

## ORIGINAL ARTICLE

# Sibutramine is safe and effective for weight loss in obese patients whose hypertension is well controlled with angiotensin-converting enzyme inhibitors

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Sibutramine treatment in obesity results in significantly greater weight reduction compared with placebo, although weight loss with sibutramine may be accompanied by small but statistically significant mean increases in blood pressure (BP). This 52-week, placebo-controlled, double-blind, randomised study investigated the effects of sibutramine 20 mg once daily or placebo on body weight in 220 obese (body mass index (BMI) 27–40 kg/m<sup>2</sup>), hypertensive patients. At randomisation, hypertension was well controlled ( $\leq 95$  mm Hg diastolic blood pressure (DBP)) with an angiotensin-converting enzyme (ACE) inhibitor, with or without concomitant thiazide diuretic therapy. Therapy for hypertension continued for the 52 weeks of the study. Sibutramine 20 mg produced significantly greater weight loss compared with placebo: 4.5 kg with sibutramine compared with 0.4 kg with placebo (last observation carried forward (LOCF);  $P \leq 0.05$ ). A total of 62 patients (42.8%) treated with sibutramine lost  $\geq 5\%$  of their body weight compared with six patients (8.3%) treated with placebo; 19 patients (13.1%) treated with sibutramine lost  $\geq 10\%$  of their body weight compared with two patients (2.8%) treated with placebo (LOCF;  $P \leq 0.05$  for both comparisons). Hypertension remained well controlled for the 52 weeks of the study with both sibutramine and placebo treatment. After 52 weeks, the differences between placebo treatment and sibutramine

treatment for both mean supine systolic blood pressure (SBP) and DBP were approximately 3 mm Hg: mean DBP was 82.8 mm Hg with placebo treatment compared with 85.5 mm Hg with sibutramine treatment (LOCF;  $P = 0.004$ ) and mean SBP was 130.4 mm Hg with placebo compared with 133.1 mm Hg with sibutramine (LOCF;  $P = 0.0497$ ; both comparisons, sibutramine vs placebo). The mean increases in SBP and DBP did not appear to change the overall risk category for coronary heart disease end points. Changes in pulse rate at week 52 were a decrease of 0.3 beats per minute (bpm) for placebo treatment compared with an increase of 5.7 bpm for sibutramine treatment ( $P < 0.001$ ). Mandated withdrawals from the study due to protocol-defined changes in BP were not statistically different between the two treatment groups. Greater favourable changes in lipid profile, serum glucose, and uric acid could be accounted for by greater weight losses occurring in the sibutramine treatment group. Sibutramine was well tolerated. This study indicates that in obese patients whose hypertension is well controlled at the outset with an ACE inhibitor, with or without concomitant thiazide diuretic therapy, sibutramine safely and effectively achieves weight loss without compromising good BP control.

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## Introduction

Obesity is a serious health problem that is additionally associated with a number of co-morbidities, including hypertension, coronary artery disease, and congestive heart failure.<sup>1,2</sup> The relative risks of hypertension, hypercholesterolaemia, and diabetes

are higher in overweight persons than in persons who are not overweight.<sup>3</sup> Higher body weight is also associated with increases in rates of mortality due to all causes,<sup>4</sup> and evidence is accumulating that supports the benefits of weight reduction.<sup>5</sup> Although short-term weight loss in obese patients can be achieved with a diet and exercise programme, patients usually start to regain the weight soon after ending such an intervention.

In selected patients, pharmacotherapy can augment reduced-energy diets, increased physical activity, and behaviour therapy to promote and

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maintain weight loss.<sup>5</sup> Sibutramine hydrochloride is an effective pharmacotherapy for weight loss in obese patients when used as an adjunct to programmes that include a reduced-calorie diet, regular exercise, and behaviour modification.<sup>6,7</sup> Sibutramine induces satiety by inhibiting the reuptake of serotonin and noradrenaline. It also increases thermogenesis and basal energy expenditure.<sup>8</sup> Long-term treatment with sibutramine maintained and improved weight loss for up to 2 years compared with placebo.<sup>7</sup>

It is generally recommended that all patients with hypertension who are above their desirable weight should be prescribed an individualised, monitored weight reduction programme involving caloric restriction and increased physical activity.<sup>9–11</sup> Based on its activity in weight reduction, sibutramine used with a general weight reduction programme should help patients with hypertension to lose weight and maintain the loss over time. However, because of its mechanism as a noradrenaline reuptake inhibitor, sibutramine has the potential to raise blood pressure (BP)<sup>12</sup> and its use in obese patients with hypertension has been questioned, even if hypertension is already well controlled. The primary objective of this study was to investigate the effects of sibutramine 20 mg once daily (higher than the currently approved doses of 10 mg and 15 mg once daily) on weight loss in obese patients whose hypertension was well controlled with an angiotensin-converting enzyme (ACE) inhibitor, with or without concomitant thiazide diuretic therapy. The secondary objectives were to evaluate the effects of sibutramine on BP and pulse rate, as well as plasma lipids, glucose, and uric acid, in these patients.

## Materials and methods

### Study design and patient population

This was a 52-week, multicentre, randomised, double-blind, placebo-controlled, parallel-group comparison of the effects of sibutramine 20 mg with those of placebo on weight loss in obese patients whose hypertension was well controlled with an ACE inhibitor, with or without concomitant thiazide diuretic therapy. Change in ACE inhibitor dose was not specifically disallowed by the protocol; however, the same dose was to be continued for the duration of the study unless a change was in the best interest of the patient. In the sibutramine treatment group, 71/146 (48.7%) patients were on concomitant diuretics and 41/74 (55.4%) were on concomitant diuretic treatment in the placebo group. Male or non-pregnant female patients of any race who were at least 18 years of age, with a body mass index (BMI)  $\geq 27$  kg/m<sup>2</sup> and  $\leq 40$  kg/m<sup>2</sup>, were eligible for inclusion in the study. Patients had to have a history of hypertension that was controlled for  $\geq 60$  days preceding the screening visit with a constant dose of an ACE inhibitor, with or without a thiazide

diuretic. The dose and nature of the medication used to control hypertension had to have been unchanged for  $\geq 60$  days preceding the screening visit.

Patients were considered for randomisation if their hypertension was well controlled at each of three qualifying consecutive run-in visits. Well-controlled hypertension was protocol-defined as a mean supine diastolic BP (DBP)  $\leq 95$  mm Hg at each qualifying visit, with an overall difference of 10 mm Hg or less between visits, without changes to the dose of the ACE inhibitor or thiazide diuretic. In addition, at each of the three qualifying consecutive run-in visits, repeat within-visit differences in individual measurements (three per visit) of supine DBP had to be within 10 mm Hg.

Exclusion criteria included increased BP secondary to a concurrent medical condition or drug therapy, mean supine pulse rate  $>95$  beats per minute (bpm) at baseline, or mean supine DBP  $>95$  mm Hg at any run-in visit. Patients were excluded if they had a clinically significant history of cardiac disease or any clinically significant abnormal cardiac condition other than hypertension, had previously been treated with sibutramine, or had had gastric surgery to reduce obesity.

### Treatment schedule

After initial screening, patients received single-blind placebo study medication during the 2- to 10-week run-in period. At the baseline visit following the run-in period, patients meeting the entry criteria were randomised in a 2:1 ratio to either sibutramine or placebo treatment taken once daily in the morning with 4 ounces of water. In addition, patients were given general dietary advice regarding weight reduction. During the initial 8-week period, patients randomised to sibutramine had their doses titrated from 5 mg to 20 mg per day in 5-mg increments every 2 weeks. Treatment of hypertension continued for the 52 weeks of the study.

After week 52, patients attended a follow-up visit within 10–14 days; those who were withdrawn early attended a follow-up visit within 10–14 days after their last study visit. A 52-week treatment period was chosen because the results of prior studies show that patients treated with sibutramine achieve maximal weight loss by about 24 weeks and maintain it while they continue treatment.<sup>6,7,13</sup>

### Safety analysis

Safety evaluation included physical examination with determination of the adverse event profile according to COSTART definitions and reasons for withdrawal from the study. Vital signs included measurement of supine pulse rate, supine systolic BP (SBP) and DBP, postural SBP and DBP, and electrocardiogram (ECG) parameters. Laboratory

measurements included lipid profile, serum glucose, uric acid, and other selected metabolic parameters.

Protocol-defined reasons for removal of a patient from the study included deterioration of the patient's clinical condition, increase in mean supine DBP >15 mm Hg from baseline, or mean supine DBP >100 mm Hg at any visit during the study period. Also included as a protocol-defined reason for withdrawal was an increase in mean supine pulse rate to  $\geq 105$  bpm at any visit during the study period, intolerable adverse events or adverse events that might cause severe or permanent harm, or violation of the study protocol.

### Statistical methodology

Statistical tests were two-tailed at a  $P \leq 0.05$  level of significance. A two-way analysis of variance procedure was used for inferential analyses on continuous variables. The Shapiro-Wilk procedure was used to assess the normality of residuals. Levene's procedure was used to assess the homogeneity of variance. The Cochran-Mantel-Haenszel procedure was used to analyse categorical data. Analysis was performed on three sets of data. The first, on the intent-to-treat patient population, used the last observation carried forward (LOCF) technique, for which missing data were replaced by the last available observation. Baseline data were not carried forward. The second analysis was an observed analysis that used only the actual data recorded for a patient. The third analysis was on data for patients who completed the study (completers analysis).

### Results

A total of 220 patients were randomised to the study—146 to the sibutramine treatment group (84/146 completed the study) and 74 to the placebo group (36/74 completed the study). Three patients, one in the sibutramine treatment group and two in the placebo treatment group, were excluded from the efficacy analyses because they had no efficacy measurements after baseline. Three patients (one in the sibutramine treatment group and two in the placebo treatment group) were categorised as protocol violators because of a change in the dose of their ACE inhibitor.

The demographics and other baseline characteristics of the randomised patients, including the ACE inhibitors (benazepril, enalapril, lisinopril) most commonly used at baseline and continued into the double-blind phase of the study, are shown in Table 1. No statistically significant differences were noted between the two treatment groups in terms of baseline and demographic characteristics, including supine and postural SBP and DBP and pulse rate, and the demographics for the groups were well matched.

**Table 1** Demographic and other baseline characteristics

	Sibutramine ( <i>n</i> = 146)	Placebo ( <i>n</i> = 74)
Age (yr)	51.5 $\pm$ 9.6	50.7 $\pm$ 9.2
Gender, <i>n</i> (%)		
Women	85 (58.2)	42 (56.8)
Men	61 (41.8)	32 (43.2)
Race, <i>n</i> (%)		
Caucasian	116 (79.5)	64 (86.5)
Black	26 (17.8)	8 (10.8)
Mexican American	3 (2.1)	2 (2.7)
Other	1 (0.7)	0
Weight (kg)	96.7 $\pm$ 16.0	99.0 $\pm$ 13.9
Height (cm)	168.9 $\pm$ 9.7	170.1 $\pm$ 9.1
BMI (kg/m <sup>2</sup> )	33.8 $\pm$ 3.6	34.2 $\pm$ 3.6
Supine SBP (mm Hg) <sup>a</sup>	129.4 $\pm$ 10.8	129.3 $\pm$ 10.9
Supine DBP (mm Hg) <sup>a</sup>	82.4 $\pm$ 5.8	82.9 $\pm$ 5.5
ACE inhibitors, <i>n</i> (%)		
Benazepril	24 (16.4)	12 (16.2)
Enalapril	25 (17.1)	10 (13.5)
Lisinopril	55 (37.7)	35 (47.3)

<sup>a</sup>SBP and DBP are the means of the baseline visit and the two preceding pretreatment visits. Values of age, weight, height, BMI, SBP, and DBP are reported as mean  $\pm$  s.d.

### Efficacy

A summary of primary efficacy results for both the LOCF and completers analyses is shown in Table 2. The sibutramine group had significantly ( $P \leq 0.05$ ) greater decreases from baseline in weight-related variables at week 52 compared with the placebo group. In the LOCF analysis, patients treated with sibutramine lost a mean of 4.5 kg, or 4.8% of their body weight, compared with a mean of 0.4 kg, or 0.3% of body weight, in patients treated with placebo ( $P \leq 0.05$ ). Patients treated with sibutramine had a significantly larger mean reduction (5.3 cm) in waist circumference, a surrogate measure of visceral fat that correlates with obesity comorbidities, compared with patients treated with placebo (1.3 cm) ( $P \leq 0.05$ ). The treatment differences in weight loss were statistically significant ( $P \leq 0.001$ ) at all visits from week 4 onward during the double-blind period for both LOCF and completers analyses as shown in Figure 1 (LOCF).

Table 2 shows a categorical analysis, the numbers and percentages of patients losing  $\geq 5\%$  and  $\geq 10\%$  of their baseline weight by week 52. When compared with the placebo group, the sibutramine group had significantly higher percentages of 5% responders (42.8% vs 8.3%, respectively, LOCF) and 10% responders (13.1% vs 2.8%, respectively, LOCF) ( $P \leq 0.05$  for both comparisons).

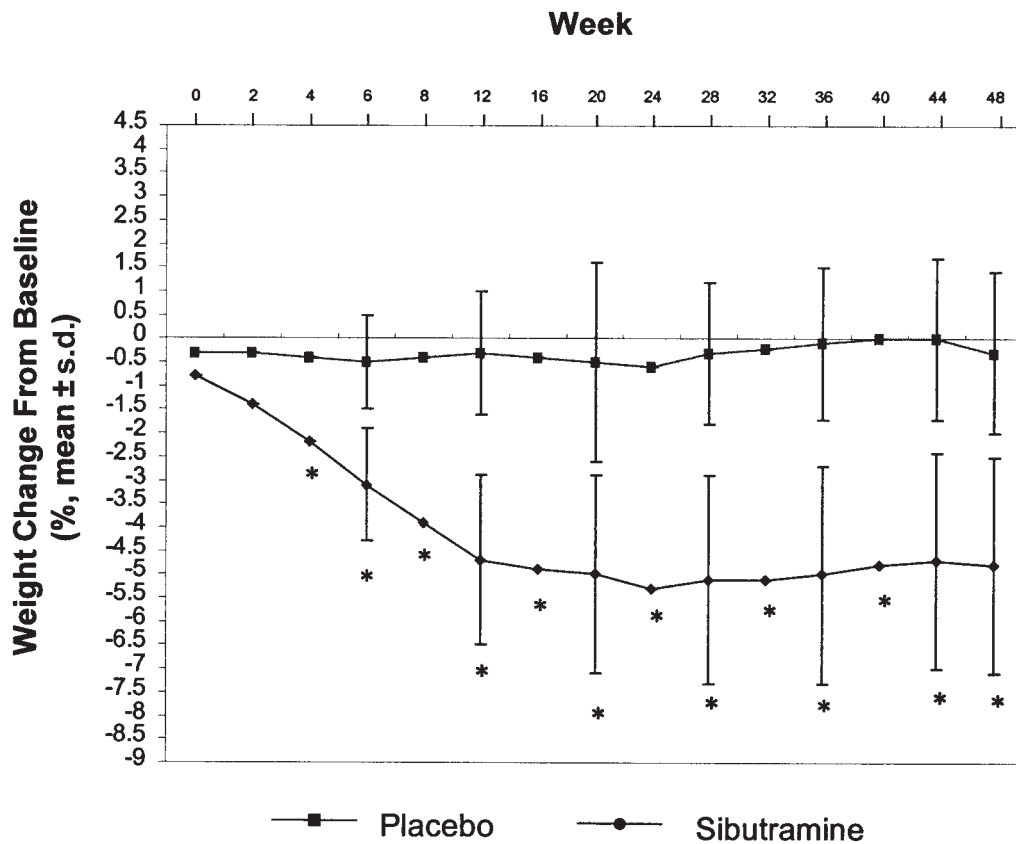
### Vital signs

Mean values for vital signs and increases and decreases from baseline at week 52 are shown in Table 3. Generally, hypertension remained well controlled for the 52-week duration of the study in both the sibutramine treatment group and the

**Table 2** Mean changes of body weight and related parameters at week 52

Patient number (%)	LOCF analysis		Completers analysis	
	Sibutramine 145 (100)	Placebo 72 (100)	Sibutramine 84 (100)	Placebo 36 (100)
Body weight (kg)	-4.5 <sup>a</sup>	-0.4	-5.5 <sup>a</sup>	-0.8
Body weight (%)	-4.8 <sup>a</sup>	-0.3	-5.8 <sup>a</sup>	-0.6
BMI (kg/m <sup>2</sup> )	-1.6 <sup>a</sup>	-0.1	-1.9 <sup>a</sup>	-0.3
Waist circumference (cm)	-5.3 <sup>a</sup>	-1.3	-5.2 <sup>a</sup>	-1.1
Hip circumference (cm)	-3.5 <sup>a</sup>	-0.6	-3.5 <sup>a</sup>	-0.3
Waist/hip ratio	-0.02	-0.01	-0.02	-0.01
Patients losing ≥5% and ≥10% of baseline weight by week 52, n (%)				
5% responders	62 (42.8) <sup>a</sup>	6 (8.3)	45 (53.6) <sup>a</sup>	4 (11.1)
10% responders	19 (13.1) <sup>a</sup>	2 (2.8)	14 (16.7)	2 (5.6)

<sup>a</sup>*P* ≤ 0.05, compared with placebo.



**Figure 1** Weight change (%; mean ± s.d.) over time with treatment with sibutramine or placebo as part of a weight loss programme (LOCF). \**P* < 0.001, sibutramine vs placebo.

placebo treatment group. At week 52, the differences between placebo treatment and sibutramine treatment for both mean SBP and mean DBP were statistically significant. At week 52, mean supine DBP was 82.8 mm Hg with placebo treatment compared with 85.5 mm Hg with sibutramine treatment (LOCF; *P* = 0.004) and mean supine SBP was 130.4 mm Hg with placebo compared with 133.1 mm Hg with sibutramine (LOCF; *P* = 0.0497; both compar-

isons, sibutramine vs placebo). Decrease in pulse rate at week 52 was -0.3 bpm for placebo treatment compared with an increase of 5.7 bpm for sibutramine treatment (LOCF; *P* < 0.001). Pulse rates at week 52 were 77.1 bpm for the sibutramine group compared with 72.8 bpm for the placebo group. There were no significant differences for changes in postural DBP in patients in the sibutramine group compared with those in the placebo group (*P* > 0.05; data not

**Table 3** Vital signs<sup>a</sup> at week 52

	LOCF analysis		Completers analysis	
	Sibutramine	Placebo	Sibutramine	Placebo
Patient number (%)	145 (100)	72 (100)	84 (100)	36 (100)
SBP (mm Hg)	133.1	130.4	133.3	131.1
Change from baseline				
Supine	3.8 <sup>b</sup>	1.1	4.3	1.4
DBP (mm Hg)	85.5	82.8	85.1	81.8
Change from baseline				
Supine	3.0 <sup>c</sup>	-0.1	3.3 <sup>c</sup>	-0.1
Pulse rate (bpm)				
Change from baseline	5.7 <sup>d</sup>	-0.3	5.6 <sup>d</sup>	0.0

<sup>a</sup>Baseline vital signs are the means of the baseline visit and the two preceding visits. <sup>b</sup> $P = 0.0497$ , sibutramine compared with placebo. <sup>c</sup> $P = 0.004$ . <sup>d</sup> $P < 0.001$ .

shown). Five patients (3.4%) in the sibutramine group and one patient (1.4%) in the placebo group were discontinued because of hypertension as defined in the protocol; the withdrawal rates in the two treatment groups for hypertension were not statistically different.

### Serum chemistry

A summary of mean increases and decreases in serum lipid variables between screening and week 52 for LOCF and completers analyses is shown in Table 4. Compared with the placebo group, the sibutramine group had greater mean decreases for total cholesterol for all patients, as well as for the 5% and the 10% responders (LOCF). Decreases in triglycerides, increases in high-density lipoprotein (HDL) cholesterol, and decreases in very low-density lipoprotein cholesterol were generally greater in the sibutramine group, for all patients as well as for the 5% and the 10% responders, compared with the placebo group ( $P \leq 0.05$ ). Greater improvements in serum lipid profile were generally associated with greater weight loss in the sibutramine group compared with the placebo group.

Throughout the study, the sibutramine group had greater mean decreases from screening levels of serum uric acid compared with the placebo group.

At week 52, the mean placebo-adjusted decreases from screening levels in serum uric acid were 0.2 mg/dL and 0.3 mg/dL for the LOCF and completers analyses, respectively. Serum glucose levels decreased with increased weight loss, with no significant differences between the sibutramine and placebo groups. The greatest serum glucose decrease (5.1 mg/dL) occurred in the 18 patients in the sibutramine group who lost  $\geq 10\%$  of their baseline body weight.

### Safety

Sibutramine 20 mg was safe and well tolerated in this patient population for the 52 weeks of the study. Twenty-seven patients discontinued because of adverse events: 23 patients (15.8%) in the sibutramine group and four patients (5.4%) in the placebo group. Although changes in BP that exceeded the protocol-defined levels requiring withdrawal were the most frequently reported adverse events leading to discontinuation, the rates of withdrawal due to hypertension in the two treatment groups were not statistically different ( $P > 0.05$ ). No increases or decreases were seen on ECG evaluations that were attributable to treatment. Other reasons for discontinuation included lack of efficacy (1/146 (0.7%) for sibutramine treatment and 6/74 (8.1%) for placebo

**Table 4** Mean changes in serum lipid variables (mg/dL) between screening and week 52

	LOCF analysis				Completers analysis			
	All placebo patients	All sibutramine patients	Sibutramine 5% responders <sup>a</sup>	Sibutramine 10% responders <sup>a</sup>	All placebo patients	All sibutramine patients	Sibutramine 5% responders	Sibutramine 10% responders
Total cholesterol	-2.2 (n = 63)	-3.8 (n = 129)	-4.8 (n = 61)	-3.5 (n = 18)	-3.6 (n = 36)	-0.9 (n = 84)	0.0 (n = 45)	-5.5 (n = 14)
HDL cholesterol	1.3 (n = 63)	4.8* (n = 129)	7.5* (n = 61)	12.3 (n = 18)	3.4 (n = 36)	8.3* (n = 84)	10.2* (n = 45)	14.8* (n = 14)
LDL cholesterol	-4.0 (n = 60)	-4.3 (n = 122)	-3.8 (n = 59)	-1.2 (n = 17)	-5.1 (n = 33)	-3.3 (n = 80)	-0.4 (n = 43)	-3.0 (n = 13)
VLDL cholesterol	-1.4 (n = 63)	-5.5* (n = 129)	-10.0* (n = 61)	-15.9* (n = 18)	-5.4 (n = 36)	-8.6 (n = 84)	-11.7 (n = 45)	-19.1* (n = 14)
Triglycerides	-7.2 (n = 63)	-27.4* (n = 129)	-49.3* (n = 61)	-78.3* (n = 18)	-26.6 (n = 36)	-42.8 (n = 84)	-57.7 (n = 45)	-94.3* (n = 14)

<sup>a</sup>The placebo group used for comparison contains all placebo patients. \*Statistically significant vs placebo,  $P \leq 0.05$ . HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

treatment) and protocol violation (6/146 (4.1%) for sibutramine treatment and 5/74 (6.8%) for placebo treatment).

Treatment-emergent adverse events were reported by 141 of the 146 patients (96.6%) in the sibutramine group, and by 65 of the 74 patients (87.8%) in the placebo group and were similar to those reported previously.<sup>6–8,13</sup> The nature, frequency, and severity of adverse events were not statistically significantly different in the sibutramine group compared with the placebo group. The majority of adverse events were of either mild or moderate severity. Headache was the most frequently reported adverse event: 41 of the 146 patients (28.1%) in the sibutramine group and 17 of the 74 patients (23.0%) in the placebo group. Dry mouth was the second most frequently reported adverse event in the sibutramine treatment group: 30 of 146 patients (20.5%) compared with 0% in the placebo treatment group. The rates of serious adverse events reported were comparable in the two treatment groups. Nine patients (6.2%) reported serious adverse events in the sibutramine group, two defined as being possibly treatment related, and five patients (6.8%) in the placebo group reported serious adverse events, with none considered to be treatment related. No deaths were reported in the study.

## Discussion

The results of this 52-week study show that, compared with placebo, sibutramine 20 mg produces statistically and clinically significant loss in body weight in mild to moderately obese patients whose hypertension is well controlled with an ACE inhibitor, with or without concomitant thiazide diuretic therapy. Overall, hypertension that was well controlled in obese patients at randomisation into the study remained well controlled in both the sibutramine and placebo treatment groups for the 52 weeks of the study. Although small, mean increases in BP were seen in the sibutramine treatment group compared with the placebo treatment group, mean BP values in both treatment groups remained generally within the ranges determined in the HOT (Hypertension Optimal Treatment) study to confer maximum protection from cardiovascular events.<sup>14</sup> Results of the HOT study showed that most cardiovascular end points show a declining frequency in relation to target BP. In the HOT study, the optimal protection against combined major cardiovascular end points was seen in the range of 80–85 mm Hg for DBP and in the range of 130–140 mm Hg for SBP.<sup>14,15</sup> Most patients in this study remained in this target range for the duration of the study. It is important to note that the dose of sibutramine used in the study, 20 mg once daily, is actually higher than the current recommended starting dose (10 mg once daily) and maximum recommended dose (15 mg once daily). Despite the higher dose, the number of patients who discontinued treatment

because of hypertension, as mandated in the study protocol, was low in both the sibutramine (3.4%) and placebo (1.4%) groups. Thus, this study shows that ACE inhibitors, used with or without concomitant thiazide diuretics, continue to control BP well when sibutramine is taken for weight reduction. However, since sibutramine can increase BP, sibutramine-treated patients should have regular monitoring of BP. The high rate of discontinuation from the study, 62/146 (43%) in the sibutramine treatment group and 38/74 (51%) in the placebo treatment group, is a limitation in interpreting the results of this study. Reasons for discontinuation from the study were not statistically significant different between the two treatment groups.

This study confirms that the use of sibutramine, in conjunction with a programme of general dietary advice, results in greater weight loss than a programme of general dietary advice alone with placebo. In addition to losing more weight, patients treated with sibutramine had significantly larger mean reductions in BMI and waist circumference—surrogate measures that correlate with the comorbidities of obesity—compared with patients treated with placebo. About five times as many patients receiving sibutramine treatment were 5% responders compared with patients receiving placebo treatment. By the end of the study, 43% to 54% (LOCF, completers) of patients treated with sibutramine lost at least 5% of their baseline body weight, a degree of weight loss often associated with improvements in comorbid conditions.<sup>10</sup> Significantly greater weight loss with sibutramine compared with placebo was associated with significantly greater improvement in serum lipid profiles. Similarly, weight loss was associated with a decrease in serum glucose, consistent with improvements in diabetic control reported in other studies with sibutramine.<sup>16,17</sup> Greater improvements in lipid profile, serum glucose, and uric acid could be accounted for by the greater weight losses occurring in the sibutramine treatment group. Sibutramine treatment reduces overall risk of coronary heart disease despite small BP increases. Calculation of the 10-year percent reduction in risk of coronary heart disease was carried out in equations developed from the results of the Framingham Heart Study. This analysis shows that greater weight loss achieved with sibutramine treatment results in a risk reduction of 0.57% over 10 years, compared with a reduction of 0.02% with placebo treatment ( $P < 0.001$ , sibutramine treatment compared with placebo treatment).<sup>18</sup>

In summary, the data from this 52-week study indicate that, compared with placebo, sibutramine 20 mg is safe, well tolerated, and produces statistically and clinically significant body weight loss in obese patients whose hypertension is well controlled with an ACE inhibitor, with or without concomitant thiazide diuretic therapy. These results confirm the safety and efficacy of sibutramine treat-

ment in those patients with hypertension controlled by calcium channel blockers.<sup>19</sup> Patients with hypertension controlled with either calcium channel blockers or ACE inhibitors can lose more weight on a programme that includes sibutramine compared with a programme that includes placebo. Effects on BP with either calcium channel blockers or ACE inhibitors are minimal with sibutramine treatment. The greater weight loss with sibutramine treatment concurred with greater improvements in the serum lipid profiles and serum glucose and uric acid levels. BP values remained in the well-controlled target range for patients in both the sibutramine and the placebo treatment groups. Although sibutramine treatment was associated with small, mean increases in BP, and modest increases in pulse rate, the percentages of patients experiencing clinically significant increases in these measures resulting in withdrawal from the study were comparable for the sibutramine and placebo groups.

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