

# Effect of Sibutramine on Weight Management and Metabolic Control in Type 2 Diabetes

A meta-analysis of clinical studies

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**OBJECTIVE** — The aim of this study was to provide a comprehensive meta-analysis of randomized controlled clinical studies on the effects of sibutramine on weight loss and glycemic control in obese subjects with type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — Controlled clinical trials assessing the effect sizes of sibutramine on weight loss effects on glycemia in obese subjects with type 2 diabetes were identified and reviewed using the Cochrane Library, Medline, EMBASE, and a manual search.

**RESULTS** — Eight placebo-controlled, double-blind, randomized trials of sibutramine were included. After sibutramine treatment, the decrease in body weight and waist circumference was significantly greater than in the placebo group. Fasting blood glucose and HbA<sub>1c</sub> significantly decreased after sibutramine treatment. Treatment benefits were seen in plasma triglycerides and HDL, without significant variations in serum total and LDL cholesterol. No differences in systolic blood pressure between the sibutramine and the placebo groups were seen, while recording of diastolic blood pressure and heart rate showed that sibutramine produced a small increase relative to placebo.

**CONCLUSIONS** — A pharmacological approach in a weight management program for patients with type 2 diabetes may be helpful in glycemic control and in the management of other risk factors. Sibutramine may help improve glucose control because it is conducive to weight loss. The reviewed data on the effect of sibutramine further enforce the recommendations that weight management may be the most important therapeutic task for most obese subjects with type 2 diabetes.

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Obesity has become a major public health concern not only in western societies but also in some developing countries and is reaching epidemic proportions. American adults have experienced a 50% increase in the prevalence of overweight and obesity, while children and adolescents have experienced a 100% increase since the 1970s (1). Coincident with this increase in obesity, the preva-

lence of type 2 diabetes has also reached epidemic proportions. About 50 million Americans exhibit metabolic syndrome, as defined in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2). It is noteworthy that the overall prevalence of the metabolic syndrome in nondiabetic adult Europeans is 15%,

with the metabolic syndrome increasing the risk of death from all causes as well as cardiovascular disease (3). The U.K. Prospective Diabetes Study provided several outcomes that can be categorized as POEM (patient-oriented evidence that matters) (4). Among them, weight loss is especially challenging for insulin- or sulfonylurea-treated diabetic patients because this therapeutical approach has been found to cause weight gain without any impact on individual or aggregate microvascular or macrovascular outcomes (5). In fact, weight gain occurred in all patients except those treated with metformin. In overweight patients, treatment with metformin decreased diabetes-related outcomes and mortality related to diabetes or other causes (6). Moreover, control of blood pressure (7) and body weight had a greater effect on complications than blood glucose control. Overweight, therefore, makes it more difficult to control blood glucose and increases the chances of cardiovascular complications in diabetic patients. Treatment with the prescription weight loss medication sibutramine could have significant benefits for overweight or obese people with insulin- or oral hypoglycemic agent-treated type 2 diabetes and with suboptimal metabolic control. The aim of this study was to provide a comprehensive meta-analysis of randomized controlled clinical studies on the effects of sibutramine on weight loss and its benefits in improving glycemic control.

## RESEARCH DESIGN AND METHODS

Randomized controlled clinical trials were searched in the current list of medical literature from the Cochrane Library, Medline, and EMBASE, and reference lists of all relevant articles were also checked. Abbott Laboratories were also contacted in order to identify unpublished data.

The key indexing terms used were “sibutramine, obesity, diabetes, clinical

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**Abbreviations:** DBP, diastolic blood pressure; SBP, systolic blood pressure.

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Table 1—Study protocols of the patients in the trials considered in the meta-analysis

	Sibutramine group		Placebo group	Study duration (months)	Antidiabetic treatment
	Drug dosage	Patients (n)	Patients (n)		
Role of sibutramine in the treatment of obese type 2 diabetic patients receiving sulphonylurea therapy (ref. 10)	15 mg	69	65	6	Sulphonylurea
A randomized trial of sibutramine in the management of obese type 2 diabetic patients treated with metformin (ref. 11)	15 mg	68	64	12	Metformin
A randomized trial of sibutramine in the management of obese Type 2 diabetic patients treated with metformin (ref. 11)	20 mg	62	64	12	Metformin
Effects of sibutramine in obese female subjects with type 2 diabetes and poor blood glucose control (ref. 14)	20 mg	29	25	6	Metformin, sulphonylurea
Weight loss with sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus (ref. 12)	5/20 mg	89	86	6	Metformin, sulphonylurea
Sibutramine is effective for weight loss and diabetic control in obesity with type 2 diabetes: a randomised, double-blind, placebo-controlled study (ref. 13)	15 mg	47	44	3	Insulin, metformin, sulphonylurea
Use of sibutramine in overweight adult Hispanic patients with type 2 diabetes mellitus: a 12-month, randomized, double-blind, placebo-controlled clinical trial (ref. 15)	10 mg	44	42	12	Glibenclamide
Health-related quality of life in a randomized placebo-controlled trial of sibutramine in obese patients with type II diabetes (ref. 16)	15 mg	114	122	12	Hypocaloric diet
One-year outcome of a combination of weight loss therapies for subjects with type 2 diabetes: a randomized trial (ref. 17)	10 mg	30	29	12	Hypocaloric diet
Total		552	541		

In all the studies, diet was reduced in calories and specific dietary recommendations were given to the patients.

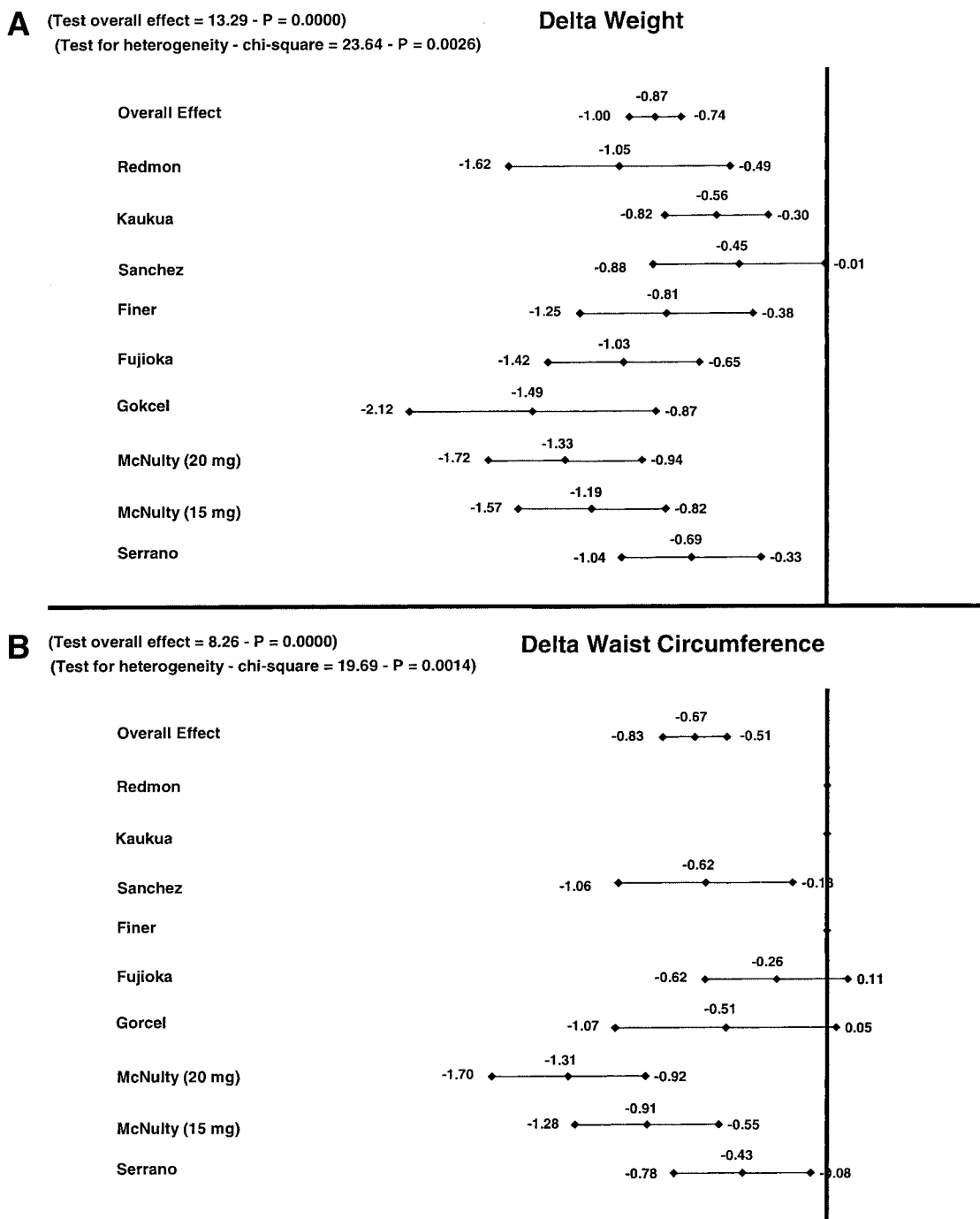
trials." Inclusion criteria were a full publication in English, a randomized controlled trial (blind, parallel, or crossover), a diagnosis of type 2 diabetes, the presence of overweight or obesity, and minimum duration of treatment with sibutramine of at least 3 months. Trials lasted until October 2004. One investigator extracted data and a second checked data extraction. Studies published in abstract form only were not included because it was impossible to judge study quality from abstract alone. The randomized controlled trial quality was assessed

following Verhagen Delphi criteria (8). The outcome measures were body weight; waist circumference; fasting blood glucose and serum insulin; HbA<sub>1c</sub>; fasting serum triglycerides; total, LDL, and HDL cholesterol; systolic (SBP) and diastolic (DBP) blood pressure; and heart rate. Results are presented as means  $\pm$  SD.

The meta-analysis was done according to the methods described by Hedges and Olkin (9) to determine the effect size for each study. The mean of a control group ( $M_c$ ) was subtracted from the mean of the experimental group ( $M_e$ )

and divided by the pooled SD of both groups:  $d = (M_e - M_c)/SD$ . In this case, SD is the square root of the weighted average of the two variances:  $s^2 = [(n_e - 1)(s_e)^2 + (n_c - 1)(s_c)^2]/(n_e + n_c - 2)$ . The degree of homogeneity or heterogeneity of the dataset and the  $\chi^2$  test was also calculated.

**RESULTS**— We found 35 articles in databases matching the search string and selected eight clinical studies that met inclusion criteria. Table 1 shows the study protocols of the trials considered in the



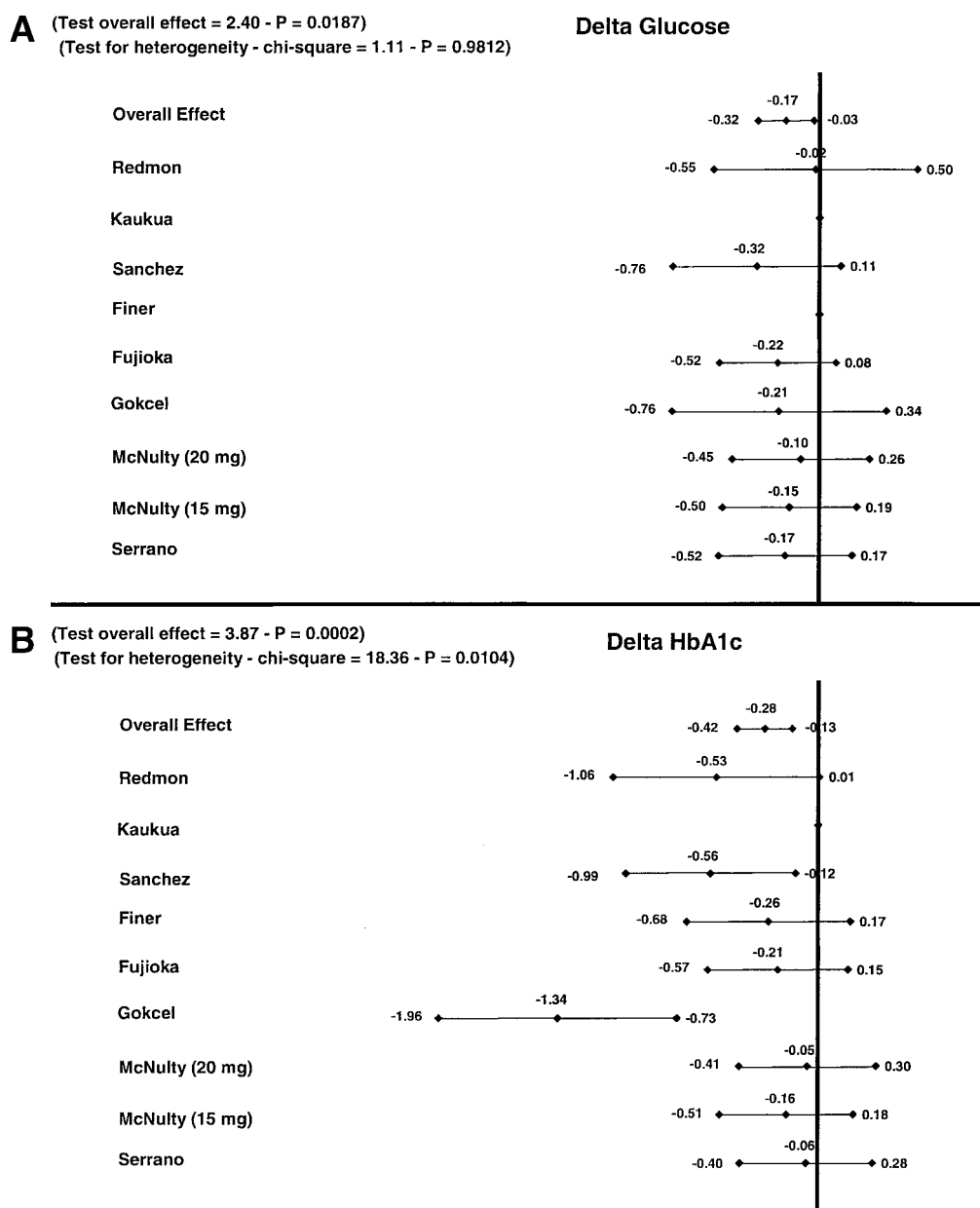
**Figure 1**—Changes in body weight (A) and waist circumference (B) in clinical studies included in the meta-analysis.

meta-analysis. One 6-month randomized controlled trial comparing sibutramine (15 mg/day) with placebo in subjects receiving sulfonylureas (10) and a 12-month randomized prospective placebo-controlled double-blind study (sibutramine 15 and 20 mg/day) in metformin-treated obese subjects (11) with type 2 diabetes were identified. In another

three studies, either metformin or sulfonylurea or insulin or diet only was the treatment of the patients (12–14). Another trial had been performed with 10 mg sibutramine for 12 months in diabetic patients treated with glibenclamide (15). In the last two studies examined, sibutramine (15 and 10 mg) had been compared with only a hypocaloric diet (16,17) for 1

year. In all the studies, diet was reduced in calories and specific dietary recommendations were given.

A total of 1,093 obese patients with type 2 diabetes (552 treated with sibutramine M163 F201 and 541 treated with placebo M123 F225) were analyzed. The mean age of the sibutramine-treated patients in all the studies was slightly lower



**Figure 2**—Changes in blood glucose (A) and HbA<sub>1c</sub> (B) in clinical studies included in the meta-analysis.

than in the placebo group, and therefore the overall effect resulted in a significant difference between the two groups ( $P = 0.0078$ ). In the study of Gokcel et al. (14), the enrolled patients were only women. The two groups were similar in terms of race; sex; body weight; waist circumference; fasting blood glucose and serum insulin; HbA<sub>1c</sub>; fasting serum triglycerides; total, LDL, and HDL cholesterol; SBP and DBP; and heart rate.

In the sibutramine-placebo comparison, body weight decreased on average  $5.533 \pm 0.225$  kg after sibutramine treatment and  $-0.900 \pm 0.169$  kg in the pla-

cebo group, and waist circumference ( $5.320 \pm 0.310$  vs.  $-1.130 \pm 0.160$  cm) significantly decreased after sibutramine. The overall effect size (standard mean difference) was 0.87 (95% CI 1.00–0.74;  $P = 0.0000$ ) on weight change (Fig. 1A) and 0.67 (0.83–0.51;  $P = 0.0000$ ) for waist circumference (Fig. 1B).

Mean changes in basal blood glucose show a small but significant variation ( $-0.17$  [95% CI 0.03–0.32];  $P = 0.0187$ ) (Fig. 2A), whereas HbA<sub>1c</sub> significantly decreased after sibutramine treatment. The overall effect size on HbA<sub>1c</sub> was  $-0.28\%$  ( $-0.13$  to  $-0.42$ ;  $P = 0.0002$ ),

with some heterogeneity ( $P = 0.0104$ ) among the studies (Fig. 2B). Treatment benefits were seen in plasma triglycerides and HDL, without significant variations in serum total and LDL cholesterol. The overall effect size on serum triglycerides was  $-0.24$  ( $-0.09$  to  $-0.39$ ;  $P = 0.0024$ ) and  $0.20$  ( $0.05$ – $0.35$ ;  $P = 0.0087$ ) for HDL (Fig. 3).

The eight trials did not report differences in SBP between the sibutramine and the placebo but showed a weak increase in DBP in the sibutramine group ( $0.22$  [95% CI 0.07–0.38;  $P = 0.0050$ ]) (Fig. 4A). Moreover, recording of heart rate

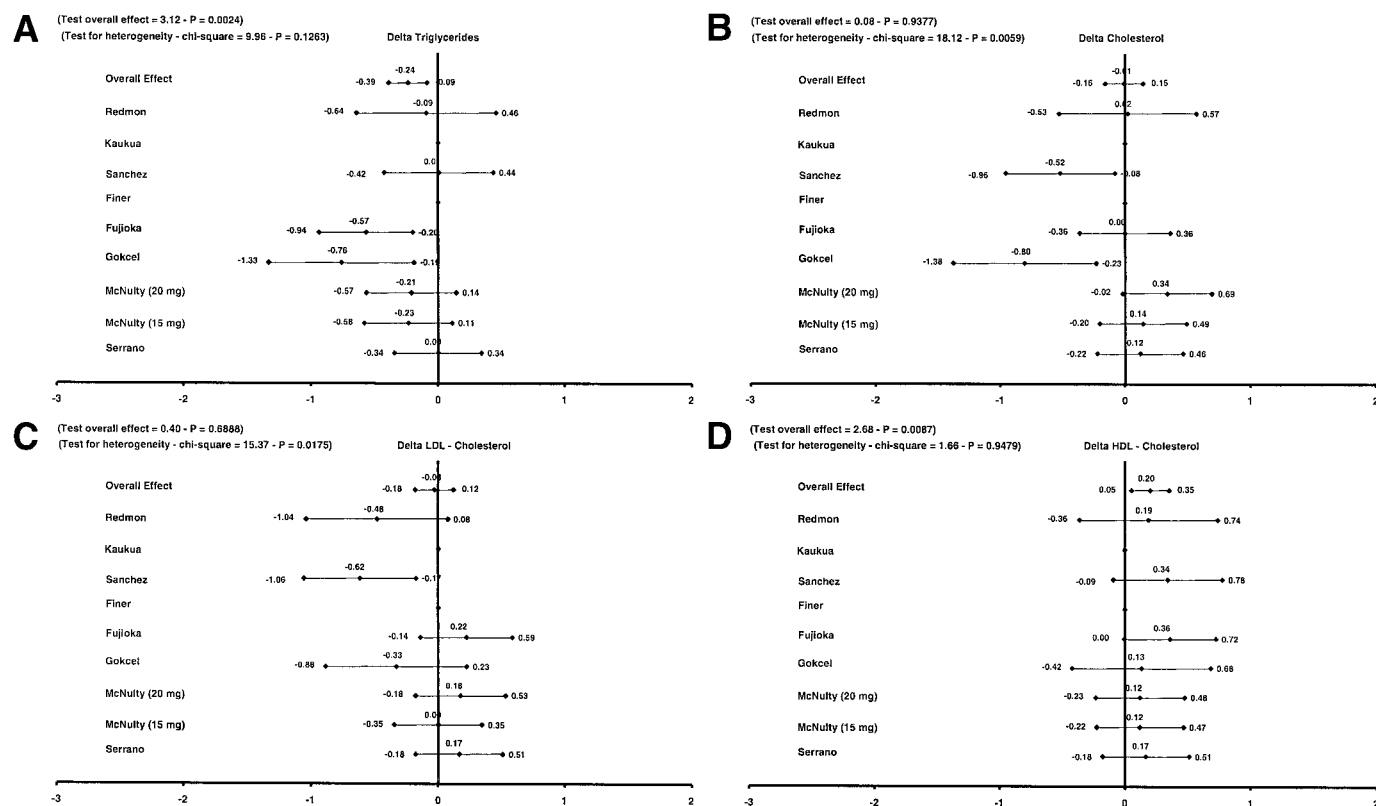


Figure 3—Changes in triglycerides (A) and total (B), LDL (C), and HDL (D) cholesterol in clinical studies included in the meta-analysis.

showed that sibutramine produced a small increase relative to placebo, either between groups or within groups over time. The overall effect size on heart rate was 0.53 (0.39–0.67;  $P = 0.0000$ ) (Fig. 4B).

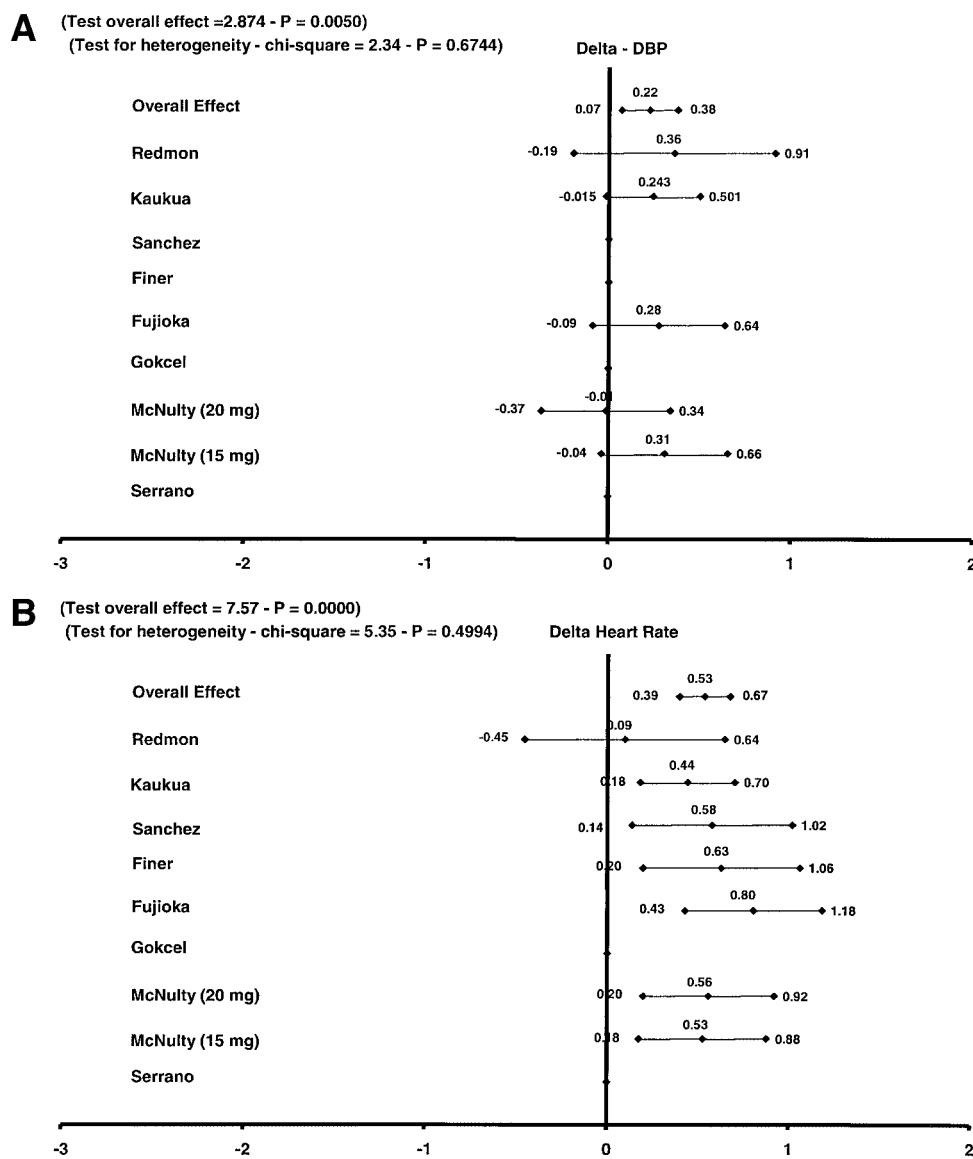
**CONCLUSIONS**— Obesity is a risk factor for type 2 diabetes, dyslipidemia, hypertension, and cardiovascular and coronary artery disease (18,19). In type 2 diabetic patients with obesity, loss of quite modest amounts of weight has been shown to bring about regression of coronary atherosclerosis (20), to increase HDL cholesterol, and to reduce triglycerides. The results of our meta-analysis clearly confirm that treatment with sibutramine is able to determine a considerable decrease in body weight that differs significantly from that reported in the placebo group. This observation further supports the therapeutic efficacy of sibutramine in reducing body weight (21–24), even in a population of obese type 2 diabetic subjects who are considered less compliant and with a limited adherence to the lifestyle advertisements. Weight loss remains the cornerstone for the great majority of

overweight diabetic patients, and glucose control and fasting glucose levels improve before major weight loss has occurred. According to Fujioka et al. (12), one can expect a 0.5% reduction in HbA<sub>1c</sub> and a 1.1-mmol/l fall in fasting plasma glucose for every 4.5-kg loss in weight.

These results demonstrate that the addition of sibutramine to the treatment with diet, oral antidiabetic agents, or insulin may improve glycemic control. This is a significant finding that could have implications on how these patients are treated in the future. Given that glycemic control reduces HbA<sub>1c</sub> levels, one would postulate that sibutramine and the resulting weight loss observed significantly ameliorated the metabolic control. In the Norfolk study, Khaw et al. (25) showed that there is a continuous relationship between HbA<sub>1c</sub> levels and cardiovascular disease and total mortality. This relationship was apparent even among persons without diabetes. However, the U.K. Prospective Diabetes Study only found a weak association between glucose control and the risk of myocardial infarction (16% reduction;  $P = 0.052$ ) (26). Each 1% reduction in HbA<sub>1c</sub> levels resulted in a

14% decrease in myocardial infarctions compared with a 37% decrease in microvascular events. Since glycemic control lowers the risk of microvascular events to a greater extent than macrovascular events (27), pharmacologic interventions targeting hypertension and dyslipidemia, preferentially affecting macrovascular disease, have markedly reduced cardiovascular events in patients with type 2 diabetes. In fact, lipid-lowering and hypertension trials in type 2 diabetes have shown significant cardiovascular benefits in persons with long-standing diabetes. Strict glycemic control must therefore be coupled with proven therapies to reduce cardiovascular events by addressing the atherogenic dyslipidemia and hypertension associated with type 2 diabetes.

The “lipid triad” (small dense LDL, hypertriglyceridemia, and low HDL levels) found in the metabolic syndrome and type 2 diabetes is associated with nearly twice the incidence of cardiovascular events compared with an isolated LDL alone (28). Patients with type 2 diabetes have average LDL levels but have an increased number of small dense LDL particles, which are highly susceptible to



**Figure 4**—Changes in DBP (A) and heart rate (B) in clinical studies included in the meta-analysis.

oxidative modification and are associated with a threefold increase in cardiovascular disease. In addition, low HDL levels deprive patients with type 2 diabetes of maximum protection from reverse cholesterol transport and exposure to potent antioxidants (paroxanase). In this context, the body weight-lowering effect of sibutramine was associated with a marked decrease in plasma triglycerides and a significant increase in HDL cholesterol in obese type 2 diabetic subjects. These results, far from indicating sibutramine as a therapeutic mean to prevent the macrovascular complications in obese type 2 diabetic patients, clearly suggest that a pharmacological approach in a weight management program may be use-

ful in metabolic control and cardiovascular complications.

At present, a major emphasis should first be on reaching appropriate blood pressure targets in patients with type 2 diabetes. Recent data from the National Health and Nutrition Examination Survey registry suggest that <15% of diabetic patients meet Joint National Committee 6 blood pressure targets (29). Finally, the new guidelines established by the Joint National Committee 7 (30) on prevention, detection, evaluation, and treatment of high blood pressure stress the use of aggressive combination drug therapy to achieve blood pressure goals in high-risk patients. Sibutramine causes weight loss, acting at the central nervous system by

promoting energy expenditure and inhibiting food intake. It also increases the sympathetic drive, heart rate, and blood pressure through its norepinephrine reuptake inhibitory effect (12,31–33), and this fact limits its use in hypertensive patients. Despite the existence of contradictory results reporting that sibutramine does not influence blood pressure (34,35), a recent meta-analysis (36) confirmed that in sibutramine-treated obese subjects, there is a slight but significant increase in both SBP and DBP. In our meta-analysis of controlled trials, no clear evidence for an effect of sibutramine treatment on SBP and only a small enhancement of DBP were observed, probably because these effects are masked or abol-



ished by the decrease in body weight, which often implies a reduction in blood pressure. However, the decrease in body weight is not sufficient to produce a reduction in the activation of the sympathetic drive by sibutramine. In fact, the heart rate, which may represent a surrogate index of the sympathetic activity, is significantly higher in sibutramine-treated patients. Moreover, we have to take into account that the cardiovascular effect of sibutramine results from a complex interaction of peripheral and central effects (37). In fact, it has been described that in young healthy subject with low sympathetic activity, the peripheral effect dominates, leading to an increased resting blood pressure. On the other hand, when sympathetic activity is increased, such as was found in a larger subgroup of obese hypertensive patients (38), the inhibitory clonidine-like effects of sibutramine seem to prevail. This hypothesis could explain the observation that sibutramine only slightly increases or leaves unmodified the resting blood pressure in a significant proportion of patients.

In summary, although only eight studies were included in the meta-analysis, the results are remarkable in revealing a substantial effect of sibutramine on weight loss as well as a considerable benefit on glycemic control and lipid profile, therefore reducing some of the cardiovascular risk factors in type 2 diabetic patients. The reviewed data further enforce the recommendations that weight management may be the most important therapeutic task for most obese type 2 diabetic individuals.

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