Optimal Treatment of Obesity-Related Hypertension
The Hypertension-Obesity-Sibutramine (HOS) Study
Jürgen Scholze, MD; Elmar Grimm, MD; Dana Herrmann, MD; Thomas Unger, MD; Ulrich Kintscher, MD

Background—Current guidelines for the treatment of hypertension do not provide specific recommendations for obese hypertensive patients. To identify an optimal treatment regimen for obese hypertensive patients, we studied the interactions between a drug-based weight loss approach by sibutramine and different antihypertensive drug regimens.

Methods and Results—This was a prospective, 16-week double-blind placebo-controlled randomized multicenter study in 171 obese hypertensive patients. After a 2-week run-in period, patients receiving 1 of the 3 antihypertensive combination therapies (felodipine 5 mg/ramipril 5 mg [n=57], verapamil 180 mg/trandolapril 2 mg [n=55], or metoprolol succinate 95 mg/hydrochlorothiazide 12.5 mg [metoprolol/hydrochlorothiazide; n=59]) were assigned randomly to sibutramine (15 mg) or placebo. Sibutramine treatment resulted in a significantly greater decrease in body weight, body mass index, and waist circumference and a significant increase in diastolic blood pressure during 24-hour blood pressure monitoring compared with placebo treatment. Sibutramine-induced weight loss and reduction of visceral obesity were markedly attenuated in the metoprolol/hydrochlorothiazide group compared with the other groups. Consistently, improvement in glucose tolerance and hypertriglyceridemia by sibutramine was abrogated in the cohort treated with metoprolol/hydrochlorothiazide compared with the other groups.

Conclusions—The present study demonstrates for the first time that an antihypertensive combination therapy regimen with angiotensin-converting enzyme inhibitors and calcium channel blockers is more advantageous than a β-blocker/diuretic–based regimen in supporting the weight-reducing actions and concomitant metabolic changes induced by sibutramine in obese hypertensive patients. These data may help to develop future comprehensive treatment strategies and guidelines for this high-risk patient population. (Circulation. 2007;115:1991-1998.)

Key Words: drugs ■ glucose ■ hypertension ■ obesity ■ metabolism

The prevalence of obesity (body mass index [BMI] ≥30 kg/m²) is increasing at dramatic rates, reaching 35.8% in the United States.1 The obesity epidemic is closely associated with a prominent rise in the incidence of hypertension, both of which result in a major increase in cardiovascular risk.2 However, current guidelines for the treatment of hypertension do not provide specific recommendations for the treatment of obese hypertensive patients.3 This lack of recommendations may be explained by the absence of prospective intervention studies combining effective antihypertensive therapy and weight loss interventions. Thus, new therapeutic regimens are required for a comprehensive targeting of body weight and blood pressure in obesity-related hypertension. Weight reduction and maintenance of weight loss are important principal steps.4 Preventive strategies and lifestyle interventions such as dietary management and physical activity should be considered first because they have been proved to be highly effective4; however, in most patients, these nonpharmacological approaches have limited sustainability, and adjuvant pharmacotherapy is required for effective weight reduction and maintenance of reduced body weight.4–6

Antihypertensive therapy in obese hypertensive patients should include compounds that exert beneficial effects beyond blood pressure lowering.7 This comprises actions that support concomitant weight-reducing therapy and positive effects on associated metabolic disorders, such as insulin resistance, glucose intolerance, and dyslipidemia.7 Correspondingly, weight-reducing medication should enhance antihypertensive treatment.7

One therapy used worldwide for weight reduction is pharmacological treatment with the selective serotonin and norepinephrine reuptake inhibitor sibutramine. Sibutramine has been shown to be a highly effective pharmacotherapy for weight loss in obese patients, mediated by increased satiety
and an enhancement of energy expenditure.\textsuperscript{8–10} However, because of its mechanism as a monoamine reuptake inhibitor, sibutramine has the potential to raise blood pressure in certain patients, which may counteract the decrease in blood pressure achieved by its weight-reducing actions.\textsuperscript{11,12}

To identify an optimal treatment regimen for obese hypertensive patients, we studied the interactions between a drug-based weight loss approach by sibutramine and different antihypertensive drug regimens in a prospective, double-blind, placebo-controlled, multicenter randomized trial in obese hypertensive patients. The primary objective of the present study was to discern the effect of different antihypertensive treatment regimens on sibutramine-induced weight loss in obese hypertensive patients. Secondary end points were to determine the effects of sibutramine-mediated weight reduction on blood pressure and lipid and glucose metabolism in obese hypertensive patients pretreated with different antihypertensive combination therapies.

**Methods**

**Patients**

Overweight and obese male and female patients (BMI 27 to 45 kg/m\(^2\)) aged 20 to 65 years with essential hypertension (systolic blood pressure [SBP] 140 to 160 mm Hg, diastolic blood pressure [DBP] 90 to 100 mm Hg) under pretreatment with a prespecified antihypertensive combination therapy were eligible for inclusion in the present study. Patients were excluded from the study if they had any of the following: secondary hypertension or obesity; a clinical history of coronary artery disease, myocardial infarction, or carditis; congestive heart failure (New York Heart Association class III and IV); supraventricular/ventricular tachycardia; renal failure; liver failure; hyperthyroidism; uncontrolled diabetes mellitus; malignancies; chronic infectious disease; alcohol/drug abuse; epilepsy; psychosis; treatment with antidepressant/neuroleptic drugs; or pretreatment with sibutramine within the last 6 months. Written informed consent was obtained from all participants.

**Study Design**

This was an investigator-initiated prospective 16-week double-blind placebo-controlled randomized study of sibutramine in obese hypertensive patients. The patient group consisted of 3 cohorts according to their antihypertensive premedication: felodipine 5 mg/trandolapril 5 mg (n = 57; 33.3%); slow-release verapamil 180 mg/trandolapril 2 mg (n = 55; 32.2%); or metoprolol succinate 95 mg/hydrochlorothiazide (HCT) 12.5 mg (n = 59; 34.5%; Table 1). General dietary guidelines (reduction of fat intake/decrease of energy density in foods and drinks) and physical activity advice (30 minutes of moderate-intensity exercise on 3 to 4 days per week) were provided. During a 2-week run-in period, the antihypertensive combination therapy and concomitant measures were stabilized, and patients had to meet the described inclusion criteria at the end of this period. When target blood pressure for inclusion was not reached, add-on antihypertensive therapy was allowed. Patients were randomized to sibutramine 10 mg or placebo. The sibutramine dose (or placebo) was increased to 15 mg after 8 weeks. The study was performed at 5 clinical research centers. The study protocol complies with the Declaration of Helsinki and with local institutional guidelines and was approved by the local ethics committees.

**Anthropometric Analysis, Blood Pressure Measurements, and Physical Mobility**

Anthropometric data that included body weight, BMI, and waist circumference and blood pressure from the day of randomization and from the end of the study were taken for statistical analysis. Blood pressure (SBP and DBP) was measured with an oscillometric semiautomatic device (Tensoval, Paul Hartmann AG, Heidenheim, Germany) in the same arm with subjects in a seated position after 5 minutes’ rest. Mean values of 3 consecutive measures and heart rate were taken for further analysis. Ambulatory 24-hour blood pressure monitoring was performed in a subset of patients (felodipine/ramipril n = 50, verapamil/trandolapril n = 46, and metoprolol/HCT n = 48; missing data were predominantly due to technical problems in 2 centers) with an automatic oscillometric device (SpaceLab, Redmond, Wash). The 24-hour means for SBP and DBP were used for further analysis. In addition, nocturnal SBP/DBP dipping status was analyzed with a nighttime period from 10 PM to 6 AM. “Nondippers” were defined as those subjects whose average SBP/DBP dipped at night <10% compared with their average daytime SBP/DBP. The percentage of patients in each group who changed from “nondipping” to “dipping” status was calculated.

A subgroup of patients (sibutramine n = 71; placebo n = 70; felodipine/ramipril n = 47; verapamil/trandolapril n = 47; and metoprolol/HCT n = 47; except for isolated cases, missing data were caused by only 1 center, which omitted this measurement in almost all patients) were asked to grade the degree of their general physical mobility (at rest and with exercise) on 11 scales between 1 and 5 each. Questionnaires were adapted from the IWQOL-Lite (Impact of Weight on Quality of Life–Lite) questionnaire.\textsuperscript{13} The summary score was transformed to a standardized scale between 0 and 100 in which low scores correspond to immobility and high scores to high mobility.

**Laboratory Measurements**

An oral glucose tolerance test was performed on the day of randomization and at the end of the study with 75 g of glucose, and blood samples were withdrawn at 0, 60, and 120 minutes for measurement of plasma glucose in a subgroup of patients (sibutramine n = 59, placebo n = 58; felodipine/ramipril n = 35, verapamil/trandolapril n = 38, and metoprolol/HCT n = 44; besides isolated missing values, the oral glucose tolerance test was omitted in patients who had diabetes mellitus). Fasting concentrations of glucose, triglycerides, glycosylated hemoglobin (HbA\(_1c\)), total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were determined in a subgroup of patients by standard laboratory methods.

**Figure 1.** Trial profile.
Statistical Analysis

Testing for baseline homogeneity across treatment groups and the 3 cohorts was performed with a t test/Mann-Whitney test or ANOVA/Kruskal-Wallis test for continuous/quantitative parameters. Treatment effects or treatment and cohort effects were calculated as changes from baseline to week 16 and assessed by 1- or 2-factor ANCOVAs with baseline values as covariates. A common coefficient for baseline in the respective study groups was assumed. The resulting least squares mean±SEM values were presented as (baseline-)adjusted changes from baseline to week 16. All study results described as mean±SEM were derived from these ANCOVA models. The comparisons of subgroups (eg, cohorts) were realized by means of linear contrasts. Qualitative differences were analyzed with χ² testing. An intention-to-treat analysis was performed with the last-observation-carried-forward method. Statistical significance was defined as P<0.05.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Results

#### Patients

A total of 171 patients were randomized into 2 treatment groups (sibutramine [n=87] and placebo [n=84]); of these, 57 (33.3%) were treated with felodipine/ramipril, 55 (32.2%) with verapamil/trandolapril, and 59 (34.5%) with metoprolol/HCT. A total of 145 patients (84.8%) completed the 16-week treatment (Figure 1). Ten patients withdrew in the sibutramine group, 5 because of adverse events (sleeping disorder, Quincke edema (ACE inhibitor–mediated), palpitation, or gastrointestinal disturbance) and 5 patients for other reasons (lost to follow-up [n=2], lack of therapy effectiveness [n=2], and protocol violation [n=1]). Sixteen patients of the placebo group withdrew from the study because of adverse events (n=5; leg edema, central nervous system disorder, palpitation, sleeping disorder, and exanthema), loss to follow-up (n=5), patient...

### TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=84)</th>
<th>Sibutramine (n=87)</th>
<th>P</th>
<th>Felodipine/Ramipril (n=57)</th>
<th>Verapamil/Trandolapril (n=55)</th>
<th>Metoprolol/HCT (n=59)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>52.3 (8.1)</td>
<td>51.6 (8.6)</td>
<td>NS*</td>
<td>53.8 (2.3)</td>
<td>51.9 (2.1)</td>
<td>51.2 (2.7)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Sex</td>
<td>37/47</td>
<td>31/56</td>
<td>NS</td>
<td></td>
<td></td>
<td>29/28</td>
<td>20/35</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>34.8 (4.3)</td>
<td>35.4 (3.9)</td>
<td>NS*</td>
<td>35.3 (4.5)</td>
<td>34.4 (3.8)</td>
<td>35.5 (3.8)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Waist, M, cm, mean (SD)</td>
<td>114.9 (11.1)</td>
<td>115.4 (9.2)</td>
<td>NS*</td>
<td>116.9 (11.4)</td>
<td>112.4 (7.7)</td>
<td>115.2 (10.8)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Waist, F, cm, mean (SD)</td>
<td>105.7 (10.8)</td>
<td>105.7 (10.8)</td>
<td>NS*</td>
<td>107.5 (10.9)</td>
<td>103.5 (9.8)</td>
<td>105.1 (10.2)</td>
<td>NS‡</td>
</tr>
<tr>
<td>SBP, mm Hg, mean</td>
<td>146.5 (10.7)</td>
<td>145.4 (10.1)</td>
<td>NS*</td>
<td>144.6 (10.6)</td>
<td>146.5 (11.2)</td>
<td>145.0 (9.7)</td>
<td>NS‡</td>
</tr>
<tr>
<td>DBP, mm Hg, mean</td>
<td>92.5 (6.7)</td>
<td>98.4 (7.4)</td>
<td>0.0053*</td>
<td>99.1 (7.5)</td>
<td>98.7 (6.7)</td>
<td>91.1 (7.4)</td>
<td>NS‡</td>
</tr>
<tr>
<td>SBP24 hours, mm Hg, mean (SD)</td>
<td>133 (12)</td>
<td>130.8 (11.1)</td>
<td>NS*</td>
<td>131.3 (12.1)</td>
<td>131.2 (10.5)</td>
<td>132.3 (12.1)</td>
<td>NS‡</td>
</tr>
<tr>
<td>DBP24 hours, mm Hg, mean (SD)</td>
<td>85.4 (13.8)</td>
<td>82.8 (12.8)</td>
<td>NS*</td>
<td>84.9 (12.5)</td>
<td>82.8 (12)</td>
<td>84.3 (15.2)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Physical mobility, mean (SD)</td>
<td>62.8 (22.9)</td>
<td>62.3 (20.7)</td>
<td>NS†</td>
<td>64.7 (24.7)</td>
<td>60.5 (20.7)</td>
<td>62.4 (19.7)</td>
<td>NS§</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>14 (16.7)</td>
<td>11 (12.6)</td>
<td>NS</td>
<td></td>
<td></td>
<td>10 (14.9)</td>
<td>10 (18.2)</td>
</tr>
<tr>
<td>oGTT, mmol/L, mean (SD)</td>
<td>0 min</td>
<td>5.4 (1)</td>
<td>NS*</td>
<td>6 (2.4)</td>
<td>5.2 (0.9)</td>
<td>5.5 (1.1)</td>
<td>NS‡</td>
</tr>
<tr>
<td></td>
<td>60 min</td>
<td>10.5 (2.8)</td>
<td>NS*</td>
<td>11.3 (4.2)</td>
<td>9.6 (3.3)</td>
<td>10.5 (2.9)</td>
<td>NS‡</td>
</tr>
<tr>
<td></td>
<td>120 min</td>
<td>7.4 (2.8)</td>
<td>NS*</td>
<td>8.6 (5.4)</td>
<td>7.2 (3.1)</td>
<td>7.9 (2.8)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>30 (35.7)</td>
<td>23 (26.4)</td>
<td>NS</td>
<td></td>
<td></td>
<td>20 (29.9)</td>
<td>19 (34.5)</td>
</tr>
<tr>
<td>Previous medication, n (%)</td>
<td>53 (63.1)</td>
<td>58 (66.7)</td>
<td>NS</td>
<td></td>
<td></td>
<td>43 (75.4)</td>
<td>40 (72.7)</td>
</tr>
<tr>
<td></td>
<td>43 (51.2)</td>
<td>46 (52.9)</td>
<td>NS</td>
<td></td>
<td></td>
<td>16 (28.1)</td>
<td>24 (43.6)</td>
</tr>
<tr>
<td></td>
<td>25 (29.8)</td>
<td>24 (27.6)</td>
<td>NS</td>
<td></td>
<td></td>
<td>21 (36.8)</td>
<td>15 (27.3)</td>
</tr>
<tr>
<td></td>
<td>13 (15.5)</td>
<td>13 (14.9)</td>
<td>NS</td>
<td></td>
<td></td>
<td>9 (15.8)</td>
<td>14 (25.5)</td>
</tr>
<tr>
<td>No. of drugs (%)</td>
<td>NS†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (2.4)</td>
<td>4 (4.6)</td>
<td>4 (7)</td>
<td>4 (7)</td>
<td>2 (3.4)</td>
<td>2 (3.4)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>32 (38.1)</td>
<td>32 (36.8)</td>
<td>23 (40.4)</td>
<td>22 (40)</td>
<td>19 (32.2)</td>
<td>2 (3.4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>31 (36.9)</td>
<td>32 (36.8)</td>
<td>18 (31.6)</td>
<td>17 (30.9)</td>
<td>28 (47.5)</td>
<td>6 (10.2)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>17 (20.2)</td>
<td>12 (13.8)</td>
<td>10 (17.5)</td>
<td>13 (23.6)</td>
<td>6 (10.2)</td>
<td>6 (10.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>2 (2.4)</td>
<td>7 (8.1)</td>
<td>2 (3.5)</td>
<td>3 (5.5)</td>
<td>4 (6.8)</td>
<td>6 (10.2)</td>
<td></td>
</tr>
</tbody>
</table>

M indicates male; F, female; SBP24 hours, 24-hour mean SBP; DBP24 hours, 24-hour mean DBP; oGTT, oral glucose tolerance test (data are plasma glucose level); and CCB, calcium channel blocker.

Twenty-four-hour blood pressure monitoring and oGTTS were performed in subgroups of patients (see Methods).

Testing for homogeneity was performed with *t* test, †Mann-Whitney test, ‡ANNOVA, §Kruskal-Wallis test, or ¥χ² test.
request (n=4), or lack of therapy effectiveness (n=2). At baseline, office DBP was higher in the placebo group than in the sibutramine group, which was not documented in the 24-hour blood pressure analysis (Table 1). Other baseline characteristics were similar among the treatment groups (Table 1). Add-on antihypertensive medication was required to reach target blood pressure before randomization in the felodipine/ramipril group (n=8; add-on therapy HCT 12.5 mg), the verapamil/trandolapril group (n=8; add-on therapy HCT 12.5 mg), and the metoprolol/HCT group (n=4; add-on therapy felodipine 5 mg).

**Body Weight, BMI, Waist Circumference, and Physical Mobility**

Sibutramine treatment resulted in a significantly greater decrease in body weight (−5.7±0.5 kg versus −1.5±0.5 kg; P<0.0001), BMI (−2.0±0.2 versus −0.5±0.2 kg/m²; P<0.0001), and waist circumference (−5.0±0.6 cm versus −0.8±0.6 cm; P<0.0001) than placebo treatment (Figure 2A). Body weight reduction of >5% occurred in 54.7% of patients in the sibutramine group compared with 14.5% in the placebo group (P<0.0001). Comparison of the 3 antihypertensive treatment regimens revealed that sibutramine-mediated enhancement of the reduction in body weight and BMI was observed in all groups (Figures 2B and 2C). However, sibutramine-induced weight loss was significantly (global comparison P=0.0124) attenuated in the metoprolol/HCT group (−3.9±0.8 kg) compared with felodipine/ramipril (−7.2±0.8 kg; pairwise comparison P=0.0037) and verapamil/trandolapril (−6.1±0.7 kg; pairwise comparison P=0.0484; Figure 2B). Consistently, the decrease in BMI by sibutramine was also attenuated in the metoprolol/HCT group (global comparison P=0.0156; Figure 2C). Pairwise comparisons of metoprolol/HCT (−1.4±0.3 kg/m²) with felodipine/ramipril (−2.4±0.3 kg/m²; P=0.0060) and verapamil/trandolapril (−2.2±0.3 kg/m²; P=0.0306) were both significant. Furthermore, the sibutramine-mediated reduction of waist circumference was not significantly discriminated from placebo in patients treated with metoprolol/HCT, which indicates that the β-blocker/diuretic regimen results in an attenuation of the beneficial actions of sibutramine on visceral obesity (Figure 2D). However, overall, the differences between the cohorts in sibutramine-treated patients were less pronounced (global com-
not statistically significant. Differences between the antihypertensive cohorts were which indicates an improved physical mobility with sibutramine placebo (sibutramine 11.9 ± 0.7 versus placebo 5.7 ± 0.8 mm Hg, P = 0.06) and verapamil/trandolapril (−1.3 ± 0.5 mm Hg; pairwise comparison P = 0.0797; Figure 4). Additional metabolic parameters were evaluated in the sibutramine (n = 74) and placebo (n = 69) groups. Consistently, with an improvement of glucose tolerance under sibutramine therapy, triglyceride levels were markedly reduced with sibutramine (−0.4 ± 0.1 mmol/L), whereas the placebo group showed almost no reduction (−0.06 ± 0.1 mmol/L, P = 0.0194 versus sibutramine). The most prominent triglyceride reduction by sibutramine was observed in the felodipine/ramipril cohort (−0.6 ± 0.2 mmol/L compared with −0.5 ± 0.2 mmol/L in the verapamil/trandolapril cohort and only −0.2 ± 0.2 mmol/L in the metoprolol/HCT cohort). Total cholesterol, low-density lipoprotein cholesterol, and HbA1c levels were decreased and high-density lipoprotein cholesterol levels were increased in the sibutramine and placebo groups; however, the differences between the treatment groups and the cohorts were not significant.

Blood Pressure and Heart Rate
Office SBP and DBP changes from baseline did not differ significantly between the sibutramine and placebo groups (SBP: −5.9 ± 1.3 mm Hg, P = 0.5494; DBP: −0.7 ± 0.8 versus −2.3 ± 0.8 mm Hg, P = 0.1785; Figure 3A). In the 24-hour blood pressure analysis, SBP was lower in both groups, whereas DBP was increased in the sibutramine group compared with placebo (SBP: −0.3 ± 1.1 versus −0.9 ± 1.2 mm Hg, P = 0.6936; DBP: 2.1 ± 0.8 versus −0.3 ± 0.8 mm Hg, P = 0.0403; Figure 3B). This rise in DBP was averaged across 24 hours. No significant differences between the sibutramine and placebo group were observed for nocturnal SBP/DBP dipping status. Comparison of changes in blood pressure responses by sibutramine and placebo in the 3 cohorts did not reveal statistically significant differences (Tables 2 and 3). Heart rate did increase in the sibutramine group (sibutramine 4.5 ± 1 bpm versus placebo −1.4 ± 1 bpm, P < 0.0001). This sibutramine-placebo difference in heart rate did not differ significantly among the 3 cohorts.

Metabolic Parameters
An oral glucose tolerance test was performed in a subgroup of patients before and after treatment. Sibutramine significantly lowered fasting glucose levels (0 minutes; before treatment 5.7 ± 0.3 mmol/L, after treatment 5.4 ± 0.2 mmol/L; P = 0.0402), whereas placebo treatment had no significant effect. Additionally, glucose tolerance at 60 minutes of the oral glucose tolerance test was markedly improved by sibutramine, whereas the placebo effect was only small (sibutramine −1.1 ± 0.3 mmol/L, P = 0.0003; placebo −0.4 ± 0.3 mmol/L, P = 0.1297). Improvement of glucose tolerance by sibutramine at 60 minutes of the oral glucose tolerance test was significantly (global comparison P = 0.0301) abrogated in the cohort treated with metoprolol/HCT (−0.1 ± 0.5 mmol/L) compared with felodipine/ramipril (−2.1 ± 0.6 mmol/L; pairwise comparison P = 0.0107) and verapamil/trandolapril (−1.3 ± 0.5 mmol/L; pairwise comparison P = 0.0797; Figure 4). Additional metabolic parameters were evaluated in the sibutramine (n = 74) and placebo (n = 69) groups. Consistently, with an improvement of glucose tolerance under sibutramine therapy, triglyceride levels were markedly reduced with sibutramine (−0.4 ± 0.1 mmol/L), whereas the placebo group showed almost no reduction (−0.06 ± 0.1 mmol/L, P = 0.0194 versus sibutramine). The most prominent triglyceride reduction by sibutramine was observed in the felodipine/ramipril cohort (−0.6 ± 0.2 mmol/L compared with −0.5 ± 0.2 mmol/L in the verapamil/trandolapril cohort and only −0.2 ± 0.2 mmol/L in the metoprolol/HCT cohort). Total cholesterol, low-density lipoprotein cholesterol, and HbA1c levels were decreased and high-density lipoprotein cholesterol levels were increased in the sibutramine and placebo groups; however, the differences between the treatment groups and the cohorts were not significant.

Discussion
The present study demonstrates that antihypertensive combination therapy with ACE inhibitors and calcium channel blockers is more advantageous than a β-blocker/diuretic-based regimen in supporting the weight-reducing actions and concomitant metabolic changes induced by sibutramine in obese hypertensive patients. The β-blocker/diuretic therapy attenuated the reduction of visceral obesity by sibutramine and abrogated the sibutramine-mediated improvement in glucose tolerance and the decrease in triglyceride levels. Sibutramine-mediated blood pressure regulation was not significantly different among the distinct antihypertensive treatment regimens.

Visceral obesity is a central component of the metabolic syndrome, and a pathophysiological link between abdominal fat and metabolic disorders such as insulin resistance, glucose intolerance, and dyslipidemia has been established.14 In addition, visceral obesity is increasingly recognized as an important risk factor for cardiovascular morbidity and mortality, and its reduction is strongly associated with a decrease in cardiovascular risk.15,16 An important and simple method to assess visceral obesity is the measurement of waist circumference.16 In the present study, sibutramine was more efficient than placebo in decreasing waist circumference. These data are consistent with other studies that demonstrated a marked reduction of visceral fat by sibutramine using either computer tomography or MRI.17,18 The combination of obesity and hypertension often requires combination therapy with an antiobesity drug and different blood pressure–lower-
sibutramine translated into an improvement in glucose tolerance brought about by sibutramine. No differences between the antihypertensive cohorts are statistically not significant.

Long-term treatment with thiazide diuretics also negatively interferes with insulin and glucose metabolism.27 In particular, HCT promotes insulin resistance and dyslipidemia in hypertensive and obese patients.27 Slight differences in previous diuretic therapy between the 3 antihypertensive treatment cohorts documented in the present study may have amplified this process and must be taken into account in interpretation of the study. However, in summary, the deleterious action of β-blockade and long-term diuretic therapy on lipid and glucose metabolism may be potentiated in combination therapy, which provides a suitable explanation for the disadvantageous effects on body weight and metabolic parameters when combined with sibutramine.

Against the background of the pharmacological actions of sibutramine as a norepinephrine uptake inhibitor, concerns have been raised that sibutramine treatment may raise blood pressure in obese patients.28 However, it is now well known that the effects of sibutramine on blood pressure during long-term treatment differ markedly from its short-term application and depend on preexisting blood pressure levels. Short-term sibutramine application significantly increases resting blood pressure in healthy normal-weight subjects, whereas a number of studies have demonstrated that long-term therapy in obese patients results in only minor changes in SBP and DBP compared with placebo.11,12 Body weight loss itself reduces blood pressure.29 Therefore, the sibutramine-induced weight loss with long-term treatment may overcome the direct effects of this substance on resting blood pressure. In the present study, in patients with modestly elevated blood pressure, 24-hour mean DBP was slightly but significantly higher in the sibutramine group than in the placebo group, which indicates that the response can be variable depending on the patient population. Against the background of the importance of DBP regulation for cardiovascular mortality and morbidity in hypertensive populations, DBP should be monitored carefully during sibutramine treatment.30

Interestingly, the actions of sibutramine on blood pressure were not significantly different among the antihypertensive treatment regimens, which suggests that with regard to blood

### TABLE 2. Office Blood Pressure Measurement

<table>
<thead>
<tr>
<th>Sibutramine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felodipine/Ramipril</td>
<td>Verapamil/Trandolapril</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>DBP, mm Hg</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>DBP, mm Hg</td>
</tr>
<tr>
<td>−4 ± 2.3</td>
<td>−0.4 ± 1.4</td>
</tr>
<tr>
<td>−5.9 ± 2.1</td>
<td>−0.2 ± 1.3</td>
</tr>
<tr>
<td>−7.8 ± 2.2</td>
<td>−1.7 ± 1.4</td>
</tr>
</tbody>
</table>

Adjusted blood pressure differences in the 24-hour blood pressure mean are shown as changes from baseline. The differences between the cohorts are statistically not significant.

### TABLE 3. Twenty-Four-Hour Ambulatory Blood Pressure Measurement

<table>
<thead>
<tr>
<th>Sibutramine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felodipine/Ramipril</td>
<td>Verapamil/Trandolapril</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>DBP, mm Hg</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>DBP, mm Hg</td>
</tr>
<tr>
<td>−0.7 ± 2</td>
<td>1.2 ± 1.4</td>
</tr>
<tr>
<td>−0.2 ± 1.8</td>
<td>2.1 ± 1.3</td>
</tr>
<tr>
<td>−0.04 ± 1.9</td>
<td>3 ± 1.4</td>
</tr>
</tbody>
</table>

Adjusted blood pressure differences in the 24-hour blood pressure mean are shown as changes from baseline. The differences between the cohorts are statistically not significant.
pressure–lowering efficacy, ACE inhibitor/calcium channel blocker combinations are equally effective as β-blocker/HCT therapy in sibutramine-treated obese hypertensive patients. However, as mentioned earlier, “pleiotropic” blood pressure–independent actions on body weight and metabolic parameters are in favor of an ACE inhibitor/calcium channel blocker combination.

In the Hypertension-Obesity-Sibutramine Study design, nonrandomized comparisons of the antihypertensive treatments were performed because this was the only way to allocate patients to study groups dependent on intrinsic characteristics of their medical history (antihypertensive pre-medication). However, because the main parameters were homogeneously distributed across the cohorts, and baseline adjustments were used throughout all analyses, we believe that this design does not constitute a limitation of the study. Nevertheless, the following limitations of the study must be taken into account: (1) No control group existed that was treated with sibutramine alone; therefore, it cannot be ruled out that all antihypertensive treatment regimens may have limited the weight loss induced by sibutramine. (2) The study had a small sample size; it was powered to detect a difference between sibutramine and placebo with regard to weight loss within the cohorts but not specifically to detect differences between the cohorts with regard to secondary (eg, circulatory or metabolic) parameters. (3) The study excluded a number of patients, including patients with coronary artery disease, congestive heart failure (New York Heart Association class III and IV), and renal failure. Thus, the present results cannot be translated to obese hypertensive patients with such comorbidities.

In summary, the present study demonstrates for the first time that antihypertensive combination therapy with ACE inhibitors and calcium channel blockers is more advantageous than a β-blocker/diuretic–based regimen in supporting the weight-reducing actions and concomitant metabolic changes induced by sibutramine in obese hypertensive patients. These data may help to develop future comprehensive treatment strategies and guidelines for this high-risk patient population.

Acknowledgments
We thank Maria Schäfer, Joachim Ruh, Brigitte Schlaak, Thea Jordan, and Renate Rusczynski for patient recruitment. We also thank Jörg Schnitker, Institut für Angewandte Statistik GmbH, Bielefeld, Germany, for the statistical analysis.

Sources of Funding
This study was supported by Abbott GmbH & Co KG. Dr Kintscher is supported by the Deutsche Forschungsgemeinschaft (DFG-GK 754-II, DFG-GK 865-II, and DFG-KI 712/3-1). Dr Unger is supported by the Deutsche Forschungsgemeinschaft (DFG-GK 754-III and DFG-GK 865-II).

Disclosures
Dr Scholze has been a member of the advisory board and speakers’ bureau of Abbott GmbH & Co KG and received research grants from Abbott GmbH & Co KG. The remaining authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

Current guidelines for the treatment of hypertension do not provide specific recommendations for the treatment of obese hypertensive patients. To identify an optimal treatment regimen for obese hypertensive patients, we studied the interactions between a drug-based weight loss approach by sibutramine and different antihypertensive drug combination regimens. This was a prospective 16-week double-blind placebo-controlled randomized multicenter study in 171 obese hypertensive patients. The present study demonstrates for the first time that an antihypertensive combination therapy with angiotensin-converting enzyme inhibitors and calcium channel blockers is more advantageous than a beta-blocker/diuretic-based regimen in supporting the weight-reducing actions and comonitant metabolic changes induced by antiobesity drug treatment in obese hypertensive patients. These results suggest that the routine combined use of a thiazide with a beta-blocker should be questioned in the management of obese hypertensive patients simultaneously treated with the antiobesity drug sibutramine. Conversely, the present data suggest that a combination regimen with angiotensin-converting enzyme inhibitors and calcium channel blockers should be preferred in such patients.
Optimal Treatment of Obesity-Related Hypertension: The Hypertension-Obesity-Sibutramine (HOS) Study
Jürgen Scholze, Elmar Grimm, Dana Herrmann, Thomas Unger and Ulrich Kintscher

Circulation. 2007;115:1991-1998; originally published online April 2, 2007;
doi: 10.1161/CIRCULATIONAHA.106.625400
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/115/15/1991

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/