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Increased Risk of Left Heart Valve Regurgitation Associated With Benfluorex Use in Patients With Diabetes Mellitus

A Multicenter Study

Christophe Tribouilloy, MD, PhD; Dan Rusinaru, MD, PhD; Sylvestre Maréchaux, MD, PhD; Antoine Jeu, MD; Stéphane Ederhy, MD; Erwan Donal, MD; Patricia Réant, MD; Elise Arnalsteen, MD; Jacques Boulanger, MD; Pierre-Vladimir Ennezat, MD, PhD; Thierry Garban, MD; Yannick Jobic, MD

Background—Benfluorex was withdrawn from European markets in June 2010 after reports of an association with heart valve lesions. The link between benfluorex and valve regurgitations was based on small observational studies and retrospective estimations. We therefore designed an echocardiography-based multicenter study to compare the frequency of left heart valve regurgitations in diabetic patients exposed to benfluorex for at least 3 months and in diabetic control subjects never exposed to the drug.

Methods and Results—This reader-blinded, controlled study conducted in 10 centers in France between February 2010 and September 2011 prospectively included 376 diabetic subjects previously exposed to benfluorex who were referred by primary care physicians for echocardiography and 376 diabetic control subjects. Through the use of propensity scores, 293 patients and 293 control subjects were matched for age, sex, body mass index, smoking, dyslipidemia, hypertension, and coronary artery disease. The main outcome measure was the frequency of mild or greater left heart valve regurgitations. In the matched sample, the frequency and relative risk (odds ratio) of mild or greater left heart valve regurgitations were significantly increased in benfluorex patients compared with control subjects: 31.0% versus 12.9% (odds ratio, 3.55; 95% confidence interval, 2.03–6.21) for aortic and/or mitral regurgitation, 19.8% versus 4.7% (odds ratio, 5.29; 95% confidence interval, 2.46–11.4) for aortic regurgitation, and 19.4% versus 9.6% (odds ratio, 2.38; 95% confidence interval, 1.27–4.45) for mitral regurgitation.

Conclusions—Our results indicate that the use of benfluorex is associated with a significant increase in the frequency of left heart valve regurgitations in diabetic patients. The natural history of benfluorex-induced valve abnormalities needs further research. (*Circulation*. 2012;126:2852-2858.)

Key Words: diabetes mellitus ■ drugs ■ echocardiography ■ regurgitation ■ valves

Exposure to amphetamine-based appetite-suppressant drugs such as fenfluramine and dexfenfluramine has been associated with life-threatening adverse effects as pulmonary hypertension and cardiac valve regurgitations,¹⁻³ leading to the withdrawal of these drugs from the US market in 1997. Benfluorex, an amphetamine derivative related to fenfluramine and dexfenfluramine in terms of structure, clinical effect, and metabolism (hypoglycemic and hypolipidemic properties), has been prescribed in Europe, Asia, and South Africa in patients with

hypertriglyceridemia and type II diabetes mellitus. It has also been used off-label as a slimming aid.

Clinical Perspective on p 2858

Benfluorex was withdrawn from the European market in 2010 after the publication of several reports suggesting a link between exposure to benfluorex and the occurrence of severe valve regurgitations as previously observed with other fenfluramine derivatives.⁴⁻⁹ A case series reported 40 cases of

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moderate or severe valve regurgitation after exposure to benfluorex.⁷ Patients in this report were highly symptomatic and frequently had multiple valve abnormalities and pulmonary arterial hypertension.⁷ Moreover, 2 case-control studies have reported an important proportion of benfluorex use in patients admitted to hospital for severe organic mitral regurgitation of unclear origin.^{8,9} In a retrospective cohort study of 2 French national databases including a large number of patients with diabetes mellitus, Weill et al¹⁰ observed a 3-fold increase in the risk of hospitalization for valve regurgitation and a 4-fold increase in the risk of valve replacement surgery in patients exposed to benfluorex. According to recent estimations, exposure to benfluorex might have been responsible for up to 3100 admissions to hospital for valvular heart disease and up to 1300 deaths resulting from valve regurgitations in France.¹¹ These data demonstrate that benfluorex has fenfluramine-like adverse effects on valve structure and function and suggest excess morbidity and mortality in exposed individuals.

However, previous studies were derived from hospital discharge records and thus do not reflect the continuum of the disease and have uncertain validity resulting from the selection of the most severe forms of valve lesions and by shifts in coding practices because of reimbursement incentives. Therefore, from a population-based perspective, we lack prospective, controlled data on the relationship between the exposure to benfluorex and the risk of valve regurgitations. To address this issue, we conducted an echocardiography-based multicenter study and prospectively included a group of diabetic patients without history of valve heart disease who had taken benfluorex for at least 3 months and a matched group of diabetic patients who had not taken this drug. Our aim was to compare the frequency of left heart valve regurgitations in patients with diabetes mellitus who had taken benfluorex and matched control subjects.

Methods

Study Design

The marketing authorization of benfluorex was suspended in France in November 2009, and the French drug regulatory agency (Agence française de sécurité sanitaire des produits de santé) issued a public health advisory inviting all patients with previous exposure to benfluorex to contact their primary care physician. Primary care physicians further referred patients to a cardiologist for echocardiography. On November 26, 2009, cardiology departments of all French university hospitals, important private clinics, and general hospitals were contacted by e-mail on behalf of the French Society of Cardiology and invited to participate in this echocardiography prospective multicenter study. Investigators (a complete list can be found in the online-only Data Supplement) were asked to prospectively enroll all consecutive diabetic patients without a history of heart valve disease who were previously exposed to benfluorex and referred by their primary care physicians for echocardiography. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL, use of hypoglycemic agents, or a history of physician-diagnosed diabetes mellitus. Ten centers participated in the present study (Centre hospitalier universitaire d'Amiens, Centre hospitalier de Beauvais, Centre hospitalier universitaire de Bordeaux, Centre hospitalier universitaire de Brest, Centre hospitalier de Compiègne, Centre hospitalier universitaire de Lille, Groupe hospitalier de l'Institut catholique de Lille, Centre hospitalier universitaire de Nantes, AP-HP Hôpital Saint Antoine Paris, and Centre hospitalier universitaire de Rennes). This observational study was approved by the ethics committee for noninterventional research at the University of Picardie, Amiens, France. Oral consent was obtained for each

enrolled patient. Only 3 exposed patients referred by their primary care physicians did not agree to participate.

Patients

All consenting benfluorex-treated patients referred by primary care physicians for echocardiography to the participating centers were enrolled in the present study if they had no history of heart valve disease and if they had at least a previous 3-month exposure to benfluorex since January 1, 2000. All patients were included after the market withdrawal of the drug, starting February 1, 2010. It is worth noting that all patients exposed to benfluorex who were referred for a second expert evaluation after an initial echocardiography were not included in the present study to avoid nonconsecutive enrollment that might contribute to an overestimation of the frequency of valve regurgitations. Patients who had been exposed to drugs that could induce valvular heart diseases (rye ergot alkaloids, fenfluramine/phentermine, dexfenfluramine, pergolide) were also excluded. During a 20-month period, 376 diabetic patients previously treated with benfluorex were included. Demographic data, cardiovascular risk factors, presence of symptoms, and echocardiography parameters were recorded. Daily doses of benfluorex, and total duration of treatment, were systematically and prospectively obtained before echocardiography. Primary care physicians were contacted by phone at the time of the echocardiography if there was doubt about medications use or exposure time.

Control Subjects

During the same time period, 411 consecutive diabetic patients without previous exposure to benfluorex or other drugs associated with valve disease and without history of valve disease who were referred by their primary care physicians to the outpatient diabetes clinics of the participating centers were approached to participate. A total of 376 patients consented and served as control subjects. Collection of data was similar to that for patients treated with benfluorex.

Echocardiography

Complete echocardiography examinations on commercially available ultrasound systems were performed in each center by experienced operators according to a standardized protocol with multiple 2-dimensional incidences and use of different Doppler modes. When possible, we obtained views of the mitral, aortic, tricuspid, and pulmonary valves. To this effect, magnified video loops were recorded in parasternal long-axis view for the aortic and mitral valves; the parasternal short-axis view for the pulmonary, tricuspid, and aortic valves; apical view for the tricuspid, mitral, and aortic valves; and subcostal view for all valves when possible. All recordings were obtained with and without Doppler color flow mapping. Echocardiography examinations were stored in digital DICOM (digital imaging and communications in medicine) format on digital versatile disks for subsequent offline analysis. All echocardiograms were read independently by 2 cardiologists who were experts in echocardiography and valvular heart diseases and were blinded to all aspects of patient history, including benfluorex use. If there was disagreement between the 2 readers, a third independent expert performed a final blinded reading and gave the final grading. The severity of valve regurgitations was expressed according to the recommendations of the European Society of Echocardiography (absence or trace, mild, moderate, severe).^{12,13} The moderate regurgitation group was subclassified into mild to moderate and moderate to severe.^{12,13} Standard 2-dimensional measurements (left ventricular end-diastolic and end-systolic diameters) were obtained from the parasternal long-axis views. Left atrium surface was calculated by planimetry from apical 4-chamber views. Left ventricular ejection fraction was calculated with the Simpson biplane method. The maximal velocity of the tricuspid regurgitation was estimated from continuous Doppler.

End Points

The primary echocardiography end point was mild or greater left heart valve regurgitation (mitral and/or aortic). Secondary end points

Table 1. Characteristics* of Patients Treated With Benfluorex and Control Subjects Before and After Matching

Variable	Overall Cohort			Matched Pairs			Standardized Difference, %
	Benfluorex (n=376)	Control Subjects (n=376)	P	Benfluorex (n=293)	Control Subjects (n=293)	P	
Age, y	63.6±10.8	65.6±12.0	0.26	63.0±10.0	64.0±12.0	0.98	9.05
Female sex, % (n)	49 (184)	43 (160)	0.08	46 (136)	45 (133)	0.80	2.01
Body mass index, kg/m ²	31.5±5.5	29.4±5.7	<0.001	30.4±4.9	30.3±5.5	0.90	1.90
Past or active smoker, % (n)	17 (63)	14 (54)	0.37	17 (50)	16 (47)	0.82	2.69
Dyslipidemia, % (n)	68 (254)	58 (218)	0.007	65 (189)	67 (197)	0.49	4.22
Hypertension, % (n)	68 (257)	67 (252)	0.70	68 (200)	69 (203)	0.86	2.15
Coronary artery disease, % (n)	14 (53)	19 (72)	0.06	16 (46)	17 (49)	0.82	2.69

Continuous variables are expressed as mean±SD; dichotomous variables, as percentage and absolute number. Subjects treated with benfluorex and control subjects were matched for age, sex, body mass index, smoking, dyslipidemia, hypertension, and coronary artery disease.

*Clinical variables used for matching.

were mild or greater mitral regurgitation and mild or greater aortic regurgitation.

Statistical Analysis

Quantitative data are presented as mean±SD. Qualitative data are presented as absolute numbers and percentages. Continuous data were compared by use of the unpaired Student *t* test or the Mann-Whitney *U* test in the case of highly skewed variables. Categorical data were compared by use of the χ^2 test or Fisher exact test as appropriate. Interreader variability was assessed with the κ statistic.

The imbalance in baseline variables between patients and control subjects was reduced by the use of propensity scores. The propensity scores for benfluorex exposure were estimated in each patient with a multivariable logistic model in a forward stepwise regression analysis.^{14,15} The variables in the model were age, sex, body mass index, smoking, dyslipidemia, hypertension, and coronary artery disease. Goodness of fit, assessed by the Hosmer-Lemeshow test ($\chi^2=9.3$; $P=0.56$), and the discriminatory power of the model (area under the receiver-operating characteristic curve, $C=0.71$) were acceptable. Propensity scores were used to match each patient to a unique control subject with a propensity score within 2% through the use of a greedy-matching algorithm that successively searched for matches by 5, 4, 3, and 2 digits. In total, 293 pairs of patients (78%) were successfully matched to individual control subjects within this tolerance. Mean propensity score in patients before matching was 0.52719 compared with 0.462365 in control subjects ($P<0.001$). After matching, mean propensity score was 0.50023 in patients, comparable to that of the control group (0.50017; $P=0.98$). The success of the propensity score matching was assessed by checking standardized differences between groups after matching, ie, the absolute difference in sample means divided by an estimate of the pooled standard deviation of the variable expressed as a percentage. Balancing was considered successful if the standardized differences were <10%. The distributions of dichotomous variables between the 2 groups in the matched cohort were compared with the use of McNemar tests. Continuous variables were compared between groups in the matched cohort through the use of paired *t* tests or Wilcoxon signed-rank tests as appropriate.

In the overall cohort, classic multivariable logistic regression adjusted for age, sex, body mass index, smoking, dyslipidemia, hypertension, and coronary artery disease was used to obtain adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the outcome variables. For the matched cohort, OR estimates and 95% CIs for the outcome variables were produced from univariate conditional logistic regression of each dichotomous variable on benfluorex exposure, conditioning on the propensity-matched pairs.

All *P* values are the result of 2-tailed tests. For all tests, a value of $P<0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 13.0 (SPSS Inc, Chicago, IL) and STATA version 10 (Stata Corp, College Station, TX).

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

Results

A total of 752 diabetic subjects (376 patients and 376 control subjects) were enrolled during a 20-month period in the participating centers. Characteristics used for propensity matching are presented in Table 1 according to exposure to benfluorex. Mean age was similar in patients and control subjects. Compared with control subjects, benfluorex patients were more frequently women, had greater body mass index, and were more often dyslipidemia. In patients exposed to benfluorex, mean dose was 352 mg (median, 450; range, 150–900 mg), and mean treatment duration 61.2 months (median, 36.5 months; range, 3–360 months). After matching, there were no statistically significant differences between the 293 benfluorex patients and the 293 control subjects in terms of variables used for matching (all standardized differences <10%; Table 1). Duration since diagnosis of diabetes mellitus was 11.7±8.8 years in benfluorex patients and 11.6±8.9 years in control subjects ($P=0.88$). Among benfluorex patients, 9.8% were on diet only, 83.2% were treated with ≤ 2 antidiabetic drugs, and 7.0% had ≥ 3 antidiabetic drugs. The distribution of antidiabetic regimens was similar among control subjects (10.1%, 83.8%, and 6.1%, respectively; all $P>0.5$). Cardiac murmurs were identified at the time of echocardiography more frequently in patients exposed to benfluorex compared with control subjects (8.5% versus 2.4%; $P<0.001$ in the total cohort).

Left Heart Valve Regurgitation

In the overall population, the frequency of mild or greater aortic and/or mitral regurgitation was 29.7% for benfluorex patients and 13.6% for control subjects ($P<0.001$). Mild aortic and/or mitral regurgitation was observed in 22.3% of patients compared with 12.8% of control subjects ($P<0.001$; Table 2). Moderate aortic and/or mitral regurgitation was also more frequent in benfluorex patients compared with control subjects (7.4% versus 0.8%; $P<0.001$; Table 2). There were no cases of severe aortic and/or mitral regurgitation. The frequency of mild or greater aortic and/or mitral regurgitation was still significantly higher in patients exposed to benfluorex compared with control subjects

Table 2. Frequency of Valvular Regurgitations According to the Degree of Severity in Patients Exposed to Benfluorex Compared With Control Subjects Before and After Matching

Valvular Regurgitations	Overall Cohort				Matched Pairs			
	Benfluorex (n=376), % (n)	Control Subjects (n=376), % (n)	OR* (95% CI)	P	Benfluorex (n=293), % (n)	Control Subjects (n=293), % (n)	OR† (95% CI)	P
Aortic and/or mitral regurgitation								
None or trace	70.2 (264)	86.4 (325)	Referent		68.9 (202)	87.0 (255)	Referent	
Mild	22.3 (84)	12.8 (48)	2.50 (1.66–3.78)	<0.001‡	24.2 (71)	12.6 (37)	2.35 (1.55–3.78)	<0.001‡
Moderate	7.4 (28)	0.8 (3)	17.6 (5.10–61.1)	<0.001‡	6.8 (20)	0.3 (1)	20.0 (2.68–149.1)	0.003‡
Severe	0 (0)	0 (0)	...		0 (0)	0 (0)	...	
Aortic regurgitation								
None or trace	80.1 (301)	95.5 (359)	Referent		80.2 (235)	95.2 (279)	Referent	
Mild	14.4 (54)	4.3 (16)	4.45 (2.44–8.13)	<0.001‡	15.4 (45)	4.4 (13)	4.20 (2.17–7.95)	<0.001‡
Moderate	5.6 (21)	0.3 (1)	35.6 (4.59–230.3)	0.001‡	4.4 (13)	0.3 (1)	14.8 (1.88–99.7)	0.013‡
Severe	0 (0)	0 (0)	...		0 (0)	0 (0)	...	
Mitral regurgitation								
None or trace	81.9 (308)	89.4 (336)	Referent		80.5 (236)	90.4 (265)	Referent	
Mild	16.0 (60)	10.1 (38)	1.94 (1.23–3.08)	0.008‡	16.7 (49)	9.6 (28)	1.92 (1.15–3.11)	0.014‡
Moderate	2.1 (8)	0.5 (2)	8.62 (1.63–45.6)	0.011‡	2.7 (8)	0.0 (0)	5.62 (1.35–38.8)	0.02‡
Severe	0 (0)	0 (0)	...		0 (0)	0 (0)	...	

Odds ratios reflect relative risk of mild and moderate regurgitations, respectively, compared to the group “none or trace” (referent).

OR indicate odds ratio; CI, confidence interval. Continuous variables are expressed as mean value \pm SD; dichotomous variables, as percentage and absolute number. Relative risks of “mild or greater” valve regurgitations are not reported in this table but are detailed in the text.

*Odds ratios for valvular regurgitations associated with benfluorex exposure were estimated by logistic regression adjusted for age, sex, body mass index, smoking, dyslipidemia, hypertension, and coronary artery disease.

†Odds ratios for valvular regurgitations associated with benfluorex exposure were estimated by propensity-based matched pairs univariate conditional logistic regression.

‡P values refer to comparisons of “mild” and “moderate” regurgitation, respectively to the group “none or trace” (referent).

after the exclusion of patients with murmurs (25.0% versus 12.5%; $P < 0.001$), patients with overt (New York Heart Association class III or IV) symptoms (29.7% versus 13.5%; $P < 0.001$), or both (29.6% versus 13.1%; $P < 0.001$). Among patients exposed to benfluorex (median duration of treatment, 36.5 months), the frequency of left heart valve regurgitations was greater in patients with treatment duration ≥ 36.5 months compared with patients with a treatment duration < 36.5 months (35% versus 23.6%; $P = 0.001$). Classic multivariable logistic regression showed increased risk of mild or greater left heart valve regurgitation associated with exposure to benfluorex (adjusted OR, 3.17; 95% CI, 2.05–4.87).

The frequency of mild or greater aortic and/or mitral regurgitation in the matched sample was significantly higher for benfluorex patients compared with control subjects (31.0% versus 12.9%; $P < 0.001$). Mild and moderate aortic regurgitation and/or mitral regurgitation were each individually more frequent in patients compared with control subjects (Table 2). Univariate conditional logistic regression on the matched pairs confirmed the risk of mild or greater aortic and/or mitral regurgitation associated with benfluorex exposure (OR, 3.55; 95% CI, 2.03–6.21). Two alternative approaches to adjustment for confounding, classic multiple logistic regression and logistic regression modeling of the matched cohorts with adjustment for the continuous propensity score, basically yielded results similar to propensity-based matched-pairs conditional logistic regression.

Adjustment for overt symptoms (class III/IV dyspnea) at the time of echocardiography and the presence of a cardiac

murmur did not change the association between exposure to benfluorex and the presence of mild or greater left heart valve regurgitations (adjusted OR, 3.01; 95% CI, 1.98–4.68).

Aortic Regurgitation

In both the total and matched samples, the frequency of mild or greater aortic regurgitation was higher in benfluorex patients than in control subjects (20.0% versus 4.6% in the total sample and 19.8% versus 4.7% in the matched sample; both $P < 0.001$). This was due to a greater frequency of mild and moderate aortic regurgitation in patients compared with control subjects (Table 2). Among exposed patients with moderate aortic regurgitation, 20 had mild to moderate regurgitation and 1 patient had moderate to severe regurgitation. The risk of mild or greater aortic regurgitation associated with benfluorex exposure was increased >5 -fold in both the overall (adjusted OR, 5.21; 95% CI, 2.80–9.67) and matched groups (OR, 5.29; 95% CI, 2.46–11.4). Exposure to benfluorex was associated with an increased risk of moderate aortic regurgitation but also mild aortic regurgitation (Table 2).

Mitral Regurgitation

The frequency of mild or greater mitral regurgitation was 18.1% in the total sample and 19.4% in the matched sample compared with 10.6%, and 9.6% in the control subjects (both $P < 0.001$). Similar to aortic regurgitation, there was a greater frequency of mild and moderate mitral regurgitation in patients compared with control subjects (Table 2). Among exposed patients with moderate mitral regurgitation, 6 had

Table 3. Other Parameters in Patients Treated With Benfluorex Compared With Control Subjects Before and After Matching

	Benfluorex (n=376)	Control Subjects (n=376)	<i>P</i>	Benfluorex (n=293)	Control Subjects (n=293)	<i>P</i>
NYHA class III–IV dyspnea, % (n)	12.2 (46)	7.4 (28)	0.028	11.3 (33)	8.5 (25)	0.11
LV ejection fraction, %	62.8±7.3	61.2±7.7	0.008	62.5±7.4	61.6±7.2	0.01
LV end-diastolic diameter, mm	50.3±6.2	48.4±6.7	<0.001	49.9±5.9	47.9±6.7	0.001
LV end-systolic diameter, mm	31.9±6.3	31.5±6.6	0.42	31.6±6.2	30.9±6.4	0.24
Left atrium surface, cm ²	20.0±5.5	20.0±5.6	0.94	19.9±5.5	19.8±5.3	0.93
TR maximal velocity, m/s	2.45±0.36	2.41±0.41	0.18	2.45±0.38	2.39±0.39	0.13

LV indicates left ventricular; NYHA, New York Heart Association; and TR, tricuspid regurgitation. Continuous variables are expressed as mean value±SD; dichotomous variables, as percentage and absolute number.

mild to moderate regurgitation and 2 had moderate to severe regurgitation. The risk of mild or greater mitral regurgitation associated with benfluorex exposure was increased >2-fold in both the overall (adjusted OR, 2.34; 95% CI, 1.42–3.84) and matched (OR, 2.38; 95% CI, 1.27–4.45) groups. Exposed patients had increased risk of moderate mitral regurgitation but also mild mitral regurgitation (Table 2).

Aortic and Mitral Regurgitation

The percentage of patients with combined mild or greater aortic and mitral regurgitation mild was significantly higher in benfluorex patients compared with control subjects (8.2% versus 1.9% in the overall sample and 8.2% versus 1.7% in the matched sample; both $P<0.001$). The risk of combined mild or greater aortic and mitral regurgitation associated with benfluorex exposure was increased ≈5-fold in the overall group (adjusted OR, 5.06; 95% CI, 2.15–11.9) and ≈4-fold among the matched pairs (OR, 4.16; 95% CI, 1.56–11.2).

Reproducibility

The κ coefficients for the interreader concordance in 3-level categorizations (none or trace, mild, moderate) of regurgitation were 0.80 for aortic regurgitation, 0.78 for mitral regurgitation, and 0.81 for aortic and/or mitral regurgitation.

Other Clinical and Echocardiography Findings

In the overall cohort, at the time of echocardiography, patients exposed to benfluorex more often had overt symptoms (12.2% versus 7.4%; $P=0.028$) and greater left ventricular ejection fraction and left ventricular end-diastolic dimensions (Table 3). The frequency of mild or greater tricuspid regurgitation was 10.5% in benfluorex patients and 8.1% in control subjects ($P=0.21$). The frequency of mild or greater pulmonary regurgitation was also similar in patients and control subjects (7.9% versus 8.7%; $P=0.93$). After matching, overt symptoms were no longer different between exposed patients and control subjects (11.3% versus 8.5%; $P=0.11$; Table 3).

Discussion

This is the first study to document an increased frequency of left heart valve regurgitations among diabetic patients who were treated with benfluorex compared with untreated diabetic subjects.

Several drugs have been incriminated in the development of heart valve disease.^{16,17} Fenfluramine and dexfenfluramine were withdrawn from the market in 1997 after reports

documenting increased risk of pulmonary hypertension¹⁸ and heart valve regurgitation^{1,19,20} in patients treated with these drugs. The main 2-dimensional echo feature of toxic heart valve regurgitating lesions is “restriction,” ie, stiffening of leaflets with retraction of leaflets or subvalvular apparatus toward the apex (for the mitral valve) and opening/closure with obvious doming of the leaflets (for the aortic valve).¹⁷ Benfluorex, a fenfluramine derivative prescribed in Europe and Asia in patients with hyperlipidemia and diabetes mellitus but also widely used off-label as an appetite suppressant, has recently been reported to have similar adverse effects on heart valves. Like fenfluramine, benfluorex may exert a serotonergic effect via its metabolite, norfenfluramine. Norfenfluramine has the capacity to activate the 5-HT(2B) serotonin receptors in heart valves, which play a significant role in the development of drug-induced fibrotic valvular disease.^{16,17} The molecular mechanism is a G-protein-mediated upregulation of transforming growth factor- β that stimulates mitogenic pathways and leads to increased production of glycosaminoglycans and collagen.^{21,22}

The risk of heart valve disease associated with exposure to benfluorex was acknowledged after the recent publication of data.^{4–11,23,24} The first case reports of valve disease and/or pulmonary hypertension in patients exposed to benfluorex were published between 2003 and 2010.^{4–6,23} Then, 40 cases of moderate or severe valve disease associated with benfluorex exposure were reported and analyzed.⁷ These cases represent the most severe presentation of benfluorex-associated valve disease and have quite homogeneous presentation: middle-aged patients, especially overweight women, suffering from symptomatic heart failure caused by significant aortic, mitral, or frequently multiple regurgitating valve lesions.⁷ The high frequency of combined aortic and mitral restrictive valve regurgitation associated with benfluorex exposure was also observed by Boudes et al²⁴ in a single-center study of hospitalized patients with restrictive valve disease. In a single-center case-control study, Frachon et al⁸ reported high exposure to benfluorex among patients hospitalized for mitral regurgitation of unclear origin (70%) compared with patients with mitral regurgitation of known origin (5.6%) and concluded that benfluorex was associated with a high risk of mitral regurgitation. This finding was confirmed by another case-control study showing that among patients with mitral regurgitation of unclear origin, exposure to benfluorex was identified in 40.9% of cases compared with

4.5% in a matched group of patients with degenerative mitral regurgitation resulting from flail leaflets.⁹

These series of observations were followed by retrospective cohort studies estimating of the risk of valvular damage, hospitalizations, valve surgery, and death associated with benfluorex exposure.^{10,11} The first cohort study by Weill et al¹⁰ used the database of the French National System of Reimbursement Information (Système national d'information inter régime de l'assurance maladie) and discharge diagnostic data from public and private hospitalizations (Programme de médicalisation des systèmes d'informations) and analyzed diabetic patients 40 to 69 years of age with reimbursements for antidiabetic drugs in 2006. The authors reported a 3-fold increase in the risk of hospital admission for mitral regurgitation and a 4-fold increase in the risk of hospitalization for aortic regurgitation and valvular replacement surgery during the first 2 years after exposure to benfluorex.¹⁰ Finally, according to a recent statistical estimation, use of benfluorex between 1976 and 2009 in France would have been responsible for ≈3100 admissions to hospital and 1300 deaths resulting from valvular regurgitation.¹¹

Our study demonstrates the association between benfluorex exposure and increased frequency of left heart valve regurgitations in prospectively included individuals with diabetes mellitus. In contrast to previous studies,^{10,11} the present study does not use hospital discharge records and therefore is not biased by the selection of the most severe forms of valve diseases and by coding practices secondary to reimbursement issues. It is a prospective multicenter study with a clear methodology and careful echocardiography examination. Thus, we included consecutive diabetic outpatients previously exposed to benfluorex who were referred for echocardiography by their general practitioner. Moreover, by propensity matching, we obtained 2 groups that were balanced in terms of baseline characteristics. Echocardiograms were read by 2 experts in echocardiography who were blinded to the treatment status, and grading of regurgitation was performed according to standard methods. We report a 31% frequency of left heart valve regurgitations in patients exposed to benfluorex compared with 13% in matched control subjects. Previous exposure for at least 3 months to benfluorex was associated in our study with a >3-fold increase in the risk of mild or greater aortic and/or mitral valve regurgitations, >5-fold increase in the risk of mild or greater aortic regurgitation, and >2-fold increase in the risk of mild or greater mitral regurgitation. The increased prevalence of left heart valve regurgitations in patients exposed to benfluorex for at least 3 months was due mainly to an increased frequency of mild regurgitations. The 3-month exposure period was chosen on the basis of older fenfluramine/phentermine studies.²

In the fenfluramine/phentermine studies, the prevalence of valve regurgitations varied considerably, ranging between 6% and 30%, and the duration of treatment was associated with development of clinical valvulopathy.^{17,25} In our study, we observed an association between the duration of benfluorex exposure and the frequency of regurgitations. As with fenfluramine/phentermine, the risk of valve damage associated with benfluorex appears to be more important for the aortic valve than for the mitral valve. In the overall cohort, patients exposed to benfluorex more often had overt symptoms, greater left ventric-

ular end-diastolic dimensions, and slightly higher left ventricular ejection fraction, probably as a result of some amount of volume overload. However, these findings probably cannot be explained solely by a higher frequency of moderate regurgitations in patients treated with benfluorex. Thus, after matching, the frequency of overt symptoms was no longer different between patients and control subjects. Mechanisms responsible for the occurrence of class III/IV dyspnea in this population are probably multiple and are often noncardiac (eg, obesity and pulmonary disease). There was no difference in left atrium size and tricuspid regurgitation maximal velocity between patients and control subjects, presumably because there were few subjects with moderate regurgitations and no cases of severe regurgitation.

The natural history of valve regurgitation after benfluorex discontinuation is unknown. It has been reported that valve regurgitations induced by fenfluramine have a variable natural history (regression, stabilization, or aggravation).^{3,25,26} A prospective follow-up study of the natural history of benfluorex-induced valve regurgitations in relation to severity at baseline is therefore needed.

Among patients exposed to benfluorex, we identified 2 cases of moderate to severe mitral regurgitation and 1 case of moderate to severe aortic regurgitation. We did not observe severe valve regurgitations according to the criteria of the European Society of Echocardiography.^{12,13} This is not surprising because severe benfluorex-induced valve regurgitations appear to be infrequent (<1 per 1000 patient-years according to Weill et al¹⁰). On the other hand patients included in the present study were referred for echocardiography because of exposure to benfluorex. Moreover, we excluded patients with previous history of heart valve disease or referred for a second expert echocardiography evaluation when an initial echocardiography raised the suspicion of some kind of valvular abnormality. Patients admitted to hospital for diagnostic workup of a valvular lesion possibly induced by benfluorex were also excluded. Therefore, the frequency of severe regurgitations was probably underestimated. Thus, this study cannot establish the real frequency of moderate and severe valve regurgitation induced by benfluorex.

The present study should be considered in the context of several limitations. It is not a randomized trial because benfluorex was withdrawn from the market. It is not a prevalence study because we excluded patients with previously suspected valve disease and patients hospitalized for valve disease. The influence of hidden or unmeasured covariates in the matching procedure cannot be excluded. Restricting the study to diabetic patients has allowed the formation of a more homogeneous study group and has simplified the recruitment of control subjects. We acknowledge that the method for selecting control subjects does not entirely preclude differential selection bias, in addition to any inherent confounding in the population. The study was conducted after the patients took the drug, and there might have been changes in valvular regurgitation in the period of time between drug discontinuation and echocardiography. Echocardiograms were performed on different echocardiography machines, and Nyquist limit, gain, and persistence were not standardized. The prevalence of valve regurgitations in a population is highly variable, depending on the characteristics of the

studied population and on the methods used to evaluate regurgitation. To the best of our knowledge, the prevalence of valve regurgitations in diabetic subjects is unknown. Finally, our results concern patients with diabetes mellitus and cannot be extrapolated to the general population.

Conclusions

Our data show that diabetic patients exposed to benfluorex have a significantly higher frequency of left heart valve regurgitations compared with matched control subjects. The risk associated with benfluorex use is greater for the aortic valve. Further work is needed to establish the natural history of this type of valve disease.

Disclosures

None.

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CLINICAL PERSPECTIVE

The aim of this population-based multicenter study was to compare the frequency of left heart valve regurgitations diagnosed by echocardiography in prospectively included diabetic patients who had taken benfluorex for at least 3 months and in matched diabetic control subjects (matched for age, sex, body mass index, smoking, dyslipidemia, hypertension, and coronary artery disease) without previous exposure to the drug. We found a significant increase in the frequency of mild or greater left heart valve regurgitations among patients treated with benfluorex compared with propensity-matched control subjects (31% vs. 13%; $P < 0.001$). Exposure to benfluorex was associated with a >3-fold increase in the risk of mild or greater left heart valve regurgitations. Furthermore, the risk of benfluorex-induced regurgitations was more important for the aortic valve compared with the mitral valve. Finally, the higher frequency of left heart valve regurgitations among benfluorex-treated patients compared with control subjects was due mainly to an increased frequency of mild regurgitations. The natural history of benfluorex-induced valve abnormalities needs further research.

Supplemental Material

APPENDIX – list of investigators

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