FDA Warning and Removal of Rosiglitazone From VA National Formulary

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Objectives: To describe changes in rosiglitazone prescribing following the US Food and Drug Administration (FDA) warning of potentially increased risk of myocardial infarction and removal from the Department of Veterans Affairs National Formulary (VANF), assess patient-level factors associated with rosiglitazone discontinuation, and evaluate changes in glucose control.

Study Design: Historical cohort.

Methods: Veterans with an active outpatient prescription for rosiglitazone on April 1, 2007, were followed until June 30, 2008. Incidence rate ratios (IRRs) of rosiglitazone discontinuation were compared over time using Poisson methods. We identified patient-level factors associated with stopping rosiglitazone using multivariable Poisson regression and compared glycated hemoglobin (A1C) values across time among patients who discontinued/continued rosiglitazone using linear mixed models.

Results: Of 95,539 veterans with an active outpatient rosiglitazone prescription, 86.7% discontinued rosiglitazone. Discontinuation rates increased significantly after the FDA warning, with IRRs from 1.6 to 1.8. After removal from the VANF, rosiglitazone discontinuation rates again increased significantly. Discontinuing rosiglitazone was associated with the FDA warning, removal from the VANF, female sex, black race, Hispanic ethnicity, comorbidity, A1C greater than 9%, and use of rosiglitazone as first- or second-line therapy. Among patients who did and did not receive a replacement medication, the mean changes in A1C from baseline were 0.12% and 0.46%, respectively. For those who continued rosiglitazone, the mean change in A1C was –0.02%.

Conclusion: The rosiglitazone discontinuation rate increased following the FDA warning and increased further following removal of rosiglitazone from the VANF. Glucose control may have declined among those who discontinued rosiglitazone.

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For author information and disclosures, see end of text.

Before October 4, 2007, rosiglitazone was available on the Department of Veterans Affairs National Formulary (VANF) for treatment of type 2 diabetes mellitus (T2DM); pioglitazone could be obtained via the nonformulary request process. However, rosiglitazone use likely changed following the US Food and Drug Administration (FDA) safety alert issued May 21, 2007, regarding the potential increased risk of myocardial infarction (MI) and cardiovascular death in patients receiving rosiglitazone and the subsequent removal of rosiglitazone from the VANF on October 4, 2007.[1] The FDA alert, which was sent to all Department of Veterans Affairs (VA) providers via established electronic distribution lists, was largely prompted by the online publication of a meta-analysis in which rosiglitazone was associated with increased MI risk (odds ratio = 1.43; 95% confidence interval [CI],1.03-1.98) compared with other diabetes medications or placebo.[2] A subsequent meta-analysis of trials with 12 or more months of follow-up (vs 24 weeks in the previous meta-analysis) confirmed the increased MI risk (relative risk = 1.42; 95% CI, 1.06-1.91).[3] The only other thiazolidinedione (TZD) available for T2DM treatment during this time was pioglitazone. A meta-analysis of pioglitazone versus non-TZDs showed a lower risk of the composite end point of death, MI, or stroke with pioglitazone (hazard ratio = 0.82; 95% CI, 0.72-0.94).[4] In addition, a nested case-control study of older patients with T2DM showed that rosiglitazone monotherapy, but not pioglitazone, was associated with increased MI risk.[5]

Given these results, as well as similar findings in a retrospective cohort study conducted by the VA,[6] regional pharmacy leaders and the VA Medical Advisory Panel removed rosiglitazone from the VANF at their October 4, 2007, meeting. Using the electronic distribution lists, VA prescribers were sent guidance recommending a discussion of the risks and benefits of continued rosiglitazone use with their patients. If patients and providers made an informed choice to continue TZD therapy, then patients could remain on rosiglitazone or change to pioglitazone. Pioglitazone was the only TZD available for new starts, but required completion of a nonformulary request.

Other studies examined the impact of safety warnings on rosiglitazone use, but none described changes in use based on its place in therapy for the treatment of T2DM.[7-11] This is important because providers may be more likely

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to discontinue rosiglitazone if other options remain available for controlling blood glucose. In addition, our study describes the effect on glucose control (ie, glycated hemoglobin [A1C]) of removing rosiglitazone from the VANF. Formulary changes are frequently made within healthcare systems to promote the use of specific medications, but the clinical consequences of these decisions rarely are examined and reported.[12-14]

Take-Away Points

After the US Food and Drug Administration (FDA) issued a safety alert in May 2007 regarding potentially increased risk of myocardial infarction in patients receiving rosiglitazone, the Department of Veterans Affairs (VA) removed it from its national formulary in October 2007.

- The rosiglitazone discontinuation rate increased following the FDA warning and increased further after its removal from the VA formulary.
- Patients receiving insulin concurrently tended to have the highest discontinuation rates, and patients receiving rosiglitazone as third-line agent had the lowest discontinuation rates.
- Among patients who discontinued rosiglitazone and did not receive replacement medication, the mean change from baseline in glycated hemoglobin was 0.46%.

The 4 primary objectives of this study were to: (1) describe changes in rosiglitazone prescribing following the FDA warning of a potentially increased risk of MI and removal of rosiglitazone from the VANF; (2) describe these changes in the context of diabetes medications used concomitantly with rosiglitazone; (3) examine the medications replacing rosiglitazone; and (4) assess patient-level factors associated with rosiglitazone discontinuation. The secondary objective was to evaluate changes in A1C levels over time among patients who did and did not discontinue rosiglitazone.

PATIENTS AND METHODS

Study Setting and Population

The cohort included veterans with an active outpatient prescription for rosiglitazone in the VA on April 1, 2007, who were chronic users of the medication. Chronic use was defined as having another prescription for rosiglitazone within the 180 days preceding the release date of the prescription that was active on April 1. The release date is the date the prescription is mailed to the patient or picked up from the VA pharmacy. For each patient, the study period was the time between the baseline date of April 1, 2007, and June 30, 2008.

Data Sources and Data Collection

The study cohort was identified retrospectively using the Pharmacy Benefits Management Services' database (version 3.0) for rosiglitazone prescriptions. The Pharmacy Benefits Management database also was used to obtain information on all antidiabetic medications prescribed in the VA during the study period. VA Medical SAS Datasets (Austin Information Technology Center, Austin, Texas) provided patient demographics and comorbidities. A1C values were obtained from the Decision Support Services database. All-cause mortality was identified from the VA Beneficiary Identification and Record Locator System files.

Outcomes

Discontinuation of the baseline rosiglitazone prescription during the study period was defined as a subsequent prescription for pioglitazone or no additional prescriptions for rosiglitazone during the 60 days following the end of the days of supply for the rosiglitazone prescription (ie, release date of rosiglitazone prescription plus days of supply plus 60 days).[15]

The place of rosiglitazone in therapy was defined in terms of concurrent prescriptions for antidiabetic medications that were active within 1 week of the baseline date. The place of rosiglitazone in therapy was categorized as; (1) *first line* if the patient had no concurrent medications at baseline (ie, monotherapy); (2) *second line* if the patient had concurrent metformin or sulfonylurea, but not both (with or without additional medications); (3) *third line* if the patient had concurrent metformin and sulfonylurea (with or without additional medications); (4) *with insulin* if the patient had concurrent insulin (with or without additional medications); or (5) *other* if the patient had concurrent medications other than those listed previously (eg, acarbose).

For those patients discontinuing rosiglitazone, we assessed the medication(s) that replaced rosiglitazone (ie, the medications released within the time period of the days of supply of rosiglitazone plus 60 days, but not dispensed during the 180 days before the rosiglitazone release date). The secondary outcome was change in A1C. The baseline A1C value was the most recent result within 3 months of the baseline date. The follow-up A1C level was the most recent result within 3 to 9 months of stopping rosiglitazone (for those who discontinued rosiglitazone) or the most recent result within 3 to 9 months of June 30, 2008 (for those who continued rosiglitazone).

Outcomes were assessed in the context of 2 key events: the May 21, 2007, FDA safety warning and the removal of rosiglitazone from the VANF on October 4, 2007. The study period was split into 3 phases accordingly: pre-FDA warning (April 1, 2007, to May 20, 2007), post FDA warning (May 21,

Table 1. Baseline Patient Characteristics by Rosiglitazone Discontinuation Status

Characteristics	Total (N = 95,539 [100%])	Discontinued (n = 82,797 [86.7%])	Continued[a] (n = 12,742 [13.3%])	*P*
Age, y, mean (SD)	67.0 (10.0)	66.9 (10.1)	67.4 (9.7)	<.0001
Male, n (%)	93,406 (97.8)	80,885 (97.8)	12,521 (98.4)	<.0001
Race, n (%)				<.0001
White	57,332 (60.0)	49,530 (59.8)	7802 (61.2)	
Black	8880 (9.3)	7985 (9.6)	895 (7.0)	
Other	2200 (2.3)	1948 (2.4)	252 (2.0)	
Unknown	27,127 (28.4)	23,334 (28.2)	3793 (29.8)	
Hispanic ethnicity, n (%)				<.0001
No	66,212 (69.3)	57,258 (69.2)	8954 (70.3)	
Yes	5570 (5.8)	5171 (6.2)	399 (3.1)	
Unknown	23,757 (24.9)	20,368 (24.6)	3389 (26.6)	
Comorbidity				
Overall Charlson Comorbidity Index score, mean (SD)	2.2 (1.6)	2.2 (1.6)	2.2 (1.5)	<.0001
Myocardial infarction, n (%)	2328 (2.4)	2078 (2.5)	250 (2.0)	.0002
Congestive heart failure, n (%)	5185 (5.4)	4680 (5.7)	505 (4.0)	<.0001
Peripheral vascular disease, n (%)	7853 (8.2)	6897 (8.3)	956 (7.5)	.002
Cerebrovascular disease, n (%)	6995 (7.3)	6149 (7.4)	846 (6.6)	.002
Chronic pulmonary diseases, n (%)	11,505 (12.0)	10,072 (12.2)	1433 (11.2)	.003
Renal disease, n (%)	9141 (9.6)	8024 (9.7)	1117 (8.8)	.001
Any malignancy, n (%)	8055 (8.4)	6983 (8.4)	1072 (8.4)	.94
Diabetes with chronic conditions, n (%)	22,783 (23.8)	19,782 (23.9)	3001 (23.6)	.40
A1C within 3 months of baseline				<.0001
<7%, n (%)	29,191 (30.6)	25,233 (30.5)	3958 (31.1)	
7%-9%, n (%)	32,567 (34.1)	28,489 (34.4)	4078 (32.0)	
>9%, n (%)	6980 (7.3)	6369 (7.7)	611 (4.8)	
Missing, n (%)	26,801 (28.1)	22,706 (27.4)	4095 (32.1)	
Mean (SD)	7.4% (1.3%)	7.4% (1.4%)	7.3% (1.2%)	<.0001
Concurrent antidiabetic medications with rosiglitazone at baseline,[b] n (%)				
Any	78,412 (82.1)	67,677 (81.7)	10,735 (84.2)	<.0001
Metformin	44,192 (46.3)	37,753 (45.6)	6439 (50.5)	<.0001
Sulfonylurea	54,832 (57.4)	46,754 (56.5)	8078 (63.4)	<.0001
Insulin	18,716 (19.6)	16,736 (20.2)	1980 (15.5)	<.0001
Other medications	2541 (2.7)	2121 (2.6)	420 (3.3)	<.0001
Place in therapy for rosiglitazone at baseline, n (%)				<.0001
First line	17,127 (17.9)	15,120 (18.3)	2007 (15.8)	
Second line	33,980 (35.6)	29,442 (35.6)	4538 (35.6)	
Third line	25,391 (26.6)	21,222 (25.6)	4169 (32.7)	
With insulin	18,716 (19.6)	16,736 (20.2)	1980 (15.5)	
Other	325 (0.3)	277 (0.3)	48 (0.4)	

A1C indicates glycated hemoglobin; SD, standard deviation.
[a]Patients who died before discontinuing rosiglitazone (n = 580 [4.6%]) were included in the "continued" group.
[b]Baseline concurrent medications were those that were active on the baseline date or within 1 week before or after the index date.

Table 2. Monthly Rosiglitazone Discontinuation Rates and Incidence Rate Ratios After FDA Warning and After Removal From the VANF

Time	Total Patients	Died[a]	Discontinued	Person-Days	Discontinuation Rate per 1000 Person-Days (95% CI)	IRR Compared With Before FDA Warning[b] (95% CI)	IRR Compared With Before Removal From VANF[c] (95% CI)
Pre-FDA warning					**2.3 (2.2-2.3)[f]**		
April 1, 2007	95,539	77	5921	2,687,809	2.2 (2.1-2.3)	0.9 (0.9-1)	0.6 (0.5-0.6)
May 1, 2007[d]	89,541	61	4120	1,752,101	2.4 (2.3-2.4)	Reference	0.6 (0.6-0.6)
Post FDA warning					**3.9 (3.9-4.0)[f]**		
June 1, 2007[d]	85,360	90	12,548	3,243,690	3.9 (3.8-3.9)	1.6 (1.6-1.7)	1.0 (1.0-1.0)
July 1, 2007	72,722	57	7975	2,138,687	3.7 (3.6-3.8)	1.6 (1.5-1.6)	1.0 (0.9-1.0)
August 1, 2007	64,690	60	8041	1,877,264	4.3 (4.2-4.4)	1.8 (1.8-1.9)	1.1 (1.1-1.1)
September 1, 2007[e]	56,589	52	6983	1,800,344	3.9 (3.8-4.0)	1.6 (1.6-1.7)	Reference
After removal from VANF					**5.3 (5.2-5.3)[f]**		
October 1, 2007[e]	49,554	25	5827	1,266,423	4.6 (4.5-4.7)	2.0 (1.9-2.0)	1.2 (1.1-1.2)
November 1, 2007	43,702	29	6614	1,215,255	5.4 (5.3-5.6)	2.3 (2.2-2.4)	1.4 (1.4-1.5)
December 1, 2007	37,059	39	6322	1,048,056	6.0 (5.9-6.2)	2.6 (2.5-2.7)	1.6 (1.5-1.6)
January 1, 2008	30,698	25	5066	874,403	5.8 (5.6-6.0)	2.5 (2.4-2.6)	1.5 (1.4-1.5)
February 1, 2008	25,607	25	3839	686,800	5.6 (5.4-5.8)	2.4 (2.3-2.5)	1.4 (1.4-1.5)
March 1, 2008	21,743	18	3198	604,242	5.3 (5.1-5.5)	2.3 (2.1-2.4)	1.4 (1.3-1.4)
April 1, 2008	18,527	9	2723	514,612	5.3 (5.1-5.5)	2.3 (2.1-2.4)	1.4 (1.3-1.4)
May 1, 2008	15,795	5	2124	442,480	4.8 (4.6-5.0)	2.0 (1.9-2.2)	1.2 (1.2-1.3)
June 1, 2008	13,666	8	1496	386,523	3.9 (3.7-4.1)	1.6 (1.6-1.7)	1.0 (0.9-1.1)

CI indicates confidence interval; FDA, US Food and Drug Administration; IRR, incidence rate ratio; VANF, Department of Veterans Affairs National Formulary.
[a]Patients died before discontinuing rosiglitazone.
[b]All *P* values were less than .001.
[c]All *P* values were less than or equal to .001, except *P* =.86, .02, and .94 for June 2007, July 2007, and June 2008, respectively.
[d]Data from May 21, 2007, through May 31, 2007, were included in June because the FDA warning was disseminated on May 21, 2007.
[e]Data from October 1, 2007, through October 4, 2007, were included in September because rosiglitazone removed from VANF on October 4, 2007.
[f]Rosiglitazone discontinuation rates were aggregated for the 3 study periods. The discontinuation rate for the entire study period was 4.0 (95% CI, 4.0-4.1) per 1000 person-days, which means that during 1000 days of observation (eg, 10 patients on rosiglitazone for 100 days), 4 would have discontinued the medication.

2007, to October 4, 2007), and after removal from the VANF (October 5, 2007, to June 30, 2008).

Statistical Analysis

Patient baseline characteristics including demographics, comorbidities as defined in the adaptation by Deyo and colleagues of the Charlson Comorbidity Index (a weighted index in which a higher score is associated with an increased risk of health outcomes such as mortality and resource use based on comorbidities coded within the year prior to baseline),[16] A1C, and place of rosiglitazone in therapy were described by rosiglitazone discontinuation status (yes or no). We compared baseline characteristics with χ^2 or *t* tests, as appropriate.

We determined the monthly rosiglitazone discontinuation rates. Using Poisson methods, we compared monthly incidence rate ratios (IRRs) in the month prior to the FDA warning (May 2007) with the IRRs in the month prior to removing rosiglitazone from the VANF (September 2007) to assess the impact of the 2 events separately. We also examined the rosiglitazone discontinuation rates across time and described the proportions of patients receiving medications to replace rosiglitazone by the place of rosiglitazone in therapy at the index date. We estimated the intervention effects (IRRs for post FDA warning vs pre-FDA warning, after removal from the VANF vs pre-FDA warning, and after removal from the VANF vs post FDA warning) and identified patient-level factors associated with stopping rosiglitazone by using multivariable Poisson regression with a robust variance estimator and fixed effects for VA medical centers. Patients who died before rosiglitazone was discontinued were coded as continuing on rosiglitazone.

To evaluate the effect on glucose control of removing rosiglitazone from the VANF, we compared A1C levels across time among patients who discontinued and continued rosiglitazone. We used a linear mixed model to account for within-patient correlation and conducted subgroup analyses of A1C levels according to insulin use at baseline.

All *P* values were 2-sided, and *P* values less than .05 were considered statistically significant. Because most tests were statistically significant due to the large sample size, we focused our interpretation on differences of a clinically significant magnitude. We used Stata release 11 (StataCorp LP, College Station, Texas) to fit the Poisson models; the remaining analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Baseline Characteristics by Rosiglitazone Discontinuation Status

On April 1, 2007, 95,539 veterans had an active outpatient prescription for rosiglitazone and were chronic users of the medication. The average age of the cohort was 67 years; 97.8% were male; 60% were white; 9.3% were black; and 30% were other/unknown race (**Table 1**). At baseline, the mean A1C was 7.4%, and 82.1% of patients received other antidiabetic medications concurrently with rosiglitazone. Rosiglitazone was first-line therapy in 17.9% of patients, second-line in 35.6%, third-line in 26.6%, used with insulin in 19.6%, and rarely prescribed with other medications not included in the second-line or third-line definitions (0.3%). By the end of the study period, 82,797 (86.7%) patients discontinued rosiglitazone. The baseline characteristics of these patients were essentially the same as those of the total cohort. Patients who continued rosiglitazone were clinically similar to the patients who discontinued the medication, except that they were less likely to be black, have a baseline A1C value higher than 9%, or receive insulin concurrently at baseline, and relatively more likely to receive rosiglitazone as third-line therapy.

Discontinuation of Rosiglitazone

The rosiglitazone discontinuation rate over the entire study period was 4.0 per 1000 person-days, which means that during 1000 days of observation (eg, 10 patients on rosiglitazone for 100 days), 4 would have discontinued the medication. The period-specific rosiglitazone discontinuation rates were about 2.3 per 1000 person-days of rosiglitazone use before the FDA warning, 3.9 per 1000 person-days after the FDA warning, and 5.3 per 1000 person-days after removal from the VANF (**Table 2**). Discontinuation rates increased significantly during the 4 months following the May 21, 2007, FDA warning, with the IRRs ranging from 1.6 to 1.8 (Table 2, **Figure 1A**). After removal from the VANF on October 4, 2007, discontinuation rates increased significantly through May 2008; compared with September 2007, the monthly IRRs ranged from 1.2 to 1.6. Discontinuation rates returned to the September 2007 level in June 2008. Rosiglitazone discontinuation rates varied with the place of rosiglitazone in therapy at the baseline date (**Figure 1B**). Patients receiving insulin concurrently tended to have the highest discontinuation rates, and those on rosiglitazone as a third-line agent had the lowest discontinuation rates.

Medications Replacing Rosiglitazone

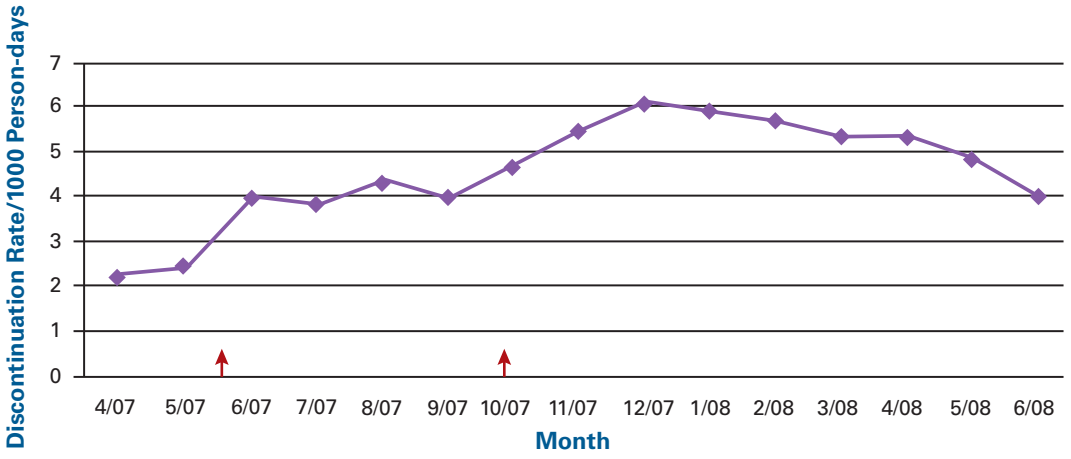
When rosiglitazone was discontinued, the proportions of patients who received another medication in its place ranged from 17.1% pre-FDA warning to 22.5% post FDA warning and 37.8% after the VANF removal. An abrupt increase in the proportion of patients starting pioglitazone in place of rosiglitazone, from 1% or fewer pre-FDA warning to 22% after VANF removal of rosiglitazone, accounts for the large increase in the proportion of patients receiving prescriptions for replacement medications (**Figure 2A**). In addition, patients receiving rosiglitazone as first-line therapy were most likely to receive a replacement medication, whereas those receiving insulin concurrently at baseline were least likely (**Figure 2B**).

Factors Associated With Discontinuation of Rosiglitazone

Compared with the pre-FDA warning period, patients were more likely (IRR = 1.81; 95% CI, 1.77-1.85) to have rosiglitazone discontinued after the FDA warning (**Table 3**). During the post VANF removal period, patients were more than twice as likely to discontinue rosiglitazone relative to baseline (IRR = 2.73; 95% CI, 2.67-2.79). The discontinuation rate was significantly higher after rosiglitazone was removed from the formulary than it was immediately after the FDA warning (IRR = 1.51; 95% CI, 1.49-1.53).

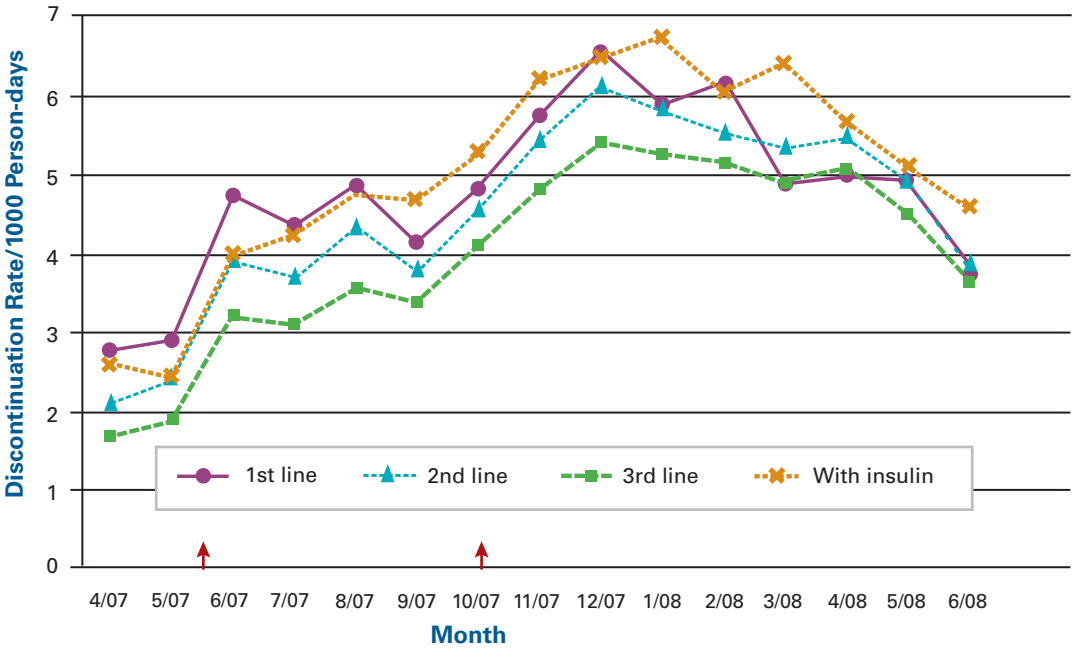
In the multivariable model (Table 3), rosiglitazone was more likely to be discontinued for patients who were female (IRR = 1.10; 95% CI, 1.05-1.15) or black (IRR = 1.05; 95% CI, 1.03-1.08). A 1-point increase in the Charlson Comorbidity Index score was associated with a 3% increase in the risk of discontinuing rosiglitazone. Compared with patients whose baseline A1C was within the range of 7% to 9%, patients whose A1C was less than 7% were less likely (IRR = 0.91, 95% CI, 0.89-0.92), and patients whose A1C was greater than 9% were more likely (IRR = 1.24; 95% CI, 1.2-1.27), to have rosiglitazone discontinued. Patients who were *not* re-

Figure 1A. Monthly Rosiglitazone Discontinuation Rates[a]



[a]Month of US Food and Drug Administration warning and month of removal from Department of Veterans Affairs National Formulary are denoted by first and second arrows, respectively.

Figure 1B. Monthly Rosiglitazone Discontinuation Rates by Place of Rosiglitazone in Therapy at the Index Date[a]



[a]Month of US Food and Drug Administration warning and month of removal from Department of Veterans Affairs National Formulary are denoted by first and second arrows, respectively.

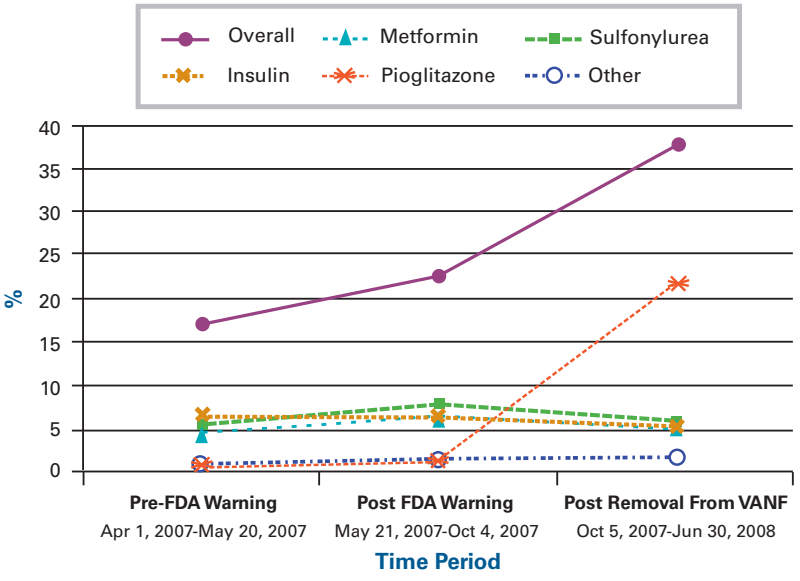
ceiving rosiglitazone as third-line therapy at the index date were 11% to 24% more likely to have it discontinued.

Change in A1C

Among patients who had rosiglitazone discontinued and received replacement medication(s), mean A1C values at baseline and after discontinuation were 7.4% and 7.5%, respectively (Table 4). For those patients who had rosiglitazone discontinued and received no new medication, mean A1C values were 7.4% at baseline and 7.9% after discontinuation. Among patients who remained on rosiglitazone, mean A1C values were the same at baseline and the end of the study (ie, 7.3% vs 7.3%).

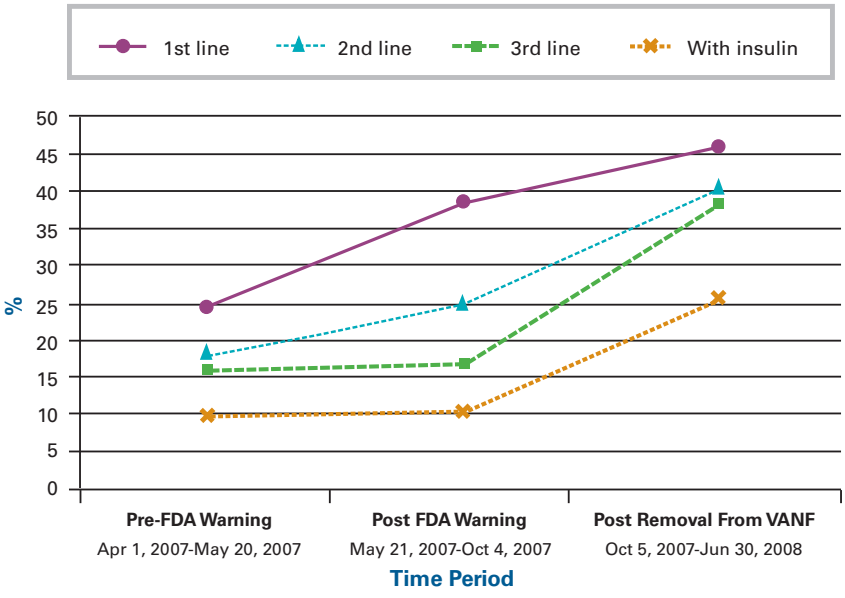
In the subset of patients who did not receive insulin concurrently at baseline, those who had rosiglitazone discontinued and received a replacement medication had mean A1C values of 7.3% at baseline and 7.5% after discontinuation. Those who

Figure 2A. Proportions of Patients Receiving Various Medications to Replace Rosiglitazone Across 3 Time Periods: Pre-FDA Warning, Post FDA Warning, and After Removal From the VANF



FDA indicates US Food and Drug Administration; VANF, Department of Veterans Affairs National Formulary.

Figure 2B. Proportions of Patients Receiving any Medication(s) to Replace Rosiglitazone Across 3 Time Periods: Pre-FDA Warning, Post FDA Warning, and After Removal From the VANF, by Rosiglitazone's Place in Therapy at the Index Date



FDA indicates US Food and Drug Administration; VANF, Department of Veterans Affairs National Formulary.

did not receive a replacement medication had mean A1C values at baseline and after discontinuation of 7.2% and 7.7%, respectively. Patients who received insulin concurrently with rosiglitazone had higher A1C values on average. Among those taking insulin who received other medication(s) to replace rosiglitazone, the mean A1C values were comparable at baseline and after discontinuation of rosiglitazone (7.9% vs 8.0%). For patients receiving insulin at baseline who had rosiglitazone discontinued and received no new medication, mean A1C values were 7.9% at baseline and 8.3% after discontinuation.

Table 3. Factors Associated With Discontinuation of Rosiglitazone[a]

Factors	IRR	95% CI	*P*
Intervention effect[b]			
Post FDA warning vs pre-FDA warning	1.81	1.77-1.85	<.001
After removal from VANF vs pre-FDA warning	2.73	2.67-2.79	<.001
After removal from VANF vs post FDA warning	1.51	1.49-1.53	<.001
Age (per year)	1.00	1.00-1.00	.23
Female	1.10	1.05-1.15	<.001
Race			
White	Reference		
Black	1.05	1.03-1.08	<.001
Other	1.02	0.97-1.07	.38
Unknown	1.02	0.99-1.04	.19
Hispanic ethnicity			
No	Reference		
Yes	1.05	1.01-1.08	.006
Missing	0.97	0.95-1.00	.04
Charlson Comorbidity Index score	1.03	1.02-1.03	<.001
Diabetes with complications	0.96	0.95-0.98	.001
Baseline A1C			
<7%	0.91	0.89-0.92	<.001
7%-9%	Reference		
>9%	1.24	1.2-1.27	<.001
Missing	0.96	0.95-0.98	<.001
Place in therapy for rosiglitazone at index date			
First line	1.24	1.22-1.27	<.001
Second line	1.11	1.09-1.13	<.001
Third line	Reference		
With insulin	1.23	1.21-1.26	<.001
Other	1.16	1.02-1.31	.02

A1C indicates glycated hemoglobin; CI, confidence interval; FDA, US Food and Drug Administration; IRR, incidence rate ratio; VANF, Department of Veterans Affairs National Formulary.
[a]Poisson regression analysis with a robust variance estimator and VA medical center specified as a fixed effect. Patients who died before rosiglitazone was discontinued were not considered to have discontinued rosiglitazone.
[b]Intervention was coded as time-varying indicators of (1) pre-FDA warning: April 1, 2007 to May 20, 2007; (2) post FDA warning: May 21, 2007, to October 4, 2007; and (3) after removal from the VANF: October 5, 2007, to June 30, 2008.

DISCUSSION

Similar to previous studies,[7-11] we found an increase in the rosiglitazone discontinuation rate following the May 21, 2007, FDA warning.[1] The rate increased still more following the removal of the medication from the VANF; 86.7% of the VA cohort had rosiglitazone discontinued, which is higher than the 62% reported in a similar study by Orrico and colleagues.[9] However, our overall follow-up period was longer (13 vs 5 months), and we further assessed rosiglitazone use following its change in formulary status. We conducted a similar study of an intervention to decrease glyburide use in elderly veterans with renal insufficiency; in that study, the baseline glyburide discontinuation rate was approximately 3 per 1000 person-days in the preintervention period and 6.1, 4.8, and 4.2 per 1000 person-days at 1, 2, and 3 months, respectively, after the intervention.[17] Although the antidiabetic medications and "interventions" were different, the discontinuation rates in the glyburide and rosiglitazone studies (ie, 2.3 per 1000 person-days at baseline and 4.6, 5.4, and 6.0 per 1000 person-days at 1, 2, and 3 months, respectively, after removal from the VANF) are fairly similar.

We also found important differences in the discontinuation rates according to rosiglitazone's place in therapy, which

Table 4. A1C Results Among Patients Who Discontinued or Continued Rosiglitazone for the Overall Cohort and the Subgroups Not Receiving and Receiving Insulin at Baseline[a]

Rosiglitazone Status	Sample Size, n	Mean (SD) Baseline A1C, %	Sample Size	Mean (SD) A1C After Rosiglitazone Was Discontinued or June 30, 2008,[b] %	Average Change in A1C (95% CI) From Baseline, %
Overall					
Discontinued with any medication replacing rosiglitazone	17,967	7.4 (1.3)	17,549	7.5 (1.4)	0.12 (0.10-0.14)
Discontinued with no medication replacing rosiglitazone	42,124	7.4 (1.4)	39,242	7.9 (1.6)	0.46 (0.44-0.47)
Continued	8647	7.3 (1.2)	8279	7.3 (1.2)	–0.02 (–0.04 to 0.10)
Not receiving insulin at baseline					
Discontinued with any medication replacing rosiglitazone	15,675	7.3 (1.3)	15,351	7.5 (1.4)	0.13 (0.11-0.15)
Discontinued with no medication replacing rosiglitazone	31,065	7.2 (1.3)	28,878	7.7 (1.6)	0.50 (0.48-0.51)
Continued	7139	7.2 (1.1)	6899	7.2 (1.2)	0.001 (–0.03 to 0.03)
Receiving insulin at baseline					
Discontinued with any medication replacing rosiglitazone	2292	7.9 (1.4)	2198	8.0 (1.5)	0.07 (0.01-0.13)
Discontinued with no medication replacing rosiglitazone	11,509	7.9 (1.5)	10,364	8.3 (1.7)	0.35 (0.32-0.38)
Continued	1508	7.7 (1.4)	1380	7.6 (1.3)	–0.09 (–0.16 to –0.01)

A1C indicates glycated hemoglobin; CI, confidence interval; SD, standard deviation.
[a]Linear mixed model to account for correlation between repeated measures within patients.
[b]A1C after rosiglitazone was discontinued among patients who discontinued rosiglitazone or A1C after June 30, 2008, for patients who continued on rosiglitazone at the end of the study.

was not evaluated in prior studies. The discontinuation rate was lowest when rosiglitazone was used as third-line therapy and generally highest when it was used in combination with insulin. Patients receiving rosiglitazone in combination with metformin and a sulfonylurea (ie, third-line therapy) likely had long-standing and more difficult to control diabetes and may have preferred to avoid insulin, so providers may have been reluctant to stop rosiglitazone. Among patients receiving concomitant insulin, providers could increase the dose of insulin as necessary when rosiglitazone was discontinued. Also, the FDA warned of an increased MI risk in patients on both insulin and rosiglitazone on November 19, 2007; this warning did not apply to pioglitazone.[18]

For patients who had rosiglitazone discontinued, approximately 29% received another medication in its place during the time periods before and after the FDA warning. The FDA warning increased the rosiglitazone discontinuation rate, but did not markedly influence the rate of replacement of rosiglitazone with other medications. However, this replacement rate increased sharply to 37.8% when rosiglitazone was removed from the VANF because providers could switch patients to pioglitazone without completing a nonformulary request. This made prescribing pioglitazone easier and accounted for the observed increase during the period after the VANF removal as the proportions of patients prescribed metformin, a sulfonylurea, or insulin in place of rosiglitazone decreased slightly. It is somewhat surprising that the proportion of patients who received pioglitazone was not higher; it is possible that some medical centers did not follow VA guidelines and limited the availability of pioglitazone.

Because of the huge sample size, all factors assessed, except for age, were statistically associated with discontinuing rosiglitazone in the multivariable model. However, the effects of the FDA warning and removal of rosiglitazone from the VANF, baseline glucose control, and rosiglitazone's place in therapy were most strongly associated with discontinuation. Providers were more likely to discontinue rosiglitazone after the FDA warning and were even more apt to do so after removal from the VANF. Although providers were notified of the FDA warning via e-mail, the change in formulary status and associated recommendations for using the medication likely resulted in a greater response because additional information regarding MI risk with the TZDs had been published.[3-5] Furthermore, VA providers were urged to discuss the risks and benefits of

continuing rosiglitazone with their patients and make a decision about continued TZD use. Thus, a concrete action was required with the change in formulary status. Studies have found that formularies can be effective in shifting prescribing practices toward preferred, or formulary, medications.[19,20] Providers also were more likely to discontinue rosiglitazone if the glucose was less well controlled (ie, baseline A1C >9% vs 7%-9%). It is possible that providers thought rosiglitazone was not contributing much to the antidiabetic regimen. Providers also were more likely to discontinue rosiglitazone when it was not being used as third-line therapy. Again, providers may have been more willing to stop the medication when other options were available.

The increase in A1C was statistically and potentially clinically significant when another medication was not prescribed in place of rosiglitazone (mean change of 0.35% in those receiving insulin concurrently at baseline and 0.5% in those not receiving insulin). Because of measurement error, some have suggested that a change of 0.5% or greater over time is clinically significant.[21] In the study by Shi and colleagues[10] of the effect of TZD safety warnings on glycemic control, the group of veterans who discontinued rosiglitazone or pioglitazone without receiving another antidiabetic medication in its place had a mean increase in their A1C of 0.27%. However, those patients who were changed to a non-TZD therapy also had an increase in their A1C (ie, 0.33%). Similar to the results of our study, patients who remained on rosiglitazone or pioglitazone had almost no change in their A1C (ie, –0.06%).[10] We used the most recent A1C result within 3 to 9 months of stopping rosiglitazone, so glucose control may have improved over time if antidiabetic medications were changed after the provider assessed the effect of discontinuing rosiglitazone.

Limitations

Although we followed a large patient cohort over time and comprehensively assessed medication data, the study has limitations. Most importantly, the project was observational and uncontrolled. However, these types of safety warnings and policy changes will not allow a controlled intervention study. Second, we may have overestimated the discontinuation rate if patients obtained rosiglitazone outside the VA system. This probably occurred infrequently because providers could switch their patients to pioglitazone without completing a nonformulary request, and rosiglitazone is only available as a brand medication, so the copay is likely higher outside the VA system. Third, the relative effect of the FDA warning may have been underestimated if the rosiglitazone discontinuation rate was increasing prior to April 1, 2007. In our data, the rate was essentially unchanged in April and May, and in the study by Starner and colleagues,[11] the average number of rosiglitazone claims per day per 1 million members was stable in January through April 2007. Rosiglitazone use started to decline in May 2007, the month of the FDA warning.[11]

Fourth, we probably underestimated the proportion of patients categorized as receiving rosiglitazone as a second- or third-line medication. Patients with a previous adverse event or contraindication to metformin or a sulfonylurea would be misclassified as receiving rosiglitazone as a first- or second-line agent. We were not able to obtain this information using administrative databases; however, were such patients categorized correctly, the discontinuation rate among those receiving rosiglitazone as first- or second-line therapy would have been even higher. Fifth, we could not assess insulin doses because the directions are not always updated when a change is made, so we did not know whether the dose was increased after rosiglitazone was stopped. Sixth, we did not know whether other medications were eventually added or changed in those with poor glucose control because we assessed medication changes within a relatively short time frame (60 days after the end of the days of supply of the last rosiglitazone prescription). Finally, we did not assess the long-term effects of this intervention because our follow-up ended in June 2008.

CONCLUSIONS

In conclusion, the rosiglitazone discontinuation rate increased following the FDA warning about a potential increased risk of MI and increased still more following its removal from the VANF. Glucose control may have declined among those who discontinued rosiglitazone without receiving another antidiabetic agent in its place.

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