Frequency of drug-induced valvular heart disease in patients previously exposed to benfluorex: a multicentre prospective study

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Received 8 March 2013; revised 11 May 2013; accepted 18 June 2013; online publish-ahead-of-print 6 September 2013

See page 3535 for the editorial comment on this article (doi:10.1093/eurheartj/eht323)

Aims
The epidemiologic link between benfluorex use and an increased global frequency of left heart valve regurgitation has been well documented. However, no data linking previous drug exposure to the frequency of diagnosis of drug-induced valvular heart disease (DI-VHD) are available. The present study was conducted to address this issue.

Methods and results
This echocardiography reader-blinded, controlled study conducted in 10 centres between February 2010 and February 2012 prospectively included 835 subjects previously exposed to benfluorex referred by primary care physicians for echocardiography. Based on blinded off-line analysis, echocardiography findings were classified as: (i) DI-VHD (+) for patients with an echocardiographic diagnosis of DI-VHD, (ii) inconclusive, and (iii) DI-VHD (−) for patients without signs of DI-VHD. Fifty-seven (6.8%) patients exposed to benfluorex were classified as DI-VHD (+), 733 (87.8%) patients were classified as DI-VHD (−), and 45 (5.4%) were classified as inconclusive. Mitral and aortic DI-VHD were reported in 43 patients (5.1%) and 30 (3.6%) patients, respectively. Longer duration of exposure, female gender, smoking, and lower BMI were independently associated with a diagnosis of DI-VHD. Good inter-observer reproducibility was observed for the echocardiography classification (Kappa = 0.83, P < 0.00001).

Conclusions
About 7% of patients without a history of heart valve disease previously exposed to benfluorex present echocardiography features of DI-VHD. Further studies are needed to study the natural history of DI-VHD and to identify risk factors for the development of drug-induced valve lesions.

Keywords
Drug-induced valvular disease • Echocardiography • Benfluorex

Introduction
Exposure to amphetamine-based appetite suppressants has been associated with serious adverse effects, such as pulmonary artery hypertension and cardiac valvular regurgitation. Benfluorex, an amphetamine derivative related to fenfluramine and dexfenfluramine in terms of structure, clinical effects, and metabolism, has been widely prescribed in Europe, Asia, and South Africa in patients with dyslipidemia and type II diabetes, but has also been widely used off-label as an appetite suppressant. Benfluorex was withdrawn from European markets in 2010 following the publication of several reports showing a link between benfluorex exposure and valvular...
Drug-induced valvular disease and benfluorex

regurgitation, as previously observed with other fenfluramine derivatives. A retrospective cohort study including a large number of patients with diabetes mellitus reported a three-fold increased risk of hospitalization for valve regurgitation and a four-fold increased risk of valve replacement surgery in patients exposed to benfluorex. A recent randomized control study comparing the effect of benfluorex and pioglitazone on glycosylated haemoglobin levels in diabetic patients showed that 1 year of benfluorex exposure was responsible for a three-fold increase in the incidence of valvular regurgitation. However, no significant changes in valvular morphology were observed between the two groups during the 1-year echocardiography follow-up. Consistent with these findings, we recently demonstrated, in a prospective multicentre case-control study, that the use of benfluorex was associated with a three-fold increase in the frequency of left heart valve regurgitation in diabetic patients. According to recent estimations, exposure to benfluorex may have been responsible for up to 3100 hospital admissions for valvular heart disease and up to 1300 deaths from valve regurgitation in France. Diagnosis of drug-induced valvular heart disease (DI-VHD) is based on morphological echocardiographic abnormalities. Valve lesions preferentially involve the mitral and/or aortic valves. The most characteristic feature is restriction of valve motion, responsible for regurgitation. Leaflet thickening is often minimal and associated for the mitral valve with thickening and shortening of the chordae tendineae. Restriction and tenting generally affect both mitral leaflets but often predominate at the posterior leaflet. For the aortic valve, echocardiographic abnormalities are often more moderate with systolic subtle dome-like appearance of the leaflets, and/or incomplete diastolic coaptation. The relationship between benfluorex exposure and higher global frequency of left heart valve regurgitation has been established. However, valvar regurgitation can be due to many aetiologies and no data linking previous drug exposure and the frequency of diagnosis of DI-VHD are available. This multicentre prospective study was designed to address this issue in a large cohort of patients previously exposed to benfluorex.

Methods

Study design

The Marketing Authorization for benfluorex was suspended in France in November 2009 and the French medicines agency (Agence Française de Sécurité Sanitaire des Produits de Santé—Afssaps) issued a public health advisory opinion inviting all patients previously exposed to benfluorex to contact their primary care physician. Primary care physicians subsequently referred patients to a cardiologist for echocardiography. On 26 November 2009, the cardiology departments of all French University Hospitals, large private clinics, and general hospitals were contacted by e-mail and invited to participate in a multicentre prospective study. Investigators (see Supplementary material online) were asked to include all consecutive patients exposed to benfluorex and referred by primary care physicians for echocardiography over a 24-month period. Ten centres participated in this study (Centre Hospitalier Universitaire d’Amiens, GCS-Groupement des Hôpitaux de l’Institut Catholique de Lille, Centre Hospitalier de Beauvais, AP-HP Hôpital Saint Antoine Paris, Centre Hospitalier Universitaire de Bordeaux, Centre Hospitalier Universitaire de Brest, Centre Hospitalier de Compiegne, Centre Hospitalier Universitaire de Lille, Centre Hospitalier Universitaire de Nantes, Centre Hospitalier Universitaire de Rennes). The non-interventional research Ethics Committee at University of Picardie, Amiens, France, approved this observational study. Oral consent was obtained from each patient.

Patients

The flow chart of the study population is detailed in Figure 1. From February 2010 to February 2012, consecutive benfluorex-exposed patients referred for echocardiography to the participating centres by their primary physician were enrolled when they presented a history of at least 3 months of exposure to benfluorex and no history of VHD. All patients who had taken benfluorex, referred for a second expert evaluation by their cardiologist after an initial echocardiography, were not included in the present study to avoid non-consecutive enrolment and overestimation of the frequency of valve lesions. Patients exposed to other drugs known to induce valvular heart disease (rye ergot alkaloids, fenfluramine/phentermine, dexfenfluramine, pergolide) were also excluded. Demographic data and cardiovascular risk factors were recorded. Daily doses of benfluorex and total duration of treatment were systematically collected at the time of echocardiography. Primary care physicians were contacted by phone at the time of echocardiography when there was any doubt concerning medication use or duration of benfluorex exposure.

Controls

The present study comprised a control group of 376 consenting diabetic patients not previously exposed to benfluorex or other drugs known to induce VHD and with no history of VHD. These patients were referred by their primary care physicians to the outpatient diabetes clinics of the participating centres. Data from this group have been reported in a previous analysis.

Echocardiography

Complete echocardiography examinations on commercially available ultrasound devices, with multiple two-dimensional views and the use of various Doppler modes, were performed in each centre by experienced operators according to a standardized protocol. Briefly, magnified video loops with and without Doppler colour flow mapping were recorded in parasternal long-axis views for the aortic and mitral valves, parasternal short-axis views for the pulmonary, tricuspid and aortic valves, apical views for the tricuspid, mitral and aortic valves, and subcostal views for all valves whenever possible. Echocardiography examinations were stored in DICOM (digital imaging and communications in medicine) format on digital versatile disks for subsequent off-line analysis. All echocardiograms of patients and controls were read independently by two cardiologists, experts in echocardiography and VHD, and blinded to all aspects of patient history including benfluorex use. When a disagreement was observed between the two readers, a third independent expert performed a final blinded reading and gave the final conclusion. Echocardiography features of DI-VHD were systematically investigated. For the mitral valve, these features were leaflet thickening, retraction towards the ventricular apex during systole (leaflet tenting), reduced valve mobility, and/or thickening and shortening of the chordae tendineae (Figure 2). For the aortic valve, these features were systolic subtle dome-like appearance of the leaflets, valvaral thickening, reduced mobility, and/or incomplete diastolic coaptation resulting in a small central triangular valve hiatus during diastole in the short-axis view with central aortic regurgitation (Figure 2). Based on blinded echocardiographic analysis, patients and controls were classified into three groups: (i) DI-VHD (+) group
comprising patients with an echocardiographic diagnosis of DI-VHD, (ii) inconclusive group, comprising patients with a doubt concerning the diagnosis of DI-VHD, and (iii) DI-VHD \( (-) \) group, comprising patients without signs of DI-VHD in whom the diagnosis of DI-VHD was rejected.

The severity of valve regurgitation was expressed according to the recommendations of the European Society of Echocardiography (absence or trace, mild, moderate, severe). Standard two-dimensional measurements (left ventricular end-diastolic and endsystolic diameters) were obtained from parasternal long-axis views. Left atrium area was calculated by planimetry from apical four-chamber views. Left ventricular ejection fraction was calculated using Simpson’s biplane method. The peak tricuspid regurgitant jet velocity was estimated using continuous Doppler.

**Figure 1** Flow chart of the study population. *Patient’s group previously reported in Tribouilloy et al., Circulation 2012;126:2852–2858.

**Figure 2** Aortic and mitral echocardiographic features suggestive of drug-induced valvular heart disease. (A) Parasternal long-axis view with systolic doming of the aortic valve, mitral valve tenting, and mitral leaflet thickening. (B) Apical long-axis view with mitral leaflet thickening, retraction towards the ventricular apex, with thickening and shortening of the chordae tendineae.

**Statistical analysis**

Continuous variables are expressed as mean ± standard deviation or median and interquartile range if Shapiro–Wilk’s normality test failed. Categorical variables are presented as absolute numbers and frequencies. Comparisons between continuous variables were performed with Student’s t-test or Mann–Whitney U-test, as appropriate. Comparisons between three groups were performed using one-way ANOVA. Comparisons between frequencies were performed using a Chi-square test or Fisher’s exact test, as appropriate. Variables associated with a diagnosis of DI-VHD in patients exposed to benfluorex on univariate analysis \( (P < 0.10) \) were entered into a complete instead of stepwise multivariate logistic regression analysis. Goodness of fit of the multivariate model was assessed by using the Hosmer–Lemeshow test to measure the model’s
calibration and by computing the area under the ROC curve to measure its discrimination. The kappa test was used to assess the concordance between the two readers concerning the classification of echocardiography findings. Statistical analysis was performed using PASW 18.0 (SPSS Inc, Issy Les Moulineaux, France). A two-tailed P-value less than 0.05 was considered to be statistically significant.

Results

Study population

One thousand consecutive patients previously exposed to benfluorex were screened for this study. One hundred sixty-five patients were excluded, as they had been exposed to other drugs known to induce valvular heart disease. The remaining 835 patients were included in the present study (Figure 1). Mean age was 59 ± 12 years and 487 (58%) were females. Four hundred twelve patients (49%) had diabetes mellitus and 455 (55%) had a history of hypertension. Mean body mass index was 31 ± 6 kg/m². Four hundred eighty-five (58%) patients had a history of dyslipidemia and 155 (19%) were smokers. Median (interquartile range) daily dose and duration of benfluorex therapy were 300 (300–450) mg and 36 (24–60) months, respectively. The main reason for benfluorex prescription was diabetes in 360 patients (43%), dyslipidemia in 120 patients (14%), slimming aid in 313 (38%), and unclear reasons in 42 patients (5%).

Diagnosis of drug-induced valvular heart disease in patients exposed to benfluorex

The frequency of echocardiography findings related to DI-VHD is presented in Table 1. Overall, 57 (6.8%) patients were classified in the DI-VHD (+) group (mitral and/or aortic valve disease), 733 (87.8%) patients were classified in the DI-VHD (−) group, and 45 (5.4%) were classified in the inconclusive group. A diagnosis of mitral DI-VHD was established in 43 (5.1%) patients, while echocardiography was inconclusive in 25 (3%) patients. A diagnosis of aortic DI-VHD was established in 30 (3.6%) patients, while echocardiography was inconclusive in 45 (5.4%) patients. Simultaneous involvement of aortic and mitral valves, considered to be related to DI-VHD, was reported in 16 patients (1.9%). The restrictive motion of the mitral or the aortic valve was the most frequent finding (85.9%) in patients with the diagnosis of DI-VHD. Mild and moderate aortic and/or mitral regurgitation was more frequent in the DI-VHD (+) group than in the DI-VHD (−) group (Table 2). The frequency of more than mild aortic and/or mitral valve regurgitation increased with the quartiles of duration of exposure to benfluorex (P = 0.047).

In the control group of 376 diabetic patients not exposed to benfluorex, only 1 (0.26%) patient was classified in the DI-VHD (+) group and presented echocardiography features involving only the mitral valve, while 9 (2.3%) patients were classified in the inconclusive group. In the group of patients exposed to benfluorex (n = 835), 412 were diabetics. Twenty-three of these 412 diabetic patients (5.6%) were classified in the DI-VHD (+) group and 18 (4.4%) were classified in the inconclusive group.

Echocardiography findings related to DI-VHD involving right-sided heart valves were not found during the blind analysis. Left ventricle (LV) ejection fraction, diameters, LA area, and peak tricuspid regurgitant jet velocity were comparable in the three groups of patients (Table 3).

As shown in Table 4, a good agreement was observed between the primary and the secondary reader for this classification into three groups (kappa value 0.83, P < 0.0001). The percentage of cases where there was a disagreement between readers was 3.47%.

Factors associated with a diagnosis of drug-induced valvular heart disease

In the 835 patients exposed to benfluorex, patients of the DI-VHD (+) group were more frequently female and smokers and had a lower body mass index than DI-VHD (−) patients (Table 5). Duration of benfluorex therapy was also significantly longer in patients of the DI-VHD (+) group compared with DI-VHD (−) patients [55 (36–104) vs. 36 (24–60) months, P = 0.015]. Figure 3 depicts the relationship between the frequency of aortic and/or mitral, mitral, aortic, and combined mitral and aortic considered to be related to DI-VHD, and the quartiles of duration of therapy. Duration of therapy was longer in the 16 patients with combined aortic and mitral valve involvement considered to be related to DI-VHD compared with those with no signs of DI-VHD [78 (48–119) months vs. 36 (24–60) months, P = 0.001] and compared with those with isolated aortic or mitral valve involvement [78 (48–119) vs. 48 (24–93) months, P = 0.06]. In multivariate logistic regression analysis, a longer duration of benfluorex therapy, female sex, smoking, and a lower BMI remained independently associated with diagnosis of DI-VHD (Table 6).

Discussion

This is the first study to investigate the frequency of echocardiography findings leading to a diagnosis of DI-VHD in a large population of patients treated with benfluorex. About 7% of patients without a history of heart valve disease previously exposed to benfluorex presented echocardiography findings consistent with DI-VHD. Overall, the presence of echocardiography features of DI-VHD in patients exposed to benfluorex was associated with longer duration of benfluorex use, female gender, smoking, and lower BMI.

The possibility that certain drugs might induce VHD was first proposed in the mid-60s with respect to ergot alkaloids used for migraine
prophylaxis (initially methysergide and then ergotamine). In 1997, DI-VHD was reported with fenfluramine and dexfenfluramine, two appetite suppressants previously demonstrated to be associated with the development of pulmonary artery hypertension. A high frequency of 33–40% of DI-VHD was then reported in patients treated for Parkinson’s disease with pergolide and cabergoline. More recently, similar cases of drug-induced VHD have been reported with prolonged use of the recreational drug, ecstasy (MDMA), and benfluorex, an amphetamine derivative structurally related to fenfluramine and dexfenfluramine. We recently demonstrated that diabetic patients exposed to benfluorex have a significantly higher frequency of left heart valve regurgitation compared with matched control subjects (31 vs. 13%, \( P < 0.0001 \)). In the present study, about 7% of patients exposed to benfluorex presented echocardiography features highly suggestive of mitral and/or aortic DI-VHD. Importantly, these echocardiography features considered to be highly suggestive of DI-VHD were defined on the basis of a blind thorough assessment and proved to be highly specific, as only 1 of 376 (0.26%) diabetic controls not exposed to drugs responsible for VHD presented such features. This study also showed a higher frequency of inconclusive echocardiography findings in the group of patients exposed to benfluorex (45 [5.4%]) compared with controls [9 [2.3%]]. As the expert cardiologists reading echocardiography were blinded to the history of

| Table 2 | Frequency of left heart valve regurgitation according to the diagnosis of drug-induced valvular heart disease (DI-VHD) |
|-----------------------------------------------|-------------------------------------------------|---------------------------------|------------------|------------------|
| Aortic regurgitation                          | DI-VHD (+) \((n = 57)\)                          | DI-VHD (-) \((n = 733)\)       | Inconclusive \((n = 45)\) | Overall \(P\)-value |
| None (n, %)                                   | 7 (12)                                         | 539 (74)                       | 7 (16)            | <0.0001         |
| Trace (n, %)                                  | 6 (11)                                         | 107 (15)                       | 4 (9)             | <0.0001         |
| Mild (n, %)                                   | 24 (42)                                        | 68 (9)                         | 27 (60)           |                 |
| Moderate (n, %)                               | 20 (35)                                        | 19 (3)                         | 7 (16)            |                 |
| Severe (n, %)                                 | 0 (0)                                          | 0 (0)                          | 0 (0)             |                 |
| Mitral regurgitation                          |                                                |                                |                   |                 |
| None (n, %)                                   | 7 (12)                                         | 335 (46)                       | 7 (16)            | <0.0001         |
| Trace (n, %)                                  | 16 (28)                                        | 316 (43)                       | 22 (49)           | <0.0001         |
| Mild (n, %)                                   | 30 (53)                                        | 75 (10)                        | 15 (33)           |                 |
| Moderate (n, %)                               | 4 (7)                                          | 7 (1)                          | 1 (2)             |                 |
| Severe (n, %)                                 | 0 (0)                                          | 0 (0)                          | 0 (0)             |                 |
| Aortic and/or mitral regurgitation            |                                                |                                |                   | <0.0001         |
| None (n, %)                                   | 0 (0)                                          | 282 (38)                       | 0 (0)             | <0.0001         |
| Trace (n, %)                                  | 4 (7)                                          | 308 (42)                       | 4 (9)             |                 |
| Mild (n, %)                                   | 31 (54)                                        | 118 (16)                       | 33 (73)           |                 |
| Moderate (n, %)                               | 22 (39)                                        | 25 (3)                         | 8 (18)            |                 |
| Severe (n, %)                                 | 0 (0)                                          | 0 (0)                          | 0 (0)             |                 |

DI-VHD (+) group includes patients with an echocardiographic diagnosis of DI-VHD; inconclusive group includes patients with a doubt concerning the diagnosis of DI-VHD; DI-VHD (-) group includes patients without signs of DI-VHD.

| Table 3 | Other echocardiographic data according to the diagnosis of drug-induced valvular heart disease (DI-VHD) |
|-----------------------------------------------|-------------------------------------------------|---------------------------------|------------------|
| LV ejection fraction (%)                      | DI-VHD (+) \((n = 57)\)                          | DI-VHD (-) \((n = 733)\)       | Inconclusive \((n = 45)\) |
|                                               | 64 ± 7                                          | 64 ± 7                          | 64 ± 7           | 0.820           |
| LV end-diastolic diameter (mm)                | 51 ± 5                                          | 50 ± 6                          | 49 ± 6           | 0.300           |
| LV end-systolic diameter (mm)                 | 31 ± 6                                          | 31 ± 6                          | 31 ± 5           | 0.813           |
| Left atrial surface (cm²)                     | 19 ± 4                                          | 19 ± 5                          | 19 ± 4           | 0.793           |
| Peak tricuspid regurgitant jet velocity (m/s) | 2.1 ± 0.9                                       | 2.2 ± 0.7                       | 2.3 ± 0.7        | 0.339           |

DI-VHD (+) group includes patients with an echocardiographic diagnosis of DI-VHD; inconclusive group includes patients with a doubt concerning the diagnosis of DI-VHD; DI-VHD (-) group includes patients without signs of DI-VHD.

LV, left ventricle.
benfluorex exposure, this result suggests that some inconclusive echocardiography findings in the benfluorex-exposed group could actually be related to drug toxicity. We have also recently reported an absolute 18% increase in the overall frequency of left heart valve regurgitation ≥ mild in patients exposed to benfluorex compared with controls. However, in the present analysis, a diagnosis of DI-VHD was observed in 6.8% of cases. This is not an unexpected finding, as the REGULATE trial elegantly demonstrated a three-fold increase in the incidence of valvular regurgitation after 1 year of benfluorex exposure, while the proportion of emergent echocardiographic morphological abnormalities was lower and, most importantly, comparable between benfluorex exposed and unexposed patients. This last finding strongly suggests that minor anatomical DI-VHD resulting in mild left heart regurgitation may be not identified by echocardiography.

The natural history of DI-VHD after discontinuation of benfluorex is unknown. Indeed, there are no data regarding outcome of these patients exposed to benfluorex. The aim of the ongoing REFLEX study in France is to investigate the natural history of DI-VHD following benfluorex exposure with a clinical and echocardiographic follow up at 1 year, 2 years, and 3 years after the index echocardiogram. Fenfluramine-induced valve regurgitation has been reported to have a variable natural history (regression, stabilization, or aggravation). Gardin et al. reported that the severity of aortic regurgitation decreased in most cases after cessation of exposure to dexfenfluramine or fenfluramine without any change in valve mobility or thickness on echocardiographic follow-up. Although the overall risk of left heart valve regurgitation ≥ mild associated with benfluorex is greater for the aortic valve than for the mitral valve, the present analysis shows that DI-VHD was more frequently diagnosed for the mitral valve. Actually, the diagnosis of DI-VHD in practice can sometimes be challenging, especially for the aortic valve, as echocardiography may not be sufficiently sensitive to detect minor structural valve changes causing only mild regurgitation.

This study reports a dose–effect relationship between the presence of highly suggestive echocardiography features and the duration of benfluorex use, as the risk of DI-VHD increased with increasing duration of exposure to benfluorex. Accordingly, a retrospective analysis of 1 million diabetic patients (including 4% of patients treated with benfluorex) reported that patients with lower cumulative doses of benfluorex were less likely to be hospitalized for VHD. However, despite a statistically significant relationship, 86% of patients in the present study who had received benfluorex for at least 5 years (the highest quartile of duration of exposure) did not present any echocardiography features suggestive of DI-VHD, indicating that multiple factors are probably involved in the pathogenesis of VHD.

Fenfluramine derivatives including benfluorex have been suspected to induce VHD via a serotonergic mechanism by increasing synaptic levels of 5-HT. Their metabolite, norfenfluramine, has a high affinity for the 5-HT2B receptor with a full agonist effect. Stimulation of the 5-HT2B receptor leads to upregulation of target genes involved in the proliferation and stimulation of valvular interstitial cells via various intracellular pathways, hence leading to drug-induced fibrotic valvular disease. This type of 5-HT2B agonist effect has also been reported for ergot alkaloids, ergotamine and methysergide, pergolide, cabergoline, MDMA, ergotamine, and methylergonovine.
a metabolite of methysergide. Interestingly, 5-HT polymorphisms have been observed to be associated with the penetrance of clinical manifestations in a number of neurological diseases. Genetic polymorphisms can therefore be expected to play a role in the pathogenesis of valve lesions in patients exposed to benfluorex. Strikingly, estradiol and progesterone, the primary female steroid hormones, exert an array of effects on the serotonergic system, including 5-HT expression. Noteworthy, the landmark report on VHD associated with fenfluramine–phentermine consisted exclusively of 24 women. Derumeaux et al. in the REGULATE study found that female gender was an independent predictor of emergent valvular regurgitation after 1-year exposure to benfluorex. The finding in the present study that female gender was independently associated with a diagnosis of DI-VHD also suggests a gender-associated susceptibility to develop these lesions. In the present study, smoking and lower body mass index were also found to be associated with a diagnosis of DI-VHD.

Limitations

This study was not a randomized trial because benfluorex has been withdrawn from the market. However, this study was prospective, echocardiograms were recorded by experienced operators according to a standardized protocol, and the echocardiography classification of the diagnosis of DI-VHD into three groups was based on blinded and reproducible examination of echocardiography recordings. It was not a prevalence study. The discovery of a new cardiac murmur by primary care physician may have induced a referral bias. To minimize referral bias, all patients with a history of cardiac murmur, with a diagnostic work-up of heart valve disease, or referred by their cardiologist were not included in the present study. Patients with a previously diagnosed VHD from another cause were also excluded because the diagnosis of DI-VHD cannot be ascertained in this context. Finally, the risk of false diagnosis of DI-VHD in the current study seems low as the diagnosis of DI-VHD was obtained in only 1 of the 376 subjects (0.26%) in the control group.

Conclusions

This study shows that echocardiography detects features considered to be highly suggestive of DI-VHD in 6.8% of patients previously exposed to benfluorex, whereas such features are very uncommon in diabetic subjects not exposed to drugs known to induce VHD. The apparent discrepancy between the absolute 18% increase in the overall frequency of heart valve regurgitation previously reported in patients exposed to benfluorex and the 6.8% frequency of echocardiographic abnormalities suggestive of DI–VHD in the present report illustrates that subtle changes in valve structure related to benfluorex not detectable by echocardiography may be responsible for mild regurgitation. Multiple factors, such as female gender, smoking, and duration of therapy, could predispose to the development of DI-VHD in patients exposed to benfluorex. Further studies are needed to identify the possible genetic, biological, and

Table 6  Variables independently associated with an echocardiographic diagnosis of drug-induced valvular heart disease (DI-VHD) in patients exposed to benfluorex on multivariate logistic regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of benfluorex therapy (/ 1-month increase)</td>
<td>1.006 (1.002–1.011)</td>
<td>0.002</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.55 (1.36–4.78)</td>
<td>0.003</td>
</tr>
<tr>
<td>Past or current smoking</td>
<td>2.57 (1.40–4.71)</td>
<td>0.002</td>
</tr>
<tr>
<td>Body mass index (/kg/m² increase)</td>
<td>0.92 (0.87–0.97)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Calibration: Hosmer–Lemeshow test, P = 0.26
Discrimination: AUC = 0.72 (0.66–0.78), P < 0.0001

Cl, confidence interval; AUC, area under the curve; OR, odds ratio. Odds ratios were calculated by using patients with no signs of drug-induced valvular heart disease [DI-VHD (−) group] as the reference group.
clinical factors that determine individual susceptibility to developing DI-VHD in patients exposed to amphetamine derivatives and to establish the natural history of this type of VHD.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

**Conflict of interest:** none declared.

**References**