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Safety Assessment of an Anti-Obesity Drug (Sibutramine)

A Retrospective Cohort Study

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Abstract

Background: Obesity is a serious and rapidly growing health problem worldwide. Few therapies are available beyond diet, exercise and bariatric surgery. A previously approved medication, sibutramine, has been withdrawn from the market due to concerns over the potential of increased risk of cardiovascular (CV) events, based on a phase IV clinical trial that included only individuals at high risk for CV events.

Objective: The aim of the study was to compare sibutramine users and matched non-users on rates of CV events, both overall and stratified by whether the patient qualified for on-label sibutramine use, using data from real-life clinical practice.

Methods: A retrospective cohort was constructed from electronic medical record data from physician office practices (mostly primary care) in the UK and Germany, using the LifeLink™ database from IMS Health Incorporated. For patients with at least one physician visit in which sibutramine was prescribed between 1 April 1999 and 31 October 2008, the date of their first such prescription was their index date. Users and non-users were matched 1 : 1 on index date (within 30 days), sex, age group (six categories), Charlson Comorbidity Index and evidence of obesity (high body mass index [BMI] or, if BMI was missing, diagnosis of obesity or very high weight relative to height). The resultant total samples analysed were 6186 in Germany and 7264 in the UK. User and non-user cohorts in the samples were compared according to the ratio of their crude incidence rates of acute myocardial infarction (AMI), stroke and either AMI or stroke per 1000 patient-years of follow-up. Cox regression analysis was used to compare the risk of CV events as a hazard ratio (HR) with 95% confidence intervals (CIs) between sibutramine user and non-user cohorts, controlling for label status and/or history of prior CV disease at baseline.

Results: The risk of AMI, stroke and either AMI or stroke was not higher among sibutramine users than comparable non-users of sibutramine in both Germany and the UK [Germany: HR 0.47 (95% CI 0.17, 1.26), 0.43 (0.23, 0.81)

and 0.44 (0.26, 0.75), respectively; UK: HR 0.44 (0.15, 1.31), 0.63 (0.25, 1.60) and 0.54 (0.27, 1.10), respectively]. Regardless of whether or not the model controlled for prior CV disease (CVD), the direction and statistical significance of the differences did not change. In the sensitivity analyses including only those without a history of CVD in the 365 days prior to the index date there was no increased risk of CV events in either Germany or the UK.

Conclusion: This study offers a framework for the safety assessment of anti-obesity drugs using an observational epidemiological study design. Large electronic health databases were used to construct retrospective cohorts to examine the risk in a population using one specific anti-obesity drug. Use of sibutramine in general practice settings was not found to increase the risk of acute CV events.

Background

Obesity has increased over the past several decades and has reached epidemic proportions worldwide.[1] According to the WHO, globally in 2008 approximately 1.5 billion adults (aged 20+ years) were overweight or obese, of whom 200 million men and 300 million women were obese. WHO further projects that by 2015 approximately 2.3 billion adults will be overweight or obese. Additionally, obesity and overweight have been associated with an increased incidence of several health conditions, particularly cardiovascular disease (CVD), and increased all-cause mortality.[2-6]

For the management of obesity, Abbott Laboratories (Abbott) launched sibutramine (sibutramine hydrochloride monohydrate; Meridia® in the US) in February 1998, and Reductil® in Europe (February 1999 in Germany, and May 2001 in the UK). Sibutramine acts centrally through norepinephrine, serotonin and dopamine reuptake inhibition. Several clinical studies have demonstrated that sibutramine results in significant weight loss compared with placebo.[7,8] However, the drug label states that it may lead to increased blood pressure and/or pulse rate in some patients, and recommends that the drug not be prescribed in patients with certain clinical conditions (table I).[9]

At the European Medicine Agency's (EMA) request, the SCOUT (Sibutramine Cardiovascular OUTcomes) study[10-13] was launched in 16 countries in more than 10 000 overweight or obese patients aged 55 years or older with a history of CVD and/or diabetes mellitus. The results indicated that sibutramine was associated with an increased risk of non-fatal acute myocardial infarction (AMI) and non-fatal stroke, but not fatal AMI/stroke or all-cause mortality. The majority of the patients enrolled in the SCOUT study would not qualify for the initiation or continuation of sibutramine therapy based on their CVD history or other contraindications, as specified in the EMA label.[9] Although anti-obesity drugs, including sibutramine, have been associated with weight loss, reviews of the literature identified that the longer-term clinical benefits in terms of cardiovascular (CV) risk reduction have not been studied.[14,15]

Because the SCOUT study was a randomized, double-blind, placebo-controlled study, including those overweight and obese patients at high risk for CV events as requested by the EMA, the results cannot be extrapolated to patients managed in a general practice setting. Thus, this study was designed to examine the real-world incidence and risk of CV events among users and matched non-users of sibutramine therapy in the UK and Germany. Additionally, another purpose of this paper is to offer a design strategy for a pharmacoepidemiological assessment of an intervention for obesity, a very complex health problem.

Methods

Study Design

The study employed a retrospective matched inception cohort design using electronic health

Table I. Contraindication status (on-label vs off-label) of matched[a] users and non-users of sibutramine in Germany and the UK

Measure	Germany			UK		
	Users [N (%)]	Non-users [N (%)]	p-Value[b]	Users [N (%)]	Non-users [N (%)]	p-Value[b]
Total study patients	3093 (100.0)	3093 (100.0)	NA	3632 (100.0)	3632 (100.0)	NA
Total no. of patients identified as on-label	1693 (54.7)	1672 (54.1)	0.9624	2221 (61.2)	2262 (62.3)	0.8062
Total no. of patients identified as off-label	1400 (45.3)	1421 (45.9)	NA	1411 (36.8)	1370 (37.7)	
Contraindications to sibutramine use[c]						
Benign prostatic hyperplasia with urinary retention	34 (1.1)	47 (1.5)	0.1486	25 (0.7)	11 (0.3)	0.0196
Uncontrolled hypertension	112 (3.6)	183 (5.9)	<0.0001	79 (2.2)	148 (4.1)	<0.0001
History of CVD, including coronary artery disease (e.g. myocardial infarction, angina pectoris), cerebrovascular disease (e.g. stroke, transient ischaemic attack), cardiac arrhythmias, congestive heart failure and peripheral arterial occlusion	449 (14.5)	476 (15.4)	0.3747	114 (3.1)	177 (4.9)	0.0002
History of major eating disorders	5 (0.2)	2 (0.1)	0.2568	1 (0.0)	1 (0.0)	1.0000
Severe hepatic impairment	1 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Severe renal impairment	4 (0.1)	6 (0.2)	0.5271	0 (0.0)	2 (0.1)	NA
Uncontrolled hyperthyroidism	86 (2.8)	67 (2.2)	0.1245	12 (0.3)	14 (0.4)	0.6949
Narrow angle glaucoma	1 (0.0)	1 (0.0)	1.0000	4 (0.1)	4 (0.1)	1.0000
Organic causes of obesity[d]	167 (5.4)	135 (4.4)	0.0656	212 (5.8)	120 (3.3)	<0.0001
Pheochromocytoma	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Psychiatric illness (specifically bipolar disorder)	604 (19.5)	557 (18.0)	0.1678	819 (22.5)	725 (20.0)	0.0167
History of tachycardia (diagnosis in previous 90 days)	33 (1.1)	35 (1.1)	0.8084	2 (0.1)	0 (0.0)	NA
Tourette's syndrome	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
BMI <27.0	91 (2.9)	91 (2.9)	1.0000	230 (6.3)	230 (6.3)	1.0000
Pregnancy and lactation (in previous 270 days)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Age less than 18 years	7 (0.2)	7 (0.2)	1.0000	8 (0.2)	8 (0.2)	1.0000
Age over 65 years	362 (11.7)	362 (11.7)	1.0000	223 (6.1)	223 (6.1)	1.0000
History of drug, medication or alcohol abuse	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Concomitant use (within the past 30 days) of MAOI or other centrally acting drugs for psychiatric disorders (e.g. depression, psychosis) or weight reduction, or tryptophan for sleep disturbances	53 (1.7)	37 (1.2)	0.0917	285 (7.8)	311 (8.6)	0.2869
Overweight (BMI ≥27 to <30 kg/m^2) and without diabetes, dyslipidemia or controlled hypertension	1 (0.0)	1 (0.0)	1.0000	3 (0.1)	7 (0.2)	0.2059

a Matched on (pseudo-) index date (within 30 days); sex; age (six categories); CCI score (four categories); and BMI score (four categories) or evidence of obesity (ICD-10 code E66 or very high weight: male ≥120 kg, female ≥100 kg).

b McNemar test of symmetry for dependent samples.

c Counts are NOT mutually exclusive. Known sensitivity to sibutramine could not be measured in these data.

d Organic causes of obesity include: congenital hypothyroidism (ICD-9: 243.x), acquired hypothyroidism (244.x) and Cushing's syndrome (255.0).

BMI = body mass index; **CCI** = Charlson Comorbidity Index; **CVD** = cardiovascular disease; **ICD** = International Classification of Diseases; **MAOI** = monamine oxidase inhibitor; **NA** = not applicable.

databases from Germany and the UK. Users and non-users of sibutramine were compared with respect to the risk of AMI, stroke and the composite of AMI and stroke.

Data Sources

The study employed IMS LifeLink™ electronic medical record (EMR)-EU data for the UK and

Germany from 1 January 1999 through 31 October 2009. The database comprises longitudinal patient-level data from office-based physician-practice data systems. Data collected included basic demographics (sex and age), height and weight, medical diagnoses (International Classification of Diseases [ICD]-10 codes), prescriptions issued by the physician and the date of the visit during which the diagnosis was made and/or the prescription was issued. In both countries, data are collected from participating primary care physicians (PCPs), including internal medicine specialists. Data from physicians treating the patient other than the physician supplying the EMR data are generally not available.

Identification of Patients and Matching Procedure

Sibutramine Users

All patients in the database for each country (Germany and the UK) who had at least one physician visit in which sibutramine was prescribed anytime during the study's index window (1 April 1999 through 31 October 2008) were identified. Sibutramine prescriptions were determined using the Anatomical Therapeutic Chemical classification system code for sibutramine (A08AA10). Physician visits were also searched for the generic drug name, and the identified visits were further validated by reviewing the brand, package description and manufacturer information associated with each prescription. Sibutramine is dispensed in 4-week (28 capsules) calendar packs. The date of the patient's first observed prescription for sibutramine was defined as his/her 'index date'. Study patients had to show evidence of continuous presence in the database throughout the 365-day period preceding their index date (pre-index period). The total period during which a patient showed activity in the database was called his/her activity period. Patients were not required to have a minimum duration of post-index follow-up. In order to ensure that patients in the sibutramine user cohort were naïve to sibutramine and other weight-loss drugs, they were excluded if they had (i) any prescriptions for sibutramine during their 365-day pre-index period; or (ii) any prescriptions for either orlistat (Xenical®) or rimonabant (Acomplia®) anytime during the 30 days immediately preceding their index date. During the study period, both orlistat and rimonabant were licensed weight loss agents in the EU. Because either the prescribed units per day or package quantity may be listed and are not consistently recorded in the EMRs databases, the duration of therapy was not included as a study variable. The exposure groups were determined by whether or not the sibutramine prescription was written (i.e. assignment by intent-to-treat).

Non-Users of Sibutramine

Non-users of sibutramine (control patients) were eligible for matching to sibutramine users if they showed evidence of continuous presence in the database for at least 366 days (equivalent to a user's 365-day pre-index period plus his/her index date) prior to an index date on which the patient had a body mass index (BMI) measurement or a diagnosis of obesity (ICD-10 code E66.x) during the study's index window (1 April 1999–31 October 2008).

Look-Back Period for Users and Non-Users of Sibutramine

The criteria for minimal and similar time periods of observation in the database for both users and non-users of sibutramine ensure that both users and non-users have comparable medical surveillance for ascertainment and treatment, thereby removing biases due to disproportionate medical care and monitoring. This also allows for an adequate time period for the assessment of patients' medical history, which was an important factor to classify patients accurately as 'on label' and 'off label'.

Matching Procedure

Matching of the study samples by demographic and selected clinical variables was performed to isolate the effect of the drug itself from these host factors, which could also affect the emergence of a CV endpoint. Matching in cohort studies can increase efficiency of estimation of the rate ratio (RR) by achieving a more balanced ratio of exposed to unexposed numbers across strata and if both the exposure and matching factor are

associated with the outcome or with each other, as with the case of our matching variables.[16]

Each sibutramine user was paired with one non-user who matched that user in terms of each of five matching criteria: (i) the non-user's index date had to fall within 30 days of the user's index date; the non-user also had to match exactly to the user in terms of (ii) sex, (iii) age group (six categories) and (iv) Charlson Comorbidity Index (CCI [modified Dartmouth-Manitoba adaptation,[17] with the specified ICD-9-clinical modification (CM) diagnosis codes translated to ICD-10 codes], categorized into four intervals); and (v) the non-user had to match the sibutramine user in terms of evidence of obesity, as follows:

- sibutramine users with a BMI score were matched according to that score (categorized into four intervals), as measured most recently prior to their index date;
- sibutramine users with missing BMI were matched on the basis of the occurrence of a diagnosis of obesity (ICD-10 codes E66.x), as measured most recently prior to their index date;
- if the user had neither a BMI score nor a diagnosis of obesity, he/she was matched according to whether or not his/her weight (measured most recently prior to his/her index date) could be considered very high for all but the tallest individuals: at least 120 kg for males (BMI of 30.0 for a man 2 metres tall [about 6.5 foot]) or 100 kg for females (BMI of 30.0 for a woman 1.8 metres tall [about 6 foot]).

The database did not allow us to distinguish fatal from non-fatal CV endpoints; hence, we used the CCI as a matching variable. Individual diseases included in the CCI are associated with certain known probability of mortality. Matching can result in an inaccurate estimate of risk if cases are not included because suitable matches cannot be found. However, since the databases we used were large, no sibutramine cases were excluded from the analysis because of the inability to find appropriate matches.

Study Sample

The LifeLink™ EMR-EU database contained 10 271 patients in Germany and 6330 patients in the UK who had at least one prescription for sibutramine anytime during the study's index window (1 April 1999–31 October 2008; figure 1). After applying the study's inclusion and exclusion criteria, the final sample size of sibutramine users eligible for matching was 3093 in Germany and 3632 in the UK. The pool of non-users of sibutramine was of sufficient size in both countries such that no eligible users were eliminated because matches were not able to be found.

Study Variables

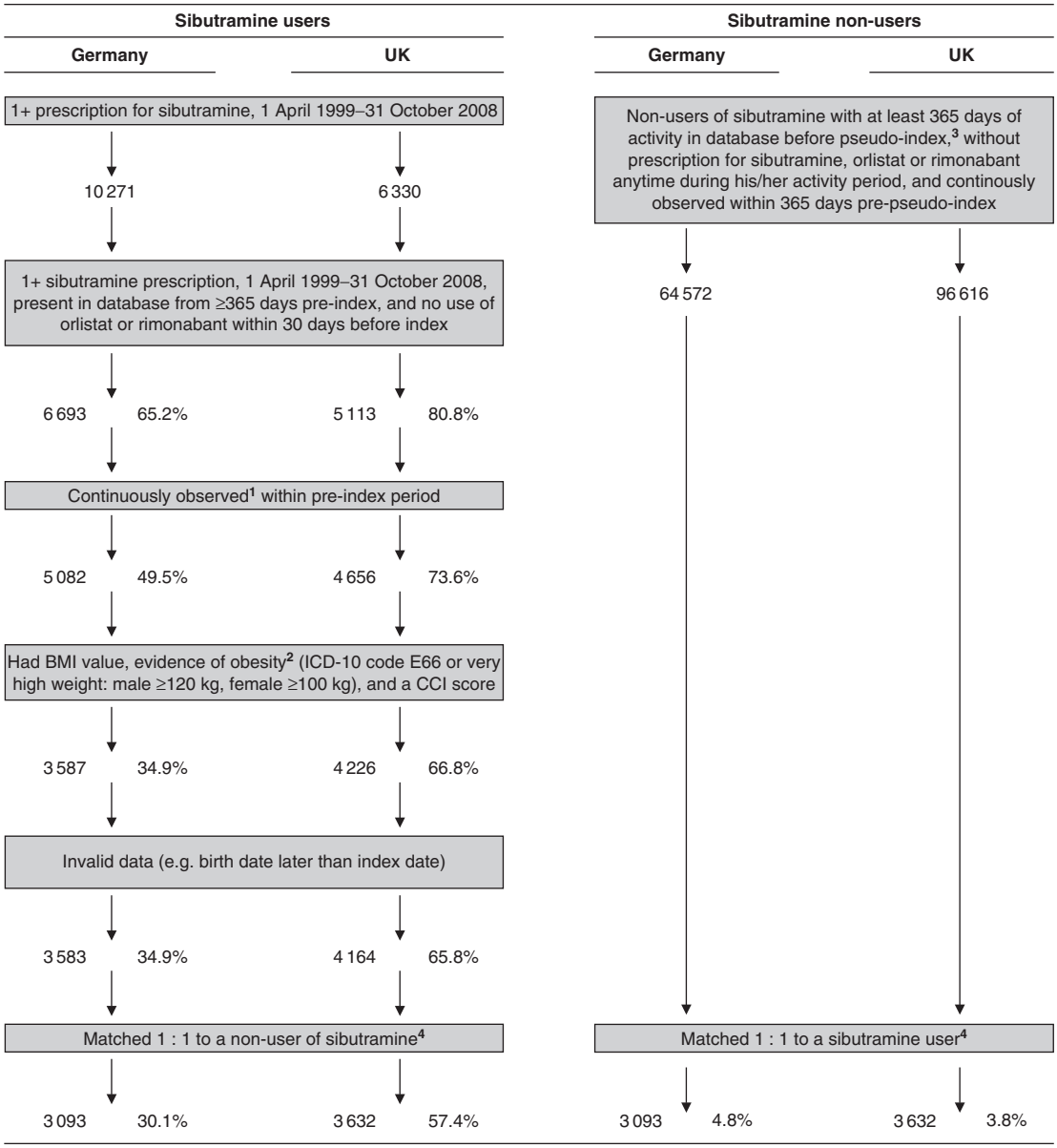
A panel of physician specialists employed by the sponsor of the study with expertise in neurology, internal medicine or cardiology provided consensus validation of the coding algorithms used for the clinical conditions classifying 'label status' and the CV endpoints.

Label Status

The final cohorts of sibutramine users and non-users were divided into two sub-cohorts – 'on-label' and 'off-label' – according to whether they met any of the criteria for contraindication to sibutramine therapy as specified in the EU label[17] that could be identified in the LifeLink™ EMR-EU data. (The ICD-9 list of contraindications used in the study is available from the corresponding author upon request.) These contraindications were measured prior to the patient's index date (table I). Furthermore, if an on-label patient was overweight (BMI of 27.0–29.9 observed within 30 days pre-index), then he/she was required to have at least one physician visit with a diagnosis or mention of either diabetes or dyslipidemia, anytime during his/her 365-day pre-index period. The EU label was used to define the conditions that determined a history of CVD. These were as follows: coronary artery disease (e.g. myocardial infarction (MI), angina pectoris), cerebrovascular disease (e.g. stroke, transient ischaemic attack), cardiac arrhythmias, congestive heart failure and peripheral arterial occlusion.

Cardiovascular (CV) Endpoints

For the purposes of this study, only the ICD-10 codes for acute-onset CV events were used in computing risk. These CV events were AMI (ICD-10 I12.x) and acute stroke (ICD-10 I60.x-I64.x).



1 At least one observation (action, prescription, diagnosis or tests) within the following two periods: pre-index: index date − 182 days AND index date − 183 days through to 365 days.

2 An existing BMI value was given top priority. If BMI was absent, ICD-10 diagnosis E66 was used. If that diagnosis was absent, a very high weight measurement (male ≥120 kg, female ≥100 kg) was used.

3 Date of BMI value or obesity diagnosis (ICD-10 code E66) within 1 April 1999–31 October 2008.

4 Matched on index date (within 30 days); sex, age group (six categories); CCI (four categories); and BMI (four categories) or evidence of obesity (ICD-10 code E66 or very high weight: male ≥120 kg, female ≥100 kg).

Fig. 1. Attrition of study population, by country. **BMI** = body mass index; **CCI** = Charlson Comorbidity Index, modified Dartmouth-Manitoba adaptation; **ICD** = International Classification of Diseases.

Data Analysis

The analysis was conducted separately for the UK and Germany. In all comparisons, a p-value <0.05 was considered statistically significant. All analyses employed SAS® version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Descriptive Analysis of Study Cohorts

The distributions of the matched cohorts of users and non-users of sibutramine in terms of each of the matching criteria were checked for any remaining differences or imbalances, using both the categorized and continuous versions of age, BMI and CCI. In addition, the matched cohorts were compared in terms of the EU-label-specified contraindications to sibutramine use during the patient's 365-day pre-index period (table I). For each categorical measure, the number and percentage of patients in each category were calculated. The statistical significance of the differences between matched sibutramine users and non-users in terms of each categorical measure, when not broken down into the on-label versus off-label sub-cohorts, was assessed using the McNemar-Bowker test for dependent samples.[18] Differences between sibutramine users and non-users when broken down by on-label versus off-label were assessed using the Pearson Chi-squared test.[19]

For continuous measures, the mean, standard deviation, median, minimum and maximum were calculated, and Student's t-test was used to assess the statistical significance of difference in mean scores between groups. The paired t-test was used for comparing matched sibutramine users and non-users when not broken down by on-label versus off-label; and the unpaired t-test was used for comparing users and non-users when broken down by on-label versus off-label.

Estimates of Incidence and Crude Rate Ratio of CV Events

The occurrence of CV events was based on the presence of one or more physician visits with a diagnosis or physician's note indicating that the patient had experienced one or more AMIs or stroke events anytime during the patient's variable-length post-index period. The crude incidence rate of each type of CV event (AMI, stroke and either AMI or stroke) per 1000 patient-years of follow-up was calculated for each cohort (sibutramine users vs matched non-users) in each country. Moreover, the RR between the sibutramine user and non-user cohorts was calculated, along with its 95% confidence intervals (CIs). These measures were also broken down by the patient's label status (on-label vs off-label) and by the following two subsets of patients: (i) those who did not experience the same type of CV event during their pre-index period; and (ii) those who had no history of any type of CVD. In addition, the number of days from the patient's index date until the occurrence of his/her first CV event of each type (AMI, stroke and either AMI or stroke) was measured for each cohort (sibutramine user vs non-user) within each sub-cohort (on-label vs off-label).

Estimates of Hazard Ratio of CV Events

Cox proportional hazards regression analysis[20] was used to compute the hazard ratios (HRs) and CIs, and to assess the difference between matched users and non-users of sibutramine experiencing each type of CV event during their post-index period, after controlling for label status (on-label vs off-label). Some differences between users and non-users may emerge even with rigorous matching and because of factors in the study samples not measured in the database. Thus, label status was used as a control variable in the computation of the adjusted hazard rates to globally capture these differences.

Patients who never experienced the relevant type of CV event anytime during their post-index period were censored as of the date of their last observed healthcare activity. This analysis was repeated: (i) in patients who had not experienced the same type of CV event during their pre-index period; (ii) with an additional control (covariate) for history of CVD (vs those with no such history); (iii) with the previous two specifications combined; and (iv) among patients who had no history of CVD.

Results

In both countries, the distributions of the matching categorical variables, sex, age group, CCI group and BMI level were not statistically

significantly different between sibutramine users and non-users (data not shown). The percentage of patients categorized as either on-label or off-label (one or more contraindications to sibutramine use) was also not significantly different between users and non-users of sibutramine in either country (table I). However, there were differences between the two cohorts in terms of the specific contraindications for sibutramine use in each country. In Germany, the only specific contraindication to sibutramine use that differed significantly between users and non-users was uncontrolled hypertension, which was significantly higher among non-users than users ($p < 0.0001$). In the UK, however, several contraindications differed significantly between users and non-users: uncontrolled hypertension (higher among non-users; $p < 0.001$), history of CVD (higher among non-users; $p < 0.05$), organic causes of obesity (higher among users; $p < 0.001$); and psychiatric illness (specifically bipolar disorder, also higher among users; $p < 0.05$).

Similarities between the matched user and non-user cohorts largely remained when they were broken down according to label status (tables II and III). The main exception was that, within the off-label cohorts in both countries, mean age differed significantly between users and non-users (Germany: 53.9 years vs 55.3 years, respectively, $p < 0.05$; UK: 47.9 years vs 49.6 years, respectively, $p = 0.05$). In addition, within the UK, but not in Germany, the mean BMI differed significantly between users and non-users (on-label: 36.9 vs 35.6, respectively, $p < 0.001$; off-label: 34.9 vs 34.0, respectively, $p < 0.05$), although the differences were numerically modest and may not reflect clinical significance.

Sibutramine users had significantly lower average mean diastolic and systolic blood pressure values than non-users within both the on-label and off-label cohorts in the UK ($p < 0.001$, except $p < 0.05$ for diastolic blood pressure among off-label patients). In Germany, there was no significant difference between users and non-users in either the on-label or off-label cohorts for both systolic and diastolic blood pressure.

Finally, in both countries the overall (regardless of label status) average duration of follow-up was significantly higher among users than non-users (Germany 1.46 years vs 1.26 years, respectively; UK 2.25 years vs 1.78 years, respectively; both $p < 0.001$). As shown in tables II and III, the direction of this difference persisted in both the on-label and off-label user and non-user cohorts in the UK. The exception was in Germany, where in the on-label cohort there was no difference in follow-up time between sibutramine users and non-users.

Table IV presents the crude rates per 1000 person-years of AMI, stroke and either AMI or stroke for sibutramine users and matched non-users overall in both Germany and the UK. Noteworthy is that the rate per 1000 person-years of AMI, stroke and AMI or stroke was higher among both the user and non-user cohorts in Germany than in the UK. Table IV also displays the RR of the user cohort to the non-user cohort and the 95% CIs around that ratio. Regardless of prior CVD history, in both Germany and the UK the RR of AMI was not significantly different between sibutramine users and matched non-users. For stroke, the risk was significantly lower among sibutramine users than among matched non-users in Germany, but was not significantly different in the UK. For AMI or stroke combined the same pattern was observed. When the analysis was restricted to those who had no prior history of CVD, there was no statistically significant difference between users and non-users for any CV event category in either country.

Table V presents the results of Cox proportional hazards regression analysis on each of the three CV events (AMI, stroke and either AMI or stroke) with cohort (sibutramine user vs non-user) as the key predictor and adjusted for label status (off-label vs on-label) as a covariate. Hazards ratios and their 95% CIs for the effects of sibutramine use compared with matched non-users are shown for each of these regression models.

Among all study patients, the risk of AMI, stroke and either AMI or stroke was statistically significantly reduced in all cohorts of sibutramine users except for stroke in the UK. In the UK, the risk of stroke was not significantly different between users and non-users, regardless of whether individuals without a prior history of CVD were excluded. Restricting the model to only those

Table II. Demographic and clinical characteristics of users and matched[a] non-users of sibutramine, by contraindication status (on-label vs off-label) in Germany

Measure	On-label			Off-label		
	Users [N (%)]	Non-users [N (%)]	p-Value[b]	Users [N (%)]	Non-users [N (%)]	p-Value[b]
Total no. of patients	1693 (50.3)	1672 (49.7)		1400 (49.6)	1421 (50.4)	
Sex						
Female	1277 (75.4)	1282 (76.7)	0.3970	1103 (78.8)	1098 (77.3)	0.3309
Male	416 (24.6)	390 (23.3)		297 (21.2)	323 (22.7)	
Age (at diagnosis [y])						
<18	0 (0.0)	0 (0.0)	0.9230	7 (0.5)	7 (0.5)	0.9765
18–29	180 (10.6)	178 (10.6)		63 (4.5)	65 (4.6)	
30–39	368 (21.7)	379 (22.7)		173 (12.4)	162 (11.4)	
40–49	484 (28.6)	476 (28.5)		280 (20.0)	288 (20.3)	
50–65	661 (39.0)	639 (38.2)		515 (36.8)	537 (37.8)	
>65	0 (0.0)	0 (0.0)		362 (25.9)	362 (25.5)	
Mean (SD)	45.1 (11.6)	45.1 (12.1)	0.9487	53.9 (14.0)	55.3 (15.4)	0.0161
CCI						
0	1107 (65.4)	1089 (65.1)	0.9527	706 (50.4)	724 (51.0)	0.9934
1–2	579 (34.2)	577 (34.5)		655 (46.8)	657 (46.2)	
3–4	7 (0.4)	6 (0.4)		38 (2.7)	39 (2.7)	
5+	0 (0.0)	0 (0.0)		1 (0.1)	1 (0.1)	
Mean (SD)	0.4 (0.6)	0.4 (0.6)	0.3980	0.7 (0.8)	0.7 (0.8)	0.7729
BMI						
Missing	1523 (90.0)	1500 (89.7)	0.8135	1122 (80.1)	1144 (80.5)	0.8080
BMI value present[c]	170 (10.0)	172 (10.3)		278 (19.9)	277 (19.5)	
<27.0	0 (0.0)	0 (0.0)	0.7218	91 (6.5)	91 (6.4)	0.8923
27.0–29.9	40 (2.4)	47 (2.8)		54 (3.9)	47 (3.3)	
30.0–34.9	68 (4.0)	65 (3.9)		75 (5.4)	78 (5.5)	
>35.0	62 (3.7)	60 (3.6)		58 (4.1)	61 (4.3)	
Mean (SD)	34.3 (5.6)	33.7 (5.1)	0.2598	30.3 (5.9)	30.3 (6.4)	0.5585
Obesity diagnosis[c,d]	1658 (97.9)	1551 (92.8)	<0.0001	1341 (95.8)	1206 (84.9)	<0.0001
High weight[c,e]	225 (13.3)	172 (10.3)	0.0069	321 (22.9)	277 (19.5)	0.0256
Blood pressure (systolic)[c]						
Missing	1545 (91.3)	1430 (85.5)	<0.0001	1216 (86.9)	1121 (78.9)	<0.0001
Value present	148 (8.7)	242 (14.5)		184 (13.1)	300 (21.1)	
Mean (SD)	135.6 (17.6)	137.0 (20.3)	0.5086	138.2 (21.8)	140.4 (22.5)	0.2794
Blood pressure (diastolic)[c]						
Missing	1552 (91.7)	1431 (85.6)	<0.0001	1222 (87.3)	1121 (78.9)	<0.0001
Value present	141 (8.3)	241 (14.4)		178 (12.7)	300 (0.0)	
Mean (SD)	83.1 (10.7)	82.9 (11.6)	0.8881	84.5 (10.3)	83.4 (11.2)	0.2517
Duration of follow-up (y)						
Mean (SD)	1.14 (1.75)	1.02 (1.78)	0.5374	1.85 (2.25)	1.54 (2.06)	0.0007
Median	0.46	0.29		1.00	0.75	
Maximum	10.44	10.34		10.46	10.37	

a Matched on (pseudo-) index date (within 30 days); sex; age (six categories); CCI (four categories); and BMI (four categories) or evidence of obesity (ICD-10 code E66 or very high weight: male ≥120 kg, female ≥100 kg).

b Pearson Chi-squared test for categorical measures; Student t-test for continuous measures.

c Based on the most recent reading in the pre-index period.

d ICD-10 code E66.

e Male ≥120 kg, female ≥100 kg.

BMI = body mass index; **CCI** = Charlson Comorbidity Index; **ICD** = International Classification of Diseases.

Table III. Demographic and clinical characteristics of users and matched[a] non-users of sibutramine, by contraindication status (on-label vs off-label) in the UK

Measure	On-label			Off-label		
	Users [N (%)]	Non-users [N (%)]	p-Value[b]	Users [N (%)]	Non-users [N (%)]	p-Value[b]
Total no. of patients	2221 (49.5)	2262 (50.5)		1411 (50.7)	1370 (49.3)	
Sex						
Female	1896 (85.4)	1970 (87.1)	0.0939	1213 (86.0)	1139 (83.1)	0.0389
Male	325 (14.6)	292 (12.9)		198 (14.0)	231 (16.9)	
Age (at diagnosis [y])						
<18	0 (0.0)	0 (0.0)	0.6215	8 (0.6)	8 (0.6)	0.3755
18–29	396 (17.8)	433 (19.1)		157 (11.1)	120 (8.8)	
30–39	594 (26.7)	615 (27.2)		284 (20.1)	263 (19.2)	
40–49	614 (27.6)	608 (26.9)		315 (22.3)	321 (23.4)	
50–65	617 (27.8)	606 (26.8)		424 (30.0)	435 (31.8)	
>65	0 (0.0)	0 (0.0)		223 (15.8)	223 (16.3)	
Mean (SD)	41.6 (11.7)	41.4 (12.5)	0.6790	47.9 (14.6)	49.6 (15.6)	0.0033
CCI						
0	1756 (79.1)	1773 (78.4)	0.7421	962 (68.2)	945 (69.0)	0.8820
1–2	464 (20.9)	487 (21.5)		443 (31.4)	420 (30.7)	
3–4	1 (0.0)	2 (0.1)		6 (0.4)	5 (0.4)	
5+	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Mean (SD)	0.2 (0.5)	0.23 (0.47)	0.8382	0.4 (0.6)	0.4 (0.6)	0.6623
BMI						
Missing	49 (2.2)	56 (2.5)	0.5509	95 (6.7)	46 (3.4)	<0.0001
BMI value present[c]	2172 (97.8)	2206 (97.5)		1316 (93.3)	1324 (96.6)	
<27.0	0 (0.0)	0 (0.0)	0.1578	175 (12.4)	229 (16.7)	<0.0001
27.0–29.9	169 (7.6)	206 (9.1)		127 (9.0)	90 (6.6)	
30.0–34.9	758 (34.1)	794 (35.1)		400 (28.3)	364 (26.6)	
>35.0	1245 (56.1)	1206 (53.3)		614 (43.5)	641 (46.8)	
Mean (SD)	36.9 (5.9)	35.6 (5.1)	<0.0001	34.9 (6.9)	34.0 (6.8)	0.0006
Obesity diagnosis[c,d]	974 (43.9)	267 (11.8)	<0.0001	610 (43.2)	179 (13.1)	<0.0001
High weight[c,e]	2197 (98.9)	2192 (96.9)	0.5757	1385 (98.2)	1322 (96.5)	0.0065
Blood pressure (systolic)[c]						
Missing	375 (16.9)	482 (21.3)	0.0002	302 (21.4)	262 (19.1)	0.1351
Value present	1846 (83.1)	1780 (78.7)		1109 (78.6)	1108 (80.9)	
Mean (SD)	128.7 (14.3)	131.7 (18.5)	<0.0001	130.8 (15.3)	134.8 (21.1)	<0.0001
Blood pressure (diastolic)[c]						
Missing	375 (16.9)	483 (21.4)	0.0001	306 (21.7)	266 (19.4)	0.1386
Value present	1846 (83.1)	1779 (78.6)		1105 (78.3)	1104 (80.6)	
Mean (SD)	80.8 (8.4)	82.1 (10.6)	<0.0001	80.8 (8.9)	81.8 (12.0)	0.0159
Duration of follow-up (y)						
Mean (SD)	1.96 (2.00)	1.49 (1.92)	<0.0001	2.71 (2.17)	2.27 (2.20)	0.0007
Median	1.23	0.62		2.10	1.61	
Maximum	8.06	8.07		8.02	8.08	

a Matched on (pseudo-) index date (within 30 days); sex; age (six categories); CCI (four categories); and BMI (four categories) or evidence of obesity (ICD-10 code E66 or very high weight: male ≥120 kg, female ≥100 kg).

b Pearson Chi-squared test for categorical measures; Student t-test for continuous measures.

c Based on the most recent reading in the pre-index period.

d ICD-10 code E66.

e Male ≥120 kg, female ≥100 kg.

BMI = body mass index; **CCI** = Charlson Comorbidity Index; **ICD** = International Classification of Diseases.

Table IV. Acute myocardial infarction or stroke incidence rates per 1000 person-years among users and matched[a] non-users of sibutramine in Germany and the UK

Measure[b]	Germany					UK				
	Users (N = 3093)		Non-users (N = 3093)			Users (N = 3632)		Non-users (N = 3632)		
	N	Rate/1000 person-years	N	Rate/1000 person-years	RR (95% CI)	N	Rate/1000 person-years	N	Rate/1000 person-years	RR (95% CI)
Total events in post-index period										
AMI	9	1.994	19	4.872	0.474 (0.215, 1.045)	17	2.076	53	8.188	0.321 (0.186, 0.553)[c]
Stroke	20	4.430	42	10.769	0.476 (0.280, 0.809)[c]	23	2.809	32	4.944	0.719 (0.422, 1.226)
AMI or stroke	29	6.424	61	15.641	0.475 (0.306, 0.738)[c]	40	4.885	85	13.132	0.471 (0.324, 0.683)[c]
Post-index period incident events[d]										
AMI	6	1.329	11	2.820	0.546 (0.202, 1.473)	5	0.611	9	1.390	0.556 (0.186, 1.656)
Stroke	15	3.323	30	7.692	0.500 (0.270, 0.927)[c]	8	0.977	10	1.545	0.800 (0.316, 2.025)
AMI or stroke	21	4.652	41	10.513	0.512 (0.303, 0.865)[c]	13	1.588	19	2.935	0.684 (0.338, 1.383)
Post-index period incident events,[d] no prior CVD [n (%)]	2644 (50.3)		2617 (40.7)			3518 (50.5)		3455 (49.5)		
AMI	5	1.405	4	1.356	1.237 (0.333, 4.602)	5	0.633	7	1.150	0.702 (0.223, 2.208)
Stroke	10	2.810	16	5.423	0.619 (0.281, 1.361)	8	1.012	10	1.642	0.786 (0.311, 1.988)
AMI or stroke	15	4.216	20	6.779	0.742 (0.381, 1.447)	13	1.645	17	2.792	0.751 (0.365, 1.544)

a Matched on (pseudo-) index date (within 30 days); sex; age (six categories); CCI score (four categories); and BMI score (four categories) or evidence of obesity (ICD-10 code E66 or very high weight: male ≥120 kg, female ≥100 kg).

b No distinction could be made between fatal and non-fatal MI and stroke events because of limitations in the data on death.

c Statistically significant beyond the 0.05 level.

d Incident events are those that occurred among those patients who did not have a similar event in the pre-index period.

AMI = acute myocardial infarction; **BMI** = body mass index; **CCI** = Charlson Comorbidity Index; **CVD** = cardiovascular disease, as defined in table I; **ICD** = International Classification of Diseases; **MI** = myocardial infarction; **RR** = rate ratio.

without a prior history of CVD, there was no significant increase in the risk of AMI, stroke or either AMI or stroke in either country.

Discussion

In this retrospective cohort epidemiological study of real-life clinical practice settings comprised predominantly of general practitioners, CV risk (AMI, stroke or the composite of AMI or stroke) was not higher among sibutramine users than among comparable non-users of sibutramine in Germany and the UK. In fact, the risk of such CV conditions among sibutramine users relative to non-users was significantly lower or non-differential. The low magnitude of CV risk among sibutramine users relative to non-users remained when controlling for prior history of CVD. Despite the absolute differences in the underlying rates of AMI and stroke in both countries, the HRs of users compared with non-users was similar overall in both countries despite the older age of all German cohorts.

Both overweight and obesity are known to be linked with increased frequency to several types of comorbidities, regardless of the type of anti-obesity treatment given.[2] Several studies have shown that obese individuals are more likely than non-obese controls to develop certain types of conditions that may increase the risk of CV complications, or that obesity itself may directly increase that risk.[2,21] Recent meta-analyses showed significantly increased risk among overweight and obese individuals for conditions such as type 2 diabetes, hypertension, stroke, coronary artery disease and congestive heart failure, as well as an increased risk of CV mortality.[2,22] Using two large population-based data sources, our study was designed to assess whether treatment of overweight and obese patients with sibutramine in clinical practice settings are related to an increased risk of non-fatal CV events, i.e. AMI, stroke and combined AMI or stroke. In order to better isolate the effect of obesity/overweight from that of pharmacological treatment upon the risk of acute CV events, we employed a design

Table V. Hazard ratios and 95% CIs from Cox regressions on acute myocardial infarction and/or stroke for sibutramine users vs matched non-users,[a] controlling for sibutramine contraindication status (on-label vs off-label) in Germany and the UK, by endpoint and patient population

Patient population	Endpoint	Germany		UK	
		No control for prior CVD [HR (95% CI)][b]	Control for prior CVD [HR (95% CI)][b]	No control for prior CVD [HR (95% CI)][b]	Control for prior CVD [HR (95% CI)][b]
All study patients	All AMI	0.421 (0.191, 0.931)[c]	0.450 (0.204, 0.996)[c]	0.291 (0.169, 0.503)[c]	0.420 (0.243, 0.728)[c]
	All stroke	0.422 (0.248, 0.719)[c]	0.442 (0.260, 0.754)[c]	0.631 (0.369, 1.079)	0.853 (0.497, 1.463)
	All AMI or stroke	0.422 (0.271, 0.656)[c]	0.445 (0.286, 0.692)[c]	0.421 (0.289, 0.613)[c]	0.590 (0.404, 0.861)[c]
Patients with no similar event within 365 days pre-index	Incident[d] AMI	0.467 (0.173, 1.263)	0.488 (0.180, 1.322)	0.438 (0.147, 1.308)	0.459 (0.153, 1.377)
	Incident[d] stroke	0.434 (0.233, 0.806)[c]	0.445 (0.239, 0.828)[c]	0.633 (0.250, 1.604)	0.613 (0.242, 1.553)
	Incident[d] AMI or stroke	0.443 (0.262, 0.749)[c]	0.456 (0.269, 0.772)[c]	0.541 (0.267, 1.095)	0.542 (0.267, 1.099)
Patients with no history of any CVD within 365 days pre-index	Incident[d] AMI	1.037 (0.278, 3.866)	NA	0.551 (0.175, 1.737)	NA
	Incident[d] stroke	0.524 (0.238, 1.155)	NA	0.613 (0.242, 1.553)	NA
	Incident[d] AMI or stroke	0.626 (0.320, 1.223)	NA	0.588 (0.285, 1.210)	NA

a Matched on (pseudo-) index date (within 30 days); sex; age group (six categories); CCI (four categories); and BMI (four categories) or evidence of obesity (ICD-10 code E66 or very high weight: male ≥120 kg, female ≥100 kg).

b All regression included sibutramine contraindication status (on-label vs off-label) as a covariate.

c Statistically significant beyond the 0.05 level.

d Incident events are those that occurred among those patients who did not have a similar event in the pre-index period.

AMI = acute myocardial infarction; **BMI** = body mass index; **CCI** = Charlson Comorbidity Index; **CVD** = cardiovascular disease, as defined in table I; **HR** = hazard ratio; **ICD** = International Classification of Diseases; **NA** = not applicable.

matching the demographic and clinical characteristics of users and non-users of sibutramine.

Regardless of whether or not label status and prior CVD were controlled for, no increased risk was found for AMI or stroke or the composite of AMI and stroke among the sibutramine users in any of the subgroups evaluated. In the sensitivity analyses where only those who had no history of CVD in the 365 days prior to their first prescription of sibutramine were included, the effect of sibutramine on CV events became non-significant in both Germany and the UK; however, this may have been due to the much smaller sample size in that analysis.

Our results are similar to the SCOUT study for the subgroup with diabetes and without pre-existing CVD who were similar to the general population of on-label sibutramine patients. This subgroup had no increased risk of CV events.[11] This finding indicates that an increased risk of non-fatal MI and non-fatal stroke in the overall SCOUT trial population was primarily driven by the subjects with pre-existing CV conditions. Indeed, the recent study by Willemen et al.[23] observed that both CV and psychiatric co-morbid conditions were more prevalent among patients who were starting sibutramine compared with non-users, suggesting that this baseline risk may translate into higher occurrence of psychiatric and CVD events during the use of anti-obesity drugs, independent of the drugs themselves. It is also worth noting that in the SCOUT study only 0.6% of patients had to discontinue treatment within the lead-in period due to cardiac disorders.[10] This proportion was similar among conformers and non-conformers (0.7% and 0.5%, respectively).[10]

There were three other studies, to the authors' knowledge, of the use of sibutramine and CV risk. In the Harrison-Woolrych et al.[24] postmarketing study of real-life use of sibutramine in New Zealand, no elevated risk of CV events, including AMI and stroke, was found. However, that study was limited in that it was based upon self-report of sibutramine use and CV events, and comparison of risk was made only to the New Zealand population. In a prescription-event monitoring (PEM) study by Perrio et al.,[25] which was postmarketing and focused on sibutramine, neither AMI nor stroke was found among events leading to discontinuation. Another study by Gaciong and Placha[26] reported no serious CV events in just 12 weeks of follow-up among 2225 sibutramine patients enrolled into the study. Despite serious limitations of these studies, none of them indicated increased risk of CV events in sibutramine users.

Our study adds further methodological strengths to previous research that used population based samples. First, we employed a quasi-experimental study design where non-users of sibutramine comparable with users of sibutramine were selected on the basis of important matching criteria, including BMI and CCI, and the RRs of these two groups were computed. Perhaps because of the similarities achieved between the groups in our study, the CV risk parameters yielded fairly precise point estimates within relatively narrow CIs. The study outcomes were investigated in two countries, which allowed for comparing and contrasting the results and therefore providing some sense of external validity. Indeed, the study results in the two countries were comparable, despite some differences in their demographic and clinical characteristics.

Nonetheless, some aspects of our study design have limitations. First, the LifeLink™ EMR-EU data were derived solely from PCPs, and in Germany those physicians do not act as 'gatekeepers' of all of a patient's healthcare, like in the UK. Consequently, CV events may not always get reported to a German patient's PCP; however, this bias is likely to be present in both databases to some extent. Second, given certain limitations regarding information on death in the available data, it was not feasible to distinguish between fatal and non-fatal CV events, to assess rates of death, or determine the effects of over-the-counter (OTC) drug use for weight reduction. However, one of the matching variables, CCI, a predictor of mortality, was not significantly different among the user and non-user subgroups. Third, the direct one-to-one matching process yielded only slightly more than 85% of sibutramine users being successfully matched to a non-user. Although this percentage provided good internal

validity, CV event rates may be somewhat underestimated. Lastly, the study follow-up time may only capture the acute-onset CV events group.

It also has to be remembered that exposure to sibutramine was assessed based on prescriptions written, thus no information on a dose and duration of exposure was included in the analysis. Other anti-obesity agent prescriptions were excluded via the study exclusion criteria (see figure 1). No exposure to OTC anti-obesity agents could be included in the analysis.

The authors emphasize that caution must be used in interpreting the absolute measures of risk as well as the corresponding HRs of the CV events presented herein. First, regarding the risk measures, the CV rates in the study populations presented herein may not be extrapolated to the general populations of Germany and the UK. Our study samples are predominantly female, and non-users are comprised of matched samples who have not had any prior prescriptions for the anti-obesity agents of sibutramine, orlistat or rimonabant. Because the label states that inadequately controlled hypertension is a contraindication to starting sibutramine, in consideration of this physicians may have initiated blood pressure control measures for those identified as hypertensive and hence the reason for the lower blood pressure levels, at least in the UK sample. Thus, this might also have an independent effect on the CV endpoint for which we did not examine specifically. Second, the HRs were not adjusted for risk factors (e.g. smoking) other than label status and/or prior history of CVD for several reasons. These reasons include the very unique subgroups within the users driven by drug indications and the lack of availability of known risk factors (e.g. smoking, physical activity, etc.) in the database. Instead, our approach to the study design was matching of the study samples by demographic and selected clinical variables. In addition, controlling for label status was performed to attempt to globally isolate the effect of the drug itself from these other factors. Although it is possible that the sample size may have not had sufficient power to detect a significant risk potentially associated with sibutramine use when adjusted for covariates, the minimum overall sample size was able to detect an RR of 2.0 (or conversely an RR of 0.5) with 95% CI, two-tailed.[27] Limiting the number of variables used in adjustment reduced the likelihood of not capturing a significant risk level. Thus, for all the above reasons, our study's risk estimates are not intended for use by a physician in making decisions about an individual patient's weight management plan.

Not shown in these results is the fact that, within both the on-label and off-label sub-cohorts and in both countries, sibutramine users had significantly lower rates of some CV events than non-users prior to starting sibutramine, possibly indicating that they may have been healthier to begin with, or more closely monitored or more intensively medically managed. This possibility is also reflected in the significantly lower average levels of blood pressure among users than non-users in the UK, and the slightly but significantly lower average age among users in both countries. Finally, additional patient characteristics (other than the matching criteria) that could have affected the outcomes were not controlled for (e.g. blood pressure and weight change over time) because of their limited availability in the database over the study period.

Obesity continues to be a complex problem that can require a multi-faceted approach to treatment.[28] Exercise and diet are the key elements of any weight-loss regimen.[29] Anti-obesity drugs, and weight loss surgery for the extremely obese, may also be necessary.[29] Yet there are few options for the growing numbers of patients who would consider using pharmaceuticals to help shed pounds. In 2010, sibutramine was removed from the market and three anti-obesity drugs (Contrave® from Takeda [Osaka, Japan]/Orexigen Therapeutics [La Jolla, CA, USA],[30] lorcaserin from Arena [San Diego, CA, USA]/Eisai [Tokyo, Japan][31] and Qnexa® from Vivus [Mountain View, CA, USA][32]) failed to get US FDA approval because of either lack of efficacy or safety concerns. Orlistat is still the lone pharmaceutical on the anti-obesity market; however, in 2012 the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted to recommend approval of both Qnexa and lorcaserin[33] and, at the time of writing, these applications are awaiting final FDA

endorsement. Nevertheless, in spite of these developments, there is a great unmet need for a safe and effective oral therapy in this therapeutic area.

As such, our study offers additional insights to patients, practitioners, anti-obesity drug manufacturers/developers and relevant regulatory authorities. The findings should help to further clarify the putative CV risks associated with anti-obesity drugs in a real-world drug setting. The results could also be used to establish appropriate guidelines and postmarketing safety studies in the use of anti-obesity agents.

Conclusions

Despite the methodological limitations of studying real-world practice, we found no evidence that, after initiating sibutramine, the risk of AMI, stroke or the composite of AMI or stroke was increased among users compared with non-users of sibutramine. In all cases, rates of the endpoints of interest in total events in the post-index period analysis were lower for sibutramine users. This study provides a framework for assessing the safety of anti-obesity agents for use in the general medical practice setting. Conducting well designed epidemiological studies, either retrospective cohort database or prospective observational, can provide timely evidence to gauge the benefits and potential risks of other anti-obesity agents. Nevertheless, the application and evaluation of this epidemiological model of safety assessment for anti-obesity drugs in other countries and healthcare systems is still warranted.

Safety studies of anti-obesity agents are challenging because of the complexity of the condition, its numerous co-morbidities and the limitations of existing electronic databases to comprehensively assess exposure and endpoints of concern. By acknowledging the limitations of our design as well as its conclusions, our study approach provides a learning springboard for others planning pharmacoepidemiology safety studies of anti-obesity agents.

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While contributing to the preparation of this study, Jerzy Tyczynski was an employee of Abbott Laboratories but is currently an employee of Astellas Pharma Global Development, Inc. Denise Oleske is an employee of Abbott Laboratories and holds stock in the company. Cheryl Ferrufino and Won Chan Lee are employees of IMS Health Inc. At the time of preparation of this study, David Klingman was an employee of IMS Health Inc., but has now retired. IMS Health Inc. was under contract to Abbott Laboratories for assistance in the design, data analysis, interpretation of the results, and review and approval of the manuscript.

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