

# Clinical Consequences of Disseminating the Rosiglitazone FDA Safety Warning

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The frequency of US Food and Drug Administration (FDA) MedWatch postmarketing drug safety alerts has increased precipitously over the past few years. In calendar year 2007, for example, MedWatch issued 161 safety warnings about drugs, medical biological and nutritional products, and medical devices.<sup>1</sup> The deluge of warnings poses a challenge for managed care organizations that may not be prepared for the patient response that often follows alerts that are widely publicized through the lay media. Often recommendations need to be quickly incorporated into treatment guidelines and clinic procedure. A case in point concerns a recently released warning about the asthma medication omalizumab, which is administered in most allergy clinics. The FDA warning advised that patients be observed for at least 2 hours postadministration and that clinic staff be prepared to manage possible life-threatening anaphylaxis.<sup>2</sup> Alerts also impact formulary selection. When an early communication about possible excess atherosclerotic plaque formation in users of the popular cholesterol-lowering agent ezetimibe was issued in 2008, it was quickly followed by removal of the drug from many health plan formularies.<sup>3</sup>

On May 21, 2007, MedWatch issued a warning concerning a possible increased risk of ischemic myocardial infarction (MI) and cardiovascular (CV) death in people receiving the widely prescribed antidiabetic drug rosiglitazone.<sup>4</sup> The alert was prompted by the *New England Journal of Medicine*'s online publication of a meta-analysis conducted by Nissen and Wolski, which combined the results of 42 clinical trials (mean duration 6 months; 14,237 total patients) that mostly compared rosiglitazone with placebo.<sup>5</sup> The results suggested a 43% increase in the rate of MI in treatment groups receiving rosiglitazone versus groups that did not. Although the findings were never presented by the authors as conclusive, the warning was broadly disseminated through the public media, raising intense patient concern and triggering the Safety, Notification, and Follow-Up (SNAFU) Committee at the Palo Alto Medical Foundation for Health Care, Research, and Education (PAMF) to notify patients and providers about the warning.

The aim of our study was to examine the clinical consequences that may have resulted from distributing the rosiglitazone FDA safety alert to both patients and providers.

As observational end points, we determined the percentage of patients who had rosiglitazone therapy discontinued as a result

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**Background:** On May 21, 2007, a safety alert was widely disseminated through the media and US Food and Drug Administration (FDA) MedWatch concerning a possible increased risk of ischemic myocardial infarction and cardiovascular death in people receiving the antidiabetic drug rosiglitazone.

**Objective:** To determine whether notification of patients and providers about an FDA safety warning influenced the decision to discontinue rosiglitazone therapy and the resulting effect on glycemic control.

**Study Design:** Retrospective electronic medical record (EMR) review.

**Methods:** EMR documentation review of 552 primary care patients with a prescription for rosiglitazone current on May 21, 2007, was conducted to determine the percentage that had rosiglitazone discontinued as a result of written notification about the FDA alert. We ascertained whether discontinuation was initiated by the physician or patient. We compared the change in glycosylated hemoglobin (A1C) values from baseline to follow-up between the group continuing on rosiglitazone and the group discontinuing therapy.

**Results:** Of 552 patients, 344 (62%) had rosiglitazone discontinued as a result of the warning. Discontinuation was initiated by the physician in 150 cases (43.6%), by the patient in 155 cases (45.1%), and was undetermined in 39 cases (11.3%). No significant difference was found in the mean change in A1C values from baseline to follow-up between the 2 groups.

**Conclusions:** Notifying patients and providers about FDA safety alerts does influence clinical decision making. The lay media should partner with the FDA to responsibly communicate drug safety information in evidence-based, understandable terms that quantify real risk.

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**For author information and disclosures, see end of text.**

### Take-Away Points

Both patients and providers are affected by notification about and media dissemination of US Food and Drug Administration (FDA) safety alerts, and such alerts do influence clinical decision making.

- Our results suggest that notification about the rosiglitazone FDA safety alert influenced both patients and providers to discontinue the drug because of safety concerns in 62% of our study population.
- Considering the impact drug safety warnings have on drug therapy, it is imperative that all recommended action be evidence based.
- The lay media should partner with the FDA and responsibly communicate drug safety information to the public in evidence-based, understandable terms that quantify real risk.

of the warning as ascertained through electronic medical record (EMR) documentation review, and whether the discontinuation of rosiglitazone was initiated by the physician or the patient. We also compared glycemic control in the group of patients who continued on rosiglitazone with that in the group who discontinued the drug by measuring the change in baseline glycosylated hemoglobin (A1C) values before and after the warning was issued.

## STUDY SETTING

The study was conducted as a retrospective EMR review at the Palo Alto Division of PAMF (PAMF/PAD) located in Northern California after approval by the PAMF Research Institute Institutional Review Board. The foundation is an affiliate of Sutter Health, a system of not-for-profit hospitals and physician organizations. PAMF/PAD is a multispecialty medical group with approximately 400 physicians that conduct 750,000 patient visits annually. Since 2002, PAMF/PAD providers have used a full-featured EMR produced by Epic Systems to document all clinical activity including computerized medication order entry; however, this EMR does not capture prescription fill history. The EMR can be queried to abstract patient-specific data such as demographic information, physician assignment, prescription and over-the-counter medication order entry information, laboratory results, diagnoses, appointment dates, and visit type(s), as well as additional patient-specific information. Documents not available electronically (eg, patient correspondence) are scanned into the record for viewing.

Unique to this study setting, the SNAFU Committee was formed at PAMF/PAD in 2004 to provide a rapid and concerted response to FDA drug safety warnings, medical product recalls, and other patient safety incidents requiring notification to patients or healthcare providers.<sup>6</sup> The SNAFU Committee is composed of key decision-making individuals who contribute their specific expertise to forming and implementing a workable course of action. Committee members include pharmacists, medical group administrators, physicians, risk

managers, the director of materials services, and a communications specialist.

On receipt of the rosiglitazone warning through FDA MedWatch, the SNAFU Committee formulated an internal action plan and sent notification to the medical staff late in the day on May 21, 2007. The notification reiterated the FDA's recommendation that an association was possible and that rosiglitazone therapy should be reconsidered

for patients at the highest risk of a cardiac event. Physicians also were told that all PAMF/PAD patients receiving rosiglitazone would be identified and informed of the alert.

A query of the EMR conducted on May 30, 2007, identified 828 patients with at least 1 prescription for rosiglitazone entered into the system in the preceding 12 months. The SNAFU Committee decided that the query should extend through May 30, 2007, to capture any prescribing of rosiglitazone that occurred near term to the alert, possibly before physicians had read the notification. All listed patients were notified about the FDA warning through letter or secured e-mail by June 4, 2007, and asked to contact their primary care physician regarding their individual treatment plan. A copy of the correspondence was scanned into each patient's EMR.

## METHODS

### Data Source and Population

The list of 828 patients generated on behalf of the SNAFU Committee was used to select our study population because it captured patients whose drug therapy was actively managed at PAMF/PAD. Listed patients who met the study inclusion criteria were eligible for evaluation. Study inclusion required that patients were assigned a primary care physician at PAMF/PAD, were not deceased, had at least 1 prescription for rosiglitazone entered into the EMR between May 1, 2006, and May 30, 2007, and had at least 1 visit (encounter) with any department within the past 18 months. Listed patients were excluded if they were not stabilized on therapy because rosiglitazone was either discontinued prior to May 21, 2007, or initiated after February 21, 2007. Patients also were excluded if they had documented nonadherence as evidenced by visit notation (**Table 1**) (eg, "Patient reports that she frequently forgets to take meds").

Patient charts were reviewed to determine the status of their rosiglitazone prescription order after notification. Patients were categorized into the continued group if the drug order was active or the discontinued group if rosiglitazone had been discontinued. The discontinuation of rosiglitazone

in response to the alert could occur at any time between May 21, 2007, and October 1, 2007, if documentation supported the reasoning that the discontinuation was due to the safety warning and not other factors such as intolerance or lack of therapeutic response.

### Chart Review Methodology and Outcome Measures

The chart review process commenced on October 1, 2007, and was independently conducted by 3 investigators. As a process check, each patient chart was reviewed by 2 investigators, and any discrepancy between the 2 reviews was rectified by a third reviewer.

The EMR of each patient was accessed through entry of their medical record number. The encounter or visit progress notes, current and historical medication lists, laboratory results, and other sections of the EMR were reviewed in order to abstract data. Reviewers verified that each patient met the study inclusion criteria with no exclusions. Next, reviewers verified that the notification letter had been sent to the patient by reviewing the copy scanned into each patient's EMR on the Encounter view and labeled as Patient Correspondence.

The Chart Review option was used to determine whether rosiglitazone had been continued or discontinued, and to abstract outcome measures. The chronology of changes made to the antidiabetic regimen was examined by filtering and sorting the Current and the Historical Medication List views. The Current Medication List contains all orders without a discontinuation or "end date," and the Historical Medication List contains an archive of the patient's previously discontinued orders. The EMR allows for the medication list to be sorted or "filtered" by pharmaceutical class. Through the selection of "antidiabetic agents" and a sort of the view by the Start Date and Stop Date columns, the chronology of medication changes was determined.

Encounter notes and documentation in close temporal proximity to the date the alert was issued (May 21, 2007) and/or that corresponded to dates where changes were made to the antidiabetic drug regimen were reviewed to determine prescription status and whether the patient or provider initiated a change in drug therapy. Of note, the end date documented in the EMR was not always the same as the actual date the medication was discontinued, especially in situations where the patient self-initiated stopping the drug. In order to correct for this, visit notes were read to verify the exact date rosiglitazone was discontinued.

■ **Table 1.** Selection of Study Population

Criteria	No.
<b>Patients with a rosiglitazone prescription current on May 21, 2007</b>	828
<b>Exclusions</b>	
Duplicate name	6
Age <18 y	1
No primary care physician assignment	44
Deceased during study period	18
Rosiglitazone discontinued before May 21, 2007	97
Rosiglitazone initiated after February 21, 2007	62
Discontinued for reasons other than alert	12
Documented medication nonadherence	36
<b>Total exclusions</b>	276
<b>Total available for group assignment</b>	552

Once rosiglitazone prescription status was determined, chart documentation of the discontinued group was further evaluated to determine the observational end point of who initiated the discontinuation of rosiglitazone, whenever possible. For discontinuation that was patient initiated, often there was evidence of a phone encounter explaining that the patient was requesting an appointment to discuss concerns regarding rosiglitazone. Other documentation found under Reason for Visit said that the patient was there to discuss the rosiglitazone warning rather than another chief complaint (eg, "Patient is here to discuss recent FDA warning regarding rosiglitazone," "Patient worried about recent news of MI risk with Avandia"). For physician-initiated discontinuation, reasoning documentation was typically found in the visit note under Plan for Diabetes Mellitus (eg, "Due to recent safety warning, will discontinue Avandia at this time").

In order to calculate and compare the changes from baseline in A1C values for the discontinued group and the continued group, baseline and follow-up A1C values were abstracted by reviewing the laboratory results recorded in the EMR. All A1C values must have been dated as drawn between the 2-year window of June 1, 2006, and May 31, 2008. The baseline A1C value for patients in the continued group was defined as the one measured most immediately prior to May 21, 2007. For the discontinued group, the baseline A1C value was defined as the one measured most immediately prior to the rosiglitazone discontinuation date. Because A1C values indicate the mean blood glucose concentration over the past 6 to 8 weeks,<sup>7</sup> the follow-up A1C value was defined as the next A1C value measured at least 8 weeks postbaseline for the continued group or as the next

■ **Table 2.** Characteristics of the Study Population (N = 552)

Variable	Discontinued Group	Continued Group
No. (percentage of total)	344 (62)	208 (38)
Mean age, y	59.28	62.64
Men	184	123
Women	160	85

measured value occurring at least 8 weeks after the rosiglitazone discontinuation date for the discontinued group. All abstracted data were entered onto a singular, password-protected Excel worksheet located on the system share drive for statistical evaluation.

### Statistical Analysis

Simple percentages were calculated to determine the observational end points of the percentage of patients who had rosiglitazone discontinued and the percentage of the discontinued group who had physician-initiated versus patient-initiated discontinuation.

Averages were calculated for the baseline and follow-up A1C values for both groups, and the mean change was calculated. The statistical significance of the difference between the mean changes in A1C values for the discontinued group and the continued group was determined by using the paired, 2-sided *t* test assuming equal variances (*P* = .05).

## RESULTS

Of the listed 828 patients identified for notification by the SNAFU Committee, 552 (67%) met the inclusion criteria and were eligible for rosiglitazone prescription status evaluation (Table 1). All 828 patients had the notification letter scanned into the EMR. Of the 552 study patients, 344 (62%) had rosiglitazone discontinued in response to the alert and composed the discontinued group, while 208 (38%) made up the continued group (Table 2). Of the 344 patients who had rosiglitazone discontinued, 142 (41%) were initially switched to pioglitazone, an alternative medication in the same thiazolidinedione class. Although both drugs cause a dose-dependent increase in congestive heart failure, pioglitazone had not been shown to share additional ischemic CV risk.

Further EMR review of the discontinued group showed that the decision to discontinue rosiglitazone was initiated by the physician in 150 (43.6%) cases, by the patient in 155 (45.1%) cases, and could not be determined by chart review in 39 (11.3%) cases. The time frame over which the drug was discontinued in response to the alert spanned from May 21, 2007, through October 22, 2007.

The majority of the discontinued group (273 [79%]) had rosiglitazone discontinued within the 6-week time period after the alert was issued, from May 21, 2007, through July 31, 2007. Later discontinuations generally occurred when the patient presented for routine diabetes follow-up or posttravel and were mostly initiated by the physician.

The changes in A1C values from baseline to follow-up were calculated for the 2 groups, and the mean changes were compared (Table 3). Of the continued group, 129 (62%) patients had both a baseline and a follow-up A1C value documented in the EMR. The mean baseline A1C was 7.26% ± 1.29%, and the mean follow-up A1C was 7.25% ± 1.31%, resulting in a mean difference of -0.5% (95% confidence interval [CI] = -0.60, -0.40). Of the discontinued group, 344 (91%) patients had both a baseline and follow-up A1C value documented in the EMR. The mean baseline A1C was 7.15% ± 1.26%, and the mean follow-up A1C was 7.2% ± 1.4%, resulting in a mean difference of 0.092% (95% CI = 0.04, 0.13). The *t* score for the differences in the group means was 0.276, showing that there was not a statistically significant difference in the mean change in A1C between the 2 groups.

## DISCUSSION

Our results show that notification about the rosiglitazone FDA safety alert did influence both patients and providers to discontinue the drug because of safety concerns in 62% of our study population. The impetus to discontinue was nearly evenly split between patients and physicians. A difference between our study population and the general population is that the activities of the SNAFU Committee ensured that most PAMF patients and providers were made aware of the alert and the recommended course of action, although wide media reporting did serve to inform the general population to a great extent. A comparable analysis that evaluated pharmacy claims for rosiglitazone from 9 commercial insurance plans similarly showed a 58.6% decrease in rosiglitazone utilization from February 2007 through December 2007, without an accompanying change in drug plan coverage.<sup>8</sup>

The content of the notification sent to PAMF patients and physicians closely mirrored the FDA recommendations and requested that patients contact their physician to discuss their individual risk profile. Providers were told to consider alternative drug therapy in those patients at “highest” cardiac risk, although no guidelines for assessing this risk or drug substitutions were suggested. Because the FDA was in the process of evaluating the evidence when the news media began reporting the

■ **Table 3.** Changes in A1C

Variable	Continued Group (n = 129)	Discontinued Group (n = 344)
Mean ± SD A1C at baseline, %	7.26 ± 1.29	7.15 ± 1.26
Mean ± SD A1C at follow-up, %	7.25 ± 1.31	7.2 ± 1.4
Mean (95% CI) difference in A1C, %	-0.5 (-0.60, -0.40)	0.092 (0.04, 0.13)
P	<.94	<.39

A1C indicates glycosylated hemoglobin; CI, confidence interval.

meta-analysis results, the information was based on the best available evidence at that time and whether the drug increased the risk of ischemic heart attack or CV death was unknown.

On June 6, 2007, FDA Commissioner Dr. Andrew C. von Eschenbach expressed concern, while explaining the FDA's position on the safety of rosiglitazone to the House Committee on Oversight and Government Reform,<sup>9</sup> that patients receiving rosiglitazone and their physicians, confused by media reports about the meta-analysis, would unnecessarily discontinue the drug and lose glycemic control. Our study showed that patient and physician concern from May 2007 through October 2007 did indeed influence the discontinuation of rosiglitazone therapy, although mean glycemic control in our population did not significantly change whether the drug was discontinued or not.

Our study was subject to the limits inherent to all retrospective chart and database reviews, including the accuracy and completeness of EMR documentation.<sup>10,11</sup> Although we verified that notification had been sent to each patient, we could not ascertain from chart review whether the notice was received or read. Physician notification sent through electronic mail was monitored to ensure that the message had been viewed by the provider. Any physician who had not viewed the notification within 7 days was called and asked to read the e-mail. Our study also was limited by the unavailability of baseline or follow-up A1C values, particularly in the continued group, where only 62% had both values documented. Because it was not possible in a retrospective review to control for the multitude of factors that affect glycemic control, the mean change in A1C is a broad indicator at best. Although visit notes were fairly complete, we could not determine which party initiated the discontinuation of rosiglitazone in 11.3% of the discontinued group. It was necessary for reviewers to decide—based on chart documentation alone—which party discontinued the drug, and we attempted to control for bias by having each patient independently reviewed twice.

## CONCLUSION

More than 2 years later, after many people discontinued rosiglitazone, the outcome trial needed to ascertain the true

risk of ischemic CV events still is not available. The situation highlights the importance of clearly communicating drug safety information to the public. Ideally, the media should partner with the FDA to responsibly communicate drug safety information to the public in evidence-based, understandable terms that quantify real risk.

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