

AN ASSESSMENT OF HEART-VALVE ABNORMALITIES IN OBESE PATIENTS TAKING DEXFENFLURAMINE, SUSTAINED-RELEASE DEXFENFLURAMINE, OR PLACEBO

NEIL J. WEISSMAN, M.D., JOHN F. TIGHE, JR., M.D., JOHN S. GOTTDIENER, M.D., AND JOHN T. GWYNNE, M.D.,
FOR THE SUSTAINED-RELEASE DEXFENFLURAMINE STUDY GROUP***ABSTRACT**

Background The appetite-suppressant drug fenfluramine, usually given in combination with phentermine, has been reported to be associated with cardiac valvular regurgitation. Concern has been raised that the *d*-enantiomer of fenfluramine, dexfenfluramine, may also cause this problem. We were able to study the question by modifying an ongoing trial comparing sustained-release dexfenfluramine with regular dexfenfluramine and placebo.

Methods We modified our randomized, double-blind, placebo-controlled study of dexfenfluramine to include echocardiographic examinations of 1072 overweight patients within a median of one month after the discontinuation of treatment. The patients (approximately 80 percent of whom were women) had been randomly assigned to receive dexfenfluramine (366 patients), investigational sustained-release dexfenfluramine (352 patients), or placebo (354 patients). The average duration of treatment was 71 to 72 days in each of the three groups. Echocardiograms were assessed in a blinded fashion.

Results When all degrees of valvular regurgitation were considered and when the two dexfenfluramine groups were combined, there was a higher prevalence of any degree of aortic regurgitation (17.0 percent vs. 11.8 percent, $P=0.03$) and any degree of mitral regurgitation (61.4 percent vs. 54.4 percent, $P=0.01$) in the active-treatment groups than in the placebo group. These differences were primarily due to a higher prevalence of physiologic, trace, or mild regurgitation. Analyses that used the criteria of the Food and Drug Administration for aortic regurgitation of mild or greater severity and mitral regurgitation of moderate or greater severity found no significant difference among the groups ($P=0.14$ to 0.75). These analyses showed that aortic regurgitation of mild or greater severity occurred in 5.0 percent of the patients in the dexfenfluramine group, 5.8 percent of those in the sustained-release dexfenfluramine group, 5.4 percent of those in the two active-treatment groups combined, and 3.6 percent of those in the placebo group. Mitral regurgitation of moderate or greater severity occurred in 1.7, 1.8, 1.8, and 1.2 percent, respectively. Aortic regurgitation of mild or greater severity, mitral regurgitation of moderate or greater severity, or both occurred in 6.5 percent, 7.3 percent, 6.9 percent, and 4.5 percent, respectively.

Conclusions We found a small increase in the prevalence of aortic and mitral regurgitation in patients treated with dexfenfluramine, and the degree of regurgitation was in most cases classified as physiologic, trace, or mild. However, the duration of therapy was short, and whether therapy of longer duration would yield the same or different results is not known. (N Engl J Med 1998;339:725-32.)

©1998, Massachusetts Medical Society.

OBESITY is associated with serious health risks, including an increased incidence of heart disease, stroke, and hypertension.^{1,2} The use of fenfluramine and phentermine increased dramatically after a report on the efficacy of the combination was published.³ In April 1996 dexfenfluramine hydrochloride, the dextrorotatory isomer of fenfluramine hydrochloride, was approved in the United States for the treatment of obesity. Dexfenfluramine, like fenfluramine, is an appetite-suppressant agent that acts by releasing serotonin and inhibiting its reuptake.⁴

Connolly and colleagues reported on 24 patients with valvular heart disease who had been treated with fenfluramine and phentermine.⁵ Another report from five centers suggested an overall prevalence of valvular regurgitation of 32.8 percent in patients treated with fenfluramine or dexfenfluramine, generally with phentermine.^{6,7} These reports and others⁸⁻¹⁰ have aroused concern that treatment with dexfenfluramine may be associated with valvular heart disease. On the basis of these reports, dexfenfluramine and fenfluramine were voluntarily withdrawn by the manufacturers on September 15, 1997. At that time, the protocol of an ongoing randomized, double-blind, placebo-controlled trial comparing dexfenfluramine (Redux, Interneuron, Lexington, Mass.), an investigational sustained-release formulation of dexfenfluramine, and placebo was amended. The study medication was discontinued and echocardiographic examinations were performed. We report here the initial echocardiographic findings.

METHODS**Patients**

The patients included in the initial randomized trial were men and women 18 years of age or older with a body-mass index (the weight in kilograms divided by the square of the height in meters) of at least 30, or of at least 27 if they had hypertension, hyperlipidemia, or diabetes mellitus. Patients were ineligible if they had unstable cardiovascular disease or other systemic disorders or

From the Division of Cardiology and the Cardiovascular Institute, Georgetown University Medical Center, Washington, D.C. (N.J.W., J.E.T., J.S.G.); and the Department of Clinical Research, Wyeth-Ayerst Research, Philadelphia (J.T.G.). Address reprint requests to Dr. Weissman at the Division of Cardiology, Georgetown University Medical Center, 3800 Reservoir Rd., NW, Washington, DC 20007-2197.

*The other members of the Sustained-Release Dexfenfluramine Study Group are listed in the Appendix.

obesity secondary to endocrinopathy. Patients who had used selective serotonin-reuptake inhibitors, other appetite-suppressant agents, or dexfenfluramine within six months before randomization were ineligible, as were patients with a history of pulmonary hypertension or other disorders listed in the product labeling.

Study Design

The study was originally designed as a randomized, double-blind, parallel-group, placebo-controlled trial comparing the efficacy and safety of an investigational sustained-release formulation of dexfenfluramine (30 mg once a day) with the efficacy and safety of the immediate-release formulation of dexfenfluramine (15 mg twice a day) and placebo. Obese outpatients were enrolled at 52 sites. Written informed consent was obtained from all the patients. The protocol and its amendments, including the addition of echocardiographic examinations and revised study objectives, were filed with the Food and Drug Administration (FDA) in an investigational-new-drug application and approved by the institutional review boards of the study sites. The study was conducted according to current FDA guidelines.

After a two-week, single-blind, controlled-diet period, the eligible patients were randomly assigned to one of the three study groups and received two identical-appearing capsules each morning and evening. Although the protocol specified a double-blind treatment period of 16 weeks, the study medication was discontinued prematurely because of the withdrawal of dexfenfluramine from the market. The patients and investigators remained blinded to the treatment assignments, and the protocol was amended to include echocardiographic examinations. This paper reports the analysis of the initial echocardiograms. Longer-term follow-up is ongoing.

Echocardiographic Assessments

Echocardiograms were recorded locally with the use of a standardized imaging protocol that included the parasternal long-axis view; the parasternal short-axis view at the aortic, mitral, and mid-papillary levels; and apical four-chamber, two-chamber, and long-axis views. Mitral, aortic, and tricuspid valves were studied by color Doppler in multiple views to determine the degree of regurgitation. The technical inability to evaluate one valve did not preclude the examination of the remaining valves. Mitral regurgitation was visually rated as none, physiologic, mild, moderate, severe, or impossible to evaluate.¹¹ Aortic regurgitation was visually rated as none, trace, mild, moderate, severe, or impossible to evaluate.¹²

In addition, morphologic features of the mitral, aortic, and tricuspid leaflets were viewed in multiple projections to assess valve thickness and mobility. A valve leaflet was considered abnormally thickened if it was ≥ 4 mm thick during diastole.¹³ Mobility was considered to be restricted if there was decreased leaflet excursion without apposition to the wall of the receiving chamber. A leaflet was categorized as severely restricted if there was no movement throughout the cardiac cycle. Pulmonary-artery pressure was estimated from tricuspid-regurgitation velocity with the modified Bernoulli equation and an assumption of a right atrial pressure of 10 mm Hg.¹⁴

The echocardiograms were interpreted at an independent central laboratory by physicians who were unaware of the patients' treatment assignments. The echocardiograms were evaluated by a second independent reviewer when any of the following conditions were present: thickening of any valve leaflet, valve-leaflet mobility considered at least moderately restricted, aortic regurgitation considered at least mild, mitral regurgitation considered at least moderate, or tricuspid-valve regurgitation considered at least moderate. The echocardiograms of 137 patients met at least one of these criteria. All discrepant readings were adjudicated by consensus. In addition, approximately 5 percent of all the other echocardiograms were read by two readers to evaluate the degree of agreement between readers, and each reader reread approximately 15 echocardiograms to evaluate intrareader agreement.

Statistical Analysis

After the addition of echocardiography and before the unblinding of the data, the statistical-analysis plan was revised. The demographic characteristics of the patients in the study groups were compared with the use of analysis of variance and chi-square statistics. The FDA criteria of aortic regurgitation of mild or greater severity and mitral regurgitation of moderate or greater severity were used to determine the presence or absence of valvular regurgitation. The proportion of patients in each group who met the FDA criteria was calculated, and Fisher's exact test was used to determine whether there were significant differences among the three study groups. The 95 percent confidence intervals for the crude odds ratios and the difference in proportions between each active treatment and placebo were also calculated with large-sample normal approximations. In addition, a stepwise multiple logistic-regression analysis was performed to identify the independent predictors of important valvular regurgitation on the basis of the FDA criteria. The variables included in the logistic-regression model were treatment group (which had to remain in the model), sex, age, body-mass index, duration of therapy, and time between discontinuation of study medication and echocardiographic examination. Treatment interactions with these variables were also investigated.

An additional analysis was performed in which the frequency of the five grades of valvular regurgitation (none, trace or physiologic, mild, moderate, or severe) was compared among the treatment groups. The nonparametric Kruskal-Wallis test with adjustment for ties was used to determine whether there were significant treatment differences with respect to the grade of valvular regurgitation. Separate analyses were performed for the aortic, mitral, and tricuspid valves. The Kruskal-Wallis test was also used to determine significant treatment differences with respect to the four grades of restricted leaflet mobility (none, minimal, moderate, and severe). Kappa statistics were used to assess interreader and intrareader variability. Spearman correlation coefficients were calculated to explore anatomical and physiologic relations. Contingency tables were used to assess interactions according to study site, and no such interactions were observed by inspection. All reported P values are nominal. After the initial evaluation of the data, we undertook multiple additional analyses, without adjustment of P values, including analyses that combined the two active-treatment groups. All statistical analyses were performed with the use of SAS statistical software (version 6.09, SAS Institute, Cary, N.C.).

RESULTS

A total of 1598 patients were screened for the study. The 1212 randomized patients (404 in each of the three groups) were predominantly obese, white, middle-aged women. A total of 1072 patients underwent echocardiography. The base-line demographic characteristics of the patients who underwent echocardiography (Table 1) and median duration of treatment (77 to 78 days) were similar in all groups. The average duration of treatment was 71 to 72 days in each of the three groups. Overall, 78.5 percent of the patients were treated for 8 weeks or longer, and 34.9 percent were treated for at least 12 weeks.

The study cohort for the primary analysis consisted of 1072 patients who underwent echocardiographic examinations within a median of 33 to 34 days after discontinuation of the study drug. The patients who underwent echocardiography were demographically similar to the randomized group as a whole, and the characteristics of the patients in the

TABLE 1. CHARACTERISTICS OF THE PATIENTS WHO HAD ECHOCARDIOGRAMS.*

CHARACTERISTIC	DEXFEN- FLURAMINE (N=366)	SUSTAINED- RELEASE DEXFEN- FLURAMINE (N=352)	PLACEBO (N=354)
Age — yr	45.1±10.9	45.1±10.5	45.1±11.9
Sex — no. (%)			
Female	299 (82)	275 (78)	287 (81)
Male	67 (18)	77 (22)	67 (19)
Race — no. (%)†			
White	308 (84)	282 (80)	297 (84)
Black	42 (11)	57 (16)	39 (11)
Other	16 (4)	13 (4)	18 (5)
Weight — kg	106±22	105±20	105±21
Body-mass index‡	38.6±6.9	38.1±7.0	38.7±6.7
Duration of treatment — days			
Mean	72.3±22.4	71.3±23.3	71.3±22.8
Median	78	78	77

*Plus-minus values are means ±SD.

†Because of rounding, percentages do not all total 100.

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

primary analysis were similar in all treatment groups. One hundred forty patients (11.6 percent) did not undergo echocardiographic examination. Ninety-three patients refused to undergo echocardiography, 24 agreed to undergo echocardiography at a later time, and 23 were lost to follow-up; the reasons for not undergoing echocardiography were evenly distributed across all treatment groups. The patients who did not undergo echocardiography were younger, were heavier, were more likely to be black, and were treated for a shorter time than those who did.

Echocardiographic Results

Not all valves could be fully evaluated in every patient. The aortic valve could be evaluated for regurgitation on 1001 of the 1072 echocardiograms (93 percent), the mitral valve on 1010 (94 percent), and the tricuspid valve on 967 (90 percent).

Valvular Regurgitation

When we used the FDA criteria of aortic regurgitation of mild or greater severity, mitral regurgitation of moderate or greater severity, or both, the prevalence of aortic regurgitation was 5.0 percent in the dexfenfluramine group, 5.8 percent in the sustained-release dexfenfluramine group, 5.4 percent in the active-treatment groups combined, and 3.6 percent in the placebo group (Table 2), and the prevalence of mitral regurgitation was 1.7, 1.8, 1.8, and 1.2 percent, respectively. The prevalence of aortic or mitral valvular regurgitation (or both) was 6.5, 7.3, 6.9, and 4.5 percent, respectively. No significant dif-

ferences among treatment groups were found when we used the FDA criteria (Table 2).

In addition, we examined valvular regurgitation according to the degree of severity. Of the patients in whom the aortic valve could be evaluated, aortic regurgitation of any severity was detected in 58 of the 342 patients (17.0 percent) in the dexfenfluramine group, 56 of the 329 (17.0 percent) in the sustained-release dexfenfluramine group, 114 of the 671 (17.0 percent) in the active-treatment groups combined, and 39 of the 330 (11.8 percent) in the placebo group. Aortic regurgitation of any severity was more frequent in the dexfenfluramine and sustained-release dexfenfluramine groups than in the placebo group, but this difference did not reach statistical significance ($P=0.06$) until both active-treatment groups were combined ($P=0.03$). The data presented in Table 3 suggest that the differences can be attributed primarily to increased trace or mild regurgitation in the active-treatment groups as opposed to increased moderate or severe regurgitation.

Of the patients in whom the mitral valve could be evaluated, mitral regurgitation of any severity occurred in 210 of the 343 patients (61.2 percent) in the dexfenfluramine group, 206 of the 334 (61.7 percent) in the sustained-release dexfenfluramine group, 416 of the 677 (61.4 percent) in the active-treatment groups combined, and 181 of the 333 (54.4 percent) in the placebo group. Most cases of mitral regurgitation were considered physiologic. When all degrees of mitral regurgitation were considered, there was a higher prevalence of regurgitation in the dexfenfluramine group ($P=0.03$), the sustained-release dexfenfluramine group ($P=0.03$), and the active-treatment groups combined ($P=0.01$) than in the placebo group. Again, the data in Table 3 suggest that the differences can be attributed primarily to increased physiologic or mild regurgitation.

Physiologic and mild tricuspid regurgitation occurred frequently in all three study groups (61.4 percent to 70.3 percent), and there were no significant differences among the dexfenfluramine group, the sustained-release dexfenfluramine group, the active-treatment groups combined, and the placebo group. Few patients (<1 percent) had moderate tricuspid regurgitation, and no patient had severe tricuspid regurgitation (Table 3). No patient had more than physiologic pulmonary regurgitation.

Multiple logistic-regression analysis indicated that treatment, when forced into the model, and age were predictors of the risk of regurgitation (as defined by the FDA criteria) and that sex, body-mass index, duration of therapy, and time between the discontinuation of the study medication and the time of echocardiography were not. There was an interaction between age and treatment in the active-treatment groups combined, with the risk of regur-

TABLE 2. PREVALENCE OF MITRAL- AND AORTIC-VALVE REGURGITATION ACCORDING TO STUDY GROUP.*

TYPE OF REGURGITATION	DEXFENFLURAMINE (N=366)	SUSTAINED-RELEASE DEXFENFLURAMINE (N=352)	COMBINED DEXFENFLURAMINE GROUPS (N=718)	PLACEBO (N=354)
Aortic valve†				
No. of echocardiograms that could be evaluated	342	329	671	330
Regurgitation absent — no. (%)	325 (95.0)	310 (94.2)	635 (94.6)	318 (96.4)
Regurgitation present — no. (%)	17 (5.0)	19 (5.8)	36 (5.4)	12 (3.6)
Odds ratio (95% CI)‡	1.4 (0.7–3.0)	1.6 (0.8–3.4)	1.5 (0.8–2.9)	
P value (pairwise vs. placebo)§	0.45	0.20	0.27	
Mitral valve¶				
No. of echocardiograms that could be evaluated	343	334	677	333
Regurgitation absent — no. (%)	337 (98.3)	328 (98.2)	665 (98.2)	329 (98.8)
Regurgitation present — no. (%)	6 (1.7)	6 (1.8)	12 (1.8)	4 (1.2)
Odds ratio (95% CI)‡	1.5 (0.4–5.2)	1.5 (0.4–5.4)	1.5 (0.5–4.6)	
P value (pairwise vs. placebo)	0.75	0.75	0.60	
Aortic or mitral valve (or both)‡¶				
No. of echocardiograms that could be evaluated	340	327	667	330
Regurgitation absent — no. (%)	318 (93.5)	303 (92.7)	621 (93.1)	315 (95.5)
Regurgitation present — no. (%)	22 (6.5)	24 (7.3)	46 (6.9)	15 (4.5)
Odds ratio (95% CI)‡	1.5 (0.7–2.9)	1.7 (0.9–3.2)	1.6 (0.9–2.8)	
P value (pairwise vs. placebo)**	0.31	0.14	0.16	

*The severity of valvular regurgitation was defined according to FDA criteria.

†Aortic-valve regurgitation was considered to be absent if it was less than mild and considered to be present if it was of mild or greater severity.

‡The odds ratio was based on the presence of regurgitation in the two active-treatment groups combined as compared with the placebo group. CI denotes confidence interval.

§P=0.43 for the difference among the dexfenfluramine, sustained-release dexfenfluramine, and placebo groups by Fisher's exact test.

¶Mitral-valve regurgitation was considered to be absent if it was less than moderate and considered to be present if it was of moderate or greater severity.

||P=0.86 for the difference among the dexfenfluramine, sustained-release dexfenfluramine, and placebo groups by Fisher's exact test.

**P=0.30 for the difference among the dexfenfluramine, sustained-release dexfenfluramine, and placebo groups by Fisher's exact test.

gitation greater than that in the placebo group in younger patients but smaller than that in the placebo group in older patients. The small number of affected patients limits the value of the analysis.

Valvular Morphology

All valve leaflets were assessed for the presence or absence of leaflet thickening and the degree of restricted mobility. The morphologic features of the aortic valve were similar in all treatment groups. Increased thickening of aortic leaflets was found in 7.4 percent of the patients in the dexfenfluramine group, 5.5 percent of those in the sustained-release dexfenfluramine group, 6.4 percent of those in the active-treatment groups combined, and 7.6 percent of those in the placebo group. Restricted mobility (of moderate or greater degree) of any aortic cusp was found in less than 1 percent of any group. There were no significant differences among study groups

in the prevalence of restricted cusp mobility in any of the three aortic leaflets (left, P=0.38; right, P=0.17; and noncoronary, P=0.12).

The mitral leaflets were also assessed for thickening and mobility. Increased mitral-leaflet thickening was uncommon (present in 2 percent of patients or less) and did not differ significantly among the treatment groups (P=0.23). However, more of the patients in the sustained-release dexfenfluramine group had posterior (P=0.01) or anterior (P=0.03) restricted mitral-leaflet mobility. There was a trend toward restricted posterior leaflet mobility in the dexfenfluramine group (P=0.07) and no evidence of restricted anterior leaflet mobility (P=0.50). When the active-treatment groups were combined, only the incidence of posterior restricted mobility was significantly different from that in the placebo group (P=0.02) (Table 4). Eight patients in the dexfenfluramine group and four in the sustained-release

TABLE 3. PREVALENCE OF AORTIC-, MITRAL-, AND TRICUSPID-VALVE REGURGITATION ACCORDING TO SEVERITY AND STUDY GROUP.*

TYPE AND SEVERITY OF REGURGITATION	DEXFENFLURAMINE (N=366)	SUSTAINED-RELEASE DEXFENFLURAMINE (N=352)	COMBINED DEXFENFLURAMINE GROUPS (N=718)	PLACEBO (N=354)
Aortic valve				
No. of echocardiograms that could be evaluated	342	329	671	330
Degree — no. (%)				
None	284 (83.0)	273 (83.0)	557 (83.0)	291 (88.2)
Trace	41 (12.0)	37 (11.2)	78 (11.6)	27 (8.2)
Mild	14 (4.1)	19 (5.8)	33 (4.9)	10 (3.0)
Moderate	3 (0.9)	0	3 (0.4)	2 (0.6)
Severe	0	0	0	0
P value (pairwise vs. placebo)†	0.06	0.06	0.03	
Mitral valve				
No. of echocardiograms that could be evaluated	343	334	677	333
Degree — no. (%)				
None	133 (38.8)	128 (38.3)	261 (38.6)	152 (45.6)
Physiologic	173 (50.4)	172 (51.5)	345 (51.0)	160 (48.0)
Mild	31 (9.0)	28 (8.4)	59 (8.7)	17 (5.1)
Moderate	6 (1.7)	5 (1.5)	11 (1.6)	4 (1.2)
Severe	0	1 (0.3)	1 (0.1)	0
P value (pairwise vs. placebo)‡	0.03	0.03	0.01	
Tricuspid valve				
No. of echocardiograms that could be evaluated	331	317	648	319
Degree — no. (%)				
None	117 (35.3)	93 (29.3)	210 (32.4)	120 (37.6)
Physiologic	198 (59.8)	209 (65.9)	407 (62.8)	180 (56.4)
Mild	16 (4.8)	14 (4.4)	30 (4.6)	16 (5.0)
Moderate	0	1 (0.3)	1 (0.2)	3 (0.9)
Severe	0	0	0	0
P value (pairwise vs. placebo)§	0.72	0.08	0.22	

*Because of rounding, not all percentages total 100.

†P=0.10 for the difference among the dexfenfluramine, sustained-release dexfenfluramine, and placebo groups by the Kruskal-Wallis test.

‡P=0.04 for the difference among the dexfenfluramine, sustained-release dexfenfluramine, and placebo groups by the Kruskal-Wallis test.

§P=0.17 for the difference among the dexfenfluramine, sustained-release dexfenfluramine, and placebo groups by the Kruskal-Wallis test.

dexfenfluramine group had moderate or severe restriction of posterior mitral-leaflet mobility (2 percent), as compared with one patient in the placebo group (<1 percent). Although there was an increased likelihood of mitral regurgitation with moderately or severely restricted posterior mitral-leaflet mobility ($P<0.001$), the degree of regurgitation was variable and the correlation with severity was poor ($r=0.18$). No patient had restricted tricuspid-leaflet mobility or thickening.

Pulmonary-Artery Pressure

Three hundred thirty-one patients (equally distributed among the study groups) had tricuspid regurgitation sufficient for the estimation of pulmonary-artery pressure. There was no significant difference in mean pulmonary-artery pressure (30 to 31 mm Hg) among the groups. The pulmonary-artery pressure was greater than 40 mm Hg in seven patients in the

dexfenfluramine group, six in the sustained-release dexfenfluramine group, and nine in the placebo group ($P=0.83$).

Variability among Readers

Variability among readers was assessed with the use of echocardiograms that met the criteria for a second evaluation, as well as a sample of normal echocardiograms. There was agreement on the presence or absence of aortic and mitral regurgitation in 39 of the 40 normal echocardiograms and agreement on the presence or absence of aortic and mitral regurgitation in 121 of the 137 selected echocardiograms (kappa, 0.81; 90 percent confidence interval, 0.73 to 0.89). The simple, overall kappa statistic for posterior mitral-leaflet mobility was 0.32. There was 100 percent concordance for intrareader variability in the assessment of the presence or absence of aortic and mitral regurgitation.

TABLE 4. RESTRICTED MOBILITY OF ANTERIOR AND POSTERIOR MITRAL-VALVE LEAFLETS ACCORDING TO STUDY GROUP.

TYPE AND DEGREE OF RESTRICTION	DEXFENFLURAMINE (N=366)	SUSTAINED-RELEASE DEXFENFLURAMINE (N=352)	COMBINED DEXFENFLURAMINE GROUPS (N=718)	PLACEBO (N=354)
Anterior leaflet				
No. of echocardiograms that could be evaluated	359	347	706	351
Degree — no. (%)				
None	357 (99.4)	342 (98.6)	699 (99.0)	351 (100)
Minimal	2 (0.6)	5 (1.4)	7 (1.0)	0
Moderate	0	0	0	0
Severe	0	0	0	0
P value (pairwise vs. placebo)*	0.50	0.03	0.10	
Posterior leaflet				
No. of echocardiograms that could be evaluated	346	330	676	341
Degree — no. (%)				
None	321 (92.8)	301 (91.2)	622 (92.0)	327 (95.9)
Minimal	17 (4.9)	25 (7.6)	42 (6.2)	13 (3.8)
Moderate	8 (2.3)	3 (0.9)	11 (1.6)	1 (0.3)
Severe	0	1 (0.3)	1 (0.1)	0
P value (pairwise vs. placebo)†	0.07	0.01	0.02	

*P=0.06 for the difference among the dexfenfluramine, sustained-release dexfenfluramine, and placebo groups by Fisher's exact test.

†P=0.05 for the difference among the dexfenfluramine, sustained-release dexfenfluramine, and placebo groups by the Kruskal-Wallis test.

DISCUSSION

We found that when all degrees of valvular regurgitation were considered and when the dexfenfluramine and sustained-release dexfenfluramine groups were combined, there was a higher prevalence of aortic and mitral regurgitation, primarily due to a higher prevalence of physiologic, trace, or mild regurgitation, in the active-treatment groups than in the placebo group. An analysis conducted with the FDA criteria (aortic regurgitation of mild or greater severity and mitral regurgitation of moderate or greater severity) found no statistical difference among the groups. Our results are based on a duration of exposure to dexfenfluramine of only two to three months.

Comparison with Previous Studies

The prevalence of mitral and aortic regurgitation (as defined according to the FDA criteria) in both dexfenfluramine groups in this study was much lower than suggested by previous reports.⁶ Because of the very high prevalence of valvular regurgitation in the general population, adequate controls are necessary. When the investigators participating in the Framingham Offspring Study used current echocardiographic color Doppler techniques,¹⁵ they reported that up to 87 percent of the general population has some degree of mitral regurgitation, 76 percent has some degree of tricuspid regurgitation, and 11 percent has some degree of aortic regurgitation. These high per-

centages reflect the ability of exquisitely sensitive technology to detect normal "physiologic" regurgitation. Most clinicians recognize that the classification of either physiologic (trace) or mild mitral regurgitation as abnormal may be inappropriate, because both occur frequently and are clinically unimportant. Aortic regurgitation is different; studies have found that less than 5 percent¹⁶⁻¹⁹ of the population has mild or greater aortic regurgitation, and consequently this is the usual cutoff for clinical significance.

Applying the FDA criteria for mitral and aortic regurgitation to the prevalence data from the Framingham study, 3.5 to 6.0 percent of the population had aortic regurgitation of mild or greater severity and 1.1 to 1.5 percent had mitral regurgitation of moderate or greater severity. The prevalence of important and unimportant valvular regurgitation in our placebo group is consistent with the findings of this epidemiologic study. Therefore, since common abnormalities (valvular regurgitation) occur frequently in any large population (including people taking appetite-suppressant drugs), comparative control groups are necessary to account for the non-drug-related regurgitation that occurs in the general population.

Connolly et al.⁵ reported on 24 patients with valvular regurgitation who were taking fenfluramine and phentermine. Seven of these patients (29 percent) had mild mitral regurgitation, 4 (17 percent) had moderate mitral regurgitation, and 10 (42 per-

cent) had severe mitral regurgitation. Aortic regurgitation was common in their study, with 19 patients (79 percent) having mild or greater regurgitation of this type. No lesions as severe as those reported by Connolly et al. were found in our population. Although Connolly et al. reported no prevalence data, a 32.8 percent prevalence, based on the FDA criteria, was reported in the *Morbidity and Mortality Weekly Report*.⁶ This prevalence also differs from our results. The high prevalence rate reported from the five centers cited in the *Morbidity and Mortality Weekly Report* may have been due to the use of combination therapy (fenfluramine and phentermine), the longer duration of therapy, selection bias, or the lack of a standardized means of conducting echocardiography or of interpreting its results.

Since the recommendation for echocardiographic screening of patients who have received appetite-suppressant drugs was published,⁶ there has been a dramatic increase in screening echocardiography. Preliminary clinical experience is in accord with our finding that the prevalence of important regurgitation in people taking appetite-suppressant drugs is much less than 30 percent.²⁰

Prevalence of Valvular Regurgitation

The prevalence of aortic regurgitation of any severity was higher in the active-treatment groups combined than in the placebo group ($P=0.03$). Although there were statistically significant differences in aortic regurgitation when the two active-treatment groups were combined, these were attributable primarily to an increase in trace regurgitation. Using the FDA criteria for aortic regurgitation of mild or greater severity, we found a difference in prevalence between the dexfenfluramine groups combined (5.4 percent) and the placebo group (3.6 percent) of 1.7 percentage points (95 percent confidence interval, -0.9 to 4.4 percentage points). These rates vary from those previously reported.⁶

Mitral regurgitation was also more common in the active-treatment groups when all categories of severity were included. The difference in the prevalence of mitral regurgitation, as defined by the FDA criteria, between the active-treatment groups combined (1.8 percent) and the placebo group (1.2 percent) was 0.6 percentage point (95 percent confidence interval, -1.0 to 2.1 percentage points), again a much lower rate than previously reported. Even if mild mitral regurgitation had been included in the analysis, the difference in prevalence between the two dexfenfluramine groups combined (10.4 percent) and the placebo group (6.3 percent) would have been only 4.1 percentage points.

Valvular Morphology

A greater prevalence of restriction in the mobility of the posterior mitral leaflet was noted in both

active-treatment groups combined than in the placebo group. Although this finding may be the best discriminator of abnormal leaflet morphology in people taking appetite-suppressant drugs, the prevalence of restricted posterior mitral-leaflet mobility was very low, and the clinical effect remains to be determined, given the weak correlation with mitral regurgitation. Moreover, restricted posterior mitral-leaflet mobility appears to occur focally on the leaflet. Its detection requires meticulous attention, because focal abnormalities can easily be missed if most of the leaflet moves normally as two-dimensional echocardiography scans through multiple planes of the valve. Given the difficulty of detection, the low prevalence, the high degree of variability among readers, and the variable association with mitral regurgitation, restricted posterior mitral-leaflet mobility may have limited value as a clinical marker of valvulopathy.

Limitations of the Study

The withdrawal of dexfenfluramine from the market limited the duration of exposure to the drug in our study. Nonetheless, the patients were treated with the study medication for a median of 77 to 78 days and underwent echocardiography after the discontinuation of treatment within a median of 34 days. Although it is possible that this duration of treatment was insufficient to cause valvular abnormalities, there have been reports of abnormalities in some patients who took the drug for one to four months.^{5,6}

We relied on a randomized control group to assess the association of dexfenfluramine and valvular regurgitation. Pretreatment echocardiography was not included in the original trial design, and patients with preexisting valvular disease were therefore not excluded from the study. In fact, the one patient with severe mitral regurgitation had undergone coronary-artery bypass surgery more than 10 years before the study, and the one patient with severely restricted posterior mitral-leaflet mobility had a history of rheumatic disease. Nonetheless, the patients were randomly assigned to the treatment groups without regard to medical history, and there appeared to be random distribution with regard to the other variables.

Clinical Implications

The difference in the prevalence of valvular regurgitation between the patients who received either type of dexfenfluramine and those who received placebo was small, and the degree of regurgitation in most affected patients was considered physiologic, trace, or mild. Although these findings are reassuring for patients who have taken dexfenfluramine for two to three months, they should not preclude the appropriate investigation of a new murmur or new symp-

toms in an individual patient with a history of dexfenfluramine use (as specified in the American College of Cardiology guidelines²¹). Future studies should explore combination therapy, the duration of therapy, the natural history of valvular regurgitation, and the pathophysiologic mechanisms of this condition.

Supported by a grant from the Wyeth–Ayerst Research Division of Wyeth Laboratories.

We are indebted to Dr. John Vance and Susan Perras, M.S.N., for their assistance in the preparation of the manuscript; and to Drs. Arthur Weyman, Curt Furberg, O. Dale Williams, Ron Brookmeyer, and Bernard Gersh for their critical review.

APPENDIX

The primary clinical investigators and study coordinators of the Sustained-Release Dexfenfluramine Study Group were J. Anderson, J. Blake, Metabolic Research Group, Lexington, Ky.; M. Basista, I. Merz, Immedi-center, Bloomfield, N.J.; W. Berger, J. Feazor, C. Maldonado, Southern California Research Center, Mission Viejo; G. Blackburn, S. Flickner, Center for Study of Nutritional Medicine, Boston; M. Block, C. DeCave, Mary L. Wilson Clinical Research Center, Phoenix, Ariz.; T. Bock, D. Wichert, Harleysville Medical Associates, Harleysville, Pa.; F. Busick, L. Taylor, Clinica Research, Waltham, Mass.; L. Charles, M. Cordeiro, S.N.J. Medical Institution, Stratford, N.J.; G. Cooper, J. Cooper, West Hills, Calif.; C. DeAbate, S. Ashby, C. Kumpf, Medical Research Center, New Orleans; M. Dreihobl, B. Richards, Centre for Health Care, San Diego, Calif.; C. Dujovne, S. Horniman, J. Hoehn, Kansas Foundation for Clinical Pharmacology, Overland Park; J. Farrell, M. Farrell, Midwest Pharmaceutical Research, St. Peters, Mo.; J. Ferguson, A. Holman, Pharmacology Research, Salt Lake City; J. Foreyt, P. Pace, Behavioral Medical Research Center, Baylor College of Medicine, Houston; A. Frank, G. Colcough, M. Blanchard, Novum, Washington, D.C.; K. Fujioka, J. Sheard, Scripps Clinic, San Diego, Calif.; H. Deodhar, M. McMahon, Clinical Research Group of Oregon, Portland; L. Gilderman, University Clinical Research Associates, Pembroke Pines, Fla.; D. Gremillion, D. Coleman, Nashville Research Associates, Nashville; L. Gringeri, P. Van Arsdale, Atlantic Clinical Research, Newtown, Pa.; J. Hartford, R. Rice, Hartford Research Group, Cincinnati; K. Hershon, L. Lazerson, North Shore Diabetes and Endocrine Associates, New Hyde Park, N.Y.; J. Hill, B. Davy, University of Colorado Health Sciences Center, Denver; W. Garland, D. Nicholls, Lawrence Clinical Research, Lawrenceville, N.J.; R. Kamrath, G. Plummer, Diablo Clinical Research, Walnut Creek, Calif.; R. Khairi, S. DeCastro, Physicians Research Group, Indianapolis; J. Lewis, J. Cimmarusti, Mitchell Pappas Associates, Sunnyvale, Calif.; T. Littlejohn, C. Theiler, Piedmont Medical Research Associates, Winston-Salem, N.C.; M. Doyle, J. Segler, Beaumont Preventive and Nutritional Clinic, Birmingham, Mich.; F. Maggiamo, J. Gilligan, Silver Lake Medical, Providence, R.I.; T. Marbury, N. Brinkman, Orlando Clinical Research Center, Orlando, Fla.; A. Mehra, M. Johnson, Joslin Center for Diabetes, Princeton, N.J.; D. Morin, J. Robbins, TriCities Research, Bristol, Tenn.; W. Mrozcek, T. Williams, Weight Loss Clinic at the Cardiovascular Center, Falls Church, Va.; R. Noveck, P. Rigo, Clinical Research Center, New Orleans; M. Passaro, E. Robinson, Medlantic C.R.C., Washington, D.C.; X. Pi-Sunyer, E. Bauza, St. Luke's–Roosevelt Hospital Center, New York; H. Resnick, J. Conner, R/D Clinical Research, Lake Jackson, Tex.; J. Rippe, S. Hess, Center for Clinical and Lifestyle Research, Shrewsbury, Mass.; J. Rosenzweig, P. Master, Joslin Diabetes Center, Boston; S. Scumpia, M. Nipp, S. Jiang, Center for Clinical Research, Austin, Tex.; D. Smith, L. Futrelle, N. Whitley, C.S.R.A. Partners in Health, Augusta, Ga.; W. Smith, B. Chiapetta, New Orleans Center for Clinical Research, New Orleans; P. Solbach, A. Desai, N. Platte, Menninger Clinic Center for Clinical Research, Topeka, Kans.; D. Sugimoto, S. Aquino, Cedar–Crosse Research Center, Chicago; S. Targum, L. Houghton, Clinical Studies, Philadelphia, Philadelphia; J. Thwainey, A. Khalifa, Michigan Clinical Research Center, Dearborn; T. Truitt, K. Warren, S. Walmer, Associated Medical Research, Melbourne, Fla.; A. Vaswani, M. Gamble, Clinical Investigator Network/NY, Garden City, N.Y.; S. Weiss, M. Hyderkahn, San Diego Endocrine and Medical Clinic, San Diego, Calif.; and J. Zavoral, J. Gillingham, Preventive Cardiology Institute at Fairview, Edina, Minn. Other participants involved in the conduct of this study were J. Tall and M. Yohe of the Georgetown Echocardiography Core Laboratory; and S. Perras, J. Kitzen, S. Nielsen and D. Sarkozy of Wyeth–Ayerst Clinical Research. Data-base management and statistical analysis were provided by Parxel International.

REFERENCES

1. Kissebah AH, Freedman DS, Peiris AN. Health risks of obesity. *Med Clin North Am* 1989;73:111-38.
2. Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. The effect of age on the association between body-mass index and mortality. *N Engl J Med* 1998;338:1-7.
3. Weintraub M, Sundaresan PR, Cox C. Long-term weight control study. VI. Individual participant response patterns. *Clin Pharmacol Ther* 1992;51:619-33.
4. Davis R, Faulds D. Dexfenfluramine — an updated review of its therapeutic use in the management of obesity. *Drugs* 1996;52:696-724.
5. Connolly HM, Cray JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine–phentermine. *N Engl J Med* 1997;337:581-8. [Erratum, *N Engl J Med* 1997;337:1783.]
6. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: U.S. Department of Health and Human Services interim public health recommendations, November 1997. *MMWR Morb Mortal Wkly Rep* 1997;46:1061-6.
7. FDA analysis of cardiac valvular dysfunction with use of appetite suppressants. Washington, D.C.: Food and Drug Administration, 1997. (See <http://www.fda.gov/cder/news/slides/sld001.htm>.) (Also available from NAPS [document no. 05472 for 16 pages], c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. This is not a multiarticle document. Remit in advance [in U.S. funds only] \$15 for the first 20 photocopies [\$0.50 per page thereafter] or \$5 for the first microfiche [\$1 per microfiche thereafter]. Outside the U.S. and Canada add postage of \$4.50 for the first 20 pages, \$1 for every 10 pages thereafter [\$1 per microfiche]. There is a \$25 invoicing fee for purchase orders.)
8. Kurz X, Van Erman A. Valvular heart disease associated with fenfluramine–phentermine. *N Engl J Med* 1997;337:1772-3.
9. Rasmussen S, Corya BC, Glassman RD. Valvular heart disease associated with fenfluramine–phentermine. *N Engl J Med* 1997;337:1773.
10. Cannistra LB, Davis SM, Bauman AG. Valvular heart disease associated with dexfenfluramine. *N Engl J Med* 1997;337:636.
11. Helmcke F, Nanda NC, Hsiung MC, et al. Color Doppler assessment of mitral regurgitation with orthogonal planes. *Circulation* 1987;75:175-83.
12. Perry GJ, Helmcke F, Nanda NC, Byard C, Soto B. Evaluation of aortic insufficiency by Doppler color flow mapping. *J Am Coll Cardiol* 1987;9:952-9.
13. Ranganathan N, Lam JH, Wigle ED, Silver MD. Morphology of the human mitral valve. II. The valve leaflets. *Circulation* 1970;41:459-67.
14. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation* 1984;70:657-62.
15. Singh JP, Evans JC, Levy D, Larson MG, Fuller DL, Lehman B. Prevalence of valvular regurgitation in a population-based cohort. *Circulation* 1997;96:Suppl I:I-541. abstract.
16. Choong CY, Abascal VM, Weyman J, et al. Prevalence of valvular regurgitation by Doppler echocardiography in patients with structurally normal hearts by two-dimensional echocardiography. *Am Heart J* 1989;117:636-42.
17. Reid CL, Gardin JM, Yunis C, Kurosaki T, Flack JM. Prevalence and clinical correlates of aortic and mitral regurgitation in a young adult population: the CARDIA Study. *Circulation* 1994;90:Suppl I:I-282. abstract.
18. Jobic Y, Slama M, Tribouilloy C, et al. Doppler echocardiographic evaluation of valve regurgitation in healthy volunteers. *Br Heart J* 1992;69:109-13.
19. Klein AL, Burstow DJ, Tajik AJ, et al. Age-related prevalence of valvular regurgitation in normal subjects: a comprehensive color flow examination of 118 volunteers. *J Am Soc Echocardiogr* 1990;3:54-63.
20. Wong J, Reddy SS, Klein AL. Anorectic drugs and valvular heart disease: a biological and clinical perspective. *Cleve Clin J Med* 1998;65:35-41.
21. Statement of the American College of Cardiology on recommendations for patients who have used anorectic drugs. Bethesda, Md.: American College of Cardiology, October 18, 1997. (See <http://www.acc.org/pubs/news/statement.html>.) (Also available from NAPS [document no. 05472 for 3 pages], c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. This is not a multiarticle document. Remit in advance [in U.S. funds only] \$15 for the first 20 photocopies [\$0.50 per page thereafter] or \$5 for the first microfiche [\$1 per microfiche thereafter]. Outside the U.S. and Canada add postage of \$4.50 for the first 20 pages, \$1 for every 10 pages thereafter [\$1 per microfiche]. There is a \$25 invoicing fee for purchase orders.)