

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

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ABSTRACT

Objectives: To evaluate the impact of risk minimisation policies on the use of rosiglitazone-containing products and on glycaemic control among patients in Denmark and the 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 the use of rosiglitazone during its entire period of availability on the European market (2000–2010) and evaluated changes in the glycosylated haemoglobin (HbA_{1c}) and fasting plasma glucose (FPG) levels among patients discontinuing this drug.

Results: During 2000–2010, 2321 patients with records in AUPD used rosiglitazone in northern Denmark and 25 428 patients with records in GPRD used it in the UK. The proportion of rosiglitazone users among all users of oral hypoglycaemic agents peaked at 4% in AUPD and at 15% in GPRD in May 2007, the month of publication of a meta-analysis showing increased cardiovascular morbidity associated with rosiglitazone use. 12 months after discontinuation of rosiglitazone-containing products, the mean change in HbA_{1c} was –0.16% (95% CI –3.4% to 3.1%) in northern Denmark and –0.17% (95% CI –0.21% to 0.13%) in the UK. The corresponding mean changes in FPG were 0.01 mmol/L (95% CI –7.3 to 7.3 mmol/L) and 0.03 mmol/L (95% CI –0.22 to 0.28 mmol/L).

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

INTRODUCTION

Since it was first marketed in the European Union in 2000, rosiglitazone has been subjected to several risk-benefit assessments, especially concerning cardiovascular safety.^{1–9} In a May 2007 meta-analysis published in

ARTICLE SUMMARY

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 the record generation mechanisms in the two databases, the results were concordant overall.
- The automated prescription and dispensation data may have imprecisely measured the time of initiation and discontinuation of medication intake.

the *New England Journal of Medicine*, Nissen and Wolski² reported increased cardiovascular morbidity associated with rosiglitazone use. 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 the potentially increased risk of ischaemic 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 Wolski¹² 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. In July 2010, Graham *et al*⁷ published a paper in *JAMA*, based on data from the 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. Following these two publications, on 22 September 2010, the EMA recommended the suspension of use of all rosiglitazone-containing products in the European Union.¹³ The European Commission subsequently mandated the suspension of the drug, citing the absence of unique therapeutic benefits outweighing its risks.¹⁴

We report the results of an EMA-commissioned study on the impact of labelling changes and findings reported in scientific publications on the utilisation of rosiglitazone-containing products in Europe. On the population level, we examined changes in the 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 (OHAs) prescribed after the postsuspension discontinuation of rosiglitazone.

METHODS

Setting and study population

This study was based on routinely collected data in medical databases in Denmark and in the UK. In Denmark, the study population included users of 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. 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 codes in AUPD and Multilex codes in 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.

The 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. The prescription length was estimated at 45 days in AUPD and 130 days in GPRD, based on the 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 patients' clinical and demographic characteristics, including sex, age, body mass index (BMI), smoking, medical diagnoses and use of other medications (lipid-lowering agents, anti-hypertensive 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 the measured glycated haemoglobin (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, respectively, were obtained from the Danish National Registry of Patients,¹⁷ AUPD, and the Laboratory Information Systems of the North and the Central Denmark Regions (the LABKA database¹⁸). The LABKA database stores the 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

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

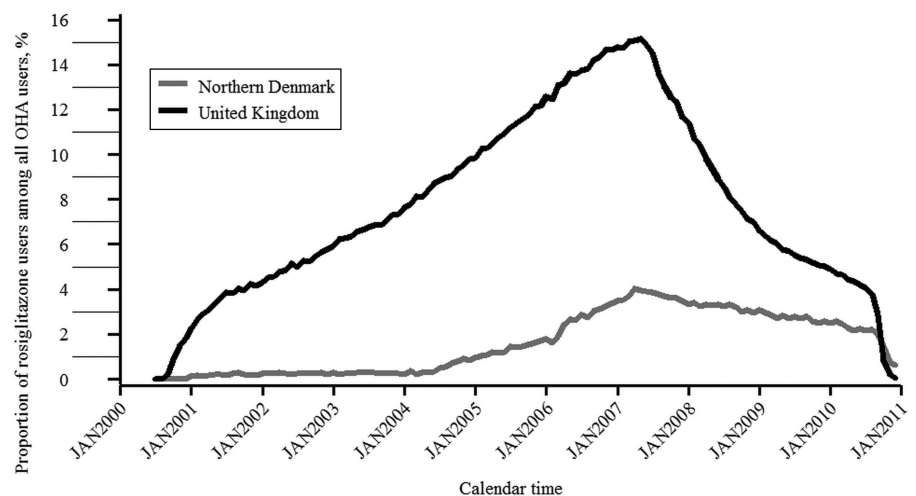


Table 1 Baseline characteristics of patients treated with rosiglitazone and other oral hypoglycaemic agents from 1 January 2000 to 31 December 2010 in northern Denmark and the UK

| Characteristic | Northern Denmark (n=67 525) | | UK (n=191 276) | |
|---|--|--|--|---|
| | Users of rosiglitazone (n=2321) 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 1 January 2000 or date of first OHA prescription, whichever came later.

†Other glucose-lowering drugs excluding insulins are acarbose, repaglinide, exenatide and liraglutide. OHA, oral hypoglycaemic agent.

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 GPRD. 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. GPRD captures prescriptions issued to patients by general practitioners, and it also includes information on patient demographics, diagnoses, referrals, hospitalisations 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 the HbA_{1c} and FPG levels, comparing values before and after the discontinuation of rosiglitazone treatment. The prediscontinuation value of a laboratory parameter was the value closest in time to the estimated

Table 2 Glycated haemoglobin (HbA_{1c}; %) before and after discontinuation of rosiglitazone among patients with available pre-discontinuation and post-discontinuation measurements, in northern Denmark and in the United Kingdom, 2000–2011

| Characteristic | Northern Denmark (n=1242) | | United Kingdom (n=9448) | | 12 months (n=8635) | |
|--|---------------------------|---------------------|-------------------------|------------------------|------------------------|------------------------|
| | 3 months (n=1496) | 6 months (n=1496) | 3 months (n=9448) | 6 months (n=12 439) | 12 months (n=8635) | 12 months (n=8635) |
| Baseline mean (SD) | 7.8 (1.7) | 7.8 (1.6) | 8.7 (2.2) | 8.5 (2.1) | 8.4 (1.9) | 8.4 (1.9) |
| Follow-up mean (SD) | 7.7 (1.5) | 7.7 (1.5) | 8.1 (1.7) | 8.2 (1.8) | 8.2 (1.8) | 8.2 (1.8) |
| Change from baseline, mean (95% CI) | -0.10 (-3.0 to 2.8) | -0.05 (-3.1 to 3.0) | -0.57 (-0.62 to -0.53) | -0.30 (-0.34 to -0.26) | -0.17 (-0.21 to -0.13) | -0.17 (-0.21 to -0.13) |
| Proportion with a clinically meaningful* increase, per cent (95% CI) | 26 (24 to 29) | 28 (26 to 30) | 23 (22 to 24) | 28 (27 to 28) | 29 (28 to 30) | 29 (28 to 30) |
| Proportion with a clinically meaningful* decrease, per cent (95% CI) | 28 (25 to 30) | 27 (25 to 29) | 40 (39 to 41) | 36 (35 to 37) | 34 (33 to 35) | 34 (33 to 35) |
| N with HbA _{1c} level >7.5% after baseline/N with baseline HbA _{1c} ≤7.5% | 160/670 | 228/827 | 1026/3286 | 1641/4672 | 1246/3408 | 1246/3408 |
| New post-discontinuation onset of loss of glycaemic control with HbA _{1c} >7.5%, per cent (95% CI)† | 24 (21 to 27) | 28 (25 to 31) | 31 (30 to 33) | 35 (34 to 36) | 37 (35 to 38) | 37 (35 to 38) |

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

†Assessed in patients without evidence of loss of glycaemic control before discontinuing rosiglitazone.

discontinuation date within 24 months before that date. We defined three non-overlapping postdiscontinuation periods as follows: 3 (90–179 days); 6 (180–359 days) and 12 months (360–479 days). We used the earliest available measurement within each postdiscontinuation period. The postdiscontinuation values were ascertained until 30 June 2011. We calculated the mean (with SD) level for HbA_{1c} and FPG before and after discontinuation, and the mean change for each postdiscontinuation period. Furthermore, we calculated the proportion of patients with a new postdiscontinuation onset of loss of glycaemic control, defined as HbA_{1c}>7.5%, and the proportion of patients with a new postdiscontinuation onset of treatment failure, defined as FPG>10 mmol/L. To capture the 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 the 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 online supplementary appendix. We used SAS software V.9.2 (SAS Inc, Cary, North Carolina, USA) to analyse the data.

RESULTS

Utilisation of rosiglitazone and patient characteristics

During the study period, 67 525 OHA users were recorded in AUPD and 191 276 in GPRD. Of these, 2321 (3.4%) persons in AUPD and 25 428 (13%) persons in GPRD received at least one prescription for a rosiglitazone-containing product. **Figure 1** shows the 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 the 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 other OHA users to have used OHAs other than metformin and sulfonylurea before the baseline. Based on data from GPRD, users of rosiglitazone-containing products were slightly more likely than other OHA users to have a BMI of ≥ 30 kg/m². BMI data for patients in Denmark were sparse (**table 1**).

Glycaemic control after discontinuation of rosiglitazone

Among all rosiglitazone users in AUPD, 1776 patients who discontinued the drug had HbA_{1c} measurements.

Table 3 HbA_{1c} (%) before and after discontinuation of rosiglitazone-containing products, among users who discontinued the drug on or after 23 September 2010 (date of 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 to 2.7) | 0.34 (−1.8 to 2.5) | −2.0 (−2.2 to −1.8) | −1.8 (−2.1 to −1.6) |
| Proportion with a clinically meaningful* increase, per cent (95% CI) | 34 (29 to 38) | 33 (29 to 38) | 14 (12 to 16) | 15 (12 to 19) |
| Proportion with a clinically meaningful* decrease, per cent 95% CI) | 13 (9.5 to 16) | 12 (9.3 to 15) | 72 (69 to 75) | 69 (64 to 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 postdiscontinuation onset of loss of glycaemic control with HbA _{1c} >7.5%, per cent (95% CI)† | 27 (22 to 32) | 27 (22 to 32) | 44 (38 to 51) | 33 (22 to 46) |

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

†Assessed in patients without evidence of loss of glycaemic control before discontinuing rosiglitazone.

Among these patients, the median duration of rosiglitazone use was 19 months (quartiles 6–38 months), and the median time from the last prediscontinuation HbA_{1c} measurement until discontinuation of rosiglitazone was 44 days (quartiles 21–78 days). In 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 prediscontinuation HbA_{1c} measurement until discontinuation of rosiglitazone was 70 days (quartiles 25–153 days). Table 2 shows changes in HbA_{1c} at 3, 6 and 12 months after discontinuation of rosiglitazone treatment at any time during the study period. At 12-month postdiscontinuation, a change of similar magnitude in the mean HbA_{1c} was observed in both databases: −0.16% (95% CI −3.4% to 3.1%) in northern Denmark, and −0.17% (95% CI −0.21% to −0.13%) in the UK. Loss of glycaemic control, defined by the 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-month postdiscontinuation.

Table 3 shows changes in HbA_{1c} among patients who discontinued rosiglitazone-containing products on or after 23 September 2010. Thus, table 3 represents the subset of patients described in table 2. In the UK data, mean HbA_{1c} changed by −1.8% (95% CI −2.1% to −1.6%) at 6-month postdiscontinuation, but the prediscontinuation 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 3, 6 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 to 7.3 mmol/L) in northern Denmark, and mean change of 0.03 mmol/L (95% CI −0.22 to 0.28 mmol/L) in the UK. Treatment failure, defined by the 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 or after 23 September 2010. 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—57% in Denmark and 42% in the UK—received a prescription for metformin. In the UK, 24% of patients had a prescription for pioglitazone, and 14% for pioglitazone and metformin. Pioglitazone was prescribed only to 4.4% of the patients in northern Denmark.

DISCUSSION

We examined the use of rosiglitazone-containing products over the entire period of their availability in Europe (2000–2010) using routinely collected data in medical databases in Denmark and in 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%, respectively, in the two countries. 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 Wolski² and subsequent regulatory warnings from the EMA. This decline occurred

Table 4 Fasting plasma glucose (FPG; mmol/L) before and after discontinuation of rosiglitazone among patients with available prediscontinuation and postdiscontinuation 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 to 8.2) | -0.27 (-8.2 to 7.6) | 0.01 (-7.3 to 7.3) | 0.27 (0.04 to 0.49) | 0.08 (-0.12 to 0.27) | 0.03 (-0.22 to 0.28) |
| Proportion with a clinically meaningful* increase, per cent (95% CI) | 40 (31 to 50) | 35 (26 to 44) | 32 (23 to 43) | 39 (36 to 43) | 40 (38 to 43) | 40 (37 to 44) |
| Proportion with a clinically meaningful* decrease, per cent (95% CI) | 39 (30 to 49) | 35 (26 to 44) | 40 (30 to 51) | 30 (27 to 33) | 33 (31 to 36) | 34 (31 to 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 postdiscontinuation onset of treatment failure, FPG >10 mmol/L, per cent (95% CI)† | 22 (13 to 33) | 23 (15 to 33) | 15 (7.3 to 26) | 16 (13 to 19) | 20 (18 to 23) | 17 (14 to 20) |

*Clinically meaningful change defined using the European Medicines Agency's definition as change of more than 10 mmol/L.

†Assessed in patients without evidence of treatment failure before discontinuing rosiglitazone.

3 years before the regulatory decision to suspend rosiglitazone in Europe. Similarly, a sharp decline in prescribing occurred in the USA 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 the 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 in the UK have stated that rosiglitazone should only be prescribed if other classes of OHAs were not effective in lowering plasma glucose concentrations. Therefore, rosiglitazone was recommended only as second-line or third-line therapy.²⁶ The high prediscontinuation 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. AUPD records purchased prescriptions, while 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 UK, data on diagnoses originate from general practitioner records. Despite these differences and the potential differences in the underlying patient populations, the results obtained from the two countries were generally consistent.

As OHAs are distributed by prescription only and need to be taken in the long term, the information we present on rosiglitazone utilisation over calendar time is likely to be accurate. The pattern of use for the two Danish regions included here mirrors the nationwide

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 | Per cent (95% CI) | Number | Per cent (95% CI) |
| Metformin | 269 | 57 (52 to 61) | 1136 | 42 (40 to 44) |
| Glimepiride | 84 | 18 (14 to 21) | 57 | 2.1 (1.6 to 2.7) |
| Metformin+sitagliptin | 49 | 10 (7.6 to 13) | 103 | 3.8 (3.1 to 4.6) |
| Sitagliptin | 45 | 9.5 (6.9 to 12) | | |
| Metformin+vildagliptin | 35 | 7.4 (5.0 to 9.7) | 641 | 24 (22 to 25) |
| Liraglutide | 26 | 5.5 (3.4 to 7.5) | | |
| Pioglitazone | 21 | 4.4 (2.6 to 6.3) | 394 | 14 (13 to 16) |
| Pioglitazone+metformin | 17 | 3.6 (1.9 to 5.3) | 351 | 13 (12 to 14) |
| Gliclazide | | | 8 | 1.7 (0.5 to 2.8) |
| Glibenclamide | 8 | 1.7 (0.5 to 2.8) | 16 | 0.6 (0.4 to 1.0) |
| Saxagliptin | 8 | 1.7 (0.5 to 2.8) | 9 | 0.3 (0.2 to 0.6) |
| Glipizide | 4 | 0.8 (0.1 to 1.7) | | |
| Vildagliptin | 4 | 0.8 (0.1 to 1.7) | 2 | 0.1 (0.0 to 0.3) |
| Repaglinide | 3 | 0.6 (0.1 to 1.3) | | |
| Exenatide | 3 | 0.6 (0.1 to 1.3) | 4 | 0.2 (0.1 to 0.4) |
| Acarbose | 2 | 0.4 (0.1 to 1.0) | | |
| Tolbutamide | 1 | 0.2 (0.1 to 0.6) | 9 | 0.3 (0.2 to 0.6) |

*Eighty-three patients had no record of another OHA after the last rosiglitazone prescription.

†Eighty-eight patients had no record of another OHA after the last rosiglitazone prescription.

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 the timing of rosiglitazone discontinuation and prescription length. We speculate that short-term changes in laboratory parameters following the discontinuation of rosiglitazone are subject to more misclassification due to errors in assigning the discontinuation status than long-term changes in these parameters. Therefore, our 12-month estimates of postdiscontinuation change in laboratory parameters may be more robust than the 3-month estimates. The information on HbA_{1c} and on FPG 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 collect laboratory data routinely 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 the 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 the patients had evidence of loss of glycaemic control on discontinuation. Most patients who discontinued rosiglitazone after EMA-mandated suspension were switched to a metformin-containing regimen.

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REFERENCES

- Home PD, Pocock SJ, Beck-Nielsen H, *et al*. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. *N Engl J Med* 2007;357:28–38.
- Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457–71.
- Psaty BM, Furberg CD. Rosiglitazone and cardiovascular risk. *N Engl J Med* 2007;356:2522–4.
- Margolis DJ, Hoffstad O, Strom BL. Association between serious ischemic cardiac outcomes and medications used to treat diabetes. *Pharmacoepidemiol Drug Saf* 2008;17:753–9.
- EMA statement on recent publication on cardiac safety of rosiglitazone (Avandia, Avandamet, Avaglim). 2009. http://www.emea.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500013467.pdf (accessed Aug 2013).
- Home PD, Pocock SJ, Beck-Nielsen H, *et al*. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009;373:2125–35.
- Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, *et al*. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA* 2010;304:411–18.
- Nissen SE. The rise and fall of rosiglitazone. *Eur Heart J* 2010;31:773–6.
- Blind E, Dunder K, de Graeff PA, *et al*. A European regulatory perspective. *Diabetologia* 2011;54:213–18.
- EMA recommends new warnings and contraindications for rosiglitazone. 2009. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500015420.pdf (accessed Aug 2013).
- European Medicines Agency confirms positive benefit-risk balance for rosiglitazone and pioglitazone. 2009. http://www.emea.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500011009.pdf (accessed Aug 2013).
- Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med* 2010;170:1191–201.
- European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim. 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/09/WC500096996.pdf (accessed Aug 2013).
- The European Commission. Commission Decision of 3.12.2010 suspending, under Article 20 of Regulation (EC) No 726/2004 of the European Parliament and of the Council, the marketing authorisation, granted by Decision C(2000)1799, for “Avandia—Rosiglitazone” a medicinal product for human use.
- Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clin Epidemiol* 2010;2:273–9.
- Clinical Practice Research Datalink. <http://www.cprd.com> (accessed Aug 2013).
- Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:30–3.
- Grann AF, Erichsen R, Nielsen AG, *et al*. Existing data sources for clinical epidemiology: the clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. *Clin Epidemiol* 2011;3:133–8.
- Danish National Indicator Project. <http://www.nip.dk> (accessed Aug 2013).
- Pedersen CB, Gotzsche H, Moller JO, *et al*. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441–9.
- Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ* 1991;302:766–8.
- Garcia Rodriguez LA, Perez Gutthann S. Use of the UK general practice research database for pharmacoepidemiology. *Br J Clin Pharmacol* 1998;45:419–25.
- Jick SS, Kaye JA, Vasilakis-Scaramozza C, *et al*. Validity of the general practice research database. *Pharmacotherapy* 2003;23:686–9.
- Shah ND, Montori VM, Krumholz HM, *et al*. Responding to an FDA warning—geographic variation in the use of rosiglitazone. *N Engl J Med* 2010;363:2081–4.
- <http://hertedoktor.dk/content/pdf/dsams%20vejledning%20for%20type2%20diabetes.pdf> (accessed Aug 2013).
- National Collaborating Centre for Chronic Conditions. *Type 2 diabetes: national clinical guideline for management in primary and secondary care (update)*. London: Royal College of Physicians, 2009.
- The Danish Medicines Agency. Polypharmacy in diabetes care. <http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=1665> (accessed May 2013).