

# A Randomized Trial of Sibutramine in the Management of Obese Type 2 Diabetic Patients Treated With Metformin

STEVEN J. McNULTY, MD<sup>1</sup>  
EHUD UR, MB, FRCP<sup>2</sup>  
GARETH WILLIAMS, MD, FRCP EDIN<sup>1</sup>

FOR THE MULTICENTER SIBUTRAMINE STUDY  
GROUP

**OBJECTIVE** — To evaluate the effects of sibutramine (15 and 20 mg/day) on weight, metabolic control, and blood pressure in metformin-treated obese subjects with type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — A 12-month randomized prospective placebo-controlled double-blind study was performed. It included 21 primary and secondary care centers in England, Canada, France, and Belgium. A total of 195 subjects (44% male) with type 2 diabetes and a BMI >27 kg/m<sup>2</sup> were studied. Changes were assessed in weight, blood pressure and resting heart rate, HbA<sub>1c</sub>, fasting glucose, and lipids.

**RESULTS** — Sibutramine induced significant weight loss ( $P < 0.001$ ) with both 15 mg/day ( $5.5 \pm 0.6$  kg at 12 months) and 20 mg/day ( $8.0 \pm 0.9$  kg), whereas placebo did not ( $0.2 \pm 0.5$  kg). Weight loss  $\geq 10\%$  was achieved by 14 and 27% of subjects receiving 15 and 20 mg, respectively, but by none given placebo. Glycemic control improved in parallel with weight loss, and subjects who lost  $\geq 10\%$  weight showed significant decreases in both HbA<sub>1c</sub> ( $1.2 \pm 0.4\%$ ,  $P < 0.0001$ ) and fasting plasma glucose (1.8 mmol/l,  $P < 0.001$ ). HDL cholesterol increased slightly with the higher dose, whereas plasma triglycerides fell with both doses, especially in subjects with weight loss of  $\geq 10\%$  (a 29% decrease,  $P < 0.01$ ). Treatment was generally well tolerated. Sibutramine treatment raised sitting diastolic blood pressure by  $\geq 5$  mmHg in a higher proportion of patients than did placebo (43% with 15 mg/day vs. 25% with placebo,  $P < 0.05$ ), but this effect was less evident in subjects who had a weight loss of  $\geq 10\%$  weight. Pulse rate increased significantly more with sibutramine, being  $\geq 10$  bpm higher in 42% of treated patients versus 17% with placebo ( $P < 0.01$ ).

**CONCLUSIONS** — Sibutramine can be an effective adjunct to metformin treatment in selected obese type 2 diabetic subjects and improves metabolic control in individuals who lose weight.

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Obesity exacerbates insulin resistance, hypertension, dyslipidemia, and atherosclerosis, the main cause of death in type 2 diabetes (1–3). It therefore impedes the management of hyperglycemia and its comorbidities in type 2

diabetes and ultimately shortens life expectancy; the risk of premature death increases progressively in subjects with a BMI >25 kg/m<sup>2</sup>, to 5-fold in men and 10-fold in women with a BMI >35 kg/m<sup>2</sup> (4,5). Weight loss confers important ben-

efits in obese type 2 diabetic patients. In subjects with a BMI between 30 and 40 kg/m<sup>2</sup>, weight loss of  $\geq 10\%$  often lowers fasting plasma glucose by 1–2 mmol/l and HbA<sub>1c</sub> by 1% (6–8)—effects comparable to those of oral hypoglycemic drugs. Unfortunately, weight loss is harder to achieve and sustain in type 2 diabetic patients than in nondiabetic people (5,7). In the U.K. Prospective Diabetes Study (UKPDS), only 5–10% of obese type 2 diabetic patients remained adequately treated by dietary and lifestyle approaches after 1 year (9).

Various anti-obesity drugs, including the fenfluramines (now withdrawn) and orlistat (10,11), have produced  $\geq 10\%$  weight loss in 20–30% of obese type 2 diabetic patients, with concomitant improvements in glycemic control. Sibutramine is a combined reuptake inhibitor of both serotonin (5-hydroxytryptamine) and norepinephrine and acts centrally to enhance satiety (12). Its structure and mode of action differ from those of the fenfluramines, which stimulate serotonin release. Sibutramine decreases food intake in rodents and humans and may also have mild thermogenic properties (12). It has achieved weight loss of  $\geq 10\%$  in 30–40% of nondiabetic obese patients (13). Sibutramine is generally well tolerated, although some patients show evidence of increased sympathetic cardiovascular tone, with mild tachycardia and rises in blood pressure (12,13).

Here, we report metabolic and cardiovascular effects of sibutramine in obese type 2 diabetic patients treated with metformin, which is widely used as first-line therapy in patients who respond inadequately to diet and lifestyle measures.

## RESEARCH DESIGN AND METHODS

This multicenter randomized placebo-controlled double-blind trial compared placebo with two dosages of sibutramine (15 and 20 mg/day) for 12 months. We studied 195 patients from two centers in the U.K. ( $n = 28$ ), eight in Canada ( $n = 116$ ), five in France ( $n = 21$ ), and six in Belgium ( $n =$

From the <sup>1</sup>Diabetes and Endocrinology Research Group, Department of Medicine, University Hospital Aintree, Liverpool, U.K.; and the <sup>2</sup>Division of Endocrinology, Dalhousie University, Halifax, Canada.

Address correspondence and reprint requests to Professor Gareth Williams, Diabetes and Endocrinology Research Group, Department of Medicine, University Hospital Aintree, Longmoor Lane, Liverpool L9 7AL, U.K. E-mail: garethw@liverpool.ac.uk.

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**Abbreviations:** UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Characteristics of the subjects randomized to each treatment group

	Placebo	15 mg sibutramine	20 mg sibutramine
n	64	68	62
M (%)	34	53	44
Age (years)	51 ± 1.1	49 ± 1.0	48 ± 1.0
Weight (kg)	100.7 ± 2.6	103.5 ± 2.2	104.3 ± 2.9
BMI (kg/m <sup>2</sup> )	36.2 ± 0.8	36.3 ± 0.7	37.5 ± 1.0
Duration of diabetes (years)	1.8 (0.4–13)	2.0 (0.4–17)	2.0 (0–22)
Duration of metformin (years)	0.6 (0.2–2.0)	0.6 (0.1–2.9)	0.6 (0.1–2.0)
Fasting plasma glucose (mmol/l)	9.1 (6.2–16.2)	9.5 (5.7–15.4)	9.2 (5.7–17.1)
HbA <sub>1c</sub> (%)	9.73 ± 0.3	9.75 ± 0.3	9.14 ± 0.2

Data are means ± SE or median (range). All group differences are nonsignificant.

30). Suitable subjects, identified from review of case notes and/or computerized clinic registers, were contacted personally or by telephone.

Inclusion criteria were as follows: type 2 diabetes (absence of ketonuria, rapid preceding weight loss, or need for insulin treatment), diabetes duration >6 months, BMI ≥27 kg/m<sup>2</sup>, duration of metformin treatment of 3 months to 2 years, fasting serum glucose 7.0–15.0 mmol/l, and age 25–70 years. Exclusion criteria comprised the following: current or previous evidence of ischemic heart disease, heart failure, or stroke; seated pulse rate >100 bpm; diastolic blood pressure >95 mmHg; total fasting serum cholesterol >7.8 mmol/l; fasting serum triglycerides >5.6 mmol/l; serum creatinine >120 μmol/l; serum liver enzymes or bilirubin levels that exceeded twice the upper limit of normal; weight change of >3 kg during the preceding 3 months; malignancy; and significant neurological or psychiatric disturbances, including alcohol or drug abuse. Excluded medications (within the previous 3 months) were anorectic agents, laxatives, β-agonists (other than inhalers), cyproheptadine, phenothiazines, anti-depressants, anti-serotonergics, barbiturates, anti-psychotics, and oral corticosteroids. Antihypertensive and lipid-lowering drugs were permitted if treatment was stable for at least 3 months. Women were excluded if they were pregnant, lactating, or of child-bearing potential while not taking adequate contraceptive precautions.

Participants (Table 1) comprised 85 men (44%) and 109 women (56%) aged 27–69 years. There were no significant differences between centers in sex distribution, age, diabetes duration, or the dosage (mean 1,250 mg/day) or duration of

metformin treatment. At entry, 70 subjects (36%) were hypertensive according to World Health Organization criteria, and 56 (29%) were taking anti-hypertensive treatment, with 17 (9%) receiving lipid-lowering drugs. Ethical approval was obtained at each site, according to the Declaration of Helsinki.

#### Study design and protocol

Eligible patients were given each center's standard dietary advice by a dietitian and/or specialist nurse and returned within 4 weeks for random allocation to 15 or 20 mg/day sibutramine or placebo. For tolerability reasons, patients in the 20-mg sibutramine group took 15 mg sibutramine daily for the first 2 weeks. Patients were reviewed every 4 weeks, when dietetic advice was reinforced, medication compliance checked by capsule count, and adverse events and medication changes recorded. Glycemic control was monitored 3-monthly by fasting glucose and HbA<sub>1c</sub>; metformin dosage was adjusted if necessary, but other antidiabetic drugs were not used.

Height, weight (in light clothes), and BMI were recorded at screening, and weight was measured 4-weekly thereafter. At randomization and at 6 and 12 months, waist and hip circumference were measured and waist-to-hip ratio was calculated. A 12-lead electrocardiogram, physical examination, and tobacco and alcohol history were recorded. Fasting blood samples and urine for standard screening were taken initially and 3-monthly thereafter. HbA<sub>1c</sub>, serum glucose, insulin, C-peptide, triglycerides, total cholesterol, and HDL cholesterol were measured, and LDL cholesterol was calculated.

#### Statistical analysis

The study required 60 patients to be evaluated per treatment group, to be 90% powered at the 5% significance level to detect a treatment effect of 0.8% in HbA<sub>1c</sub>, assuming a variability of 1.3%. The minimum differences from placebo (at 90% power and 5% significance level) that could be detected by the study were 0.65 and 0.67% for sibutramine dosages of 15 and 20 mg, respectively. Analyses, performed by the Biostatistics Section, Knoll Limited, were based on the intention-to-treat populations using the last observation carried forward.

Changes from baseline to end point in body weight, anthropometry, and metabolic measures were analyzed using ANCOVA, with factors for treatment group and country and the relevant baseline as a covariate. Pairwise comparisons between each sibutramine group and placebo were carried out using Fisher's protected least-squares difference test. Metabolic measures were ranked before analysis, and Hodges-Lehmann estimates of treatment differences were determined. Analyses were also carried out on within-group changes, stratified by weight loss (<5, ≥5, and ≥10%) using one-sample *t* tests. The proportions of subjects within these categories were compared between sibutramine and placebo groups using χ<sup>2</sup> tests. All tests were two-tailed and carried out at the 5% level.

**RESULTS**— A total of 68 patients were assigned to 15 mg/day sibutramine, 62 to 20 mg/day sibutramine, and 64 to placebo. The groups were well matched at baseline (Table 1). There were 50 patients who withdrew prematurely (19 in the 15 mg/day sibutramine group, 13 in the 20 mg/day sibutramine group, and 18 in the placebo group). There were no significant group differences in reasons or numbers of withdrawals, and an imputation analysis indicated that this drop-out rate is unlikely to have influenced the outcome.

#### Effects on weight and anthropometry

Placebo-treated patients showed no consistent weight change at any time; 88% of subjects (56 of 63) either gained weight or lost <5%, whereas only 12% lost ≥5%, and none lost ≥10% (Table 2 and Fig. 1). With 15 mg/day sibutramine, average weight fell steadily over 6 months to 5.3 kg (~6%) below baseline and was then

**Table 2—Overall effects on weight and anthropometry in groups treated with placebo or 15 or 20 mg/day sibutramine**

Variable	Treatment group	Baseline	Change	$D^c$	95% CI for $D^c$	
Weight (kg)	Placebo	100.7 ± 2.6	-0.2 ± 0.5	—	—	
	15 mg sibutramine	103.5 ± 2.2	-5.5 ± 0.6‡	-5.1 ± 0.9*	-7.0 to -3.3	
	20 mg sibutramine	104.3 ± 2.9	-8.0 ± 0.9‡	-7.8 ± 1.0*	-9.7 to -5.9	
BMI (kg/m <sup>2</sup> )	Placebo	36.2 ± 0.8	-0.1 ± 0.2	—	—	
	15 mg sibutramine	36.3 ± 0.7	-2.0 ± 0.2‡	-1.9 ± 0.3*	-2.6 to -1.2	
	20 mg sibutramine	37.5 ± 1.0	-2.9 ± 0.3‡	-2.9 ± 0.3*	-3.6 to -2.2	
Circumference						
	Waist (cm)	Placebo	112.0 ± 2.0	0.2 ± 0.6	—	—
		15 mg sibutramine	113.5 ± 1.6	-4.7 ± 0.7‡	-4.9 ± 0.9*	-6.7 to -3.0
20 mg sibutramine		113.0 ± 1.9	-6.6 ± 0.7‡	-6.8 ± 1.0*	-8.7 to -4.9	
Hip (cm)	Placebo	119.4 ± 1.6	0.0 ± 0.7	—	—	
	15 mg sibutramine	116.9 ± 1.6	-3.0 ± 0.6‡	-3.0 ± 1.0*	-5.0 to -1.0	
	20 mg sibutramine	119.1 ± 2.1	-6.1 ± 1.0‡	-6.1 ± 1.0*	-8.2 to -4.1	
Waist to hip ratio	Placebo	93.9 ± 1.2	-0.3 ± 0.7	—	—	
	15 mg sibutramine	97.5 ± 1.2	-1.6 ± 0.6‡	-1.4 ± 0.9	-3.1 to 0.3	
	20 mg sibutramine	95.3 ± 1.2	-1.1 ± 0.7	-0.9 ± 0.9	-2.6 to 0.8	

Data are means ± SE or medians (range).  $D^c$ , treatment group difference (i.e., sibutramine minus placebo). \* $P < 0.001$ , † $P < 0.01$ .

maintained throughout treatment. The 20-mg dose caused consistently greater weight loss, averaging 8 kg (~8%) below baseline from 8 months to the end of treatment.

Significantly more sibutramine-treated subjects lost ≥5% weight (46 and 65% with 15 and 20 mg, respectively), whereas 14% of subjects receiving 15 mg/day and 27% of subjects taking 20 mg lost ≥10%.

BMI and hip and waist circumferences also fell significantly in both sibutramine-treated groups compared with placebo—more so with the higher dose (Table 2). Waist circumference, an independent predictor of cardiovascular risk (14), was reduced by 4.7 ± 0.7 cm with 15 mg sibutramine and by 6.6 ± 0.7 cm with 20 mg sibutramine (both  $P < 0.001$ ), whereas placebo caused no significant change (0.2 ± 0.6 cm,  $P > 0.05$ ).

Waist circumference fell by ≥5 cm in 46% (15 mg) and 63% (20 mg) of sibutramine-treated patients but in only 18% with placebo. For waist circumference reductions of ≥10 cm, the corresponding figures were 14% (15 mg), 29% (20 mg), and 0% (placebo).

### Effects on glycemic control

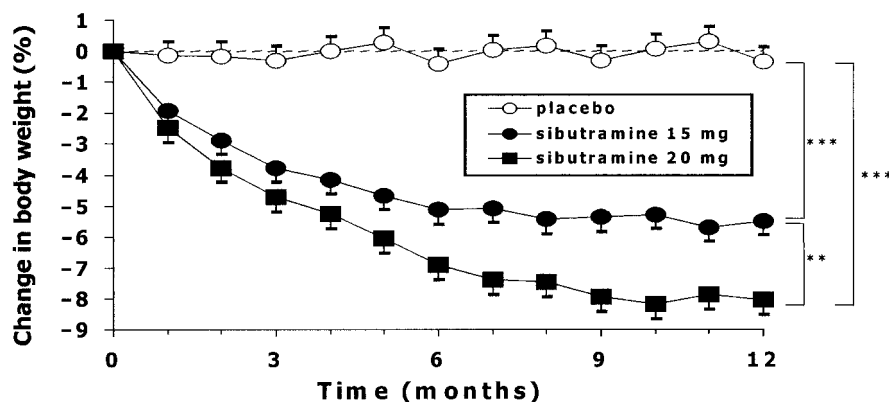
Overall, HbA<sub>1c</sub> concentrations did not change significantly among the treatment groups (Table 3), but it fell significantly (0.7 ± 0.3%,  $P < 0.02$ ) in subjects who lost 5–10% of weight and significantly further (1.2 ± 0.4%,  $P < 0.0001$ ) in those losing ≥10%. Among the sibutramine-treated patients, percentage weight loss was significantly correlated with the fall in HbA<sub>1c</sub> ( $r = 0.43$ ,  $P < 0.001$ , for the 15-mg group and  $r = 0.32$ ,  $P < 0.02$ , for the 20-mg group), but no correlation was seen in the placebo group, where average weight was unchanged ( $r = 0.5$ ,  $P = 0.73$ ). Fall in HbA<sub>1c</sub> correlated significantly with percentage reduction in waist circumference in both sibutramine treatment groups (15 mg:  $r = 0.43$ ,  $P < 0.001$ ; 20 mg:  $r = 0.30$ ,  $P < 0.05$ ) and with placebo ( $r = 0.51$ ,  $P < 0.001$ ).

Fasting plasma glucose similarly showed no overall differences between the three treatment groups but fell significantly by 1.8 mmol/l ( $P < 0.001$ ) in patients (sibutramine-treated only) who lost ≥10%. Fasting plasma insulin showed no significant changes with 15 mg sibutramine or placebo, but the final concentration was significantly decreased with 20 mg sibutramine compared with placebo (Table 3).

Metformin dosage was reduced in five patients (7%) receiving 15 mg sibutramine and in six patients (10%) with the 20-mg dosage, but in only one subject (2%) given placebo.

### Effects on blood lipids

Baseline lipid levels (Table 3) were representative of those seen in moderately obese type 2 diabetic patients treated with metformin (15). Neither total nor LDL cholesterol showed any significant changes in any treatment group, but HDL cholesterol showed slight but significant rises of 0.1 mmol/l with both 15 and 20 mg sibutramine. The total cholesterol-to-HDL cholesterol ratio showed a slight but statistically significant fall (10%) with 15 mg sibutramine but no significant change with 20 mg sibutramine. In sub-



**Figure 1—Changes in weight from baseline in obese type 2 diabetic patients treated with placebo (n = 68), 15 mg/day sibutramine (n = 62), and 20 mg/day sibutramine (n = 64). Data are means ± SE. Statistical significance of differences between final data points: \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .**

Table 3—Overall effects on metabolic measures in groups treated with placebo or 15 or 20 mg/day sibutramine

Variable Treatment group	Baseline	Change	D <sup>c</sup>	95% CI for D <sup>c</sup>
Fasting glucose (mmol/l)				
Placebo	9.1 (6.2–16.2)	0.2 (–6.8 to 9.3)	—	—
15 mg sibutramine	9.5 (5.7–15.4)	–0.3 (–6.3 to 8.5)	–0.2	–1.0 to 0.7
20 mg sibutramine	9.2 (5.7–17.1)	–0.1 (–5.7 to 7.7)	–0.2	–1.0 to 0.5
HbA <sub>1c</sub> (%)				
Placebo	9.73 ± 0.27	–0.22 ± 0.24	—	—
15 mg sibutramine	9.75 ± 0.26	–0.56 ± 0.27	–0.34 ± 0.33	–0.99 to 0.31
20 mg sibutramine	9.14 ± 0.24	–0.32 ± 0.23	–0.10 ± 0.34	–0.76 to 0.57
Fasting insulin (pmol/l)				
Placebo	108.0 (30–402)	–3.0 (–210 to 228)	—	—
15 mg sibutramine	114.0 (30–372)	–7.2 (–168 to 246)	–6.0	–24.0 to 12.0
20 mg sibutramine	96.0 (30–540)	–33.0 (–492 to 84)*	–18.0*	–30.0 to 0.0
Cholesterol (mmol/l)				
Total				
Placebo	5.8 (3.5–7.3)	–0.2 (–1.3 to 1.4)	—	—
15 mg sibutramine	5.4 (3.4–7.4)	–0.1 (–2.6 to 1.1)	0.0	–0.2 to 0.3
20 mg sibutramine	5.5 (2.8–8.0)	0.0 (–1.6 to 1.3)	0.1	–0.1 to 0.3
HDL				
Placebo	1.1 (0.6–5.7)	0.0 (–4.9 to 0.3)	—	—
15 mg sibutramine	1.0 (0.3–2.3)	0.1 (–1.4 to 0.6)*	0.1	0.0 to 0.2
20 mg sibutramine	1.1 (0.7–2.3)	0.1 (–0.8 to 0.7)†	0.1	0.0 to 0.1
LDL				
Placebo	3.5 (1.1–5.4)	–0.2 (–1.8 to 1.2)	—	—
15 mg sibutramine	3.2 (0.6–5.2)	–0.2 (–2.1 to 0.9)	0.0	–0.2 to 0.3
20 mg sibutramine	3.2 (1.1–5.8)	–0.1 (–1.2 to 1.1)	0.1	–0.1 to 0.3
Total cholesterol-to-HDL cholesterol ratio				
Placebo	5.0 (1.1–10.2)	0.0 (–1.8 to 7.1)	—	—
15 mg sibutramine	5.8 (2.8–13.3)	–0.3 (–3.3 to 13.5)	–0.5‡	–0.9 to –0.2
20 mg sibutramine	4.8 (2.2–7.9)	–0.5 (–8.5 to 2.8)	–0.2	–0.5 to 0.1
Triglycerides (mmol/l)				
Placebo	2.4 (0.6–5.7)	0.1 (–1.8 to 3.4)	—	—
15 mg sibutramine	2.4 (0.6–7.2)	–0.2 (–3.3 to 3.4)	–0.2	–0.6 to 0.1
20 mg sibutramine	2.2 (0.6–4.2)	–0.2 (–1.7 to 6.3)‡	–0.3‡	–0.6 to 0.0

Data are means ± SE or median (range). D<sup>c</sup>, treatment group difference (i.e., sibutramine minus placebo). \*P < 0.001, †P < 0.05, ‡P < 0.01.

jects who lost ≥5 or ≥10% weight, total cholesterol-to-HDL cholesterol ratio also showed modest but significant falls of 8% (P = 0.011) and 16% (P = 0.002), respectively.

Triglyceride levels did not alter significantly with placebo or 15 mg sibutramine but fell significantly by 0.2 mmol/l (9%) with 20 mg sibutramine. In subjects losing ≥5 and ≥10% weight, triglycerides fell significantly by 0.3 mmol/l (13%, P < 0.01) and 0.8 mmol/l (29%, P < 0.01), respectively.

### Cardiovascular effects

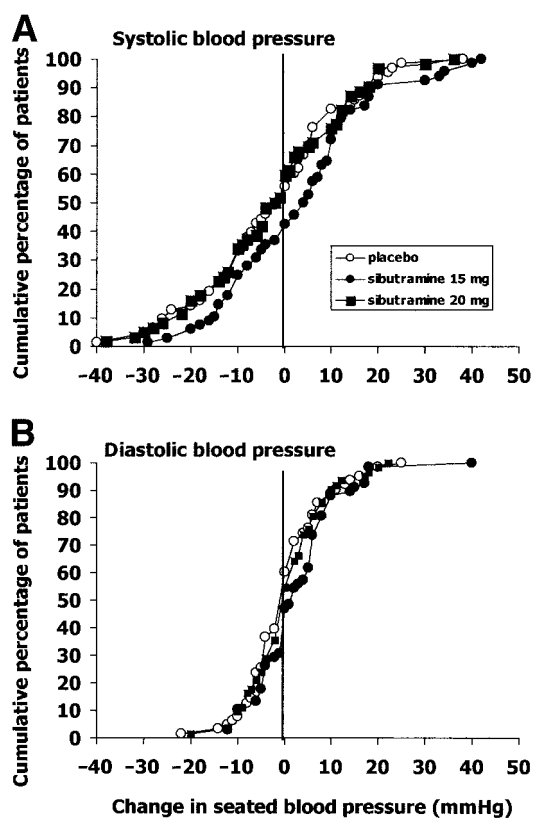
Individual blood pressure responses varied widely in all three treatment groups. A few sibutramine-treated patients showed marked blood pressure rises, but systolic

and diastolic blood pressure also rose in some placebo-treated patients, being higher at completion than at baseline in over 40% of cases (Fig. 2 and Table 4).

Blood pressure rises during sibutramine treatment were more apparent when measured sitting; standing systolic pressure showed no consistent group differences. Mean systolic and diastolic blood pressures were significantly higher at completion in the group receiving 15 mg/day (by 4 and 3 mmHg, respectively), but there was no significant rise in the group receiving 20 mg/day. Final systolic blood pressure (sitting) was ≥10 mmHg higher at the endpoint than at baseline in 36 and 29% of patients receiving 15 and 20 mg sibutramine, respectively, and in 24% of those given placebo (all differ-

ences: NS). For a diastolic blood pressure rise of ≥5 mmHg, the corresponding figures were 43% with 15 mg sibutramine (P < 0.05 vs. placebo), 26% with 20 mg sibutramine (NS vs. placebo), and 25% with placebo.

Blood pressure changes were influenced by weight change. With 15 mg sibutramine, systolic blood pressure did not change significantly in subjects who lost ≥5 or ≥10% weight, whereas the ≥5% responders with 20 mg sibutramine showed a mean placebo-subtracted fall of 4.6 ± 2.0 mmHg (P = 0.053 vs. all placebo subjects). Placebo-treated subjects who lost ≥5% weight showed a systolic decrease of 3.3 ± 1.4 mmHg. For >5% weight loss, mean placebo-subtracted diastolic changes were 2.0 ± 1.5 with 15



**Figure 2**—Cumulative plot of changes in systolic and diastolic blood pressure (A and B, respectively), measured while sitting, during treatment with placebo, 15 mg sibutramine, or 20 mg sibutramine. The differences shown represent the baseline value subtracted from the final value.

mg sibutramine (NS vs. placebo,  $1.5 \pm 1.0$  mmHg) and  $-0.9 \pm 1.4$  mmHg (NS vs. placebo) for 20 mg sibutramine. For  $>10\%$  weight loss, mean placebo-subtracted changes were  $1.7 \pm 2.2$  and  $1.0 \pm 1.8$  mmHg, respectively (both NS vs. placebo).

Pulse rate increased significantly more in both sibutramine groups than with placebo (Table 4). Final pulse rate was  $\geq 10$  bpm higher than at baseline in 17% of placebo-treated patients, significantly fewer ( $P < 0.01$ ) than with 15 mg (41%) and 20 mg (44%) sibutramine.

**CONCLUSIONS**— Management of type 2 diabetes often fails to meet the stringent treatment targets for glycemia, lipids, blood pressure, and other cardiovascular risk factors. The importance of obesity as a determinant of cardiovascular outcome has generally been neglected, despite accumulating evidence that it plays a crucial role (14,16). In the UKPDS (17), only metformin-treated patients enjoyed a significant reduction in cardiovascular events, whereas those receiving insulin or sulfonylureas did not. Glycemic control was no better with metformin, but weight gain was substantially less (by an

average of 4 kg) than with insulin or sulfonylureas. An independent cardioprotective effect of metformin cannot be excluded, but other data suggesting that weight loss reduces cardiovascular risk (18) point to metformin's anti-obesity action. Unfortunately, obesity is particu-

larly difficult to treat in type 2 diabetic patients (19), as highlighted by the overall failure of our placebo group to lose weight, despite regular dietary and lifestyle advice (Fig. 1).

Here, sibutramine was an effective anti-obesity agent in a substantial proportion of these patients. Average weight loss at 12 months was 5.5 kg with 15 mg sibutramine and 8 kg with 20 mg sibutramine, whereas placebo-treated patients lost no weight at all. Similarly, waist circumference was significantly reduced, by an average of 4.7 cm and 6.6 cm with 15 and 20 mg sibutramine, respectively. The usual tendency of obese type 2 diabetic patients to continue gaining weight is clearly illustrated by the placebo group, of whom 19% gained  $>2$  kg during the 12-month study. Sibutramine treatment significantly prevented weight gain, with only one subject taking 15 mg sibutramine and no subjects taking 20 mg sibutramine gaining  $>2$  kg.

Weight loss of  $\geq 10\%$  confers important metabolic and cardiovascular benefits in obese type 2 diabetic patients (6). This target was achieved by 14 and 27% of subjects taking 15 and 20 mg sibutramine, respectively, but by none given placebo. Loss of  $\geq 5\%$  weight, which may bring lesser benefits to some patients, was achieved by 46 and 65% of subjects taking 15 and 20 mg sibutramine, respectively, but by only 11% with placebo. These outcomes are comparable with

**Table 4**—Overall cardiovascular effects (seated vital signs) during treatment with placebo or sibutramine

Variable	Treatment group	Baseline	Change	D <sup>c</sup>	95% CI for D <sup>c</sup>
Systolic blood pressure (mmHg)					
	Placebo	$132.9 \pm 1.9$	$-0.2 \pm 2.0$		
	15 mg sibutramine	$131.5 \pm 2.1$	$4.4 \pm 1.9^*$	$4.6 \pm 2.2^\dagger$	0.3 to 8.8
	20 mg sibutramine	$130.5 \pm 2.0$	$-1.5 \pm 2.0$	$-1.3 \pm 2.2$	-5.6 to 3.1
Diastolic blood pressure (mmHg)					
	Placebo	$82.1 \pm 1.1$	$0.5 \pm 1.1$		
	15 mg sibutramine	$82.8 \pm 1.2$	$3.3 \pm 1.1^\dagger$	$2.8 \pm 1.2^\dagger$	0.4 to 5.3
	20 mg sibutramine	$81.3 \pm 1.2$	$0.4 \pm 1.0$	$0.0 \pm 1.3$	-2.5 to 2.4
Pulse (bpm)					
	Placebo	$74.8 \pm 1.0$	$-0.8 \pm 1.2$		
	15 mg sibutramine	$76.4 \pm 1.3$	$5.1 \pm 1.5^*$	$5.9 \pm 1.7^*$	2.5 to 9.4
	20 mg sibutramine	$75.0 \pm 1.2$	$5.0 \pm 1.4^*$	$5.8 \pm 1.8^\ddagger$	2.3 to 9.3

Data are means  $\pm$  SE or medians (range). D<sup>c</sup>, treatment group difference (i.e., sibutramine minus placebo). \* $P < 0.01$ ,  $^\dagger P < 0.05$ ,  $^\ddagger P < 0.001$ .

those of orlistat in obese type 2 diabetes (11).

Significant improvements in glycemic control accompanied weight loss. With  $\geq 10\%$  weight loss (only achieved in subjects taking sibutramine), mean  $HbA_{1c}$  fell by 1.2% and fasting glucose by 2 mmol/L—effects comparable to those of oral antihyperglycemic agents (20). Lesser improvements were seen with weight loss of 5–10%, but  $HbA_{1c}$  fell by  $>1\%$  (a recognized efficacy threshold for antidiabetic drugs) in 86% of patients receiving 15 mg sibutramine. In addition, metformin dosage could be reduced in a higher proportion of sibutramine-treated patients because of improved glycemic control. Interestingly, a good glycemic response ( $HbA_{1c}$  decrease  $>2\%$ ) was predicted not only by  $\geq 10\%$  weight loss, but also by an initial  $HbA_{1c}$  of  $>9.2\%$  (data not shown); thus, poorly controlled obese type 2 diabetic patients may gain the most from weight loss and anti-obesity medication.

Serum lipids showed relatively modest changes with sibutramine treatment and weight loss (Table 3)—notably a 10% rise in HDL cholesterol and a fall in triglycerides that averaged 29% in subjects (sibutramine-treated only) who lost  $>10\%$  in weight. Lipid changes were generally less impressive than those reported with sibutramine in other populations, for example, the STORM study in nondiabetic obese subjects (21); the fact that our patients were already receiving metformin, which has favorable lipid-modifying effects (15), may partly explain this. Nonetheless, there is now firm evidence that lipid changes of the magnitude seen in our 10% responders will tend to diminish atherogenic risk (22).

Sibutramine was generally well tolerated, with no excess of withdrawals over placebo. Commonly described side effects (dry mouth, constipation, and insomnia) were as previously reported, with no indication that these damaged compliance. Sibutramine's central sympathomimetic action can increase pulse rate and blood pressure. Hypertension is a particular concern in type 2 diabetes: in the UKPDS, improved blood pressure control (144/82 mmHg) reduced cardiovascular events by 25% as compared with "routine" levels of 154/87 mmHg (23). The risk-benefit balance of interventions that might raise blood pressure must therefore be carefully evaluated. Here, sibutramine

tended to increase blood pressure in more patients than placebo, and a few individuals showed marked rises (Fig. 2). This tendency was offset by weight loss; at completion, only 10 (37%) of those subjects losing  $\geq 10\%$  weight showed a rise of  $\geq 5$  mmHg in systolic blood pressure.

Our data underscore the common problems of hypertension in obese type 2 diabetic patients. Initially, 32% of our patients had both systolic and diastolic blood pressure readings above the American Diabetes Association's currently recommended levels (135/80 mmHg). Moreover, hypertension progressed in some cases, perhaps after further weight gain or arterial stiffening (24): 39% of our placebo patients showed  $>5$  mmHg increases in systolic pressure during the study, and an additional 11% exceeded both American Diabetes Association thresholds. At present, the balance of risk between increased blood pressure versus the metabolic and other benefits of weight loss cannot be accurately determined. However, modeling the effects of sibutramine in obese type 2 diabetic patients using data from the Framingham (25) and Munster (26) studies suggests that the overall cardiovascular impact of sibutramine is favorable (K. Lauterback, personal communication). Both sibutramine dosages significantly increased heart rate. Tachycardia has also been associated with cardiovascular events (27), but may represent a marker of risk rather an independent pathophysiological factor; no clinical trials have yet specifically assessed the impact of tachycardia or of interventions that lower heart rate.

In conclusion, sibutramine was an effective anti-obesity agent in type 2 diabetic patients, of whom nearly 20% achieved weight loss of  $\geq 10\%$ , and over 50% achieved a loss of  $\geq 5\%$ . Patients losing  $\geq 10\%$  showed improvements in glycemic control that were comparable with those achieved by oral hypoglycemic agents. Thus, sibutramine is a potentially valuable adjunct to the medical management of appropriately selected obese type 2 diabetic patients. Individual responses in weight,  $HbA_{1c}$ , and blood pressure should be carefully evaluated, and long-term treatment should be considered only in subjects who lose  $>5\%$  weight and whose blood pressure does not rise.

## APPENDIX

### Investigators for the Multicenter Sibutramine Study Group

Canada: Ellen Burgess, Ronald Elisioff, Lawrence Leiter, Simon Rabkin, Hugh Tildesley, Gregory Bondy, Stephanie Kaiser, Vincent Woo, and Ehud Ur; Belgium: Andre Scheen, Michel Letiexhe, Isabel Dumont, Luc Van Gaal, Paul Van Crombrugge, Frank Nobels, Gerard Lamberigts, Bart Keymeulen, and Kris Poppe; U.K.: Gareth Williams, Steven McNulty, and Kevin Hardy; France: Marc Leutenegger, Corinne Le Borgne, Reginald Mira, Gérard Cathelineau, Arnaud Cocaul, and Nabil Assad.

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