

Review Article

Benfluorex and Mortality: A Fresh Perspective

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Benfluorex, a drug related to fenfluramine, has been sold under the trade name “Mediator” by Servier Laboratories and was introduced to the French market in 1976, licenced for the treatment of type 2 diabetes and dyslipidemia. Although the evidence that benfluorex increases the risk of mild valvular regurgitant abnormalities is convincing, it is also apparent that no data exist from which to calculate the risk of death attributable to benfluorex use. Despite this, two studies have attempted to make such estimates, the results of which have been the focus of much media attention. In this review, we attempt to provide a further assessment of the evidence base, explore the limitations of the estimates of death that have been made, and calculate the population risk of mild valvular regurgitation and hospitalisation attributable to benfluorex use. We conclude that the previously published estimates of deaths attributed to the use of this agent are unsafe, based on unfounded assumptions, and are highly likely to be inaccurate.

1. Introduction

In 2011 a media storm occurred as a result of claims that benfluorex, a Servier-manufactured drug used to treat type 2 diabetes and dyslipidemia, was responsible for “between 500 and 2000 deaths” since its introduction in 1976 [1]. We were intrigued by how readily the figures were accepted by both lay and scientific communities with little detailed examination of how they had been derived. We therefore aimed to investigate for ourselves the validity of these estimates of deaths attributable to benfluorex use.

2. Epidemiology and Assessment of Valvular Heart Disease

It is helpful to briefly outline the known epidemiology and assessment of heart valve lesions to provide a context for the following discussions.

The Euro Heart Survey reported findings on 5001 men and women aged 19 to 101 years recruited across 25 European countries after assessment for valvular heart disease [2]. In this study, of those with native heart valves, 33.9% had aortic

stenosis, 24.8% mitral regurgitation, 10.4% aortic regurgitation, and 9.5% mitral stenosis. 20.2% had multiple lesions and 1.2% had involvement of right-sided valves. Of those with aortic stenosis, degeneration was the cause in 81.9%; the figure for aortic regurgitation was 50.3%. Mitral regurgitation in native valves was found to be degenerative in 61.3%; in contrast 85.4% of cases of mitral stenosis (MS) were found to be of rheumatic origin.

Thus valvular heart disease is common in the general population. The majority of cases are mild; indeed, in an American study [3], the population prevalence in a cohort defined following referral for symptoms was lower than that in a large sample of the free living community suggesting that much disease is subclinical. Nkomo et al. [3] examined two large cohorts: firstly 11,911 randomly selected adults who had been assessed prospectively with echocardiography (that is as part of a prospective study in the absence of a clinical indication), pooled from several small cohorts; and secondly a community study of 16,501 adults in Olmsted County, who had been assessed by clinically indicated echocardiography. In the population cohort (40% black, 59% white, and 1% other) the prevalence of all heart valve disease was similar in men and women and there was an increase with age, such

that the prevalence was 0.7% at 18 to 44 years, 0.4% at 45 to 54 years, 1.9% at 55 to 64 years, 8.5% at 65 to 74 years, and 13.2% at 75 years or above.

This demonstrates an increase in prevalence by age for regurgitant lesions, the type associated with medication such as fenfluramine and benfluorex. When extrapolated to the US population, based on the census in 2000, the overall prevalence of valve disease was estimated to be 2.5% (95% CI: 2.2–2.7%). Interestingly, the overall prevalence of heart valve lesions in the Olmsted County community echocardiography cohort was lower than that in the prospective population cohort, at 1.8%, adjusted to the US population. This cohort had a much greater prevalence of white than black participants (90.3% and 2.7%, resp.), but no analysis by factors such as ethnic origin, comorbidity, or anthropometric measures was given. The disparity did appear to be greater for women, suggesting that there may be under referral compared with men. Another explanation for this disparity is that much of the valve disease in the population does not present to medical attention. As these studies did not report serial echocardiograms, it is difficult to be sure of the duration of any detected prevalent lesion, and therefore the true significance of lesions that do not present to medical attention; this disparity does suggest, however, that mild lesions may not have a significant adverse effect, a notion consistent with other data [4].

There are very few data describing the natural history of valve disease in populations, particularly regarding mild disease of the sort most commonly associated with medication use. Echocardiography is necessary to detect valvular heart disease reliably, but there is good evidence of marked interoperator variability in diagnosis, and, importantly, obesity reduces the ability to clearly detect mild disease. Thus knowledge of the suspected diagnosis or drug exposure may well influence interpretation of echocardiogram results, as has been demonstrated in a US study. The natural history of drug induced valvular heart disease is also unclear, with studies potentially subject to a range of confounding factors, not least the interpretation of serial echocardiographic scans. However, the available evidence relating to fenfluramine exposure suggests that resulting disease is usually mild and that it may remain stable or even improve after cessation of the causative agent.

3. Overview of the Evidence Linking Benfluorex Consumption to Drug-Induced Valvular Heart Disease

3.1. Background. Benfluorex, a drug related to fenfluramine, has been sold under the trade name “Mediator” by Servier Laboratories and was introduced to the French market in 1976. The initial marketing authorisation for this medication in 1974 was for the following approved indications: treatment of type II diabetic patients with body mass index greater than 25 kg/m² in combination with an appropriate diet, and secondary treatment of adult hypercholesterolaemia and hypertriglyceridaemia. In the late 1990, dexfenfluramine, a

molecule related to benfluorex, was associated with regurgitant heart valve lesions in two case-control studies; in 2003 the first case report was published in which a heart valve lesion was attributed to benfluorex [5]. Three further case reports followed [6–8] and were supplemented by one cohort [9] and three case-control studies [10–12] which consistently indicated that benfluorex consumption was associated with an increased risk of regurgitant valve lesions. Findings consistent with the observational data (in terms of direction of association, but not always in terms of effect size) have come from the results of the Servier-sponsored REGULATE study [13], a randomised double-blind controlled trial of benfluorex versus pioglitazone specifically aimed at evaluating echocardiographic heart valve changes. Furthermore, there is mechanistic evidence suggesting that drugs such as benfluorex and fenfluramine might act on heart valves via a serotonergic mechanism involving 5HT_{2b} receptors. Although fenfluramine derivatives have been associated with pulmonary hypertension, the evidence linking benfluorex to this condition is much weaker, comprising a recent case series [14] and clinical study [15], neither of which allows any definite conclusions to be made regarding causality.

Whilst there is little disagreement about whether benfluorex, as with other related medications, might cause heart valve lesions, there is much debate as to the natural history and potential severity of these lesions, whether other factors might be important, such as genetic predisposition [16], and the likelihood of resulting death. Since 1976, two deaths linked to benfluorex use have been recorded as case reports, in 2003 [5] and 2008 [17]. An analysis of deaths potentially attributable to benfluorex was made as a report to Afssaps, the French regulator, on a case-by-case basis by Weill et al. in 2010, and the total number of deaths attributable to benfluorex use in France was estimated as 500 by Hill [18] in 2011 and 1300 by Fournier and Zureik [19] in 2012.

Overall, the evidence base convincingly demonstrates a causal association between benfluorex and DIVHD but does not allow calculation of the risk of hospitalisation or death attributable to benfluorex consumption. In the remaining part of this review, we will describe in detail some of the key studies which have attempted to relate benfluorex use to DIVHD, hospitalization, and death.

3.2. Case-Control Studies. Two case-control studies compared benfluorex use in patients with regurgitant heart valve lesions of unknown aetiology with that in patients with defined diagnoses, for example, degenerative disease. Both studies were relatively small and could not satisfactorily account for potential confounding factors such as disease severity, comorbidities, and/or body mass index. Additionally there were methodological issues such as the use of case-control methods for a rare exposure, the lack of logistic regression analysis [10], and inappropriate use of propensity scoring [11]. Use of controls with defined causes of valvulopathy is also problematic, resulting in the potential for selection bias, and prevents generalisation to the whole population.

Most recently, as part of the government funded screening of individuals previously exposed to benfluorex, Tribouilloy et al. [12] conducted a high quality study of 376 diabetic subjects previously exposed to benfluorex and 376 nonexposed controls. The inclusion criteria for both benfluorex users and controls included no history of heart valve disease and no exposure to other drugs that could induce valvular heart diseases (rye ergot alkaloids, fenfluramine/phentermine, dexfenfluramine, and pergolide). The severity of valve regurgitations was recorded from echocardiograms by cardiologists blinded to patient history. Using propensity scores, a matched cohort of 293 exposed and 293 nonexposed individuals was derived. In both the matched and unmatched samples left-sided mild to moderate valvular regurgitation was more common in the benfluorex exposed group. Thus, in the matched sample, 31% of the benfluorex group and 12.9% of the nonexposed group had left-sided valvular regurgitation (OR: 3.55, 95% CI: 2.03–6.21). The majority of these lesions were mild. The methodology is sound and the results are consistent with other papers. However, it is clear that this study does not give any information regarding the risk of death attributable to benfluorex use.

3.3. Cohort Study. Weill et al. [9] studied a cohort of 1,048,173 patients aged 40 to 69 years old with reimbursement for an antidiabetic drug in 2006 using data from the French healthcare databases. We describe this study, known as CNAMI, in rather more detail, as it has been used as the basis for estimates of the risk of death attributable to benfluorex use. Benfluorex users (4.1%) were patients with at least one reimbursement in 2006, regardless of dose or number of reimbursements; nonusers were patients with no reimbursement between 2006 and 2008. The outcome was a hospital diagnosis of valvular insufficiency of any cause. The risk of valvular insufficiency was 75.9 per 100,000 in benfluorex users versus 26.6 per 100,000 in nonusers. Adjusting for age, sex, and hospital diagnosis of cardiovascular disease, the relative risk of valvular insufficiency was 3.1 (95% CI: 2.4 to 4.0) in benfluorex users versus nonusers. Data from the SNIIR-AM database are only available for a period of 2 years plus the current year [20] and include both new (incident) and existing (prevalent) benfluorex users; thus it is unknown for how long patients had been taking the drug, or indeed even whether they had taken it at all following reimbursement, and “nonusers” may have taken benfluorex prior to 2006. Information on other medications known to cause DIVHD, such as ergot alkaloids and fenfluramine/phentermine, is lacking. Important confounders such as body mass index and duration of diabetes were not addressed. Additionally, although the data are quoted as person years at risk, time to event data and censoring information including death and loss to followup do not appear to have been taken into account. The authors assume that all patients remained at risk in the database between 2006 and 2008. However, there is an immortal time period at the start of the study where in 2006 it was not possible for both exposed and nonexposed patients to have the outcome, and treatment use could change over time

for both users and nonusers. Selection bias may have arisen from the inability to exclude patients with mild to moderate forms of vascular disease at the start of the study. Finally, although the French healthcare database used covers 86% of the population, concerns have been raised over the accuracy of recorded diagnoses, particularly of comorbid conditions. Weill et al. followed this study with a descriptive paper [21] (and addendum [22]) forming a report to the French regulator describing the characteristics of 64 individuals who had died after having been exposed to benfluorex. Clearly the design of this study, lacking a control group and relying on summary data rather than medical notes, does not allow accurate attribution of cause of death to be made. Indeed benfluorex is very unlikely to be involved positively in many of the deaths (e.g., metastatic cancer, splenic abscess) and it is difficult to see how this study and similar studies with admission for valvulopathy as the endpoint [23, 24] really take us forward in terms of attributable risk of death.

3.4. Intervention Study (REGULATE). The Servier-sponsored REGULATE trial [13] was a double-blind, parallel-group, multicentre, randomised, and noninferiority trial designed to compare the efficacy and safety of benfluorex and pioglitazone in type II diabetes patients. The interventions were benfluorex (150–450 mg/day) or pioglitazone (30–45 mg/day) and followup was over one year. The primary outcome in terms of efficacy was change in HbA1c and safety was assessed by blinded longitudinal echocardiographic evaluation of cardiac and valvular status, according to American Society of Cardiology guidelines [25], with images assessed as a batch at the end of the study. Thus grade 1 is termed “trivial trace” and grade 2 “mild.” The distribution of valvular disease was well matched between the groups. Overall, 51% had at least one abnormality on any valve, 17% had grade 1, and 15% had grade 2 aortic regurgitation; 61% had grade 1 and 59% had grade 2 mitral valve regurgitation with only 1% grade 3. There were no other grade 3 measurements at any other valves.

Amongst patients with repeat echocardiographic assessment (310 benfluorex and 305 pioglitazone), there were eight participants with new morphological abnormalities (valve thickening or calcification) in the benfluorex group, compared with four in the pioglitazone group (OR 1.99, 95% CI: 0.59–6.69). 27% of the benfluorex group (82 participants) and 11% of the pioglitazone group (33 participants) experienced a new valvular regurgitant lesion or worsening of an existing lesion by one or more grade (OR 2.97, 95% CI: 1.91–4.63). The vast majority of these were to grade 1 (trivial trace) with only 3 in each group progressing to grade 2 (mild); there were no cases in either group of more severe progression. The main limitation of this study is the short duration of followup, particularly considering that in the general population, benfluorex could be used for many years. The study clearly demonstrates, in this randomised, double-blind design, that benfluorex is associated with at least mild regurgitant lesions but unfortunately cannot tell us about their longer term natural history.

4. Estimate of Risk of Death Attributable to Benfluorex Consumption

Despite the lack of any data on the risk of death attributable to benfluorex use in any population, two published attempts have been made to estimate the total number of deaths associated with benfluorex use from 1976 until it was removed from the market in 2009.

4.1. Hill, Presse Medicale 2011. Hill, in 2011 [18], used data from Weill et al. [9] regarding the relative risk of hospitalisation associated with benfluorex use and information supplied by Servier to Afssaps regarding the number of boxes of benfluorex officially issued since 1976 to estimate the number of deaths attributable to benfluorex use.

In the first part of the paper, Professor Hill makes some interesting observations regarding the difference between “imputability”, that is, the likelihood of a particular cause of death in an individual clinical scenario, and “attributable mortality,” an epidemiological concept in which the fraction of the overall mortality attributable to use of the medication is defined at the population level. The assumptions underlying the measure of attributable risk are firstly that the risk factor (benfluorex) is causally associated with the outcome of interest and secondly that there is no confounding or bias in the measures of risk in exposed and unexposed groups. The evidence that benfluorex may cause regurgitant valvular heart lesions is substantial, and whilst the individual observational studies have significant limitations, the consistency of direction between cohort, case-control, and randomised controlled trial evidence is as conclusive as can reasonably be expected. However, this general association becomes more problematic when it is put in terms of specific numbers and used for extrapolation to the entire population. Despite the discussion of imputability and attributable risk, the author neglects the fact that no epidemiological data exist regarding the attributable risk of death due to benfluorex.

Three key issues must be examined here: firstly, the number of people at risk (clearly related to the number of boxes of medication sold) since 1976; secondly, the relative risk of hospitalisation or surgery associated with benfluorex use; and thirdly, the relative risk of death following hospitalisation or surgery associated with benfluorex use.

4.1.1. Number of Boxes Issued. A major potential problem with the estimation of the number of people at risk is that there is evidence that benfluorex was used off label for weight loss, even in people who were not diabetic. However, the total number of boxes sold between 1976 and 2009 (data supplied by Servier to Afssaps), 145 million, should include all use, regardless of whether it was licensed or unlicensed.

The study uses data from the paper, by Weill et al. [26], of the cohort of 303,000 benfluorex users in 2006 on which to base their extrapolations alongside information on the number of boxes of benfluorex these patients consumed. In the cohort benfluorex users were followed up for 4 years for hospitalization (from 2006 to 2009) and 4.6 years for mortality (2006 to July 31, 2010), and they reported

556 hospitalized for valvular regurgitation and 58 deaths. However, this cohort contains both new (incident) and existing (prevalent) drug users. Hill makes an assumption that benfluorex users had 1.1 years after exposure to treatment prior to 2006 and 3.7 years followup from 2006 onwards for hospitalization (4.3 years for mortality). The basis behind this assumption is weak, based on guesswork, and will naturally have measurement error. The author then includes 597 hospitalizations for valvular insufficiency and lesions and 64 deaths, based on the addendum by Weill et al. to CNAM2 [22]. They then inflate the 597 hospitalizations by a factor of 4.8/3.7 to estimate hospitalizations that would have occurred prior to 2006 bringing the total to 774 (the 64 deaths inflated by a factor of 5.4/4.3 making a total of 80). We are told that the 303,000 benfluorex users consumed 10.3 million boxes of the drug between 2006 and 2009. To estimate consumption that occurred prior to 2006, the author makes a further assumption that users would be in the middle of their treatment and estimate that 6.5 million boxes were used prior to 2006, making a rounded total of 17 million boxes. Again there will be a large amount of measurement error associated with this estimate of boxes consumed. The author then inflates the 774 hospitalizations up by a factor of 145/17 to estimate the total number of hospitalizations for all 145 million boxes consumed in France between 1976 and 2009 bringing the total up to 6602 hospitalizations (the 80 deaths also inflated by 145/17 making a total of 682 deaths).

4.1.2. Attributable Risk for Hospitalisation for Valvular Disease.

To estimate the number of hospitalizations attributable to benfluorex use the author uses the estimate of attributable risk from the cohort of diabetic benfluorex users in the earlier study by Weill et al. [9] which was 67.7% (RR 3.1–1/3.1), making the assumption that the attributable risk in diabetic benfluorex users is the same as in all benfluorex users. The authors therefore state that 4500 hospitalizations (67.7% of the 6602 hospitalizations) are attributable to benfluorex between 1976 and 2009. This is unlikely to be true given that, in the cohort of all 303,000 benfluorex users, the rate of hospitalization was 46 per 100,000 person years compared to a rate of 75.9 per 100,000 in diabetic benfluorex users. Hence the attributable risk has been overestimated, and hence the total number of hospitalizations for valvular insufficiency.

4.1.3. Attributable Risk for Death due to Benfluorex. There are no epidemiological data on which to base a figure for the attributable fraction of deaths related to benfluorex use and the major assumption made by Hill [18] is that the risk of death for valvular disease associated with benfluorex use is identical to the risk of death associated with other causes of valvular disease; the resulting attributable fraction is thus identical to that for hospitalisation (hence 465 (67.7%) of the 682 deaths are assumed attributable to benfluorex), leading to the implicit assumption that the risk of death following hospitalisation is the same for all causes of valvulopathy. In fact, if it is assumed that all patients with valvular heart disease who die do so after admission to hospital (a further assumption implicit in the analysis, and one which is clearly

unlikely to be valid for the whole population), then the key issue is whether the prognosis of valvular heart disease varies by aetiology.

There are several important reasons why it is unlikely that the risk of death associated with valvulopathy due to benfluorex will be the same as that due to other aetiologies. It must be acknowledged that these are hypotheses, and that there are insufficient data to confirm or refute in every case. This being the case, however, it is important that they are taken into account, when assessing the confidence with which to accept the estimates of mortality associated with benfluorex.

Firstly, even if two lesions of different origin result in similar haemodynamic consequences, the aetiological factors are likely to mean that risk of death, either due to medical complication such as heart failure or occurrence of complication following surgery, is different between causes. An example might be functional mitral regurgitation occurring as a consequence of ischaemic cardiomyopathy compared with mitral regurgitation due to benfluorex used for weight loss in an otherwise healthy patient. Clearly the associated ischaemic heart disease will substantially change the mortality risk in the first patient.

Secondly, users of benfluorex may not have the same demographic and comorbidity profile as nonusers. That is, benfluorex was prescribed for a particular indication and that indication might influence prognosis (confounding by indication). The effect of this is likely to be different according to indication, either licensed (diabetes, dyslipidemia) or unlicensed (weight loss). Thus benfluorex users are likely to be at higher risk of metabolic syndrome, hypertension, and chronic renal impairment (all associated with obesity/diabetes/dyslipidemia), all of which have implications for reduced survival than benfluorex nonusers who might present with degenerative valvulopathy. As body mass index or weight was not reported in the CNAMI [9] study, it is impossible to gauge whether there are differences in these parameters between the benfluorex treated and untreated cohorts, but in the case-control study by Frachon et al. [10], unexplained mitral or aortic regurgitation was associated with greater BMI, in addition to a higher frequency of benfluorex use. This consideration applies both to the comparison of diabetic benfluorex users and nondiabetic controls and to benfluorex users and nonusers within a diabetic population such as studied by Weill et al. in CNAMI [9].

Thirdly, the reason for obtaining admission coding of valvular heart disease might not be similarly distributed across different aetiologies. These underlying reasons were not recorded in CNAMI [9] but might have included factors such as diagnostic investigation, preoperative workup, and general workup for multiple disease, in addition to a medical emergency, for example, heart failure [27]. The distribution of these reasons and their associated prognoses will be affected by symptom presentation, previous investigations, and comorbidities, none of which are adequately assessed in CNAMI, but which are likely to be differentially associated with different aetiologies. An example might be a functional insufficiency secondary to ischaemic cardiomyopathy in a patient admitted for optimisation of their medical condition,

carrying a poor prognosis, but a haemodynamically similar valvular lesion in an otherwise well diabetic might be admitted for preoperative workup, associated with a good prognosis.

Fourthly, the cause of drug-induced valvular disease is liable to vary over time, that is the dose and duration of medication use will vary between individuals, and within an individual's usage over time. Serial echocardiographic evidence pertaining to fenfluramine use suggests that non-progression and improvement of lesion severity are possible once treatment has ceased [28, 29], and both CNAM2 [21, 22] and the analysis of Koenig [30] suggest decreasing risk with time since cessation of benfluorex treatment. CNAMI suggested a dose effect with benfluorex [9]. Thus changes in treatment dose and duration following a hospital admission for valvular heart disease might impact prognosis and risk of death.

Finally, the distribution of deaths between hospital and community might differ between aetiologies. This is perhaps less likely in developed countries such as France with excellent healthcare provision, but even within such populations there is evidence of differential utilisation of health services according to socioeconomic and ethnic indices [31–34]. Therefore, where such factors are associated with aetiology, for example, rheumatic heart disease in those of African origin [2], there might be differential attendance at hospital.

There are further major methodological limitations. Firstly the data from the epidemiological study on which it is based [9] has major limitations in terms of bias and confounding, as described earlier. Secondly, due to the cohort of 303,000 benfluorex users in 2006 not being an incident cohort, several assumptions have to be made regarding duration of exposure to treatment prior to 2006 and the number of boxes of drug consumed, that will have a large measurement error associated with it. Thirdly, there are no epidemiological data on the attributable risk of benfluorex on mortality in all users, and the figure for hospitalisation in diabetic patients has to be used instead, which is a strong assumption and likely an overestimate, with associated measurement error. Hill describes the importance of differentiating between “imputable” mortality and “attributable” mortality but fails to highlight the fact that epidemiological data on the attributable risk of mortality in benfluorex users do not exist. Finally and most importantly, there are no epidemiological data to suggest any association of benfluorex and mortality, let alone a causal association. To conclude, it is clear there is no basis behind the author's conclusions relating to the estimates of the totality of hospitalizations for valvular insufficiency and death.

4.2. Fournier and Zureik, Pharmacoepidemiology and Drug Safety 2012. Fournier and Zureik [19] used a similar method to Hill [18] in their attempt to estimate the number of deaths attributable to benfluorex use, but with two important differences. Firstly they assumed a threshold of cumulative benfluorex dose (30 boxes), below which an adverse effect would not be expected; secondly, they used the mortality estimates derived from the Olmsted County study by Nkomo

et al. [3] as the risk of death associated with hospitalisation for valvular heart disease in patients taking benfluorex. Again, there are major concerns regarding the estimates and assumptions relating to number of patients exposed, attributable risk of hospitalization, and attributable risk of death. The second point has been addressed in the preceding section.

4.2.1. Estimate of Number of Exposed Patients. As the cohort study contains both prevalent and incident benfluorex users, the authors need to estimate the number of boxes of benfluorex used prior to 2006 and use a figure of 9 million (in contrast to the figure of 6.5 million assumed above by Hill [18]) which works out at 30 boxes per person (9,000,000/303,336). They state that the mean dose of benfluorex per user and per day was 246 mg in 2006, corresponding to 1.67 boxes per user per month (30 tablets of 150 mg benfluorex in each box with recommended daily dose of 450 mg). The authors make an assumption and estimate that 54% of boxes are sold to people that have already consumed 30 boxes. They make a further assumption that the risk of valvular insufficiency only applies to the 31st box consumed and beyond (despite no evidence for a thresholded effect) and therefore to 54% of the 145 million boxes, which is 78,300,000 boxes. In the cohort study the 597 admissions for valvular insufficiency occurred in patients that had consumed 10,317,567 boxes between 2006 and 2009. The authors assume that all 597 admissions relate to the 31st box and beyond. To extrapolate the 597 hospitalizations to the whole period between 1976 and 2009, they multiple up by a factor of 78,300,000/10,317,567, giving a total of 4531 hospitalizations. The attributable risk of hospitalization due to benfluorex in diabetic patients of 67.7% is then used to get an estimate of 3069 hospitalizations attributable to the drug (this is much lower than the estimate of 4500 by Hill in the other paper).

4.2.2. Risk of Death. The relative risk of death associated with benfluorex use is a key part of the calculations in both studies, and as in the study of Hill, the assumptions underlying the use of the data from Olmsted County by Fournier and Zureik require detailed examination.

Firstly, it is important to ask how similar are the Olmsted County population to that of the CNAMI study [9], on which the estimates of hospital admission are based. Clearly there are major differences. In Olmsted County, the age range was from 18 to more than 75 years old, 46.6% were men, and included both mitral and aortic regurgitant and stenotic lesions; indeed 31.5% of the lesions were aortic stenosis. In contrast the age range for CNAMI was 40–69 years, 56.4% benfluorex users were female, and only regurgitant lesions were included. Haemodynamic consequences clearly vary by valve lesion (in the Nkomo population cohort, patients with mitral regurgitation showed left ventricular enlargement without hypertrophy, whereas those with aortic stenosis had left ventricular hypertrophy without enlargement). The Nkomo paper does not give mortality estimates for specific valvular lesions, and it is difficult to deduce this information from other studies, but it is intuitively likely that different

valve lesions will be associated with different rates of mortality. Indeed, the severity of valve disease and ventricular dysfunction has been clearly demonstrated to predict survival [35–37]. There is a lack of detail on comorbidities in both studies (only classification to a chronic diagnosis group, ALD, is used in CNAMI, and survival rates were adjusted for age, sex, left ventricular ejection fraction, hypertension, diabetes, and coronary artery disease in the Nkomo analysis), together with an absence of information on body mass index, smoking, and alcohol intake. Ethnicity is estimated on the basis of the 2000 census in Olmsted County (90.3% white and 2.7% black), but no data are given in the CNAMI study.

Thus the two cohorts differ markedly in terms of age range and valvular diagnosis, and given the lack of further detail could differ substantially in terms of other risk factors for mortality, namely, comorbidities, smoking and alcohol intake, body mass index, and ethnicity. It is notable in the Nkomo study that although the adjusted risk of death in Olmsted County was 1.75 (95% CI: 1.61–1.90; $P < 0.001$), in the population-based study the adjusted relative risk of death associated with valvular disease was 1.36 (95% CI: 1.15–1.62, $P < 0.0001$). Whilst it can be argued that it is appropriate to use the estimate derived from a cohort based on clinically indicated echocardiograms, when comparing the French and US cohorts, the subsequent extrapolation to the entire French population is problematic. It also presupposes that indications and thresholds for hospitalisation are identical in Olmsted County and France; that is, the hospitalised population is similar in terms of disease severity in each case. The disease severity is not detailed in either paper, and anecdotally, given the very different health care systems in France and the US, it is unlikely that every person has the same chance of hospitalisation in both places. There is certainly evidence of geographic variations in care within countries [38]. Given these uncertainties, it might have been more appropriate for Fournier and Zureik to extend their sensitivity analysis to include the lower limit of the population sample-based estimate of mortality (1.15).

It is apparent, therefore, that there are major differences between the French CNAMI and the US Olmsted County cohorts. The differences that are conclusively demonstrated include age range and distribution of valvular diagnoses. Differences that are likely but cannot be documented because of inadequate data include body mass index, comorbidities, other medication use, smoking and alcohol consumption, and ethnicity, all of which are likely to influence mortality. Fundamentally, the key consideration is that the Nkomo paper gives mortality estimates in the general population and in a hospital-based cohort, but not in a cohort exposed to benfluorex. The use of the Nkomo estimate in the French paper can therefore really only be justified in terms of its being the only such estimate available and not in terms of its being correct. This being the case, the number of deaths estimated from the French cohort becomes difficult to support with any certainty.

Thus, in relation to attributable mortality, Fournier and Zureik make a very strong assumption. They use the RR of death of 1.75 in patients with diagnosed valvular disease

relative to the general population estimated by Nkomo et al. and work out the attributable risk (RR 1.75–1/1.75) as 43% and assume that this applies to patients using benfluorex (this estimate of attributable risk of mortality is lower than the estimate of 67.7% assumed by Hill). The authors then apply this attributable risk to the number of hospitalizations and arrive at an estimate of 1320 deaths (much higher than the estimate of Hill). Within the literature there are no data on mortality attributed to benfluorex use and the authors are making a very strong assumption in applying their chosen estimate of attributable risk of mortality to hospitalized French patients. Hill took a different approach with extrapolations based on the 64 deaths occurring within the cohort of 303,000 benfluorex users. If we apply the workings out and calculations Fournier and Zureik have made to these 64 deaths, the extrapolation to the whole period between 1976 and 2009 would be $64 * (78,300,000/10,317,567) * 0.43$, equivalent to 209 deaths, a much lower figure.

4.3. Data Presentation. Furthermore, these estimates of attributable mortality have been presented as total figures, rather than as rates per 100,000 person-years or even as total numbers per calendar year: even if the rates were accurate, if presented in this way, they would be much less immediately alarming. The annual number of deaths attributable to benfluorex based on the papers of Hill and Zureik would then be between 15 and 39. The total annual deaths attributable to diabetes mellitus in France was 29,590 in 2001, rising to 32,156 in 2006 (5.5 and 6.1% of total population deaths, resp.) [39]; thus, as a fraction of the total deaths, the estimates from these two papers might account for 0.05 to 0.1% of deaths amongst diabetics annually and between 0.003 and 0.007% total deaths annually. It is interesting that the data were not presented with reference to the denominator and clearly might not have achieved such widespread attention had they been presented in this way. The many reasons why these estimates are highly unlikely to be correct make the enthusiastic coverage by both the scientific and lay media even more concerning.

5. An Alternative Approach to Estimating the Risk of Mild DIVHD and Hospitalization Attributable to Benfluorex

It is possible, however, to derive meaningful estimates of the risk of new trivial trace (grade 1) or mild (grade 2) DIVHD in diabetic patients attributable to benfluorex using published data. In the REGULATE trial, there were 82 new cases of grade 1 or 2 regurgitation at mitral, aortic, or tricuspid valves in benfluorex users. Notably, the vast majority were of progression to trivial trace (grade 1, $n = 79$), with 3 cases of progression to grade 2 (mild) disease. There were 33 new cases of trivial trace ($n = 30$) or mild regurgitation ($n = 3$) at these valves in the pioglitazone group. From these figures we estimate the attributable risk to be 15.6 extra cases per 100 per year (risk in benfluorex (82/310) – risk in pioglitazone (33/305) = $0.2645 - 0.1082 = 0.1563 = 15.6$

per 100). Expressing this as the number needed to treat to harm (NNTH), for every 7 diabetic patients treated with benfluorex, the medication might cause one trivial trace or mild valvular regurgitant lesion over 12 months. Attributable risk can also be expressed as a proportion (also known as the aetiologic fraction) of exposure to benfluorex, estimated to be 59.0% (RR = $0.2645/0.1082 = 2.44$) (proportional attributable risk = $(2.44 - 1)/2.44 = 59.0\%$). This means that in patients with type 2 diabetes taking benfluorex, 59.0% of grades 1-2 valvular regurgitation may be due to benfluorex, with the vast majority of these being grade 1 (trivial trace).

However, whilst these figures initially appear high, it is important to realize that the overall impact of benfluorex on disease in the population depends on how common (prevalent) its use is in diabetic patients. The cohort study by Weill et al. [9] estimated the prevalence of benfluorex use in diabetic patients to be 4.1%. The impact at the population level is assessed using the population attributable risk, where we estimate that 5.6% of minor valvular regurgitation is attributable to benfluorex (population attributable risk = $(0.041 * 1.44)/1 + (0.041 * 1.44)$). The estimate of attributable risk at the population level is much lower as the use of benfluorex is very rare (uncommon) in diabetic patients. Furthermore, the vast majority of the emergent valve lesions associated with benfluorex use in the REGULATE study were grade 1 (trivial trace), which appears not to be associated with long-term morbidity and mortality [4, 40].

A second approach is to use the cohort study by Weill et al. [9] to estimate the risk of hospitalization attributable to benfluorex. Here the risk difference for hospitalization was 49.2 per 100,000 (risk in benfluorex (65/85,677) – risk in nonusers (532/1,996,711) = $49.2/100,000$) with an NNTH of 2033; thus for every 2033 diabetic patients treated with benfluorex, the medication might cause one hospitalization for valvular insufficiency. The attributable risk of hospitalization for valvular insufficiency in benfluorex users was 67.7% (RR 3.1-1/RR 3.1 = 67.7%). At the population level the attributable risk is 7.9% (population attributable risk = $(0.041 * 2.1)/1 + (0.041 * 2.1)$). To put this into context in terms of absolute numbers of the 1,048,173 diabetic patients in 2006, a total of 597 (comprised of 65 benfluorex users + 532 nonusers) (0.06%) hospitalizations for valvular insufficiency occurred between 2007 and 2008 (or rather 28.7 per 100,000 person years ($597/2,083,288 = 28.7$ per 100,000)). Of these 597 (100%) of hospitalizations 65 (10.9%) were in benfluorex users. The potential impact of eliminating exposure to benfluorex might have prevented 44 (7.4%) of hospitalizations that occurred between 2007 and 2008 in the population of diabetic patients (67.7% of the hospitalizations of those taking benfluorex).

Thus it is possible to estimate the population attributable risk associated with benfluorex use for emergence of new trivial trace/mild valvular changes and for hospitalization. There are clearly limitations with the approaches we have adopted, mainly as a result of the limitations of the underlying data, which we have elucidated earlier in this paper. Furthermore, it is clear that the existing evidence base does not permit such estimates to be made for moderate or severe valvular changes, or, crucially, for risk of death.

6. Conclusion

In conclusion, the recent estimates of mortality attributable to benfluorex use are based on unfounded assumptions and are highly likely to be inaccurate. These estimates should have been viewed with extreme caution and the necessity for further enquiry, rather than with the wholesale acceptance which has been observed in both the scientific and lay media.

7. Summary Points

- (i) Valvular heart disease is common in the general population. In an European study, of those with native heart valves, 33.9% had aortic stenosis, 24.8% mitral regurgitation, 10.4% aortic regurgitation, and 9.5% mitral stenosis.
- (ii) The overall prevalence of valve disease was estimated to be 2.5% in the US population.
- (iii) There is a convincing evidence base demonstrating a causal association between benfluorex use and mild to moderate drug induced valvular heart disease (DIVHD) in diabetic patients.
- (iv) There are no epidemiological studies describing the influence of benfluorex use on mortality.
- (v) It is possible to derive meaningful estimates of the risk of trivial trace/mild DIVHD in diabetic patients attributable to benfluorex using published data. In patients with type 2 diabetes taking benfluorex, 59.0% of trivial trace/mild valvular regurgitation may be due to benfluorex use. The estimate of attributable risk at the population level is much lower, estimated at 5.6%, as the use of benfluorex is uncommon in diabetic patients, and the vast majority of this figure is due to trivial trace (American grade 1) changes.
- (vi) Despite the lack of data on the risk of death attributable to benfluorex use, two published attempts have been made to estimate the number of deaths associated with benfluorex consumption.
- (vii) The recent estimates of mortality attributable to benfluorex use are based on unfounded assumptions and are highly likely to be inaccurate. These estimates should have been viewed with extreme caution.

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