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Risk Management and Outcomes of Adverse Events to Pioglitazone in Primary Care in the UK

An Observational Study

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Abstract

Background: Pioglitazone is an antidiabetic drug that belongs to the thiazolidinedione (TZD) class of insulin-sensitizing agents. Adverse events to pioglitazone of potential severity are listed in the 'special warnings and special precautions for use' section of the pioglitazone summary of product characteristics (SPC), with recommendations for monitoring and management.

Objective: To describe the risk management and outcomes of recognized TZD class effects in patients prescribed pioglitazone.

Methods: An observational study of risk management and event outcomes for the adverse events of cardiac failure, fluid retention/oedema, weight gain, anaemia and abnormal liver function tests (LFTs) was performed. Patients were identified from within a prescription-event monitoring (PEM) post-marketing cohort of first-users of pioglitazone. Patients with pre-existing events or alternative causes, or with no possibility of collecting further information, were excluded. Outcomes included (i) the method of detection of the adverse event, i.e. whether the patient or the prescriber identified the problem; (ii) whether responsibility for risk management was taken at a primary- or secondary-care level; (iii) interventions taken to manage the event, including discontinuation of treatment; (iv) resolution and/or other outcomes of the event; and (v) general practitioner (GP) opinion of relatedness of the event to pioglitazone.

Results: Acute events such as cardiac failure and oedema were more likely to be detected by the patient presenting with the event rather than at regular follow-up. GPs were more likely to take responsibility for management of abnormal LFTs, anaemia and oedema events, whereas hospital admissions occurred mainly in patients with cardiac failure (45.3%). Pioglitazone was stopped in more than 50% of each type of event, apart from anaemia. Oedema events were the most likely to resolve (87.6%) and anaemia the least likely (42.9%). Oedema events were the most likely to be attributed to the drug by GPs, whereas cardiac failure was the event least attributed to pioglitazone.

Conclusions: Timely drug withdrawal and/or interventions such as corrective treatment or referral to a specialist can lead to successful resolution of class-effect adverse events of pioglitazone. Regular follow-up of patients on antidiabetic agents is essential to detect certain events, but more acute events are more likely to be reported spontaneously. Treatment options for patients with diabetes mellitus and cardiovascular risk factors are limited, requiring careful benefit-risk assessment of pioglitazone use in these patients and careful monitoring for signs of worsening cardiac function.

Background

Pioglitazone is an antidiabetic agent that was launched in the UK market in November 2000. It belongs to a class of insulin-sensitizing agents known as thiazolidinediones (TZDs), which act by stimulating the peroxisome proliferator-activated receptor (PPAR)-γ. Pioglitazone is the third TZD to be marketed, preceded by troglitazone and rosiglitazone. Troglitazone was withdrawn from the UK market within a few months of its launch in December 1997 after a number of reports of severe hepatic adverse events.[1] A recent review of rosiglitazone safety has highlighted risks of cardiac failure, myocardial infarction and fractures in women.[2]

After the marketing of pioglitazone, the 'special warnings and special precautions for use' section of the UK Summary of Product Characteristics (SPC) highlighted important adverse events from premarketing and early postmarketing studies, which required monitoring as part of the risk management of the product. The requirement for more proactive pharmacovigilance has been highlighted by the development of International Conference on Harmonisation documentation[3] (incorporated into pharmacovigilance regulations in the EU), which recommends regulatory request of post-authorization studies to investigate safety risks identified at the licensing stage, potential risks and any key missing information.[4]

The events of interest for this drug are cardiac failure, oedema, weight gain, anaemia and abnormal liver function. Diabetes mellitus is an independent risk factor for cardiac failure,[5] which is an important cause of mortality and morbidity in diabetic patients.[6] Pioglitazone may exacerbate or precipitate cardiac failure by causing fluid retention, and is contraindicated in patients with cardiac failure or a history of cardiac failure (New York Heart Association [NYHA] class I–IV).[7] A number of mechanisms have been suggested for the development of fluid retention with TZDs,[8] and it is thought to be dose-dependent and exacerbated by concomitant insulin therapy.[9] Weight gain with pioglitazone may be explained by the redistribution of lipids from visceral to subcutaneous deposits[10] or by an increase in plasma volume.[11] Haemodilution results in a small number of patients taking pioglitazone presenting with anaemia.[7] Monitoring of liver enzymes prior to initiating therapy with pioglitazone and periodically during treatment is recommended, and pioglitazone is contraindicated in patients with hepatic impairment.[7]

Prescription-event monitoring (PEM) studies are postmarketing cohort studies that can detect and characterize safety issues for newly marketed medicines.[12] Within a PEM study on pioglitazone,[13] a case-series analysis of the events recommended to be monitored was performed to investigate the detection, risk management and outcomes of these events in a 'real life' primary-care setting, named the Pioglitazone Event Management and Outcome (PEMO) study.

Methods

The pioglitazone PEM study included 12 772 patients with the first prescription of pioglitazone between November 2000 and June 2001.[13] The methodology of PEM has been previously

described elsewhere.[12] Events[1] meeting the following criteria were identified for inclusion into the PEMO study:

(i) event term matching one of the following lower level terms in the Drug Safety Research Unit (DSRU) dictionary:

- cardiac failure, left ventricular failure, congestive cardiac failure
- oedema, fluid retention, swollen ankles/limbs
- weight gain
- anaemia
- abnormal liver function test (LFT)

(ii) the event was known to have occurred whilst taking pioglitazone or within 7 days of drug cessation.

A medical doctor performed a review of all identified events and applied the following exclusion criteria: (i) pre-existing events, e.g. those given as past medical history; (ii) alternative (non-pioglitazone) cause for event provided by a general practitioner (GP) or considered to be more likely based on information on the PEM questionnaire; (iii) other medically related event of interest of greater significance reported on the same patient visit chosen for follow-up (e.g. weight gain excluded where both oedema and weight gain reported on the same date); (iv) non-incident event (in the case of multiple reports); (v) no further information possible, e.g. event of interest was fatal; and (vi) the patient had left the practice.

An event-specific questionnaire was sent to the patient's GP for each event of interest and included demographics, past medical history (diabetes and other related conditions, including those related to events of interest), initiation and discontinuation of pioglitazone therapy, detection, management and outcome of the event, and whether the GP suspected the event was related to pioglitazone. Test results were requested where applicable, e.g. LFTs, urea and electrolytes, full blood count analysis, and height and weight/body mass index. GPs were reimbursed for administrative costs to complete the questionnaires. To increase response rates, questionnaires were sent a second time to initial non-responders.

The PEM study was conducted in accordance with the international ethical guidelines for biomedical research prepared by the Council for International Organisations of Medical Sciences in collaboration with the WHO in 2002.[14] The method of study also complies with the guidelines on the practice of ethics committees in medical research involving human subjects, as issued by the Royal College of Physicians[15] and the UK Department of Health.[16] Patient confidentiality was maintained throughout by using unique identifiers provided by the GP.

Data were entered using Access® 2000 (Microsoft Corp., Redmond, WA, USA) and analysed with Stata version 9.2 (Stata Corporation, College Station, TX, USA). Summary data for tables were calculated on the event denominator, and additional information for the text was calculated using the patient denominator. 'Don't know' and unspecified responses were categorized as missing data and were excluded from calculations of proportions and summary statistics (medians, interquartile range [IQR]), with the frequency of missing data presented in tables for reference.

Results

The process of identification of events and the formation of the sample for the PEMO study is shown in figure 1. Overall, 5.9% of the pioglitazone cohort reported at least one of the events to their GP. The response rate was 67.8%.

Patient Characteristics

The median patient age was 65 years (range 22–95 years); 38.6% (n = 177) were male, and weight gain and oedema events were reported predominantly in females. The median duration of diabetes prior to starting pioglitazone was 6 years (ranging from starting treatment at the time of diabetes diagnosis to 37 years). Glycosylated

1 An event was defined as 'any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter into the patient's notes'.

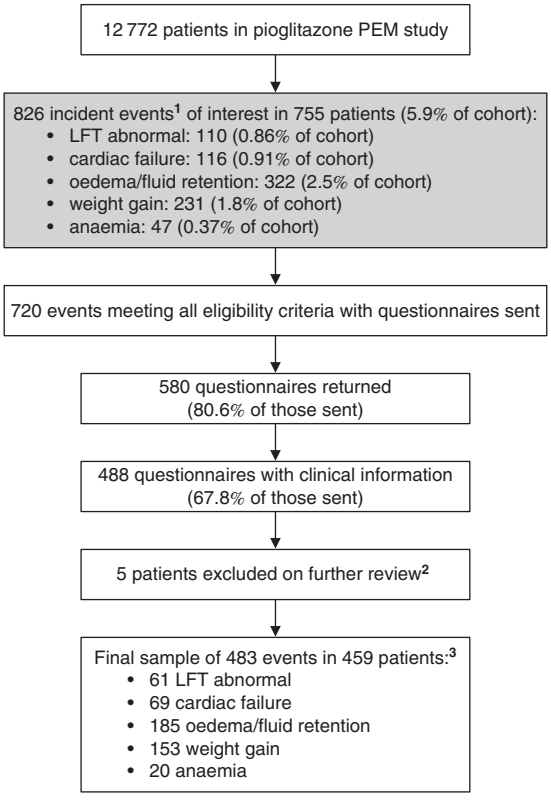

Fig. 1. Identification of events for the PEMO (Pioglitazone Event Management and Outcome) study. **1** Includes on-treatment and off-treatment events. **2** Four cardiac failures that had a fatal outcome on the day of the event, with one cardiac failure occurring before pioglitazone was started. **3** Four hundred and thirty-six patients with one event, 14 patients with oedema plus weight gain, 5 patients with oedema plus cardiac failure, 1 patient with each of oedema plus cardiac failure plus anaemia, weight gain plus cardiac failure, weight gain plus abnormal liver function test (LFT) and abnormal LFT plus anaemia. **PEM** = prescription-event monitoring.

haemoglobin (HbA_{1c}) test results in the 3 months prior to starting pioglitazone had a median value of 8.8% (IQR 8.0–9.8%; n = 426). Blood glucose results in the 3 months prior to starting pioglitazone (not specified whether fasting or random sugars) had a median value of 11.7 mmol/L (IQR 9.8–14.9 mmol/L; n = 259). Pioglitazone was initiated by the GP for 65.0% (n = 288) of patients, by a hospital doctor for 34.8% (n = 154) of patients and under shared care for one patient. Demographic characteristics, past medical history and initiator of pioglitazone treatment stratified by the event of interest are displayed in table I. Sulphonylureas were taken by 64.8% of patients with reported concomitant antidiabetic medications (193/298) and metformin by 48.7% (145/298). Concurrent use of insulin at the time of the event was reported in 18 patients (6.0% of those specifying concurrent medications and 3.9% of the cohort).

The proportions of patients with a previous medical history of conditions were as follows: liver conditions 6.3% (n = 29), cardiovascular conditions 43.6% (n = 200), obesity 49.5% (n = 227) and haematological conditions 3.9% (n = 18). The distribution of these conditions stratified by the event reported is given in table I. Patients with a history of cardiovascular conditions were 1.6-fold more likely to be started on pioglitazone by the consultant than the GP (odds ratio 1.6; 95% CI 1.1, 2.4; p = 0.019; n = 442); there was no difference with the other conditions.

Event Characteristics

Cardiac Failure

Of the 64 cardiac failure events, 31.3% (n = 20) were reported as congestive cardiac failure, 31.3% (n = 20) as left ventricular failure, 34.4% (n = 22) as cardiac failure and 3.1% (n = 2) as acute heart failure. Males accounted for 68.8% (n = 44) of the cardiac failure events. A history of ischaemic heart disease was reported in 26.6% (n = 17) of patients, hypertension in 17.2% (n = 11) and atrial fibrillation in 15.6% (n = 10). More than one of these three cardiovascular risk factors for cardiac failure was reported in 17.2% (n = 11) of patients. Other cardiovascular risk factors included mitral regurgitation, poor left ventricular function, cerebral/peripheral vascular disease, congestive cardiomyopathy and angina/chest pain.

Oedema and Weight Gain

Where sex was known, females accounted for 69.6% (n = 128) of patients reported to have oedema events and 71.2% (n = 109) of weight gain events. Where severity of oedema was provided (n = 171), it was generalized for 4.1% (n = 7) of patients, up to the leg for 33.9% (n = 58), and foot and ankle for 60.2% (n = 103), with facial oedema

reported in a further three patients. Of the 18 patients with concurrent insulin use reported, nine had oedema events and six had weight gain events. For the 98 patients for whom an increase in weight was calculable from the 3 months before the event was reported and the time of the event, the average weight gain was 4.3 kg (SD 3.5).

Anaemia

For patients with reports of anaemia (n = 17) or low haemoglobin (n = 3), the median haemoglobin value at the time of the event was 10.9 (range 5.5–12.6) for males (n = 7) and 11.4 (range 11.0–11.5) for females (n = 5) where haemoglobin results were provided. Approximately one-third of anaemias had also been reported in the 3 months before starting pioglitazone (table I).

Hepatic Events

Information collated from both the PEM and PEMO questionnaires showed 'raised AST/ALT' was the abnormal component of the LFT panel in 59% (n = 36) of events. Where the values of transaminases were specified (23 AST, 36 ALT), nine results (in eight patients – eight ALT and one AST) were >3 times the upper limit of normal (ULN). Abnormal LFT was the event most likely to have been reported in the 3 months before starting pioglitazone (table I).

Event Management and Outcome

The detection of the event by the prescriber or presentation by the patient and subsequent management of events is summarized in table II. Events were most commonly detected during

Table I. Characteristics of patients stratified by event group[a]

Characteristic	Cardiac failure (n = 64)	Oedema (n = 185)	Weight gain (n = 153)	Anaemia (n = 20)	Abnormal LFT (n = 61)
Median age, y (IQR)	74 (64–78)	67 (57–75)	62 (54–69)	69 (66–73)	59 (50–68)
no data		1	2		
No. males (%)	44 (68.8)	57 (31.0)	44 (28.8)	11 (55.0)	31 (50.8)
no data		1			
Median duration of diabetes mellitus, y (IQR)	8 (4–12)	7 (3–11)	5 (2–8)	8 (5–11)	5 (2–9)
no data	4	3	11		
Initiator of pioglitazone therapy					
General practitioner [n (%)]	35 (56.5)	123 (68.7)	91 (61.1)	13 (68.4)	40 (70.2)
Hospital doctor [n (%)]	27 (43.5)	56 (31.3)	57 (38.3)	6 (31.6)	17 (29.8)
Shared [n (%)]	0	0	1 (0.7)	0	0
No data (n)	2	6	4	1	4
Medical history at the time of starting pioglitazone[b]					
Liver condition [n (%)]	2 (3.1)	11 (6.0)	6 (3.9)	0	12 (19.7)
Cardiovascular disease [n (%)]	42 (65.6)	81 (43.8)	54 (35.3)	8 (40.0)	22 (36.1)
Obesity [n (%)]	27 (42.2)	98 (53.0)	83 (54.3)	6 (30.0)	25 (41.0)
Haematological abnormality [n (%)]	1 (1.6)	9 (4.9)	5 (3.3)	2 (10.0)	3 (4.9)
Event also occurred in the 3 months prior to starting pioglitazone[c]					
Yes [n (%)]	7 (12.5)	22 (14.5)	8 (7.2)	4 (30.8)	17 (40.5)
No [n (%)]	49 (87.5)	130 (85.5)	103 (92.8)	9 (69.2)	25 (59.5)
No data (n)	8	33	42	7	19

a Each patient is unique within each column, but patient data can contribute to more than one column.

b More than one element of medical history can be ticked per event record.

c Information only available on follow-up questionnaire.

IQR = interquartile range; **LFT** = liver function test.

Table II. Management and outcome of events

Parameter	Cardiac failure (n = 64)	Oedema (n = 185)	Weight gain (n = 153)	Anaemia (n = 20)	Abnormal LFT (n = 61)
Detection of the event					
During regular follow-up [n (%)]	8 (15.1)	82 (46.9)	105 (75.0)	11 (68.8)	57 (96.6)
Patient presented with the problem [n (%)]	45 (84.9)	93 (53.1)	35 (25.0)	5 (31.3)	2 (3.4)
No data (n)	11	10	13	4	2
Responsibility for management					
GP [n (%)]	16 (27.1)	130 (74.3)	79 (57.3)	11 (61.1)	45 (77.6)
Hospital doctor [n (%)]	21 (35.6)	21 (12.0)	24 (17.4)	2 (11.1)	3 (5.2)
Shared [n (%)]	22 (37.3)	24 (13.7)	35 (25.4)	5 (27.8)	10 (17.2)
No data (n)	5	10	15	2	3
Intervention for management (more than one category possible per event)					
No action taken [n (%)]	1 (3.1)[a]	66 (35.7)	66 (43.1)	4 (20.0)	36 (59.0)
Treatment with other drugs [n (%)]	43 (67.2)	80 (43.2)	43 (28.1)	8 (40.0)	5 (8.2)
Referral [n (%)]	10 (15.6)	15 (8.1)	15 (9.8)	4 (20.0)	13 (21.3)
Hospital admission [n (%)]	29 (45.3)	6 (3.2)	1 (0.7)	2 (10.0)	0
Discontinuation of pioglitazone[b]					
Stopped [n (%)]	37 (59.7)	116 (62.7)	98 (64.1)	8 (40.0)	38 (62.3)
Not stopped [n (%)]	25 (40.3)	69 (37.3)	55 (36.0)	12 (60.0)	23 (37.7)
Cessation known to be due to event [n (%)]	23 (62.2)	85 (73.3)	76 (77.6)	2 (25.0)	32 (84.2)
Resolution of event after discontinuation of pioglitazone					
Yes [n (%)]	11 (42.3)	63 (75.9)	37 (59.7)	2 (40.0)	20 (55.6)
No [n (%)]	15 (57.7)	20 (24.1)	25 (40.3)	3 (60.0)	16 (44.4)
No data (n)	11	33	36	3	2
Outcome					
Event resolved [n (%)]	36 (63.2)	120 (87.6)	46 (47.9)	6 (42.9)	36 (67.9)
Event not resolved [n (%)]	4 (7.0)	15 (11.0)	49 (51.0)	7 (50.0)	16 (30.2)
Patient died (all causes) [n (%)]	17 (29.8)[c]	2 (1.5)[d]	0	0	1 (1.9)[e]
No data (n)	7	48	57	6	8
GP's opinion about whether event related to drug (n = 305)					
Yes [n (%)]	10 (27.0)	74 (61.2)	71 (80.7)	4 (28.6)	13 (31.0)
No [n (%)]	27 (73.0)	17 (38.8)	17 (19.3)	10 (71.4)	29 (69.1)
No data (n)	27	64	65	6	19

a Although the GP ticked 'no action', it was stated that symptoms resolved after pioglitazone was stopped.

b Two missing responses for cardiac failure events.

c Causes of death not due to event (non-cardiovascular causes) were bronchiectasis (n = 1), cerebral haemorrhage (n = 1), chronic obstructive pulmonary disease (n = 1), death cause unspecified (n = 2).

d Causes of death not due to event were renal failure, death cause unspecified.

e Cause of death not due to event was metastatic carcinoma.

GP = general practitioner; **LFT** = liver function test.

regular follow-up appointments with the GP (59.4%; n = 263) followed by the patient presenting with the problem (40.6%; n = 180). Almost all abnormal LFTs were detected during regular follow-up or monitoring by the GP (96.6%), whereas cardiac failures were mostly detected when the patient presented with the problem (84.9%). Overall, GPs took responsibility for management for more than half the events, but hospital doctors played a larger role in management

of cardiac failure, either alone or together with the GP (72.9%), whereas abnormal LFTs were managed by the GP either alone or in shared responsibility with a hospital doctor (94.8%). Cardiac failure events had the highest rate of hospital admissions (45%) and a high proportion (67%) were managed by treatment with other drugs. A more conservative approach was most likely to be taken with abnormal LFT events, with 59% having no intervention (excluding drug cessation).

Pioglitazone was not stopped in 38.3% (n = 184) of events, and not all discontinuations of pioglitazone were directly attributable to the occurrence of the event, with the proportion of events reported to lead to treatment withdrawal varying from 84.2% for abnormal LFTs to 25% for anaemia (table II). Excluding events of interest, the most common reasons for stopping pioglitazone in patients in the PEMO study were impaired diabetic control (n = 31) and ineffectiveness of the drug (n = 15).

Outcome information is summarized in table II. Outcomes were not available for 26.1% of events. Of all events with an outcome, 68.3% were reported to have resolved. For events in patients in which pioglitazone was discontinued that have outcomes, 62.7% (n = 133) resolved, with the highest proportion of resolution for oedema and weight gain events. Of the 20 deaths reported, only deaths in patients with cardiac failure events had causes of death within the same system organ class as the event (cardiovascular). GPs provided an opinion on whether they thought the event was related to pioglitazone for 62.5% of events, with relatedness varying from 27.0% for cardiac failure to 80.7% for weight gain.

Discussion

This questionnaire-based study provides an insight into the management and outcome of five important adverse events with a widely used antidiabetic agent. It demonstrates that GPs were key players in prescribing this novel antidiabetic agent and managing potential treatment-related adverse events. It also showed that within the context of a disease with multiple outcomes and with limited treatment options, prioritization of glycaemic control may lead to off-label use in patients with previous relevant medical history or risk factors for adverse events.

Patients with cardiac failure events were the most likely to have had pioglitazone initiated in hospital, possibly due to cardiovascular safety concerns with TZDs or patients with a longer history of diabetes and/or worsening control being more likely to be admitted and have a subsequent treatment review. Although it was not possible to compare PEMO subjects with patients who have a previous medical history of the five events of interest, it was apparent that a history of such events had not prevented prescribers from prescribing pioglitazone, even though pioglitazone is known to cause or exacerbate these conditions. Even though pioglitazone is contraindicated in patients with cardiac failure or history of cardiac failure (NYHA class I–IV),[7] 12% of the patients with cardiac failure events had experienced cardiac failure in the 3 months prior to starting pioglitazone. The decision to start pioglitazone may be explained by limited therapeutic options in diabetes and consequent channelling of patients onto novel medications. Alternatively, potential favourable cardiovascular effects of pioglitazone such as improvement in endothelial function, decrease in vascular inflammation and decrease in C-reactive protein levels[17] may lead to prescribers evaluating the benefit-risk profile of pioglitazone therapy as favourable in these patients. Cardiac failure events were also more likely to have hospital participation in management, likely due to the nature of the event and the necessity of further investigations that can be performed only in a hospital setting.

According to the SPC, pioglitazone should not be initiated in patients with ALT >2.5 times the ULN or with hepatic impairment.[7] However, we do not know which of the 40% of patients with abnormal LFTs had previously had abnormal results during the 3 months prior to starting pioglitazone and the proportion of patients who had transaminases >2.5 times the ULN, due to the difficulty in the GPs providing test results.

The high rates of discontinuation of pioglitazone following adverse events suggest that the possible consequences of these events were well known by the managing physicians. As would be expected, the management of abnormal LFT events had a low rate of corrective treatment or referral, but had the highest proportion of patients where pioglitazone was known to be stopped due to the event. As another member of the same class (troglitazone) was withdrawn from the market due to hepatotoxicity, GPs may have been more proactive in withdrawing pioglitazone when abnormal LFTs were detected, thereby complying with recommendations in the SPC. The lowest rates of recovery during the observation period were seen in weight gain and anaemia events, possibly due to pre-existing conditions, or the longer time required to correct haemoglobin values or reduce weight once acquired.

GPs were requested to indicate whether they thought the event was related to pioglitazone, although this was not a formal causality assessment and many factors may have lead to this subjective assessment. However, the GP assessments seem to be quite strongly influenced by standard parameters used in assessing causality,[18] i.e. whether the event was pre-existing, whether the treatment was withdrawn and whether the event subsequently resolved. For example, cardiac failure events occurred in patients with a high proportion of pre-existing cardiovascular disease, two-thirds of which did not resolve, with a resulting assessment of no relation of the event with the drug for 73% of events. On the contrary, oedema, related to possible onset of cardiac failure in the SPC, had a much lower rate of pre-existence (14.5%), and a higher rate of recovery, resulting in a higher level of attribution of the event as a side effect of the drug (61.2%).

This study has merit because it presents results from 'real life' clinical experiences and demonstrates the feasibility of performing a follow-up study on events or topics of interest arising within a PEM cohort, e.g. to assess risk management at the postmarketing stage. The regulatory requirements for risk management in the EU require the assessment of risk minimization activities to ensure their effectiveness,[19] and we have demonstrated the feasibility of this through implementing a PEM study with targeted follow-up. However, it is clear that the results of such studies must be used in the evolution of the risk management of a product, as they may reveal that the measures that have been put in place are effective or they may show that subsets of the population are at greater risk and require tighter protective measures. The questionnaire response rate was good (68%), although some difficulties by GPs in retrieving required clinical information (e.g. laboratory test results) were apparent, thus restricting the analysis. However, we have stated the frequency of missing data of the major outcomes, and believe this is not unusual in a records-based study, although future studies of this kind could be better moulded to GP data storage and retrieval systems. The study is also validated by its demonstration of characteristics of diabetes epidemiology. For example, patients with cardiac failure tended to be older than the median cohort age (74 vs 65 years) and were reported more frequently in men. These results were found be consistent with those of the Framingham heart study, which showed that the incidence of cardiac failure increased with age and had male predominance.[20] The Framingham study also showed that coronary heart disease and hypertension are the dominant precursors for cardiac failure,[20] and these were also the most frequently reported cardiovascular co-morbidities in patients with cardiac failure events at the time of starting pioglitazone in our cohort. Obesity was a common co-morbidity across the cohort, which has been shown to be an independent risk factor for diabetes.[20]

Conclusions

GPs play an important role in the therapeutic management of patients with diabetes, including the detection and management of adverse events. Patients with pre-existing risk factors for the event or relevant past medical history, particularly cardiovascular history, were still prescribed pioglitazone in this observational cohort, most likely due to limited treatment options. The

benefit-risk of pioglitazone use in patients with cardiovascular risk factors was more likely to be assessed by consultants than GPs, again demonstrating the necessity for developing antidiabetic agents with a more favourable benefit-risk profile that can be confidently prescribed in primary care for this large group of patients. Timely drug withdrawal for other class-effect events commonly leads to a positive outcome, particularly for oedema and weight gain.

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