



# Predictors for change to thiazolidinedione prescribing in the UK following the rosiglitazone cardiovascular safety warning

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**Predictors for change to thiazolidinedione prescribing in the UK following the rosiglitazone cardiovascular safety warning**

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Changes and predictors for change to thiazolidinedione prescribing in the UK primary care following the  
rosiglitazone safety warning

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Short report

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### Abstract

**Objective** To investigate switching from thiazolidinediones, and predictors for switching treatment, after publication of a meta-analysis reporting an increased risk of myocardial infarction associated with rosiglitazone use.

**Research design and methods** Using THIN UK primary care database, the number of people with Type 2 diabetes prescribed either thiazolidinedione; rosiglitazone (n=10,062) or pioglitazone (n=4,454) and the rate of switching from thiazolidinediones (n=3,301 and 1,106 respectively), were computed for each month, May 2006 to January 2008. The probability of switching post-publication, May 2007 to January 2008, was modelled by logistic regression in a forward stepwise model. Variables included demographics, history of ischaemic heart disease (IHD), heart failure (HF) or stroke, risk factors for IHD, glucose-lowering and cardiovascular drug use, HbA1c and diabetes duration.

**Results** There was a sharp increase in switching from both thiazolidinediones in summer 2007; rosiglitazone prescription numbers then decreased while pioglitazone prescribing increased. Switching from rosiglitazone was associated with IHD (adjusted odds ratio OR 1.72; 95% confidence intervals CI 1.47-2.00), insulin treatment (OR 5.10; 95% CI 3.21-8.10), HF (OR 2.26; 95% CI 1.62-3.18), recent sulphonylurea prescription (OR 1.33; 95% CI 1.17-1.51) sex (OR males v females 0.79; 95% CI 0.70, 0.90) and duration of therapy. Switching from pioglitazone was associated with HF (OR 3.05; 95% CI 1.77-5.26), duration of therapy, and number of glucose lowering treatments.

**Conclusions** Prescribing habits for both thiazolidinediones changed immediately following the safety warning. IHD was associated with switching from rosiglitazone; otherwise reasons for change appear to be complex, not directly related to the findings of the meta-analysis.

**Key words:** Diabetes; Prescribing habits; Thiazolidinedione; Cardiovascular disease; Safety.

**Abbreviations:** CVD, cardiovascular disease, CHD, coronary heart disease; TZD, Thiazolidinediones; THIN, The Health Information Network; MI, myocardial infarction; NHS, National Health Service; BNF, British National Formulary; ROC, receiver operating characteristic.

**Running title:** Thiazolidinedione prescribing after a rosiglitazone safety warning.

**Presented at:** Oral presentation at Diabetes UK.

**What is already known about this topic?**

Previous work from a number of countries suggests that the well publicized report of an association between rosiglitazone and cardiovascular disease resulted in a decrease in rosiglitazone prescriptions but an increase in pioglitazone prescribing.

**What does this article add?**

Our more detailed analysis shows that there was also a peak in switching from pioglitazone (despite an overall increase in prescriptions) and that the meta-analysis was not the sole reason for change.

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**Introduction**

In May 2007, Nissen et al reported a meta-analysis of 42 randomised clinical trials with various control groups, showing a statistically significant increased risk of myocardial infarction (MI) and a non-significant increase in cardiovascular death in those treated with rosiglitazone.<sup>1</sup> This analysis aroused extensive debate about the methods,<sup>2</sup> but the results received wide publicity<sup>3,4,5</sup> Subsequent North American and Scottish studies reported a decrease in rosiglitazone claims or prescriptions and an increase in pioglitazone use shortly after May 2007.<sup>6,7,8,9</sup> The percentage of rosiglitazone users with increased cardiovascular risk also decreased<sup>7</sup> but the characteristics of individual patients were not investigated. Any change in prescribing habits may be due to reasons other than the meta-analysis as there were reports about the association of thiazolidinediones with heart failure<sup>10</sup> and fractures<sup>11</sup> around the same time period. We investigated the impact of the meta-analysis and its subsequent publicity on patient treatment in the UK and examined which patient characteristics predicted treatment switching.

**Patients and Methods**

All study populations, prescribing and patient characteristics were identified from the THIN Database. THIN is an observational database containing UK primary care records. Details of demographics, primary care diagnoses and prescription treatment, secondary care diagnoses and deaths are routinely recorded. This study included those 267 practices (2.1 million patients) with electronic links to pathology laboratories. The protocol was approved by a Cambridgeshire 4 (UK) Ethics Committee.

Cohort 1 comprised permanently registered patients who received one or more prescriptions for either rosiglitazone or pioglitazone between May 2006 and January 2008. Prescriptions for anti-diabetic treatments (BNF 6.1.1 and 6.1.2<sup>12</sup>) issued for each study month were identified and patients were categorised as switched (another prescription for an anti-diabetic drug, but no repeat of that TZD treatment, within 112 days), continued treatment (another prescription for that TZD within 112 days) or ended anti-diabetic treatment (no further prescriptions for any anti-diabetic drug within 112 days).

Cohort 2, a subset of cohort 1, included those patients who received a prescription for a TZD during May 2007 to assess which characteristics were associated with subsequent treatment switching. Patients with less than six months prior registration, who had treatment breaks of 112 days or more in the year to May 2007, who were co-prescribed both TZDs in May 2007 or who ended anti-diabetic treatments were excluded. For those who switched TZD treatment the index date was the date of the last TZD prescription. For non-switchers an index date was assembled by randomly allocating the distribution (by calendar month) of the switchers to the non-switchers. Patient characteristics at the index date were identified including age, sex, duration of diabetes and most recent HbA<sub>1c</sub> and anti-diabetic and cardiovascular (BNF categories 2.2, 2.4, 2.5 and 2.6) drugs on, or in the previous, 112 days. Any history of ischaemic heart disease, heart failure, hypertension or cerebrovascular disease was identified. Other cardiovascular disease risk factors comprised hyperlipidaemia (a diagnosis or a blood result of total cholesterol: high density lipoprotein ratio >4.5 or a total cholesterol >5.2mmol/l); a body mass index >30 kg/m<sup>2</sup> within two years and smoking status.

**Analysis**

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For each month, 1<sup>st</sup> May 2006 to 31<sup>st</sup> January 2008, the number of patients prescribed a TZD, and the percentage number who then switched, was estimated from Cohort 1. The analysis was run after partitioning by TZD, and excluding those who stopped treatment.

In cohort 2 separate models were fitted for each type of TZD. The probability of being a switcher was modelled by logistic regression with variables significant at the  $p < 0.001$  level in a forward stepwise procedure included in the model. We used a strict  $< 0.001$  cut-off rule in the forward stepwise algorithms due to the high number of switchers. The predictive power of an individual variable and a comparison of sensitivity and specificity were assessed using the 'C-index'<sup>13, 14</sup> (the area under the curve of a receiver operating characteristic (ROC) plot).<sup>15</sup> Note that a variable with no predictive ability has a C-index of 0.5 and a variable with perfect predictive power has a C-index of 1.

## Results

In cohort 1, 3,301 (33%) of 10,062 rosiglitazone users switched and 5,203 (52%) continued treatment, while 1,106 (25%) of 4,454 pioglitazone users switched and 2,802 (63%) continued treatment. The remaining patients ended treatment and were excluded. Prescribing of rosiglitazone dropped sharply after May 2007 then gradually increased without returning to pre-May 2007 levels (Figure 1). Switching from rosiglitazone increased reaching a peak of 9% in July 2007, over three times the mean May 2006 to April 2007 rate of change. Switching from pioglitazone also peaked in July 2007 although there remained a gradual increase in pioglitazone prescriptions throughout the study period (Figure 1).

Figure 1

In Cohort 2, 1,388 (28%) of 4,909 patients who had a prescription for rosiglitazone in May 2007, and 311 (21%) of 1,759 patients with a prescription for pioglitazone, switched therapy (Table 1). The results of the multivariate logistic regression are shown in Table 2. Ischaemic heart disease, recent prescription for insulin, duration of TZD use, history of heart failure, recent prescription for a sulphonylurea and sex were significant in the forward stepwise procedure for switching from rosiglitazone (Table 2) but were not highly predictive of a switch when plotted on a ROC curve, area under the curve (AUC) 0.63. The variables for pioglitazone (heart failure, TZD duration and number of other glucose lowering therapies) had a greater ability to predict a switch with an AUC of 0.71 (figure 2).

Tables 1 and 2

The most common glucose-lowering agent both pre and post-switch (Table 3) for both rosiglitazone and pioglitazone users was metformin, with or without a sulphonylurea. The pioglitazone cohort most commonly stopped TZD therapy without adding an alternative agent (59%), although 5% were prescribed a regimen which included rosiglitazone. Rosiglitazone users were more diverse post-index date; including 32% switched to pioglitazone (tables 3 and 4).

*Tables 3 and 4 and Figure 2 could be available as only an electronic file.*

## Discussion

A distinct change in prescribing habits for TZDs occurred in the UK in the weeks after publication of the controversial meta-analysis.<sup>1</sup> Although the meta-analysis included only clinical trials of rosiglitazone, a peak in switching was seen for both TZDs. The number of pioglitazone prescriptions continued to increase

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whereas rosiglitazone prescriptions did not return to pre-May 2007 levels. The continued increase in pioglitazone prescription numbers, and switching from rosiglitazone to pioglitazone in almost a third of patients, suggests that many prescribers were aware of safety issues specifically relating to rosiglitazone. A range of patient characteristics was associated with switching from TZD therapy. Given that these characteristics were often not related to cardiovascular disease and, even together, they were not highly predicative of change, suggests that the reasons for switching were complex, but, particularly in the rosiglitazone cohort, could be simply due to non-specific safety concerns.

A similar decrease in rosiglitazone use with parallel increase in pioglitazone claims after May 2007 has been reported in three North American<sup>6-8</sup> and one Scottish study<sup>9</sup>. The studies did not investigate switching in individual patients so neither the peak in switching from pioglitazone nor predictors of change were reported. One study reported that there was no statistically significant difference in the number of patients on rosiglitazone with either heart failure, ischaemic heart disease or a current supply of either a nitrate or insulin between May and December 2007, but the decrease became significant with any of these risk factors.<sup>7</sup>

The switching pattern in the current study may have been due to a general concern about TZD safety. An increase in heart failure and oedema in TZD treated patients, particularly when co-prescribed insulin,<sup>10</sup> had received further coverage in the medical literature throughout 2007.<sup>5, 16, 17</sup> Switching was more common in patients with heart failure, with a recent insulin prescription the strongest predictor of change in the rosiglitazone users. Similarly, the finding that switching from rosiglitazone was less common in males may be related to a reported increased risk of fractures in women,<sup>11</sup> which was reported directly to some UK health care professionals during 2007.<sup>18-20</sup> More switching early in treatment may reflect physicians' reluctance to alter an established, well tolerated regimen. More switching from pioglitazone in those on more anti-diabetic agents might be expected within a progression from oral treatments to insulin as glycaemic control worsens. However, a shift to insulin was not common and poor glycaemic control was not a strong predictor for change.

These findings provide a 'real life' picture of changes to prescribing habits but the reason for change had to be assumed from recorded patient characteristics. While this design allowed nine months for patients to be reviewed, we found a peak in switching of TZD immediately after the publication. Cardiovascular risk factors may have been more predictive of switching had the time window been shorter.

In conclusion, there was a sudden increase in switching from both TZDs shortly after a controversial meta-analysis raised safety concerns with rosiglitazone therapy. Reasons for change for many patients seem not directly related to the publication but possibly partially due to general safety concerns with these agents.



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## Transparency

### Funding

The study was funded by Eli Lilly. Eli Lilly had the right to comment on the manuscript but with no restriction on publication.

### Declaration of financial/other relationships

Gillian Hall has received funding for research and payment for consultancy from a number of pharmaceutical companies and from charities and has no direct stock holding in any pharmaceutical company. Helen Smith and Bradley Curtis are employees of Eli Lilly. Alex McMahon has no conflict of interest to declare.

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**Table 1 Characteristics of switchers at index date and crude odds ratios comparing switchers with those who continued therapy (Cohort 2)**

	Rosiglitazone (n=4,909)		Pioglitazone (n=1,477)	
	Number who switched (% in category)	Crude odds ratio (95% CI)	Number who switched (% in category)	Crude odds ratio (95% CI)
Total	1388 (28.27)	-	311 (21.06)	-
Female	623 (30.57)	reference	140 (22.95)	reference
Male	765 (26.65)	0.83 (0.73, 0.94)	171 (19.72)	0.82 (0.64, 1.06)
Age				
≤45	108 (26.15)	reference	25 (21.19)	reference
45- 55	217 (25.14)	0.95 (0.73, 1.24)	47 (19.92)	0.93 (0.54, 1.6)
56-65	397 (26.59)	1.02 (0.8, 1.31)	97 (21.18)	1.00 (0.61, 1.64)
66-75	435 (30.44)	1.24 (0.97, 1.58)	98 (22.27)	1.07 (0.65, 1.75)
>75	231 (32.49)	1.36 (1.04, 1.78)	44 (19.56)	0.9 (0.52, 1.57)
HbA1c				
<7.5	791 (26.25)	reference	137 (15.97)	reference
≥7.5	596 (31.72)	1.3 (1.15, 1.48)	173 (28.22)	2.07 (1.61, 2.67)
unknown	1 (5.88)	-	1 (16.67)	-
Duration of TZD therapy:				
≤6 months	287 (36.75)	reference	121 (39.93)	reference
6 months-1 yr	256 (32.2)	0.82 (0.66, 1.01)	53 (25.6)	0.52 (0.35, 0.76)
1- 2 yr	382 (27)	0.64 (0.53, 0.77)	55 (16.08)	0.29 (0.2, 0.42)
>2 yr	463 (24.14)	0.55 (0.46, 0.66)	82 (13.12)	0.23 (0.16, 0.31)
Duration of diabetes :				
≤5 yr	441 (25.94)	reference	81 (19.15)	reference
5- 10 yr	522 (28.08)	1.11 (0.96, 1.29)	115 (19.79)	1.04 (0.76, 1.43)
>10 yr	425 (31.48)	1.31 (1.12, 1.54)	115 (24.31)	1.36 (0.98, 1.87)
History of:				
Cardiovascular drug use	1161 (29.03)	1.23 (1.04, 1.45)	258 (21.04)	1.00 (0.71, 1.39)
IHD	376 (38.6)	1.82 (1.57, 2.11)	76 (26.67)	1.48 (1.1, 2.0)
Heart failure	79 (51.97)	2.85 (2.06, 3.94)	26 (39.39)	2.57 (1.54, 4.28)
Cerebrovascular disease	129 (36.03)	1.47 (1.18, 1.85)	34 (25.0)	1.28 (0.85, 1.93)
Hyperlipidaemia	1194 (28.5)	1.08 (0.9, 1.29)	264 (21.52)	1.18 (0.84, 1.67)
Hypertension	915 (29.87)	1.24 (1.09, 1.41)	196 (20.55)	0.92 (0.71, 1.19)
Smoking:				
Non-smoker	492 (26.99)	reference	119 (20.95)	reference
Smoker	172 (25.86)	1.15 (1.01, 1.32)	34 (17.00)	1.08 (0.83, 1.42)
Ex-smoker	724 (29.92)	0.94 (0.77, 1.16)	158 (22.28)	0.77 (0.51, 1.18)
Obesity	486 (28.59)	0.98 (0.86, 1.12)	204 (20.63)	0.92 (0.70, 1.20)
Number of risk factors*				
0	30 (26.55)	reference	4 (15.38)	reference
1	228 (27.64)	1.06 (0.68, 1.65)	54 (23.68)	1.71 (0.56, 5.17)
2	506 (26.66)	1.01 (0.65, 1.55)	121 (20.37)	1.41 (0.48, 4.16)
3	572 (30.74)	1.23 (0.8, 1.89)	126 (22.42)	1.59 (0.54, 4.7)
4	52 (24.53)	0.9 (0.53, 1.52)	6 (8.96)	0.54 (0.14, 2.1)

\*Risk factors include hypertension, smoking, obesity or hyperlipidaemia.

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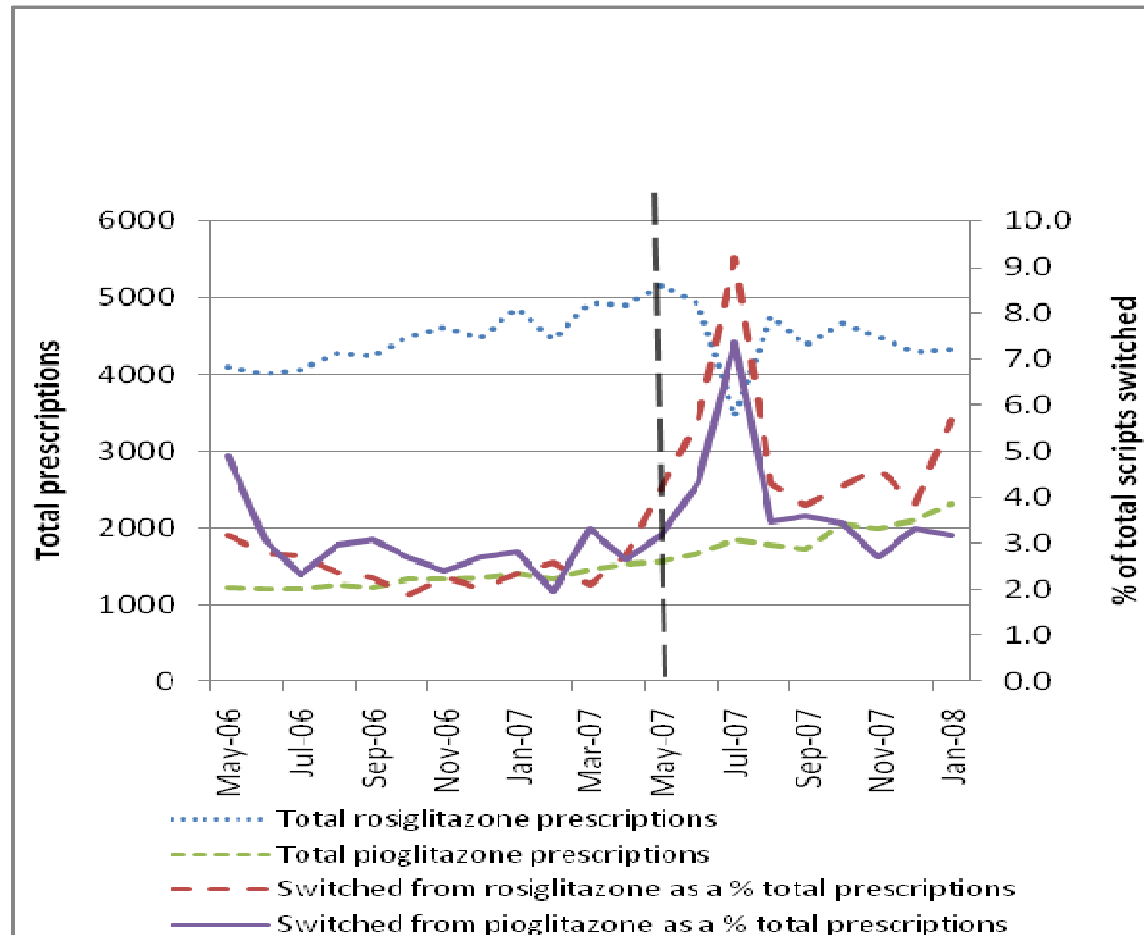
Table 2 Multivariate logistic regression\* odds ratio (95% confidence intervals)

Variable	Rosiglitazone	Pioglitazone
Current insulin	5.10 (3.21, 8.10)	-
Heart failure	2.26 (1.62, 3.18)	3.05 (1.77, 5.26)
Ischaemic heart disease	1.72 (1.47, 2.00)	-
Current sulphonylurea	1.33 (1.17, 1.51)	-
Male	0.79 (0.70, 0.90)	-
Duration of TZD therapy (<6 months as reference)		
6 months – 1 year	0.78 (0.63, 0.97)	0.55 (0.37, 0.81)
1-2 years	0.61 (0.50, 0.74)	0.29 (0.20, 0.42)
>2 years	0.53 (0.44, 0.64)	0.23 (0.16, 0.32)
Number of current glucose lowering therapies (1 as reference)		
2	-	2.09 (1.02, 4.31)
3	-	2.61 (1.26, 5.40)
4	-	10.44 (3.57, 30.56)

\*including those variables significant at p<0.001 in the forward stepwise model,

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**Figure 1** Number of patients who received a TZD prescription and the percentage who switched after this prescription



Changes and predictors for change to thiazolidinedione prescribing in the UK primary care following the rosiglitazone safety warning – extra tables

Table 3 Glucose lowering agents prescribed in the 112 days pre and post switching from rosiglitazone

Treatment in addition to rosiglitazone pre-index date	Treatment post-index date															
	Total	MF	MF + SU	MF + PG	MF + SU + PG	SU	MF + INS	SU + PG	MF + SU + INS	PG	INS	MF + other	SU + INS	MF + SU + other	SU+ other	* <10 pts
MF	523	190	60	194	15	10	22	0	2	2	2	14	0	1	0	11
MF + SU	519	16	198	7	168	28	23	5	37	0	5	0	5	9	2	16
SU	197	0	25	1	4	90	3	51	1	1	2	0	6	0	6	7
None	68	11	5	3	0	12	1	2	0	29	1	0	0	0	0	4
MF + INS	22	0	0	0	0	0	13	0	1	0	3	0	0	0	0	5
MF + SU + INS	13	0	1	0	0	0	1	0	7	0	3	0	0	0	0	1
MF + MG	10	0	0	1	0	0	1	0	0	0	0	0	0	0	0	8
INS	9	0	0	0	0	0	1	0	0	0	7	0	0	0	0	1
MF + SU+other	8	0	0	0	1	0	0	0	0	0	0	0	0	3	0	4
SU+ INS	5	0	0	0	0	1	0	0	1	0	1	0	2	0	0	0
MF + other	4	1	0	0	0	0	0	0	0	0	0	0	0	0	1	2
MF+SU+ MG	3	0	0	0	0	0	0	0	2	0	0	0	0	0	0	1
MG.	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
MF +SU + INS+other	2	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
Other	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
MG+INS	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
SU+MG	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Total	1388	218	289	206	188	142	66	58	51	32	25	14	13	13	10	63

MF = metformin; SU= sulphonylurea; MG. = meglitinides; PG= pioglitazone  
\*treatment combinations with less than 10 patients post-index date. across all post-index date treatment regimens.

Changes and predictors for change to thiazolidinedione prescribing in the UK primary care following the rosiglitazone safety warning – extra tables

**Table 4 Glucose lowering agents prescribed in the 112 days pre and post switching from pioglitazone**

Treatment pre-index date in addition to pioglitazone	Treatment post-index date									
	Total	MF + SU	MF	SU	MF + INS	INS	MF + SU + RG	MF + SU + INS	MF + SU + other	*with <10 patients
MF + SU	112	59	3	5	9	1	15	9	6	5
MF	90	19	52	1	1	2	0	0	0	15
SU	57	11	1	33	0	0	0	0	0	12
MF + INS	13	0	0	0	10	1	0	0	0	2
INS	10	0	0	0	0	9	0	0	0	1
None	9	0	4	2	0	2	0	0	0	1
MF + SU + INS	7	0	0	0	2	0	0	4	0	1
MF + SU+other	6	1	0	0	1	0	0	0	4	0
SU + INS	3	0	0	0	0	0	0	0	0	3
SU + other	2	0	0	0	0	0	0	0	1	1
MF + other	1	0	0	0	0	0	0	0	1	0
MF+ SU + MG.	1	0	0	0	0	0	0	0	0	1
Total	311	90	60	41	23	15	15	13	12	42

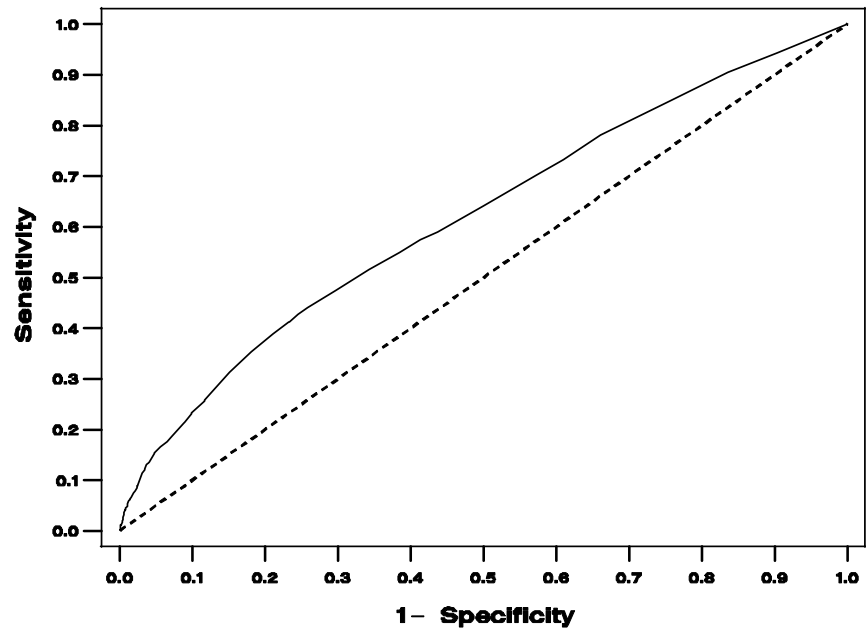
MF = metformin; SU= sulphonylurea; MG = meglitinides; INS = insulin; RG=rosiglitazone.

\*treatment combinations with less than 10 patients post-index date across all pre-index date treatment regimens.

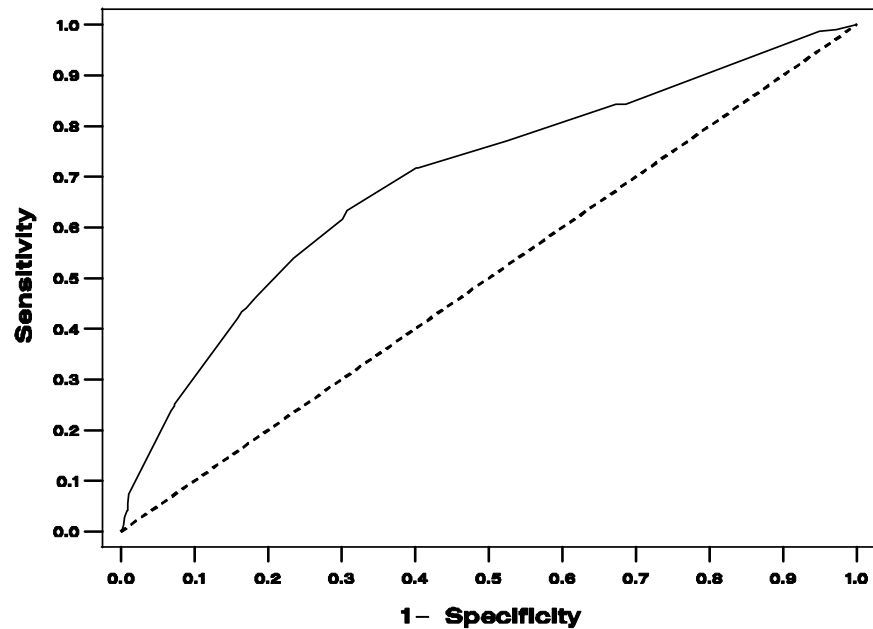


Changes and predictors for change to thiazolidinedione prescribing in the UK primary care following the rosiglitazone safety warning – extra tables

Figure 2 ROC curve including variables significant in the forward stepwise analysis



A Rosiglitazone



B Pioglitazone