# Weight-reducing drug therapy and hypertension

The obesity epidemic is closely associated with a prominent rise in the incidence of hypertension, and both obesity and hypertension independently cause a major increase in cardiovascular risk. To reduce body weight, nonpharmacological approaches have limited success, and adjuvant pharmacotherapy is often required for effective weight reduction and maintenance of reduced body weight. In this literature review, we examined the clinical effect of the anti-obesity drugs orlistat, rimonabant and sibutramine on blood pressure, and if this effect was attributed to a change in body weight. We found a blood pressure decrease under treatment with orlistat and rimonabant, which was more pronounced in subjects with pre-existing hypertension. The decrease in blood pressure corresponded to the loss of body weight and waist circumference, with no evidence of a substance-specific effect beyond that. Findings for sibutramine were more complex. Sibutramine has central sympatholytic and peripheral sympathomimetic effects. The peripheral sympathomimetic effects, via norepinephrine reuptake inhibition, may slightly increase the blood pressure in normotensive subjects with a relatively low central sympathetic drive. By contrast, the central sympatholytic effects of sibutramine may predominate in hypertensive patients with a high sympathetic tone, leading to sustained reductions in blood pressure.

**KEYWORDS: hypertension treatment, obesity, orlistat, pharmacological, rimonabant, sibutramine**

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Obesity has reached epidemic proportions throughout the industrialized world, particularly in the USA where 66% of adults are currently categorized as overweight patients, and 34% are obese (defined as having a body mass index [BMI] greater than 30 g/m$^2$) [1,101]. Obesity and several of its comorbidities, such as Type 2 diabetes, hypertension and premature atherosclerosis, belong to a set of cardiovascular risk factors known as the metabolic syndrome [2,3].Of those, hypertension and obesity are also independently associated with increased cardiovascular risk and premature mortality [4–7].

Many epidemiological studies have demonstrated associations between BMI and blood pressure, and there is good evidence to suggest that obesity is a causal factor in the development of hypertension in obese subjects [8,9]. For example, findings from the Third National Health and Nutrition Examination Survey (NHANES III) show that the risk of hypertension increases with increasing weight in both men and women [10]. Abdominal obesity, in particular, is associated with a higher prevalence of hypertension and cardiovascular disease [11,12].

Therefore, treatment of the metabolic syndrome concentrates primarily on increased physical activity and generalized weight loss. A meta-analysis of randomized, controlled trials showed weight loss to be important for preventing and treating hypertension, reflected in blood pressure reductions that were -1.05 mmHg for systolic blood pressure and -0.92 mmHg for diastolic blood pressure when expressed per kilogram of weight loss [13]. However, weight loss interventions utilizing a reduced-energy diet and exercise are only associated with moderate weight loss over a period of 6 months [14], and treatment success, defined as clinically meaningful weight loss that can be maintained for longer periods, is limited [15,16].

To further investigate whether nonpharmacologic interventions can prevent hypertension in the long term, the TOHP II trial was initiated. In this study, a weight reduction of 4.5 kg over 30 months led to a reduction of the hypertension incidence by 65%, but only 13% of the patients accomplished the weight goal [17].

Since most patients do not achieve and maintain sufficient weight loss with dietary changes and exercise alone, a combination of diet and exercise with anti-obesity drugs may be useful [18]. Anti-obesity agents produce a moderate weight loss for longer periods than diet and exercise alone [14].

This article summarizes the effect of the three anti-obesity substances, orlistat, rimonabant and sibutramine, on blood pressure, and whether this

part of future medicine fsg

effect was caused only by changes in body weight, by the pharmacological properties of the individual compound, or by both. For all three agents, appropriate study results could be identified with a treatment period of up to 4 years.

## Orlistat

Orlistat is a potent and selective inhibitor of pancreatic lipase that reduces the intestinal digestion of fat. In a number of long-term clinical trials, in conjunction with lifestyle modifications, orlistat has been shown to promote weight loss [19,20].

After 4 years of double-blind treatment, the XENical® in the Prevention of Diabetes in Obese Subjects (XENDOS) study showed a weight difference of 2.8 kg in the orlistat group compared with lifestyle modification plus placebo. The authors also reported a decrease in blood pressure for the treatment group whose systolic and diastolic values were 1.5 and 0.7 mmHg lower, respectively. Accordingly, the additional blood pressure decrease produced by orlistat was 0.54 mmHg/kg of weight loss [21].

In a meta-analysis by Sharma and Golay on hypertensive patients with a BMI between 28 and 43 kg/m$^2$, the mean weight loss was 8% with orlistat and 4% in the placebo group. There was no significant difference in blood pressure between the placebo and orlistat group overall, but in patients with a weight loss of more than 10%, the decrease of mean systolic pressure was doubled compared with patients with a weight reduction below 10% [22].

Sjöström, Rössner, Davidson and Hauptmann found, in four controlled studies in predominantly normotensive patients, an average weight reduction between 1 and 8% of body weight for the orlistat treatment groups, with a mean diastolic blood pressure decrease of only 1–2 mmHg as a result of orlistat treatment [23].

Richelsen investigated the effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet (VLED). After 8 weeks of VLED treatment, a reduction in blood pressure was observed, with a reduction of 12.5 mmHg in systolic blood pressure and 7.4 mmHg in diastolic blood pressure. However, after 3 years there was no significant difference in the two study groups regarding blood pressure, while there was a better weight loss maintenance in the orlistat group [24].

In summary, as was to be expected given the local effectiveness of orlistat, the blood pressure reduction seen for orlistat treatment can be attributed to the achieved weight loss with no further drug-specific effect.

## Rimonabant

The endocannabinoid system, consisting of the cannabinoid type 1 receptor ($CB_1$) and endogenous lipid-derived ligands, seems to modulate energy homeostasis as well as glucose and lipid metabolism, both through central orexigenic and peripheral metabolic effects in adipose tissue, liver and skeletal muscle [25,26]. In addition to weight, metabolic processes of the carbohydrates and lipid metabolism are the primary systems influenced [27]. In animal data, cannabinoids decrease blood pressure in hypertensive rodents primarily owing to decreased cardiac contractility. Rimonabant, as a specific antagonist on the $CB_1$, induced in hypertensive rats a marked and sustained increase in cardiac contractility and blood pressure [28].

Rimonabant is approved in Europe, but not yet in the USA, owing to an increased risk of neurological and psychiatric side effects (please see Authors' note at the end of the article). In clinical data, rimonabant has been shown to produce substantial general weight loss, related waist circumference reduction and improvements in multiple cardiovascular and metabolic risk factors such as insulin resistance, glucose tolerance and dyslipidemia [27,29–30], all of which are linked to fat mass.

The Rimonabant in Obesity (RIO)-North America Trial, a Phase III, multicenter, randomized, double-blind, placebo-controlled trial of 3045 overweight and obese patients, showed that systolic and diastolic blood pressures tended to decrease slightly but not significantly in patients receiving either 5 or 20 mg of rimonabant [30].

In a meta-analysis of pooled RIO study results, Ruilope *et al.* further investigated the effect of rimonabant on blood pressure [31]. In Phase III, the RIO-Trial-Programme featured multinational, randomized, double-blind, placebo-controlled studies with 6620 overweight or obese patients. At study entry, 37% of patients had hypertension, 71% of whom were receiving antihypertensive treatment. After 1 year of treatment, average systolic blood pressure decreased by 0.8 mmHg for rimonabant 20 mg/day, compared with a small increase of 0.3 mmHg for placebo; diastolic blood pressure decreased by 0.8 mmHg versus a 0.3 mmHg reduction for placebo. In a subgroup of hypertensive patients, the systolic blood pressure change was significant, with a 7.5 mmHg reduction with rimonabant versus only 4.7 mmHg for placebo. However, there was no effect of rimonabant on blood pressure beyond that expected from weight loss alone. Reductions were more pronounced in

patients with dyslipidemia and Type 2 diabetes. There were no blood pressure-related adverse incidents in the rimonabant patients [31].

The Strategy To Reduce Atherosclerosis Development InVolving Administration of Rimonabant – the Intravascular Ultrasound Study (STRADIVARIUS) trial investigated whether rimonabant reduced the progression of coronary disease in patients with abdominal obesity and metabolic syndrome. Atheroma volumes were measured in 839 patients by coronary intravascular ultrasonography, and after 18 months of treatment, the study failed to show a significant effect for rimonabant on disease progression compared with placebo. In this study, mean systolic blood pressure was slightly increased both in the rimonabant and the placebo groups [32].

The increased systolic blood pressure could have been one of the causes behind the negative result of STRADIVARIUS, and a long-term cardiovascular outcome trial in 17,000 patients with a high risk of cardiovascular events is currently underway to further define the role of rimonabant in the treatment of metabolic risk factors (Clinicaltrials.gov identifier: NCT00263042 [102]).

In conclusion, in clinical data the antihypertensive effect of rimonabant seems to be mediated via weight reduction with no additional specific drug effects.

## Sibutramine

Sibutramine, a serotonin and norepinephrine reuptake inhibitor, has been approved for long-term management of obesity [33].

Its main effect is reducing intake by promoting early satiety after eating and limiting the fall in energy expenditure during weight loss. In the randomized, placebo-controlled, Sibutramine Trial on Obesity Reduction and Maintenance (STORM) trial with 605 obese patients, James *et al.* demonstrated that adding sibutramine to diet and lifestyle counseling led to doubled weight loss. There was a three- to four-fold increase in the number of patients who achieved 5–10% weight loss in the treatment group compared with placebo.

Furthermore, sibutramine was found to slightly increase heart rate and cause a small rise in blood pressure [33–35].

The effects of sibutramine on weight loss and blood pressure have been evaluated in a meta-analysis of 21 studies by Kim *et al.* Sibutramine produced a significant overall weight loss and a significant increase in both systolic and diastolic blood pressure. A subgroup analysis found the effect on systolic blood pressure to be dose-dependent in subjects weighing greater than 92 kg and in younger individuals. Older individuals with a body weight of more than 92 kg showed a greater rise in diastolic blood pressure [35]. A review by Arterburn *et al.* on 25 trials regarding the effects of sibutramine on blood pressure and heart rate produced a statistically heterogeneous analysis on blood pressure changes. As a consequence, blood pressure results could not be pooled [36].

A 12-week, open-label study in over 6000 obese German subjects found a significantly different effect of sibutramine treatment on blood pressure in normotensive versus hypertensive subjects [37].

While normotensive subjects developed a slight increase in blood pressure, consistent with the findings of the studies mentioned before, hypertensive patients showed a significant decrease in blood pressure. This decrease was more pronounced in individuals with a higher baseline blood pressure, leading to the hypothesis that the effects of sibutramine on blood pressure may depend on baseline blood pressure values, which likely reflect baseline sympathetic tone [37].

Dividing these patients into groups with hypertension from stage 1–3 also showed similar results. Previous obesity studies with sibutramine, such as STORM [33] or Intervall [34], also fit this scheme. While only 25% of normotensive subjects showed a blood pressure decrease, 99% of patients with hypertension stage two showed a substantial blood pressure decrease [37].

Moreover, in an analysis of two German placebo-controlled, long-term studies using sibutramine, the authors reported that while sibutramine significantly reduced weight, it did not change systolic blood pressure [38].

The blood pressure-lowering effects of sibutramine are compatible with an emerging hypotheses regarding the complex and opposing peripheral and central effects of sibutramine on sympathetic activity in normotensive or hypertensive obese subjects. The peripheral sympathomimetic effects of norepinephrine reuptake inhibition may increase blood pressure of normotensive subjects with relatively low central sympathetic drive. However, the central sympatholytic effects of sibutramine may predominate in hypertensive patients with high sympathetic tone, so that sustained reductions in blood pressure may occur. This hypothesis is further supported by direct microneurography analysis in individuals with increased baseline sympathetic activity, showing a blockage of sympathetic activity by sibutramine [39,40].

The Sibutramine Cardiovascular OUTcomes (SCOUT) trial, the first outcome trial with an anti-obesity agent, is a randomized, double-blind

comparison of sibutramine versus placebo in addition to standard care in obese subjects with an increased risk of cardiovascular disease. Most patients had conditions that are explicitly contraindicated under the current label, for example, patients with coronary heart disease or hypertension stage one. Data from the initial single-blind period of SCOUT with sibutramine over a period of 6 weeks indicate a reduction of body weight by 2.2 kg and of waist circumference by 2 cm. Systolic blood pressure fell significantly by 3 mmHg – 1.36 mmHg per 1 kg and the heart rate increased by 1.5 beats/min. Two consecutive increases in blood pressure were observed in only 4.7% of subjects of this high-risk population. For the 10,742 subjects, the median BP changes to baseline was a reduction of 7.5/2.5 mmHg for hypertensive subjects with a weight loss above 5% [41].

While all European and American guidelines recommend a change of lifestyle, and weight reduction in particular, to treat hypertension, none mention specific pharmacological therapies for obesity-related hypertension [42].

A number of smaller studies have demonstrated certain advantages of antihypertensive therapy with angiotensin-converting enzyme (ACE) inhibitors compared with calcium channel blockers. Other studies showed that β-blockers and diuretics achieve a less effective metabolic outcome [43,44].

A recent study on hypertensive, obese patients demonstrated for the first time that a sibutramine-based weight loss therapy in conjunction with β-blockers and diuretics achieves a significantly smaller degree of weight loss as compared with a sibutramine-based therapy in combination with ACE inhibitors and calcium channel blockers. Furthermore, it has been demonstrated that β-blockers, together with diuretics, can neutralize the positive sibutramine-induced effects on the glucose metabolism and, consequently, weight reduction [45].

Therefore, it may be concluded that β-blockers, if administered chronically, may induce weight increase and may also prevent an intended weight loss.

With regard to its effect on blood pressure, sibutramine appears to have a dual effect, increasing the blood pressure in normotensive individuals and decreasing it in hypertensive subjects.

## Conclusion

Summarizing the clinical studies, the blood pressure decrease under treatment with the lipase inhibitor orlistat and the $CB_1$ inhibitor rimonabant corresponds to the loss of body weight and waist circumference. Beyond that, no references to substance-specific blood pressure-lowering effects exist.

The effect of sibutramine is more complex. Central sympatholytic and peripheral sympathomimetic effects can be observed. The peripheral sympathomimetic effects via norepinephrine reuptake inhibition may slightly increase blood pressure of normotensive subjects with a relatively low central sympathetic drive. However, the central sympatholytic effects of sibutramine may predominate in hypertensive patients with a higher sympathetic activity, so that sustained reductions in blood pressure can occur. These data might be construed to challenge the assumption and labeling precaution that sibutramine should be used with particular caution in patients with high blood pressure.

## Future perspective

Research over the past few years has provided an unprecedented expansion of knowledge regarding the molecular mechanism regulating body fat [46].

There are drugs approved for uses other than weight loss (e.g., growth hormones and growth hormone fragments, such as exanitide, pramlintide, atomoxetine and somatostatin), which resulted in weight loss in clinical trials. Their influence on blood pressure remains to be investigated [47].

In addition, there are several new drugs with clinical data or in clinical studies targeting different molecular mechanisms regulating body fat. For example, the neuropeptide-Y receptor antagonists, leptin, serotonin 2C receptor antagonists, PYY 3–36, oxyntomodulin, ghrelin antagonists, melanin-concentrating hormone receptor-1 antagonist and oleoylestrone [48]. However, leptin and drugs that activate the melanocortin system raise blood pressure and heart rate, whereas ghrelin lowers sympathetic nervous system activity, which suggests that a ghrelin antagonist will most likely cause the opposite effect [49,50].

The development of safe and effective pharmacologic strategies for managing obesity and its complications will likely proceed at a more rapid pace in future, as drug development is now more sophisticated than in the past. At the same time, one of the most difficult challenges is to develop a successful drug capable of suppressing appetite and increasing thermogenesis without causing sympathetic nervous system activation and hypertension.

## Executive summary

***Hypertension & obesity***

- Hypertension and obesity are independently associated with increased cardiovascular risk and premature mortality.

***Lifestyle modification***

- Lifestyle modifications are important for preventing and treating hypertension.
- Weight reduction may lower blood pressure. However, long-term success is limited.

***Orlistat***

- Orlistat is a lipase inhibitor.
- It promotes weight loss when used in combination with lifestyle modifications.
- Blood pressure decrease corresponds to weight loss.

***Rimonabant***

- Rimonabant is a cannabinoid type 1 receptor blocker.
- Rimonabant promotes weight loss when used in combination with lifestyle modifications.
- Blood pressure decrease corresponds to weight loss.

***Sibutramine***

- Sibutramine is a serotonin and norepinephrine reuptake inhibitor.
- It promotes weight loss in addition to lifestyle modifications.
- Sibutramine has central sympatholytic and peripheral mimetic effects.
- The peripheral sympathicomimetic effects of norepinephrine uptake may slightly increase blood pressure.
- The central sympatholytic effects may predominate in hypertensive patients with a higher sympathetic nerve activity.
- Reductions in blood pressure may occur.
- β-blockers may induce weight increase and may also prevent an intended weight loss in a sibutramine-based therapy.

It is hoped that by combining various types of medication or by combining medication with other weight-loss strategies, including surgical therapy [51], a higher degree of weight loss will be achieved, as well as reducing cardiovascular disease.

## Authors' note

*Following submission of this article, referring to the recommendations of the European Medicines Agency (EMEA), rimonabant has been, as of October 24th 2008, temporarily withdrawn from sale due to psychiatric side effects.*


## Financial & competing interests disclosure

*Prof. Dr Scholze has been a member of the Advisory Board of Abbott GmbH & Co. KG and received honoraria for lectures on all of the three discussed anti-obesity drugs. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

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