Prescribing pattern of glucose lowering drugs in the United Kingdom in the last decade: a focus on the effects of safety warnings about rosiglitazone

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Several safety alerts regarding the cardiotoxicity of thiazolidinediones have been launched by regulatory agencies starting from May 2007.
- Several studies, mainly in the United States, have assessed the prescription pattern of the glucose lowering drugs in a short period around the publication of the FDA safety alert of rosiglitazone in May 2007.
- Until now only one study has described the prescription pattern of glucose lowering drugs in a European country (the Netherlands) for a long period of time and none in the United Kingdom.

WHAT THIS STUDY ADDS

- After the safety alerts in May 2007 the prescription pattern of thiazolidinediones changed, with an increase in the use of pioglitazone and a decrease in the use of rosiglitazone.
- After May 2007, high risk patients with type 2 diabetes mellitus were preferably newly treated with pioglitazone rather than rosiglitazone
- As a result of the alerts an increase in the frequency of switching between rosiglitazone and pioglitazone was observed.

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AIM

In the last decade, new glucose lowering drugs (GLDs) have been launched, and also several warnings regarding their safety. The cardiovascular safety of thiazolidinediones (TZD) has been questioned. We analyzed the prescription pattern of GLDs from 2000 to November 2009 in the United Kingdom (UK) using the THIN database with special focus on the effects of the safety warnings about rosiglitazone issued in May 2007 and January 2008.

METHODS

Annual prevalence and incidence of GLD prescriptions were measured. For TZD, the monthly prevalence and incidence of prescription were calculated from May 2006 to January 2009. The switching pattern around the FDA alert and the characteristics of subjects starting treatment with TZD before and after the alerts were observed.

RESULTS

The prevalence of prescriptions of GLDs increased during the 10 year period, metformin increasing more than three times. Rosiglitazone prevalence showed an increased trend until May 2007, (2.3/1000 person-years) and decreased thereafter (January 2009: 1.1/1000 person-years). The use of pioglitazone increased surpassing rosiglitazone from April 2008 onwards. The incidence of rosiglitazone use decreased sharply after May 2007 (0.8/1000 person-years). The prevalence of use of other therapies remained rather stable from 2000 to 2007 but increased afterwards. After May 2007, rosiglitazone users were increasingly switched to pioglitazone. There was an increased proportion of new users of pioglitazone with cardiovascular risk after the alerts.

CONCLUSIONS

The prescription of GLDs in the UK has increased in the last decade. For TZDs, it changed after May 2007 as well as the characteristics of the subjects treated with them.

Introduction

The goal of type 2 diabetes mellitus (T2DM) treatment is to reduce blood glucose concentrations, thus preventing complications. Life style changes and therapeutic strategies such as use of metformin, sulfonylureas and insulin have been the usual standard of treatment. In the last decade, several new glucose lowering drugs (GLDs) have been marketed, such as meglitinides (repaglinide and nateglinide), glucagon-like peptide 1 receptor agonists (GLP1-R: exenatide and liraglutide), dipeptidyl peptidase-4 inhibitors (DPP4-inhibitors: vildagliptin, sitagliptin and saxagliptin) and the insulin sensitizers thiazolidinediones (TZD), troglitazone (withdrawn from the market in the United Kingdom (UK) in December 1997 due to hepatotoxicity), rosiglitazone and pioglitazone (marketed in 2000) [1].

The guidelines for the management of hyperglycaemia in T2DM, issued by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) in 2006, recommended metformin and life-style changes as the first line treatment for all newly diagnosed patients with T2DM. TZD, baseline insulin and sulfonylureas were indicated as second line therapy [2].

In the last years, the cardiovascular safety of rosiglitazone has been questioned and the regulatory agencies have launched several warnings based on the results of postmarketing studies. In 2007, Nissen *et al.* published a meta-analysis of randomized clinical trials reporting a 40% increase in the risk of myocardial infarction with rosiglitazone [3]. On the same day (May 21, 2007) the US Food and Drug Administration (FDA) issued a safety alert about this increased cardiovascular risk [4]. On January 24, 2008, the European Medicines Agency (EMA) issued a similar safety alert warning health professionals against the use of rosiglitazone in patients with ischaemic heart disease and/or peripheral arterial disease [5].

Based on the growing body of evidence about rosiglitazone's cardiovascular risk, the treatment guidelines were updated in 2008 and from 2009 onwards the use of rosiglitazone was not recommended anymore [6, 7].

Finally, on September 23, 2010, the EMA recommended the suspension of rosiglitazone marketing in the European Union (EU) [8], while the FDA restricted its use to patients successfully treated with this drug, whose glycaemia could not be controlled with other GLDs and who, after consulting healthcare professionals, did not wish to switch to pioglitazone therapy [9].

Studies in the USA assessed the short term effect of the FDA safety warning on the prescription patterns of GLDs. Stewart *et al.* [10] reported that the use of rosiglitazone fell after the warning (more than 50% of the number of fills), while Shi *et al.* found that 45% of veterans with diabetes mellitus discontinued TZD after the FDA safety warning [11].

Several drug utilization studies about GLDs have been previously conducted in some European Countries (Italy [12], France [13], Germany [14] and UK [15]). However, these investigations analyzed a study period prior to the rosiglitazone safety warnings and as a consequence could not explore the effect of these alerts on GLD use. Recently, Ruiter *et al.* [16] analyzed the dispensing patterns of GLDs and the impact of European warnings [EMA press releases and Direct Health Professional Communications (DHPCs)] in the Netherlands from 1998 to 2008. To our knowledge this is the only paper that has studied the use of these types of medications for a long period of time. The objective of this study was to analyze the prescription pattern of GLDs in the UK general population from 2000 to 2009, with special focus on the effects of the safety warnings about rosiglitazone issued by both agencies, the FDA and the EMA in May 2007 and January 2008 respectively, in the use of TZD and other GLDs specifically in patients with T2DM.

Methods

Data source

The data source for this study was The Health Improvement Network (THIN) general practice database from the UK. The general practitioners (GPs) in the UK serve as gatekeepers to medical care for patients and file all their relevant medical details. Overall, by the end of 2009, 479 practices contributed data to the THIN database, that represents 5.7% (9.15 million) of the UK general population [17]. This database contains anonymized medical records concerning information about patients' demographics, drug prescriptions written, medical diagnoses, laboratory results, referrals to specialists and lifestyle characteristics. Read codes are used for registering medical conditions and the Multilex/BNF (British National Formulary) coding system for drug prescriptions. The approval of the Scientific Review Committee was obtained for this study.

Study population

The source population comprised all subjects from the UK registered in the THIN database from January 1, 2000 to November 24 2009 (last data drawn at the time of the analysis) with at least 1 year of valid record in the database. Within this population, all patients with a diagnosis of T2DM who received at least one GLD during the study period were considered as user of a GLD.

Glucose lowering drugs

Information on GLD use was obtained from the prescription files. GLDs used in the analysis were grouped by class into insulins (all types), biguanides (metformin), sulfonylureas (glibenclamide, chlorpropamide, tolbutamide, glibornuride, tolazamide, glipizide, gliquidone, gliclazide, glimepiride, acetohexamide, glymidine), TZD (rosiglitazone, pioglitazone) and others [dipeptidyl peptidase-4

(DPP-4) inhibitors, meglitinides, glucagon-like peptide-1 receptor (GLP-1R) agonists, alpha glucosidase inhibitors]. TZDs included both individual compounds and fixed combinations (metformin/rosiglitazone and metformin/pioglitazone). The duration covered by each prescription was calculated as the total number of units per prescription divided by the prescribed daily number of these units.

Data analysis

For each GLD class, annual prevalence of use and 95% confidence interval (95% CI) from 2000 to November 2009 was measured. Annual prevalence of use was defined as the number of GLD users divided by mid-year (1 July) estimate of the number of subjects alive and registered in the database in the observation year. Annual incidence of use was calculated as the number of new users of each GLD class (i.e. subjects with no GLD prescription of the same class in the previous year) divided by the time period contributed from subjects alive and registered in THIN in the observation year. Among TZD, monthly prevalence and incidence of use were calculated for individual compounds and fixed combinations from 1 year prior the first warning from the FDA to 1 year after the warning from the EMA (May 2006–January 2009).

To observe if safety warnings led to the prescription TZDs in different types of patients, demographic and clinical characteristics of new users (i.e. subjects with a first prescription of rosiglitazone or pioglitazone recorded in the database in the specified periods) of TZD at the time of the first prescription were explored in three different consecutive periods of similar length: (i) within 6 months prior FDA warning (period 1: November 21 2006 to 21 May 2007), (ii) between the FDA and EMA warnings (period 2: May 22 2007 to January 24 2008) and (iii) within 6 months after the EMA warning (period 3: January 25 2008–July 24 2008). The following characteristics were explored at the time of the first TZD prescription: age, sex, concomitant use of insulin (i.e. duration of the last prescription of insulin covers the date of the first prescription of the TZD), history of heart failure, myocardial infarction, or cerebrovascular disorders, primary hypertension, angina, obesity or lipid metabolism disorder.

Changes in the TZD user characteristics were explored using linear contrasts and the Cochran–Armitage test for trend for continuous and categorical variables, respectively. All tests were two tailed and a *P* value of less than 0.05 was considered as statistically significant.

Furthermore, the switching pattern of GLDs was analyzed 1 year before and 1 year after the FDA alert in May 2007. A switch from a drug 'A' to a drug 'B' was defined as the start of a prescription of drug B during treatment duration covered by a prescription of drug A (but not on the first day of drug A treatment). Additional requirements for a switch were that drug B was not prescribed in the 180 days before the switch, and that there was no refill of prescriptions of A in the year following the switch. To

ensure data completeness, patients were only considered eligible for a switch if observation data were available 180 days prior and 365 days following the start of the prescription of drug B. Only users eligible for a switch were included in the denominator when computing the proportion of switchers. TZD alone and fixed combinations were analyzed separately.

Annual and monthly prevalence and incidence rates were calculated using Jerboa® v2.9.21, a custom-built software written in Java™ developed within the EU-ADR project [18]. All other analyses were carried out using SAS v9.2 (Cary, North Carolina, USA). Switching graphs were done using Cytoscape v2.8.1 [19].

Results

A total of 5 312 567 subjects were registered in THIN from 1 January 2000 to 24 November 2009. Among them, we identified 178 674 (3.4%) T2DM subjects receiving overall 9 369 167 prescriptions for GLDs during the study period. Of GLD users, 715 (0.4%) subjects received a TZD (alone or as a fixed combination) as the first line treatment [351 (49.1%) rosiglitazone, 182 (25.5%) pioglitazone and 182 (25.5%) with combinations containing TZD].

An increase in the prevalence of use of GLDs was observed during the 10 year period (Figure 1), with metformin increasing more than three times (2000: 6.9 per 1000; 2009: 22.7 per 1000). The use of TZD (alone and as fixed combinations) increased from 2000 (0.2 per 1000) to 2007 (5.2 per 1000), while their use progressively decreased in the following years (2009: 4.8 per 1000). Prevalence of use of the category 'other' remained rather stable from 2000 to 2007 (0.5–0.7/1000) but it increased in the following years (2008: 0.9 per 1000; 2009: 1.6 per 1000).

As regard to new use of GLDs (Figure 2), metformin use almost doubled during the study period (from 2.0/1000 person-years in 2000 to 3.5/1000 person-years in 2009). TZD incidence of use increased from 2000 to 2006 and decreased thereafter (0.2/1000 person-years in 2000; 1.6/1000 person-years in 2006; 1.2/1000 person-years in 2007; 0.8/1000 person-years in 2009). The incidence of use of the drugs in the category 'other' increased 10 times, from 0.2/1000 person-years to 1.1/1000 person-years between 2007 and 2009.

The monthly prevalence of rosiglitazone use (Figure 3) showed an increasing trend until May 2007, (2.3/1000 py) whereas it decreased thereafter (1.1/1000 person-years in January 2009). The use of pioglitazone increased surpassing rosiglitazone use from April 2008 onwards. The incidence of rosiglitazone use decreased sharply after May 2007 until August of the same year (0.8/1000 person-years in May 2007 and 0.2/1000 person-years in August 2007) and later it remained stable (Figure 4). At the end of the period (January 2009) the incidence of pioglitazone use was higher than that of rosiglitazone. Use of the fixed

Figure 1
Annual prevalence of prescription of glucose lowering drugs from 2000 to 2009 in the United Kingdom. Prevalence is reported by class and calendar year. Thiazolidinediones group includes alone and fixed combinations. Others group includes alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, meglitinides, glucagon like-1 analogues. —♦—, others; —■—, sulfonylureas; —▲—, biguanides; —×—, insulins; —●—, thiazolidinediones

Figure 2
Annual incidence of prescription of glucose lowering drugs from 2000 to 2009 in the United Kingdom. Incidence is reported by class and calendar year. Thiazolidinediones group includes alone and fixed combinations. Others group includes alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, meglitinides, glucagon like-1 analogues. —♦—, others; —■—, sulfonylureas; —▲—, biguanides; —×—, insulins; —●—, thiazolidinediones

combinations rosiglitazone/metformin and pioglitazone/metformin followed the same pattern as that of the TZDs alone.

With regards to the characteristics of patients who started TZDs (Table 1), rosiglitazone users were less likely to have a history of coronary heart disease (MI and/or angina, $P_{\text{trend}} < 0.001$) and concomitant use of insulin ($P_{\text{trend}} = 0.011$) after the warnings as compared with the previous period. Users of pioglitazone who initiated the treatment after the safety warning were older ($P_{\text{trend}} = 0.001$), more likely to be male ($P_{\text{trend}} = 0.001$), to

have a history of myocardial infarction (MI) ($P_{\text{trend}} = 0.005$) and a history of cerebrovascular disease ($P_{\text{trend}} = 0.033$) as compared with those starting the drug before the safety warning.

In the analysis of the pattern of switching (Figure 5), we found that 8.4% of subjects on rosiglitazone changed to pioglitazone after the FDA alert (May 2007) as compared with 0.6% who changed before May 2007. In addition, 9.1% switched from the fixed combination metformin/rosiglitazone to metformin alone after the alert, while 2.2% did the same switch in the period before the warning.

Figure 3

Monthly prevalence of prescription of thiazolidinediones from May 2006 to January 2009 in the United Kingdom. Prevalence is reported by specific thiazolidinedione or the fixed combination and calendar year. ◆, rosiglitazone; ■, pioglitazone; ▲, metformin/rosiglitazone; ✕, metformin/pioglitazone

Figure 4

Monthly incidence of use of thiazolidinediones from May 2006 to January 2009 in the United Kingdom. Incidence is reported by specific thiazolidinedione or the fixed combination and calendar year. ◆, rosiglitazone; ■, pioglitazone; ▲, metformin/rosiglitazone; ✕, metformin/pioglitazone

Discussion

In this retrospective, population-based drug utilization study we observed an increase in the use of GLDs in the years 2000–2009 in UK primary care. In line with current guidelines and previous drug utilization studies [10, 15], metformin was constantly the most frequently prescribed GLD in patients with T2DM. A study conducted in the UK general population from 2000 to 2006 [10] documented that biguanides were more frequently used than sulfonylureas since 2001. The change in the prevalence of use of metformin over sulfonylureas could be due to results from studies such as the UKPDS where it was shown that obese patients who received metformin had gained less weight and had less hypoglycaemic events compared with users of insulin and sulfonylureas [19]. Fillion *et al.* reported an

increasing trend in the use of GLDs in the same period of time in the UK, with the greatest relative increase observed in TZD use [15]. In 2007 we detected an increase in the use of GLDs other than biguanides and sulfonylureas. This finding may be attributed to the marketing of new drugs such as exenatide (marketed in 2007) and liraglutide (marketed in 2009). Similarly, Hurren *et al.* [20], reported that the use of insulin and other drugs such as sitagliptin and exenatide increased in the USA after the safety alert regardless of whether the subject continued or not with the TZD. Regarding the use of TZD, the prevalence of use decreased after 2007 but not steeply. This could be mainly explained by the reduced number of new users of TZD after the alert. In addition, 8.4% of rosiglitazone users switched to pioglitazone, after the FDA alert in May 2007. The same finding was observed in the Ontario Drug

Table 1

Characteristics of new users of rosiglitazone and pioglitazone before, after and between the FDA and EMA warnings

	Rosiglitazone				Pioglitazone			
	Period 1	Period 2	Period 3	<i>P</i> _{trend}	Period 1	Period 2	Period 3	<i>P</i> _{trend}
Number of new users	1972	923	269	–	788	2024	2476	–
TZD as first GLD drug ever (%)	44 (2.23)	18 (1.95)	4 (1.49)	–	21 (2.66)	14 (0.69)	10 (0.40)	–
Age (SD) (years)	61.70 (12.38)	61.40 (12.39)	61.18 (13.23)	0.523	61.51 (12.73)	63.04 (11.93)	63.09 (11.78)	0.001
Male (%)	1135 (57.56)	516 (55.90)	150 (55.76)	0.390	433 (54.95)	1159 (57.26)	1503 (60.70)	0.001
Users with concomitant use of insulin (%)	18 (0.91)	15 (1.63)	7 (2.60)	0.011	50 (6.35)	96 (4.74)	66 (2.67)	<0.001
Angina (%)	222 (11.26)	82 (8.88)	15 (5.58)	0.001	93 (11.80)	258 (12.75)	277 (11.19)	0.343
History of myocardial infarction (%)	182 (9.23)	75 (8.13)	14 (5.20)	0.031	68 (8.63)	171 (8.45)	276 (11.15)	0.005
History of coronary heart disease*	314 (15.92)	122 (13.22)	23 (8.55)	<0.001	126 (15.99)	340 (16.80)	434 (17.53)	0.296
History of congestive heart failure (%)	45 (2.28)	14 (1.52)	5 (1.86)	0.286	30 (3.81)	68 (3.36)	64 (2.58)	0.053
History of hypertension (%)	1011 (51.27)	473 (51.25)	139 (51.67)	0.934	403 (51.14)	1095 (54.10)	1330 (53.72)	0.357
Obesity (%)	419 (21.25)	214 (23.19)	70 (26.02)	0.055	164 (20.81)	485 (23.96)	542 (21.89)	0.927
Lipid metabolism disorders (%)	551 (27.94)	249 (26.98)	81 (30.11)	0.806	217 (27.54)	669 (33.05)	745 (30.09)	0.772
History of cerebrovascular disease (%)	77 (3.90)	23 (2.49)	8 (2.97)	0.112	24 (3.05)	70 (3.46)	111 (4.48)	0.033

Period 1: 21 November 2006 to 21 May 2007, Period 2: 22 May 2007 to 24 January 2008), Period 3: 25 January 2008 to 24 July 2008. GLD, Glucose lowering drug; *P*_{trend}, *P* value for trend; SD, standard deviation; TZD, thiazolidenedione. *History of coronary heart disease comprises angina and/or history of myocardial infarction.

Figure 5

Switching pattern of glucose lowering drugs in patients with T2DM before May 21 2007 (A) and after (B) May 21 2007. The percentage reflects the proportion of subjects who were on drug A and changed to drug B

Benefits Database [21], reporting a dramatic decline in rosiglitazone use and an increase in new use of pioglitazone after the same warning. This progressive decrease in the use of rosiglitazone with a corresponding increase in the prevalence of use of pioglitazone suggests that some patients who were on rosiglitazone treatment could have been progressively switched to pioglitazone. The steep change in the use of TZD after May 2007 was not observed after the EMA alert in January 2008. This was also observed by Ruiter *et al.* [16] in the Netherlands, where no significant change in dispensing prescribed by GPs ($P=0.18$) was found after the EMA alert in January 2008.

Looking at the switching pattern we observed that most of rosiglitazone users switched to pioglitazone. Switching from rosiglitazone to pioglitazone was probably supported by previous publications where pioglitazone was not associated with ischaemic cardiovascular risk [22].

However in July 2011, pioglitazone was suspended in France [23] due to reports of bladder cancer associated to this drug. The EMA and FDA issued warnings concerning this possible association [24, 25]. The EMA restricted its use only to certain subjects where other therapies had failed or are not suitable.

Interestingly, also users of combination metformin/rosiglitazone tended to switch to pioglitazone and to a greater extent to metformin alone. Hall *et al.* [26] studied the switching pattern using the THIN database as well. Despite the different definition for switchers, the authors of this study reported that 33% of subjects on rosiglitazone changed the prescription to another glucose lowering treatment, 55% continued treatment with a TZD (rosiglitazone or pioglitazone) and 25% suspended rosiglitazone and did not have further prescriptions for a GLD 6 months after the FDA alert.

In our study we also investigated the characteristics of subjects who started treatment with a TZD in three different periods and we observed significant changes after the alerts. The proportion of male and older patients who started pioglitazone increased after the alerts, but decreased in new rosiglitazone users. Gender and advancing age are well known cardiovascular risk factors. Likewise, patients with cerebrovascular disease and myocardial infarction were more likely to be treated with pioglitazone than rosiglitazone, especially after the EMA alert. Altogether these findings highlight the change in the treatment of T2DM high-risk patients from rosiglitazone to pioglitazone. Interestingly there was an increase in the proportion of subjects receiving concomitant treatment with insulin with rosiglitazone even when the regulatory agencies alerted about the increased risk of oedema using both drugs concomitantly. Starner *et al.* [27] found that more than 50% of subjects at risk were at risk due to the concomitant use of insulin with rosiglitazone. The treatment guidelines [28] recommend to reduce or stop this combination to avoid oedema and excessive weight gain although it is also mentioned that TZD could be useful in lowering HbA1c and minimizing the required insulin dose. Therefore physicians could have considered treating some subjects with both medications.

As mentioned before, the meta-analysis published by Nissen and Wolski [3] and the safety alert issued by the FDA [4] were both published on the same day (May 21 2007). Therefore, it is not possible to determine which document drove the change in the prescription of GLDs. One limitation of the study is that we were not able to separate the effect of the alerts issued in May and August 2007 and therefore, the decrease of the prescription pattern of rosiglitazone could be not only because of the alert in May but also due to the alert in August 2007. We could not assess the effect of the suspension of rosiglitazone in the EU because at the time of the analysis the most up to date data available were the cut-off as of November 24 2009.

On the other hand we were able to assess the pattern of use of GLDs since the introduction of rosiglitazone and pioglitazone into the market in 2000 and for a period of almost 10 years in a large database with high quality of data.

In conclusion, the prescription of GLDs in the UK has increased in the last 10 years. Metformin was consistently the first line treatment. The prescription of other therapies including the new agents based on incretin mechanism increased from 2007 onwards. The pattern of TZD prescriptions changed after May 2007 after the launch of the FDA safety alert. Rosiglitazone use, which was suspended in the EU in 2010, decreased dramatically after the first safety warnings, partly in favour of pioglitazone. Such a pattern of TZD use was particularly evident for patients at higher cardiovascular risk.

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Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and claim no conflict of interest related to the submitted work. Miriam Sturkenboom occasionally conducts unconditional research for pharmaceutical companies including Pfizer, Boehringer, Lilly and AstraZeneca.

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