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## Effect of Sibutramine on Cardiovascular Outcomes in Overweight and Obese Subjects

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### ABSTRACT

#### BACKGROUND

The long-term effects of sibutramine treatment on the rates of cardiovascular events and cardiovascular death among subjects at high cardiovascular risk have not been established.

#### METHODS

We enrolled in our study 10,744 overweight or obese subjects, 55 years of age or older, with preexisting cardiovascular disease, type 2 diabetes mellitus, or both to assess the cardiovascular consequences of weight management with and without sibutramine in subjects at high risk for cardiovascular events. All the subjects received sibutramine in addition to participating in a weight-management program during a 6-week, single-blind, lead-in period, after which 9804 subjects underwent random assignment in a double-blind fashion to sibutramine (4906 subjects) or placebo (4898 subjects). The primary end point was the time from randomization to the first occurrence of a primary outcome event (nonfatal myocardial infarction, nonfatal stroke, resuscitation after cardiac arrest, or cardiovascular death).

#### RESULTS

The mean duration of treatment was 3.4 years. The mean weight loss during the lead-in period was 2.6 kg; after randomization, the subjects in the sibutramine group achieved and maintained further weight reduction (mean, 1.7 kg). The mean blood pressure decreased in both groups, with greater reductions in the placebo group than in the sibutramine group (mean difference, 1.2/1.4 mm Hg). The risk of a primary outcome event was 11.4% in the sibutramine group as compared with 10.0% in the placebo group (hazard ratio, 1.16; 95% confidence interval [CI], 1.03 to 1.31;  $P=0.02$ ). The rates of nonfatal myocardial infarction and nonfatal stroke were 4.1% and 2.6% in the sibutramine group and 3.2% and 1.9% in the placebo group, respectively (hazard ratio for nonfatal myocardial infarction, 1.28; 95% CI, 1.04 to 1.57;  $P=0.02$ ; hazard ratio for nonfatal stroke, 1.36; 95% CI, 1.04 to 1.77;  $P=0.03$ ). The rates of cardiovascular death and death from any cause were not increased.

#### CONCLUSIONS

Subjects with preexisting cardiovascular conditions who were receiving long-term sibutramine treatment had an increased risk of nonfatal myocardial infarction and nonfatal stroke but not of cardiovascular death or death from any cause. (Funded by Abbott; ClinicalTrials.gov number, NCT00234832.)

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**O**BESITY AND EXCESS WEIGHT ARE ESCALATING public health concerns because they increase the prevalence of associated conditions such as diabetes mellitus and the risk of premature death.<sup>1,2</sup> More than 80% of even highly motivated patients are unable to achieve weight loss with dietary and lifestyle modifications alone.<sup>3</sup>

Sibutramine is a norepinephrine and serotonin reuptake inhibitor that was approved for weight management in patients who are unable to lose weight by means of diet and exercise alone. Sibutramine induces satiety (resulting in reduced food intake) and an increase in energy expenditure.<sup>4,5</sup> In some patients, sibutramine increases blood pressure, pulse rate, or both, owing to its sympathomimetic effects.<sup>6</sup> Sibutramine is not indicated for patients with a history of cardiovascular disease; otherwise, treatment with sibutramine is recommended for no more than 1 to 2 years in patients who achieve a 5% weight loss. The Sibutramine Cardiovascular Outcomes (SCOUT) trial evaluated the long-term effects of sibutramine treatment combined with diet and exercise on the rates of cardiovascular events and cardiovascular death among subjects who were at high cardiovascular risk.

## METHODS

### STUDY DESIGN AND POPULATION

The SCOUT trial was a randomized, double-blind, placebo-controlled, multicenter trial that was conducted from January 2003 through March 2009 at 298 centers in 16 countries in Europe, Central America, South America, and Australia. The trial protocol has been described elsewhere.<sup>7,8</sup>

Eligible subjects included men and women, 55 years of age or older, with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 27 and no more than 45; subjects were also eligible if they had a BMI of at least 25 and less than 27 and a waist circumference of at least 102 cm in the case of men or 88 cm in the case of women. Subjects were required to have a history of cardiovascular disease (defined as coronary artery disease, stroke, or peripheral arterial occlusive disease), type 2 diabetes mellitus with at least one other cardiovascular risk factor (hypertension, dyslipidemia, current smoking, or diabetic nephropathy), or both. Subjects who were enrolled in the study were categorized as belonging to one

of three prespecified cardiovascular-risk groups: diabetes only (DM-only group), cardiovascular disease only (CV-only group), or both (CV-DM group). Exclusion criteria were symptoms of heart failure greater than New York Heart Association functional class II, blood pressure higher than 160/100 mm Hg, a pulse rate of more than 100 beats per minute, scheduled cardiac surgery or coronary angioplasty, or a weight loss of more than 3 kg within the previous 3 months.

All subjects underwent a 6-week lead-in period with single blinding (of the subjects), during which they received sibutramine at a dose of 10 mg per day as well as advice regarding diet and exercise, so that subjects with early and persistent increases in blood pressure or pulse rate could be identified and excluded from randomization. After this lead-in period, eligible subjects were randomly assigned, in a double-blind manner, to receive sibutramine, at a dose of 10 mg per day, or placebo, in a 1:1 ratio; an increase in the dose of sibutramine to 15 mg per day was permitted according to the investigator's judgment, if weight loss was not sufficient. All subjects participated in individualized cardioprotective diet and exercise programs that were designed to result in a reduction in calories of 600 kcal per day.<sup>9</sup> Physicians were instructed to ensure that subjects received optimal management of medical conditions such as diabetes, hypertension, or dyslipidemia, according to national guidelines. Anthropometric measurements were obtained and vital signs assessed monthly for the first 3 months and every 3 months thereafter in the case of subjects taking a study drug and annually in the case of subjects who discontinued the study drug. Assessments to ascertain illness and death were performed in all patients every 3 months, and laboratory testing and electrocardiography were performed annually.

Subjects who continued in the study were followed until the final visit, which occurred between November 2008 and March 2009; in the case of subjects who had discontinued the study drug, follow-up data were obtained until March 2009. The duration of individual treatment was calculated as the time from randomization to the final visit.

### OUTCOME MEASURES AND ADVERSE EVENTS

The primary outcome was the time from randomization to the first occurrence of a primary outcome event. The primary outcome events were

nonfatal myocardial infarction, nonfatal stroke, resuscitation after cardiac arrest, and cardiovascular death. Death from any cause was a secondary outcome. A full list of the secondary outcomes is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. Potential outcome events were evaluated by the event adjudication committee with the use of prespecified criteria.

Adverse events were reported if they were serious or contributed to discontinuation of the study drug. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 12.0, with the use of the medical terms provided by the investigators.

#### STUDY OVERSIGHT

The study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines. The study protocol was approved by the relevant ethics committee for each participating site. All subjects gave written informed consent. The study was designed by the executive steering committee (see the Appendix), in cooperation with the sponsor (Abbott Laboratories). Data were collected, managed, and analyzed by the sponsor, with the assistance of MDS Pharma Services and oversight by the executive steering committee. The study was monitored by an independent data and safety monitoring committee. The initial draft of the manuscript was written by the first author. All the authors contributed to subsequent drafts and had unrestricted access to the data during this process. All the authors made the decision to submit the manuscript for publication and assume responsibility for the accuracy and completeness of the data. The protocol, including the statistical analysis plan, is available at NEJM.org. All the authors attest that the study was performed in accordance with the protocol and the statistical analysis plan.

#### STATISTICAL ANALYSIS

We estimated that we would need to enroll 9000 subjects (4500 in each group) and to continue the study until 2160 confirmed primary outcome events had occurred to have 80% power to detect an 11.4% reduction in the hazard ratio with sibutramine as compared with placebo, or vice versa, assuming a 7% annual event rate<sup>10-14</sup> with placebo and a 30% rate of discontinuation of sibutramine, at a two-sided type I error rate of 0.05. Owing to a low rate of primary outcome

events, recruitment was restricted after 15 months to the highest cardiovascular-risk group (CV-DM), with the result that the CV-DM group represented 60% of the overall study population. In addition, recruitment was extended from 2 years to 2.8 years, and study follow-up was extended from 5 years to 6 years. It was agreed to stop the trial after 6 years, at which time 49% of the predicted primary outcome events had occurred. This rate allowed the detection of a 15.9% reduction in the hazard ratio with 80% power.

Prespecified time-to-event analyses of the rates of primary outcome events and of death from any cause in the intention-to-treat population were performed with the use of a Cox model, with factors for treatment, country, sex, and age (at the beginning of the lead-in period) as covariates. Estimates of hazard ratios, 95% confidence intervals, and log-rank P values were calculated within the Cox model framework. Secondary analyses of interactions between treatment and cardiovascular-risk group were evaluated with the use of Cox models. A sensitivity analysis was conducted that was restricted to the period during which the subjects were receiving the study drug.

Mean changes in body weight and vital signs from the baseline of the lead-in period to each scheduled study visit were evaluated longitudinally with the use of a mixed-effects model for repeated measures,<sup>15</sup> including factors for treatment; country; sex; age; baseline values for body weight, systolic blood pressure, diastolic blood pressure, and pulse rate; visit; interaction between treatment and visit; and interaction between baseline values and visit. The following covariance structures were considered: unstructured, compound symmetric, first-order autoregressive, and Toeplitz. The covariance structure that provided the best fit according to Akaike's information criterion was used in the analysis.

All statistical analyses were performed with the use of SAS software, version 9.1.3 (SAS Institute). All statistical tests were two-tailed. P values of less than 0.05 were considered to indicate statistical significance, unless otherwise specified. No statistical imputation was performed for missing data.

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## RESULTS

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#### SUBJECTS

A total of 9804 of the 10,744 subjects (91.3%) completed the lead-in period, were randomly as-

signed to a group, and were given a study drug; 4906 subjects were given sibutramine, and 4898 placebo (Fig. 1). The mean age of the subjects was 63.2 years (range, 51 to 88). At baseline, demographic and other characteristics were generally similar between the sibutramine and placebo groups and among the cardiovascular-risk groups (Table 1).

The mean duration of study treatment after randomization was 3.4 years (interquartile range, 2.1 to 4.7), during which 40.2% of the subjects in the sibutramine group and 42.3% of those in the placebo group permanently discontinued the study drug. A total of 41,408 person-years of data were accrued for primary outcome events (20,626 in the sibutramine group and 20,782 in the placebo group). At the end of the study, the status with respect to death was unknown in 95 subjects (1.0%) and the status with respect to nonfatal primary outcome events was unknown in 397 subjects (4.0%).

#### CHANGES IN WEIGHT, BLOOD PRESSURE, AND PULSE

During the 6-week lead-in period, when all the subjects received sibutramine, there was a mean weight loss of 2.6 kg in the cohort that subsequently underwent randomization. After randomization, there was a further reduction in weight in the sibutramine group (maximum mean additional weight loss, 1.7 kg at 12 months) and a mean increase in weight in the placebo group (0.7 kg by month 12). Thereafter, both groups had a limited increase in mean weight (Fig. 2A). Similar mean weight-change profiles were observed in analyses of the subjects according to cardiovascular-risk group.

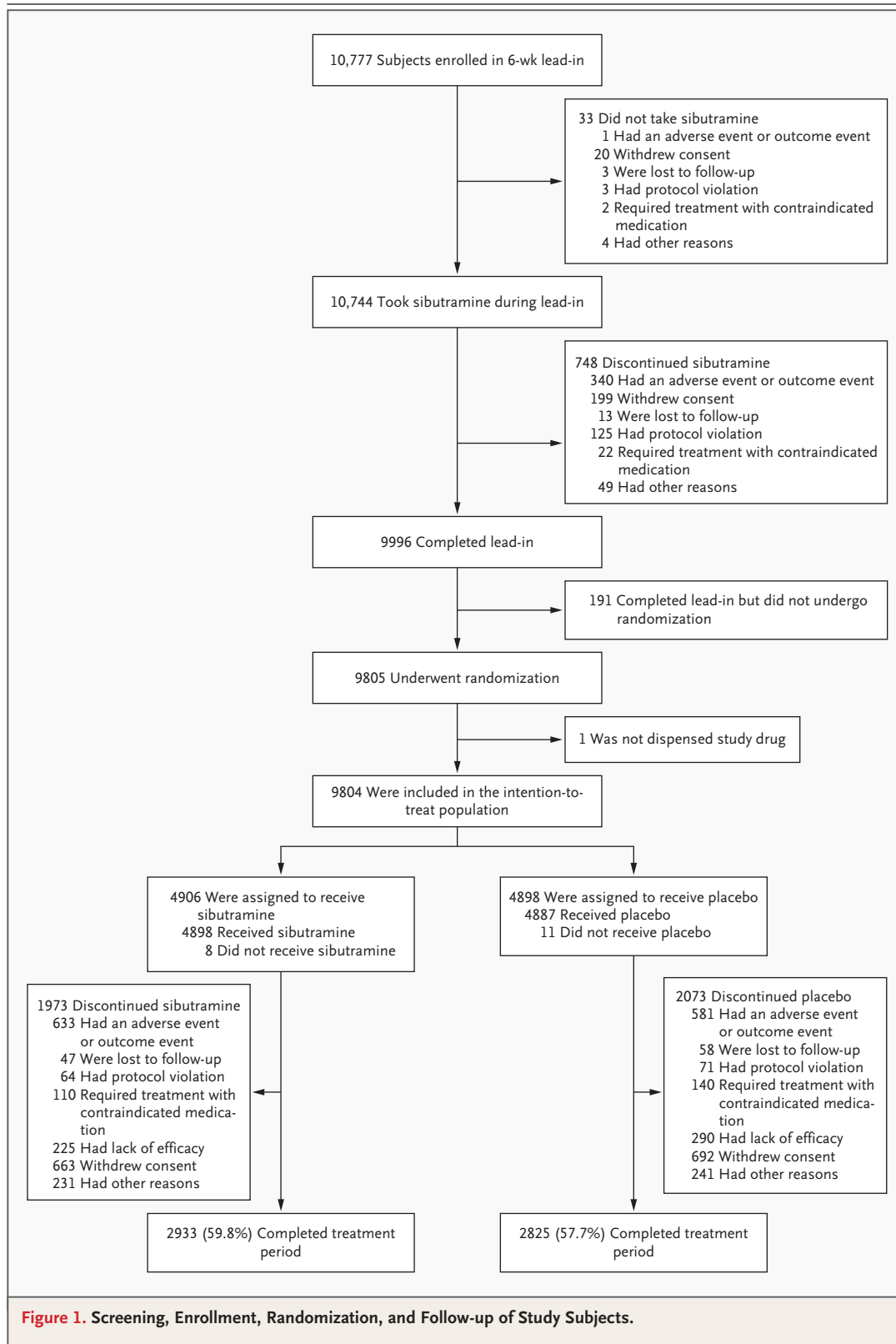
There was a mean decrease in blood pressure during the lead-in period (reductions of 4.7 mm Hg systolic and 1.7 mm Hg diastolic). Mean blood pressure remained below initial values in both groups throughout the treatment period but was consistently higher in the sibutramine group than in the placebo group, with mean differences between the groups ranging from  $-0.3$  to  $1.2$  mm Hg systolic and from  $0.6$  to  $1.4$  mm Hg diastolic. Pulse rate was also consistently higher in the sibutramine group than in the placebo group, with mean differences between the groups ranging from  $2.2$  to  $3.7$  beats per minute (Fig. 2B, 2C, and 2D). Similar changes and differences

were observed in analyses of the subjects according to cardiovascular-risk group.

#### PRIMARY OUTCOME EVENTS AND DEATH FROM ANY CAUSE

The risk of a primary outcome event was increased by 16% in the sibutramine group as compared with the placebo group (hazard ratio, 1.16; 95% confidence interval [CI], 1.03 to 1.31;  $P=0.02$ ), with overall incidences of 11.4% and 10.0%, in the two groups, respectively (Fig. 3). The individual rates of nonfatal myocardial infarction and stroke, which were components of the primary outcome event, were also increased in the sibutramine group (hazard ratio for nonfatal myocardial infarction, 1.28; 95% CI, 1.04 to 1.57;  $P=0.02$ ; hazard ratio for nonfatal stroke, 1.36; 95% CI, 1.04 to 1.77;  $P=0.03$ ). No significant between-group difference was observed with respect to cardiovascular death (hazard ratio, 0.99; 95% CI, 0.82 to 1.19;  $P=0.90$ ). Resuscitation after cardiac arrest occurred in 0.2% or less of the subjects in each group. No significant difference was observed between the study groups with respect to death from any cause (hazard ratio with sibutramine, 1.04; 95% CI, 0.91 to 1.20;  $P=0.54$ ). A sensitivity analysis that was restricted to the period during which the subjects were receiving the study drug showed similar results with respect to primary outcome events (hazard ratio with sibutramine, 1.17; 95% CI, 1.02 to 1.35;  $P=0.02$ ).

In an analysis of the three cardiovascular-risk groups, the increases in nonfatal primary outcome events were seen in the CV-only and CV-DM groups but not in the DM-only group (Fig. 3). The times to the primary outcome events and to death from any cause for the overall population are shown in Figure 4. Respective results according to cardiovascular-risk group are provided in the Supplementary Appendix. Although the treatment-event profiles for the primary outcome differed among the three cardiovascular-risk groups, no significant interaction was seen between treatment and cardiovascular risk group ( $P=0.58$  for the interaction), but the analysis had limited statistical power, as evidenced by the wide confidence interval in the CV-only group (hazard ratio, 1.28; 95% CI, 0.92 to 1.78;  $P=0.15$ ) and the DM-only group (hazard ratio, 1.01; 95% CI, 0.74 to 1.38;  $P=0.95$ ).



**Figure 1.** Screening, Enrollment, Randomization, and Follow-up of Study Subjects.

**Table 1. Demographic and Clinical Characteristics of the Subjects at Screening, According to Treatment and Cardiovascular-Risk Group.\***

Variable	Overall		DM Only		CV Only		CV+DM	
	Placebo (N=4898)	Sibutramine (N=4906)	Placebo (N=1178)	Sibutramine (N=1207)	Placebo (N=793)	Sibutramine (N=759)	Placebo (N=2901)	Sibutramine (N=2906)
Male sex — no. (%)	2843 (58.0)	2807 (57.2)	454 (38.5)	472 (39.1)	543 (68.5)	476 (62.7)	1832 (63.2)	1845 (63.5)
White race — no. (%)†	4722 (96.4)	4733 (96.5)	1137 (96.5)	1163 (96.4)	779 (98.2)	744 (98.0)	2781 (95.9)	2794 (96.1)
Age — yr	63.3±6.2	63.2±6.1	62.1±5.6	61.8±5.5	63.2±6.2	63.3±5.9	63.8±6.3	63.7±6.3
Age >65 yr — no. (%)	1650 (33.7)	1631 (33.2)	304 (25.8)	282 (23.4)	255 (32.2)	256 (33.7)	1085 (37.4)	1079 (37.1)
Body weight — kg	96.2±15.5	96.3±15.4	97.2±15.8	98.2±16.4	95.4±15.2	94.9±14.9	96.0±15.5	95.8±15.1
Body-mass index‡								
Men	33.7±4.1	33.6±4.1	34.7±4.3	35.0±4.5	33.1±3.9	33.2±3.8	33.5±4.1	33.4±4.0
Women	35.4±4.8	35.7±4.9	36.5±4.9	36.9±4.9	34.2±4.6	34.0±4.5	35.0±4.6	35.3±4.8
Waist circumference — cm								
Men	114.4±10.8	114.4±10.6	116.6±11.3	117.6±11.9	112.5±10.0	112.9±10.1	114.4±10.8	114.0±10.1
Women	109.1±11.3	109.5±11.6	110.8±11.6	111.8±11.6	104.5±11.1	103.4±10.9	109.1±10.8	109.5±11.3
Blood pressure								
Systolic — mm Hg	138.2±12.6	138.2±12.9	140.5±12.2	140.9±12.3	136.1±13.0	136.0±13.1	137.8±12.5	137.7±12.9
Diastolic — mm Hg	77.9±8.4	77.8±8.4	78.2±8.3	78.6±8.2	78.6±8.5	78.2±8.5	77.5±8.3	77.4±8.5
Systolic >145 mm Hg — no. (%)	1494 (30.5)	1532 (31.2)	431 (36.6)	474 (39.3)	210 (26.5)	187 (24.6)	842 (29.0)	859 (29.6)
Diastolic >90 mm Hg — no. (%)	175 (3.6)	177 (3.6)	51 (4.3)	54 (4.5)	50 (6.3)	49 (6.5)	70 (2.4)	70 (2.4)
Pulse — beats/min	71.2±10.1	71.1±10.2	74.2±10.2	74.4±10.3	67.9±9.5	68.2±9.8	70.8±9.8	70.5±10.0
Glycated hemoglobin in subjects with diabetes — %	7.5±1.4	7.5±1.5	7.5±1.4	7.5±1.4	7.0±1.4	6.8±0.9	7.5±1.4	7.5±1.5
Cholesterol — mg/dl§								
Total	195.0±44.3	194.5±44.1	206.4±43.1	204.3±41.8	197.4±39.7	199.5±42.8	189.6±45.1	189.0±44.7
LDL	110.2±38.0	109.9±37.0	120.0±37.9	118.3±35.8	115.7±35.6	116.3±37.0	104.7±37.7	104.6±36.7
VLDL	36.2±14.6	35.9±14.6	35.3±13.9	35.4±14.3	33.4±12.8	33.0±13.5	37.5±15.2	37.0±15.0
HDL								
Men	43.0±10.0	43.0±9.9	43.8±10.1	43.8±9.7	45.0±9.3	45.7±10.0	42.2±10.2	42.1±9.7
Women	50.6±11.5	50.7±11.6	51.7±11.7	51.2±11.5	53.2±11.0	55.1±12.5	49.1±11.2	49.2±11.2
Triglycerides — mg/dl								
Men	206.0±135.4	204.8±133.8	208.9±139.7	211.7±182.5	177.9±89.7	182.3±104.3	213.8±144.6	209.2±125.2
Women	194.8±106.4	191.2±103.0	187.8±92.0	184.9±93.1	167.5±68.5	156.1±63.9	206.5±120.6	205.6±115.0

Medications — no. (%)	3034 (61.9)	2983 (60.8)	392 (33.3)	409 (33.9)	548 (69.1)	542 (71.4)	2084 (71.8)	2017 (69.4)
Beta-blocker	3792 (77.4)	3826 (78.0)	862 (73.2)	896 (74.2)	512 (64.6)	502 (66.1)	2397 (82.6)	2408 (82.9)
ACE inhibitor or ARB¶	1796 (36.7)	1861 (37.9)	386 (32.8)	403 (33.4)	249 (31.4)	267 (35.2)	1151 (39.7)	1185 (40.8)
Calcium-channel blocker	3877 (79.2)	3832 (78.1)	485 (41.2)	470 (38.9)	734 (92.6)	698 (92.0)	2644 (91.1)	2644 (91.0)
Aspirin	3235 (66.0)	3288 (67.0)	515 (43.7)	549 (45.5)	575 (72.5)	564 (74.3)	2136 (73.6)	2162 (74.4)
Statin	466 (9.5)	492 (10.0)	126 (10.7)	119 (9.9)	51 (6.4)	40 (5.3)	288 (9.9)	330 (11.4)
Fibrate	1227 (25.1)	1250 (25.5)	302 (25.6)	311 (25.8)	1 (0.1)	10 (1.3)	919 (31.7)	925 (31.8)
Insulin	2856 (58.3)	2888 (58.9)	901 (76.5)	955 (79.1)	10 (1.3)	6 (0.8)	1938 (66.8)	1919 (66.0)
Other medication for diabetes**	2360 (48.2)	2310 (47.1)	557 (47.3)	548 (45.4)	298 (37.6)	283 (37.3)	1492 (51.4)	1467 (50.5)
Diuretic								

\* Plus-minus values are means  $\pm$ SD. The diabetes mellitus (DM)—only group comprised subjects with a history of type 2 diabetes mellitus and with at least one other risk factor (i.e., hypertension controlled on medication, dyslipidemia, current cigarette smoking, or diabetic nephropathy with evidence of microalbuminuria) but no history of protocol-specified coronary artery disease, cerebrovascular disease, or peripheral arterial occlusive disease. The cardiovascular (CV)—only group comprised subjects who had a history of protocol-specified coronary artery disease, cerebrovascular disease, or peripheral arterial occlusive disease but did not have a history of type 2 diabetes mellitus with at least one other risk factor. The CV-DM group comprised subjects with a history of protocol-specified coronary artery disease, cerebrovascular disease, or peripheral arterial occlusive disease and a history of type 2 diabetes mellitus with at least one other risk factor. In the case of 60 subjects (26 in the placebo group and 34 in the sibutramine group), there was insufficient information to classify them into one of the three cardiovascular-risk groups. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and VLDL very-low-density lipoprotein.

† Race was determined by the investigator.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

¶ The category of angiotensin-converting–enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) includes drug classes of ACE inhibitors, angiotensin II–receptor blockers, and spironolactone.

|| The category of aspirin includes drug classes of aspirin, any anticoagulant agent, and any antiplatelet drug.

\*\* The category of other medication for diabetes includes biguanides (i.e., metformin), sulfonylureas, thiazolidinediones, and meglitinide.

## ADVERSE EVENTS

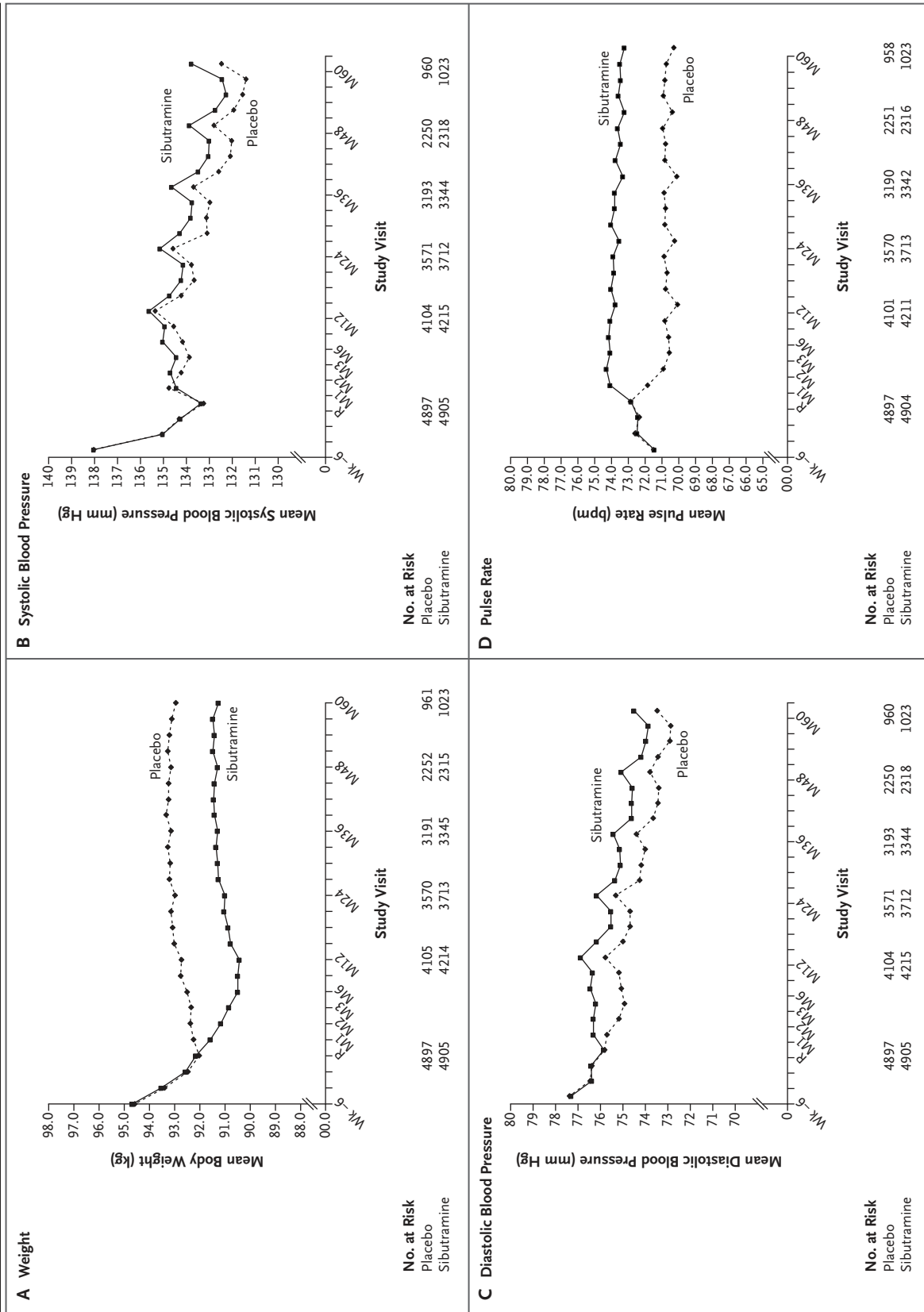
Serious adverse events and adverse events leading to permanent discontinuation of the study drug were evaluated regardless of whether they were adjudicated as cardiovascular outcome events. Adverse events resulting in discontinuation of the study drug occurred in 13.6% of the subjects in the sibutramine group and 12.4% of the subjects in the placebo group. The most common adverse event in both groups was myocardial infarction. Serious adverse events were reported in 42.1% of the subjects in the sibutramine group and 40.5% in the placebo group. Adverse events with an incidence of at least 0.5% or with a significant between-group difference (for a summary, see the Supplementary Appendix) are those reported by investigators and do not necessarily reflect adjudicated primary outcome events. A review of serious adverse events showed that there were significantly more reports of myocardial ischemia and ischemic stroke in subjects taking sibutramine than in subjects taking placebo and significantly more reports of second-degree atrioventricular block and acute pancreatitis in subjects taking placebo than in subjects taking sibutramine.

## DISCUSSION

The SCOUT trial evaluated the long-term effects of sibutramine, as compared with placebo, on the incidence of cardiovascular disease and death among high-risk subjects who were participating in diet and exercise programs. Intentional modest weight loss has been shown to reduce the severity of obesity-related illness and associated cardiovascular risk factors.<sup>16–18</sup> To date, however, long-term weight management has not been shown to reduce morbidity or mortality except after bariatric surgery.<sup>19,20</sup>

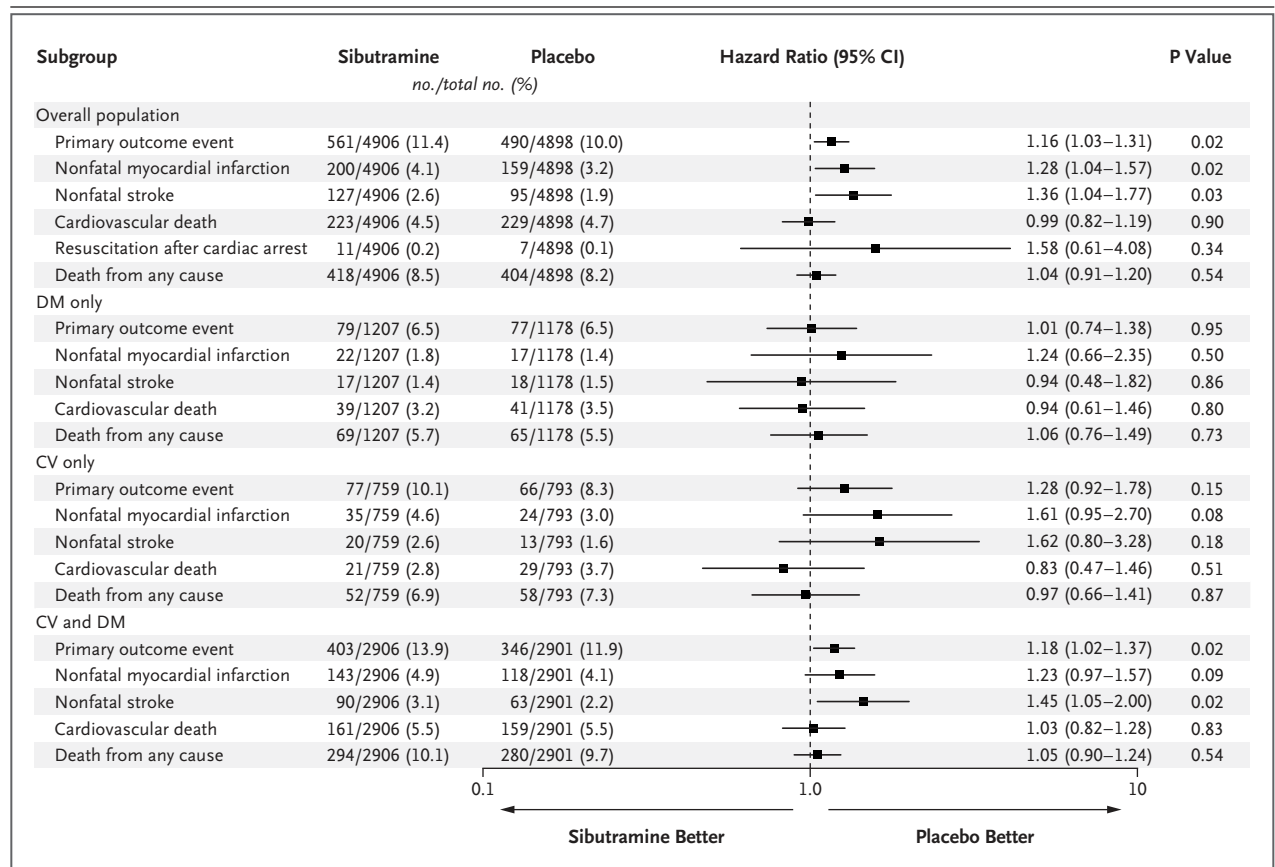
In the SCOUT trial, event rates in the sibutramine group were lower than expected, and the sibutramine group lost more weight than the placebo group and maintained the weight loss. However, the risk of a primary outcome event was increased by 16% in the sibutramine group as compared with the placebo group ( $P=0.02$ ). This increase was due to a higher incidence of nonfatal events (myocardial infarction and stroke), with no significant difference between the study groups in the incidence of cardiovascular death or death from any cause. An analysis of the three cardiovascular-risk groups showed that the risk





**Figure 2. Mean Weight, Blood Pressure, and Pulse Rate from Lead-in Period to the Final Visit.**

Analyses were performed on data from the intention-to-treat population. In Panel A,  $P=0.001$  for the comparison between sibutramine and placebo at all time points from month (M) 1 to month 60. In Panel B,  $P=0.05$  at months 2, 3, 15, 18, 24, 30, 33, 51, 57, and 60;  $P=0.01$  from month 36 to month 48, and  $P=0.001$  at months 6 and 27. In Panel C,  $P=0.001$  at all time points from month 1 to month 48 and at months 54 and 57, and  $P=0.01$  at months 51 and 60. In Panel D,  $P=0.001$  at all time points from month 1 to month 60. R denotes randomization.



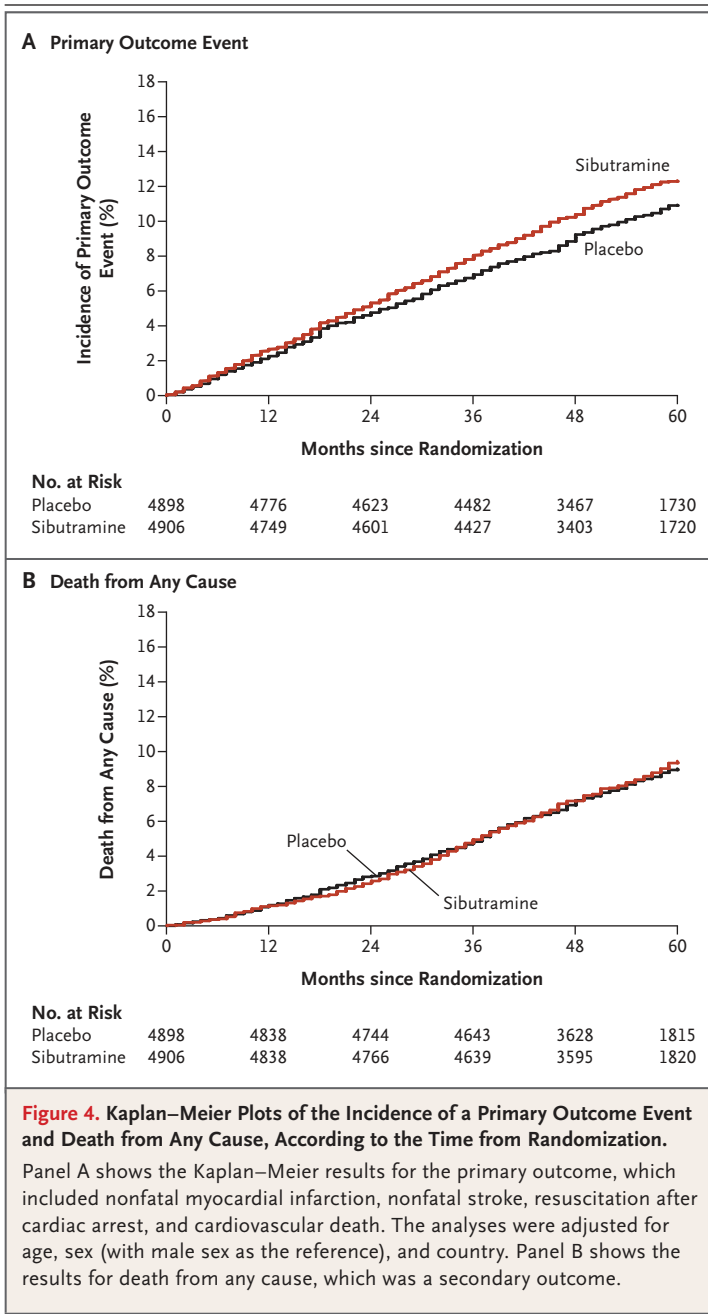
**Figure 3. Hazard Ratios in the Total Cohort and the Three Cardiovascular-Risk Groups.**

Hazard ratios for the primary end point, individual components of the primary end point, and death from any cause (a secondary end point) are shown in the overall population and in the three cardiovascular-risk subgroups; hazard ratios for resuscitation after cardiac arrest are shown for the overall population only, owing to the small number of events in the three cardiovascular-risk subgroups. The diabetes mellitus (DM)-only group comprised subjects with a history of type 2 diabetes mellitus and with at least one other risk factor (i.e., hypertension controlled on medication, dyslipidemia, current cigarette smoking, or diabetic nephropathy with evidence of microalbuminuria) but no history of protocol-specified coronary artery disease, cerebrovascular disease, or peripheral arterial occlusive disease. The cardiovascular (CV)-only group comprised subjects who had a history of protocol-specified coronary artery disease, cerebrovascular disease, or peripheral arterial occlusive disease but did not have a history of type 2 diabetes mellitus with at least one other risk factor. The CV-DM group comprised subjects with a history of protocol-specified coronary artery disease, cerebrovascular disease, or peripheral arterial occlusive disease and a history of type 2 diabetes mellitus with at least one other risk factor. In the case of 60 patients (34 in the sibutramine group and 26 in the placebo group), there was insufficient information to classify them into one of the three cardiovascular-risk groups.

of nonfatal events was increased among sibutramine-treated subjects who had preexisting cardiovascular conditions (i.e., the CV-only and CV-DM groups) but was not evident in the DM-only group, in which the subjects did not have a history of cardiovascular disease. An analysis of the effect of treatment did not show significant differences among the three risk groups.

Possible explanations for the excess of nonfatal events in subjects receiving sibutramine include the recognized effect of increased blood pressure on cardiovascular outcomes<sup>21-25</sup> and the

combined peripheral and central sympathomimetic effects of sibutramine.<sup>26</sup> Despite a decrease in mean blood pressure in both study groups during the lead-in period, the mean blood pressure after the subjects underwent randomization remained consistently and significantly higher in the subjects taking sibutramine than in those taking placebo, although the mean difference was small (1 to 2 mm Hg). The mean pulse rate was also consistently higher in the sibutramine group than in the placebo group over the course of the treatment period, and an elevated resting pulse



rate is an independent predictor of cardiovascular risk.<sup>27–29</sup> Elevated blood pressure or pulse rate has typically been associated with increases in both nonfatal and fatal events; a selective effect on nonfatal events has been observed previously.<sup>29</sup>

The weight loss that was achieved in both study groups during the lead-in period was largely maintained over the course of the study (mean

duration, 3.4 years). The long-term maintenance of reduced weight in placebo-treated subjects is unusual but may relate to the fact that our cohort was older than the cohorts in most obesity trials; it is known that weight tends to stabilize in subjects who are older than 60 years of age,<sup>30</sup> whereas younger subjects gain about 1 kg per year.<sup>31,32</sup>

During the 6-year study period in the SCOUT trial, the incidence of cardiovascular disease was reduced in most of Europe and Australia, and there were improvements in the medical management of cardiovascular disease.<sup>33–35</sup> In addition, the optimal medical management of blood pressure, blood glucose levels, and lipid levels was repeatedly emphasized throughout the trial. The original expectation of an annual incidence rate of 7.0% in the placebo group was based on data that were available almost a decade ago, when the trial was initially designed. Despite the fact that we selectively recruited subjects with the highest cardiovascular risk (with the result that 60% of the subjects were in the CV–DM group) and extended the trial period, less than half the predicted primary outcome events occurred. The decision not to extend the trial further in order to accumulate more primary outcome events was made because approximately 40% of the subjects had discontinued treatment, and further discontinuations could have undermined the trial's validity.

Our study has some limitations. First, because the overall event rate was lower than originally intended, the statistical power of the study, especially for potential subgroup analyses, was reduced. Second, for ethical and practical reasons, no true placebo group (i.e., a group that received no treatment at all) was included. Safety considerations also required that all the subjects receive an initial 6-week course of treatment with sibutramine in addition to advice on lifestyle modification in order to exclude from randomization subjects who had a sensitivity to sibutramine; thus, the weight changes that were seen in the placebo group after randomization may have resulted from the initial effects of sibutramine rather than from diet and exercise alone. No data on background events in similar populations that did not receive active weight management or initial sibutramine treatment are available for comparison. Third, in order to achieve the primary

objective of the SCOUT trial, high-risk subjects were selectively recruited; the vast majority did not meet the treatment criteria specified on the current sibutramine label. Only high-risk subjects who tolerated sibutramine during the 6-week lead-in period and met additional criteria for randomization were eligible for long-term treatment in the study; the exclusion of the subjects at highest risk may have minimized differences in outcomes between the study groups. Fourth, the subjects in the SCOUT trial continued to receive therapy for up to 6 years, regardless of the weight loss they achieved, in order to minimize the number of subjects who discontinued the study drug, and this could have altered the risk-benefit ratio of sibutramine. The discontinuation rates of 40 and 42% in the sibutramine and placebo groups, respectively, although less than those predicted on the basis of previous obesity trials,<sup>36,37</sup> exceeded the rates reported in trials of cardiovascular outcomes in nonobese subjects<sup>13</sup> and may have led to some convergence of the two groups. Finally, the repeated reinforcement of individualized cardioprotective diet and exercise programs and the observed maintenance of weight loss in both groups may also have limited the treatment differences. Despite these limitations, the trial allowed us to assess the effect of intentional modest weight loss with sibutramine on the risks of cardiovascular events and death with the usual intention-to-treat approach among patients at high cardiovascular risk.

In conclusion, the SCOUT trial showed that among subjects who were receiving long-term treatment with sibutramine, those with preexisting cardiovascular conditions had an increased risk of nonfatal myocardial infarction and nonfatal stroke but not of cardiovascular death or death from any cause. On the basis of these re-

sults, sibutramine should continue to be excluded from use in patients with preexisting cardiovascular disease.

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#### APPENDIX

The following investigators participated in the Sibutramine Cardiovascular Outcomes (SCOUT) trial: **Executive Steering Committee:** W.P.T. James (chair), I.D. Caterson, W. Coutinho, N. Finer, L.F. Van Gaal, A.P. Maggioni, A.M. Sharma, C. Torp-Pedersen. **Data and Safety Monitoring Board:** C. Pepine (chair), S. Pocock, H. Drexler (deceased), K. Swedberg, P. Sleight, P. Armstrong, D. Kerr. **Event Adjudication Committee:** G. Dagenais (chair), J. Brophy, A. Avezum, P. Bogaty, G. Fabbri, M. Galli, P. Hildebrandt, J. Mann, J. Ostergren, D. Sherman, F. Zannad. **National Leaders:** D. Colquhoun, G. Hollanders, A. Costa e Forti, R. Cifkova, S. Toubro, O. Ziegler, W.A. Scherbaum, J. Jordan, L. Halmy, E. Ferrannini, F. Santini, C. Gonzalez, K. Narkiewicz, N. Hancu, J. Payer, J. Pascual, J. Wilding. **Investigators:** *Australia:* L. Campbell, D. Carey, D. Colquhoun, M. Gerstman, J. Karrasch, J. Lefkowitz, J. Marks, S. Marks, R. Moses, P. Phillips, J. Proietto, D. Roberts, P. Roberts-Thomson, J. Shaw, R. Simpson, B. Singh, W. Singleton Jeffries, B. Stuckey. *Belgium:* J. Boland, C. Brohet, F. Coucke, P. Dendale, G. Hollanders, G. Jouret, J. Kolanowski, M. Kutnowski, F. Martens, E. Muls, F. Peiffer, H. Penninckx, A. Scheen, D. Schoors, M. Vaerenberg, J. Van Cleemput, P. Van Crombrugge, M. Van Kuyk, A. Verhaegen, B. Wollaert. *Brazil:* D. Campos de Albuquerque, J. Appolinario, A. Costa e Forti, A. Fernando de Godoy Matos, J. Luiz Gross, A. Halpern, J.F. Kerr Saraiva, R. Milagres, G. Repetto, H. Lacerda Suplicy, M.T. Zanella. *Czech Republic:* J. Bednarova, V. Cepelak, P. Cerny, R. Cifkova, V. Hainer, P. Havranek, M. Homza, P. Jansa, M. Karlicek, J. Kolesar, I. Kotik, D. Kucera, J. Kuchar, M. Kunc, M. Kvapil, A. Linhart, V. Machova, J.

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## REFERENCES

1. International Obesity Taskforce prevalence data: global obesity prevalence in adults. London: The International Association for the Study of Obesity. (Accessed August 2, 2010, at <http://www.iof.org/database/index.asp>.)
2. McPherson K, Marsh T, Brown M. Foresight: tackling obesity: future choices — modelling future trends in obesity and the impact on health. 2nd ed. London: U.K. Government Office for Science, 2007.
3. Wing RR, Hill JO. Successful weight loss maintenance. *Annu Rev Nutr* 2001; 21:323-41.
4. Lean M, Finer N. ABC of obesity. Management: part II — drugs. *BMJ* 2006; 333:794-7.
5. Halford JCG, Boyland EJ, Cooper SJ, et al. The effects of sibutramine on the microstructure of eating behaviour and energy expenditure in obese women. *J Psychopharmacol* 2010;24:99-109.
6. Florentin M, Liberopoulos EN, Elisaf MS. Sibutramine-associated adverse effects: a practical guide for its safe use. *Obes Rev* 2008;9:378-87.
7. James WPT. The SCOUT study: risk-benefit profile of sibutramine in overweight high-risk cardiovascular patients. *Eur Heart J* 2005;7:Suppl:L44-L48.
8. Torp-Pedersen C, Catterson I, Coutinho C, et al. Cardiovascular responses to weight management and sibutramine in high-risk subjects: an analysis from the SCOUT trial. *Eur Heart J* 2007;28:2915-23.
9. Lean ME, James WP. Prescription of diabetic diets in the 1980s. *Lancet* 1986; 1:723-5.
10. Heart Protection Study. Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360:7-22.
11. The HOPE (Heart Outcomes Prevention Evaluation) Study: the design of a large, simple randomized trial of an angiotensin-converting enzyme inhibitor (ramipril) and vitamin E in patients at high risk of cardiovascular events. *Can J Cardiol* 1996;12:127-37.
12. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999;341:410-8.
13. The Long-Term Intervention with Pravastatin Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57.
14. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease. *Lancet* 1994;344: 1383-9.
15. Mallinckrodt CH, Lane PW, Schnell D, Peng Y, Mancuso JP. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. *Drug Inf J* 2008;42:303-19.
16. Tuck ML, Sowers J, Dornfeld L, Kledzik G, Maxwell M. The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients. *N Engl J Med* 1981;304:930-3.
17. Lyznicki JM, Young DC, Riggs JA, Davis RM. Obesity: assessment and management in primary care. *Am Fam Physician* 2001;63:2185-96.
18. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr* 1992;56:320-8.
19. Sjöström L, Narbro K, Sjöström CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007;357:741-52.
20. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007;357:753-61.
21. Ness AR, Gunnell D, Hughes J, Elwood PC, Davey SG, Burr ML. Height, body mass index, and survival in men with coronary disease: follow up of the

- Diet and Reinfarction Trial (DART). *J Epidemiol Community Health* 2002;56:218-9.
22. Lawes CMM, Vander Hoorn S, Law MT, Elliott P, McMahon S, Rodgers A. Blood pressure and the burden of coronary heart disease. In: Marmot M, Elliott P, eds. *Coronary heart disease epidemiology: from aetiology to public health*. 2nd ed. Oxford, England: Oxford Medical Publications, 2005:152-73.
23. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomized trials. *BMJ* 2008;336:1121-3.
24. Turnbull F, Woodward M, Neal B, et al. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. *Eur Heart J* 2008;29:2669-80.
25. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005;165:1410-9.
26. Heusser K, Tank J, Diedrich A, et al. Influence of sibutramine treatment on sympathetic vasomotor tone in obese subjects. *Clin Pharmacol Ther* 2006;79:500-8.
27. Palatini P, Benetos A, Grassi G, et al. Identification and management of the hypertensive patient with elevated heart rate: statement of a European Society of Hypertension Consensus Meeting. *J Hypertens* 2006;24:603-10.
28. Palatini P. Elevated heart rate: a "new" cardiovascular risk factor? *Prog Cardiovasc Dis* 2009;52:1-5.
29. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet* 2008;372:817-21.
30. Barr ELM, Magliano DJ, Zimmet PZ, et al. The Australian Diabetes, Obesity and Lifestyle Study: tracking the accelerating epidemic: its causes and outcomes. Melbourne, Australia: International Diabetes Institute, 2006.
31. Gordon-Larsen P, Hou N, Sidney S, et al. Fifteen-year longitudinal trends in walking patterns and their impact on weight change. *Am J Clin Nutr* 2009;89:19-26.
32. Heitmann BL, Garby L. Patterns of long-term weight changes in overweight developing Danish men and women aged between 30 and 60 years. *Int J Obes Relat Metab Disord* 1999;23:1074-8.
33. Gregg EW, Cheng YJ, Cadwell BL, et al. Secular trends in cardiovascular disease risk factors according to body mass index in US adults. *JAMA* 2005;293:1868-74. [Erratum, *JAMA* 2005;294:182.]
34. Sever PS, Poulter NR, Dahlöf B, Wedel H. Different time course for prevention of coronary and stroke events by atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Trial — Lipid-Lowering Arm (ASCOT-LLA). *Am J Cardiol* 2005;96:Suppl:39F-44F.
35. Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;373:1083-96.
36. Patel MR, Donahue M, Wilson PW, Califf RM. Clinical trial issues in weight-loss therapy. *Am Heart J* 2006;151:633-42.
37. Johansson K, Neovius K, DeSantis SM, Rössner S, Neovius M. Discontinuation due to adverse events in randomized trials of orlistat, sibutramine and rimonabant: a meta-analysis. *Obes Rev* 2009;10:564-75.

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