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Rosiglitazone use and post-discontinuation glycaemic control in two European countries, 2000-2010

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Article summary

Article focus (up to three bullet points on the research questions or hypotheses addressed);

- Rosiglitazone is a second-line oral hypoglycaemic agent, which was sold in the European Union starting in 2000; in a series of regulatory decision, its use was restricted and ultimately suspended in Europe in September 2010
- This article examines utilization of rosiglitazone in Denmark and the United Kingdom, in 2000-2010
- On the patient level, this article explores changes in glycaemic control following discontinuation of rosiglitazone

Key messages (up to three bullet points showing the key messages or significance of the study)

- Following a 2007 publication of a meta-analysis showing increased cardiovascular morbidity associated with rosiglitazone, use of the drug declined sharply and irreversibly in Denmark and in the UK; this predated the official suspension of the drug by the European Medicines Agency in 2010
- On the patient level, observed mean changes in fasting plasma glucose and glycated haemoglobin A1c were slight in patients who discontinued rosiglitazone

Strengths and limitations of this study

- The study makes use of population based routine medical databases in two European countries, which are likely to reflect typical clinical practice
- Despite differences in record generation mechanisms in the two databases, results were overall concordant
- Automated prescription and dispensation data may have imprecisely measured initiation and discontinuation of medication intake

Abstract

Objectives To evaluate the impact of risk minimisation policies on use of rosiglitazone-containing products and on glycaemic control among patients in Denmark and the United Kingdom (UK).

Design, setting and participants We used population-based data from the Aarhus University Prescription Database (AUPD) in northern Denmark and the General Practice Research Database (GPRD) in the UK.

Main outcome measures We examined use of rosiglitazone during its entire period of availability on the European market (2000–2010) and evaluated changes in glycated haemoglobin-A_{1c} (HbA_{1c}) and fasting plasma glucose (FPG) levels among patients discontinuing this drug.

Results During 2000–2010, 2,321 patients with records in the AUPD used rosiglitazone in northern Denmark and 25,428 patients with records in the GPRD used it in the UK. The proportion of rosiglitazone users among all users of oral hypoglycaemic agents (OHA) peaked at 4% in the AUPD and 15% in the GPRD in May 2007. Twelve months after discontinuation of rosiglitazone-containing products, the mean change in HbA_{1c} was –0.16% (95% confidence interval [CI]: –3.4%, 3.1%) in northern Denmark and –0.17% (95% CI: –0.21%, 0.13%) in the UK. Corresponding mean changes in FPG were 0.01 mmol/L (95% CI: –7.3 mmol/L, 7.3 mmol/L) and 0.03 mmol/L (95% CI: –0.22 mmol/L, 0.28 mmol/L).

Conclusions Publication of evidence concerning potential cardiovascular risks of rosiglitazone was associated with a irreversible decline in use of rosiglitazone-containing products in Denmark and the UK. Mean changes in HbA_{1c} and FPG after drug discontinuation were slight.

Key words: diabetes mellitus, drug safety, glucose-lowering drugs, rosiglitazone, thiazolidinediones

Introduction

Since first marketed in the European Union in 2000, rosiglitazone has been subject to several risk-benefit assessments, especially concerning cardiovascular safety [1-9]. In a May 2007 meta-analysis published in the *New England Journal of Medicine*, Nissen and Wolski reported increased cardiovascular morbidity associated with rosiglitazone use [2]. In 2008, the European Medicines Agency (EMA) amended the rosiglitazone product label, adding coronary syndrome to the list of contraindications and inserting a warning about potentially increased risk of ischemic events [10]. At the time of this label amendment, EMA concluded "that the benefits of [...] rosiglitazone [...] in the treatment of type 2 diabetes continue to outweigh their risks" [11]. In June 2010, Nissen and Wolski updated their meta-analysis, confirming the finding of an increased risk of myocardial infarction (but not the original finding of increased all-cause mortality) in association with rosiglitazone use [12]. In July 2010, Graham and colleagues published a paper in *JAMA*, based on data from US Medicare beneficiaries, showing increased risks of several cardiovascular events, as well as all-cause mortality, in a comparison of rosiglitazone users with pioglitazone users [7]. Following these two publications, on 22 September 2010, the EMA recommended suspension of use of all rosiglitazone-containing products in the European Union [13]. The European Commission subsequently mandated suspension of the drug, citing absence of unique therapeutic benefits outweighing its risks [14].

Here we report results of an EMA-commissioned study on the impact of labelling changes and findings reported in scientific publications on utilisation of rosiglitazone-containing products in Europe. On the population level, we examined changes in use of rosiglitazone-containing products over the entire period when rosiglitazone was available on the market. On the patient level, we assessed the impact of rosiglitazone discontinuation on glycaemic control and reported oral hypoglycaemic agents prescribed after post-suspension discontinuation of rosiglitazone.

Methods

Setting and study population. This study was based on routinely collected data in Danish and United Kingdom (UK) medical databases. In Denmark, the study population included users of oral hypoglycaemic agents (OHAs) identified in the Aarhus University Prescription Database (AUPD) [15]. The database's catchment area covers the North and Central Regions of Denmark (hereafter referred to as 'northern Denmark'), with a combined population in mid-2010 of 1,834,595 persons, which is about one-third of the Danish population. The AUPD captures reimbursed prescriptions redeemed in the regions' outpatient pharmacies since 1998. In the UK, OHA users were identified from the General Practice Research Database (GPRD), currently also known as the Clinical Practice Research Datalink.

We identified patients in each database with a prescription for any OHA between 1 January 2000 and 31 December 2010, encompassing the entire period of rosiglitazone availability in Europe. We defined OHA users as persons who received at least one prescription for any OHA during the study period. Prescriptions for OHAs were identified using Anatomical Therapeutic Chemical (ATC) codes in the AUPD and Multilex codes in the GPRD. People could have received prescriptions for multiple OHAs during the study period, including rosiglitazone. Our use of the term 'rosiglitazone' includes all preparations of the drug.

Start of rosiglitazone use was defined as the date of the first-recorded prescription for a rosiglitazone-containing product. Patients were assumed to have discontinued rosiglitazone therapy in the absence of a record of a new rosiglitazone prescription during a period encompassing the estimated length of at least two prescriptions. Prescription length was estimated at 45 days in AUPD and 130 days in the GPRD, based on observed intervals between prescriptions and knowledge about typical clinical practice in Denmark, as well as the prescribing instructions in the British Monthly Index of Medications in the UK.

To describe the study population, we obtained data on participants' clinical and demographic characteristics, including sex, age, body mass index (BMI), smoking, medical diagnoses, and use of other medications (lipid-lowering agents, antihypertensive agents,

diuretics, nitrates, and antiplatelet agents). These characteristics were measured as of 1 January 2000 for patients who started an OHA before 2000 and on the date of the first OHA prescription for those who started thereafter. We used records from routine laboratory tests to obtain data on measured glycated haemoglobin-A_{1c} (HbA_{1c}) and fasting plasma glucose (FPG) levels.

Data sources. In northern Denmark, data on hospital-based medical diagnoses, prescription medications, and laboratory test results were obtained, respectively, from the Danish National Registry of Patients (DNRP [16]), from the AUPD, and from the Laboratory Information Systems of the North and the Central Denmark Regions (LABKA [17]). The LABKA database stores results of laboratory tests performed at hospital-based laboratories. Patients are referred to these laboratories by hospitals, general practitioners, and specialists. Data on smoking and BMI were obtained from the Danish National Indicator Project database (http://www.nip.dk). All data were linked on the individual level using the universal personal identifier [18]. The GPRD is a longitudinal database that has collected data from over 450 general practices in the UK since 1987, covering a representative 6% sample of the UK population. The GPRD captures prescriptions issued to patients by general practitioners, and it also includes information on patient demographics, diagnoses, referrals, hospitalizations, and laboratory test results [19-22].

Statistical analysis. First, we examined changes in the proportion of rosiglitazone users among all users of OHAs in the two countries between 2000 and 2010. Second, we compared distributions of demographic and clinical characteristics between rosiglitazone users and users of other OHAs. Third, we examined changes in HbA_{1c} and FPG levels, comparing values before and after discontinuation of rosiglitazone treatment. The pre-discontinuation value of a laboratory parameter was the value closest in time to the estimated discontinuation date within 24 months before that date. We defined three non-overlapping post-discontinuation periods as follows: 3 months (90–179 days post-discontinuation); 6 months (180–359 days post-discontinuation); and 12 months (360–479 days post-discontinuation). We used the earliest available measurement within each post-discontinuation period. The post-discontinuation

values were ascertained through 30 June 2011. Using the pre-discontinuation and post-discontinuation values, we calculated the mean (with standard deviation) level for HbA_{1c} and FPG before and after discontinuation and the mean change for each post-discontinuation period. Furthermore, we calculated the proportion of patients with new post-discontinuation onset of loss of glycaemic control, defined as of HbA_{1c} >7.5%, and the proportion of patients with new post-discontinuation onset of treatment failure, defined as FPG >10 mmol/L. To capture new onset, these proportions first were computed among patients without evidence of treatment failure/loss of glycaemic control before discontinuing rosiglitazone. We then calculated the proportions of patients with clinically meaningful changes in HbA_{1c} (change >0.6%) and FPG (change >10%) after discontinuation of rosiglitazone. Finally, we examined changes in HbA_{1c} levels in patients who discontinued the drug on or after 23 September 2010, presumably in response to the EMA's suspension of the drug, and reported the first OHA prescribed to patients who discontinued rosiglitazone after its suspension. The algorithms used to define variables in this project are provided in the Appendix. We used SAS software version 9.2 (SAS Inc., Cary, NC, USA) to analyse the data.

Ethical approval. This study was approved by the Danish Data Protection Agency (record number 2009-41-3866) and by the Independent Scientific Advisory Committee of the GPRD. There was no patient contact, and informed consent was therefore not required.

Results

During the study period, 67,525 OHA users were recorded in the AUPD and 191,276 in the GPRD. Of these, 2,321 (3.4%) persons in the AUPD and 25,428 (13%) persons in the GPRD received at least one prescription for a rosiglitazone-containing product. Figure 1 shows changes in the proportion of rosiglitazone users among all OHA users within the study period. This proportion peaked at 4% in northern Denmark and at 15% in the UK in May 2007, and rapidly decreased thereafter, with virtually no rosiglizatone users remaining after 2010.

Table 1 compares demographic and clinical characteristics of users of rosiglitazone and users of other OHAs. Rosiglitazone users tended to be younger, but were more likely to have had a prescription history of lipid-lowering or antihypertensive agents. Rosiglitazone users were more likely than the other OHA users to have used OHAs other than metformin and sulfonylurea previously. Based on data from the GPRD, users of rosiglitazone-containing products were slightly more likely than other OHA users to have a BMI of ≥30 kg/m^2 (Table 1).

Glycaemic control after discontinuation of rosiglitazone. Among all rosiglitazone users in the LABKA 1776 who discontinued the drug had HbA_{1c} measurements available. The mean duration of rosiglitazone use in these patients was 24.1months (standard deviation 21.1), median 18.8. In the GPRD there were 21145 rosiglitazone users with HbA_{1c} measurements. The mean duration of use in these patients was 30.3 (standard deviation 25.5), median, 24,0 . Table 2 shows changes in HbA_{1c} at three, six, and 12 months after discontinuation of rosiglitazone treatment at any time during the study period. At 12 months post-discontinuation, a change of similar magnitude in the mean HbA_{1c} was observed in both the LABKA (Denmark) and Laboratory (UK) databases: –0.16% (95% confidence interval [CI]: –3.4%, 3.1%) in northern Denmark, and –0.17% (95% CI: –0.21%, -0.13%) in the UK. Loss of glycaemic control, defined by new onset of HbA_{1c}>7.5%, was registered for up to 29% of patients during the 12-month follow-up period in Denmark and for up to 37% of patients in the UK. Similar proportions of patients had HbA_{1c} values consistent with a clinically meaningful decrease (>0.6%) at 12 months.

Table 3 shows changes in HbA_{1c} after discontinuation of rosiglitazone-containing products on or after 23 September 2010. Thus, Table 3 represents subset of patients described in Table 2. In the UK data, mean HbA1c decreased by 1.8% at six months post-discontinuation (95% CI: –2.1%, –1.6%), but the pre-discontinuation mean HbA_{1c} in this group was 10%. A larger proportion of patients in the UK than in Denmark had evidence of loss of glycaemic control and a substantially larger proportion of patients in the UK

experienced a clinically meaningful decrease in HbA1c after discontinuation of rosiglitazone compared with Denmark (Table 3).

Table 4 shows changes in FPG at three, six, and 12 months after discontinuation of rosiglitazone. At 12 months post-discontinuation, there was virtually no change seen in either of the databases: mean change = 0.01 mmol/L (95% CI: –7.3 mmol/L; 7.3 mmol/L) in Denmark and mean change = 0.03 mmol/L (95% CI: –0.22 mmol/L; 0.28 mmol/L) in the UK. Treatment failure, defined by new onset of FPG >10 mmol/L during one of the follow-up periods, was observed in a maximum of 23% of patients in Denmark and 20% in the UK. The number of persons with available measurements for Denmark, however, was small (Table 4). Table 5 shows the distribution of OHA prescribed to patients after terminating rosiglitazone on 23 September 2010 or later. The majority of patients switched to another OHA (82% in Denmark; 97% in the UK) after the last recorded pioglitazone prescription. The majority of patients – 56.8% in Denmark and 41.7% in the UK – received a prescription for meformin. In the UK, 23.6% of patients had a prescription for pioglitazone, and 14.5% for pioglitazone + metformin. Pioglitazone was prescribed only to 4.4% of the patients in northern Denmark.

Discussion

We examined use of rosiglitazone-containing products over the entire period of availability of this drug in Europe (2000–2010) using routinely collected data in medical databases in Denmark and the UK. Overall, the drug was more widely used in the UK than in Denmark, with the proportion of rosiglitazone users among all users of OHA peaking at 15% and 4% in the two countries, respectively. The timing of both peaks, which marked the beginning of a steep decline in use, coincided with the May 2007 publication of the meta-analysis by Nissen and Wolski [2] and subsequent regulatory warnings from the EMA. This decline occurred three years before the regulatory decision to suspend rosiglitazone in Europe. Similarly, a sharp decline in prescribing occurred in the United States after the FDA added a boxed warning to the rosiglitazone label in May 2007 [23]. On the patient level, discontinuation of rosiglitazone was associated with a slight overall decrease in the mean level of glycated

haemoglobin. However, close to one-third of patients had evidence consistent with loss of glycaemic control during the 12 months of follow-up, including patients who discontinued rosiglitazone after the EMA decision to suspend the drug. The majority of patients who discontinued rosiglitazone after suspension started receiving metformin.

While on the market, rosiglitazone represented a larger proportion of all OHA use in the UK than in Denmark. This may reflect conservative recommendations issued in Denmark, suggesting that treatment first be attempted with metformin, sulfonurea, and insulin [24]. Guidelines from the National Institute for Health and Clinical Excellence (NICE) in the UK stated that rosiglitazone should only be prescribed if other classes of OHA were not effective in lowering plasma glucose concentrations.Therefore rosiglitazone was recommended only as second or third line therapy [25]. The high pre-discontinuation level of HbA_{1c} in UK patients who discontinued rosiglitazone following the drug suspension is also consistent with this guideline. Among patients terminating rosiglitazone after the drug was suspended, a larger proportion of UK patients compared with their Danish counterparts experienced a clinically meaningful decrease in glycated haemoglobin. The pre-discontinuation values among the UK patients were substantially higher. We thus attribute this to the result of patients with poor glycaemic control coming to medical attention.

The data presented here were obtained from medical databases that provide data on routine and independent registration of health-related events in two European countries. Such data are likely to reflect typical clinical practice. The data from the two data systems are also complementary. The AUPD records filled prescriptions, while the GPRD records prescriptions issued by general practitioners. Furthermore, the databases draw on different health sectors for information on patient characteristics. In Denmark data on diagnoses originate from hospital discharge summaries, while GPRD data on diagnoses originate from general-practitioner records. Despite these differences and potential differences in the underlying patient populations, the results obtained from the two data systems were generally consistent.

Because OHA are distributed by prescription only and need to be taken long-term, the information we present on rosiglitazone utilization over calendar time is likely to be accurate.

The pattern of use for the two Danish regions mirrors the nationwide pattern reported by the Danish Medicines Agency [26]. However, because automated prescription records provide no information on timing of drug intake, we had to make assumptions about timing of rosiglitazone discontinuation and prescription length. We speculate that short-term changes in laboratory parameters following discontinuation of rosiglitazone are subject to more misclassification due to errors in assigning the discontinuation status than are long-term changes in these parameters. Therefore, our 12-month estimates of post-discontinuation change in laboratory parameters may be more robust than the 3-month estimates. The information on glycated haemoglobin A_{1c} and on fasting plasma glucose originated from routinely collected laboratory data, although patients with laboratory measurements may differ from the entire population of rosiglitazone-treated patients. For example, physicians may be less likely to routinely collect laboratory data for patients with less severe diabetes.

In summary, a decline in use of rosiglitazone occurred immediately following the May 2007 publication of a meta-analysis describing adverse cardiac side effects of this drug [2]. Changes in glycaemic control after discontinuation of rosiglitazone were small on average during the 12 month follow-up period, although about one-third of patients had evidence of loss of glycaemic control upon discontinuation. Most patients were switched to a metformin-containing regimen.

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Contribution statement

V. Ehrenstein participated in conception and design of the study, led the writing, and contributed to data analysis. R. K. Hernandez contributed to study design and data analysis in the GPRD. S. P. Ulrichsen conducted the data analyses in Denmark, J. Rungby contributed to study design and analysis, and provided clinical expertise, T.L. Lash participated in conception and design of the study, A.H. Riis contributed to data analysis of the AUPD data, L. Li contributed to data analysis of the GPRD data, H.T. Sørensen oversaw the study and provided clinical expertise, and S. S. Jick participated in conception and design of the study. All authors participated in revisions of the manuscript draft for intellectual content.

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Competing interest statement

All authors have completed the ICMJE uniform disclosure form at and declare: being funded by the EMA (through institutional contracts and subcontracts) for this work; no

financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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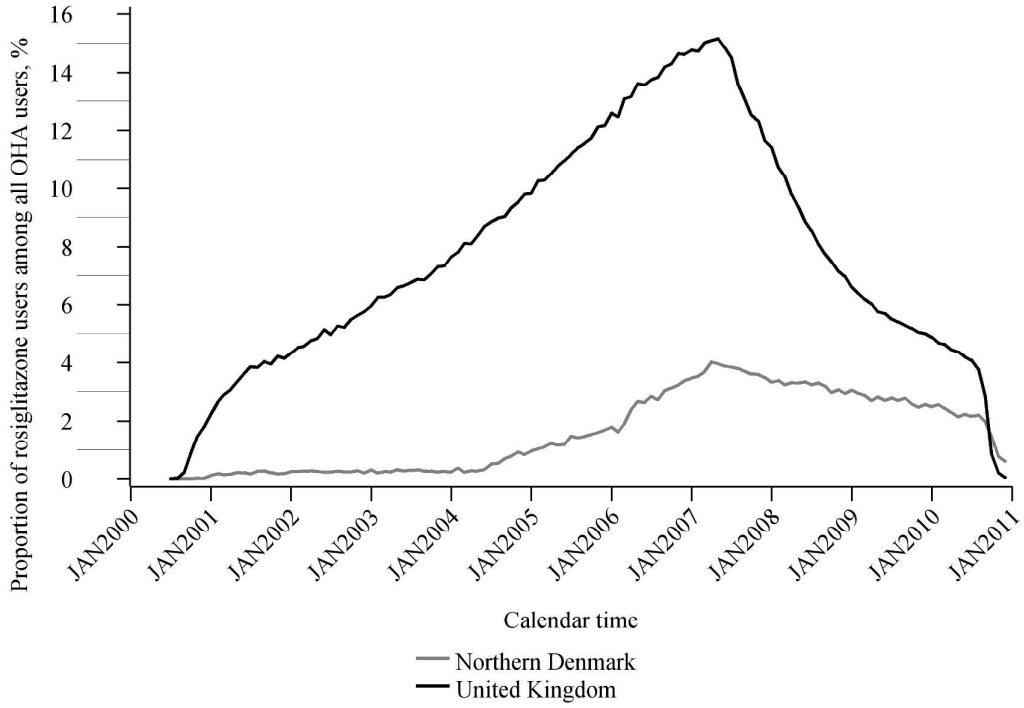
Figure 1. Proportion of users of rosiglitazone among all users of oral hypoglycaemic agents (OHA), 2000-2010.



Note: The maximum points of both graphs correspond to May 2007, the month of publication of the initial meta-analysis by Nissen and Wolski.[2]

Table 1. Baseline characteristics of patients treated with rosiglitazone and other oral hypoglycaemic agents from 1 January 2000 to 31 December 2010 in northern Denmark and the United Kingdom.

Characteristic	Northern Denmark (n=67,525)		United Kingdom (n=191,276)	
	Users of rosiglitazone (n=2,321) N (%)	Users of other oral hypoglycaemic agents (n=65,204) N (%)	Users of rosiglitazone (n=25,428) N (%)	Users of other oral hypoglycaemic agents (n=165,848) N (%)
Age group, years				
<35	83 (3.6)	3,999 (6.1)	589 (2.3)	9,358 (5.6)
35-44	286 (12)	4,967 (7.6)	2,469 (9.7)	13,192 (8.0)
45-54	595 (26)	10,219 (16)	5,513 (22)	25,023 (15)
55-64	757 (33)	16,751 (26)	7,661 (30)	38,668 (23)
65-74	444 (19)	15,724 (24)	6,434 (25)	42,030 (25)
75-84	147 (6.3)	10,423 (16)	2,426 (9.5)	28,430 (17)
≥85	9 (0.39)	3,121 (4.8)	336 (1.3)	9,147 (5.5)
Sex				
Female	976 (42)	30,845 (47)	11,259 (44)	78,772 (48)
Male	1,345 (58)	34,359 (53)	14,169 (56)	87,076 (53)
Charlson comorbidity index				
0	1,694 (73)	41,183 (63)	16,646 (65)	95,607 (58)
1-2	561 (24)	19,470 (30)	7,925 (31)	57,984 (35)
3+	66 (2.8)	4,551 (7.0)	857 (3.4)	12,257 (7.4)
History of OHA use before baseline*				
Metformin	2,279 (98)	51,022 (78)	23,836 (94)	144,881 (87)
Sulfonylurea	1,730 (74)	39,931 (61)	19,489 (77)	90,682 (55)
Pioglitazone	81 (3.5)	196 (0.30)	9,297 (37)	14,194 (8.6)
DPP 4 Inhibitor	517 (22)	4,149 (6.4)	2,242 (8.8)	5,882 (3.6)
Other oral glucose-lowering drugs**	497 (21)	5,530 (8.5)	2,582 (10)	5,725 (3.5)
History of other medication use				
Lipid lowering agents	1,939 (84)	40,327 (62)	22,223 (87)	114,378 (69)

Antihypertensive agents	1,991 (86)	48,016 (74)	21,846 (86)	126,897 (77)
Diuretics	1,404 (60)	34,650 (53)	13,516 (53)	73,225 (44)
Nitrates	351 (15)	9,456 (14)	52 (0.20)	322 (0.19)
Antiplatelet agents	1,409 (61)	33,060 (51)	2,878 (11)	15,223 (9.2)
Smoking				
Current	175 (7.5)	2,451 (3.8)	4,499 (18)	28,120 (17)
Former	215 (9.3)	3,121 (4.8)	6,102 (24)	43,985 (27)
Never	258 (11)	3,534 (5.4)	11,699 (46)	75,119 (45)
Missing	1,673 (72)	56,098 (86)	3,128 (12)	18,624 (11)
Body mass index category, kg/m^2				
< 18.5	2 (0.09)	32 (0.05)	35 (0.14)	623 (0.38)
18.5 – <25	51 (2.2)	1,257 (1.9)	2,675 (11)	21,634 (13)
25 – <30	177 (7.6)	3,257 (5.0)	7,458 (29)	49,463 (30)
≥ 30	462 (20)	5,454 (8.4)	11,225 (44)	66,725 (40)
Missing	1,629 (70)	55,204 (85)	4,035 (16)	27,403 (17)

*Baseline date was January 1, 2000 or date of first OHA prescription, whichever came later.
**Other glucose-lowering drugs excluding insulins are acarbose, repaglinide, exenatide, and liraglutide.

Table 2. Glycated haemoglobin (%) before and after discontinuation of rosiglitazone among patients with available pre-and post-discontinuation measurements, in northern Denmark and in the United Kingdom, 2000-2011.

Characteristic	Northern Denmark			United Kingdom		
	3 months (n=1,242)	6 months (n=1,496)	12 months (n=1,162)	3 months (n=9,448)	6 months (n=12,439)	12 months (n=8,635)
Baseline mean (SD)	7.8 (1.7)	7.8 (1.6)	7.9 (1.7)	8.7 (2.2)	8.5 (2.1)	8.4 (1.9)
Follow-up mean (SD)	7.7 (1.5)	7.7 (1.5)	7.7 (1.5)	8.1 (1.7)	8.2 (1.8)	8.2 (1.8)
Change from baseline, mean (95% CI)	-0.10 (-3.0; 2.8)	-0.05 (-3.1; 3.0)	-0.16 (-3.4; 3.1)	-0.57 (-0.62; -0.53)	-0.30 (-0.34; -0.26)	-0.17 (-0.21; -0.13)
Proportion with a clinically meaningful* increase, percent (95% CI)	26 (24; 29)	28 (26; 30)	28 (26; 31)	23 (22; 24)	28 (27; 28)	29 (28; 30)
Proportion with a clinically meaningful* decrease, percent (95% CI)	28 (25; 30)	27 (25; 29)	30 (27; 32)	40 (39; 41)	36 (35; 37)	34 (33; 35)
N with HbA_{1c} level>7.5% after baseline/N with baseline HbA_{1c} ≤7.5%	160/670	228/827	179/610	1,026/3,286	1,641/4,672	1,246/3,408
New post-discontinuation onset of loss of glycaemic control with HbA_{1c} >7.5%, percent (95% CI)[b]	24 (21; 27)	28 (25; 31)	29 (26; 33)	31 (30; 33)	35 (34; 36)	37 (35; 38)

*Clinically meaningful change defined using to the European Medicines Agency's definition as change of more than 0.6% (% is the test unit)
CI=confidence interval; HbA_{1c}=glycated haemoglobin A; SD=standard deviation

Table 3. Glycated haemoglobin (%) before and after discontinuation of rosiglitazone-containing products, among users who discontinued the drug on or after 23 September 2010 (date of the EMA's recommendation to suspend rosiglitazone), in northern Denmark and in the United Kingdom.

Characteristic	Northern Denmark		United Kingdom	
	3 months (n=376)	6 months (n=455)	3 months (n=1081)	6 months (n=338)
Baseline mean (SD)	7.1 (1.2)	7.1 (1.2)	10 (2.5)	10 (2.5)
Follow-up mean (SD)	7.5 (1.5)	7.4 (1.4)	8.0 (2.0)	8.3 (2.1)
Change from baseline, mean (95% CI)	0.40 (-1.9; 2.7)	0.34 (-1.8; 2.5)	-2.0 (-2.2; -1.8)	-1.8 (-2.1; -1.6)
Proportion with a clinically meaningful increase[a], percent (95% CI)	34 (29;38)	33 (29;38)	14 (12; 16)	15 (12; 19)
Proportion with a clinically meaningful decrease[a], percent (95% CI)	13 (9.5; 16)	12 (9.3; 15)	72 (69; 75)	69 (64; 74)
N with HbA_{1c} level>7.5% after baseline/N with baseline HbA_{1c} ≤7.5%	76/285	94/350	87/196	18/55
New post-discontinuation onset of loss of glycaemic control with HbA_{1c} >7.5%, percent (95% CI)[b]	27 (22; 32)	27 (22; 32)	44 (38;51)	33 (22; 46)

[a]Clinically meaningful change defined using to the European Medicines Agency's definition as change of more than 0.6% (% is the test unit)

CI=confidence interval; HbA_{1c}=glycated haemoglobin A; SD=standard deviationnce interval

Table 4. Fasting plasma glucose (mmol/L) before and after discontinuation of rosiglitazone among patients with available pre-and post-discontinuation laboratory measurements, in northern Denmark and in the United Kingdom, 2000-2011.

Characteristic	Northern Denmark			United Kingdom		
	3 months (n=95)	6 months (n=109)	12 months (n=77)	3 months (n=820)	6 months (n=1,256)	12 months (n=800)
Baseline mean (SD)	9.5 (3.6)	9.3 (3.4)	9.1 (3.5)	8.6 (3.2)	8.7 (3.2)	8.7 (3.4)
Follow-up mean (SD)	9.2 (3.7)	9.0 (3.4)	9.1 (3.5)	8.8 (3.2)	8.8 (3.1)	8.7 (3.1)
Change from baseline, mean (95% CI)	-0.38 (-9.0; 8.2)	-0.27 (-8.2;7.6)	0.01 (-7.3; 7.3)	0.27 (0.04; 0.49)	0.08 (-0.12; 0.27)	0.03 (-0.22; 0.28)
Proportion with a clinically meaningful increase*, percent (95% CI)	40 (31; 50)	35 (26; 44)	32 (23; 43)	39 (36; 43)	40 (38; 43)	40 (37; 44)
Proportion with a clinically meaningful decrease*, percent (95% CI)	39 (30; 49)	35 (26; 44)	40 (30; 51)	30 (27; 33)	33 (31; 36)	34 (31; 38)
N with FPG >10 mmol/L after baseline/N with baseline FPG ≤10 mmol/L	14/65	18/79	8/54	98/610	182/911	99/583
New post-discontinuation onset of treatment failure, FPG>10 mmol/L, percent (95% CI)	22 (13; 33)	23 (15; 33)	15 (7.3; 26)	16 (13, 19)	20 (18; 23)	17 (14; 20)

*Clinically meaningful change defined using to the European Medicines Agency's definition as change of more than 10 mmol/L.
CI=confidence interval; HbA_{1c}=glycated haemoglobin A; SD=standard deviation

Table 5. Oral hypoglycaemic agents (OHA) prescribed to patients after terminating rosiglitazone on 23 September 2010 or later.

	Aarhus University Prescription Database, Denmark (n=474*)		General Practice Research Database, United Kingdom (n=2810**)	
	Number	Percent (95% CI)	Number	Percent (95% CI)
Metformin	269	56.8 (52.3; 61.2)	1,136	41.7 (39.9; 43.6)
Glimepiride	84	17.7 (14.3; 21.2)	57	2.1 (1.6; 2.7)
Metformin+sitagliptin	49	10.3 (7.6; 13.1)		
Sitagliptin	45	9.5 (6.9; 12.1)	103	3.8 (3.1; 4.6)
Metformin+vildagliptin	35	7.4 (5.0; 9.7)		
Liraglutide	26	5.5 (3.4; 7.5)		
Pioglitazone	21	4.4 (2.6; 6.3)	641	23.6 (22.0; 25.2)
Pioglitazone + metformin			394	14.5 (13.2; 15.9)
Gliclazide	17	3.6 (1.9; 5.3)	351	12.9 (11.7; 14.2)
Glibenclamide	8	1.7 (0.5; 2.8)	16	0.6 (0.4; 1.0)
Saxagliptin	8	1.7 (0.5; 2.8)		
Glipizide	4	0.8 (0.1; 1.7)	9	0.3 (0.2; 0.6)
Vildagliptin	4	0.8 (0.1; 1.7)		
Repaglinide	3	0.6 (0.1; 1.3)	2	0.1 (0.0; 0.3)
Exenatide	3	0.6 (0.1; 1.3)		
Acarbose	2	0.4 (0.1; 1.0)	4	0.2 (0.1; 0.4)
Tolbutamide	1	0.2 (0.1; 0.6)	9	0.3 (0.2; 0.6)

*83 patients had no record of another OHA after the last rosiglitazone prescription.
**88 patients had no record of another OHA after the last rosiglitazone prescription

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	N/A
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	x
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	x
Objectives	3	State specific objectives, including any prespecified hypotheses	x
Methods			
Study design	4	Present key elements of study design early in the paper	x
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	x
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	x
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	x
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	x
Study size	10	Explain how the study size was arrived at	x
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	x
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	x
		(*b*) Describe any methods used to examine subgroups and interactions	x
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	x
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	x
		(b) Indicate number of participants with missing data for each variable of interest	x
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	x
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	x
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	x
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	x
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	x
Generalisability	21	Discuss the generalisability (external validity) of the study results	x
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	x

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Re: bmjopen-2013-003424 - Rosiglitazone use and post-discontinuation glycaemic control in two European countries, 2000-2010

11 July 2013

Dear Editor:

At your request, we are providing point-by-point responses to the peer review comments at BMJ. Please do not hesitate to let us know if additional revision or discretional changes as outlined below are necessary in your opinion.

With kind regards,

Vera Ehrenstein on behalf of the authors

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REVIEWER 1.

The data on HbA1c and FPG are of limited value. The authors do not present any information on what proportion of patients who stopped taking rosiglitazone were switched to other oral hypoglycaemic agents. It is difficult to believe that there were not such switches. Thus, a meaningful interpretation of the changes in glycemic control is not possible.

Response: *We agree that the data on post-rosiglitazone hypoglycaemic agents is important for the interpretation of the changes in glycaemic control. We added Table 5 to the manuscript, whereby we report the distribution of oral hypoglycaemic drugs prescribed after discontinuation of rosiglitazone. We also added text to the end of the Results section to describe the findings.*

REVIEWER 2.

1. It would be important addition to the paper to describe the agents that individuals switched to after coming off rosiglitazone. This may be something to consider in the glycaemic control analysis.

Response*: Same response as above (REVIEWER 1)*

2. It would be ideal to have minimum exposure to rosiglitazone to include in the glycaemic control study. It is unclear what the mean median exposure time was and how it was distributed.

Response. *We agree that information on median exposure to rosiglitazone is important in interpreting the data on glycaemic control. We have added this information to the results section.. In the table below, we provide distribution of the length of rosiglitazone treatment in the two databases.* ***This information is not incorporated in the current submission, but we will be happy to do so if advised by Editor/referees.***

Duration of rosiglitazone treatment (in months) among patients with available baseline HbA1c measurements before stopping rosiglitazone (Table 2 of the manuscript)

	N	Mean	Std	Median	25th quartile	75th quartile
Time (in months) from start to end of rosiglitazone treatment (Northern Denmark)	1776	24.09	21.11	18.77	5.72	38.12
Time (in months) from start to end of rosiglitazone treatment (United Kingdom)	21145	30.16	25.50	24.00	8.00	47.00

3. The baseline HbA1c is also important to consider the exposure to rosiglitazone. It would be also important to get some sense of the distribution of how far the look back was. Was it close r to the 24-months or to the discontinuation date.

Response. *We agree that information on recency of pre-discontinuation HbA1c measurement is important to consider. In the table below, we provide distribution of time between the baseline HbA1c measurement and the discontinuation of rosiglitazone.* ***This information is not incorporated in the current submission, but we will be happy to do so if advised by Editor/referees.***

Time (days) from baseline HbA1c measurement until discontinuation of rosiglitazone

	N	Mean	Std	Median	25th quartile	75th quartile
Days from last HbA1c measurement to rosiglitazone discontinuation (Northern Denmark)	1776	71.75	94.51	44.00	21.00	78.00
Days from last HbA1c measurement to rosiglitazone discontinuation (United Kingdom)	21145	108.22	114.67	70.00	25.00	153.00

4. In the table comparing the baseline the OHA selection, it would be important to consider the difference in HbA1c values between the two groups.

Response*. It was not the goal of the study to compare HbA1c in the 2 groups thus Table 1 provides no inferential comparison, only distribution of patient characteristics with and without use of rosiglitazone. We included all users of OHA during the study period to show characteristics of medicinally treated diabetic patients in the two countries.*

5. It is unclear how the other OHA group is identified. It looks like a bulk of this group had prior OHA use. What is this population.

Response*. We identified all users of other OHAs within each database during the study time period. See the second paragraph in the Methods section for details. We have added additional text to clarify who the OHA users were.*

6. What is Table 2. Are these all users who ever discontinued rosiglitazone? The discontinuation prior to 2007 is for different reasons compared to after 2007. This is not addressed in the manuscript. The analysis also needs to be done here.

Response*. Table 2 shows all those who ever discontinued rosiglitazone. Table 3 shows patients who discontinued rosiglitazone post-suspension. We agree with the reviewer that reasons for discontinuation*

are different before and after 2007, and especially before and after 2010. After the suspension of rosiglitazone, in September 2010, the patients had to be taken off the drug.

7. While the specific warnings and restrictions went into effect in September 2010 the decrease in use started in May 2007. This needs to be considered and addressed in the manuscript.

Response. *There were several warnings: some went in effect shortly after the publication of the 2007 analysis. In September 2010 rosiglitazone was suspended in Europe. Please see Discussion, first paragraph for relevant text.*

8. The authors do a nice job of looking at glycaemic control in many different ways. While the HbA1c of 7.5% may be a guideline driven threshold, there isn't strong evidence based for this cut-point. Would it be better to look at poor glycaemic control cutpoint of 9%?

Response: *We used the guideline-driven threshold to make our results comparable to results of other studies. Furthermore, decisions relevant to pioglitazone were most likely driven by the guidelines' values. We therefore respectfully retain current analyses in the manuscript.*

Result

The results section can be much stronger. There needs to be some information on what individuals switched to. The comparison group for other OHA is still not clear…. Is it truly everyone else. If so, a large amount was on previous OHAs. If so, are incident cases included? Thou should most likely be removed as incident case typically would not get rosiglitazone and thus would be an inappropriate comparison group.

Response: *See response above to Reviewer #1 and Reviewer #2 comment 1. We have added a table to the manuscript. Assuming that by 'comparison group' the reviewer means persons exposed to OHAs other than rosiglitazone in Table 1, we reported characteristics of new and prevalent users of oral hypoglycaemic agents who had at least one prescription of rosiglitazone vs. another OHA during the study period (2000-2010). No inferential comparison is intended in Table 1.We have clarified this in the Methods section.*

Interpretation and conclusion

The discussion for this manuscript can be much stronger. Given the real contribution here, there is relatively little on the impact of these changes on the surrogate outcomes. Ideally the discussion would focus around rates of use, agents that were changed to, and glycaemic control.

Response: *Rates of rosiglitazone use are presented in the Figure. Conclusion about the glycaemic control has been provided at the end of the Discussion section.*

Rosiglitazone use and post-discontinuation glycaemic control in two European countries, 2000-2010

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**Dr. Hernandez was affiliated with BCDSP at the time the work for this project was conducted.

Words: abstract 241, main text 2,~~471~~553

1 Figure, 5 Tables

Article summary

Article focus (up to three bullet points on the research questions or hypotheses addressed);

- Rosiglitazone is a second-line oral hypoglycaemic agent, which was sold in the European Union starting in 2000; in a series of regulatory decision, its use was restricted and ultimately suspended in Europe in September 2010
- This article examines utilization of rosiglitazone in Denmark and the United Kingdom, in 2000-2010
- On the patient level, this article explores changes in glycaemic control following discontinuation of rosiglitazone

Key messages (up to three bullet points showing the key messages or significance of the study)

- Following a 2007 publication of a meta-analysis showing increased cardiovascular morbidity associated with rosiglitazone, use of the drug declined sharply and irreversibly in Denmark and in the UK; this predated the official suspension of the drug by the European Medicines Agency in 2010
- On the patient level, observed mean changes in fasting plasma glucose and glycated haemoglobin A1c were slight in patients who discontinued rosiglitazone

Strengths and limitations of this study

- The study makes use of population based routine medical databases in two European countries, which are likely to reflect typical clinical practice
- Despite differences in record generation mechanisms in the two databases, results were overall concordant
- Automated prescription and dispensation data may have imprecisely measured initiation and discontinuation of medication intake

Abstract

Objectives To evaluate the impact of risk minimisation policies on use of rosiglitazone-containing products and on glycaemic control among patients in Denmark and the United Kingdom (UK).

Design, setting and participants We used population-based data from the Aarhus University Prescription Database (AUPD) in northern Denmark and the General Practice Research Database (GPRD) in the UK.

Main outcome measures We examined use of rosiglitazone during its entire period of availability on the European market (2000–2010) and evaluated changes in glycated haemoglobin-A_{1c} (HbA_{1c}) and fasting plasma glucose (FPG) levels among patients discontinuing this drug.

Results During 2000–2010, 2,321 patients with records in the AUPD used rosiglitazone in northern Denmark and 25,428 patients with records in the GPRD used it in the UK. The proportion of rosiglitazone users among all users of oral hypoglycaemic agents (OHA) peaked at 4% in the AUPD and 15% in the GPRD in May 2007. Twelve months after discontinuation of rosiglitazone-containing products, the mean change in HbA_{1c} was –0.16% (95% confidence interval [CI]: –3.4%, 3.1%) in northern Denmark and –0.17% (95% CI: –0.21%, 0.13%) in the UK. Corresponding mean changes in FPG were 0.01 mmol/L (95% CI: –7.3 mmol/L, 7.3 mmol/L) and 0.03 mmol/L (95% CI: –0.22 mmol/L, 0.28 mmol/L).

Conclusions Publication of evidence concerning potential cardiovascular risks of rosiglitazone was associated with a irreversible decline in use of rosiglitazone-containing products in Denmark and the UK. Mean changes in HbA_{1c} and FPG after drug discontinuation were slight.

Key words: diabetes mellitus, drug safety, glucose-lowering drugs, rosiglitazone, thiazolidinediones

Introduction

Since first marketed in the European Union in 2000, rosiglitazone has been subject to several risk-benefit assessments, especially concerning cardiovascular safety [1-9]. In a May 2007 meta-analysis published in the *New England Journal of Medicine*, Nissen and Wolski reported increased cardiovascular morbidity associated with rosiglitazone use [2]. In 2008, the European Medicines Agency (EMA) amended the rosiglitazone product label, adding coronary syndrome to the list of contraindications and inserting a warning about potentially increased risk of ischemic events [10]. At the time of this label amendment, EMA concluded "that the benefits of [...] rosiglitazone [...] in the treatment of type 2 diabetes continue to outweigh their risks" [11]. In June 2010, Nissen and Wolski updated their meta-analysis, confirming the finding of an increased risk of myocardial infarction (but not the original finding of increased all-cause mortality) in association with rosiglitazone use [12]. In July 2010, Graham and colleagues published a paper in *JAMA*, based on data from US Medicare beneficiaries, showing increased risks of several cardiovascular events, as well as all-cause mortality, in a comparison of rosiglitazone users with pioglitazone users [7]. Following these two publications, on 22 September 2010, the EMA recommended suspension of use of all rosiglitazone-containing products in the European Union [13]. The European Commission subsequently mandated suspension of the drug, citing absence of unique therapeutic benefits outweighing its risks [14].

Here we report results of an EMA-commissioned study on the impact of labelling changes and findings reported in scientific publications on utilisation of rosiglitazone-containing products in Europe. On the population level, we examined changes in use of rosiglitazone-containing products over the entire period when rosiglitazone was available on the market. On the patient level, we assessed the impact of rosiglitazone discontinuation on glycaemic control and reported oral hypoglycaemic agents prescribed after post-suspension discontinuation of rosiglitazone.

Methods

Setting and study population. This study was based on routinely collected data in Danish and United Kingdom (UK) medical databases. In Denmark, the study population included users of oral hypoglycaemic agents (OHAs) identified in the Aarhus University Prescription Database (AUPD) [15]. The database's catchment area covers the North and Central Regions of Denmark (hereafter referred to as 'northern Denmark'), with a combined population in mid-2010 of 1,834,595 persons, which is about one-third of the Danish population. The AUPD captures reimbursed prescriptions redeemed in the regions' outpatient pharmacies since 1998. In the UK, OHA users were identified from the General Practice Research Database (GPRD), currently also known as the Clinical Practice Research Datalink.

We identified patients in each database with a prescription for any OHA between 1 January 2000 and 31 December 2010, encompassing the entire period of rosiglitazone availability in Europe. We defined OHA users as persons ~~with~~ who received at least one ~~OHA~~ prescription for any OHA during the study period. Prescriptions for OHAs ~~, including rosiglitazone,~~ were identified using Anatomical Therapeutic Chemical (ATC) codes in the AUPD and Multilex codes in the GPRD ~~.~~. People could have received prescriptions for multiple OHAs during the study period, including rosiglitazone. Our use of the term 'rosiglitazone' includes all preparations of the drug.

Start of rosiglitazone use was defined as the date of the first-recorded prescription for a rosiglitazone-containing product. Patients were assumed to have discontinued rosiglitazone therapy in the absence of a record of a new rosiglitazone prescription during a period encompassing the estimated length of at least two prescriptions. Prescription length was estimated at 45 days in AUPD and 130 days in the GPRD, based on observed intervals between prescriptions and knowledge about typical clinical practice in Denmark, as well as the prescribing instructions in the British Monthly Index of Medications in the UK.

To describe the study population, we obtained data on participants' clinical and demographic characteristics, including sex, age, body mass index (BMI), smoking, medical diagnoses, and use of other medications (lipid-lowering agents, antihypertensive agents,

diuretics, nitrates, and antiplatelet agents). These characteristics were measured as of 1 January 2000 for patients who started an OHA before 2000 and on the date of the first OHA prescription for those who started thereafter. We used records from routine laboratory tests to obtain data on measured glycated haemoglobin-A_{1c} (HbA_{1c}) and fasting plasma glucose (FPG) levels.

Data sources. In northern Denmark, data on hospital-based medical diagnoses, prescription medications, and laboratory test results were obtained, respectively, from the Danish National Registry of Patients (DNRP [16]), from the AUPD, and from the Laboratory Information Systems of the North and the Central Denmark Regions (LABKA [17]). The LABKA database stores results of laboratory tests performed at hospital-based laboratories. Patients are referred to these laboratories by hospitals, general practitioners, and specialists. Data on smoking and BMI were obtained from the Danish National Indicator Project database (http://www.nip.dk). All data were linked on the individual level using the universal personal identifier [18]. The GPRD is a longitudinal database that has collected data from over 450 general practices in the UK since 1987, covering a representative 6% sample of the UK population. The GPRD captures prescriptions issued to patients by general practitioners, and it also includes information on patient demographics, diagnoses, referrals, hospitalizations, and laboratory test results [19-22].

Statistical analysis. First, we examined changes in the proportion of rosiglitazone users among all users of OHAs in the two countries between 2000 and 2010. Second, we compared distributions of demographic and clinical characteristics between rosiglitazone users and users of other OHAs. Third, we examined changes in HbA_{1c} and FPG levels, comparing values before and after discontinuation of rosiglitazone treatment. The pre-discontinuation value of a laboratory parameter was the value closest in time to the estimated discontinuation date within 24 months before that date. We defined three non-overlapping post-discontinuation periods as follows: 3 months (90–179 days post-discontinuation); 6 months (180–359 days post-discontinuation); and 12 months (360–479 days post-discontinuation). We used the earliest available measurement within each post-discontinuation period. The post-discontinuation

values were ascertained through 30 June 2011. Using the pre-discontinuation and post-discontinuation values, we calculated the mean (with standard deviation) level for HbA_{1c} and FPG before and after discontinuation and the mean change for each post-discontinuation period. Furthermore, we calculated the proportion of patients with new post-discontinuation onset of loss of glycaemic control, defined as of HbA_{1c} >7.5%, and the proportion of patients with new post-discontinuation onset of treatment failure, defined as FPG >10 mmol/L. To capture new onset, these proportions first were computed among patients without evidence of treatment failure/loss of glycaemic control before discontinuing rosiglitazone. We then calculated the proportions of patients with clinically meaningful changes in HbA_{1c} (change >0.6%) and FPG (change >10%) after discontinuation of rosiglitazone. Finally, we examined changes in HbA_{1c} levels in patients who discontinued the drug on or after 23 September 2010, presumably in response to the EMA's suspension of the drug, and reported the first OHA prescribed to patients who discontinued rosiglitazone after its suspension. The algorithms used to define variables in this project are provided in the Appendix. We used SAS software version 9.2 (SAS Inc., Cary, NC, USA) to analyse the data.

Ethical approval. This study was approved by the Danish Data Protection Agency (record number 2009-41-3866) and by the Independent Scientific Advisory Committee of the GPRD. There was no patient contact, and informed consent was therefore not required.

Results

During the study period, 67,525 OHA users were recorded in the AUPD and 191,276 in the GPRD. Of these, 2,321 (3.4%) persons in the AUPD and 25,428 (13%) persons in the GPRD received at least one prescription for a rosiglitazone-containing product. Figure 1 shows changes in the proportion of rosiglitazone users among all OHA users within the study period. This proportion peaked at 4% in northern Denmark and at 15% in the UK in May 2007, and rapidly decreased thereafter, with virtually no rosiglizatone users remaining after 2010.

Table 1 compares demographic and clinical characteristics of users of rosiglitazone and users of other OHAs. Rosiglitazone users tended to be younger, but were more likely to have had a prescription history of lipid-lowering or antihypertensive agents. Rosiglitazone users were more likely than the other OHA users to have used OHAs other than metformin and sulfonylurea previously. Based on data from the GPRD, users of rosiglitazone-containing products were slightly more likely than other OHA users to have a BMI of ≥30 kg/m^2 (Table 1).

Glycaemic control after discontinuation of rosiglitazone. Among all rosiglitazone users in the LABKA 1776 who discontinued the drug had HbA_{1c} measurements available. The mean duration of rosiglitazone use in these patients was 24.1months (standard deviation 21.1), median 18.8. In the GPRD there were 21145 rosiglitazone users with HbA_{1c} measurements. The mean duration of use in these patients was 30.3 (standard deviation 25.5), median, 24,0 . Table 2 shows changes in HbA_{1c} at three, six, and 12 months after discontinuation of rosiglitazone treatment at any time during the study period. At 12 months post-discontinuation, a change of similar magnitude in the mean HbA_{1c} was observed in both the LABKA (Denmark) and Laboratory (UK) databases: –0.16% (95% confidence interval [CI]: –3.4%, 3.1%) in northern Denmark, and –0.17% (95% CI: –0.21%, -0.13%) in the UK. Loss of glycaemic control, defined by new onset of HbA_{1c}>7.5%, was registered for up to 29% of patients during the 12-month follow-up period in Denmark and for up to 37% of patients in the UK. Similar proportions of patients had HbA_{1c} values consistent with a clinically meaningful decrease (>0.6%) at 12 months.

Table 3 shows changes in HbA_{1c} after discontinuation of rosiglitazone-containing products on or after 23 September 2010. Thus, Table 3 represents subset of patients described in Table 2. In the UK data, mean HbA1c decreased by 1.8% at six months post-discontinuation (95% CI: –2.1%, –1.6%), but the pre-discontinuation mean HbA_{1c} in this group was 10%. A larger proportion of patients in the UK than in Denmark had evidence of loss of glycaemic control and a substantially larger proportion of patients in the UK

experienced a clinically meaningful decrease in HbA1c after discontinuation of rosiglitazone compared with Denmark (Table 3).

Table 4 shows changes in FPG at three, six, and 12 months after discontinuation of rosiglitazone. At 12 months post-discontinuation, there was virtually no change seen in either of the databases: mean change = 0.01 mmol/L (95% CI: –7.3 mmol/L; 7.3 mmol/L) in Denmark and mean change = 0.03 mmol/L (95% CI: –0.22 mmol/L; 0.28 mmol/L) in the UK. Treatment failure, defined by new onset of FPG >10 mmol/L during one of the follow-up periods, was observed in a maximum of 23% of patients in Denmark and 20% in the UK. The number of persons with available measurements for Denmark, however, was small (Table 4). Table 5 shows the distribution of OHA prescribed to patients after terminating rosiglitazone on 23 September 2010 or later. The majority of patients switched to another OHA (82% in Denmark; 97% in the UK) after the last recorded pioglitazone prescription. The majority of patients – 56.8% in Denmark and 41.7% in the UK – received a prescription for meformin. In the UK, 23.6% of patients had a prescription for pioglitazone, and 14.5% for pioglitazone + metformin. Pioglitazone was prescribed only to 4.4% of the patients in northern Denmark.

Discussion

We examined use of rosiglitazone-containing products over the entire period of availability of this drug in Europe (2000–2010) using routinely collected data in medical databases in Denmark and the UK. Overall, the drug was more widely used in the UK than in Denmark, with the proportion of rosiglitazone users among all users of OHA peaking at 15% and 4% in the two countries, respectively. The timing of both peaks, which marked the beginning of a steep decline in use, coincided with the May 2007 publication of the meta-analysis by Nissen and Wolski [2] and subsequent regulatory warnings from the EMA. This decline occurred three years before the regulatory decision to suspend rosiglitazone in Europe. Similarly, a sharp decline in prescribing occurred in the United States after the FDA added a boxed warning to the rosiglitazone label in May 2007 [23]. On the patient level, discontinuation of rosiglitazone was associated with a slight overall decrease in the mean level of glycated

haemoglobin. However, close to one-third of patients had evidence consistent with loss of glycaemic control during the 12 months of follow-up, including patients who discontinued rosiglitazone after the EMA decision to suspend the drug. The majority of patients who discontinued rosiglitazone after suspension started receiving metformin.

While on the market, rosiglitazone represented a larger proportion of all OHA use in the UK than in Denmark. This may reflect conservative recommendations issued in Denmark, suggesting that treatment first be attempted with metformin, sulfonurea, and insulin [24]. Guidelines from the National Institute for Health and Clinical Excellence (NICE) in the UK stated that rosiglitazone should only be prescribed if other classes of OHA were not effective in lowering plasma glucose concentrations.Therefore rosiglitazone was recommended only as second or third line therapy [25]. The high pre-discontinuation level of HbA_{1c} in UK patients who discontinued rosiglitazone following the drug suspension is also consistent with this guideline. Among patients terminating rosiglitazone after the drug was suspended, a larger proportion of UK patients compared with their Danish counterparts experienced a clinically meaningful decrease in glycated haemoglobin. The pre-discontinuation values among the UK patients were substantially higher. We thus attribute this to the result of patients with poor glycaemic control coming to medical attention.

The data presented here were obtained from medical databases that provide data on routine and independent registration of health-related events in two European countries. Such data are likely to reflect typical clinical practice. The data from the two data systems are also complementary. The AUPD records filled prescriptions, while the GPRD records prescriptions issued by general practitioners. Furthermore, the databases draw on different health sectors for information on patient characteristics. In Denmark data on diagnoses originate from hospital discharge summaries, while GPRD data on diagnoses originate from general-practitioner records. Despite these differences and potential differences in the underlying patient populations, the results obtained from the two data systems were generally consistent.

Because OHA are distributed by prescription only and need to be taken long-term, the information we present on rosiglitazone utilization over calendar time is likely to be accurate.

The pattern of use for the two Danish regions mirrors the nationwide pattern reported by the Danish Medicines Agency [26]. However, because automated prescription records provide no information on timing of drug intake, we had to make assumptions about timing of rosiglitazone discontinuation and prescription length. We speculate that short-term changes in laboratory parameters following discontinuation of rosiglitazone are subject to more misclassification due to errors in assigning the discontinuation status than are long-term changes in these parameters. Therefore, our 12-month estimates of post-discontinuation change in laboratory parameters may be more robust than the 3-month estimates. The information on glycated haemoglobin A_{1c} and on fasting plasma glucose originated from routinely collected laboratory data, although patients with laboratory measurements may differ from the entire population of rosiglitazone-treated patients. For example, physicians may be less likely to routinely collect laboratory data for patients with less severe diabetes.

In summary, a decline in use of rosiglitazone occurred immediately following the May 2007 publication of a meta-analysis describing adverse cardiac side effects of this drug [2]. Changes in glycaemic control after discontinuation of rosiglitazone were small on average during the 12 month follow-up period, although about one-third of patients had evidence of loss of glycaemic control upon discontinuation. Most patients were switched to a metformin-containing regimen.

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Disclaimer

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Contribution statement

V. Ehrenstein participated in conception and design of the study, led the writing, and contributed to data analysis. R. K. Hernandez contributed to study design and data analysis in the GPRD. S. P. Ulrichsen conducted the data analyses in Denmark, J. Rungby contributed to study design and analysis, and provided clinical expertise, T.L. Lash participated in conception and design of the study, A.H. Riis contributed to data analysis of the AUPD data, L. Li contributed to data analysis of the GPRD data, H.T. Sørensen oversaw the study and provided clinical expertise, and S. S. Jick participated in conception and design of the study. All authors participated in revisions of the manuscript draft for intellectual content.

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Competing interest statement

All authors have completed the ICMJE uniform disclosure form at and declare: being funded by the EMA (through institutional contracts and subcontracts) for this work; no

financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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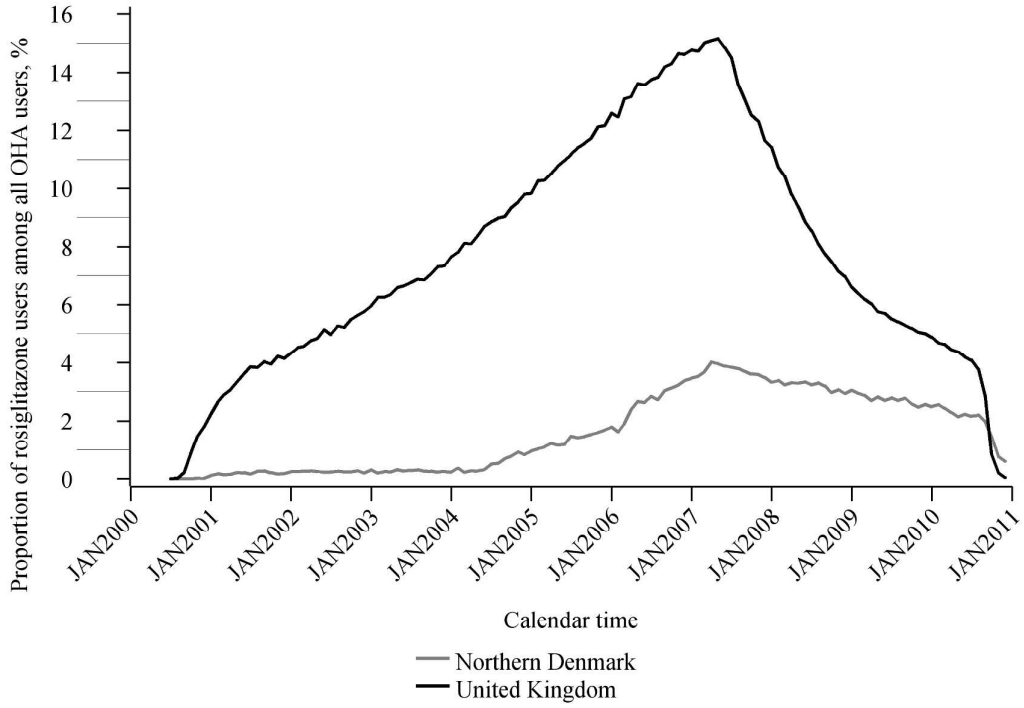
Figure 1. Proportion of users of rosiglitazone among all users of oral hypoglycaemic agents (OHA), 2000-2010.



Note: The maximum points of both graphs correspond to May 2007, the month of publication of the initial meta-analysis by Nissen and Wolski.[2]

Table 1. Baseline characteristics of patients treated with rosiglitazone and other oral hypoglycaemic agents from 1 January 2000 to 31 December 2010 in northern Denmark and the United Kingdom.

Characteristic	Northern Denmark (n=67,525)		United Kingdom (n=191,276)	
	Users of rosiglitazone (n=2,321) N (%)	Users of other oral hypoglycaemic agents (n=65,204) N (%)	Users of rosiglitazone (n=25,428) N (%)	Users of other oral hypoglycaemic agents (n=165,848) N (%)
Age group, years				
<35	83 (3.6)	3,999 (6.1)	589 (2.3)	9,358 (5.6)
35-44	286 (12)	4,967 (7.6)	2,469 (9.7)	13,192 (8.0)
45-54	595 (26)	10,219 (16)	5,513 (22)	25,023 (15)
55-64	757 (33)	16,751 (26)	7,661 (30)	38,668 (23)
65-74	444 (19)	15,724 (24)	6,434 (25)	42,030 (25)
75-84	147 (6.3)	10,423 (16)	2,426 (9.5)	28,430 (17)
≥85	9 (0.39)	3,121 (4.8)	336 (1.3)	9,147 (5.5)
Sex				
Female	976 (42)	30,845 (47)	11,259 (44)	78,772 (48)
Male	1,345 (58)	34,359 (53)	14,169 (56)	87,076 (53)
Charlson comorbidity index				
0	1,694 (73)	41,183 (63)	16,646 (65)	95,607 (58)
1-2	561 (24)	19,470 (30)	7,925 (31)	57,984 (35)
3+	66 (2.8)	4,551 (7.0)	857 (3.4)	12,257 (7.4)
History of OHA use before baseline*				
Metformin	2,279 (98)	51,022 (78)	23,836 (94)	144,881 (87)
Sulfonylurea	1,730 (74)	39,931 (61)	19,489 (77)	90,682 (55)
Pioglitazone	81 (3.5)	196 (0.30)	9,297 (37)	14,194 (8.6)
DPP 4 Inhibitor	517 (22)	4,149 (6.4)	2,242 (8.8)	5,882 (3.6)
Other oral glucose-lowering drugs**	497 (21)	5,530 (8.5)	2,582 (10)	5,725 (3.5)
History of other medication use				
Lipid lowering agents	1,939 (84)	40,327 (62)	22,223 (87)	114,378 (69)

Antihypertensive agents	1,991 (86)	48,016 (74)	21,846 (86)	126,897 (77)
Diuretics	1,404 (60)	34,650 (53)	13,516 (53)	73,225 (44)
Nitrates	351 (15)	9,456 (14)	52 (0.20)	322 (0.19)
Antiplatelet agents	1,409 (61)	33,060 (51)	2,878 (11)	15,223 (9.2)
Smoking				
Current	175 (7.5)	2,451 (3.8)	4,499 (18)	28,120 (17)
Former	215 (9.3)	3,121 (4.8)	6,102 (24)	43,985 (27)
Never	258 (11)	3,534 (5.4)	11,699 (46)	75,119 (45)
Missing	1,673 (72)	56,098 (86)	3,128 (12)	18,624 (11)
Body mass index category, kg/m^2				
< 18.5	2 (0.09)	32 (0.05)	35 (0.14)	623 (0.38)
18.5 – <25	51 (2.2)	1,257 (1.9)	2,675 (11)	21,634 (13)
25 – <30	177 (7.6)	3,257 (5.0)	7,458 (29)	49,463 (30)
≥ 30	462 (20)	5,454 (8.4)	11,225 (44)	66,725 (40)
Missing	1,629 (70)	55,204 (85)	4,035 (16)	27,403 (17)

*Baseline date was January 1, 2000 or date of first OHA prescription, whichever came later.
**Other glucose-lowering drugs excluding insulins are acarbose, repaglinide, exenatide, and liraglutide.

Table 2. Glycated haemoglobin (%) before and after discontinuation of rosiglitazone among patients with available pre-and post-discontinuation measurements, in northern Denmark and in the United Kingdom, 2000-2011.

Characteristic	Northern Denmark			United Kingdom		
	3 months (n=1,242)	6 months (n=1,496)	12 months (n=1,162)	3 months (n=9,448)	6 months (n=12,439)	12 months (n=8,635)
Baseline mean (SD)	7.8 (1.7)	7.8 (1.6)	7.9 (1.7)	8.7 (2.2)	8.5 (2.1)	8.4 (1.9)
Follow-up mean (SD)	7.7 (1.5)	7.7 (1.5)	7.7 (1.5)	8.1 (1.7)	8.2 (1.8)	8.2 (1.8)
Change from baseline, mean (95% CI)	-0.10 (-3.0; 2.8)	-0.05 (-3.1; 3.0)	-0.16 (-3.4; 3.1)	-0.57 (-0.62; -0.53)	-0.30 (-0.34; -0.26)	-0.17 (-0.21; -0.13)
Proportion with a clinically meaningful* increase, percent (95% CI)	26 (24; 29)	28 (26; 30)	28 (26; 31)	23 (22; 24)	28 (27; 28)	29 (28; 30)
Proportion with a clinically meaningful* decrease, percent (95% CI)	28 (25; 30)	27 (25; 29)	30 (27; 32)	40 (39; 41)	36 (35; 37)	34 (33; 35)
N with HbA_{1c} level>7.5% after baseline/N with baseline HbA_{1c} ≤7.5%	160/670	228/827	179/610	1,026/3,286	1,641/4,672	1,246/3,408
New post-discontinuation onset of loss of glycaemic control with HbA_{1c} >7.5%, percent (95% CI)[b]	24 (21; 27)	28 (25; 31)	29 (26; 33)	31 (30; 33)	35 (34; 36)	37 (35; 38)

*Clinically meaningful change defined using to the European Medicines Agency's definition as change of more than 0.6% (% is the test unit)
CI=confidence interval; HbA_{1c}=glycated haemoglobin A; SD=standard deviation

Table 3. Glycated haemoglobin (%) before and after discontinuation of rosiglitazone-containing products, among users who discontinued the drug on or after 23 September 2010 (date of the EMA's recommendation to suspend rosiglitazone), in northern Denmark and in the United Kingdom.

Characteristic	Northern Denmark		United Kingdom	
	3 months (n=376)	6 months (n=455)	3 months (n=1081)	6 months (n=338)
Baseline mean (SD)	7.1 (1.2)	7.1 (1.2)	10 (2.5)	10 (2.5)
Follow-up mean (SD)	7.5 (1.5)	7.4 (1.4)	8.0 (2.0)	8.3 (2.1)
Change from baseline, mean (95% CI)	0.40 (-1.9; 2.7)	0.34 (-1.8; 2.5)	-2.0 (-2.2; -1.8)	-1.8 (-2.1; -1.6)
Proportion with a clinically meaningful increase[a], percent (95% CI)	34 (29;38)	33 (29;38)	14 (12; 16)	15 (12; 19)
Proportion with a clinically meaningful decrease[a], percent (95% CI)	13 (9.5; 16)	12 (9.3; 15)	72 (69; 75)	69 (64; 74)
N with HbA_{1c} level>7.5% after baseline/N with baseline HbA_{1c} ≤7.5%	76/285	94/350	87/196	18/55
New post-discontinuation onset of loss of glycaemic control with HbA_{1c} >7.5%, percent (95% CI)[b]	27 (22; 32)	27 (22; 32)	44 (38;51)	33 (22; 46)

[a]Clinically meaningful change defined using to the European Medicines Agency's definition as change of more than 0.6% (% is the test unit)

CI=confidence interval; HbA_{1c}=glycated haemoglobin A; SD=standard deviationnce interval

Table 4. Fasting plasma glucose (mmol/L) before and after discontinuation of rosiglitazone among patients with available pre-and post-discontinuation laboratory measurements, in northern Denmark and in the United Kingdom, 2000-2011.

Characteristic	Northern Denmark			United Kingdom		
	3 months (n=95)	6 months (n=109)	12 months (n=77)	3 months (n=820)	6 months (n=1,256)	12 months (n=800)
Baseline mean (SD)	9.5 (3.6)	9.3 (3.4)	9.1 (3.5)	8.6 (3.2)	8.7 (3.2)	8.7 (3.4)
Follow-up mean (SD)	9.2 (3.7)	9.0 (3.4)	9.1 (3.5)	8.8 (3.2)	8.8 (3.1)	8.7 (3.1)
Change from baseline, mean (95% CI)	-0.38 (-9.0; 8.2)	-0.27 (-8.2;7.6)	0.01 (-7.3; 7.3)	0.27 (0.04; 0.49)	0.08 (-0.12; 0.27)	0.03 (-0.22; 0.28)
Proportion with a clinically meaningful increase*, percent (95% CI)	40 (31; 50)	35 (26; 44)	32 (23; 43)	39 (36; 43)	40 (38; 43)	40 (37; 44)
Proportion with a clinically meaningful decrease*, percent (95% CI)	39 (30; 49)	35 (26; 44)	40 (30; 51)	30 (27; 33)	33 (31; 36)	34 (31; 38)
N with FPG >10 mmol/L after baseline/N with baseline FPG ≤10 mmol/L	14/65	18/79	8/54	98/610	182/911	99/583
New post-discontinuation onset of treatment failure, FPG>10 mmol/L, percent (95% CI)	22 (13; 33)	23 (15; 33)	15 (7.3; 26)	16 (13, 19)	20 (18; 23)	17 (14; 20)

*Clinically meaningful change defined using to the European Medicines Agency's definition as change of more than 10 mmol/L.
CI=confidence interval; HbA_{1c}=glycated haemoglobin A; SD=standard deviation

Table 5. Oral hypoglycaemic agents (OHA) prescribed to patients after terminating rosiglitazone on 23 September 2010 or later.

	Aarhus University Prescription Database, Denmark (n=474*)		General Practice Research Database, United Kingdom (n=2810**)	
	Number	Percent (95% CI)	Number	Percent (95% CI)
Metformin	269	56.8 (52.3; 61.2)	1,136	41.7 (39.9; 43.6)
Glimepiride	84	17.7 (14.3; 21.2)	57	2.1 (1.6; 2.7)
Metformin+sitagliptin	49	10.3 (7.6; 13.1)		
Sitagliptin	45	9.5 (6.9; 12.1)	103	3.8 (3.1; 4.6)
Metformin+vildagliptin	35	7.4 (5.0; 9.7)		
Liraglutide	26	5.5 (3.4; 7.5)		
Pioglitazone	21	4.4 (2.6; 6.3)	641	23.6 (22.0; 25.2)
Pioglitazone + metformin			394	14.5 (13.2; 15.9)
Gliclazide	17	3.6 (1.9; 5.3)	351	12.9 (11.7; 14.2)
Glibenclamide	8	1.7 (0.5; 2.8)	16	0.6 (0.4; 1.0)
Saxagliptin	8	1.7 (0.5; 2.8)		
Glipizide	4	0.8 (0.1; 1.7)	9	0.3 (0.2; 0.6)
Vildagliptin	4	0.8 (0.1; 1.7)		
Repaglinide	3	0.6 (0.1; 1.3)	2	0.1 (0.0; 0.3)
Exenatide	3	0.6 (0.1; 1.3)		
Acarbose	2	0.4 (0.1; 1.0)	4	0.2 (0.1; 0.4)
Tolbutamide	1	0.2 (0.1; 0.6)	9	0.3 (0.2; 0.6)

*83 patients had no record of another OHA after the last rosiglitazone prescription.
**88 patients had no record of another OHA after the last rosiglitazone prescription

Rosiglitazone use and post-discontinuation glycaemic control in two European countries, 2000-2010

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Rosiglitazone use and post-discontinuation glycaemic control in two European countries, 2000-2010

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Article summary

Article focus

- Rosiglitazone is a second-line oral hypoglycaemic agent, which was sold in the European Union starting in 2000; after a series of regulatory decisions, its use was first restricted and ultimately suspended in Europe, in September of 2010
- This study examines utilization of rosiglitazone in Denmark and the United Kingdom (UK) in 2000-2010
- On the patient level, this study explores changes in glycaemic control following discontinuation of rosiglitazone

Key messages

- Following a 2007 publication of a meta-analysis showing increased cardiovascular morbidity associated with rosiglitazone, use of the drug declined sharply and irreversibly in Denmark and in the UK; this predated the official suspension of the drug by the European Medicines Agency, in 2010
- On the patient level, observed mean changes in fasting plasma glucose and glycated haemoglobin A_{1c} were slight in patients who discontinued rosiglitazone

Strengths and limitations of this study

- The study makes use of population-based routine medical databases in two European countries, which are likely to reflect typical clinical practice
- Despite differences in record generation mechanisms in the two databases, results were overall concordant
- Automated prescription and dispensation data may have imprecisely measured time of initiation and discontinuation of medication intake

Abstract

Objectives To evaluate the impact of risk minimisation policies on use of rosiglitazone-containing products and on glycaemic control among patients in Denmark and the United Kingdom (UK).

Design, setting and participants We used population-based data from the Aarhus University Prescription Database (AUPD), in northern Denmark and from the General Practice Research Database (GPRD), in the UK.

Main outcome measures We examined use of rosiglitazone during its entire period of availability on the European market (2000–2010) and evaluated changes in glycated haemoglobin-A_{1c} (HbA_{1c}) and fasting plasma glucose (FPG) levels among patients discontinuing this drug.

Results During 2000–2010, 2321 patients with records in the AUPD used rosiglitazone in northern Denmark and 25,428 patients with records in the GPRD used it in the UK. The proportion of rosiglitazone users among all users of oral hypoglycaemic agents (OHA) peaked at 4% in the AUPD and at 15% in the GPRD, in May 2007, the month of publication of a meta-analysis showing increased cardiovascular morbidity associated with rosiglitazone use. Twelve months after discontinuation of rosiglitazone-containing products, the mean change in HbA_{1c} was –0.16% (95% confidence interval [CI]: –3.4%, 3.1%) in northern Denmark and –0.17% (95% CI: –0.21%, 0.13%) in the UK. Corresponding mean changes in FPG were 0.01 mmol/L (95% CI: –7.3 mmol/L, 7.3 mmol/L) and 0.03 mmol/L (95% CI: –0.22 mmol/L, 0.28 mmol/L).

Conclusions Publication of evidence concerning potential cardiovascular risks of rosiglitazone was associated with an irreversible decline in use of rosiglitazone-containing products in Denmark and the UK. Mean changes in HbA_{1c} and FPG after drug discontinuation were slight.

INTRODUCTION

Since first marketed in the European Union, in 2000, rosiglitazone has been subject to several risk-benefit assessments, especially concerning cardiovascular safety.[1-9] In a May 2007 meta-analysis published in the *New England Journal of Medicine*, Nissen and Wolski reported increased cardiovascular morbidity associated with rosiglitazone use[2]. In 2008, the European Medicines Agency (EMA) amended the rosiglitazone product label, adding coronary syndrome to the list of contraindications and inserting a warning about potentially increased risk of ischemic events.[10] At the time of this label amendment, EMA concluded "that the benefits of [...] rosiglitazone [...] in the treatment of type 2 diabetes continue to outweigh their risks".[11] In June 2010, Nissen and Wolski updated their meta-analysis, confirming the finding of an increased risk of myocardial infarction (but not the original finding of increased all-cause mortality) in association with rosiglitazone use[12]. In July 2010, Graham and colleagues published a paper in *JAMA*, based on data from US Medicare beneficiaries, showing increased risks of several cardiovascular events, as well as all-cause mortality, in a comparison of rosiglitazone users with pioglitazone users.[7] Following these two publications, on 22 September 2010, the EMA recommended suspension of use of all rosiglitazone-containing products in the European Union.[13] The European Commission subsequently mandated suspension of the drug, citing absence of unique therapeutic benefits outweighing its risks.[14]

Here we report results of an EMA-commissioned study on the impact of labelling changes and findings reported in scientific publications on utilisation of rosiglitazone-containing products in Europe. On the population level, we examined changes in use of rosiglitazone-containing products over the entire period when rosiglitazone was available on the European market. On the patient level, we assessed the impact of rosiglitazone discontinuation on glycaemic control and reported oral hypoglycaemic agents prescribed after post-suspension discontinuation of rosiglitazone.

METHODS

Setting and study population

This study was based on routinely collected data in medical databases in Denmark and in the United Kingdom (UK). In Denmark, the study population included users of oral hypoglycaemic agents (OHAs) identified in the Aarhus University Prescription Database (AUPD).[15] The database's catchment area covers the North and Central Regions of Denmark (hereafter referred to as 'northern Denmark'), with a combined population in mid-2010 of 1.8 million persons, which is about one-third of the Danish population. The AUPD captures reimbursed prescriptions redeemed in the regions' outpatient pharmacies since 1998. In the UK, OHA users were identified from the General Practice Research Database (GPRD), currently also known as the Clinical Practice Research Datalink.[16]

We identified patients in each database with a prescription for any OHA between 1 January 2000 and 31 December 2010, encompassing the entire period of rosiglitazone availability in Europe. We defined OHA users as persons who received at least one prescription for any OHA during the study period. Prescriptions for OHAs were identified using Anatomical Therapeutic Chemical (ATC) codes in the AUPD and Multilex codes in the GPRD. People could receive prescriptions for multiple OHAs, including rosiglitazone, during the study period. Our use of the term 'rosiglitazone' includes all preparations of the drug.

Start of rosiglitazone use was defined as the date of the first-recorded prescription for a rosiglitazone-containing product. Patients were assumed to have discontinued rosiglitazone therapy in the absence of a record of a rosiglitazone prescription refill during a period encompassing the estimated length of at least two prescriptions. Prescription length was estimated at 45 days in AUPD and 130 days in the GPRD, based on observed intervals between prescriptions and knowledge about typical prescribing practice in Denmark, as well as on the prescribing instructions in the British Monthly Index of Medications in the UK.

To describe the study population, we obtained data on participants' clinical and demographic characteristics, including sex, age, body mass index (BMI), smoking, medical

diagnoses, and use of other medications (lipid-lowering agents, antihypertensive agents, diuretics, nitrates, and antiplatelet agents). These characteristics were measured as of 1 January 2000 for patients who started an OHA before 2000 and on the date of the first OHA prescription for those who started thereafter. We used records from routine laboratory tests to obtain data on measured glycated haemoglobin-A_{1c} (HbA_{1c}) and fasting plasma glucose (FPG) levels.

Data sources

In northern Denmark, data on hospital-based medical diagnoses, prescription medications, and laboratory test results were obtained, respectively, from the Danish National Registry of Patients (DNRP[17]), from the AUPD, and from the Laboratory Information Systems of the North and the Central Denmark Regions (the LABKA database[18]). The LABKA database stores results of laboratory tests performed at hospital-based laboratories. Patients are referred to these laboratories by hospitals, general practitioners, and specialists. Data on smoking and BMI were obtained from the Danish National Indicator Project diabetes database.[19] All data were linked on the individual level using the universal personal identifier.[20] In the UK all data were obtained from the GPRD. The GPRD is a longitudinal database that has collected data from over 450 general practices in the UK since 1987, covering a representative 6% sample of the UK population. The GPRD captures prescriptions issued to patients by general practitioners, and it also includes information on patient demographics, diagnoses, referrals, hospitalizations, and laboratory test results.[16 21-23]

Statistical analysis

First, we examined changes in the proportion of rosiglitazone users among all users of OHAs in the two countries between 2000 and 2010. Second, we compared distributions of demographic and clinical characteristics between rosiglitazone users and users of other OHAs. Third, we examined changes in HbA_{1c} and FPG levels, comparing values before and after discontinuation of rosiglitazone treatment. The pre-discontinuation value of a laboratory parameter was the value closest in time to the estimated discontinuation date within 24 months before that date. We defined three non-overlapping post-discontinuation periods as follows: 3

months (90–179 days); 6 months (180–359 days); and 12 months (360–479 days). We used the earliest available measurement within each post-discontinuation period. The post-discontinuation values were ascertained through 30 June 2011. We calculated the mean (with standard deviation) level for HbA_{1c} and FPG before and after discontinuation and the mean change for each post-discontinuation period. Furthermore, we calculated the proportion of patients with new post-discontinuation onset of loss of glycaemic control, defined as HbA_{1c} >7.5%; and the proportion of patients with new post-discontinuation onset of treatment failure, defined as FPG >10 mmol/L. To capture new onset, these proportions were computed among patients without evidence of treatment failure/loss of glycaemic control before discontinuing rosiglitazone. We then calculated the proportions of patients with clinically meaningful changes in HbA_{1c} (change >0.6%) and FPG (change >10%) after discontinuation of rosiglitazone. Finally, we examined changes in HbA_{1c} levels in patients who discontinued the drug on or after 23 September 2010, presumably in response to the EMA's suspension of the drug. We also reported the distribution of the first OHA prescribed after rosiglitazone suspension. The algorithms used to define variables in this project are provided in the Appendix. We used SAS software version 9.2 (SAS Inc., Cary, NC, USA) to analyse the data.

Ethical approval

This study was approved by the Danish Data Protection Agency (record number 2009-41-3866) and by the Independent Scientific Advisory Committee of the GPRD. There was no patient contact, and informed consent was therefore not required.

RESULTS

Utilisation of rosiglitazone and patient characteristics

During the study period, 67,525 OHA users were recorded in the AUPD and 191,276 in the GPRD. Of these, 2,321 (3.4%) persons in the AUPD and 25,428 (13%) persons in the GPRD received at least one prescription for a rosiglitazone-containing product. Figure 1 shows changes in the proportion of rosiglitazone users among all OHA users during the study period. This proportion peaked at 4% in northern Denmark and at 15% in the UK in May

2007, and rapidly decreased thereafter, with virtually no rosiglitazone users remaining after 2010.

Table 1 compares demographic and clinical characteristics of users of rosiglitazone with users of other OHAs. Rosiglitazone users tended to be younger, but were more likely to have had a prescription history of lipid-lowering or antihypertensive agents. Rosiglitazone users were more likely than the other OHA users to have used OHAs other than metformin and sulfonylurea before starting rosiglitazone. Based on data from the GPRD, users of rosiglitazone-containing products were slightly more likely than other OHA users to have a BMI of ≥30 kg/m^2. BMI data for patients in Denmark were sparse (Table 1).

Glycaemic control after discontinuation of rosiglitazone

Among all rosiglitazone users in the AUPD, 1776 patients who discontinued the drug had HbA_{1c} measurements. Among these patients, the median duration of rosiglitazone use was 19 months (quartiles, 6–38 months), and the median time from the last pre-discontinuation HbA_{1c} measurement until discontinuation of rosiglitazone was 44 days (quartiles, 21–78 days). In the GPRD, there were 21,145 rosiglitazone users with HbA_{1c} measurements. Among these patients, the median duration of rosiglitazone use was 24 months (quartiles, 8–47 months) and the median time from the last pre-discontinuation HbA_{1c} measurement until discontinuation of rosiglitazone was 70 days (quartiles, 25–153 days). Table 2 shows changes in HbA_{1c} at three, six, and 12 months after discontinuation of rosiglitazone treatment at any time during the study period. At 12 months post-discontinuation, a change of similar magnitude in the mean HbA_{1c} was observed in both databases: –0.16% (95% confidence interval [CI]: –3.4%, 3.1%) in northern Denmark, and –0.17% (95% CI: –0.21%, -0.13%) in the UK. Loss of glycaemic control, defined by new onset of HbA_{1c}>7.5%, was registered for up to 29% of patients during the 12-month follow-up period in Denmark and for up to 37% of patients in the UK. Similar proportions of patients had HbA_{1c} values consistent with a clinically meaningful decrease (>0.6%) at 12 months post-discontinuation.

Table 3 shows changes in HbA_{1c} among patients who discontinued rosiglitazone-containing products on or after 23 September 2010. Thus, Table 3 represents subset of patients

described in Table 2. In the UK data, mean HbA_{1c} decreased by 1.8% (95% CI: –2.1%, –1.6%) at six months post-discontinuation, but the pre-discontinuation mean HbA_{1c} in this group was 10%. A larger proportion of patients in the UK than in Denmark had evidence of loss of glycaemic control and a substantially larger proportion of patients in the UK experienced a clinically meaningful decrease in HbA_{1c} after discontinuation of rosiglitazone compared with Denmark (Table 3).

Table 4 shows changes in FPG at three, six, and 12 months after discontinuation of rosiglitazone. At 12 months, there was virtually no change seen in either of the databases: mean change of 0.01 mmol/L (95% CI: –7.3 mmol/L; 7.3 mmol/L) in northern Denmark, and mean change of 0.03 mmol/L (95% CI: –0.22 mmol/L; 0.28 mmol/L) in the UK. Treatment failure, defined by new onset of FPG >10 mmol/L during one of the follow-up periods, was observed in a maximum of 23% of patients in northern Denmark and 20% in the UK. The number of persons with available measurements for northern Denmark, however, was small (Table 4). Table 5 shows the distribution of OHA prescribed to patients who discontinued rosiglitazone on 23 September 2010 or later. The majority of the patients switched to another OHA (82% in northern Denmark; 97% in the UK) after the last recorded rosiglitazone prescription. The majority of patients – 56.8% in Denmark and 41.7% in the UK – received a prescription for metformin. In the UK, 23.6% of patients had a prescription for pioglitazone, and 14.5% for pioglitazone and metformin. Pioglitazone was prescribed only to 4.4% of the patients in northern Denmark.

DISCUSSION

We examined use of rosiglitazone-containing products over the entire period of availability of this drug in Europe (2000–2010) using routinely collected data in medical databases in Denmark and in the United Kingdom. Overall, the drug was more widely used in the UK than in Denmark, with the proportion of rosiglitazone users among all users of OHA peaking at 15% and 4% in the two countries, respectively. The timing of both peaks, which marked the beginning of a steep decline in use, coincided with the May 2007 publication of

the meta-analysis by Nissen and Wolski[2] and subsequent regulatory warnings from the EMA. This decline occurred three years before the regulatory decision to suspend rosiglitazone in Europe. Similarly, a sharp decline in prescribing occurred in the United States after the FDA added a boxed warning to the rosiglitazone label in May 2007.[24] On the patient level, discontinuation of rosiglitazone was associated with a slight overall decrease in the mean level of glycated haemoglobin. However, close to one-third of patients had evidence consistent with loss of glycaemic control during the 12 months of follow-up, including patients who discontinued rosiglitazone after the EMA decision to suspend the drug. Most patients who discontinued rosiglitazone after the EMA-mandated suspension started receiving metformin.

Meaning of the findings

While on the market, rosiglitazone represented a larger proportion of all OHA use in the UK than in Denmark. This may reflect conservative recommendations issued in Denmark, suggesting that treatment first be attempted with metformin, sulfonurea, and insulin.[25] Guidelines from the National Institute for Health and Clinical Excellence (NICE) in the UK stated that rosiglitazone should only be prescribed if other classes of OHA were not effective in lowering plasma glucose concentrations. Therefore rosiglitazone was recommended only as second or third line therapy.[26] The high pre-discontinuation level of HbA_{1c} in UK patients who discontinued rosiglitazone following the drug suspension is also consistent with this guideline. Among patients terminating rosiglitazone after the drug was suspended, a larger proportion of UK patients compared with their Danish counterparts experienced a clinically meaningful decrease in glycated haemoglobin. The pre-discontinuation values among the UK patients were substantially higher, probably reflecting heightened medical attention drawn to patients with poor glycaemic control.

Strengths and weaknesses

The data presented here were obtained from medical databases containing data on routine and independent registration of health-related events in two European countries. Such data are therefore likely to reflect typical clinical practice. The data from the two data systems are also complementary. The AUPD records purchased prescriptions, while the GPRD records

prescriptions issued by general practitioners. Furthermore, the databases draw on different health sectors for information on patient characteristics: in Denmark data on diagnoses originate from hospital discharge summaries, while in the GPRD, data on diagnoses originate from general-practitioner records. Despite these differences and potential differences in the underlying patient populations, the results obtained from the two countries were generally consistent.

Because OHA are distributed by prescription only and need to be taken long-term, the information we present on rosiglitazone utilization over calendar time is likely to be accurate. The pattern of use for the two Danish regions included here mirrors the nationwide pattern reported by the Danish Medicines Agency.[27] However, because automated prescription records provide no information on the exact timing of drug intake, we had to make assumptions about timing of rosiglitazone discontinuation and prescription length. We speculate that short-term changes in laboratory parameters following discontinuation of rosiglitazone are subject to more misclassification due to errors in assigning the discontinuation status than are long-term changes in these parameters. Therefore, our 12-month estimates of post-discontinuation change in laboratory parameters may be more robust than the 3-month estimates. The information on glycated haemoglobin A_{1c} and on fasting plasma glucose originated from routinely collected laboratory data, although patients with laboratory measurements may differ from the entire population of rosiglitazone-treated patients. For example, physicians may be less likely to routinely collect laboratory data for patients with less severe diabetes.

Conclusion

In summary, a decline in use of rosiglitazone occurred immediately following the May 2007 publication of a meta-analysis describing adverse cardiac side effects of this drug. Changes in glycaemic control were, on average, small during 12 months after discontinuation of rosiglitazone, although about one-third of patients had evidence of loss of glycaemic control upon discontinuation. Most patients who discontinued rosiglitazone after EMA-mandated suspension were switched to a metformin-containing regimen.

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DISCLAIMER

This document expresses the opinions of the authors of the paper, and may not be understood or quoted as being made on behalf or of reflecting the position of the European Medicines Agency or one of its committees or working parties.

CONTRIBUTION STATEMENT

V. Ehrenstein participated in conception and design of the study, led the writing, and contributed to data analysis. R. K. Hernandez contributed to study design and data analysis in the GPRD. S. P. Ulrichsen conducted the data analyses in Denmark, J. Rungby contributed to study design and analysis, and provided clinical expertise, T.L. Lash participated in conception and design of the study, A.H. Riis contributed to data analysis of the AUPD data, L. Li contributed to data analysis of the GPRD data, H.T. Sørensen oversaw the study and provided clinical expertise, and S. S. Jick participated in conception and design of the study. All authors participated in revisions of the manuscript draft for intellectual content.

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Competing interest statement

All authors have completed the ICMJE uniform disclosure form at and declare: being funded by the EMA (through institutional contracts and subcontracts) for this work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Data Sharing

Additional unpublished data from the study relate to changes in glycaemic control before suspension of rosiglitazone in the EU. The data are available to the investigators and from the investigators, upon request.

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FIGURE LEGEND

Figure 1. Proportion of users of rosiglitazone among all users of oral hypoglycaemic agents (OHA), 2000-2010 in northern Denmark and in the United Kingdom The maximum points of both graphs correspond to May 2007, the month of publication of the initial meta-analysis by Nissen and Wolski.[2]

TABLES

Table 1. Baseline characteristics of patients treated with rosiglitazone and other oral hypoglycaemic agents from 1 January 2000 to 31 December 2010 in northern Denmark and the United Kingdom.

Characteristic	Northern Denmark (n=67,525)		United Kingdom (n=191,276)	
	Users of rosiglitazone (n=2,321) N (%)	Users of other oral hypoglycaemic agents (n=65,204) N (%)	Users of rosiglitazone (n=25,428) N (%)	Users of other oral hypoglycaemic agents (n=165,848) N (%)
Age group, years				
<35	83 (3.6)	3999 (6.1)	589 (2.3)	9358 (5.6)
35-44	286 (12)	4967 (7.6)	2469 (9.7)	13,192 (8.0)
45-54	595 (26)	10,219 (16)	5513 (22)	25,023 (15)
55-64	757 (33)	16,751 (26)	7661 (30)	38,668 (23)
65-74	444 (19)	15,724 (24)	6434 (25)	42,030 (25)
75-84	147 (6.3)	10,423 (16)	2426 (9.5)	28,430 (17)
≥85	9 (0.39)	3121 (4.8)	336 (1.3)	9147 (5.5)
Sex				
Female	976 (42)	30,845 (47)	11,259 (44)	78,772 (48)
Male	1345 (58)	34,359 (53)	14,169 (56)	87,076 (53)
Charlson comorbidity index				
0	1694 (73)	41,183 (63)	16,646 (65)	95,607 (58)
1-2	561 (24)	19,470 (30)	7925 (31)	57,984 (35)
3+	66 (2.8)	4551 (7.0)	857 (3.4)	12,257 (7.4)
History of OHA use before baseline*				
Metformin	2279 (98)	51,022 (78)	23,836 (94)	144,881 (87)
Sulfonylurea	1730 (74)	39,931 (61)	19,489 (77)	90,682 (55)
Pioglitazone	81 (3.5)	196 (0.30)	9297 (37)	14,194 (8.6)
DPP 4 Inhibitor	517 (22)	4149 (6.4)	2242 (8.8)	5882 (3.6)
Other oral glucose-lowering drugs**	497 (21)	5530 (8.5)	2582 (10)	5725 (3.5)
History of other medication use				
Lipid lowering agents	1939 (84)	40,327 (62)	22,223 (87)	114,378 (69)

Antihypertensive agents	1991 (86)	48,016 (74)	21,846 (86)	126,897 (77)
Diuretics	1404 (60)	34,650 (53)	13,516 (53)	73,225 (44)
Nitrates	351 (15)	9456 (14)	52 (0.20)	322 (0.19)
Antiplatelet agents	1409 (61)	33,060 (51)	2878 (11)	15,223 (9.2)
Smoking				
Current	175 (7.5)	2451 (3.8)	4499 (18)	28,120 (17)
Former	215 (9.3)	3121 (4.8)	6102 (24)	43,985 (27)
Never	258 (11)	3534 (5.4)	11,699 (46)	75,119 (45)
Missing	1673 (72)	56,098 (86)	3128 (12)	18,624 (11)
Body mass index category, kg/m^2				
< 18.5	2 (0.09)	32 (0.05)	35 (0.14)	623 (0.38)
18.5 – <25	51 (2.2)	1257 (1.9)	2675 (11)	21,634 (13)
25 – <30	177 (7.6)	3257 (5.0)	7458 (29)	49,463 (30)
≥ 30	462 (20)	5454 (8.4)	11,225 (44)	66,725 (40)
Missing	1629 (70)	55,204 (85)	4035 (16)	27,403 (17)

*Baseline date was January 1, 2000 or date of first OHA prescription, whichever came later.
**Other glucose-lowering drugs excluding insulins are acarbose, repaglinide, exenatide, and liraglutide.

Table 2. Glycated haemoglobin (%) before and after discontinuation of rosiglitazone among patients with available pre-and post-discontinuation measurements, in northern Denmark and in the United Kingdom, 2000-2011.

Characteristic	Northern Denmark			United Kingdom		
	3 months (n=1242)	6 months (n=1496)	12 months (n=1162)	3 months (n=9448)	6 months (n=12,439)	12 months (n=8635)
Baseline mean (SD)	7.8 (1.7)	7.8 (1.6)	7.9 (1.7)	8.7 (2.2)	8.5 (2.1)	8.4 (1.9)
Follow-up mean (SD)	7.7 (1.5)	7.7 (1.5)	7.7 (1.5)	8.1 (1.7)	8.2 (1.8)	8.2 (1.8)
Change from baseline, mean (95% CI)	-0.10 (-3.0; 2.8)	-0.05 (-3.1; 3.0)	-0.16 (-3.4; 3.1)	-0.57 (-0.62; -0.53)	-0.30 (-0.34; -0.26)	-0.17 (-0.21; -0.13)
Proportion with a clinically meaningful* increase, percent (95% CI)	26 (24; 29)	28 (26; 30)	28 (26; 31)	23 (22; 24)	28 (27; 28)	29 (28; 30)
Proportion with a clinically meaningful* decrease, percent (95% CI)	28 (25; 30)	27 (25; 29)	30 (27; 32)	40 (39; 41)	36 (35; 37)	34 (33; 35)
N with HbA_{1c} level>7.5% after baseline/N with baseline HbA_{1c} ≤7.5%	160/670	228/827	179/610	1,026/3,286	1,641/4,672	1,246/3,408
New post-discontinuation onset of loss of glycaemic control with HbA_{1c} >7.5%, percent (95% CI)[b]	24 (21; 27)	28 (25; 31)	29 (26; 33)	31 (30; 33)	35 (34; 36)	37 (35; 38)

*Clinically meaningful change defined using to the European Medicines Agency's definition as change of more than 0.6% (% is the test unit)

CI, confidence interval; HbA_{1c},glycated haemoglobin A; SD, standard deviation

Table 3. Glycated haemoglobin (%) before and after discontinuation of rosiglitazone-containing products, among users who discontinued the drug on or after 23 September 2010 (date of the EMA's recommendation to suspend rosiglitazone), in northern Denmark and in the United Kingdom.

Characteristic	Northern Denmark		United Kingdom	
	3 months (n=376)	6 months (n=455)	3 months (n=1081)	6 months (n=338)
Baseline mean (SD)	7.1 (1.2)	7.1 (1.2)	10 (2.5)	10 (2.5)
Follow-up mean (SD)	7.5 (1.5)	7.4 (1.4)	8.0 (2.0)	8.3 (2.1)
Change from baseline, mean (95% CI)	0.40 (-1.9; 2.7)	0.34 (-1.8; 2.5)	-2.0 (-2.2; -1.8)	-1.8 (-2.1; -1.6)
Proportion with a clinically meaningful* increase, percent (95% CI)	34 (29;38)	33 (29;38)	14 (12; 16)	15 (12; 19)
Proportion with a clinically meaningful* decrease, percent (95% CI)	13 (9.5; 16)	12 (9.3; 15)	72 (69; 75)	69 (64; 74)
N with HbA_{1c} level>7.5% after baseline/N with baseline HbA_{1c} ≤7.5%	76/285	94/350	87/196	18/55
New post-discontinuation onset of loss of glycaemic control with HbA_{1c} >7.5%, percent (95% CI)[b]	27 (22; 32)	27 (22; 32)	44 (38;51)	33 (22; 46)

Clinically meaningful change defined using to the European Medicines Agency's definition as change of more than 0.6% (% is the test unit)
CI, confidence interval; HbA_{1c}, glycated haemoglobin A; SD, standard deviation

Table 4. Fasting plasma glucose (mmol/L) before and after discontinuation of rosiglitazone among patients with available pre-and post-discontinuation laboratory measurements, in northern Denmark and in the United Kingdom, 2000-2011.

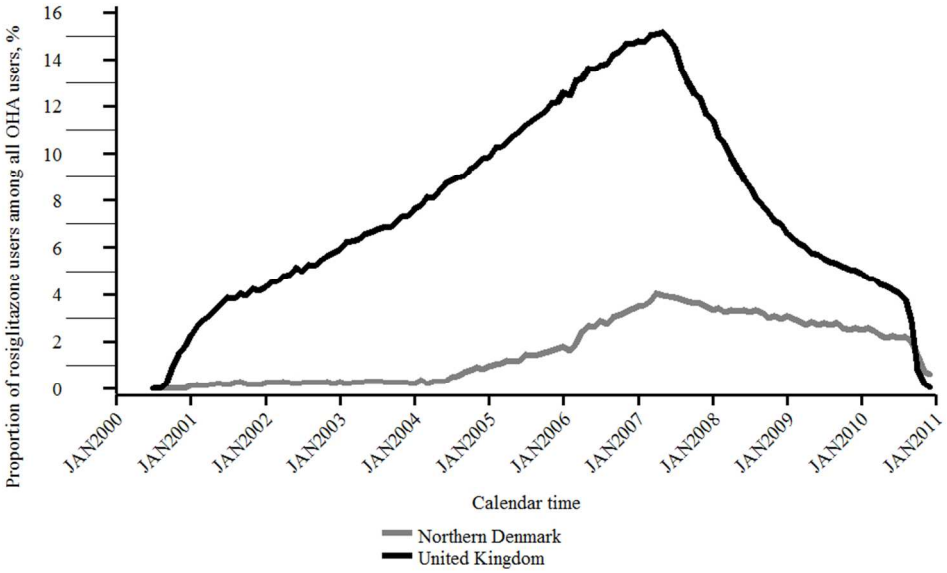
Characteristic	Northern Denmark			United Kingdom		
	3 months (n=95)	6 months (n=109)	12 months (n=77)	3 months (n=820)	6 months (n=1256)	12 months (n=800)
Baseline mean (SD)	9.5 (3.6)	9.3 (3.4)	9.1 (3.5)	8.6 (3.2)	8.7 (3.2)	8.7 (3.4)
Follow-up mean (SD)	9.2 (3.7)	9.0 (3.4)	9.1 (3.5)	8.8 (3.2)	8.8 (3.1)	8.7 (3.1)
Change from baseline, mean (95% CI)	-0.38 (-9.0; 8.2)	-0.27 (-8.2;7.6)	0.01 (-7.3; 7.3)	0.27 (0.04; 0.49)	0.08 (-0.12; 0.27)	0.03 (-0.22; 0.28)
Proportion with a clinically meaningful* increase, percent (95% CI)	40 (31; 50)	35 (26; 44)	32 (23; 43)	39 (36; 43)	40 (38; 43)	40 (37; 44)
Proportion with a clinically meaningful* decrease, percent (95% CI)	39 (30; 49)	35 (26; 44)	40 (30; 51)	30 (27; 33)	33 (31; 36)	34 (31; 38)
N with FPG >10 mmol/L after baseline/N with baseline FPG ≤10 mmol/L	14/65	18/79	8/54	98/610	182/911	99/583
New post-discontinuation onset of treatment failure, FPG>10 mmol/L, percent (95% CI)	22 (13; 33)	23 (15; 33)	15 (7.3; 26)	16 (13, 19)	20 (18; 23)	17 (14; 20)

*Clinically meaningful change defined using to the European Medicines Agency's definition as change of more than 10 mmol/L.
CI, confidence interval; HbA_{1c}, glycated haemoglobin A; SD, standard deviation

Table 5. Oral hypoglycaemic agents (OHA) prescribed to patients after terminating rosiglitazone on 23 September 2010 or later.

	Aarhus University Prescription Database, northern Denmark (n=474*)		General Practice Research Database, United Kingdom (n=2810[+])	
	Number	Percent (95% CI)	Number	Percent (95% CI)
Metformin	269	56.8 (52.3; 61.2)	1136	41.7 (39.9; 43.6)
Glimepiride	84	17.7 (14.3; 21.2)	57	2.1 (1.6; 2.7)
Metformin+sitagliptin	49	10.3 (7.6; 13.1)		
Sitagliptin	45	9.5 (6.9; 12.1)	103	3.8 (3.1; 4.6)
Metformin+vildagliptin	35	7.4 (5.0; 9.7)		
Liraglutide	26	5.5 (3.4; 7.5)		
Pioglitazone	21	4.4 (2.6; 6.3)	641	23.6 (22.0; 25.2)
Pioglitazone + metformin			394	14.5 (13.2; 15.9)
Gliclazide	17	3.6 (1.9; 5.3)	351	12.9 (11.7; 14.2)
Glibenclamide	8	1.7 (0.5; 2.8)	16	0.6 (0.4; 1.0)
Saxagliptin	8	1.7 (0.5; 2.8)		
Glipizide	4	0.8 (0.1; 1.7)	9	0.3 (0.2; 0.6)
Vildagliptin	4	0.8 (0.1; 1.7)		
Repaglinide	3	0.6 (0.1; 1.3)	2	0.1 (0.0; 0.3)
Exenatide	3	0.6 (0.1; 1.3)		
Acarbose	2	0.4 (0.1; 1.0)	4	0.2 (0.1; 0.4)
Tolbutamide	1	0.2 (0.1; 0.6)	9	0.3 (0.2; 0.6)

*83 patients had no record of another OHA after the last rosiglitazone prescription.
[+]88 patients had no record of another OHA after the last rosiglitazone prescription



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Appendix: Algorithms used to identify variables in the study titled:

Rosiglitazone use and post-discontinuation glycaemic control in two European countries, 2000-2010

Diagnostic codes used to Abstract the Danish National Registry of Patients

Disease/condition	ICD-8 code	ICD-10 code
Diabetes type 1	249.00; 249.06; 249.07; 249.09	E10.0, E10.1; E10.9
Diabetes type 2	250.00; 250.06; 250.07; 250.09	E11.0; E11.1; E11.9
Acute myocardial infarction	410	I21, I22, I23
Ischemic heart disease (acute and chronic)	411-414	I20, I24, I25
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49;	I50, I11.0, I13.0, I13.2
Other cardiac disease	393–398, 400–404	I05–I09
Peripheral vascular disease	440, 441, 442, 443, 444, 445	I70, I71, I72, I73, I74, I77
Ischemic stroke	430-438 (cerebrovascular disease)	I63-64
Alcoholism	291, 303, 577.10, 571.09, 571.10	F10.1-F10.9, G31.2, G62.1, G72.1, I42.6, K29.2, K86.0, Z72.1
Obesity	277.99	E65-E66
Mild liver disease	571, 573.01, 573.04	B18, K70.0–K70.3, K70.9, K71, K73, K74, K76.0
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00–456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Deep vein thrombosis	451.00	I81, I82
Pulmonary embolism	450.99	I26

ICD-8: http://www.sst.dk/Indberetning%20og%20statistik/Klassifikationer/SKS_download.aspx
ICD-10: http://apps.who.int/classifications/apps/icd/icd10online/

Diagnostic codes used to compute Charlson Comorbidity Index

Disease	ICD-8 code	ICD-10 code
Myocardial infarction	410	I21;I22;I23
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	430-438	I60-I69; G45; G46
Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86
Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28
Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes type1 Diabetes type2	249.00; 249.06; 249.07; 249.09 250.00; 250.06; 250.07; 250.09	E10.0, E10.1; E10.9 E11.0; E11.1; E11.9
Hemiplegia	344	G81; G82
Moderate to severe renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes with end organ damage type1 type2	 249.01-249.05; 249.08 250.01-250.05; 250.08	 E10.2-E10.8 E11.2-E11.8
Any tumor	140-194	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96
Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	195-198; 199	C76-C80
AIDS	079.83	B21-B24

Anatomical Therapeutic Chemical (ATC) codes used to abstract the Aarhus University Prescription Database

Drug	ATC code
Drugs used in diabetes	A10
Insulins and analogues for injection, fast-acting	A10AB
Insulins and analogues for injection, intermediate-acting	A10AC
Insulins and analogues for injection, intermediate-acting combined with fast-acting	A10AD
Insulins and analogues for injection, long-acting	A10AE
Insulins and analogues for inhalation	A10AF
Rosiglitazone preparations	A10BG02 rosiglitazone A10BD03 rosiglitazone+metformin A10BD04 rosiglitazone+glimepiride
Biguanides	A10BA
Sulfonamides, urea derivatives	A10BB
Sulfonamides (heterocyclic)	A10BC
Combinations of oral blood glucose lowering drugs	A10BD (except A10BD03 and A10BD04)
Thiazolidinediones other than rosiglitazone	A10BG03 (pioglitazone)
Alpha glucosidase inhibitors	A10BF
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH
Other blood glucose lowering drugs, excl. insulins	A10BX
Lipid-lowering drugs including statins	C10A
Antihypertensive agents	C07 (beta blockers) C08 (calcium channel blockers) C09, C09 (ACE-inhibitors and angiotensin blockers)
Diuretics (loop, potassium sparing, thiazide)	C03
Nitrates	C01DA
Antiplatelet agents (anti-thrombotic)	B01A

ATC classification: http://www.whocc.no/atc_ddd_index/

Codes used to identify laboratory tests accodring to the International Union of Pure and Applied Chemistry (IUPAC)

Test	IUPAC codes
Fasting blood glucose	ASS00203, ASS00204, DNK35842, NPU02193, NPU02195, NPU08509, NPU08972, NPU22069
HbA1c	NPU02307,NPU03835
Haemoglobin (anaemia)	NPU02319, AAA00359, AAA00137, AAA00115
Alanintransaminase	DNK05051,NPU19651
Albumin/creatinine ratio (urine)	ASS00023, ASS00024, ASS00194, AAA00760,DNK05289, NPU03918, NPU03929, 10913
Serum creatinine	NPU18016, NPU01807
Total cholesterol	NPU01566
LDL cholesterol	NPU01568, NPU10171
HDL cholesterol	NPU01567, NPU10157
Triglycerides	NPU03620

IUPAC codes: http://www.sst.dk/NPU

Diagnostic codes used to abstract the General Practice Research Database

Diabetes (includes both non-specific and Type II)

13AB.00 DIABETIC LIPID LOWERING DIET
13AC.00 DIABETIC WEIGHT REDUCING DIET
2BBF.00 RETINAL ABNORMALITY - DIABETES RELATED
2G51000 FOOT ABNORMALITY - DIABETES RELATED
2G5A.00 O/E - RIGHT DIABETIC FOOT AT RISK
2G5B.00 O/E - LEFT DIABETIC FOOT AT RISK
3882.00 DIABETES WELL BEING QUESTIONNAIRE
3883.00 DIABETES TREATMENT SATISFACTION QUESTIONNAIRE
42W..00 HB. A1C - DIABETIC CONTROL
42WZ.00 HB. A1C - DIABETIC CONTROL NOS
42c..00 HBA1 - DIABETIC CONTROL
66A..00 DIABETIC MONITORING
66A2.00 FOLLOW-UP DIABETIC ASSESSMENT
66A3.00 DIABETIC ON DIET ONLY
66A4.00 DIABETIC ON ORAL TREATMENT
66A8.00 HAS SEEN DIETICIAN - DIABETES
66A9.00 UNDERSTANDS DIET - DIABETES
66AD.00 FUNDOSCOPY - DIABETIC CHECK
66AG.00 DIABETIC DRUG SIDE EFFECTS
66AH.00 DIABETIC TREATMENT CHANGED
66AH000 CONVERSION TO INSULIN
66AI.00 DIABETIC - GOOD CONTROL
66AJ.00 DIABETIC - POOR CONTROL
66AJ.11 UNSTABLE DIABETES
66AJ100 BRITTLE DIABETES
66AJz00 DIABETIC - POOR CONTROL NOS
66AK.00 DIABETIC - COOPERATIVE PATIENT
66AL.00 DIABETIC-UNCOOPERATIVE PATIENT
66AM.00 DIABETIC - FOLLOW-UP DEFAULT
66AN.00 DATE DIABETIC TREATMENT START
66AO.00 DATE DIABETIC TREATMENT STOPP.
66AP.00 DIABETES: PRACTICE PROGRAMME
66AQ.00 DIABETES: SHARED CARE PROGRAMME
66AR.00 DIABETES MANAGEMENT PLAN GIVEN
66AS.00 DIABETIC ANNUAL REVIEW
66AT.00 ANNUAL DIABETIC BLOOD TEST
889A.00 DIAB MELLIT INSULIN-GLUCOSE INFUS ACUTE MYOCARDIAL INFARCT
8A12.00 DIABETIC CRISIS MONITORING
8A13.00 DIABETIC STABILISATION
8CA4100 PT ADVISED RE DIABETIC DIET
8H2J.00 ADMIT DIABETIC EMERGENCY

C10..00 DIABETES MELLITUS
C100.00 DIABETES MELLITUS WITH NO MENTION OF COMPLICATION
C100100 DIABETES MELLITUS, ADULT ONSET, NO MENTION OF COMPLICATION
C100111 MATURITY ONSET DIABETES
C100112 NON-INSULIN DEPENDENT DIABETES MELLITUS
C100z00 DIABETES MELLITUS NOS WITH NO MENTION OF COMPLICATION
C101.00 DIABETES MELLITUS WITH KETOACIDOSIS
C101100 DIABETES MELLITUS, ADULT ONSET, WITH KETOACIDOSIS
C101y00 OTHER SPECIFIED DIABETES MELLITUS WITH KETOACIDOSIS
C101z00 DIABETES MELLITUS NOS WITH KETOACIDOSIS
C102.00 DIABETES MELLITUS WITH HYPEROSMOLAR COMA
C102100 DIABETES MELLITUS, ADULT ONSET, WITH HYPEROSMOLAR COMA
C102z00 DIABETES MELLITUS NOS WITH HYPEROSMOLAR COMA
C103.00 DIABETES MELLITUS WITH KETOACIDOTIC COMA
C103100 DIABETES MELLITUS, ADULT ONSET, WITH KETOACIDOTIC COMA
C104.00 DIABETES MELLITUS WITH RENAL MANIFESTATION
C104.11 DIABETIC NEPHROPATHY
C104100 DIABETES MELLITUS, ADULT ONSET, WITH RENAL MANIFESTATION
C104y00 OTHER SPECIFIED DIABETES MELLITUS WITH RENAL COMPLICATIONS
C104z00 DIABETES MELLITIS WITH NEPHROPATHY NOS
C105.00 DIABETES MELLITUS WITH OPHTHALMIC MANIFESTATION
C105100 DIABETES MELLITUS, ADULT ONSET, + OPHTHALMIC MANIFESTATION
C105y00 OTHER SPECIFIED DIABETES MELLITUS WITH OPHTHALMIC COMPLICATN
C105z00 DIABETES MELLITUS NOS WITH OPHTHALMIC MANIFESTATION
C106.00 DIABETES MELLITUS WITH NEUROLOGICAL MANIFESTATION
C106.11 DIABETIC AMYOTROPHY
C106.12 DIABETES MELLITUS WITH NEUROPATHY
C106.13 DIABETES MELLITUS WITH POLYNEUROPATHY
C106100 DIABETES MELLITUS, ADULT ONSET, + NEUROLOGICAL MANIFESTATION
C106y00 OTHER SPECIFIED DIABETES MELLITUS WITH NEUROLOGICAL COMPS
C106z00 DIABETES MELLITUS NOS WITH NEUROLOGICAL MANIFESTATION
C107.00 DIABETES MELLITUS WITH PERIPHERAL CIRCULATORY DISORDER
C107.11 DIABETES MELLITUS WITH GANGRENE
C107.12 DIABETES WITH GANGRENE
C107100 DIABETES MELLITUS, ADULT, + PERIPHERAL CIRCULATORY DISORDER
C107200 DIABETES MELLITUS, ADULT WITH GANGRENE
C107z00 DIABETES MELLITUS NOS WITH PERIPHERAL CIRCULATORY DISORDER
C108y00 OTHER SPECIFIED DIABETES MELLITUS WITH MULTIPLE COMPS
C108z00 UNSPECIFIED DIABETES MELLITUS WITH MULTIPLE COMPLICATIONS
C109.00 NON-INSULIN-DEPENDENT DIABETES MELLITUS
C109.11 NIDDM - NON-INSULIN DEPENDENT DIABETES MELLITUS
C109.12 TYPE 2 DIABETES MELLITUS
C109.13 TYPE II DIABETES MELLITUS

C109000 NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH RENAL COMPS
C109011 TYPE II DIABETES MELLITUS WITH RENAL COMPLICATIONS
C109100 NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH OPHTHALM COMPS
C109111 TYPE II DIABETES MELLITUS WITH OPHTHALMIC COMPLICATIONS
C109200 NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH NEURO COMPS
C109211 TYPE II DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS
C109300 NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH MULTIPLE COMPS
C109400 NON-INSULIN DEPENDENT DIABETES MELLITUS WITH ULCER
C109411 TYPE II DIABETES MELLITUS WITH ULCER
C109500 NON-INSULIN DEPENDENT DIABETES MELLITUS WITH GANGRENE
C109511 TYPE II DIABETES MELLITUS WITH GANGRENE
C109600 NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH RETINOPATHY
C109611 TYPE II DIABETES MELLITUS WITH RETINOPATHY
C109700 NON-INSULIN DEPENDANT DIABETES MELLITUS - POOR CONTROL
C109711 TYPE II DIABETES MELLITUS - POOR CONTROL
C109900 NON-INSULIN-DEPENDENT DIABETES MELLITUS WITHOUT COMPLICATION
C109A00 NON-INSULIN DEPENDENT DIABETES MELLITUS WITH MONONEUROPATHY
C109A11 TYPE II DIABETES MELLITUS WITH MONONEUROPATHY
C109B00 NON-INSULIN DEPENDENT DIABETES MELLITUS WITH POLYNEUROPATHY
C109B11 TYPE II DIABETES MELLITUS WITH POLYNEUROPATHY
C109C00 NON-INSULIN DEPENDENT DIABETES MELLITUS WITH NEPHROPATHY
C109C11 TYPE II DIABETES MELLITUS WITH NEPHROPATHY
C109D00 NON-INSULIN DEPENDENT DIABETES MELLITUS WITH HYPOGLYCA COMA
C109D11 TYPE II DIABETES MELLITUS WITH HYPOGLYCAEMIC COMA
C109E00 NON-INSULIN DEPEND DIABETES MELLITUS WITH DIABETIC CATARACT
C109E11 TYPE II DIABETES MELLITUS WITH DIABETIC CATARACT
C109F00 NON-INSULIN-DEPENDENT D M WITH PERIPHERAL ANGIOPATH
C109F11 TYPE II DIABETES MELLITUS WITH PERIPHERAL ANGIOPATHY
C109G00 NON-INSULIN DEPENDENT DIABETES MELLITUS WITH ARTHROPATHY
C109G11 TYPE II DIABETES MELLITUS WITH ARTHROPATHY
C109H00 NON-INSULIN DEPENDENT D M WITH NEUROPATHIC ARTHROPATHY
C109H11 TYPE II DIABETES MELLITUS WITH NEUROPATHIC ARTHROPATHY
C10A.00 MALNUTRITION-RELATED DIABETES MELLITUS
C10A000 MALNUTRITION-RELATED DIABETES MELLITUS WITH COMA
C10A100 MALNUTRITION-RELATED DIABETES MELLITUS WITH KETOACIDOSIS
C10B.00 DIABETES MELLITUS INDUCED BY STEROIDS
C10B000 STEROID INDUCED DIABETES MELLITUS WITHOUT COMPLICATION
C10y.00 DIABETES MELLITUS WITH OTHER SPECIFIED MANIFESTATION
C10y100 DIABETES MELLITUS, ADULT, + OTHER SPECIFIED MANIFESTATION
C10yy00 OTHER SPECIFIED DIABETES MELLITUS WITH OTHER SPEC COMPS

C10yz00 DIABETES MELLITUS NOS WITH OTHER SPECIFIED MANIFESTATION
C10z.00 DIABETES MELLITUS WITH UNSPECIFIED COMPLICATION
C10z100 DIABETES MELLITUS, ADULT ONSET, + UNSPECIFIED COMPLICATION
C10zz00 DIABETES MELLITUS NOS WITH UNSPECIFIED COMPLICATION
C350011 BRONZED DIABETES
Cyu2.00 [X]DIABETES MELLITUS
Cyu2000 [X]OTHER SPECIFIED DIABETES MELLITUS
F171100 AUTONOMIC NEUROPATHY DUE TO DIABETES
F345000 DIABETIC MONONEURITIS MULTIPLEX
F35z000 DIABETIC MONONEURITIS NOS
F372.00 POLYNEUROPATHY IN DIABETES
F372.11 DIABETIC POLYNEUROPATHY
F372.12 DIABETIC NEUROPATHY
F372000 ACUTE PAINFUL DIABETIC NEUROPATHY
F372100 CHRONIC PAINFUL DIABETIC NEUROPATHY
F372200 ASYMPTOMATIC DIABETIC NEUROPATHY
F381300 MYASTHENIC SYNDROME DUE TO DIABETIC AMYOTROPHY
F381311 DIABETIC AMYOTROPHY
F3y0.00 DIABETIC MONONEUROPATHY
F420.00 DIABETIC RETINOPATHY
F420000 BACKGROUND DIABETIC RETINOPATHY
F420100 PROLIFERATIVE DIABETIC RETINOPATHY
F420200 PREPROLIFERATIVE DIABETIC RETINOPATHY
F420300 ADVANCED DIABETIC MACULOPATHY
F420400 DIABETIC MACULOPATHY
F420500 ADVANCED DIABETIC RETINAL DISEASE
F420z00 DIABETIC RETINOPATHY NOS
F440700 DIABETIC IRITIS
F464000 DIABETIC CATARACT
G73y000 DIABETIC PERIPHERAL ANGIOPATHY
K01x100 NEPHROTIC SYNDROME IN DIABETES MELLITUS
M037200 CELLULITIS IN DIABETIC FOOT
M271000 ISCHAEMIC ULCER DIABETIC FOOT
M271100 NEUROPATHIC DIABETIC ULCER - FOOT
M271200 MIXED DIABETIC ULCER - FOOT
N030000 DIABETIC CHEIROARTHROPATHY
N030011 DIABETIC CHEIROPATHY
N030100 DIABETIC CHARCOT ARTHROPATHY
Q441.00 NEONATAL DIABETES MELLITUS
R054200 [D]GANGRENE OF TOE IN DIABETIC
R054300 [D]WIDESPREAD DIABETIC FOOT GANGRENE
ZC2C800 DIETARY ADVICE FOR DIABETES MELLITUS
ZC2CA00 DIETARY ADVICE FOR TYPE II DIABETES
ZL22500 UNDER CARE OF DIABETIC LIAISON NURSE
ZV65312 [V]DIETARY COUNSELLING IN DIABETES MELLITUS

ZV6DA00 [V]ADMITTED FOR COMMENCEMENT OF INSULIN
ZV6DB00 [V]ADMITTED FOR CONVERSION TO INSULIN
13B1.00 Diabetic diet
U602300 [X]Insul/oral hypoglyc drugs caus adverse eff therapeut use
8A17.00 Self monitoring of blood glucose
8A18.00 Self monitoring of urine glucose+
C11y000 Steroid induced diabetes
C100100 DIABETES MELLITUS, ADULT ONSET, NO MENTION OF COMPLICATION
C100111 MATURITY ONSET DIABETES
C100112 NON-INSULIN DEPENDENT DIABETES MELLITUS
C101100 DIABETES MELLITUS, ADULT ONSET, WITH KETOACIDOSIS
C102100 DIABETES MELLITUS, ADULT ONSET, WITH HYPEROSMOLAR COMA
C103100 DIABETES MELLITUS, ADULT ONSET, WITH KETOACIDOTIC COMA
C104100 DIABETES MELLITUS, ADULT ONSET, WITH RENAL MANIFESTATION
C105100 DIABETES MELLITUS, ADULT ONSET, + OPHTHALMIC MANIFESTATION
C106100 DIABETES MELLITUS, ADULT ONSET, + NEUROLOGICAL MANIFESTATION
C107100 DIABETES MELLITUS, ADULT, + PERIPHERAL CIRCULATORY DISORDER
C107200 DIABETES MELLITUS, ADULT WITH GANGRENE
C107400 NIDDM WITH PERIPHERAL CIRCULATORY DISORDER
C109.00 NON-INSULIN-DEPENDENT DIABETES MELLITUS
C109.11 NIDDM - NON-INSULIN DEPENDENT DIABETES MELLITUS
C109.12 TYPE 2 DIABETES MELLITUS
C109.13 TYPE II DIABETES MELLITUS
C109000 NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH RENAL COMPS
C109011 TYPE II DIABETES MELLITUS WITH RENAL COMPLICATIONS
C109012 TYPE 2 DIABETES MELLITUS WITH RENAL COMPLICATIONS
C109100 NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH OPHTHALM COMPS
C109111 TYPE II DIABETES MELLITUS WITH OPHTHALMIC COMPLICATIONS
C109112 TYPE 2 DIABETES MELLITUS WITH OPHTHALMIC COMPLICATIONS
C109200 NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH NEURO COMPS
C109211 TYPE II DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS
C109212 TYPE 2 DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS
C109300 NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH MULTIPLE COMPS
C109400 NON-INSULIN DEPENDENT DIABETES MELLITUS WITH ULCER
C109411 TYPE II DIABETES MELLITUS WITH ULCER
C109412 TYPE 2 DIABETES MELLITUS WITH ULCER
C109500 NON-INSULIN DEPENDENT DIABETES MELLITUS WITH GANGRENE
C109511 TYPE II DIABETES MELLITUS WITH GANGRENE
C109600 NON-INSULIN-DEPENDENT DIABETES MELLITUS WITH RETINOPATHY
C109611 TYPE II DIABETES MELLITUS WITH RETINOPATHY
C109612 TYPE 2 DIABETES MELLITUS WITH RETINOPATHY
C109700 NON-INSULIN DEPENDANT DIABETES MELLITUS - POOR CONTROL
C109711 TYPE II DIABETES MELLITUS - POOR CONTROL
C109712 TYPE 2 DIABETES MELLITUS - POOR CONTROL

C109900 NON-INSULIN-DEPENDENT DIABETES MELLITUS WITHOUT COMPLICATION
C109A00 NON-INSULIN DEPENDENT DIABETES MELLITUS WITH MONONEUROPATHY
C109B00 NON-INSULIN DEPENDENT DIABETES MELLITUS WITH POLYNEUROPATHY
C109B11 TYPE II DIABETES MELLITUS WITH POLYNEUROPATHY
C109C00 NON-INSULIN DEPENDENT DIABETES MELLITUS WITH NEPHROPATHY
C109C11 TYPE II DIABETES MELLITUS WITH NEPHROPATHY
C109C12 TYPE 2 DIABETES MELLITUS WITH NEPHROPATHY
C109D00 NON-INSULIN DEPENDENT DIABETES MELLITUS WITH HYPOGLYCA COMA
C109D11 TYPE II DIABETES MELLITUS WITH HYPOGLYCAEMIC COMA
C109D12 TYPE 2 DIABETES MELLITUS WITH HYPOGLYCAEMIC COMA
C109E00 NON-INSULIN DEPEND DIABETES MELLITUS WITH DIABETIC CATARACT
C109E11 TYPE II DIABETES MELLITUS WITH DIABETIC CATARACT
C109E12 TYPE 2 DIABETES MELLITUS WITH DIABETIC CATARACT
C109F00 NON-INSULIN-DEPENDENT D M WITH PERIPHERAL ANGIOPATH
C109F11 TYPE II DIABETES MELLITUS WITH PERIPHERAL ANGIOPATHY
C109F12 TYPE 2 DIABETES MELLITUS WITH PERIPHERAL ANGIOPATHY
C109G00 NON-INSULIN DEPENDENT DIABETES MELLITUS WITH ARTHROPATHY
C109G11 TYPE II DIABETES MELLITUS WITH ARTHROPATHY
C109H00 NON-INSULIN DEPENDENT D M WITH NEUROPATHIC ARTHROPATHY
C109H11 TYPE II DIABETES MELLITUS WITH NEUROPATHIC ARTHROPATHY
C109H12 TYPE 2 DIABETES MELLITUS WITH NEUROPATHIC ARTHROPATHY
C109J00 INSULIN TREATED TYPE 2 DIABETES MELLITUS
C109J11 INSULIN TREATED NON-INSULIN DEPENDENT DIABETES MELLITUS
C109J12 INSULIN TREATED TYPE II DIABETES MELLITUS
C109K00 HYPEROSMOLAR NON-KETOTIC STATE IN TYPE 2 DIABETES MELLITUS
C10D.00 DIABETES MELLITUS AUTOSOMAL DOMINANT TYPE 2
C10D.11 MATURITY ONSET DIABETES IN YOUTH TYPE 2
C10F.00 TYPE 2 DIABETES MELLITUS
C10F.11 TYPE II DIABETES MELLITUS
C10F000 TYPE 2 DIABETES MELLITUS WITH RENAL COMPLICATIONS
C10F100 TYPE 2 DIABETES MELLITUS WITH OPHTHALMIC COMPLICATIONS
C10F200 TYPE 2 DIABETES MELLITUS WITH NEUROLOGICAL COMPLICATIONS
C10F300 TYPE 2 DIABETES MELLITUS WITH MULTIPLE COMPLICATIONS
C10F400 TYPE 2 DIABETES MELLITUS WITH ULCER
C10F500 TYPE 2 DIABETES MELLITUS WITH GANGRENE
C10F600 TYPE 2 DIABETES MELLITUS WITH RETINOPATHY
C10F700 TYPE 2 DIABETES MELLITUS - POOR CONTROL
C10F900 TYPE 2 DIABETES MELLITUS WITHOUT COMPLICATION
C10FA00 TYPE 2 DIABETES MELLITUS WITH MONONEUROPATHY
C10FB00 TYPE 2 DIABETES MELLITUS WITH POLYNEUROPATHY
C10FC00 TYPE 2 DIABETES MELLITUS WITH NEPHROPATHY

C10FD00 TYPE 2 DIABETES MELLITUS WITH HYPOGLYCAEMIC COMA
C10FE00 TYPE 2 DIABETES MELLITUS WITH DIABETIC CATARACT
C10FF00 TYPE 2 DIABETES MELLITUS WITH PERIPHERAL ANGIOPATHY
C10FG00 TYPE 2 DIABETES MELLITUS WITH ARTHROPATHY
C10FH00 TYPE 2 DIABETES MELLITUS WITH NEUROPATHIC ARTHROPATHY
C10FJ00 INSULIN TREATED TYPE 2 DIABETES MELLITUS
C10FK00 HYPEROSMOLAR NON-KETOTIC STATE IN TYPE 2 DIABETES MELLITUS
C10FL00 TYPE 2 DIABETES MELLITUS WITH PERSISTENT PROTEINURIA
C10FL11 TYPE II DIABETES MELLITUS WITH PERSISTENT PROTEINURIA
C10FM00 TYPE 2 DIABETES MELLITUS WITH PERSISTENT MICROALBUMINURIA
C10FN00 TYPE 2 DIABETES MELLITUS WITH KETOACIDOSIS
C10FP00 TYPE 2 DIABETES MELLITUS WITH KETOACIDOTIC COMA
C10FQ00 TYPE 2 DIABETES MELLITUS WITH EXUDATIVE MACULOPATHY
C10y100 DIABETES MELLITUS, ADULT, + OTHER SPECIFIED MANIFESTATION
C10z100 DIABETES MELLITUS, ADULT ONSET, + UNSPECIFIED COMPLICATION

Acute Myocardial Infarction

323..00 ECG: MYOCARDIAL INFARCTION
3233.00 ECG: ANTERO-SEPTAL INFARCT
3234.00 ECG:POSTERIOR/INFERIOR INFARCT
3235.00 ECG: SUBENDOCARDIAL INFARCT
3236.00 ECG: LATERAL INFARCTION
323Z.00 ECG: MYOCARDIAL INFARCT NOS
889A.00 DIAB MELLIT INSULIN-GLUCOSE INFUS ACUTE MYOCARDIAL INFARCT
G30..00 ACUTE MYOCARDIAL INFARCTION
G30..13 CARDIAC RUPTURE FOLLOWING MYOCARDIAL INFARCTION (MI)
G30..15 MI - ACUTE MYOCARDIAL INFARCTION
G30..17 SILENT MYOCARDIAL INFARCTION
G300.00 ACUTE ANTEROLATERAL INFARCTION
G301.00 OTHER SPECIFIED ANTERIOR MYOCARDIAL INFARCTION
G301000 ACUTE ANTEROAPICAL INFARCTION
G301100 ACUTE ANTEROSEPTAL INFARCTION
G301z00 ANTERIOR MYOCARDIAL INFARCTION NOS
G302.00 ACUTE INFEROLATERAL INFARCTION
G303.00 ACUTE INFEROPOSTERIOR INFARCTION
G304.00 POSTERIOR MYOCARDIAL INFARCTION NOS
G305.00 LATERAL MYOCARDIAL INFARCTION NOS
G306.00 TRUE POSTERIOR MYOCARDIAL INFARCTION
G307.00 ACUTE SUBENDOCARDIAL INFARCTION
G307000 ACUTE NON-Q WAVE INFARCTION
G308.00 INFERIOR MYOCARDIAL INFARCTION NOS
G309.00 ACUTE Q-WAVE INFARCT
G30X.00 ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF UNSPECIF SITE
G30y.00 OTHER ACUTE MYOCARDIAL INFARCTION

G30y000 ACUTE ATRIAL INFARCTION
G30y100 ACUTE PAPILLARY MUSCLE INFARCTION
G30y200 ACUTE SEPTAL INFARCTION
G30yz00 OTHER ACUTE MYOCARDIAL INFARCTION NOS
G30z.00 ACUTE MYOCARDIAL INFARCTION NOS
G35..00 SUBSEQUENT MYOCARDIAL INFARCTION
G31y100 MICROINFARCTION OF HEART
G350.00 SUBSEQUENT MYOCARDIAL INFARCTION OF ANTERIOR WALL
G351.00 SUBSEQUENT MYOCARDIAL INFARCTION OF INFERIOR WALL
G35X.00 SUBSEQUENT MYOCARDIAL INFARCTION OF UNSPECIFIED SITE
G30..11 Attack - heart
G30..12 Coronary thrombosis
G30..14 Heart attack
G30..16 Thrombosis - coronary
G30A.00 Mural thrombosis
G5yy600 Atrial thrombosis
G5yy700 Left ventricular thrombosis
G5yy800 Right ventricular thrombosis
G307100 Acute non-ST segment elevation myocardial infarction
G30B.00 Acute posterolateral myocardial infarction
G30X000 Acute ST segment elevation myocardial infarction
G38..00 POSTOPERATIVE MYOCARDIAL INFARCTION
G380.00 POSTOPERATIVE TRANSMURAL MYOCARDIAL INFARCTION ANTERIOR WALL
G381.00 POSTOPERATIVE TRANSMURAL MYOCARDIAL INFARCTION INFERIOR WALL
G384.00 POSTOPERATIVE SUBENDOCARDIAL MYOCARDIAL INFARCTION

Any Cardiovascular Disease

G311.00 Preinfarction syndrome
G311.11 Crescendo angina
G311.13 Unstable angina
G311.14 Angina at rest
G311100 Unstable angina
G311200 Angina at rest
G311300 Refractory angina
G311400 Worsening angina
G311500 Acute coronary syndrome
G311z00 Preinfarction syndrome NOS
G33..00 Angina pectoris
G330.00 Angina decubitus
G330000 Nocturnal angina
G330z00 Angina decubitus NOS

G331.00	Prinzmetal's angina
G331.11	Variant angina pectoris
G33z.00	Angina pectoris NOS
G33z000	Status anginosus
G33z100	Stenocardia
G33z200	Syncope anginosa
G33z300	Angina on effort
G33z400	Ischaemic chest pain
G33z600	New onset angina
G33z700	Stable angina
G33zz00	Angina pectoris NOS
Gyu3000	[X] Other forms of angina pectoris
14A5.00	H/O: angina pectoris
14AJ.00	H/O: Angina in last year
662K.00	Angina control
662K000	Angina control - good
662K100	Angina control - poor
662K200	Angina control - improving
662K300	Angina control - worsening
662Kz00	Angina control NOS
8B27.00	Antianginal therapy
G33z500	Post infarct angina
323..00	ECG: myocardial infarction
3233.00	ECG: antero-septal infarct.
3234.00	ECG: posterior/inferior infarct
3235.00	ECG: subendocardial infarct
3236.00	ECG: lateral infarction
323Z.00	ECG: myocardial infarct NOS
G30..00	Acute myocardial infarction
G300.00	Acute anterolateral infarction
G30..11	Attack - heart
G30..12	Coronary thrombosis
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..16	Thrombosis - coronary
G30..17	Silent myocardial infarction
G301.00	Other specified anterior myocardial infarction
G301000	Acute anteroapical infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction

G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G307100	Acute non-ST segment elevation myocardial infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction
G30y200	Acute septal infarction
G31y100	Microinfarction of heart
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G30A.00	Mural thrombosis
G5yy600	Atrial thrombosis
G5yy700	Left ventricular thrombosis
G5yy800	Right ventricular thrombosis
14A3.00	H/O: myocardial infarct <60
14A4.00	H/O: myocardial infarct >60
14AH.00	H/O: Myocardial infarction in last year
3232.00	ECG: old myocardial infarction
G32..00	Old myocardial infarction
G32..11	Healed myocardial infarction
G32..12	Personal history of myocardial infarction
G30..13	Cardiac rupture following myocardial infarction (MI)
G310.00	Postmyocardial infarction syndrome
G310.11	Dressler's syndrome
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
G36..00	Certain current complication follow acute myocardial infarct
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
Gyu3500	[X] Subsequent myocardial infarction of other sites
Gyu3600	[X] Subsequent myocardial infarction of unspecified site

G38..00	Postoperative myocardial infarction
G380.00	Postoperative transmural myocardial infarction anterior wall
G381.00	Postoperative transmural myocardial infarction inferior wall
G382.00	Postoperative transmural myocardial infarction other sites
G383.00	Postoperative transmural myocardial infarction unspec site
G384.00	Postoperative subendocardial myocardial infarction
G38z.00	Postoperative myocardial infarction, unspecified
ZV71900	[V]Observation for suspected myocardial infarction
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
G312.00	Coronary thrombosis not resulting in myocardial infarction
G311000	Myocardial infarction aborted
G311011	MI - myocardial infarction aborted
792..00	Coronary artery operations
792..11	Coronary artery bypass graft operations
7920.00	Saphenous vein graft replacement of coronary artery
7920.11	Saphenous vein graft bypass of coronary artery
7920000	Saphenous vein graft replacement of one coronary artery
7920100	Saphenous vein graft replacement of two coronary arteries
7920200	Saphenous vein graft replacement of three coronary arteries
7920300	Saphenous vein graft replacement of four+ coronary arteries
7920y00	Saphenous vein graft replacement of coronary artery OS
7920z00	Saphenous vein graft replacement coronary artery NOS
7921.00	Other autograft replacement of coronary artery
7921.11	Other autograft bypass of coronary artery
7921000	Autograft replacement of one coronary artery NEC
7921100	Autograft replacement of two coronary arteries NEC
7921200	Autograft replacement of three coronary arteries NEC
7921300	Autograft replacement of four of more coronary arteries NEC
7921y00	Other autograft replacement of coronary artery OS
7921z00	Other autograft replacement of coronary artery NOS
7922.00	Allograft replacement of coronary artery
7922.11	Allograft bypass of coronary artery
7922000	Allograft replacement of one coronary artery
7922100	Allograft replacement of two coronary arteries
7922200	Allograft replacement of three coronary arteries
7922300	Allograft replacement of four or more coronary arteries
7922y00	Other specified allograft replacement of coronary artery
7922z00	Allograft replacement of coronary artery NOS
7924.00	Revision of bypass for coronary artery
7924000	Revision of bypass for one coronary artery
7924100	Revision of bypass for two coronary arteries
7924200	Revision of bypass for three coronary arteries
7924300	Revision of bypass for four or more coronary arteries
7924400	Revision of connection of thoracic artery to coronary artery
7924500	Revision of implantation of thoracic artery into heart

7924y00	Other specified revision of bypass for coronary artery
7924z00	Revision of bypass for coronary artery NOS
7925.00	Connection of mammary artery to coronary artery
7925.11	Creation of bypass from mammary artery to coronary artery
7925000	Double anastomosis of mammary arteries to coronary arteries
7925011	LIMA sequential anastomosis
7925012	RIMA sequential anastomosis
7925100	Double implant of mammary arteries into coronary arteries
7925200	Single anast mammary art to left ant descend coronary art
7925300	Single anastomosis of mammary artery to coronary artery NEC
7925311	LIMA single anastomosis
7925312	RIMA single anastomosis
7925400	Single implantation of mammary artery into coronary artery
7925y00	Connection of mammary artery to coronary artery OS
7925z00	Connection of mammary artery to coronary artery NOS
7926.00	Connection of other thoracic artery to coronary artery
7926000	Double anastom thoracic arteries to coronary arteries NEC
7926100	Double implant thoracic arteries into coronary arteries NEC
7926200	Single anastomosis of thoracic artery to coronary artery NEC
7926300	Single implantation thoracic artery into coronary artery NEC
7926y00	Connection of other thoracic artery to coronary artery OS
7926z00	Connection of other thoracic artery to coronary artery NOS
7927.00	Other open operations on coronary artery
7927000	Repair of arteriovenous fistula of coronary artery
7927100	Repair of aneurysm of coronary artery
7927200	Transection of muscle bridge of coronary artery
7927300	Transposition of coronary artery NEC
7927400	Exploration of coronary artery
7927y00	Other specified other open operation on coronary artery
7927z00	Other open operation on coronary artery NOS
7927500	Open angioplasty of coronary artery
7928.00	Transluminal balloon angioplasty of coronary artery
7928.11	Percutaneous balloon coronary angioplasty
7928000	Percut transluminal balloon angioplasty one coronary artery
7928100	Percut translum balloon angioplasty mult coronary arteries
7928200	Percut translum balloon angioplasty bypass graft coronary a
7928300	Percut translum cutting balloon angioplasty coronary artery
7928y00	Transluminal balloon angioplasty of coronary artery OS
7928z00	Transluminal balloon angioplasty of coronary artery NOS
7929.00	Other therapeutic transluminal operations on coronary artery
7929000	Percutaneous transluminal laser coronary angioplasty
7929100	Percut transluminal coronary thrombolysis with streptokinase
7929111	Percut translum coronary thrombolytic therapy- streptokinase
7929200	Percut translum inject therap subst to coronary artery NEC
7929300	Rotary blade coronary angioplasty

7929400	Insertion of coronary artery stent
7929500	Insertion of drug-eluting coronary artery stent
7929600	Percutaneous transluminal atherectomy of coronary artery
7929y00	Other therapeutic transluminal op on coronary artery OS
7929z00	Other therapeutic transluminal op on coronary artery NOS
793G.00	Perc translumin balloon angioplasty stenting coronary artery
793G000	Perc translum ball angio insert 1-2 drug elut stents cor art
793G100	Perc tran ball angio ins 3 or more drug elut stents cor art
793G200	Perc translum balloon angioplasty insert 1-2 stents cor art
793G300	Percutaneous cor balloon angiop 3 more stents cor art NEC
793Gz00	Perc translum balloon angioplasty stenting coronary art NOS
792B.00	Repair of coronary artery NEC
792B000	Endarterectomy of coronary artery NEC
792B100	Repair of rupture of coronary artery
792B200	Repair of arteriovenous malformation of coronary artery
792By00	Other specified repair of coronary artery
792Bz00	Repair of coronary artery NOS
792C.00	Other replacement of coronary artery
792C000	Replacement of coronary arteries using multiple methods
792Cy00	Other specified replacement of coronary artery
792Cz00	Replacement of coronary artery NOS
792D.00	Other bypass of coronary artery
792Dy00	Other specified other bypass of coronary artery
792Dz00	Other bypass of coronary artery NOS
792y.00	Other specified operations on coronary artery
792z.00	Coronary artery operations NOS
790H300	Revascularisation of wall of heart
ZV45800	[V]Presence of coronary angioplasty implant and graft
ZV45L00	[V]Status following coronary angioplasty NOS
SP07600	Coronary artery bypass graft occlusion
ZV45K00	[V]Presence of coronary artery bypass graft
ZV45K11	[V]Presence of coronary artery bypass graft – CABG
G31..00	Other acute and subacute ischaemic heart disease
G31y.00	Other acute and subacute ischaemic heart disease
G31y.00	Other acute and subacute ischaemic heart disease
G31y000	Acute coronary insufficiency
G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G31y300	Transient myocardial ischaemia
G31yz00	Other acute and subacute ischaemic heart disease NOS
G34y.00	Other specified chronic ischaemic heart disease
G34y000	Chronic coronary insufficiency
G34y100	Chronic myocardial ischaemia
G34yz00	Other specified chronic ischaemic heart disease NOS
G34z.00	Other chronic ischaemic heart disease NOS

G34z000	Asymptomatic coronary heart disease
G3...00	Ischaemic heart disease
G3...13	IHD – Ischaemic heart diease
G3y..00	Other specified ischaemic heart disease
G3z..00	Ischaemic heart disease NOS
G34..00	Other chronic ischaemic heart diease
G343.00	Ischaemic cardiomyopathy
G344.00	Silent myocardial ischaemia
G3...12	Atherosclerotic heart disease
G3...11	Arteriosclerotic heart disease
G342.00	Atherosclerotic cardiovascular disease
G5y2.00	Cardiovascular arteriosclerosis unspecified
G34..00	Other chronic ischaemic heart disease
G340.00	Coronary atherosclerosis
G340.11	Triple vessel disease of the heart
G340.12	Coronary artery disease
G340000	Single coronary vessel disease
G340100	Double coronary vessel disease
G670.00	Cerebral atherosclerosis
G670.11	Precerebral atherosclerosis
G70..00	Atherosclerosis
G70..11	Arteriosclerosis
G700.00	Aortic atherosclerosis
G700.11	Aorto-iliac disease
G701.00	Renal artery atherosclerosis
G702.00	Extremity artery atheroma
G702000	Monckeberg's medial sclerosis
G702z00	Extremity artery atheroma NOS
G70y.00	Other specified artery atheroma
G70y000	Carotid artery atherosclerosis
G70y011	Carotid artery disease
G70z.00	Arteriosclerotic vascular disease NOS
Gyu7000	[X]Atherosclerosis of other arteries
G58..00	Heart failure
G58..11	Cardiac failure
G580.00	Congestive heart failure
G580.11	Congestive cardiac failure
G580.12	Right heart failure
G580.13	Right ventricular failure
G580.14	Biventricular failure
G580000	Acute congestive heart failure
G580100	Chronic congestive heart failure
G580200	Decompensated cardiac failure
G580300	Compensated cardiac failure
G581.00	Left ventricular failure

G581.11 Asthma - cardiac
G581.12 Pulmonary oedema - acute
G581.13 Impaired left ventricular function
G581000 Acute left ventricular failure
G582.00 Acute heart failure
G58z.00 Heart failure NOS
G58z.11 Weak heart
G58z.12 Cardiac failure NOS
G5y3.00 Cardiomegaly
G5y3.11 Dilatation - cardiac
G5y3000 Atrial dilatation
G5y3100 Ventricular dilatation
G5y3200 Cardiac dilatation NOS
G5y3300 Atrial hypertrophy
G5y3400 Ventricular hypertrophy
G5y3411 Left ventricular hypertrophy
G5y3500 Cardiac hypertrophy NOS
G5y3z00 Cardiomegaly NOS
8B29.00 Cardiac failure therapy
R2y1000 [D]Cardiorespiratory failure
324..00 ECG:left ventricle hypertrophy
325..00 ECG:right ventricle hypertrop.
G232.00 Hypertensive heart&renal dis wth (congestive) heart failure
G234.00 Hyperten heart&renal dis+both(congestv) heart and renal fai
G21z011 Cardiomegaly - hypertensive
G31y000 Acute coronary insufficiency
G34y000 Chronic coronary insufficiency
G1yz100 Rheumatic left ventricular failure
SP11111 Heart failure as a complication of care
SP11200 Cardiorespiratory failure as a complication of care
SP11100 Cardiac insufficiency as a complication of care
P6yy200 Congenital cardiomegaly
Q48y100 Congenital cardiac failure
Q490.00 Neonatal cardiac failure
14A6.00 H/O: heart failure
14AM.00 H/O: Heart failure in last year

Congestive Heart Failure

G58..00 Heart failure
G58..11 Cardiac failure
G580.00 Congestive heart failure
G580.11 Congestive cardiac failure
G580.12 Right heart failure
G580.13 Right ventricular failure

G580.14 Biventricular failure
G580000 Acute congestive heart failure
G580100 Chronic congestive heart failure
G580200 Decompensated cardiac failure
G580300 Compensated cardiac failure
G581.00 Left ventricular failure
G581.11 Asthma - cardiac
G581.12 Pulmonary oedema - acute
G581.13 Impaired left ventricular function
G581000 Acute left ventricular failure
G582.00 Acute heart failure
G58z.00 Heart failure NOS
G58z.11 Weak heart
G58z.12 Cardiac failure NOS
G5y3.00 Cardiomegaly
G5y3.11 Dilatation - cardiac
G5y3000 Atrial dilatation
G5y3100 Ventricular dilatation
G5y3200 Cardiac dilatation NOS
G5y3300 Atrial hypertrophy
G5y3400 Ventricular hypertrophy
G5y3411 Left ventricular hypertrophy
G5y3500 Cardiac hypertrophy NOS
G5y3z00 Cardiomegaly NOS
8B29.00 Cardiac failure therapy
R2y1000 [D]Cardiorespiratory failure
324..00 ECG:left ventricle hypertrophy
325..00 ECG:right ventricle hypertrop.
G232.00 Hypertensive heart&renal dis wth (congestive) heart failure
G234.00 Hyperten heart&renal dis+both(congestv) heart and renal fai
G21z011 Cardiomegaly - hypertensive
G31y000 Acute coronary insufficiency
G34y000 Chronic coronary insufficiency
G1yz100 Rheumatic left ventricular failure
SP11111 Heart failure as a complication of care
SP11200 Cardiorespiratory failure as a complication of care
SP11100 Cardiac insufficiency as a complication of care
P6yy200 Congenital cardiomegaly
Q48y100 Congenital cardiac failure
Q490.00 Neonatal cardiac failure
14A6.00 H/O: heart failure
14AM.00 H/O: Heart failure in last year

Peripheral Vascular Disease

RG73..00	Other peripheral vascular disease
RG73..11	Peripheral ischaemic vascular disease
RG73..12	Ischaemia of legs
RG73..13	Peripheral ischaemia
RG731.00	Thromboangiitis obliterans
RG731000	Buerger's disease
RG731100	Presenile gangrene
RG731z00	Thromboangiitis obliterans NOS
RG73y.00	Other specified peripheral vascular disease
RG73y000	Diabetic peripheral angiopathy
RG73y100	Peripheral angiopathic disease EC NOS
RG73y200	Acrocyanosis
RG73y400	Acroparaesthesia - Schultze's type
RG73y600	Acroparaesthesia - unspecified
RG73y700	Erythrocyanosis
RG73y800	Erythromelalgia
RG73y811	Erythralgia
RG73yz00	Other specified peripheral vascular disease NOS
RG73z.00	Peripheral vascular disease NOS
RG73z000	Intermittent claudication
RG73z011	Claudication
RG73z100	Spasm of peripheral artery
RG73zz00	Peripheral vascular disease NOS

Transient Ischemic Attack / Stroke

G63..00	Precerebral arterial occlusion
G63..11	Infarction - precerebral
G63..12	Stenosis of precerebral arteries
G630.00	Basilar artery occlusion
G631.00	Carotid artery occlusion
G631.11	Stenosis, carotid artery
G631.12	Thrombosis, carotid artery
G632.00	Vertebral artery occlusion
G634.00	Carotid artery stenosis
G63y.00	Other precerebral artery occlusion
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G63z.00	Precerebral artery occlusion NOS
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction - cerebral
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis

G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G64z400	Infarction of basal ganglia
G65..00	Transient cerebral ischaemia
G65..11	Drop attack
G65..12	Transient ischaemic attack
G65..13	Vertebro-basilar insufficiency
G650.00	Basilar artery syndrome
G650.11	Insufficiency - basilar artery
G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome
G652.00	Subclavian steal syndrome
G653.00	Carotid artery syndrome hemispheric
G654.00	Multiple and bilateral precerebral artery syndromes
G655.00	Transient global amnesia
G656.00	Vertebrobasilar insufficiency
G65y.00	Other transient cerebral ischaemia
G65z.00	Transient cerebral ischaemia NOS
G65z000	Impending cerebral ischaemia
G65z100	Intermittent cerebral ischaemia
G65zz00	Transient cerebral ischaemia NOS
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G669.00	Cerebral palsy, not congenital or infantile, acute

G680.00	Sequelae of subarachnoid haemorrhage
G681.00	Sequelae of intracerebral haemorrhage
G682.00	Sequelae of other nontraumatic intracranial haemorrhage
G683.00	Sequelae of cerebral infarction
G68W.00	Sequelae/other + unspecified cerebrovascular diseases
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs

Chronic Liver Disease

A707.00 CHRONIC VIRAL HEPATITIS
A707000 CHRONIC VIRAL HEPATITIS B WITH DELTA-AGENT
A707100 CHRONIC VIRAL HEPATITIS B WITHOUT DELTA-AGENT
A707200 CHRONIC VIRAL HEPATITIS C
A707X00 CHRONIC VIRAL HEPATITIS, UNSPECIFIED
C310400 GLYCOGENOSIS WITH HEPATIC CIRRHOSIS
J61..00 CIRRHOSIS AND CHRONIC LIVER DISEASE
J610.00 ALCOHOLIC FATTY LIVER
J612.00 ALCOHOLIC CIRRHOSIS OF LIVER
J612.11 FLORID CIRRHOSIS
J612.12 LAENNEC'S CIRRHOSIS
J612000 ALCOHOLIC FIBROSIS AND SCLEROSIS OF LIVER
J613.00 ALCOHOLIC LIVER DAMAGE UNSPECIFIED
J613000 ALCOHOLIC HEPATIC FAILURE
J614.00 CHRONIC HEPATITIS
J614000 CHRONIC PERSISTENT HEPATITIS
J614100 CHRONIC ACTIVE HEPATITIS
J614111 AUTOIMMUNE CHRONIC ACTIVE HEPATITIS
J614200 CHRONIC AGGRESSIVE HEPATITIS
J614300 RECURRENT HEPATITIS
J614400 CHRONIC LOBULAR HEPATITIS
J614y00 CHRONIC HEPATITIS UNSPECIFIED
J614z00 CHRONIC HEPATITIS NOS
J615.00 CIRRHOSIS - NON ALCOHOLIC
J615.11 PORTAL CIRRHOSIS
J615000 UNILOBULAR PORTAL CIRRHOSIS
J615100 MULTILOBULAR PORTAL CIRRHOSIS
J615111 POSTNECROTIC CIRRHOSIS OF LIVER
J615200 MIXED PORTAL CIRRHOSIS
J615300 DIFFUSE NODULAR CIRRHOSIS
J615400 FATTY PORTAL CIRRHOSIS
J615500 HYPERTROPHIC PORTAL CIRRHOSIS
J615600 CAPSULAR PORTAL CIRRHOSIS

J615700 CARDIAC PORTAL CIRRHOSIS
J615711 CONGESTIVE CIRRHOSIS
J615800 JUVENILE PORTAL CIRRHOSIS
J615811 CHILDHOOD FUNCTION CIRRHOSIS
J615812 INDIAN CHILDHOOD CIRRHOSIS
J615900 PIGMENTARY PORTAL CIRRHOSIS
J615A00 PIPE-STEM PORTAL CIRRHOSIS
J615B00 TOXIC PORTAL CIRRHOSIS
J615C00 XANTHOMATOUS PORTAL CIRRHOSIS
J615D00 BACTERIAL PORTAL CIRRHOSIS
J615E00 CARDITUBERCULOUS CIRRHOSIS
J615F00 SYPHILITIC PORTAL CIRRHOSIS
J615G00 ZOOPARASITIC PORTAL CIRRHOSIS
J615H00 INFECTIOUS CIRRHOSIS NOS
J615y00 PORTAL CIRRHOSIS UNSPECIFIED
J615z00 NON-ALCOHOLIC CIRRHOSIS NOS
J615z11 MACRONODULAR CIRRHOSIS OF LIVER
J615z12 CRYPTOGENIC CIRRHOSIS OF LIVER
J615z13 CIRRHOSIS OF LIVER NOS
J615z14 LAENNEC'S CIRRHOSIS, NON-ALCOHOLIC
J615z15 HEPATIC FIBROSIS
J616.00 BILIARY CIRRHOSIS
J616000 PRIMARY BILIARY CIRRHOSIS
J616100 SECONDARY BILIARY CIRRHOSIS
J616200 BILIARY CIRRHOSIS OF CHILDREN
J616z00 BILIARY CIRRHOSIS NOS
J617000 CHRONIC ALCOHOLIC HEPATITIS
J61y.00 OTHER NON-ALCOHOLIC CHRONIC LIVER DISEASE
J61y000 CHRONIC YELLOW LIVER ATROPHY
J61y100 NON-ALCOHOLIC FATTY LIVER
J61y700 STEATOSIS OF LIVER
J61yz00 OTHER NON-ALCOHOLIC CHRONIC LIVER DISEASE NOS
J61z.00 CHRONIC LIVER DISEASE NOS
J62..00 LIVER ABSCESS AND SEQUELAE OF CHRONIC LIVER DISEASE
J625.00 [X] HEPATIC FAILURE
J625.11 [X] LIVER FAILURE
J62y.00 OTHER SEQUELAE OF CHRONIC LIVER DISEASE
J62y.11 HEPATIC FAILURE NOS
J62y.12 LIVER FAILURE NOS
J62y.13 HEPATIC FAILURE
J62z.00 LIVER ABSCESS AND CHRONIC LIVER DISEASE CAUSING SEQUELAE NOS
J635300 TOXIC LIVER DISEASE WITH CHRONIC PERSISTENT HEPATITIS
J635400 TOXIC LIVER DISEASE WITH CHRONIC LOBULAR HEPATITIS
J635500 TOXIC LIVER DISEASE WITH CHRONIC ACTIVE HEPATITIS
J635600 TOXIC LIVER DISEASE WITH FIBROSIS AND CIRRHOSIS OF LIVER

SP14200 HEPATIC FAILURE AS A COMPLICATION OF CARE
SP14211 LIVER FAILURE AS A COMPLICATION OF CARE

Venous Thromboembolism (both deep venous thrombosis and pulmonary embolism)

G801.11 Deep vein thrombosis
G801.12 Deep vein thrombosis, leg
G801.13 DVT - Deep vein thrombosis
G822.00 Embolism and thrombosis of the vena cava
G80y.11 Phlebitis and/or thrombophlebitis of iliac vein
G80y200 Phlebitis of the external iliac vein
G80y400 Thrombophlebitis of the common iliac vein
G80y600 Thrombophlebitis of the external iliac vein
G80y800 Phlebitis and thrombophlebitis of the iliac vein
G801.00 Deep vein phlebitis and thrombophlebitis of the leg
G801000 Phlebitis of the femoral vein
G801100 Phlebitis of the popliteal vein
G801200 Phlebitis of the anterior tibial vein
G801400 Phlebitis of the posterior tibial vein
G801500 Deep vein phlebitis of the leg unspecified
G801600 Thrombophlebitis of the femoral vein
G801700 Thrombophlebitis of the popliteal vein
G801A00 Thrombophlebitis of the posterior tibial vein
G801B00 Deep vein thrombophlebitis of the leg unspecified
G801z00 Deep vein phlebitis and thrombophlebitis of the leg NOS
G401.00 Pulmonary embolism
G401.12 Pulmonary embolus

Oral Hypoglycemic Agents

ORAL ANTIDIABETICS_sulfonylureas
2108 Acetohexamide
2110 Tolazamide
2115 Tolbutamide
2116 Glibenclamide (aka Glyburide)
2133 Glibornuride
2139 Glipizide
2148 Gliclazide
2159 Glimepiride
2140 Gliquidone
2120 Chlorpropamide

ORAL ANTIDIABETICS_Acarbose
2157 Acarbose

ORAL ANTIDIABETICS_Biguanides
2122 Metformin

ORAL ANTIDIABETICS_Glinides
2161 Repaglinide
2165 Nateglinide

Dipeptidyl peptidase 4 inhibitors
1079 SITAGLIPTIN

Oral Antidiabetics_PPAR agonists
2163 ROSIGLITAZONE
2167 ROSIGLITAZONE AND METFORMIN
2160 TROGLITAZONE
2162 PIOGLITAZONE
51050 ROSIGLITAZONE + GLIMEPIRIDE
51067 PIOGLITAZONE / METFORMIN

Insulin

2103 INSULIN
2109 (CZI CRYSTILLIN ZINC INSULIN
2111 INSULIN ZINC SUSPENSION
2112 INSULIN ZINC SUSPENSION EXTENDED
2125 DEPOT-INSULIN CS
2128 GLOBIN ZINC INSULIN INJECTION
2129 KOMB-INSULIN
2136 INSULIN NOVO-RAPITARD
2138 INSULIN LEO
2141 LONG INSULIN
2144 INSULIN CS
2151 INSULIN HUM NPH W ISOPHANE
2154 INSULIN HUM NPH W NEUTRAL/SOLUBLE

2158 PRO-HUMAN INSULIN LISPRO
16221 INSULINS & ORAL ANTIDIABETIC AGENTS
51007 INSULIN PORC ZINK / LENTE SEMILENTE
51008 INSULIN BEEF
02170 HUMALOG

Statins

1214 PRAVASTATIN
1217 FLUVASTATIN
1218 ATORVASTATIN
1219 CERIVASTATIN
1220 SIMVASTATIN
1221 ROSUVASTATIN CALCIUM
1222 EZETIMIBE + SIMVASTATIN
19103 SIMVASTATIN
1212 LOVASTATIN

Antihypertensive Agents

ACE-inhibitors_P
2202 IMIDAPRIL HCL
4555 CAPTOPRIL
4559 ENALAPRIL
4566 LISINOPRIL
4574 PERINDOPRIL
4575 RAMIPRIL
4578 CILAZAPRIL
4580 FOSINOPRIL
4592 MOEXIPRIL
4609 TRANDOLAPRIL
5776 QUINAPRIL
4584 Benazepril

ACE-inhibitor combinations
4618 PERINDOPRIL + INDAPAMIDE

ACE-inhibitors and diuretics
4569 CAPTOPRIL W HYDROCHLORTH
4577 LISINOPRIL W HYDROCHLORO
4581 ENALAPRIL W HYDROCHLOROT
4590 benazepril hydrochlorothiazide

ACE-inhibitors and calcium channel blockers
4598 FELODIPINE+RAMIPRIL

Angiotensin II antagonists
4589 LOSARTAN
4596 VALSARTAN
4615 TELMISARTAN
4617 EPROSARTAN

6202 AMIAS (=Candesartan)
6203 APROVEL (= Irbesartan)
24518 OLMESARTAN MEDOXOMIL

Angiotensin II inhibitors and diuretics
4595 COZAAR-COMP
6207 IRBESARTAN+HYDROCHLOROTH

Beta-blockers incl. Combination with diuretics
1320 ACEBUTOLOL HCL
1321 TIMOLOL MALEATE
1326 ATENOLOL
4561 ATENOLOL W CHLORTHALIDON
4562 NADOLOL W BENDROFLUMETHI
4568 ATENOLOL W NIFEDIPINE
4583 CELIPROLOL
4611 NEBIVOLOL
5710 PROPRANOLOL
5723 OXPRENOLOL HCL
5732 PINDOLOL
5754 NADOLOL
5757 CLOPAMIDE W PINDOLOL
5769 BETAXOLOL
5770 TIMOLOL,AMILORIDE,HYDROC
5773 OXPRENOLOL W CYCLOPENTHI
5778 ESMOLOL
6140 METOPROLOL
6178 PROPRANOLOL W BENDROFLUA
6180 METOPROLOL W HYDROCHLORO
6182 METOPROLOL W CHLORTHALID
6184 SOTALOL W HYDROCHLOROTHI
6185 TIMOLOL W BENDROFLUAZIDE
6188 BISOPROLOL FUMARATE
6191 CARTEOLOL HCL TABLETS
6196 BISOPROLOLFUMARATE W HYD
6798 AMILORIDE,ATENOLOL,HYDRO
16704 FUROSEMIDE W PENBUTOLOL
6164 LABETALOL HCL
6166 SOTALOL HCL
6198 CARVEDILOL
6797 HYDROCHLOROTHIAZIDE W AC
4594 TENBEN
4599 HYDROCHLOROTHIAZIDE+TIMO
5731 alprenolol
6160 bupranolol hcl

1327 penbutolol
16704 furosemide w penbutolol

Calcium channel blockers
4579 FELODIPINE SR
4587 LACIDIPINE
4591 DILTIATEM + HYDROCHLOROT
4597 NISOLDIPINE
4598 FELODIPINE+RAMIPRIL
4607 ISRADIPINE
5733 VERAPAMIL
5779 VERAPAMIL HCL 180MG/2MG
6136 AMLODIPINE
6145 NIFEDIPINE
6148 PERHEXILINE MALEATE
6156 LIDOFLAZINE
6175 DILTIAZEM
6189 NIMODIPINE
6187 NICARDIPINE
6204 ZANIDIP
6205 MIBEFRADIL

Diuretics

Thiazides
6716 Bendrofluazide
4527 Benzthiazide
6746 Chlorothiazide
6734 Hydrochlorothiazide
4524 Cyclopenthiazide
6737 Polythiazide
6742 Chlorthalidone (thiazide-like)
6574 Mefruside (thiazide-like)
6770 Xipamide (thiazide-like)
6758 Metolazone
6748 Hydroflumethiazide
6764 Clopamide
16703 Clopamide with potassium
4554 Indapamide

Loop diuretics
6718 Furosemide
6756 Bumetanide
16711 Torasemide
6720 Ethacrynic acid

Kalium-sparing diuretics
6719 Triamterene
6753 Amiloride
6701 Spironolactone
6420 Metyrapone

Diuretics/combinations
6702 Acetazolamide
16710 Bumetanide + amiloride
6794 Furosemide + amiloride
6795 Furosemide + triamterene
6785 Chlorthalidone + triamterene
6721 Hydrochlorothiazide + triamterene
6796 Furosemide + spironolactone
6717 SPIRONOLACTONE W HYDROCHLOROTHIAZIDE
6763 Spironolactone + thiazides
6750 Amiloride + hydrochlorothiazide
4576 Amiloride + cyclopenthiazide

Thiazides with antihypertensives
4561 ATENOLOL W CHLORTHALIDONE
6798 AMILORIDE,ATENOLOL,HYDROCHLOROTHIAZIDE

4594 Atenolol
6797 Acebutolol
6196 Bisoprolol
4562 Nadolol
5773 Oxprenolol
5757 Pindolol
5770 TIMOLOL,AMILORIDE,HYDROCHLORTHIAZIDE
6185 Timolol
4556 PROPRANOLOL W HYDROCHLORTHIAZIDE
6178 Propranolol
6180 METOPROLOL W HYDROCHLOROTHIAZIDE
6182 Metoprolol
6184 Sotalol
4569 Captopril
4581 Enalaparil
4608 Quinapril
4577 Lisinopril
4591 Diltiazem
4515 RESERPINE W HYDROCHLOROTHIAZIDE PLUS
4525 CYCLOPENTHIAZIDE W POTASSIUM CHLORIDE
4517 METHYLCLOTHIAZIDE W DESERPIDINE

4530 CYCLOPENTHIAZIDE,RESERPINE,POTASSIUM CHLORIDE
4532 GUANETHIDINE,CYCLOPENTHIAZIDE,POTASSIUM CHLORIDE
4536 HYDROFLUMETHIAZIDE,KCL,RAUWOLFIA,SERPENTHE
4539 GUANETHIDINE W HYDROCHLOROTHIAZIDE
4544 BUTABARBITAL,HYDROCHLOROTHIAZIDE,RESERPINE
4552 CLONIDINE W CHLORTHIAZIDE
4557 HYDRALAZINE W HYDROCHLOROTHIAZIDE
4564 METHOSERPIDINE W BENZTHIAZIDE
4582 LISINOPRIL W HYDROCHLOROTHIAZIDE
4585 ALKAVERVIR W EPITHIAZIDE
4590 BENAZEPRIL, HYDROCHLOROTHIAZIDE
4599 HYDROCHLOROTHIAZIDE+TIMOLOL+AMILORIDE
4601 METHYLDOPA W HYDROCHLOROTHIAZIDE
4602 (METHYLCLOTHIAZIDE W DESERPIDINE
4603 METHYLDOPA W CHLOROTHIAZIDE
6146 RESERPIN,DIHYDRALAZINE,HYDROCHLOROTHIAZIDE,KCL
6207 IRBESARTAN+HYDROCHLOROTHIAZIDE
6707 HYDROCHLOROTHIAZIDE W POTASSIUM CHLORIDE
6711 BENDROFLUMETHIAZIDE W POTASSIUM CHLORIDE
6723 METHYLCLOTHIAZIDE
6728 BENDROFLUMETHIAZIDE,RAUWOLFIA SERP,KCL
6735 TRICHLORMETHIAZIDE
6736 HYDROCHLOROTHIAZIDE W MEPROBAMATE
6738 TRICHLOMETHIAZIDE W RESERPINE
6739 CHLOROTHIAZIDE W RESERPINE
6741 (GUANETHIDINE W HYDROCHLOROTHIAZIDE
6744 CYCLOTHIAZIDE W POTASSIUM CHLORIDE
6749 CYCLOTHIAZIDE
6750 HYDROCHLOROTHIAZIDE W AMILORIDE HCL
6762 POLYTHIAZIDE W RESERPINE
6771 BUTHIAZIDE
6783 (SPIRONOLACTONE W HYDROCHLOROTHIAZID
6789 TRIAMTERINE W BENZTHIAZIDE
6792 (AMILORIDE W HYDROCHLOROTHIAZIDE
9001 CRYPTENAMINE W METHYCLOTHIAZIDE
16701 CHLOROTHIAZIDE W SPIRONOLACTONE
16702 CHLOROTHIAZIDE W SPIRONOLACTONE,LACTOSE
16709 ETHIAZIDE
40007 HYDROCHLOROTHIAZIDE OR PLACEBO STUDY
6731 QUINETHAZONE
4545 DIHYDROERG,CLOPAMIDE,RESERPINE
5758 PINDOLOL W CLOPAMIDE
6742 CHLORTHALIDONE
6782 CHLORTHALIDONE/POT.CHLORIDE
6150 RESERPIN,MEFRUSID,INOSITONICOT

4618 PERINDOPRIL + INDAPAMIDE
6752 CLOREXOLONE
6733 MERSALYL SODIUM
9198 PHENOBARBITAL W THEOBROMINE
4551 RESERPINE W FUROSEMIDE
6768 FUROSEMIDE W POTASSIUM
6793 (FUROSEMIDE W POTASSIUM
16704 FUROSEMIDE W PENBUTOLOL
6759 BUMETANIDE W POTASSIUM CHLORIDE
4605 PIRETANIDE
6790 TIENILIC ACID
6784 ETHACRYNIC ACID W TRASICOR
6766 ETOZOLIN
6781 LASIX W SPIRONOLACTON
6783 (SPIRONOLACTONE W HYDROCHLOROTHIAZID
6786 SPIRONOLACTONE W COMBINATIONS
16701 CHLOROTHIAZIDE W SPIRONOLACTONE
16702 CHLOROTHIAZIDE W SPIRONOLACTONE,LACTOSE
16708 POTASSIUM CANRENOATE
16712 EPLERENONE
4599 HYDROCHLOROTHIAZIDE+TIMOLOL+AMILORIDE
4616 TRIAMTERINE+AMILORIDE
16710 BUMETANIDE W AMILORIDE
4616 TRIAMTERINE+AMILORIDE
6765 BEMETIZIDE W TRIAMTERENE
6789 TRIAMTERINE W BENZTHIAZIDE

Nitrates

B06106 NITROGLYCERINE EXT.RELEASE
B06127 NITROGLYCERIN
B06167 NITROGLYCERIN + ISOSORBIDEDNITRAT
B06171 NITROGLYCERIN W COMBINATIONS
B06174 NITROGLYCERINE DISC
B06176 ISOSORBIDE MONONITRATE
B06206 ISOSORBIDE MONONITRATE+ASPIRIN
B06128 ISOSORBIDE DINITRATE
B06141 SODIUM NITROPRUSSIDE
B06153 AMYL NITRITE

Antiplatelet Agents

1923 EPOPROSTENOL
1928 ABCIXIMAB
1930 CLOPIDOGREL

5528	TICLOPIDIN
6105	DIPYRIDAMOLE
6201	DIPYRIDAMOLE 200MG/ASPIR
4979	Aloxiprin
1937	Tirofiban

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	N/A
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	x
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	x
Objectives	3	State specific objectives, including any prespecified hypotheses	x
Methods			
Study design	4	Present key elements of study design early in the paper	x
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	x
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	x
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	x
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	x
Study size	10	Explain how the study size was arrived at	x
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	x
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	x
		(*b*) Describe any methods used to examine subgroups and interactions	x
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	x
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	x
		(b) Indicate number of participants with missing data for each variable of interest	x
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	x
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	x
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	x
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	x
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	x
Generalisability	21	Discuss the generalisability (external validity) of the study results	x
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	x

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Rosiglitazone use and post-discontinuation glycaemic control in two European countries, 2000-2010

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**Dr. Hernandez was affiliated with BCDSP at the time the work for this project was conducted.

Key words: diabetes mellitus, drug safety, glucose-lowering drugs, rosiglitazone, thiazolidinediones

Words: abstract 2~~41~~58, main text 2,622~~553~~

1 Figure, 5 Tables

Article summary

Article focus ~~(up to three bullet points on the research questions or hypotheses addressed);~~

- Rosiglitazone is a second-line oral hypoglycaemic agent, which was sold in the European Union starting in 2000; ~~in~~ after a series of regulatory decisions, its use was first restricted and ultimately suspended in Europe, in September of 2010
- This ~~article~~ study examines utilization of rosiglitazone in Denmark and the United Kingdom (UK), in 2000-2010
- On the patient level, this ~~article~~ study explores changes in glycaemic control following discontinuation of rosiglitazone

Key messages ~~(up to three bullet points showing the key messages or significance of the study)~~

- Following a 2007 publication of a meta-analysis showing increased cardiovascular morbidity associated with rosiglitazone, use of the drug declined sharply and irreversibly in Denmark and in the UK; this predated the official suspension of the drug by the European Medicines Agency, in 2010
- On the patient level, observed mean changes in fasting plasma glucose and glycated haemoglobin A_{1c} were slight in patients who discontinued rosiglitazone

Strengths and limitations of this study

- The study makes use of population-based routine medical databases in two European countries, which are likely to reflect typical clinical practice
- Despite differences in record generation mechanisms in the two databases, results were overall concordant
- Automated prescription and dispensation data may have imprecisely measured time of initiation and discontinuation of medication intake

Abstract

Objectives To evaluate the impact of risk minimisation policies on use of rosiglitazone-containing products and on glycaemic control among patients in Denmark and the United Kingdom (UK).

Design, setting and participants We used population-based data from the Aarhus University Prescription Database (AUPD), in northern Denmark and from the General Practice Research Database (GPRD), in the UK.

Main outcome measures We examined use of rosiglitazone during its entire period of availability on the European market (2000–2010) and evaluated changes in glycated haemoglobin-A_{1c} (HbA_{1c}) and fasting plasma glucose (FPG) levels among patients discontinuing this drug.

Results During 2000–2010, 2,321 patients with records in the AUPD used rosiglitazone in northern Denmark and 25,428 patients with records in the GPRD used it in the UK. The proportion of rosiglitazone users among all users of oral hypoglycaemic agents (OHA) peaked at 4% in the AUPD and at 15% in the GPRD, in May 2007, the month of publication of a meta-analysis showing increased cardiovascular morbidity associated with rosiglitazone use. Twelve months after discontinuation of rosiglitazone-containing products, the mean change in HbA_{1c} was –0.16% (95% confidence interval [CI]: –3.4%, 3.1%) in northern Denmark and –0.17% (95% CI: –0.21%, 0.13%) in the UK. Corresponding mean changes in FPG were 0.01 mmol/L (95% CI: –7.3 mmol/L, 7.3 mmol/L) and 0.03 mmol/L (95% CI: –0.22 mmol/L, 0.28 mmol/L).

Conclusions Publication of evidence concerning potential cardiovascular risks of rosiglitazone was associated with an irreversible decline in use of rosiglitazone-containing products in Denmark and the UK. Mean changes in HbA_{1c} and FPG after drug discontinuation were slight.

INTRODUCTION

Since first marketed in the European Union, in 2000, rosiglitazone has been subject to several risk-benefit assessments, especially concerning cardiovascular safety.[1-9] In a May 2007 meta-analysis published in the *New England Journal of Medicine*, Nissen and Wolski reported increased cardiovascular morbidity associated with rosiglitazone use[2]. In 2008, the European Medicines Agency (EMA) amended the rosiglitazone product label, adding coronary syndrome to the list of contraindications and inserting a warning about potentially increased risk of ischemic events.[10] At the time of this label amendment, EMA concluded "that the benefits of [...] rosiglitazone [...] in the treatment of type 2 diabetes continue to outweigh their risks".[11] In June 2010, Nissen and Wolski updated their meta-analysis, confirming the finding of an increased risk of myocardial infarction (but not the original finding of increased all-cause mortality) in association with rosiglitazone use[12]. In July 2010, Graham and colleagues published a paper in *JAMA*, based on data from US Medicare beneficiaries, showing increased risks of several cardiovascular events, as well as all-cause mortality, in a comparison of rosiglitazone users with pioglitazone users.[7] Following these two publications, on 22 September 2010, the EMA recommended suspension of use of all rosiglitazone-containing products in the European Union.[13] The European Commission subsequently mandated suspension of the drug, citing absence of unique therapeutic benefits outweighing its risks.[14]

Here we report results of an EMA-commissioned study on the impact of labelling changes and findings reported in scientific publications on utilisation of rosiglitazone-containing products in Europe. On the population level, we examined changes in use of rosiglitazone-containing products over the entire period when rosiglitazone was available on the European market. On the patient level, we assessed the impact of rosiglitazone discontinuation on glycaemic control and reported oral hypoglycaemic agents prescribed after post-suspension discontinuation of rosiglitazone.

METHODS

Setting and study population

This study was based on routinely collected data in medical databases in ~~Danish~~ Denmark and in the United Kingdom (UK) ~~medical databases~~. In Denmark, the study population included users of oral hypoglycaemic agents (OHAs) identified in the Aarhus University Prescription Database (AUPD).[15] The database's catchment area covers the North and Central Regions of Denmark (hereafter referred to as 'northern Denmark'), with a combined population in mid-2010 of 1.8 million ~~34,595~~ persons, which is about one-third of the Danish population. The AUPD captures reimbursed prescriptions redeemed in the regions' outpatient pharmacies since 1998. In the UK, OHA users were identified from the General Practice Research Database (GPRD), currently also known as the Clinical Practice Research Datalink.[16]

We identified patients in each database with a prescription for any OHA between 1 January 2000 and 31 December 2010, encompassing the entire period of rosiglitazone availability in Europe. We defined OHA users as persons who received at least one prescription for any OHA during the study period. Prescriptions for OHAs were identified using Anatomical Therapeutic Chemical (ATC) codes in the AUPD and Multilex codes in the GPRD. People could ~~have~~ received prescriptions for multiple OHAs, including rosiglitazone, during the study period ~~, including rosiglitazone~~. Our use of the term 'rosiglitazone' includes all preparations of the drug.

Start of rosiglitazone use was defined as the date of the first-recorded prescription for a rosiglitazone-containing product. Patients were assumed to have discontinued rosiglitazone therapy in the absence of a record of a ~~new~~ rosiglitazone prescription refill during a period encompassing the estimated length of at least two prescriptions. Prescription length was estimated at 45 days in AUPD and 130 days in the GPRD, based on observed intervals between prescriptions and knowledge about typical ~~clinical~~ prescribing practice in Denmark, as well as on the prescribing instructions in the British Monthly Index of Medications in the UK.

To describe the study population, we obtained data on participants' clinical and demographic characteristics, including sex, age, body mass index (BMI), smoking, medical

diagnoses, and use of other medications (lipid-lowering agents, antihypertensive agents, diuretics, nitrates, and antiplatelet agents). These characteristics were measured as of 1 January 2000 for patients who started an OHA before 2000 and on the date of the first OHA prescription for those who started thereafter. We used records from routine laboratory tests to obtain data on measured glycated haemoglobin-A_{1c} (HbA_{1c}) and fasting plasma glucose (FPG) levels.

Data sources

In northern Denmark, data on hospital-based medical diagnoses, prescription medications, and laboratory test results were obtained, respectively, from the Danish National Registry of Patients (DNRP[17]), from the AUPD, and from the Laboratory Information Systems of the North and the Central Denmark Regions (the LABKA database[18]). The LABKA database stores results of laboratory tests performed at hospital-based laboratories. Patients are referred to these laboratories by hospitals, general practitioners, and specialists. Data on smoking and BMI were obtained from the Danish National Indicator Project diabetes database.[19] (http://www.nip.dk). All data were linked on the individual level using the universal personal identifier.[20] In the UK all data were obtained from the GPRD. The GPRD is a longitudinal database that has collected data from over 450 general practices in the UK since 1987, covering a representative 6% sample of the UK population. The GPRD captures prescriptions issued to patients by general practitioners, and it also includes information on patient demographics, diagnoses, referrals, hospitalizations, and laboratory test results.[16 21-23]

Statistical analysis

First, we examined changes in the proportion of rosiglitazone users among all users of OHAs in the two countries between 2000 and 2010. Second, we compared distributions of demographic and clinical characteristics between rosiglitazone users and users of other OHAs. Third, we examined changes in HbA_{1c} and FPG levels, comparing values before and after discontinuation of rosiglitazone treatment. The pre-discontinuation value of a laboratory parameter was the value closest in time to the estimated discontinuation date within 24 months before that date. We defined three non-overlapping post-discontinuation periods as follows: 3

months (90–179 days ~~post-discontinuation~~); 6 months (180–359 days ~~post-discontinuation~~); and 12 months (360–479 days ~~post-discontinuation~~). We used the earliest available measurement within each post-discontinuation period. The post-discontinuation values were ascertained through 30 June 2011. ~~Using the pre-discontinuation and post-discontinuation values, we~~ We calculated the mean (with standard deviation) level for HbA_{1c} and FPG before and after discontinuation and the mean change for each post-discontinuation period. Furthermore, we calculated the proportion of patients with new post-discontinuation onset of loss of glycaemic control, defined as ~~of~~ HbA_{1c} >7.5%~~;~~ and the proportion of patients with new post-discontinuation onset of treatment failure, defined as FPG >10 mmol/L. To capture new onset, these proportions ~~first~~ were computed among patients without evidence of treatment failure/loss of glycaemic control before discontinuing rosiglitazone. We then calculated the proportions of patients with clinically meaningful changes in HbA_{1c} (change >0.6%) and FPG (change >10%) after discontinuation of rosiglitazone. Finally, we examined changes in HbA_{1c} levels in patients who discontinued the drug on or after 23 September 2010, presumably in response to the EMA's suspension of the drug~~,~~ We also ~~and~~ reported the distribution of the first OHA prescribed ~~to patients who discontinued rosiglitazone~~ after rosiglitazone ~~its~~ suspension. The algorithms used to define variables in this project are provided in the Appendix. We used SAS software version 9.2 (SAS Inc., Cary, NC, USA) to analyse the data.

Ethical approval

This study was approved by the Danish Data Protection Agency (record number 2009-41-3866) and by the Independent Scientific Advisory Committee of the GPRD. There was no patient contact, and informed consent was therefore not required.

RESULTS

Utilisation of rosiglitazone and patient characteristics

During the study period, 67,525 OHA users were recorded in the AUPD and 191,276 in the GPRD. Of these, 2,321 (3.4%) persons in the AUPD and 25,428 (13%) persons in the GPRD received at least one prescription for a rosiglitazone-containing product. Figure 1

shows changes in the proportion of rosiglitazone users among all OHA users ~~within~~ during the study period. This proportion peaked at 4% in northern Denmark and at 15% in the UK in May 2007, and rapidly decreased thereafter, with virtually no rosiglitazone users remaining after 2010.

Table 1 compares demographic and clinical characteristics of users of rosiglitazone ~~and~~ with users of other OHAs. Rosiglitazone users tended to be younger, but were more likely to have had a prescription history of lipid-lowering or antihypertensive agents. Rosiglitazone users were more likely than the other OHA users to have used OHAs other than metformin and sulfonylurea ~~previously~~before starting rosiglitazone. Based on data from the GPRD, users of rosiglitazone-containing products were slightly more likely than other OHA users to have a BMI of ≥30 kg/m^2. BMI data for patients in Denmark were sparse (Table 1).

Glycaemic control after discontinuation of rosiglitazone~~.~~

Among all rosiglitazone users in the ~~LABKA~~ AUPD, 1776 patients who discontinued the drug had HbA_{1c} measurements ~~available~~. Among these patients, t~~T~~he ~~mean~~ median duration of rosiglitazone use ~~in these patients~~ was ~~24~~19~~.1~~ months (~~standard deviation 21.1), median 18.8~~quartiles, 6–38 months)~~.~~, and the median time from the last pre-discontinuation HbA_{1c} measurement until discontinuation of rosiglitazone was 44 days (quartiles, 21–78 days). In the GPRD, there were 21,145 rosiglitazone users with HbA_{1c} measurements. Among these patients, t~~T~~he ~~mean~~ median duration of rosiglitazone use was ~~use in these patients was 30.3 (standard deviation 25.5), median,~~ 24~~.0~~ months (quartiles, 8–47 months) and the median time from the last pre-discontinuation HbA_{1c} measurement until discontinuation of rosiglitazone was 70 days (quartiles, 25–153 days). Table 2 shows changes in HbA_{1c} at three, six, and 12 months after discontinuation of rosiglitazone treatment at any time during the study period. At 12 months post-discontinuation, a change of similar magnitude in the mean HbA_{1c} was observed in both ~~the LABKA (Denmark) and Laboratory (UK)~~ databases: –0.16% (95% confidence interval [CI]: –3.4%, 3.1%) in northern Denmark, and –0.17% (95% CI: –0.21%, -0.13%) in the UK. Loss of glycaemic control, defined by new onset of HbA_{1c}>7.5%, was registered for up to 29% of patients during the 12-month follow-up period in Denmark and for

up to 37% of patients in the UK. Similar proportions of patients had HbA_{1c} values consistent with a clinically meaningful decrease (>0.6%) at 12 months post-discontinuation.

Table 3 shows changes in HbA_{1c} ~~after~~ among patients who ~~discontinuation~~ discontinued~~of~~ rosiglitazone-containing products on or after 23 September 2010. Thus, Table 3 represents subset of patients described in Table 2. In the UK data, mean HbA_{1c} decreased by 1.8% (95% CI: –2.1%, –1.6%) at six months post-discontinuation ~~(95% CI: –2.1%, –1.6%)~~, but the pre-discontinuation mean HbA_{1c} in this group was 10%. A larger proportion of patients in the UK than in Denmark had evidence of loss of glycaemic control and a substantially larger proportion of patients in the UK experienced a clinically meaningful decrease in HbA_{1c} after discontinuation of rosiglitazone compared with Denmark (Table 3).

Table 4 shows changes in FPG at three, six, and 12 months after discontinuation of rosiglitazone. At 12 months ~~post-discontinuation~~, there was virtually no change seen in either of the databases: mean change of ~~=~~–0.01 mmol/L (95% CI: –7.3 mmol/L; 7.3 mmol/L) in northern Denmark, and mean change of ~~=~~–0.03 mmol/L (95% CI: –0.22 mmol/L; 0.28 mmol/L) in the UK. Treatment failure, defined by new onset of FPG >10 mmol/L during one of the follow-up periods, was observed in a maximum of 23% of patients in northern Denmark and 20% in the UK. The number of persons with available measurements for northern Denmark, however, was small (Table 4). Table 5 shows the distribution of OHA prescribed to patients ~~after~~ who ~~terminating~~discontinued rosiglitazone on 23 September 2010 or later. The majority of the patients switched to another ~~-~~OHA (82% in northern Denmark; 97% in the UK) after the last recorded ~~pioglitazone~~ rosiglitazone prescription. The majority of patients – 56.8% in Denmark and 41.7% in the UK – received a prescription for metformin. In the UK, 23.6% of patients had a prescription for pioglitazone, and 14.5% for pioglitazone and ~~+~~ metformin. Pioglitazone was prescribed only to 4.4% of the patients in northern Denmark.

DISCUSSION

We examined use of rosiglitazone-containing products over the entire period of availability of this drug in Europe (2000–2010) using routinely collected data in medical

databases in Denmark and in the United Kingdom. Overall, the drug was more widely used in the UK than in Denmark, with the proportion of rosiglitazone users among all users of OHA peaking at 15% and 4% in the two countries, respectively. The timing of both peaks, which marked the beginning of a steep decline in use, coincided with the May 2007 publication of the meta-analysis by Nissen and Wolski[2] and subsequent regulatory warnings from the EMA. This decline occurred three years before the regulatory decision to suspend rosiglitazone in Europe. Similarly, a sharp decline in prescribing occurred in the United States after the FDA added a boxed warning to the rosiglitazone label in May 2007.[24] On the patient level, discontinuation of rosiglitazone was associated with a slight overall decrease in the mean level of glycated haemoglobin. However, close to one-third of patients had evidence consistent with loss of glycaemic control during the 12 months of follow-up, including patients who discontinued rosiglitazone after the EMA decision to suspend the drug. ~~The majority of~~Most patients who discontinued rosiglitazone after the EMA-mandated suspension started receiving metformin.

Meaning of the findings

While on the market, rosiglitazone represented a larger proportion of all OHA use in the UK than in Denmark. This may reflect conservative recommendations issued in Denmark, suggesting that treatment first be attempted with metformin, sulfonurea, and insulin.[25] Guidelines from the National Institute for Health and Clinical Excellence (NICE) in the UK stated that rosiglitazone should only be prescribed if other classes of OHA were not effective in lowering plasma glucose concentrations. Therefore rosiglitazone was recommended only as second or third line therapy.[26] The high pre-discontinuation level of HbA_{1c} in UK patients who discontinued rosiglitazone following the drug suspension is also consistent with this guideline. Among patients terminating rosiglitazone after the drug was suspended, a larger proportion of UK patients compared with their Danish counterparts experienced a clinically meaningful decrease in glycated haemoglobin. The pre-discontinuation values among the UK patients were substantially higher, probably reflecting heightened medical attention drawn to

~~We thus attribute this to the result of~~ patients with poor glycaemic control ~~coming to medical attention~~.

Strengths and weaknesses

The data presented here were obtained from medical databases containing ~~that provide~~ data on routine and independent registration of health-related events in two European countries. Such data are therefore likely to reflect typical clinical practice. The data from the two data systems are also complementary. The AUPD records ~~filled~~ purchased prescriptions, while the GPRD records prescriptions issued by general practitioners. Furthermore, the databases draw on different health sectors for information on patient characteristics: ~~.~~ ~~I~~In Denmark data on diagnoses originate from hospital discharge summaries, while in the GPRD, data on diagnoses originate from general-practitioner records. Despite these differences and potential differences in the underlying patient populations, the results obtained from the two ~~data systems~~countries were generally consistent.

Because OHA are distributed by prescription only and need to be taken long-term, the information we present on rosiglitazone utilization over calendar time is likely to be accurate. The pattern of use for the two Danish regions included here mirrors the nationwide pattern reported by the Danish Medicines Agency.~~.~~[27]~~.~~ However, because automated prescription records provide no information on the exact timing of drug intake, we had to make assumptions about timing of rosiglitazone discontinuation and prescription length. We speculate that short-term changes in laboratory parameters following discontinuation of rosiglitazone are subject to more misclassification due to errors in assigning the discontinuation status than are long-term changes in these parameters. Therefore, our 12-month estimates of post-discontinuation change in laboratory parameters may be more robust than the 3-month estimates. The information on glycated haemoglobin A_{1c} and on fasting plasma glucose originated from routinely collected laboratory data, although patients with laboratory measurements may differ from the entire population of rosiglitazone-treated patients. For example, physicians may be less likely to routinely collect laboratory data for patients with less severe diabetes.

Conclusion

In summary, a decline in use of rosiglitazone occurred immediately following the May 2007 publication of a meta-analysis describing adverse cardiac side effects of this drug.[2] Changes in glycaemic control after discontinuation of rosiglitazone were, on average, small on average during the 12 months after discontinuation of rosiglitazone follow-up period, although about one-third of patients had evidence of loss of glycaemic control upon discontinuation. Most patients who discontinued rosiglitazone after EMA-mandated suspension were switched to a metformin-containing regimen.

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DISCLAIMER

This document expresses the opinions of the authors of the paper, and may not be understood or quoted as being made on behalf or of reflecting the position of the European Medicines Agency or one of its committees or working parties.

CONTRIBUTION STATEMENT

V. Ehrenstein participated in conception and design of the study, led the writing, and contributed to data analysis. R. K. Hernandez contributed to study design and data analysis in the GPRD. S. P. Ulrichsen conducted the data analyses in Denmark. J. Rungby contributed to study design and analysis, and provided clinical expertise, T.L. Lash participated in

conception and design of the study, A.H. Riis contributed to data analysis of the AUPD data, L. Li contributed to data analysis of the GPRD data, H.T. Sørensen oversaw the study and provided clinical expertise, and S. S. Jick participated in conception and design of the study. All authors participated in revisions of the manuscript draft for intellectual content.

This study has received the ENCePP Study Seal (Reference number ENCEPP/SDPP/1777).

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Competing interest statement

All authors have completed the ICMJE uniform disclosure form at and declare: being funded by the EMA (through institutional contracts and subcontracts) for this work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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FIGURE LEGEND

Figure 1. Proportion of users of rosiglitazone among all users of oral hypoglycaemic agents (OHA), 2000-2010 in northern Denmark and in the United Kingdom. The maximum points of both graphs correspond to May 2007, the month of publication of the initial meta-analysis by Nissen and Wolski.[2]

TABLES

Table 1. Baseline characteristics of patients treated with rosiglitazone and other oral hypoglycaemic agents from 1 January 2000 to 31 December 2010 in northern Denmark and the United Kingdom.

Characteristic	Northern Denmark (n=67,525)		United Kingdom (n=191,276)	
	Users of rosiglitazone (n=2,321) N (%)	Users of other oral hypoglycaemic agents (n=65,204) N (%)	Users of rosiglitazone (n=25,428) N (%)	Users of other oral hypoglycaemic agents (n=165,848) N (%)
Age group, years				
<35	83 (3.6)	3,999 (6.1)	589 (2.3)	9,358 (5.6)
35-44	286 (12)	4,967 (7.6)	2,469 (9.7)	13,192 (8.0)
45-54	595 (26)	10,219 (16)	5,513 (22)	25,023 (15)
55-64	757 (33)	16,751 (26)	7,661 (30)	38,668 (23)
65-74	444 (19)	15,724 (24)	6,434 (25)	42,030 (25)
75-84	147 (6.3)	10,423 (16)	2,426 (9.5)	28,430 (17)
≥85	9 (0.39)	3,121 (4.8)	336 (1.3)	9,147 (5.5)
Sex				
Female	976 (42)	30,845 (47)	11,259 (44)	78,772 (48)
Male	1,345 (58)	34,359 (53)	14,169 (56)	87,076 (53)
Charlson comorbidity index				
0	1,694 (73)	41,183 (63)	16,646 (65)	95,607 (58)
1-2	561 (24)	19,470 (30)	7,925 (31)	57,984 (35)
3+	66 (2.8)	4,551 (7.0)	857 (3.4)	12,257 (7.4)
History of OHA use before baseline*				
Metformin	2,279 (98)	51,022 (78)	23,836 (94)	144,881 (87)
Sulfonylurea	1,730 (74)	39,931 (61)	19,489 (77)	90,682 (55)
Pioglitazone	81 (3.5)	196 (0.30)	9,297 (37)	14,194 (8.6)
DPP 4 Inhibitor	517 (22)	4,149 (6.4)	2,242 (8.8)	5,882 (3.6)
Other oral glucose-lowering drugs**	497 (21)	5,530 (8.5)	2,582 (10)	5,725 (3.5)
History of other medication use				
Lipid lowering agents	1,939 (84)	40,327 (62)	22,223 (87)	114,378 (69)

Antihypertensive agents	1,991 (86)	48,016 (74)	21,846 (86)	126,897 (77)
Diuretics	1,404 (60)	34,650 (53)	13,516 (53)	73,225 (44)
Nitrates	351 (15)	9,456 (14)	52 (0.20)	322 (0.19)
Antiplatelet agents	1,409 (61)	33,060 (51)	2,878 (11)	15,223 (9.2)
Smoking				
Current	175 (7.5)	2,451 (3.8)	4,499 (18)	28,120 (17)
Former	215 (9.3)	3,121 (4.8)	6,102 (24)	43,985 (27)
Never	258 (11)	3,534 (5.4)	11,699 (46)	75,119 (45)
Missing	1,673 (72)	56,098 (86)	3,128 (12)	18,624 (11)
Body mass index category, kg/m^2				
< 18.5	2 (0.09)	32 (0.05)	35 (0.14)	623 (0.38)
18.5 – <25	51 (2.2)	1,257 (1.9)	2,675 (11)	21,634 (13)
25 – <30	177 (7.6)	3,257 (5.0)	7,458 (29)	49,463 (30)
≥ 30	462 (20)	5,454 (8.4)	11,225 (44)	66,725 (40)
Missing	1,629 (70)	55,204 (85)	4,035 (16)	27,403 (17)

*Baseline date was January 1, 2000 or date of first OHA prescription, whichever came later.
**Other glucose-lowering drugs excluding insulins are acarbose, repaglinide, exenatide, and liraglutide.

Table 2. Glycated haemoglobin (%) before and after discontinuation of rosiglitazone among patients with available pre-and post-discontinuation measurements, in northern Denmark and in the United Kingdom, 2000-2011.

Characteristic	Northern Denmark			United Kingdom		
	3 months (n=1,242)	6 months (n=1,496)	12 months (n=1,162)	3 months (n=9,448)	6 months (n=12,439)	12 months (n=8635)
Baseline mean (SD)	7.8 (1.7)	7.8 (1.6)	7.9 (1.7)	8.7 (2.2)	8.5 (2.1)	8.4 (1.9)
Follow-up mean (SD)	7.7 (1.5)	7.7 (1.5)	7.7 (1.5)	8.1 (1.7)	8.2 (1.8)	8.2 (1.8)
Change from baseline, mean (95% CI)	-0.10 (-3.0; 2.8)	-0.05 (-3.1; 3.0)	-0.16 (-3.4; 3.1)	-0.57 (-0.62; -0.53)	-0.30 (-0.34; -0.26)	-0.17 (-0.21; -0.13)
Proportion with a clinically meaningful* increase, percent (95% CI)	26 (24; 29)	28 (26; 30)	28 (26; 31)	23 (22; 24)	28 (27; 28)	29 (28; 30)
Proportion with a clinically meaningful* decrease, percent (95% CI)	28 (25; 30)	27 (25; 29)	30 (27; 32)	40 (39; 41)	36 (35; 37)	34 (33; 35)
N with HbA_{1c} level>7.5% after baseline/N with baseline HbA_{1c} ≤7.5%	160/670	228/827	179/610	1,026/3,286	1,641/4,672	1,246/3,408
New post-discontinuation onset of loss of glycaemic control with HbA_{1c} >7.5%, percent (95% CI)[b]	24 (21; 27)	28 (25; 31)	29 (26; 33)	31 (30; 33)	35 (34; 36)	37 (35; 38)

*Clinically meaningful change defined using to the European Medicines Agency's definition as change of more than 0.6% (% is the test unit)
CI, confidence interval; HbA_{1c},glycated haemoglobin A; SD, standard deviation

Table 3. Glycated haemoglobin (%) before and after discontinuation of rosiglitazone-containing products, among users who discontinued the drug on or after 23 September 2010 (date of the EMA's recommendation to suspend rosiglitazone), in northern Denmark and in the United Kingdom.

Characteristic	Northern Denmark		United Kingdom	
	3 months (n=376)	6 months (n=455)	3 months (n=1081)	6 months (n=338)
Baseline mean (SD)	7.1 (1.2)	7.1 (1.2)	10 (2.5)	10 (2.5)
Follow-up mean (SD)	7.5 (1.5)	7.4 (1.4)	8.0 (2.0)	8.3 (2.1)
Change from baseline, mean (95% CI)	0.40 (-1.9; 2.7)	0.34 (-1.8; 2.5)	-2.0 (-2.2; -1.8)	-1.8 (-2.1; -1.6)
Proportion with a clinically meaningful* increase, percent (95% CI)	34 (29;38)	33 (29;38)	14 (12; 16)	15 (12; 19)
Proportion with a clinically meaningful* decrease, percent (95% CI)	13 (9.5; 16)	12 (9.3; 15)	72 (69; 75)	69 (64; 74)
N with HbA_{1c} level>7.5% after baseline/N with baseline HbA_{1c} ≤7.5%	76/285	94/350	87/196	18/55
New post-discontinuation onset of loss of glycaemic control with HbA_{1c} >7.5%, percent (95% CI)[b]	27 (22; 32)	27 (22; 32)	44 (38;51)	33 (22; 46)

Clinically meaningful change defined using to the European Medicines Agency's definition as change of more than 0.6% (% is the test unit)

CI, confidence interval; HbA_{1c}, glycated haemoglobin A; SD, standard deviation

Table 4. Fasting plasma glucose (mmol/L) before and after discontinuation of rosiglitazone among patients with available pre-and post-discontinuation laboratory measurements, in northern Denmark and in the United Kingdom, 2000-2011.

Characteristic	Northern Denmark			United Kingdom		
	3 months (n=95)	6 months (n=109)	12 months (n=77)	3 months (n=820)	6 months (n=1,256)	12 months (n=800)
Baseline mean (SD)	9.5 (3.6)	9.3 (3.4)	9.1 (3.5)	8.6 (3.2)	8.7 (3.2)	8.7 (3.4)
Follow-up mean (SD)	9.2 (3.7)	9.0 (3.4)	9.1 (3.5)	8.8 (3.2)	8.8 (3.1)	8.7 (3.1)
Change from baseline, mean (95% CI)	-0.38 (-9.0; 8.2)	-0.27 (-8.2;7.6)	0.01 (-7.3; 7.3)	0.27 (0.04; 0.49)	0.08 (-0.12; 0.27)	0.03 (-0.22; 0.28)
Proportion with a clinically meaningful* increase, percent (95% CI)	40 (31; 50)	35 (26; 44)	32 (23; 43)	39 (36; 43)	40 (38; 43)	40 (37; 44)
Proportion with a clinically meaningful* decrease, percent (95% CI)	39 (30; 49)	35 (26; 44)	40 (30; 51)	30 (27; 33)	33 (31; 36)	34 (31; 38)
N with FPG >10 mmol/L after baseline/N with baseline FPG ≤10 mmol/L	14/65	18/79	8/54	98/610	182/911	99/583
New post-discontinuation onset of treatment failure, FPG>10 mmol/L, percent (95% CI)	22 (13; 33)	23 (15; 33)	15 (7.3; 26)	16 (13, 19)	20 (18; 23)	17 (14; 20)

*Clinically meaningful change defined using to the European Medicines Agency's definition as change of more than 10 mmol/L.
CI, confidence interval; HbA_{1c}, glycated haemoglobin A; SD, standard deviation

Table 5. Oral hypoglycaemic agents (OHA) prescribed to patients after terminating rosiglitazone on 23 September 2010 or later.

	Aarhus University Prescription Database, northern Denmark (n=474*)		General Practice Research Database, United Kingdom (n=2810[+])	
	Number	Percent (95% CI)	Number	Percent (95% CI)
Metformin	269	56.8 (52.3; 61.2)	1136	41.7 (39.9; 43.6)
Glimepiride	84	17.7 (14.3; 21.2)	57	2.1 (1.6; 2.7)
Metformin+sitagliptin	49	10.3 (7.6; 13.1)		
Sitagliptin	45	9.5 (6.9; 12.1)	103	3.8 (3.1; 4.6)
Metformin+vildagliptin	35	7.4 (5.0; 9.7)		
Liraglutide	26	5.5 (3.4; 7.5)		
Pioglitazone	21	4.4 (2.6; 6.3)	641	23.6 (22.0; 25.2)
Pioglitazone + metformin			394	14.5 (13.2; 15.9)
Gliclazide	17	3.6 (1.9; 5.3)	351	12.9 (11.7; 14.2)
Glibenclamide	8	1.7 (0.5; 2.8)	16	0.6 (0.4; 1.0)
Saxagliptin	8	1.7 (0.5; 2.8)		
Glipizide	4	0.8 (0.1; 1.7)	9	0.3 (0.2; 0.6)
Vildagliptin	4	0.8 (0.1; 1.7)		
Repaglinide	3	0.6 (0.1; 1.3)	2	0.1 (0.0; 0.3)
Exenatide	3	0.6 (0.1; 1.3)		
Acarbose	2	0.4 (0.1; 1.0)	4	0.2 (0.1; 0.4)
Tolbutamide	1	0.2 (0.1; 0.6)	9	0.3 (0.2; 0.6)

*83 patients had no record of another OHA after the last rosiglitazone prescription.

[+]88 patients had no record of another OHA after the last rosiglitazone prescription

Correction

Ehrenstein V, Hernandez RK, Ulrichsen SP, *et al*. Rosiglitazone use and post-discontinuation glycaemic control in two European countries, 2000–2010. *BMJ Open* 2013;3:e003424. In the section 'Ethics approval' the record number with the Danish Data Protection Agency is incorrect. The sentence should read: '**Ethics approval** This study was approved by the Danish Data Protection Agency (record number 2004-41-4693) and by the Independent Scientific Advisory Committee of the GPRD.'

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