Journal of the American College of Cardiology
© 1999 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 34, No. 4, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(99)00321-6

Low Prevalence of Valvular Heart Disease in 226 Phentermine-Fenfluramine Protocol Subjects Prospectively Followed for up to 30 Months

Andrew J. Burger, MD, FACC,* Howard B. Sherman, MD,* Mark J. Charlamb, MD,* Juhee Kim, MS,† Laura A. Asinas, JD,† Stacy R. Flickner, RD,† George L. Blackburn, MD, PHD†

Boston, Massachusetts

OBJECTIVES This investigation sought to determine the effect of phentermine-fenfluramine (phen-fen) on the prevalence of valvular heart disease in 226 obese subjects enrolled in a prospective, strict weight loss, research protocol.

BACKGROUND Early reports have suggested that the use of phen-fen for weight loss may be associated with increased valvular heart disease. Such reports were based on small numbers of patients, limited data on dose and duration of phen-fen therapy, and no correlation with matched controls.

METHODS All subjects underwent transthoracic echocardiography for significant valvular lesions within a mean of 97 days from the manufacturer's announcement of the voluntary withdrawal of fenfluramine and dexfenfluramine. All echocardiograms were interpreted by two independent readers.

RESULTS The study population included 183 women and 43 men with a mean age of 46.9 ± 8.9 years and mean starting body mass index of 39.8 ± 7.7 kg/m^2. Using the Food and Drug Administration criteria, significant aortic regurgitation was detected in 15 subjects (6.6%) and mitral regurgitation in 3 subjects (1.3%). Only one patient had significant regurgitation of both aortic and mitral valves. No valves had severe regurgitation. Significant valvular disease did not correlate with the dose or duration of phen-fen therapy. Furthermore, the prevalence of valvular regurgitation is comparable to the normal offspring in the Framingham Heart Study, who are similar in age, gender, and geographical location.

CONCLUSIONS Phen-fen therapy is associated with a low prevalence of significant valvular regurgitation. Valvular regurgitation in our subjects may reflect age-related degenerative changes. (J Am Coll Cardiol 1999;34:1153–8) © 1999 by the American College of Cardiology

Phentermine and fenfluramine (phen-fen) are medications that are prescribed as anorectic agents for the treatment of obesity. In 1996, the total number of prescriptions for these drugs exceeded 18 million (1), even though the Food and Drug Administration (FDA) has never approved their combination use. In August 1997, researchers at the Mayo Clinic reported on 24 women with echocardiographic evidence of unusual valvular pathology and regurgitation involving both right- and left-sided heart valves (2). Following the Mayo Clinic report, numerous anecdotal reports and several small, nonrandomized observational surveys have described significant, unsuspected cardiac pathology in patients formerly on phen-fen with reported prevalence of valvular disease up to 38% (3).

See page 1159

The pathologic valvular changes in patients on phen-fen are felt to resemble those seen in patients with carcinoid syndrome and ergot-alkaloid–induced valvular heart disease: fibroplasia involving the valvular endocardium of both right- and left-sided valves (2,4–6). These changes resemble chronic rheumatic valve disease, but without evidence of valvular stenosis. Subvalvular involvement, including chordal thickening and retraction, has been noted with variable degrees of valvular regurgitation (5). To what extent these changes are fixed or reversible is not yet known, because no long-term prospective trials have been performed.

We now report the echocardiographic findings in a cohort of 226 subjects who received phen-fen for treatment of obesity and who were followed prospectively over the period September 1994 through September 1997. All sub-

From the *Division of Cardiology and †Center for the Study of Nutrition Medicine, Beth Israel Deaconess Medical Center, West Campus, Harvard Medical School, Boston, Massachusetts. No financial support was received for this echocardiographic study.

Manuscript received June 16, 1998; revised manuscript received May 27, 1999, accepted June 11, 1999.

Abbreviations and Acronyms
ECG = electrocardiogram
FDA = Food and Drug Administration
phen-fen = phentermine-fenfluramine

jects were offered transthoracic echocardiographic evaluation soon after the announcement on September 15, 1997, of the voluntary withdrawal of fenfluramine and dexfenfluramine from the U.S. market (7). Specific attention was given to any morphologic abnormalities of either right- or left-sided heart valves, as well as the presence and extent of valvular regurgitation.

METHODS

Weight-loss study. Participants in this echocardiographic study were derived from a larger population of 591 subjects participating in a four-year prospective, nonrandomized, open-label study of combination therapy with phentermine resin and *dl*-fenfluramine to promote and sustain weight loss (8). All subjects were followed at the Center for the Study of Nutrition Medicine. The study was approved by the Institutional Review Board and granted investigational new drug status by the FDA (IND no. 45,962).

Study subjects consisted of male and female volunteers with body mass indexes >27 kg/m^2 at baseline, age range 18 to 69 years old, baseline heart rate <90 beats/min, and blood pressure $<160/95$ mm Hg. To meet entry criteria, subjects must have had no prior adverse reactions to central nervous system stimulants or other weight-loss agents, no history of regular laxative use, no use of diet supplements or investigational drugs within 30 days of baseline, and no evidence of significant cardiac, immunologic, hepatic, renal, pulmonary, hematologic, metabolic, neurologic or psychiatric dysfunction. Women who were lactating, pregnant, or planning to become pregnant were excluded. Subjects with a positive drug screen for cocaine or a history of substance abuse within the previous two years were also excluded.

All participants had a baseline medical and nutritional history, physical examination, laboratory tests, and an electrocardiogram (ECG). Nutritional medicine consultation, dietary monitoring, and psychological screening were also performed. All subjects were seen every two weeks for the first two months and on a monthly basis thereafter. Participants had more extensive clinical visits at 6, 12, 18, 24 and 30 months, which included a history, physical examination, laboratory tests, and dietary questionnaire and consultation.

Because of the reported association of valvular heart disease with phen-fen and the FDA recommendations, the study was stopped prematurely, and drug therapy was discontinued in all patients. Combination phen-fen use was stopped after up to 30 months of drug therapy.

Medication schedule and dose changes. Dosing of phen-fen started at one 15-mg capsule of phentermine resin and one 20-mg tablet of *dl*-fenfluramine daily, and was titrated up to 30 mg and 60 mg, respectively. This was done to maximize appetite control and minimize side effects. The period of active drug treatment lasted up to 30 months as an adjuvant to diet, exercise, and behavior-modification programs.

Echocardiographic examination. The Beth Israel Deaconess Medical Center notified all study participants concerning phen-fen with two separate registered letters and offered them a free echocardiographic examination. Of the original 591 participants, 226 subjects were self-referred for, and underwent, echocardiographic evaluations within a mean of 97 days from the manufacturer's voluntary withdrawal of fenfluramine and dexfenfluramine from the U.S. market. All subjects continued to be followed after the drugs were discontinued according to the protocol, which involved routine clinic visits with a research nurse and physician and follow-up telephone calls with patients or their personal physicians. All subjects who did not return for an echocardiographic examination were doing well clinically, and they either refused to have an echocardiogram or had one done elsewhere.

Standard transthoracic two-dimensional echocardiography, color flow mapping, and continuous wave and pulse Doppler examinations were performed (Hewlett-Packard, Model 2500 or 5500, Andover, Massachusetts). Images were recorded on VHS tapes. All studies were reviewed and evaluated by two independent and experienced echocardiographers. The severity of a regurgitant lesion was assessed on a qualitative scale of trace, mild, moderate, or severe, using previously described methods (9,10). When tricuspid regurgitation was present, pulmonary artery pressure was estimated using the modified Bernoulli equation. Disagreement between readers on the presence of trace versus mild regurgitation occurred in four patients with aortic regurgitation and seven patients with mitral regurgitation; there was complete agreement on normal studies and moderate regurgitation. Whenever a discrepancy existed between readings, the more severe grading of valvular regurgitation was used. Significant valvular disease was determined using the FDA case definition—that is, mild or greater aortic regurgitation or mitral regurgitation $\geq$ moderate. Results were archived in the Beth Israel Deaconess Medical Center Cor Cardiology Database.

Statistical analysis. Statistical analysis was done using a commercially available statistical software program (SPSS, Version 6, Chicago, Illinois). Demographic, clinical, and echocardiographic characteristics of the subjects were compared using independent two-sample *t* tests and chi-square tests. Univariate analysis was used to identify differences in clinical variables in patients with and without valvular disease. Differences were considered statistically significant at the $p < 0.05$ level.

Table 1. Characteristics of the Study Population

	Echo* (n = 226)	No Echo (n = 365)
Age (yr)	46.9 ± 8.9†	44.3 ± 10
Start body mass index (kg/m^2)	39.8 ± 7.7	40.3 ± 9.1
Finish body mass index (kg/m^2)	35.9 ± 7.2	36.8 ± 8.7
Pulse (beats/min)	68 ± 8	69 ± 9
Blood pressure (mm Hg)	120 ± 14/75 ± 14	122 ± 15/77 ± 10
Glucose (mg/dl)	94 ± 27	97 ± 38
Cholesterol (mg/dl)	215 ± 37	213 ± 46
HDL (mg/dl)	51.5 ± 16	50.6 ± 19
Triglycerides (mg/dl)	163 ± 86	156 ± 99
Diabetes mellitus	7 (3%)	19 (5%)
Hypertension	43 (19%)	88 (24%)
"Heart murmur"	19 (8%)	18 (4.9%)
Cigarette smoking ≥1 ppd‡	4 (1.9%)	13 (3.5%)
Alcohol use (>4 drinks/wk)	15 (6.9%)	36 (9.8%)

*Echo = echocardiographic evaluation; †mean value ± SD; ‡ppd = packs per day.

RESULTS

The study population consisted of 183 women (81%) and 43 men (19%), with a mean age of 46.9 ± 8.9 years and a mean starting weight 110 ± 25.2 kg (Table 1). All subjects had normal baseline ECGs and glucose levels. The mean cholesterol level was 215 ± 37 mg/dl. At time of entry into the study, 19 subjects said that they had a prior history of a "heart murmur." On our echocardiographic evaluation, only 2 of the 19 subjects had mild aortic regurgitation. Seven subjects had type II diabetes and 43 had hypertension. No significant differences in baseline characteristics except age were found between those subjects undergoing echocardiography and those who did not. The subjects with echocardiograms were slightly older.

Concomitant psychotropic and cardiac drug use was present in 132 of 226 subjects. Twenty-seven subjects (20%) were on serotonin reuptake inhibitors at some point during the study. Five of 16 patients with significant valvular heart disease (31%) took serotonin reuptake inhibitors, whereas 22 of the 116 without valvular heart disease (19%) used them (p = NS). Other psychotropic drugs included tricyclic antidepressants in 10 subjects and amphetamines in 2 subjects. Cardiac drug use, including diuretics, occurred in 26 subjects (20%). Four of 16 subjects with valvular heart disease (25%) took cardiac medications; 22 of 116 subjects without valvular heart disease (19%) used cardiac drugs (p = NS).

The most common side effect of phen-fen use at any time during the study was a dry mouth, which occurred in 191 subjects (87%). Other common side effects included "not feeling oneself" (83%), somnolence (61%), sleep disturbance (60%), headache (59%) and confusion (51%).

Table 2. Valvular Regurgitation* (n = 226)

Valves	None	Trace	Mild	Moderate
Aortic	171 (76%)	40 (18%)	12 (5%)	3 (1%)
Mitral	70 (31%)	130 (58%)	23 (10%)	3 (1%)
Tricuspid	85 (38%)	131 (58%)	10 (4%)	0
Pulmonic	178 (79%)	46 (20%)	2 (1%)	0

*No valve had severe regurgitation.

Echocardiographic findings. Transthoracic echocardiography was performed on our subjects, with close attention to valve morphology and extent of valvular insufficiency (Table 2). In our study population of 226 subjects, only 18 subjects (8%) had significant valvular regurgitation as defined by FDA criteria. No subjects had severe regurgitation of any valve. Of the 18 subjects with significant valve lesions, the most common significant finding was mild or greater aortic insufficiency in 15 subjects and 3 subjects with moderate mitral regurgitation.

Of all the subjects with aortic regurgitation, 40 had only trace aortic insufficiency, 12 had mild aortic insufficiency, and only 3 subjects had moderate aortic insufficiency. In terms of mitral regurgitation, 156 subjects (69%) had some degree of mitral regurgitation, with most subjects (85%) having only trace mitral regurgitation, 23 subjects having mild and only 3 subjects with moderate mitral insufficiency. Tricuspid valve regurgitation was seen in 141 subjects (62%), with 93% of these subjects having only trace tricuspid regurgitation. Only two subjects had mild pulmonic insufficiency. No patients had moderate or severe tricuspid or pulmonic regurgitation.

Most subjects with valve disease in our study had regurgitation involving only a single heart valve. Six subjects (3%) had involvement of both aortic and mitral valves, and two of these subjects also had mild tricuspid regurgitation. Only one patient (0.5%) had significant regurgitation of both aortic and mitral valves by FDA criteria. Overall, aortic valve disease represented the highest proportion of cases of significant valvular regurgitation, followed by mitral, tricuspid and pulmonic, in declining order of prevalence.

For the purpose of analyzing the effect of phen-fen dose on the prevalence of valvular regurgitation, we divided subjects into low- and high-dose subgroups (Table 3). Low-dose subjects were those taking <3 tablets per day, with phen-fen combinations of 1–1, 1–0, or 0–1 tablets. High-dose groups were those taking ≥3 tablets, with phen-fen combinations of 2–1, 1–2, 2–2, or 3–2 tablets. Using FDA criteria for significant valvular regurgitation, no significant differences were noted between groups when separated by drug dose. We also analyzed the distribution of valvular abnormalities by duration of medication. Again, no significant differences were found between groups with

Table 3. Valvular Regurgitation by Dose and Duration of Medication

Duration	Phen-fen*	Aortic Regurgitation (Mild or greater)	Mitral Regurgitation (Moderate or greater)
≤6 months	Low	0	1
(n = 44)	High	2	1
7–12 months	Low	5	1
(n = 82)	High	2	0
13–18 months	Low	1	0
(n = 53)	High	1	0
19–24 months	Low	0	0
(n = 33)	High	2	0
>24 months	Low	0	0
(n = 14)	High	2	0
Total	Low	6	2
(n = 226)	High	9	1

*Low dose: Fewer than 3 tablets (phen-fen combinations of 1-1, 0-1, 1-0). High dose: Equal to or greater than 3 tablets (2-1, 1-2, 2-2, 3-2).

valvular regurgitation when differentiated by duration of drug therapy.

Univariate comparisons were performed for multiple baseline variables between those subjects with significant valvular heart disease (n = 18) and those without valvular disease (n = 208). The variables analyzed and their matched values in both groups are shown in Table 4. No significant differences were found between those with and without valvular heart disease when compared by phentermine or fenfluramine dose, age, start/finish weights, percentage weight loss, body mass index, baseline mean heart rate, blood pressure, fasting cholesterol or serum glucose measurements.

Table 4. Comparison of Groups With and Without Valvular Heart Disease

	VHD* (n = 18)	No VHD (n = 208)	p Value
Fen dose (mg)	29.4 ± 10.3	27.2 ± 10.9	0.43
Phen dose (mg)	17.6 ± 5.9	17.7 ± 6.0	0.96
Mean duration (months)	12.9 ± 8.6	12.3 ± 7.3	0.76
Age (yrs)	48.3 ± 10.9	46.9 ± 8.9	0.54
Start weight (kg)	108.2 ± 28.6	110.4 ± 24.9	0.73
Finish weight (kg)	96.3 ± 22.4	99.8 ± 23.8	0.56
% Weight loss	10.2 ± 7.0	9.5 ± 6.9	0.69
BMI† (kg/m^2)	40.1 ± 8.7	39.6 ± 7.6	0.77
Mean heart rate	69.0 ± 8.2	68.0 ± 8.5	0.62
SBP‡ (mm Hg)	122.9 ± 15.9	120.1 ± 14.8	0.45
DBP§ (mm Hg)	78.5 ± 10.7	75.5 ± 10.2	0.25

*VHD = valvular heart disease (by FDA criteria); †BMI = body mass index; ‡SBP = systolic blood pressure; §DBP = diastolic blood pressure; data are mean value ± SD.

Table 5. Prevalence of Valvular Heart Disease in the Framingham Heart Study Compared With Our Phen-fen Subjects

	Phen-fen Subjects (%)	Framingham Heart Study (%)
Aortic Regurgitation		
Mild	5.3	4.4
Moderate	1.3	0.5
Mitral Regurgitation		
Mild	10.2	17.5
Moderate	1.3	1.6
Tricuspid Regurgitation		
Mild	4.4	15.7
Moderate	0	1

DISCUSSION

Our echocardiographic investigation involved subjects taking phen-fen combination therapy within the guidelines of a strict, medically supervised study protocol, with a single central echocardiographic reading center, and extensive data collection regarding numerous potential confounding variables. Early reports describing the prevalence of valvular heart disease associated with phen-fen in less well-defined study populations have found significant valvular pathology in up to 38% of cases (3); this is much higher than previously reported Doppler studies of randomly derived samples from the general population (11,12). In our study population, only 18 subjects (8%) had significant valvular regurgitation of the aortic or mitral valves by FDA criteria. These findings question the contribution of phen-fen therapy as an independent risk factor for valvular regurgitation.

Valvular regurgitation in normal subjects. Singh and colleagues (12) have recently reported their retrospective analysis of valvular regurgitation in a population-based cohort of subjects from the Framingham Heart Study (Table 5). This represents the closest control population to our group, and is derived from a similar geographic area. A total of 1,663 men (age 55 ± 10 years) and 1,966 women (age 54 ± 10 years) underwent routine two-dimensional and color flow echocardiography with close attention to valvular regurgitation. In their cohort, 1.6% of subjects had moderate or greater mitral regurgitation, whereas 4.8% had mild or greater aortic insufficiency. In our population, 1.3% of subjects had moderate or greater mitral regurgitation and 6.6% had mild or greater aortic insufficiency, which is similar to the Framingham population sample. Thus, it appears that a significant proportion of healthy men and women have detectable valvular regurgitation by color flow Doppler, and that valvular abnormalities may represent age-related degenerative changes. In addition, the FDA's criteria for aortic regurgitation may be too narrow, and the case definition for pathologic regurgitation may need to be modified or made age specific.

Valvular disease with phen-fen. In September 1997, the FDA received independent echocardiographic prevalence surveys of patients from five different areas who had received dexfenfluramine or fenfluramine alone or in combination with phentermine (3). Most subjects (87%) were women, with sample sizes ranging from 20 to 115 patients (total patients = 284), with a mean age of 48 years (range 46 to 51 years), and median duration of drug exposure of 14 months (range 6 to 30 months). The median dose of fenfluramine was 40 mg/day (20 to 60 mg/day), phentermine 30 mg/day (15 to 37.5 mg/day) and dexfenfluramine 30 mg/day (15 to 30 mg/day). Although the methodology of these surveys differed, the prevalence of valvular disease meeting the FDA case definition for significant valvular regurgitation was similar in all five surveys, and ranged from 30.0% to 38.3% (overall: 32.8%). The prevalence of valvular abnormalities was increased with drug use ≥6 months. However, our data in a similar age population showed a significantly lower prevalence of valvular heart disease and no relationship to dose or duration of phen-fen use.

A recent report from Khan et al. (13) described the effects of three appetite-suppressant drugs in a modified study, which included echocardiography to evaluate the presence of valve disease in patients after they stopped taking the drugs. Using FDA criteria, valve regurgitation was present in 25.2% of patients (n = 163) taking phen-fen, 12.8% of patients (n = 39) given dexfenfluramine, and 22.6% of patients (n = 31) taking dexfenfluramine and phentermine. Their results may differ from our investigation owing to the much higher dose and duration of drug therapy. In addition, echocardiography was performed much earlier in their study, with 18% of patients taking drugs at the time of the echocardiogram, and another 20% within 30 days of stopping medications.

Another recent investigation by Weissman et al. (14) evaluated the use of dexfenfluramine on valvular heart disease. Their study compared echocardiograms of 1,072 patients taking dexfenfluramine hydrochloride, sustained-release dexfenfluramine or placebo. Using the FDA case definition, significant aortic regurgitation was seen in only 5% of dexfenfluramine patients, 5.8% of patients on sustained-release dexfenfluramine, and 3.6% on placebo; significant mitral regurgitation occurred in 1.7%, 1.8%, and 1.2% of patients, respectively. Overall, no statistically significant increase occurred in the prevalence of clinically relevant heart valve regurgitation following dexfenfluramine use for up to three months compared with placebo. These findings are consistent with our own results, as well as those of the Framingham Heart Study, and they suggest that the short-term use of dexfenfluramine is not associated with a significant increased risk for valve disease.

The anorectic action of fenfluramine may be mediated through the activation of serotonergic pathways in the brain; phentermine is a noradrenergic agent, which interferes with the pulmonary clearance of serotonin. Histopathologic changes noted in prior studies of patients on phen-fen are characterized by fibroplasia involving the valvular endocardium, which are microscopically identical to those seen in patients with ergot-alkaloid–induced and carcinoid valve disease (2,4–6). Twenty percent of our subjects were taking serotonin reuptake inhibitors, yet there was no increased prevalence of valvular heart disease in those taking serotonin reuptake inhibitors compared with those not taking these drugs.

Study limitations. Although all subjects were followed in a prospective, carefully controlled investigational protocol and multiple readers at one center interpreted all echocardiograms, there are limitations to our study. First, our study did not have a control group and not all subjects had an echocardiographic evaluation. However, the prevalence of valvular disease in our study was similar to the prevalence in the Framingham Heart Study. In addition, no significant differences in baseline characteristics were found between those subjects with and without echocardiographic examinations, and all subjects currently are asymptomatic and doing well clinically.

Second, inherent inaccuracies exist in differentiating relatively mild degrees of valvular regurgitation, especially using qualitative scoring systems; our study is no different from previous reports in this regard. The differentiation of trace from mild degrees of valvular regurgitation is subjective, and both intra- and interobserver variations are to be expected. We accounted for this by using multiple readers, and we recorded the largest degree of valvular regurgitation for the purpose of data analysis.

Third, in a study population such as ours and the Framingham Heart Study, most valve lesions occurred in asymptomatic individuals without a history of heart murmurs. Prior random population surveys have shown that only 17% of all patients with echocardiographic evidence of valvular heart disease have audible heart murmurs (3). Given that historical and physical examinations do not appear sensitive enough to assess the true prevalence of valvular lesions in such a population, and that few subjects had pretreatment echocardiograms for comparison, selection bias could play a significant role in the final analysis of any given population.

Fourth, neither direct inspection nor histopathologic confirmation was performed in any patient. Therefore, our study does not address the issue of whether or not histologic changes secondary to phen-fen use (which were not visible macroscopically by transthoracic echocardiography) may still have occurred. Finally, our study did not address the development of significant valvular disease in the future. Long-term, prospective studies will be needed to answer that question.

Acknowledgments

We are indebted to Maureen P. McGuire, RDCS, chief echocardiographic technician, and Ann McNamara, RN, for their assistance in the project. Wyeth-Ayerst Laborato-

ries (fenfluramine) and Medeva Pharmaceuticals (phentermine) provided support and drugs for the weight-loss study. Boston Obesity/Nutrition Research Center (DK 46200-04) provided support for the development of the weight-loss database.

Reprint requests and correspondence: Dr. Andrew J. Burger, Beth Israel Deaconess Medical Center, West Campus, Noninvasive Cardiology Laboratory, Baker-3, 1 Deaconess Road, Boston, Massachusetts 02215. E-mail: aburger@caregroup.harvard.edu.

REFERENCES

1. Langreth R. Critics claim diet clinics misuse obesity drugs. Wall Street Journal, March 31, 1997:B8.
2. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997;337: 581–8.
3. Bowen R, Glicklich A, Khan M, et al. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: U.S. Department of Health and Human Services Interim Public Health Recommendations. MMWR 1997;46:1061–6.
4. Pellikka PA, Tajik AJ, Khanderia BK, et al. Carcinoid heart disease: clinical and echocardiographic spectrum in 74 patients. Circulation 1993;87:1188–96.
5. Redfield MM, Nicholson WJ, Edwards WD, et al. Valve disease associated with ergot alkaloid use: echocardiographic and pathologic correlations. Ann Int Med 1992;117:50–2.
6. Robiolio PA, Rigolin VH, Wilson JS, et al. Carcinoid heart disease: correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. Circulation 1995;92:790–5.
7. Pondimin and Redux to Be Voluntarily Withdrawn. Wyeth-Ayerst Company Press Release, Philadelphia, September 15, 1997.
8. Weintraub M. Long-term weight control study: conclusions. Clin Pharmacol Ther 1992;51:642–6.
9. Helmcke F, Nanda NC, Hsiung MC, et al. Color Doppler assessment of mitral regurgitation with orthogonal planes. Circulation 1987;75: 175–83.
10. Perry GJ, Helmcke F, Nanda NC, et al. Evaluation of aortic insufficiency by Doppler color flow mapping. J Am Coll Cardiol 1987;9:952–9.
11. 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.
12. Singh JP, Evans JC, Levy D, et al. Prevalence of valvular regurgitation in a population-based cohort: Framingham heart study (abstr). Circulation 1997;96:I-541.
13. Khan MA, Herzog CA, St. Peter JV, et al. The prevalence of cardiac valvular insufficiency assessed by transthoracic echocardiography in obese patients treated with appetite-suppressant drugs. N Engl J Med 1998;339:713–8.
14. Weissman NJ, Tighe JF, Gottdiener JS, et al. An assessment of heart-valve abnormalities in obese patients taking dexfenfluramine, sustained-release dexfenfluramine, or placebo. N Engl J Med 1998; 339:725–32.