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ORIGINAL REPORT

Benfluorex and valvular heart disease: a cohort study of a million people with diabetes mellitus

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ABSTRACT

Purpose To evaluate and quantify in diabetic patients treated with benfluorex in France, a fenfluramine-derivated product, a possible increase in risk of valvular heart disease, previously suggested by several published case reports.

Methods This was a French comparative cohort study using data from two large national linked databases, health insurance system (SNIIRAM) and hospitalization (PMSI). Patients aged 40–69 years with reimbursement for oral antidiabetic and/or insulin in 2006 were eligible. Exposed patients were defined as patients with at least one benfluorex reimbursement in 2006. Selected admission diagnoses of interest in 2007 and 2008 PMSI databases were valvular insufficiency for any cause, mitral insufficiency, aortic insufficiency, and valvular replacement surgery with cardiopulmonary bypass. Relative risks (RR) were adjusted on gender, age, and history of chronic cardiovascular disease.

Results A total of 1 048 173 diabetic patients were included, with 43 044 (4.1%) exposed to benfluorex. The risk of hospitalization in 2007 and 2008 for any cardiac valvular insufficiency was higher in the benfluorex group: crude RR = 2.9 [95% confidence interval 2.2–3.7] and adjusted RR = 3.1 [2.4–4.0], with a lower risk for patients with lower cumulative dose of benfluorex. Adjusted RR for mitral insufficiency and aortic insufficiency admissions were 2.5 [1.9–3.7] and 4.4 [3.0–6.6], respectively. Adjusted RR for valvular replacement surgery was 3.9 [2.6–6.1].

Conclusions Benfluorex in diabetic patients was significantly associated with hospitalization for valvular heart disease in the 2 years following benfluorex exposure. Linkage between SNIIRAM and PMSI databases is in France a valuable tool to quantify the risk of serious adverse drug reactions. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — benfluorex; valvular heart disease; adverse effects; health insurance system; reimbursement databases; pharmacoepidemiology

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INTRODUCTION

Fenfluramine was introduced first on the US market in 1973 as an anorexic agent. In 1997, most of fenfluramine-derivative products (except benfluorex) were withdrawn from European and United States markets following case reports of rare but serious cardiovascular adverse drug reactions in patients exposed to these products, together with results of observational studies. In a case-control study, the use of anorexic drugs including mainly derivatives of fenfluramine was associated with an increased risk of primary pulmonary hypertension with an odds ratio of 6.3 (95%CI 3.0–13.2).[1] A second study in 24 women with no evidence of cardiovascular disease before the initiation of fenfluramine–phentermine therapy strongly suggested a causal association of this combination in the occurrence of unusual valvular heart disease.[2] One year later the results of two case-control studies including patients who received only fenfluramine showed a significant association between the use of fenfluramine derivative and valvular heart regurgitation.[3,4]

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Benfluorex, a fenfluramine-derivative drug is used in South-eastern Asia and in Europe. In France, benfluorex was available for use in patients with high blood levels of triglycerides or overweight patients and diabetes, i.e., with a body mass index (BMI) $\geq 25\,kg/m^2$, combined with an appropriate diet. Benfluorex was marketed in 1975 in France. Several published case reports have suggested that this derivative of fenfluramine might be also associated with cardiac valvular regurgitation and serious pulmonary arterial hypertension.[5–7] Following re-assessment of the benefit-risk balance in patients with hypertriglyceridemia, a decision of the French medicine drug agency (AFSSAPS) on 5 April 2007 limited benfluorex use to the second indication in diabetic population.

We report in the present paper the methodology and results of this comparative cohort study using a vast national medico-administrative database representing the most part of French population, to evaluate and quantify a possible increase in risk of cardiac valvular regurgitation associated to benfluorex use in diabetic patients. Results of this benfluorex study were transmitted to AFSSAPS in October 2009. The French medicine drug agency carried out an overall review of the safety of benfluorex and decided to suspend its marketing authorization on 30 November 2009.

METHODS

In France, the National Health Insurance Scheme, composed of several specific regimes, covers the whole population, that is to say 63.4 million inhabitants in 2008. The general regime, the Health Insurance Fund for Salaried Workers (CNAMTS), covers approximately 86% of the population residing in France. The National Health Insurance Fund for Agricultural Workers and Farmers (MSA) and the one for the Self-employed (RSI) represent 5% each, and 12 additional schemes cover the remaining 4%. Its information system namely SNIIRAM for ''Système National Inter-Régime de l'Assurance Maladie'' contains individualized, anonymous, and exhaustive data on all health spending reimbursements.[8] This information can be linked to the French hospital discharge database (PMSI: Programme de Médicalisation des Systèmes d'Information), which provides medical information for all patients discharged from hospitals, including ICD-10 (10th version of International Classification of Diseases) diagnostic codes.[9] The SNIIRAM implementation has received the agreement of the data protection agency (CNIL).

We conducted a comparative cohort study using anonymous data from individuals covered by the general regime, i.e., 55 million people. For them, the matching rate between reimbursement and hospital discharge database is 97%. The reimbursement database exhaustively records all health care expenditures that are reimbursed, including medicinal products and outpatient medical and nursing care, prescribed or executed by any health care professional (general practitioners, specialists, nurses, clinical lab biologists, pharmacists, etc.). This medico-administrative database does not inform directly about medical indication of each reimbursement, but provides status of patients about many chronic diseases that are considered as severe and costly long-term diseases ''ALD'' (''Affection de longue durée''). These ALD diseases are 100%-reimbursed on request from patient or his family and the general practitioner, after agreement of a social security physician, and are coded according to ICD-10 classification. They were concerning 8.3 millions of people in the French general scheme on 31 December 2008.[10] Short-term stay admissions in public and private hospitals are recorded and documented in PMSI, in particular discharge diagnoses that are provided with ICD-10 codes. Moreover, diagnosis-related groups ''GHM'' (''Groupe Homogène de Malades'') are also available, in order to classify patients in subgroups according to medical procedures and discharge diagnoses.

Eligible patients were all diabetic patients from the general scheme with a pharmacological treatment for diabetes mellitus in 2006, aged 40–69 years and alive on 31 December 2006. Treatment for diabetes mellitus was defined as at least three reimbursements in 2006 for any oral antidiabetic and/or insulin (Anatomical Therapeutic Chemical (ATC) code A10 excluding benfluorex). This definition is the one used to estimate the prevalence of treated diabetic patients in France[11] and in the Entred 2007 study as well[12] which was a study conducted on a randomized sample of about 10 000 French diabetic patients in order to characterize and evaluate the health status of people treated for diabetes. We selected only diabetic patients in this cohort since benfluorex marketing authorization in France was restricted in 2007 to this population. We limited our study to the 40–69 years age class that included ages of patients in published case reports.[5–7]

Exposed patients were individuals with at least one benfluorex reimbursement in 2006, whatever the dose and number of reimbursements. Non-exposed patients were defined by no benfluorex reimbursement in 2006–2008. Linkage with French hospitalization database allowed search in exposed and non-exposed patients for the following discharge diagnoses (ICD-10 codes), both in 2007 and 2008: cardiac valvular insufficiency for

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any cause (I051, I061, I071, I340, I351, and I361), mitral insufficiency (I051 and I340), and aortic insufficiency (I061 and I351). Moreover, a valvular replacement surgery for valvular insufficiency of any cause was identified with the following diagnosis-related groups (GHM): 05C02Z, 05C03V, and 05C03W.

We also identified patients with one of the four ALD for a cardiovascular disease as it may influence the propensity to develop valvular heart disease. We thus retained the four following diseases: coronary heart disease, severe heart failure, lower limb arteriopathy, and cerebrovascular disease with disability.

Benfluorex was available as 150 mg tablets. The recommended daily dose was 450 mg for most of patients. We classified patients according to their cumulative benfluorex doses in two groups: less than 40.5 g corresponding approximately to a 1–3 month-treatment and more than 41 g for treatments of 4 months and up to 1 year.

Univariate and bivariate analyses were conducted to describe the patients included and to compare baseline characteristics between benfluorex-exposed patients and non-exposed patients (Chi-square test). The relative risk (RR) of hospitalization for cardiac valvular insufficiency for benfluorex-exposed patients compared to non-exposed patients was calculated. Adjustment on age, gender, and ALD for a cardiovascular long-term disorder was performed using the Cochran–Mantel–Haenszel method. Additional subgroup analyses focused on the detailed admission diagnosis (mitral insufficiency and aortic insufficiency) and valvular replacement surgery for valvular insufficiency as well as on the benfluorex cumulative dose. The *p*-values of less than 0.05 were considered as being of statistical significance. All analyses were performed with the SAS statistical package.

RESULTS

Description of the cohort population

A total of 1 048 173 patients aged 40–69 years with at least three successive reimbursements for any antidiabetic drug in 2006 were included. Of these, 43 044 (4.1%) were exposed in 2006 to benfluorex. Benfluorex-treated patients were slightly younger than non-exposed patients (mean age: 57.3 years vs. 58.3 years; $p < 0.001$) and were more often female (56.4% vs. 42.0%, $p < 0.001$).

A higher exposure to benfluorex was found in female aged 45–49 years (6.5%) and a lower in male 65–69 years (2.6%). The rate of patients with ALD for a cardiovascular disease in 2006 increased with age in both groups and was significantly higher after 55 years in the group unexposed to benfluorex (Table 1).

Table 1. Cohort Patients Demographics and cardiovascular disease frequency at time of inclusion in 2006

	Overall *n*	Non-exposed patients	Benfluorex-exposed patients	*p*-value
	1 048 173	*n* = 1 005 129	*n* = 43 044	
Mean age of patients (years)	58.2	58.3	57.3	$p < 0.001$
Female patients (*n*)	**446 073**	**94.6%**	**5.4%**	
Mean age of patients (years)	58.1	58.3	57.3	$p < 0.01$
Age distribution (%)				
40–44 (years)	24 291	93.9%	6.1%	$p < 0.001$
45–49 (years)	41 708	93.5%	6.5%	
50–54 (years)	69 569	93.8%	6.2%	
55–59 (years)	100 239	94.1%	5.9%	
60–64 (years)	102 846	94.8%	5.2%	
65–69 (years)	107 420	95.8%	4.2%	
Male patients (*n*)	**602 100**	**96.9%**	**3.1%**	
Mean age of patients (years)	58.3	58.3	57.5	$p < 0.05$
Age distribution (%)				
40–44 (years)	27 988	96.7%	3.3%	$p < 0.001$
45–49 (years)	51 030	96.4%	3.6%	
50–54 (years)	91 193	96.5%	3.5%	
55–59 (years)	145 963	96.7%	3.3%	
60–64 (years)	148 315	97.0%	3.0%	
65–69 (years)	137 611	97.4%	2.6%	
Presence of a cardiovascular disease (ALD)* according to age and exposure				
40–44 (years)	52 279	2.9%	2.9%	NS
45–49 (years)	92 738	5.1%	5.5%	NS
50–54 (years)	160 762	7.2%	6.9%	NS
55–59 (years)	246 202	9.0%	8.4%	$p < 0.05$
60–64 (years)	251 161	10.3%	9.4%	$p < 0.01$
65–69 (years)	245 031	11.6%	10.8%	$p < 0.05$

*Cardiovascular diseases (ALD): coronary heart disease, severe heart failure, lower limb arteriopathy, and cerebrovascular disease with disability.

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Table 2. Hospitalization rates by age class and gender in 2007 for cardiac regurgitation valvular insufficiency (number for 100 000 diabetic patients)

Age class (years)	Male	Female
40–44	3.6	4.1
45–49	11.8	19.2
50–54	36.2	15.8
55–59	21.9	29.9
60–64	39.1	28.2
65–69	48.0	38.2
Overall	32.6	26.9

Hospitalizations in 2007 for cardiac valvular insufficiency diagnosis were also dramatically increasing with age from 4/100 000 in patients aged 40–44 years to more than 40/100 000 in 65–69 years patients. They occurred more often in men (Table 2).

Relation between exposure to benfluorex and hospitalization for cardiac valvular regurgitation

The absolute risk of hospitalization in 2007 and 2008 for a diagnosis of cardiac valvular insufficiency was 76/100 000 person-years in the benfluorex-exposed group versus 27/100 000 in the non-exposed group, i.e., a crude relative risk (cRR) of 2.9 [95%CI 2.2–3.7] and an adjusted relative risk (aRR) of 3.1 [95%CI 2.4–4.0]. Adjusted RR of mitral and aortic insufficiency admissions were 2.6 [95%CI 1.9–3.7] and 4.4 [95%CI 3.0–6.6], respectively, while aRR of hospitalization for valvular replacement surgery was 3.9 [95%CI 2.6–6.1] (Table 3).

A possible dose–effect relationship was searched for the risk of hospitalization for cardiac valvular insufficiency in 2007 and 2008. We found that patients with lower cumulative doses in 2006 were less likely to be hospitalized for such a diagnosis, and a dose–effect relationship was observed within the two dose classes (less than 40.5 g and more than 41 g) compared to non-exposed patients (Table 4). However, analysis of the three subgroups included in the highest class of (more than 41 g) failed to show a highest RR for the last subgroup dose (more than 135 g).

DISCUSSION

In this cohort study performed in more than one million people with diabetes, we found a positive relationship between benfluorex reimbursement in 2006 and at least one admission for cardiac valvular insufficiency in 2007 and 2008. There was a threefold increase in the risk of cardiac valvular insufficiency and particularly mitral insufficiency, and a fourfold increase for aortic insufficiency and valvular replacement surgery.

Table 3. Risk of hospitalization in 2007 and 2008 for a diagnosis of cardiac valvular insufficiency in diabetic patients exposed or not to benfluorex in 2006

	Events/patient-years		Incidence *per* 100 000 patient-years in 2007 and 2008		Relative risks	
Admission diagnosis	Non-exposed	Benfluorex-exposed	Non-exposed	Benfluorex-exposed	Crude RR [CI 95%]	Adjusted* RR [CI 95%]
Any Valvular insufficiency	532/1 997 611	65/85 677	27	76	2.9 [2.2–3.7]	3.1 [2.4–4.0]
Mitral insufficiency	350/1 997 694	37/85 689	18	43	2.5 [1.8–3.5]	2.6 [1.9–3.7]
Aortic insufficiency	170/1 997 792	29/85 699	9	34	4.0 [2.7–5.9]	4.4 [3.0–6.6]
Replacement surgery for valvular insufficiency	53/1 997 791	24/85 699	8	28	3.7 [2.4–5.6]	3.9 [2.6–6.1]

*Adjustment on age, gender, and ALD for a cardiovascular disease.

Table 4. Relationship between benfluorex cumulative dose in 2006 and risk of hospitalization in 2007 and 2008 for cardiac valvular insufficiency in 40–69 years diabetic patients

Cumulative dose of benfluorex in 2006 (g)	Effective (patient-years)	Incidence of hospitalizations for valvular regurgitation surgery in 2007 and 2008 for 100 000 benfluorex-exposed patient-years	Crude relative risk [CI 95%]	Adjusted† relative risk [CI 95%]
0	1 997 611	26.6	1.0	1.0
<41*	31 961	50.1	1.9 [1.1–3.1]	2.1 [1.3–3.5]
≥41	53 716	91.2	3.4 [2.6–4.6]	3.6 [2.7–4.8]
Subgroups analysis for highest doses				
41–90	20 400	73.5	2.7 [1.7–4.6]	3.1 [1.8–5.1]
91–135	16 091	99.4	3.7 [2.3–6.1]	4.0 [2.4–6.5]
≥136	17 225	104.5	3.9 [2.5–6.3]	3.9 [2.4–6.2]

* 41 g is equivalent to nearly 3 months treatment with recommended daily dose.
† Adjustment on age, gender, and ALD for a cardiovascular disease.

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A cohort study design was used since reimbursement and hospitalization data are collected prospectively in health insurance general scheme and PMSI databases, allowing follow-up of patients and comparisons between exposed and non-exposed groups with determination of RR. As a result, there were some differences between the two groups since no randomization was applied for their constitution. In particular, there was a higher proportion of females in the benfluorex group compared to the non-exposed group. We adjusted our analysis on three variables including gender, since it was observed in the whole cohort that such diseases affected more often male patients. The database PMSI has already been used for descriptive studies to evaluate data such as prevalence, incidence, management, and costs of a given disease in hospitalized patients.[13–15] The use of two linked databases in SNIIRAM was necessary in our study as they are complementary, particularly about admission diagnoses since PMSI database does not inform precisely about etiology. It was therefore not possible to use only data from PMSI in diabetic patients as there are many diagnoses corresponding to valvular regurgitation (e.g., degenerative, rheumatic, postendocarditis, congenital, ischemic, secondary to left ventricular failure, postradiation, valvular tumor, etc.) but for instance only two codes for mitral insufficiency (I051 Rheumatic mitral insufficiency and I340 Mitral (valve) insufficiency, except rheumatic) in ICD-10 classification. A search on criteria such as ''regurgitation valvular disease of any cause'' would have limited potential classification bias, but would have reduced the statistical power of the study.

A possible increase in the risk of regurgitation valvular occurrence in diabetic patients was then assessed in benfluorex users with the use of both diagnoses admissions and reimbursement data. Information on drug reimbursement is routinely and exhaustively teletransmitted by all French pharmacists through the national health insurance network. The collect of hospitalization data in the PMSI database is also routinely achieved by ATIH since every hospital physician in France has to record all discharge diagnoses in electronic standardised discharge summaries concerning any patient hospital stay, together with the main medical procedures that have been realized. Linkage between these two databases (that are independent in term of data collection) contributes to reduce selection bias both on discharge diagnoses and drug exposures.

Several factors may however influence the values of RR found in the present study. Firstly, assessment of exposure in health insurance databases relies upon reimbursement with the postulate that a patient has actually been treated, but it cannot be excluded that some patients were not exposed at all or discontinued their treatment prematurely. Number of exposed patients and cumulative doses as well may be therefore overestimated. Moreover, confusion between individuals in a large database at the national level may occur, particularly between members of the same family, but such confusions are considered to be rare in patients with chronic treatments (in contrast to patients who have occasional reimbursements). For example, a French survey in 2002 about lipid-lowering drugs identified up to 5% confounding errors between individuals but only in new users with just one reimbursement.[16] Furthermore, a recent study comparing French data from health insurance claims and patient interviews in the assessment of drug utilization showed that concordance on exposure to a given drug between these two data sources was the highest for antidiabetic drugs ($\kappa = 0.93$) followed by cardiovascular drugs.[17]

We also did not have the possibility to access to data from periods earlier than 2006 in order to check possible exposures to benfluorex in some patients unexposed in 2006, as the French law restricted SNIIRAM data storage to a period of 2 years plus the year being. The RR might be underestimated if the events of interest were attributed to diabetic patients that were actually exposed to benfluorex before 2006 and considered as non-exposed in our cohort study.

It has to be noted that not all diabetic patients were concerned by benfluorex indication, as they had to present high blood levels of triglycerides (until AFSSAPS decision in April 2007) or should overweight as precised in Marketing Authorization. In France in 2007, 80% of type 2 diabetic patients had a BMI ≥ 25 versus 44% among type 1 diabetic patients.[12] Inclusion in our study of type 1 diabetic patients who were less likely to be prescribed benfluorex than patients with type 2 diabetes may have contributed to underestimate the calculated RR, even if type 1 is a minority: it was accounting in France for 6.6 and 5.6% of diabetic patients in 2001 and 2007, respectively.[12,18]

The non specificity of terms ''valvular insufficiency for any cause'' including particularly degenerative or rheumatic valvulopathy which are the main causes of mitral insufficiency in this 40-69 years population could have also underestimated the RR, while however minimizing classification bias.

Moreover, the dose–effect relationship which was observed between 2006 benfluorex exposure and heart valvular disease occurrence could suggest that a higher

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RR might be observed with a follow-up greater than 2 years.

Overall taking account of these points, the RR we found might therefore be higher.

In addition to the observed increase in risk associated with benfluorex in our study, several arguments support benfluorex causality.

First, a pharmacological mechanism has been previously described for serotoninergic fenfluramine derivatives. Benfluramine, like fenfluramine, and dexfenfluramine, is known to be metabolized into active metabolite norfenfluramine. The mechanism explaining such adverse drug reaction remains unclear despite the role of serontonin release previously discussed. Several studies have suggested the involvement of 5-HT_{2B} receptors in the cardiac valvular heart disease induced by ergot derivatives or appetite suppressant drugs derivated from amphetamine (fenfluramine and dexfenfluramine).[19–22]

Second, an dose–effect relationship was observed in our study concerning benfluorex exposure in 2006. However, a formal demonstration should be done by using exhaustive exposure through possibly several years for each benfluorex user. Unfortunately, due to the storage restrictions imposed on SNIIRAM data, we were not able to take into account the previous reimbursements for patients who initiated benfluorex before 2006.

Third, our results are in agreement with results of two observational studies.[23–25] The first study included 27 cases with unexplained mitral insufficiency and 54 controls with mitral insufficiency with an identified medical cause. This case-control study conducted in cardiology and cardiac surgery units in a large French university hospital showed a strong association between benfluorex exposure and mitral regurgitation.

However, our conclusions only concern the 40–69 years diabetic population. Our analysis restricted to this population with adjustment on age, gender, and known cardiovascular diseases has limited the influence of possible confounding factors.

Data from Health Insurance databases have already been useful to monitor the incidence of a severe disease and the possible impact of therapeutics.[26] Data mining methods are also currently being studied to be applied on such databases in order to enhance the postmarketing surveillance of safety of drugs.[27] A recent review included 110 articles published about French studies using reimbursement databases in several other fields such drug utilization and cost-effectiveness assessment.[8] Despite its limitations, this study using data from the SNIIRAM system confirms that French medico-administrative databases may be helpful to study drug safety and assess an RR especially if a linkage between hospitalization and reimbursement databases is performed. Moreover, a linkage with a third database collecting medical causes of death in France will add in the future crucial information. Concerning benfluorex, this original pharmacoepidemiological study allows to confirm data from the spontaneous notification[5–7] which remains the first step to detect a pharmacovigilance signal.

CONCLUSION

Use of Benfluorex in diabetic patients was significantly associated 2 years following benfluorex exposure to mitral and/or aortic valvular regurgitation and valvular replacement surgery with cardiopulmonary bypass. This adverse drug reaction of this fenfluramine-like product was rare (less than 1/1000 patient-years) but potentially serious. The results of our study were transmitted to the French Medicine drug agency (AFSSAPS) in October 2009 to contribute to the re-assessment of the benefit-risk balance of this product. Following AFSSAPS decision to suspend its marketing authorization in November 2009, European Medicines Agency (EMA) also recommended on 18 December 2009 the withdrawal of all medicines containing benfluorex in the European Union, because "*their risks, particularly the risk of heart valve disease are greater than their benefits*."[28]

CONFLICT OF INTEREST

No private company sponsored this project. All authors are employees from public institutions. D. S. has been

KEY POINTS

- Benfluorex, a fenfluramine-derivated drug, in diabetic patients was significantly associated with hospitalization for cardiac valvular regurgitation in the 2 years following benfluorex exposure.
- Patients exposed to benfluorex had a threefold increase in the risk of mitral regurgitation, and a fourfold increase for aortic regurgitation and valvular replacement surgery.
- Linkage between French reimbursement database (SNIIRAM) and hospitalization database (PMSI) is a valuable tool to study in a real setting serious adverse drugs reactions which may have been poorly assessed or even remained unknown for many years.

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