundant G-protein-coupled receptor in the brain [27]. In addition, CB1 is expressed in various human peripheral tissues involved in the pathogenesis of obesity-associated metabolic disease [28]. In animals, genetic deletion or pharmacological inhibition of the CB1 receptor is associated with weight loss. Rimonabant, the first clinically utilized CB1 receptor antagonist, was tested in a large phase III program in different patient populations (RIO – Rimonabant in Obesity) [29–32]. Nondiabetic patients treated with rimonabant 20 mg/day lost additional 5 kg of body weight and 4 cm waist circumference compared with placebo. The response was slightly attenuated in diabetic patients. Weight loss was accompanied by favorable changes in triglycerides, high-density lipoprotein,

and fasting insulin among others. In patients with type 2 diabetes, hemoglobin A1c decreased 0.7% with rimonabant treatment. Based on statistical analysis, approximately 50% of the improvement in lipid measurements and glucose metabolism could be attributed to weight loss, thereby suggesting that rimonabant might have weight-independent influences on metabolism through ill-defined actions in peripheral tissues [33]. Rimonabant did not interfere with weight loss-induced changes in blood pressure [34]. These observations created much hope in the obesity community. Yet, in a placebo-controlled trial, rimonabant did not affect coronary atheroma volume assessed by intravascular ultrasound in patients with established coronary artery disease [35].

CRESCENDO was a randomized, double-blind, and placebo-controlled outcomes trial [36]. Patients aged at least 55 years with abdominal obesity defined as waist circumference of at least 88 cm in women and at least 102 cm in men were eligible. Patients had to have a history of cardiovascular disease in the 3 years before inclusion, or at least two major cardiovascular risk factors. Initially, type 2 diabetes mellitus was regarded as equivalent to existing cardiovascular disease. Due to the low event rate in this group, type 2 diabetes mellitus was reclassified as cardiovascular risk factor during the trial. Unlike the SCOUT trial, CRESCENDO did not have a lead-in-phase. Patients were randomized in a 1 : 1 fashion to treatment with 20 mg rimonabant or placebo. The primary endpoint was occurrence of myocardial infarction, stroke, or cardiac death. The study was event driven with an estimated minimum follow-up of 33 and maximum of 50 months.

CRESCENDO enrolled 18 695 patients, 9381 in the rimonabant and 9314 in the placebo group. Compared with SCOUT, an even larger proportion of patients received antihypertensives, platelet inhibitors, and lipid-lowering drugs. After mean follow-up of 13.8 months, regulatory agencies in several European countries requested premature discontinuation of the study due to the EMA decision to suspend marketing authorization. At this point, roughly half of the events that were required to attain sufficient statistical power had occurred. Overall, rimonabant did not reduce occurrence of the primary endpoint (hazard ratio 0.97, 95% confidence interval 0.84–1.12 compared with placebo). In patients with overt cardiovascular disease, cardiovascular event rate in the first year was virtually identical in rimonabant-treated and in placebo-treated patients. Afterward, the event rate appeared to diverge. However, the number of patients was not sufficient to assess potential beneficial actions of rimonabant later on. In patients at cardiovascular risk without overt cardiovascular disease, the event rate was identical in both treatment groups throughout the trial. All-cause mortality was not significantly different between groups. Gastrointestinal and neuropsychiatric side effects, which were particularly carefully sought for, were more common with rimonabant treatment. Of note, four completed suicides occurred in the rimonabant and one in the placebo group. Remarkably, the authors did not provide a comprehensive analysis of data. Indeed, changes in body weight, waist circumference, blood pressure, glucose metabolism, or any other cardiovascular risk factor were not reported.

The many obstacles, both in terms of benefit and efficacy of weight loss medications, resulted in a rather strong position of regulatory agencies regarding approval of new drugs. For example, the selective serotonin 5-HT2c agonist lorcaserin showed efficacy comparable with sibutramine and rimonabant in terms of achieved weight loss, and adverse reactions were relatively mild in a recent phase III trial [37]. Yet, residual concerns about valvulopathy and specific concerns about breast tumors in preclinical studies swayed the risk to benefit balance for many Food and Drug Administration (FDA) panel members. [http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM225631.pdf]. Similarly, an FDA panel recently voted against approval of a phentermine/topiramate combination [http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM224180.pdf].

Both SCOUT and CRESCENDO suggest that in obese patients at high cardiovascular risk, drug treatment of obesity is of no significant benefit. One possible conclusion is that drug treatment of obesity is a hopeless task and that further research in this area is prone to failure. Indeed, large pharmaceutical companies nowadays are much less inclined to getting involved in the 'dirty' obesity business than a few years ago. After SCOUT and CRESCENDO, our enthusiasm for weight loss medications is substantially reduced. Yet, the large number of obese patients with and without hypertension will not simply go away. Therefore, we suggest that reasons for the negative results of SCOUT and CRESCENDO should be investigated thoroughly before the concept of drug-induced weight loss is completely put to rest. Both studies employed a somewhat half-hearted lifestyle intervention as evidenced by a rather limited weight loss in the control group. Furthermore, CRESCENDO and SCOUT included patients at a particularly high cardiovascular risk. Most patients received medications known to improve cardiovascular risk, including antiplatelet and lipid-lowering drugs. Perhaps, weight loss cannot add much further improvement in this setting. It is also possible that weight loss is less beneficial or even harmful in late stage obesity. Indeed, several studies suggest that in heart failure, cancer, and severe renal failure, increased adiposity may be protective [38]. The phenomenon is commonly referred to as 'reverse epidemiology'. Possibly, weight loss medications could be considered in earlier stages of the disease [39]. For example, the

lipase inhibitor orlistat, which reduced fat uptake from the gut, decreased the incidence of type 2 diabetes mellitus, though to a lesser degree than intense lifestyle interventions [40]. Finally, drug-specific untoward effects ought to be considered. The slight increase in blood pressure with sibutramine may have been sufficient to drive an increase in cardiovascular events. Remarkably, medications that are commonly used for the treatment of depression or neuropathic pain share the same pharmacological target. Indeed, depressive patients treated with medications active at the norepinephrine transporter have an increased risk for arterial hypertension [41]. Perhaps, prescription of these medications should be scrutinized in patients at high cardiovascular risk. Similarly, one of the main reasons leading to rimonabant's withdrawal off the market was drug or mechanism of action-specific, namely, psychiatric side effects. On the other hand, recent insights into neuroendocrine mechanisms regulating body weight as well as identification of genes controlling satiety and energy expenditure provide an expanding list of potential molecular targets for novel antiobesity drugs. Possibly, combination therapy may be required as it is in other cardiovascular and metabolic disorders.

The potency, durability, and health outcomes of bariatric surgery are impressive, and concerns regarding the efficacy and safety of weight loss drugs provide us with a clinical dilemma when dealing with obese patients who have failed lifestyle measures. Recently, the safety of bariatric surgery has been highlighted with 30-day mortalities of 0.09 and 0.3%, respectively in two large US series [42,43]. There is also accumulating evidence that surgery is cost-effective and may be dominant, that is, it reduces healthcare costs [44,45]. Uptake of bariatric surgery is very low, at best serving less than 2% of those eligible and in most countries less than 1%. There are concerns about equity of access and the provision of a long-term chronic disease management aftercare.

While surgery needs to be more broadly available, and clinical pathways established, a more flexible approach to bariatric care is needed. We need to develop the multidisciplinary evaluation and management programs for those with refractory obesity and its related diseases. Such programs work well for heart disease, cancer, and diabetes, and have flexibility to adapt to new evidence and emerging therapies. A staged comprehensive bariatric care model would incorporate the ability to combine lifestyle, nutrition, drugs, surgery, devices, and emerging therapies to adequately manage this serious chronic relapsing condition. The management of hypertension provides an example of such staging. Such 'obesity' programs will need to be implemented within communities and involve primary, secondary, and tertiary levels of care. We need to be prepared for the challenges and opportunities ahead.

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