Title of paper: Geographic Variation in Rosiglitazone use Surrounding FDA Warnings in the Department of Veterans Affairs

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ABSTRACT

Background: Geographic variation in the use of prescription drugs, particularly those deemed harmful by the Food and Drug Administration (FDA), may lead to variation in patient exposure to adverse drug events. One such drug is the glucose-lowering drug, rosiglitazone, for which the FDA issued a safety alert on May 21, 2007, following the publication of a meta-analysis that suggested a 43% increase in the risk of myocardial infarction with rosiglitazone. This alert was followed by a black box warning on August 14, 2007, that was updated three months later. While large declines have been documented in rosiglitazone use in clinical practice, little is known about how the use of rosiglitazone and other glucose-lowering drugs varied within the Department of Veterans Affairs (VA), surrounding the FDA alerts. Understanding this variation within integrated health systems is essential to formulating policies that enhance patient protection and quality of care.

Objective: To document variation in the use of rosiglitazone and other glucose-lowering drugs across twenty-one Veterans Integrated Service Networks (VISNs).

Methods: We conducted a retrospective analysis of drug use patterns for all major diabetes drugs in a national cohort of 550,550 diabetes veterans from 2003-08. This included the time periods when rosiglitazone was added to (November 2003), and removed from (October 2007), the VA national formulary (VANF). We employed multivariable logistic regression models to statistically estimate the association between a patient's location and his odds of using rosiglitazone.

Results: Aggregate rosiglitazone use increased monotonically from 7.7%, in the quarter it was added to the VANF (November 4, 2003), to a peak of 15.3% in the quarter when FDA issued the safety alert. Rosiglitazone use decreased sharply afterwards, reaching 3.4% by the end of the study period (September 30, 2008). The use of pioglitazone, another glucose-lowering drug in the same class as rosiglitazone, was low when FDA issued the safety alert (0.4%), but increased sharply afterwards, reaching 3.6% by the end of the study period. Insulin use increased monotonically, metformin use remained relatively flat, and sulfonylurea use exhibited a general declining trend throughout the study period. Statistically significant geographic variation was observed in rosiglitazone use throughout the study period. The prevalence range, defined as the range of minimum to maximum use across VISNs was 3.7%-12.4% in the first quarter (January

1 to March 31, 2003), 1.0-5.5% in the last quarter of study period (July 1 to September 30, 2008) and reached a peak of 9.6-25.5% in the quarter when FDA safety alert was issued (April 1 to March 31, 2007). In five VISNs, peak rosiglitazone use occurred before FDA issued the safety alert. The odds ratio of using rosiglitazone in a given VISN varied from 0.55 (95% CI, 0.52-0.59; VISN 10) to 1.58 (95% CI, 1.50-1.66; VISN 15), with VISN 1 being the reference region. The variation was higher in the periods after the FDA issued the safety alert. Much less variation was observed in the use of pioglitazone, metformin, sulfonylurea, and insulin.

Conclusions:

Our results show statistically significant variation in the way VISNs within the VA responded to the FDA alerts, suggesting a need for mechanisms that disseminate information and guidelines for drug use in a consistent and reliable manner. Further study of regions that adopted ideal practices earlier may provide lessons for regional leadership and practice culture within integrated healthcare systems.

What is already known about this subject

- Following the safety alert by the US Food and Drug Administration (FDA) in May 2007 regarding potentially increased risk of myocardial infarction in patients receiving rosiglitazone, substantial declines in rosiglitazone use were observed in clinical practice, by as much as 75% overall, and as much as 87% within the Department of Veterans Affairs (VA).
- There was substantial regional variation in the use of rosiglitazone following the FDA warnings for the drug, outside of the VA.

What this study adds

- This is the first study to document geographic variation in rosiglitazone use within the VA, both before and after the FDA safety alert. Statistically significant regional variation was found in rosiglitazone use throughout our study period, including the time periods when rosiglitazone was added into, and removed from, the VA national formulary. Much less variation was observed in the use of other glucose-lowering drugs.
- Rosiglitazone use decreased sharply following the FDA safety alert (78% in 15 months). During the same period, insulin and pioglitazone use increased, while metformin and sulfonylurea use decreased.
- A better understanding of geographical variation can help policymakers and health system administrators in developing effective mechanisms for disseminating drug use guidelines to their clinicians.

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INTRODUCTION

Clinicians face a constant challenge of deciding whether to prescribe newly available medications and when to stop medications based on newly discovered adverse drug effects, particularly when the Food and Drug Administration (FDA) issues warnings.[1,2] This challenge is heightened for drugs with FDA "boxed" warnings, its strongest labeling requirements for high-risk medicines.[1] Previous research has shown that clinician response to FDA warnings may be inadequate, which has the potential to jeopardize patient health.[1,3] Additionally, there may be geographic variation in clinician response to the FDA warnings, implying that patients' location may determine their extent of exposure to the potential risk of adverse drug events. Understanding this variation is critical to policymakers and health system administrators responsible for communicating guidelines for drug use to their clinicians, particularly in integrated healthcare systems, where the nature and extent of the observed variation may influence their actions.

One of the landmark examples of a boxed FDA warning is for the glucose lowering drug rosiglitazone. On May 21, 2007, the FDA issued a safety alert on rosiglitazone,[4] following the publication of a meta-analysis that suggested a 43% increase in the risk of myocardial infarction (MI) with rosiglitazone.[5] On August 14, 2007, the FDA issued a boxed warning for the drug that was updated three months later.[6,7] As a result of these warnings, large declines in rosiglitazone prescriptions were observed in clinical practice in the United States.[3,8–15]

A large body of research, led by The Dartmouth Atlas of Health Care,[16] has documented significant geographic variation in the cost, quantity, and quality of healthcare in the United States. Within the Department of Veterans Affairs (VA), the largest integrated healthcare system in the United States, studies have documented significant geographic variation in various aspects of patient care and outcomes.[17–19] However, there is relatively limited literature documenting geographic variation in drug use in an integrated healthcare system such as the VA; Shah et al. is one study that previously documented significant geographic variation in rosiglitazone prescriptions in a non-VA setting.[3]

To better understand the geographic variation in rosiglitazone use, we conducted a retrospective analysis of a national cohort of veterans over a six-year period. The VA is divided into 21 regions, called the Veterans Integrated Service Networks (VISNs). VISNs provide integrated

care to veterans based on geographic location and differ by regional leadership and policies, thus providing a useful setting to investigate geographic variation.

The VA can influence the prescribing behavior of its clinicians by adding or removing drugs from its national formulary (VANF); the formulary composition is the same across all the VISNs. To prescribe a non-formulary drug, a physician must first make a request, which is reviewed by a pharmacist. If the request is approved, the drug is provided to the patient as part of normal VA care and does not affect patient benefits.[20] Rosiglitazone was added to the VANF on November 4, 2003. The VA communicated the FDA alert for rosiglitazone internally on the same day it was issued, on May 21, 2007. After an internal investigation, the VA removed rosiglitazone from the VANF on October 4, 2007, and recommended, through its newsletter, that clinicians discuss the risks and benefits of continued rosiglitazone use with their patients.

We evaluated the use of rosiglitazone and other major glucose-lowering drugs within the VA and documented the geographic differences throughout our study period. We statistically estimated the effect that a patient's VISN had on his odds of using rosiglitazone. To our knowledge, this is the first study that identifies geographic variation in rosiglitazone use in the VA and covers three key events: rosiglitazone's addition to the VANF, the FDA safety alert for rosiglitazone, and rosiglitazone's removal from the VANF.

METHODS

Data

We constructed a longitudinal dataset over a six-year period that included the three key events mentioned above. Our study cohort consisted of patients from across the 21 VISNs, who were 40 years or older on October 1, 2002 and had diabetes. Patients were included if they met one of the following two criteria: (a) at least one diabetes medication filled between October 1, 2002 and September 30, 2003, (b) two or more ICD-9 diagnostic codes (250.xx) present for inpatient care and outpatient visits between October 1, 2001 and September 30, 2003. This criteria is known to have 93% sensitivity and 98% specificity for identifying diabetes.[21] Since glucose monitoring is an essential part of diabetes management, our cohort includes only those patients, for whom HbA_{1C} values are available at baseline. Further, we excluded patients with missing values of enrollment priority, date of death, and patient identifiers, resulting in 550,550 unique patients (Figure 1 shows the patient sample selection flowchart). We aggregated healthcare data of all

included patients on a quarterly basis, resulting in 9,829,507 unique patient-quarter observations. A quarter was defined according to a calendar year (e.g., 2003Q1: 01/01/2003 – 03/31/2003). 2003Q3 served as the baseline period with 2003Q4-2008Q3 serving as the observation period.

Variables

The main outcome variable of interest was a binary indicator of whether a veteran was using rosiglitazone. The key predictor variable was the patient's VISN, determined by where his primary care provider is located. The current VISN-network structure was established in March 1995 with a goal to decentralize decision-making and provide greater consistency in the quality of care system-wide.[22] Appendix Table A1 lists all the VISNs including the larger geographic region in which each VISN is located, where we adopted the definition of region from Egede et al.[23]

Covariates and potential risk factors included patient demographics at baseline: age, gender, race, marital status, and enrollment priority. Additionally, we included Charlson comorbidity index at baseline, as defined by Deyo et al.,[24] and the patient's duration of diabetes. Other covariates included the patients' use of other glucose-lowering drugs, their lab results, and whether they experienced any diabetes-related clinical events including cardiovascular complications, microvascular complications, and hypoglycemia in the same time period.

The glucose lowering medications were classified as either injectable (insulin) or oral (metformin, sulfonylurea, pioglitazone, rosiglitazone). Pioglitazone, belonging to the same thiazolidinedione class of medications as rosiglitazone, was never on the VANF. Metformin, sulfonylurea, and insulin were on the VANF through the entire study period. A patient was considered to be **using** a drug if he possessed at least a 30-day supply of drug in a given quarter, irrespective of the dosage. The 30-day supply threshold also serves as a proxy for medication adherence. Drug use was measured as the percentage of total patients in that VISN and/or time period. All numbers represent the usage at the end of each quarter.

Lab results were continuous, time-varying variables and included glucose levels (HbA_{1C}), triglycerides, cholesterol (HDL, LDL, total), blood pressure (systolic, diastolic), and body mass index. We implemented the "last observation carried forward" method to populate the missing lab values,[25] and created clinically relevant categorical variables (see Appendix Table A2 for

ranges and categories). When multiple values were observed for a given measure in a quarter, we averaged those values..

At the organizational level, we included the facility where the patient's primary care provider is located (719 total) and the facility's parent station (128 total). Facility-level covariates included the number of operating beds and indicators for the following: affiliation with a teaching hospital, urban location, and whether it was a community-based outpatient clinic.

Statistical Analysis

We summarized the baseline characteristics of our cohort, at the VISN and the aggregate VA level, as means ± SD and/or percentage of patients. We compared patients' demographic and clinical characteristics as well as overall facility characteristics between the 21 VISN's using analysis of variance (ANOVA). We compared drug use across time periods using generalized linear model (GLM), where we included the first three quarters of the calendar year 2003 (2003Q1-2003Q3) to show how rosiglitazone's addition to the VANF affected the usage patterns of all glucose-lowering drugs.

We used the following measures to capture variation in the use of drugs: (a) *variation factor*: ratio of maximum to minimum use across all the VISNs, and (b) *range*: difference between maximum and minimum use across all the VISNs. We employed a fixed-effects multivariate logistic regression models to statistically estimate the association between patients' location (VISN) and their likelihood of using rosiglitazone, expressed as odds ratio (OR). We conducted this regression analysis for three separate time periods: the entire study period (20 quarters), pre-warning periods (14 quarters), and post-warning periods (the last 6 quarters). All statistical tests used a two-tailed α=0.05 level of significance. All standard errors were robust and corrected for clustering at the patient level. All statistical analyses were conducted using Stata (version 12, StataCorp, College Station, TX) and SAS (version 9.3, SAS Institute Inc, Cary, NC).

RESULTS

Baseline Characteristics

We observed statistically significant differences in patient demographic and clinical characteristics between the VISNs (Table 1). The average age of the cohort was 66.9 years,

ranging from 64.9 years (VISN 17) to 69.4 years (VISN 3). Approximately 13% of the overall cohort was non-Hispanic black but that fraction ranged from 2.6% (VISN 23) to 32.2% (VISN 5). The average HbA_{1C} ranged from 7.1% (VISN 4) to 7.6% (VISN 5). Sulfonylurea and metformin were the two most frequently prescribed glucose-lowering drugs, with 49.1% and 37% of the total cohort using the drugs, respectively. Thirty percent of our cohort belonged to the VISNs in the South region. On average, the annual mortality rate of our cohort was 5.2%, consistent with previous literature.[26]

Patterns of Medication Usage: Temporal Trend

Figure 2 shows the usage patterns for various diabetes drugs at the aggregate national level. Unless otherwise noted, p-values<0.0001.

Aggregate rosiglitazone use increased from 7.7% (N=42,477) in 2003Q4, when it was added to the VANF, to a peak of 15.3% (N=70,598) in 2007Q2, when the FDA issued the safety alert. Rosiglitazone use decreased afterwards, reaching 10.3% (N= 45,934, when it was removed from the VANF (2007Q4). The rate of decrease in rosiglitazone use accelerated subsequently, reaching 3.4% (N= 14,321) by the end (2008Q3), a 78% reduction in 15 months following the FDA safety alert.

The use of pioglitazone, which was never on VANF, remained low throughout the observation period. After an initial increase (from 2.3% to 2.9% in the first three quarters), pioglitazone use started to decrease, reaching 0.4% in 2007Q2. However, in the time periods following rosiglitazone's removal from the VANF, pioglitazone use increased rapidly, reaching 3.6% by the end of the study period.

The use of other three drugs (metformin, sulfonylurea, insulin) increased for the first 3 quarters until rosiglitazone was added to VANF (2007Q2). However, the trend was different in the following periods. Metformin use remained relatively stable, increasing by 1.2% during the time when rosiglitazone was on VANF (37.4% in 2003Q4 to 37.8% in 2007Q2) but decreasing 2.5% afterwards. Comparatively, sulfonylurea use exhibited an overall declining trend, going from a high of 49.7% in 2003Q4 to 44.9% in 2007Q2 and 41.7% in 2008Q3, an overall decline of 16.1%. Insulin use, on the other hand, increased monotonically throughout, ranging from 24.1% in 2003Q4, to 29.5% in 2007Q2, and 32.8% in 2008Q3. This implies an overall increase of

36.2% in insulin use, and a particularly steep increase of 11.5% in 15 months following rosiglitazone's removal from the VANF.

Patterns of Medication Usage: Geographic Variation

There were differences in rosiglitazone use between the VISNs throughout the study period (Table 2 and Appendix Figure A1). At the time of its addition to the VANF (2003Q4), rosiglitazone use ranged from 4.4% (VISN 4, Mid-Atlantic) to 14.5% (VISN 19, Midwest), a variation factor of 3.3. In 2007Q2, when FDA issued the safety alert, VISN 23 (Midwest) and VISN 17 (South) had the lowest (9.6%) and highest (25.5%) levels of use, respectively (variation factor=2.7). The variation factor increased rapidly afterwards, reaching 5.4 by the end of the study period. In contrast, the range of rosiglitazone use remained steady until 2005Q2, when it was 9.6%, increased afterwards to a peak of 16%, but decreased to 4.5% in the end.

There were geographic differences in the timing of peak use in each VISN. For example, in VISN 11 (Midwest), rosiglitazone use reached a peak use of 17.5% in 2004Q4. In contrast, in VISN 17 (South), rosiglitazone use remained low until 2005Q2, but then increased sharply, from 9.1% to a peak of 25.5% in 2007Q2. The lowest level of peak use occurred in VISN 23 (Midwest), at 9.6%, which was also one of the VISNs where rosiglitazone use was consistently low. There were five VISNs, in which peak rosiglitazone use occurred before the FDA issued the safety alert: VISN 5 (2003Q2, p-value=.022, Mid-Atlantic), VISN 7 (2006Q4, p-value=.007, South), VISN 11 (2004Q4, p-value=<.0001, Midwest), VISN 16 (2007Q1, p-value=.007, South), and VISN 19 (2005Q4, p-value=.023, Midwest).

Some variation was observed in pioglitazone use, particularly during the periods when rosiglitazone was not in the VANF; however, the results should be tempered by the fact that, in absolute terms, pioglitazone use remained relatively low, except for VISN 17, a region where we observed the following interesting features. First, pioglitazone use in VISN 17 was very high until 2005Q4; for example, in 2005Q2, pioglitazone use was almost eight times the maximum use across the rest of the VISNs. Second, the timing of the decline in pioglitazone use coincided with that of the rise in rosiglitazone use. Finally, total thiazolidinedione use was the highest in VISN 17 before the FDA issued the safety alert. Metformin, sulfonylurea, and insulin use exhibited relatively less variation. Table 2 lists the use of various drugs, expressed in terms of

quartiles: maximum, first (25th percentile), second (median), third (75th percentile), minimum. Appendix Figure A2 visually depicts the pattern of drug use by VISN.

Estimating the Region Effect

We found statistically significant geographic variation in rosiglitazone use after controlling for all observable covariates (Table 3 and Appendix Figure A3). With VISN 1 serving as the reference region, the odds ratio (OR) varied from 0.55 (95% CI, 0.52-0.59; VISN 10, Mid-Atlantic) to 1.58 (95% CI, 1.50-1.66; VISN 15, Midwest). The post-warning periods exhibited a higher variation (OR range: 0.50-1.67) compared to pre-warning periods (OR range: 0.57-1.55). Overall, patients located in the South region (VISNs 7,8,16, and 17) were most likely to use rosiglitazone. Further, ORs for VISNs in the South region decreased the most, on average, from pre- to post-warning period. In absolute terms, the OR decreased from pre- to post-warning periods for all but 5 VISNs: 2 (Northeast), 4 (Mid-Atlantic), 15 (Midwest),18 (West) and 23 (Midwest). A complete list of variables and the ORs (with 95% CIs) can be found in Appendix Table A3.

For sensitivity analysis, we changed the threshold level of days supply employed for classifying whether a patient is a user of the drug from 30 days to 45 days and 60 days. The regression results for the entire observation period (Appendix Table A4) reveal that OR's did not change in any meaningful way, regardless of which threshold level was used. In addition, we conducted an analysis where we used a thirty-day equivalent (TDE) as an alternate measure of drug use. This means that instead of drug use being a binary variable, it was a categorical variable with four values - 0, 1, 2, and 3, depending on whether the days supply for a drug was 0 days, 1-29 days, 30-59 days or greater than 60 days, respectively, in a given quarter.[27] In general, we observed similar results in terms of the absolute values as well as ordering of VISN based on ORs (Appendix Table A5).

DISCUSSION

Aggregate rosiglitazone use in the VA declined by 78% in 15 months following the FDA safety alert for the drug, indicating a swift response by the VA clinicians, and highlighting the potential strength of mechanisms through which the VA communicates the FDA warnings to its clinicians. This response is similar to previously published studies in a non-VA setting, most notably to that of Shah et al., who reported a 75% decline in monthly rosiglitazone prescriptions dispensed in 30

months following the FDA alert.[3] The increase in pioglitazone and insulin use following the FDA alert suggests that the VA clinicians used them as alternatives to rosiglitazone.

We found considerable geographic variation in rosiglitazone use throughout the study period. The two-fold increase in the variation factor from 2007Q2 to 2008Q3 is higher than what an earlier study of non-VA data reported,[3] and more than what was observed for metformin, sulfonylureas, and insulin. Further, this variation persisted after controlling for patient and facility-level covariates that may be associated with rosiglitazone prescriptions. Our regression analysis revealed that the patient's VISN significantly, and differentially, affected his odds of using rosiglitazone. While the geographic variation, both in terms of the variation factor and odds ratio, increased after the FDA warnings, our conclusions should be tempered by the fact that the range as well as the actual rosiglitazone use decreased substantially after the FDA warnings.

In the United States, where large geographic differences in incidence of diabetes, glycemic control, and medication adherence exist,[23,28–30] geographic variation in drug use may not be surprising. This variation has been attributed to clinicians' practice styles and how they translate FDA warnings into practice.[3,11] Within the VA, we expected less variation in drug use given that the VA has a closed pharmacy and a national formulary use across all VISNs, a relatively homogeneous population with well-established eligibility criteria for veterans, and a physician workforce that is salaried with financial incentives that are unaffected by practice patterns. Moreover, many administrative policies are uniform across all VISNs, and adherence to clinical guidelines and VA policy are frequently used as facility performance indicators.

We believe that some of the variation may be explained by the fact that local practice patterns spill over to the VA since (a) many VA clinicians practice outside of the VA (e.g., those affiliated with teaching hospitals) and may behave similar to non-VA clinicians,[17,31] and (b) veterans who receive the initial prescription from the non-VA clinicians may get it subsequently refilled from a VA clinician.[31] For rosiglitazone, which exhibited a persistently high variation, more than that of other drugs, there may be other contributing factors. First, some physicians may have continued to prescribe rosiglitazone to their patients for whom they thought the benefits outweighed the added potential risk. Moreover, since the decision to discontinue rosiglitazone may come from either the patient or the physician,[32] patients may have decided to

discontinue rosiglitazone at different times. It must be noted that the boxed warning did not explicitly prohibit the use of rosiglitazone. Second, increased pharmacist's role has been linked to better prescribing behavior of doctors.[33,34] In this instance, pharmacists may have been better integrated to clinical practice in some VISNs than in others, which may have led to some variation. Finally, many patients, particularly those with stable diabetes and/or those living in rural areas, may visit their clinicians infrequently (e.g., twice a year) and have their medications mailed to them for use between visits, leading to the variation in when they stopped using rosiglitazone. We note that the fraction of people living in rural areas ranged from 0.1% (VISN 1) to 30.9% (VISN 6).

Our analysis reveals other interesting patterns. In five VISNs, peak rosiglitazone use occurred before the FDA issued the safety alert, suggesting that some clinicians may have learned about the harmful effects of rosiglitazone earlier than others. For example, VISN 11, where rosiglitazone use started to decline the earliest, is also the location of VA Diabetes Quality Enhancement Research Initiative, whose mission is to conduct translational research to improve diabetes care.[35] Presumably, geographic proximity to information sources allows clinicians to have quicker access to relevant information.[3,36] Finally, VISN 10, where the likelihood of rosiglitazone use was the lowest, is home to Cleveland Clinic, the affiliation of the authors of the 2007 study that linked rosiglitazone to an increased MI risk.[5]

Limitations

Our study has several limitations. First, our data is restricted to the VA and does not include prescriptions or services that patients may have obtained from outside of the VA. The cost of medications is lower in the VA than in the private sector. Therefore, it is quite likely that most veterans obtained their diabetes medications from the VA and, consequently, we estimate the effect of omitting non-VA data to be relatively small. Further, the overwhelming majority of our cohort is male (98.2%) and non-Hispanic White (71.2%). While this may not be fully representative of true composition of diabetes patients, we believe that the policy implications from our results are still valid. Second, we aggregated our data into quarters, which prevents us from analyzing trends at a more granular level. Third, our findings may have been impacted by the rules we used to identify whether a patient is using a medication. As discussed above, our sensitivity analyses on different rules show this effect to be minimal. Fourth, patients whose

primary care facility is located in rural location may have lacked access to appropriate and evidence-based medical care, contributing to the observed geographic variation. However, our results don't change in any meaningful way when we limit the data to patients whose primary care facility lies in an urban location (Appendix Table A6). Fifth, we did not compare active versus passive dissemination of FDA advisories that may evoke a different clinician response; we leave this for future study. Finally, we did not explore or analyze causes of variation, for example, why pioglitazone (rosiglitazone) was high (low) in VISN 17. We also leave this as future work.

CONCLUSIONS

In examining the largest healthcare system in the United States, our study strengthens the argument that local practice patterns of care affect how clinicians learn and translate the FDA warnings into practice, given the significant geographic variation observed. From a policy perspective, our study highlights the need for mechanisms to disseminate information and guidelines for drug use in a consistent and reliable manner, and ensure a system wide clinical adherence to FDA warnings, noted to be of utmost importance for patient safety.[37] Finally, our study reveals opportunities for learning from high-performing divisions of the system to increase the overall efficiency. This has the potential to reduce the geographic variation in clinician response and ultimately improve the timeliness and quality of patient care.

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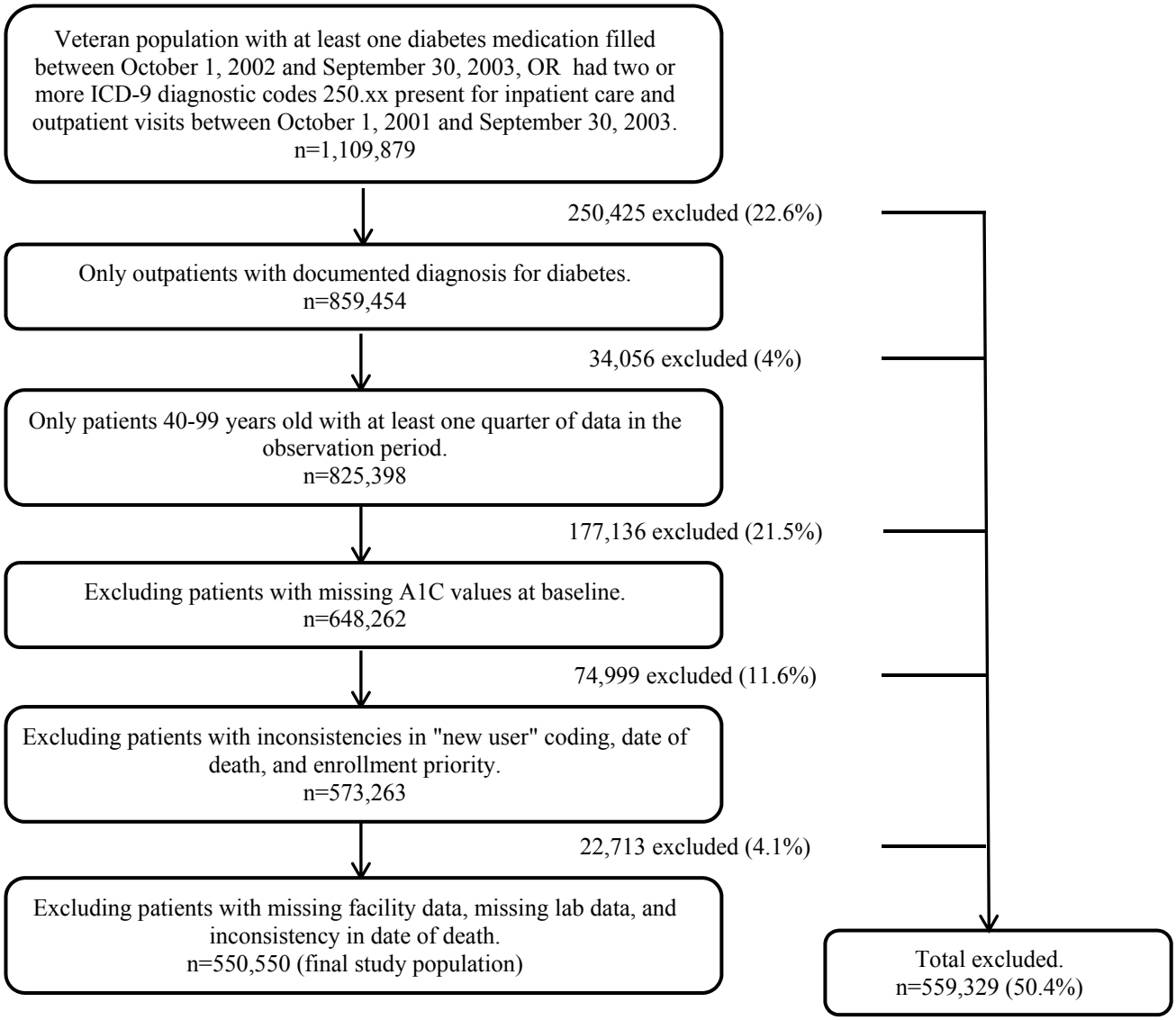


Figure 1: Flowchart of Patient Sample Selection

Table 1: Baseline Characteristics of Patients and Region by VISN [a,b]

VISN [a]	All	VISN 1	VISN 2	VISN 3	VISN 4	VISN 5	VISN 6	VISN 7	VISN 8	VISN 9	VISN 10
Region [b]	--	Northeast	Northeast	Northeast	Mid-Atlantic	Mid-Atlantic	Mid-Atlantic	South	South	Mid-Atlantic	Mid-Atlantic
Patient Population	550,550	22,240	15,283	23,176	33,429	13,904	27,008	34,355	50,821	26,454	20,644
Patient characteristics											
Male	98.2	98.3	98.2	98.9	98.5	97.9	97.9	98.0	98.4	98.5	98.3
Married	64.9	61.2	63.1	57.9	66.6	56.0	65.9	68.2	69.7	68.1	62.9
Race/ethnicity											
Non-Hispanic White	71.2	86.1	82.7	68.1	80.6	54.1	59.9	59.3	69.9	76.4	77.5
Non-Hispanic Black	12.9	4.4	6.5	20.2	9.6	32.2	23.5	27.4	7.6	12.5	12.6
Age, years, mean ± SD	66.9±10.5	68.5±10.2	68±10.6	69.4±10.4	68.6±10.1	66.4±10.8	64.9±10.6	65±10.6	68.6±10.2	65.7±10.4	67.5±10.6
<65	40.1	32.9	35.4	30.0	32.4	41.5	48.0	47.3	32.9	44.9	37.7
65-74	32.3	34.2	32.2	33.5	34.4	31.8	30.4	31.0	34.9	31.6	31.7
≥75	27.6	32.9	32.4	36.6	33.2	26.7	21.6	21.7	32.2	23.5	30.5
Diabetes duration, yrs.											
<3	41.2	38.5	38.0	35.4	43.0	39.8	41.1	39.4	43.3	39.6	46.6
≥3	58.8	61.5	62.0	64.6	57.0	60.2	58.9	60.6	56.7	60.4	53.4
Risk factors											
BMI, kg/m^2, mean±SD	30.9±5.9	31±5.7	31.5±5.9	29.9±5.4	31±5.8	30.6±5.9	30.8±5.8	30.6±5.8	29.9±5.4	30.7±5.9	31±6
≥25	61.5	52.2	65.9	60.8	63.3	60.2	58.7	65.9	59.0	65.0	70.8
Missing	29.1	40.9	26.1	27.6	27.8	28.9	32.2	22.7	29.8	24.2	18.7
A1C, % [b], mean±SD	7.3±1.4	7.1±1.3	7.3±1.3	7.2±1.4	7.1±1.3	7.6±1.6	7.4±1.5	7.3±1.5	7.4±1.4	7.2±1.4	7.4±1.4
≥7.0	52.0	48.2	52.6	50.7	47.2	60.0	55.2	51.3	54.4	50.9	56.3
LDL-C, mg/dL, mean±SD	100.4±31.9	95.8±29.4	99.8±30.3	103.2±30.9	101.9±30.7	105.4±32.4	103.7±32.7	94.1±37	99±31	101.9±32.1	100.2±32.3
≥100	32.8	25.3	28.1	45.2	27.0	45.2	38.0	34.8	35.9	35.8	39.3
Missing	30.2	35.9	38.3	10.6	44.0	15.2	25.0	17.7	20.1	26.4	14.1
Systolic BP, mm Hg, mean±SD	137.3±18.1	135.3±17.4	136.2±17	134.2±17.4	137.4±18.3	138.3±18.5	138.6±18.7	138±18.3	136.6±17.7	138.2±18.2	138.7±18.7
≥140	31.8	25.3	30.0	27.8	33.0	35.7	32.5	34.6	29.8	35.6	37.7
Missing	24.5	34.0	25.1	25.5	21.1	18.7	28.6	20.7	26.8	20.0	15.9
Medication use [c]											
Sulfonylureas	49.1	50.2	50.0	49.8	50.2	39.8	48.9	50.2	51.5	51.6	49.0
Metformin	37.0	35.3	30.7	29.9	39.0	22.4	42.1	37.4	35.1	41.8	39.3
Rosiglitazone	7.4	8.4	8.2	7.9	4.3	10.9	5.9	4.5	8.3	6.2	4.8
Pioglitazone	2.7	0.9	0.6	1.2	4.4	0.2	1.9	2.9	4.2	1.3	0.8
Insulin	23.5	21.5	21.5	17.9	21.1	22.4	26.1	25.6	22.6	24.0	23.0

VISN [a]	All	VISN 1	VISN 2	VISN 3	VISN 4	VISN 5	VISN 6	VISN 7	VISN 8	VISN 9	VISN 10
Region [b]	--	Northeast	Northeast	Northeast	Mid-Atlantic	Mid-Atlantic	Mid-Atlantic	South	South	Mid-Atlantic	Mid-Atlantic
Facility characteristics [d]											
Parent station	69.1	72.1	20.6	61.8	86.2	83.1	95.8	80.5	69.6	65.3	56.8
VA medical center	78.3	66.9	75.3	89.4	80.4	90.1	95.8	86.7	72.5	87.3	62.5
Urban Location	87.6	69.1	81.7	99.1	79.4	94.8	99.9	87.2	96.8	87.7	85.1
Teaching-Affiliated	70.8	73.7	68.4	77.1	65.9	83.1	95.8	75.4	69.6	74.0	56.8
No. of outpatient beds											
<300	70.5	88.2	93.0	54.8	67.3	65.4	65.2	68.9	54.5	77.7	64.8
≥300	29.5	11.8	7.0	45.2	32.7	34.6	34.8	31.1	45.5	22.3	35.2

VISN=veterans integrated service network; BMI=body mass index; LDL= low-density lipoprotein; SBP= systolic blood pressure; VA= veterans affairs

SI conversion factors: To convert LDL to mmol/L, multiply values by 0.0259.

[a] p-value < .001 for all the variables based on one-way analysis of variance (ANOVA).

[b] All reported values are percentage of patients, unless otherwise specified.

[c] Details on VISNs can be found at http://www.va.gov/directory/guide/division_flsh.asp?dnum=1.

[d] The percentages represent the number of patients whose primary care facility has the below listed characteristic(s).

[e] A patient could use a single medication or in conjunction with other diabetes medication(s); the categories are not exclusive.

Table 1: Baseline Characteristics of Patients and Region by VISN (contd.) [a,b]

VISN [a]	VISN 11	VISN 12	VISN 15	VISN 16	VISN 17	VISN 18	VISN 19	VISN 20	VISN 21	VISN 22	VISN 23
Region [b]	Midwest	Midwest	Midwest	South	South	West	Midwest	West	West	West	Midwest
Patient Population	25,384	24,571	28,383	52,527	27,706	25,284	11,109	13,206	20,086	25,188	29,792
Patient characteristics											
Male	98.2	98.4	98.3	98.1	97.9	97.8	97.7	97.2	97.8	97.9	98.4
Married	63.2	63.1	67.3	67.8	69.0	67.5	64.5	61.8	57.0	52.1	69.4
Race/ethnicity											
Non-Hispanic White	76.7	72.4	76.5	67.5	62.7	70.6	78.3	79.4	63.4	58.6	84.3
Non-Hispanic Black	11.9	14.1	9.8	19.3	12.8	4.4	4.1	3.1	11.1	13.6	2.6
Age, years, mean ± SD	67±10.5	68.1±10.3	67.1±10.5	65.6±10.4	64.9±10.6	66.5±10.4	66.5±10.6	65.5±10.5	65.9±10.6	65.3±10.5	68.7±10.2
<65	39.2	34.4	39.0	45.8	49.0	42.1	42.7	46.3	45.6	47.2	31.8
65-74	32.0	34.3	32.7	31.1	29.2	31.9	31.2	30.2	30.0	30.6	35.1
≥75	28.8	31.3	28.3	23.2	21.8	26.0	26.2	23.5	24.4	22.2	33.0
Diabetes duration, yrs.											
<3	43.6	45.3	43.6	41.6	40.5	39.5	38.0	34.9	39.4	40.7	43.4
≥3	56.4	54.7	56.4	58.4	59.5	60.5	62.0	65.1	60.6	59.3	56.6
Risk factors											
BMI, kg/m^2, mean±SD	31.6±6.2	31.2±5.8	31.2±6.1	31±5.9	31.2±6	30.6±5.9	30.8±6	32±6.3	31±6.1	31±6.1	31.5±5.9
≥25	59.6	49.5	63.7	64.4	73.0	59.4	60.1	52.6	63.7	60.4	56.5
Missing	33.0	44.1	27.0	26.0	16.5	30.6	29.9	41.5	26.5	29.7	36.9
A1C, % [b], mean±SD	7.3±1.4	7.2±1.3	7.3±1.3	7.4±1.4	7.2±1.4	7.3±1.3	7.4±1.4	7.4±1.3	7.3±1.4	7.2±1.4	7.1±1.3
≥7.0	53.1	50.6	53.9	53.5	46.7	53.2	53.6	56.1	53.3	49.7	47.4
LDL-C, mg/dL, mean±SD	100.7±31.5	94.4±29.1	112.4±29.7	102±31.7	101.6±31.3	98.9±30.4	97.1±31.2	103.1±32.9	102.1±31.7	103.8±32.5	95.6±29.3
≥100	31.1	24.0	26.9	32.0	29.3	37.3	32.1	35.4	37.4	31.4	24.3
Missing	33.4	36.7	57.9	34.8	39.8	17.5	25.0	29.8	22.9	38.3	38.6
Systolic BP, mm Hg, mean±SD	137.5±18.5	133.6±16.6	137.9±18.4	138.5±18.3	139.7±18.4	138.3±17.7	135.8±17.6	138.3±18.5	136.8±17.5	135.9±17.6	135.5±17.9
≥140	30.6	18.9	34.9	34.9	41.3	31.7	28.5	27.6	31.3	29.6	29.5
Missing	27.2	42.2	20.2	22.0	13.8	27.5	25.4	36.8	23.6	24.0	23.6
Medication use [c]											
Sulfonylureas	49.5	49.4	52.7	49.0	46.9	49.2	46.6	48.3	38.9	48.6	50.7
Metformin	41.7	37.5	33.0	33.8	36.8	34.7	40.2	43.9	38.9	42.1	40.9
Rosiglitazone	10.2	4.2	5.6	9.4	5.9	5.9	13.7	9.2	13.6	11.0	4.8
Pioglitazone	4.1	2.3	2.4	3.7	10.0	0.7	0.2	0.8	1.2	0.1	4.1
Insulin	27.3	23.0	24.4	24.1	23.4	24.6	25.4	26.9	21.1	22.8	24.2

VISN [a]	VISN 11	VISN 12	VISN 15	VISN 16	VISN 17	VISN 18	VISN 19	VISN 20	VISN 21	VISN 22	VISN 23
Region [b]	Midwest	Midwest	Midwest	South	South	West	Midwest	West	West	West	Midwest
Facility characteristics [d]											
Parent station	69.7	72.8	32.9	73.6	54.6	85.1	72.4	88.3	62.2	82.6	52.0
VA medical center	77.8	72.8	91.3	75.1	63.9	73.3	72.4	78.7	64.1	82.6	82.7
Urban Location	85.8	80.9	83.6	83.7	86.7	88.8	70.5	82.9	94.1	99.2	88.6
Teaching-Affiliated	58.4	59.2	81.1	73.7	54.6	85.1	43.9	53.0	54.2	91.2	65.2
No. of outpatient beds											
<300	80.1	54.0	76.1	73.7	31.2	99.6	99.8	89.3	83.5	70.3	73.3
≥300	19.9	46.0	23.9	26.3	68.8	0.4	0.2	10.7	16.5	29.7	26.7

VISN=veterans integrated service network; BMI=body mass index; LDL= low-density lipoprotein; SBP= systolic blood pressure; VA= veterans affairs

SI conversion factors: To convert LDL to mmol/L, multiply values by 0.0259.

[a] p-value < .001 for all the variables based on one-way analysis of variance (ANOVA).

[b] All reported values are percentage of patients, unless otherwise specified.

[c] Details on VISNs can be found at http://www.va.gov/directory/guide/division_flsh.asp?dnum=1.

[d] The percentages represent the number of patients whose primary care facility has the below listed characteristic(s).

[e] A patient could use a single medication or in conjunction with other diabetes medication(s); the categories are not exclusive.

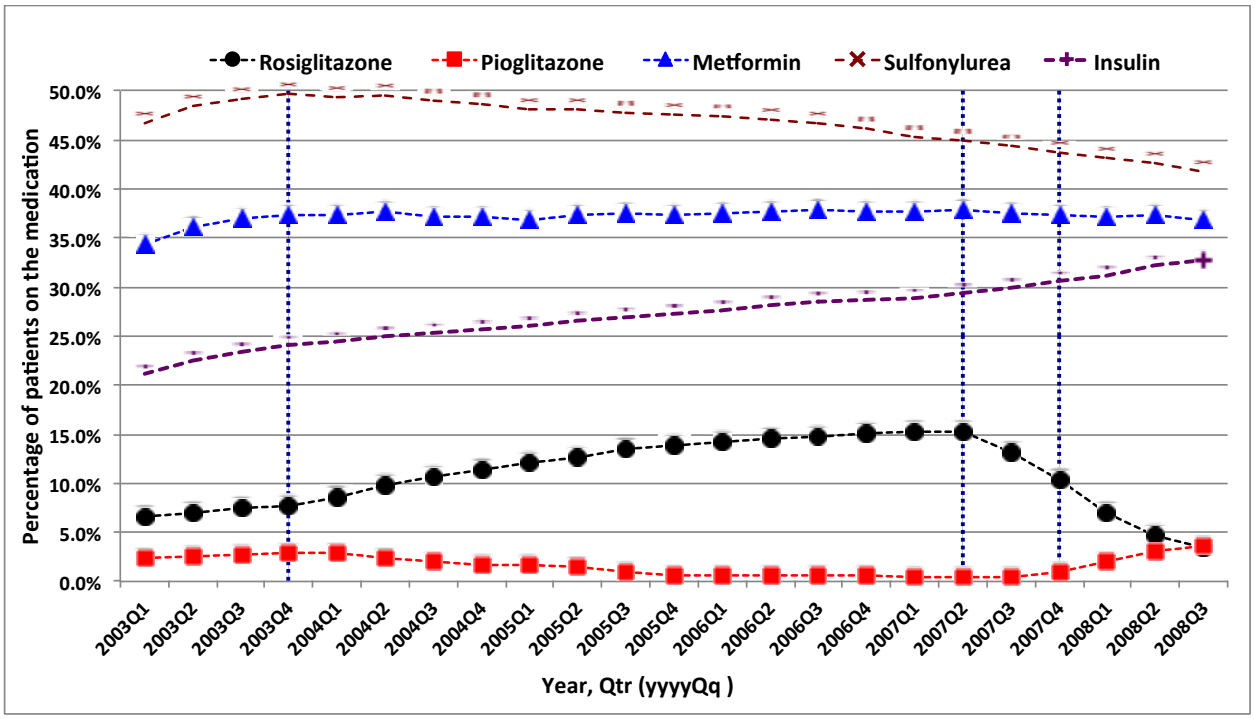


Figure 2: Aggregate Use of Various Glucose-Lowering Medications as a Percentage of Total Population.

Data were aggregated at the quarterly level and included only patients who survived up to that quarter. The three vertical lines represent the quarter in which (1) left (2003Q4): rosiglitazone was made available in the VA national formulary (VANF), (2) middle (2007Q2): FDA issued a safety alert related to rosiglitazone, (3) right (2007Q4): rosiglitazone was removed from the VANF.

Table 2: Geographic Variation in the Use of Various Glucose-Lowering Drugs.

Year, Qtr (yyyyQq)		2003Q4	2004Q4	2005Q4	2007Q2	2007Q4	2008Q3
Rosiglitazone	Maximum	14.5%	17.5%	21.6%	25.5%	17.8%	5.5%
	25th percentile	9.5%	12.7%	16.3%	16.8%	11.8%	4.1%
	Median	8.0%	10.5%	12.3%	13.3%	9.2%	3.4%
	75th percentile	6.0%	9.2%	11.1%	11.8%	8.0%	2.6%
	Minimum	4.4%	6.9%	8.8%	9.6%	6.6%	1.0%
Pioglitazone	Maximum	11.6%	14.0%	2.9%	1.1%	2.8%	6.8%
	25th percentile	3.9%	1.2%	0.9%	0.5%	1.0%	4.2%
	Median	1.6%	0.9%	0.4%	0.3%	0.9%	3.2%
	75th percentile	0.8%	0.5%	0.2%	0.2%	0.7%	3.0%
	Minimum	0.1%	0.1%	0.1%	0.1%	0.2%	0.8%
Metformin	Maximum	44.3%	44.3%	44.9%	44.8%	44.3%	43.1%
	25th percentile	41.1%	40.8%	40.9%	40.2%	39.4%	38.5%
	Median	37.5%	36.8%	37.3%	38.3%	38.0%	37.8%
	75th percentile	35.1%	34.8%	34.4%	36.1%	36.2%	35.5%
	Minimum	24.4%	27.5%	28.5%	29.7%	29.8%	29.6%
Sulfonylurea	Maximum	54.8%	53.2%	51.6%	47.5%	46.1%	44.3%
	25th percentile	50.6%	49.6%	48.6%	46.2%	45.1%	43.4%
	Median	50.1%	48.8%	47.6%	44.5%	43.2%	41.1%
	75th percentile	48.1%	48.2%	46.8%	43.6%	42.4%	40.7%
	Minimum	39.4%	37.0%	39.6%	41.1%	40.1%	38.3%
Insulin	Maximum	28.1%	30.4%	32.8%	36.4%	37.6%	39.5%
	25th percentile	25.2%	27.1%	29.1%	31.4%	32.6%	34.8%
	Median	24.1%	25.9%	27.1%	29.6%	30.9%	33.3%
	75th percentile	22.5%	24.3%	25.5%	27.5%	28.4%	30.6%
	Minimum	18.5%	19.3%	20.6%	21.5%	22.4%	23.7%

Key time periods: (a) 2003Q4: rosiglitazone was made available in the VA national formulary (VANF), (b) 2007Q2: FDA issued a safety alert related to rosiglitazone, (c) 2007Q4: rosiglitazone was removed from the VANF, (d) 2008Q3: end of study period.

Table 3: Odds Ratios (95% CIs) Representing the Odds of a Veteran with Type 2 Diabetes Receiving a Rosiglitazone Prescription.

VISN	All Time Periods 2003Q4 - 2008Q3	Pre-Warning Period 2003Q4 - 2007Q1	Post-warning Period 2007Q2 - 2008Q3
1 (reference)	1.00	1.00	1.00
2	0.92** (0.86 - 0.98)	0.89*** (0.83 - 0.95)	0.98 (0.90 - 1.05)
3	0.87*** (0.83 - 0.92)	0.96 (0.91 - 1.02)	0.63*** (0.59 - 0.67)
4	0.84*** (0.80 - 0.89)	0.83*** (0.78 - 0.87)	0.88*** (0.83 - 0.93)
5	0.82*** (0.77 - 0.88)	0.87*** (0.82 - 0.93)	0.68*** (0.63 - 0.74)
6	0.68*** (0.65 - 0.72)	0.70*** (0.66 - 0.74)	0.65*** (0.61 - 0.69)
7	0.93** (0.88 - 0.97)	1.01 (0.96 - 1.06)	0.72*** (0.68 - 0.77)
8	1.43*** (1.36 - 1.49)	1.49*** (1.42 - 1.56)	1.28*** (1.21 - 1.35)
9	0.82*** (0.78 - 0.86)	0.82*** (0.78 - 0.87)	0.82*** (0.77 - 0.88)
10	0.55*** (0.52 - 0.59)	0.57*** (0.53 - 0.61)	0.50*** (0.46 - 0.54)
11	0.80*** (0.76 - 0.84)	0.91*** (0.86 - 0.96)	0.52*** (0.48 - 0.56)
12	0.80*** (0.75 - 0.84)	0.82*** (0.77 - 0.86)	0.73*** (0.68 - 0.78)
15	1.58*** (1.50 - 1.66)	1.55*** (1.46 - 1.63)	1.67*** (1.57 - 1.78)
16	1.29*** (1.23 - 1.34)	1.32*** (1.26 - 1.38)	1.19*** (1.13 - 1.25)
17	1.35*** (1.29 - 1.42)	1.43*** (1.36 - 1.51)	1.25*** (1.18 - 1.33)
18	0.68*** (0.65 - 0.72)	0.68*** (0.64 - 0.72)	0.69*** (0.65 - 0.74)
19	1.16*** (1.09 - 1.24)	1.28*** (1.20 - 1.37)	0.83*** (0.77 - 0.90)
20	0.60*** (0.56 - 0.64)	0.61*** (0.57 - 0.65)	0.58*** (0.54 - 0.63)
21	1.51*** (1.43 - 1.59)	1.55*** (1.47 - 1.63)	1.39*** (1.31 - 1.48)
22	1.18*** (1.13 - 1.25)	1.21*** (1.15 - 1.28)	1.10** (1.03 - 1.17)
23	0.58*** (0.55 - 0.61)	0.57*** (0.54 - 0.61)	0.60*** (0.56 - 0.65)
Observations	7,626,779	5,245,146	2,381,633
Pseudo R^2	0.105	0.0919	0.134

CI=confidence interval; VISN=veterans integrated services network.
***p<0.001; **p<0.01; *p<0.05
The F-test for the joint significance of all the coefficients resulted in p-value < 0.0001.
All standard errors are robust and standard errors are clustered at the individual patient level.
The multivariate regression includes controls for demographics and clinical characteristics of a patient, the charcteristics of the patient's primary care facility, and time dummies.
Similar results were found when individual-level random effect was included; the correlation between coefficients obtained from the two sets of regression was 0.98.

APPENDIX

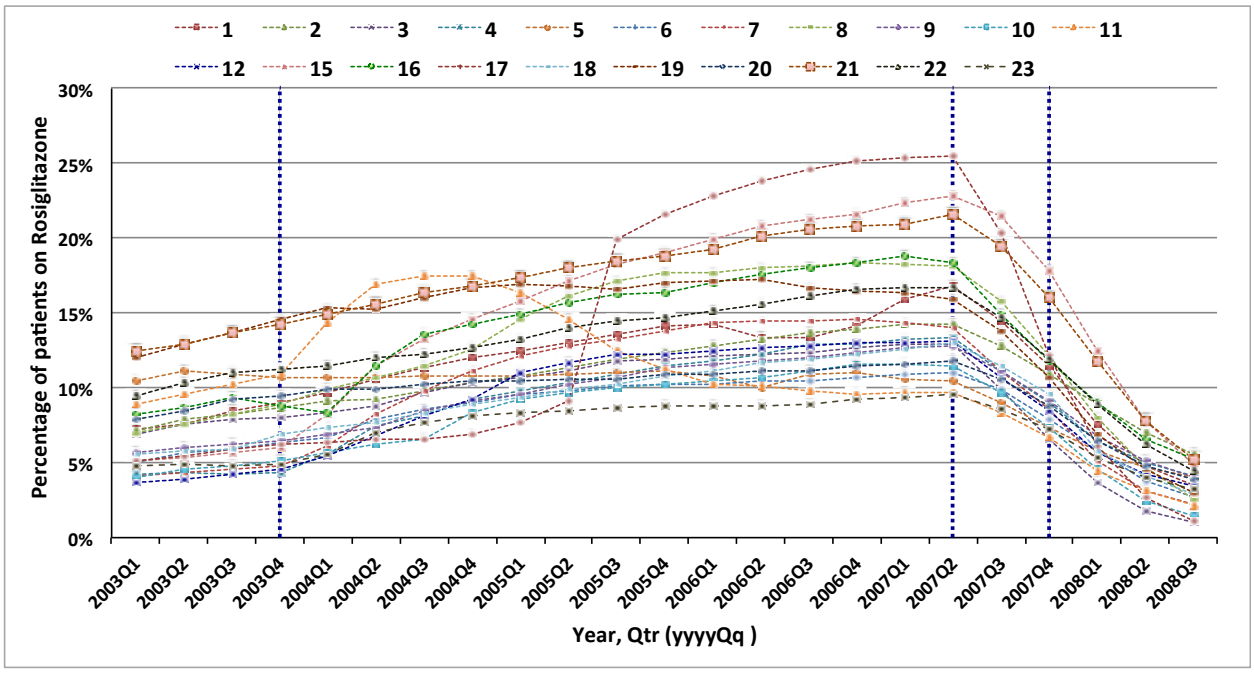
Appendix Table A1: List of Veterans Integrated Service Systems (VISNs).

VISN	Geographical Region	Description
1	Northeast	VA New England Healthcare System
2	Northeast	VA Health Care Upstate New York
3	Northeast	VA NY/NJ Veterans Healthcare Network
4	Mid-Atlantic	VA Stars & Stripes Healthcare Network
5	Mid-Atlantic	VA Capitol Health Care Network
6	Mid-Atlantic	VA Mid-Atlantic Health Care Network
7	South	The Southeast Network
8	South	VA Sunshine Healthcare Network
9	Mid-Atlantic	VA Mid South Healthcare Network
10	Mid-Atlantic	VA Healthcare System of Ohio
11	Midwest	Veterans In Partnership
12	Midwest	VA Great Lakes Health Care System
15	Midwest	VA Heartland Network
16	South	South Central VA Health Care Network
17	South	VA Heart of Texas Health Care Network
18	West	VA Southwest Health Care Network
19	Midwest	Rocky Mountain Network
20	West	Northwest Network
21	West	Sierra Pacific Network
22	West	Desert Pacific Healthcare Network
23	Midwest	VA Midwest Health Care Network

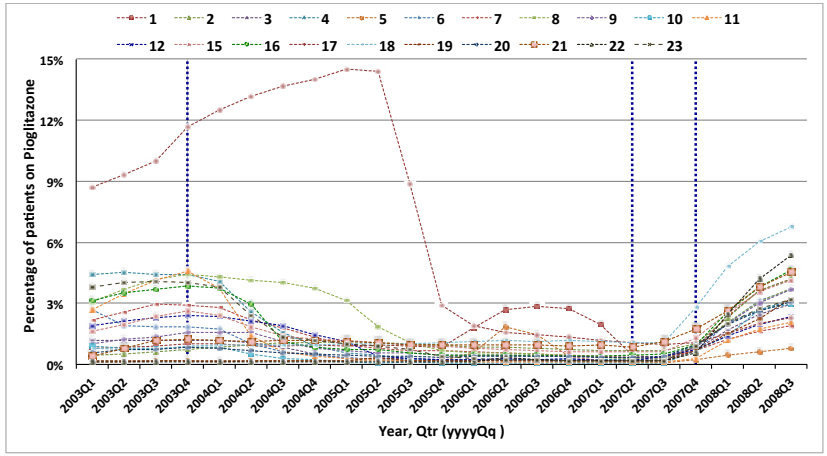
Appendix Table A2: Range and Categories for Various Measures of Lab Data.

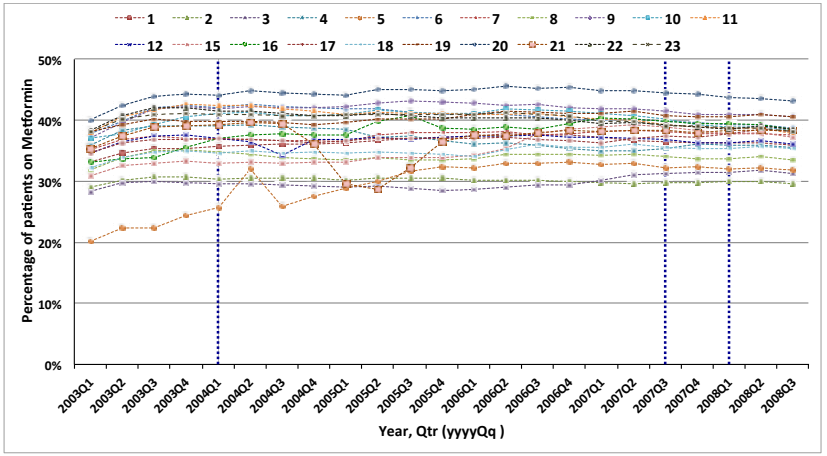
Measure	Range	Categories
BMI, kg/m^2	10-70	BMI<18.5 18.5≤BMI<25 25≤BMI<30 30≤BMI<35 35≤BMI<40 BMI≥40
HbA_{1C}, %	3-20	HbA_{1C} <6 6≤ HbA_{1C} <7 7≤ HbA_{1C} <8 8≤ HbA_{1C} <9 HbA_{1C} ≥9
LDL, mg/dL	20-300	LDL<70 70≤LDL<100 130≤LDL<160 130≤LDL<160 160≤LDL<190 LDL≥190
HDL, mg/dL	20-200	HDL<40 40≤HDL<60 HDL≥60
TCH, mg/dL TCH, mg/dL	50-500	TCH<200 200≤TCH<240 TCH≥240
TGL, mg/dL	20-800	TGL<150 150≤TGL<200 200≤TGL<500 TGL≥500
SBP, mm Hg	30-300	SBP<120 120≤SBVP<140 140≤SBP<160 SBP≥160
DBP, mm Hg	20-250	DBP<80 80≤DBP<90 90≤DBP<100 DBP≥100

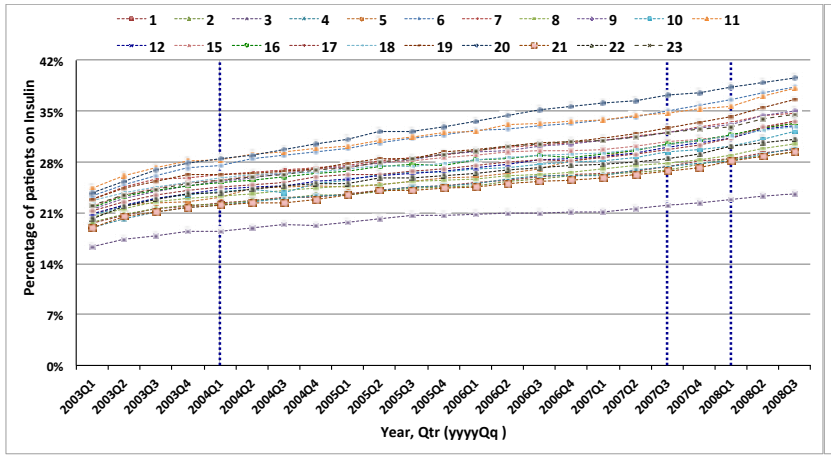
BMI=body mass index; LDL= low-density lipoprotein; HDL= high-density lipoprotein; TCH= total cholesterol; TGL=triglycerides; SBP= systolic blood pressure; DBP=diastolic blood pressure.

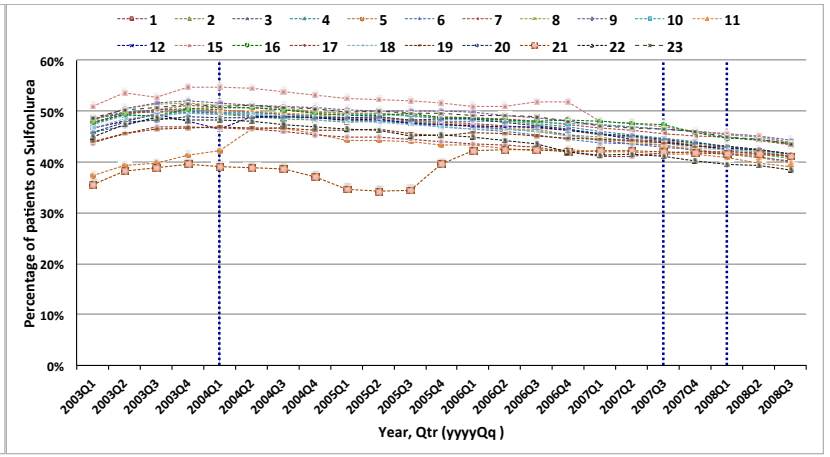


Appendix Figure A1: Rosiglitazone Use as a Percentage of Total Population within each VISN.
Data is aggregated at the quarterly level and includes only patients who survived up to that quarter. The three vertical lines represent the quarter in which (1) left (2003Q4): rosiglitazone was made available in the VA national formulary (VANF), (2) middle (2007Q2): FDA issued a safety alert related to rosiglitazone, (3) right (2007Q4): rosiglitazone was removed from the VANF.



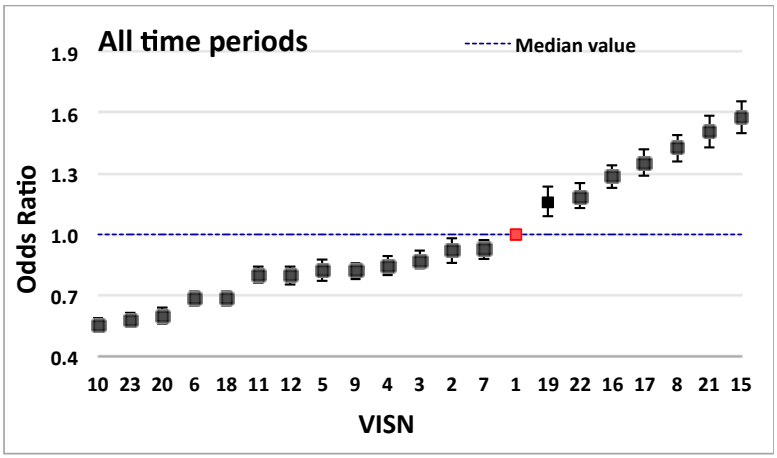


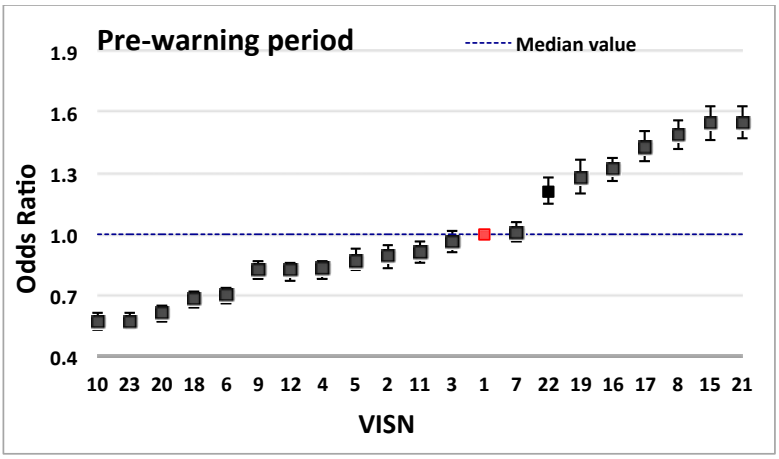


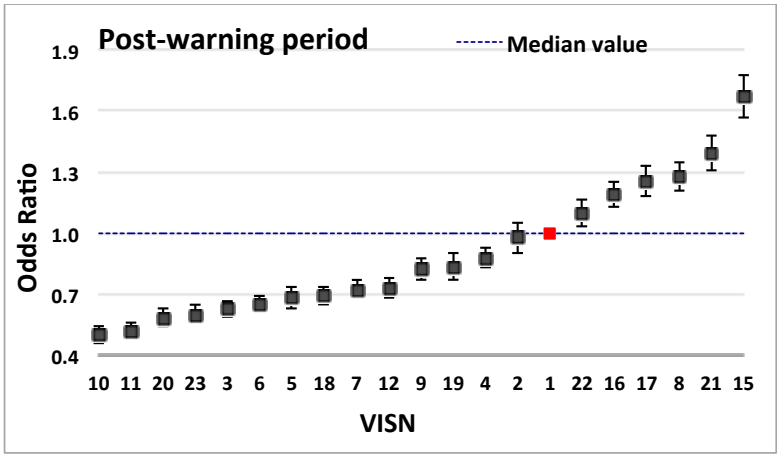


Appendix Figure A2: (Clockwise from Left) Pioglitazone, Metformin, Sulfonylurea, and Insulin Use as a Percentage of Total Population within each VISN.

Data is aggregated at the quarterly level and includes only patients who survived up to that quarter. The three vertical lines represent the quarter in which (1) left (2003Q4): rosiglitazone was made available in the VA national formulary (VANF), (2) middle (2007Q2): FDA issued a safety alert related to rosiglitazone, (3) right (2007Q4): rosiglitazone was removed from the VANF.







Appendix Figure A3: Odds Ratios (ORs) and their 95% CIs of a Veteran with Type 2 Diabetes Receiving a Prescription of Rosiglitazone.
The VISNs on x-axis are arranged according to increasing value of OR (from left to right) in each of (a) all time periods, (b) pre-warning periods, and (c) post-warning periods. VISN 10 served as the reference region (OR=1.0).

Appendix Table A3: Odds Ratios (95% CIs) Representing the Odds of a Veteran with Type 2 Diabetes Receiving a Rosiglitazone Prescription (All Variables).

Variable	All Time Periods 2003Q4 - 2008Q3	Pre-Warning Periods 2003Q4 - 2007Q1	Post-warning Periods 2007Q2 - 2008Q3
VISN 2	0.92** (0.86 - 0.98)	0.89*** (0.83 - 0.95)	0.98 (0.90 - 1.05)
VISN 3	0.87*** (0.83 - 0.92)	0.96 (0.91 - 1.02)	0.63*** (0.59 - 0.67)
VISN 4	0.84*** (0.80 - 0.89)	0.83*** (0.78 - 0.87)	0.88*** (0.83 - 0.93)
VISN 5	0.82*** (0.77 - 0.88)	0.87*** (0.82 - 0.93)	0.68*** (0.63 - 0.74)
VISN 6	0.68*** (0.65 - 0.72)	0.70*** (0.66 - 0.74)	0.65*** (0.61 - 0.69)
VISN 7	0.93** (0.88 - 0.97)	1.01 (0.96 - 1.06)	0.72*** (0.68 - 0.77)
VISN 8	1.43*** (1.36 - 1.49)	1.49*** (1.42 - 1.56)	1.28*** (1.21 - 1.35)
VISN 9	0.82*** (0.78 - 0.86)	0.82*** (0.78 - 0.87)	0.82*** (0.77 - 0.88)
VISN 10	0.55*** (0.52 - 0.59)	0.57*** (0.53 - 0.61)	0.50*** (0.46 - 0.54)
VISN 11	0.80*** (0.76 - 0.84)	0.91*** (0.86 - 0.96)	0.52*** (0.48 - 0.56)
VISN 12	0.80*** (0.75 - 0.84)	0.82*** (0.77 - 0.86)	0.73*** (0.68 - 0.78)
VISN 15	1.58*** (1.50 - 1.66)	1.55*** (1.46 - 1.63)	1.67*** (1.57 - 1.78)
VISN 16	1.29*** (1.23 - 1.34)	1.32*** (1.26 - 1.38)	1.19*** (1.13 - 1.25)
VISN 17	1.35*** (1.29 - 1.42)	1.43*** (1.36 - 1.51)	1.25*** (1.18 - 1.33)
VISN 18	0.68*** (0.65 - 0.72)	0.68*** (0.64 - 0.72)	0.69*** (0.65 - 0.74)
VISN 19	1.16*** (1.09 - 1.24)	1.28*** (1.20 - 1.37)	0.83*** (0.77 - 0.90)
VISN 20	0.60*** (0.56 - 0.64)	0.61*** (0.57 - 0.65)	0.58*** (0.54 - 0.63)
VISN 21	1.51*** (1.43 - 1.59)	1.55*** (1.47 - 1.63)	1.39*** (1.31 - 1.48)
VISN 22	1.18*** (1.13 - 1.25)	1.21*** (1.15 - 1.28)	1.10** (1.03 - 1.17)
VISN 23	0.58*** (0.55 - 0.61)	0.57*** (0.54 - 0.61)	0.60*** (0.56 - 0.65)
2004Q1	1.11*** (1.10 - 1.12)	1.11*** (1.10 - 1.12)	
2004Q2	1.27*** (1.25 - 1.28)	1.27*** (1.25 - 1.28)	
2004Q3	1.41*** (1.39 - 1.43)	1.41*** (1.39 - 1.42)	
2004Q4	1.60*** (1.58 - 1.62)	1.60*** (1.58 - 1.62)	
2005Q1	1.76*** (1.74 - 1.79)	1.76*** (1.73 - 1.78)	
2005Q2	1.81*** (1.79 - 1.84)	1.81*** (1.78 - 1.83)	
2005Q3	1.96*** (1.93 - 1.99)	1.94*** (1.92 - 1.97)	
2005Q4	2.08*** (2.05 - 2.12)	2.06*** (2.03 - 2.09)	
2006Q1	2.16*** (2.13 - 2.20)	2.14*** (2.11 - 2.18)	
2006Q2	2.17*** (2.13 - 2.20)	2.15*** (2.12 - 2.18)	
2006Q3	2.21*** (2.17 - 2.24)	2.19*** (2.15 - 2.22)	
2006Q4	2.31*** (2.28 - 2.35)	2.29*** (2.25 - 2.33)	
2007Q1	2.40*** (2.36 - 2.43)	2.37*** (2.33 - 2.41)	
2007Q2	2.36*** (2.32 - 2.40)		
2007Q3	1.89*** (1.86 - 1.92)		0.80*** (0.79 - 0.80)
2007Q4	1.47*** (1.44 - 1.50)		0.62*** (0.61 - 0.62)
2008Q1	0.98* (0.96 - 1.00)		0.40*** (0.40 - 0.41)
2008Q2	0.61*** (0.60 - 0.62)		0.24*** (0.24 - 0.25)
2008Q3	0.43*** (0.42 - 0.44)		0.17*** (0.17 - 0.17)
male	1.37*** (1.29 - 1.44)	1.34*** (1.26 - 1.42)	1.44*** (1.34 - 1.54)
married	1.14*** (1.12 - 1.16)	1.15*** (1.13 - 1.17)	1.10*** (1.08 - 1.12)
Age=55-64 yrs	1.08*** (1.06 - 1.11)	1.09*** (1.07 - 1.12)	1.05*** (1.02 - 1.08)
Age=65-74 yrs	1.03* (1.00 - 1.05)	1.05*** (1.02 - 1.07)	0.97* (0.94 - 1.00)
Age=75+ yrs	0.84*** (0.82 - 0.86)	0.86*** (0.84 - 0.89)	0.77*** (0.74 - 0.80)
Race=Non-Hispanic Black	0.94*** (0.91 - 0.96)	0.94*** (0.92 - 0.97)	0.91*** (0.88 - 0.94)
Race=Hispanic	1.17*** (1.13 - 1.22)	1.20*** (1.15 - 1.25)	1.10*** (1.05 - 1.15)
Race=Others	1.09*** (1.07 - 1.12)	1.08*** (1.06 - 1.11)	1.11*** (1.08 - 1.15)
Diabetes Duration=1yrs	0.92*** (0.89 - 0.96)	0.91*** (0.88 - 0.94)	0.95* (0.91 - 1.00)
Diabetes Duration=2yrs	1.05* (1.01 - 1.09)	1.04* (1.00 - 1.08)	1.06** (1.02 - 1.11)

Variable	All Time Periods 2003Q4 - 2008Q3	Pre-Warning Periods 2003Q4 - 2007Q1	Post-warning Periods 2007Q2 - 2008Q3
Diabetes Duration=3yrs	1.06** (1.02 - 1.10)	1.05* (1.01 - 1.09)	1.07** (1.02 - 1.13)
Diabetes Duration=4yrs	1.10*** (1.05 - 1.14)	1.09*** (1.05 - 1.14)	1.11*** (1.06 - 1.17)
Diabetes Duration=5yrs	1.16*** (1.12 - 1.21)	1.16*** (1.11 - 1.21)	1.17*** (1.11 - 1.23)
Diabetes Duration=6yrs	1.24*** (1.20 - 1.29)	1.25*** (1.20 - 1.29)	1.23*** (1.18 - 1.29)
Enrollment Priority=2	1.04* (1.01 - 1.07)	1.04* (1.01 - 1.08)	1.03 (0.99 - 1.07)
Enrollment Priority=3	1.04* (1.01 - 1.07)	1.04* (1.01 - 1.07)	1.03 (0.99 - 1.07)
Enrollment Priority=4	0.86*** (0.79 - 0.92)	0.84*** (0.78 - 0.91)	0.89* (0.81 - 0.99)
Enrollment Priority=5	1.04** (1.01 - 1.06)	1.04*** (1.02 - 1.07)	1.01 (0.98 - 1.04)
Enrollment Priority=6	1.10* (1.02 - 1.18)	1.10* (1.02 - 1.19)	1.08 (0.99 - 1.19)
Enrollment Priority=7	1.19*** (1.13 - 1.26)	1.20*** (1.14 - 1.27)	1.18*** (1.10 - 1.25)
Enrollment Priority=8	1.25*** (1.22 - 1.29)	1.27*** (1.24 - 1.31)	1.20*** (1.16 - 1.24)
Charlson Score=1	0.87*** (0.86 - 0.89)	0.88*** (0.86 - 0.90)	0.85*** (0.83 - 0.87)
Charlson Score=2	0.92*** (0.90 - 0.95)	0.93*** (0.90 - 0.95)	0.91*** (0.88 - 0.94)
Charlson Score=3	0.81*** (0.78 - 0.83)	0.81*** (0.78 - 0.84)	0.77*** (0.74 - 0.80)
18.5≤BMI<25	1.35*** (1.18 - 1.54)	1.34*** (1.16 - 1.54)	1.38** (1.12 - 1.72)
25≤BMI<30	1.76*** (1.54 - 2.01)	1.73*** (1.50 - 2.00)	1.83*** (1.48 - 2.27)
30≤BMI<35	2.29*** (2.00 - 2.61)	2.26*** (1.96 - 2.60)	2.37*** (1.91 - 2.93)
35≤BMI<40	2.77*** (2.42 - 3.18)	2.76*** (2.39 - 3.18)	2.84*** (2.29 - 3.51)
BMI≥40	3.44*** (3.00 - 3.94)	3.45*** (2.99 - 3.98)	3.46*** (2.79 - 4.28)
6≤ HbA1C <7	1.57*** (1.53 - 1.62)	1.55*** (1.50 - 1.59)	1.66*** (1.60 - 1.73)
7≤ HbA1C <8	2.25*** (2.18 - 2.31)	2.17*** (2.11 - 2.23)	2.54*** (2.44 - 2.64)
8≤ HbA1C <9	2.46*** (2.39 - 2.54)	2.38*** (2.31 - 2.46)	2.79*** (2.67 - 2.91)
HbA1C ≥9	2.23*** (2.16 - 2.31)	2.17*** (2.11 - 2.25)	2.48*** (2.37 - 2.59)
70≤LDL<100	1.19*** (1.18 - 1.21)	1.19*** (1.17 - 1.21)	1.20*** (1.18 - 1.23)
130≤LDL<160	1.22*** (1.20 - 1.24)	1.23*** (1.21 - 1.25)	1.19*** (1.16 - 1.22)
130≤LDL<160	1.05*** (1.02 - 1.07)	1.06*** (1.03 - 1.09)	1.02 (0.98 - 1.06)
160≤LDL<190	0.94** (0.91 - 0.98)	0.95* (0.91 - 0.99)	0.92* (0.87 - 0.98)
LDL≥190	1.03 (0.98 - 1.09)	1.04 (0.99 - 1.11)	1.00 (0.92 - 1.09)
40≤HDL<60	1.26*** (1.24 - 1.28)	1.25*** (1.23 - 1.27)	1.30*** (1.27 - 1.32)
HDL≥60	1.19*** (1.15 - 1.23)	1.18*** (1.14 - 1.22)	1.21*** (1.16 - 1.26)
150≤TGL<200	1.20*** (1.18 - 1.22)	1.21*** (1.19 - 1.22)	1.19*** (1.16 - 1.21)
200≤TGL<500	1.41*** (1.39 - 1.43)	1.43*** (1.41 - 1.45)	1.37*** (1.35 - 1.40)
TGL≥500	1.60*** (1.55 - 1.66)	1.65*** (1.59 - 1.71)	1.48*** (1.40 - 1.56)
200≤TCH<240	1.21*** (1.19 - 1.23)	1.23*** (1.21 - 1.26)	1.13*** (1.09 - 1.16)
TCH≥240	1.70*** (1.65 - 1.75)	1.73*** (1.68 - 1.79)	1.55*** (1.48 - 1.63)
120≤SBVP<140	1.00 (0.99 - 1.01)	0.99 (0.98 - 1.01)	1.03*** (1.02 - 1.05)
140≤SBP<160	0.97*** (0.96 - 0.99)	0.96*** (0.95 - 0.98)	1.00 (0.98 - 1.02)
SBP≥160	0.95*** (0.92 - 0.97)	0.95*** (0.93 - 0.97)	0.93*** (0.89 - 0.96)
80≤DBP<90	0.69*** (0.69 - 0.70)	0.70*** (0.69 - 0.71)	0.69*** (0.67 - 0.70)
90≤DBP<100	0.54*** (0.53 - 0.56)	0.55*** (0.54 - 0.57)	0.51*** (0.49 - 0.54)
DBP≥100	0.40*** (0.38 - 0.43)	0.41*** (0.38 - 0.43)	0.39*** (0.35 - 0.43)
Ind. for AMI event	0.86*** (0.82 - 0.91)	0.90*** (0.85 - 0.95)	0.76*** (0.68 - 0.84)
Ind. for Hypoglycemic event	1.39*** (1.33 - 1.45)	1.44*** (1.38 - 1.51)	1.24*** (1.15 - 1.34)
Ind. for Stroke	1.00 (0.97 - 1.04)	1.01 (0.97 - 1.05)	0.98 (0.93 - 1.04)
Ind. for CHF	0.71*** (0.59 - 0.86)	0.75** (0.61 - 0.91)	0.54** (0.37 - 0.80)
Ind. for LEA	0.97 (0.88 - 1.07)	1.02 (0.92 - 1.13)	0.83* (0.72 - 0.96)
Ind. for Retinopathy	1.41*** (1.34 - 1.48)	1.46*** (1.38 - 1.54)	1.24*** (1.14 - 1.35)
Ind. for Nephropathy	1.46*** (1.42 - 1.49)	1.48*** (1.44 - 1.51)	1.44*** (1.39 - 1.48)
Ind. for Insulin Use	0.89*** (0.88 - 0.90)	0.94*** (0.92 - 0.95)	0.77*** (0.75 - 0.79)
Ind. for Metformin Use	1.25*** (1.23 - 1.26)	1.23*** (1.21 - 1.25)	1.28*** (1.26 - 1.31)
Ind. for Sulfonylurea Use	2.27*** (2.24 - 2.30)	2.19*** (2.16 - 2.22)	2.53*** (2.48 - 2.58)
Ind. for Pioglitazone Use	0.75*** (0.73 - 0.78)	0.44*** (0.42 - 0.45)	1.88*** (1.81 - 1.95)
Ind. for Other medication Use	2.22*** (2.14 - 2.31)	2.29*** (2.20 - 2.39)	2.02*** (1.93 - 2.12)

Variable	All Time Periods 2003Q4 - 2008Q3	Pre-Warning Periods 2003Q4 - 2007Q1	Post-warning Periods 2007Q2 - 2008Q3
Ind. for University Affiliation	0.97 (0.94 - 1.00)	0.98 (0.95 - 1.01)	0.94** (0.90 - 0.98)
Dedicated Diabetes unit	1.14*** (1.10 - 1.18)	1.14*** (1.10 - 1.19)	1.11*** (1.06 - 1.16)
Urban location	1.21*** (1.18 - 1.24)	1.22*** (1.18 - 1.25)	1.20*** (1.16 - 1.24)
No. patients who died=6-25	0.89*** (0.87 - 0.92)	0.90*** (0.87 - 0.92)	0.88*** (0.85 - 0.91)
No. of patients who died=26-50	0.72*** (0.69 - 0.74)	0.72*** (0.69 - 0.74)	0.70*** (0.67 - 0.74)
No. of patients who died=51-75	0.66*** (0.64 - 0.68)	0.65*** (0.63 - 0.68)	0.67*** (0.64 - 0.70)
No. of patients who died=75+	0.57*** (0.55 - 0.60)	0.59*** (0.56 - 0.61)	0.50*** (0.48 - 0.53)
Dist. to parent station=1-50 mi.	0.80*** (0.78 - 0.83)	0.80*** (0.77 - 0.83)	0.82*** (0.79 - 0.86)
Dist. to parent station=51+ mi.	0.94*** (0.91 - 0.97)	0.95** (0.91 - 0.98)	0.91*** (0.88 - 0.95)
No. of op. Beds=1-150	0.84*** (0.80 - 0.88)	0.83*** (0.79 - 0.87)	0.89*** (0.84 - 0.95)
No. of op. Beds=151-300	0.92** (0.88 - 0.97)	0.92*** (0.87 - 0.96)	0.98 (0.92 - 1.04)
No. of op. Beds=300+	0.84*** (0.80 - 0.88)	0.82*** (0.78 - 0.86)	0.92** (0.87 - 0.98)
Facility Type=CBOC	0.86*** (0.82 - 0.90)	0.86*** (0.82 - 0.91)	0.85*** (0.80 - 0.90)
Facility Type=Other	1.34*** (1.28 - 1.41)	1.44*** (1.36 - 1.51)	1.05 (0.99 - 1.11)
Observations	7,626,779	5,245,146	2,381,633
Pseudo R^2	0.105	0.0919	0.134

***p<0.001; **p<0.01; *p<0.05
CI=confidence interval; VISN=veterans integrated services network; Ind=indicator; CHF=Coronary Heart Failure; LEA= lower extremity amputation; CBOC= Community-Based community center.
All reference categories were omitted.
All standard errors are robust and standard errors are clustered at the individual patient level.

Appendix Table A4: Odds Ratios (95% CIs) Representing the Odds of a Veteran with Type 2 Diabetes Receiving a Rosiglitazone Prescription as a function of level of threshold (Days Supply).

VISN	All Time Periods Threshold = 30 Days Supply	All Time Periods Threshold = 45 Days Supply	All Time Periods Threshold = 60 Days Supply
1 (Reference)	1.00	1.00	1.00
2	0.92** (0.86 - 0.98)	0.91** (0.85 - 0.97)	0.92** (0.86 - 0.98)
3	0.87*** (0.83 - 0.92)	0.86*** (0.81 - 0.91)	0.86*** (0.81 - 0.91)
4	0.84*** (0.80 - 0.89)	0.84*** (0.80 - 0.88)	0.84*** (0.80 - 0.89)
5	0.82*** (0.77 - 0.88)	0.83*** (0.77 - 0.88)	0.83*** (0.78 - 0.89)
6	0.68*** (0.65 - 0.72)	0.70*** (0.66 - 0.74)	0.71*** (0.67 - 0.75)
7	0.93** (0.88 - 0.97)	0.89*** (0.85 - 0.94)	0.88*** (0.84 - 0.93)
8	1.43*** (1.36 - 1.49)	1.44*** (1.37 - 1.51)	1.45*** (1.38 - 1.52)
9	0.82*** (0.78 - 0.86)	0.84*** (0.79 - 0.88)	0.85*** (0.81 - 0.90)
10	0.55*** (0.52 - 0.59)	0.56*** (0.53 - 0.60)	0.57*** (0.54 - 0.61)
11	0.80*** (0.76 - 0.84)	0.80*** (0.76 - 0.85)	0.81*** (0.77 - 0.85)
12	0.80*** (0.75 - 0.84)	0.77*** (0.72 - 0.81)	0.76*** (0.72 - 0.80)
15	1.58*** (1.50 - 1.66)	1.61*** (1.53 - 1.70)	1.63*** (1.55 - 1.72)
16	1.29*** (1.23 - 1.34)	1.24*** (1.19 - 1.30)	1.23*** (1.17 - 1.28)
17	1.35*** (1.29 - 1.42)	1.38*** (1.31 - 1.45)	1.38*** (1.32 - 1.45)
18	0.68*** (0.65 - 0.72)	0.67*** (0.63 - 0.71)	0.67*** (0.63 - 0.71)
19	1.16*** (1.09 - 1.24)	1.18*** (1.11 - 1.25)	1.20*** (1.12 - 1.27)
20	0.60*** (0.56 - 0.64)	0.61*** (0.57 - 0.65)	0.62*** (0.58 - 0.66)
21	1.51*** (1.43 - 1.59)	1.53*** (1.45 - 1.61)	1.55*** (1.47 - 1.64)
22	1.18*** (1.13 - 1.25)	1.20*** (1.14 - 1.26)	1.20*** (1.14 - 1.27)
23	0.58*** (0.55 - 0.61)	0.59*** (0.55 - 0.62)	0.59*** (0.56 - 0.63)
Observations	7,626,779	7,626,779	7,626,779
Pseudo R^2	0.105	0.104	0.103

CI=confidence interval; VISN=veterans integrated services network.
***p<0.001; **p<0.01; *p<0.05
All drugs were classified according to the chosen threshold of days supply.
The F-test for the joint significance of all the coefficients resulted in p-value < 0.0001.
All standard errors are robust and standard errors are clustered at the individual patient level.
The multivariate regression includes controls for demographics and clinical characteristics of a patient, the charcteristics of the patient's primary care facility, and time dummies.

Appendix Table A5: Odds Ratios (95% CIs) Representing the Odds of a Veteran with Type 2 Diabetes Receiving a Rosiglitazone Prescription where the outcome variable is a categorical variable that takes four values: 0,1,2,3.

VISN	All Time Periods TDE=1	All Time Periods TDE=2	All Time Periods TDE=3
1 (Reference)	1.00	1.00	1.00
2	0.87*** (0.81 - 0.94)	0.85*** (0.78 - 0.92)	0.92* (0.86 - 0.99)
3	1.05 (0.98 - 1.12)	0.95 (0.89 - 1.02)	0.85*** (0.80 - 0.90)
4	0.90*** (0.84 - 0.95)	0.81*** (0.76 - 0.87)	0.84*** (0.80 - 0.89)
5	0.81*** (0.75 - 0.88)	0.75*** (0.69 - 0.81)	0.84*** (0.78 - 0.90)
6	0.62*** (0.58 - 0.66)	0.57*** (0.53 - 0.60)	0.71*** (0.67 - 0.75)
7	1.23*** (1.16 - 1.30)	1.05 (0.99 - 1.11)	0.88*** (0.84 - 0.93)
8	1.29*** (1.21 - 1.36)	1.25*** (1.18 - 1.33)	1.48*** (1.41 - 1.56)
9	0.73*** (0.68 - 0.78)	0.70*** (0.66 - 0.75)	0.85*** (0.80 - 0.90)
10	0.46*** (0.43 - 0.50)	0.47*** (0.44 - 0.51)	0.57*** (0.53 - 0.60)
11	0.82*** (0.76 - 0.87)	0.76*** (0.72 - 0.82)	0.81*** (0.77 - 0.86)
12	0.97 (0.91 - 1.04)	0.94 (0.88 - 1.01)	0.75*** (0.71 - 0.80)
15	1.32*** (1.24 - 1.41)	1.31*** (1.23 - 1.39)	1.67*** (1.58 - 1.77)
16	1.61*** (1.53 - 1.70)	1.41*** (1.33 - 1.48)	1.24*** (1.19 - 1.30)
17	1.32*** (1.25 - 1.40)	1.21*** (1.14 - 1.29)	1.39*** (1.32 - 1.46)
18	0.80*** (0.75 - 0.85)	0.72*** (0.67 - 0.77)	0.66*** (0.62 - 0.70)
19	1.00 (0.93 - 1.08)	0.93 (0.86 - 1.01)	1.22*** (1.14 - 1.30)
20	0.57*** (0.52 - 0.61)	0.53*** (0.49 - 0.57)	0.61*** (0.57 - 0.66)
21	1.24*** (1.16 - 1.32)	1.25*** (1.17 - 1.33)	1.60*** (1.52 - 1.69)
22	1.09** (1.02 - 1.16)	1.10** (1.03 - 1.17)	1.22*** (1.16 - 1.29)
23	0.57*** (0.53 - 0.61)	0.51*** (0.47 - 0.55)	0.59*** (0.55 - 0.62)
Observations	7,626,779		
Pseudo R^2	0.0981		

CI=confidence interval; VISN=veterans integrated services network; TDE=Thirty Day Equivalent.
***p<0.001; **p<0.01; *p<0.05
DS=0 → TDE=0; DS=1-29 → TDE=1; DS=30-59 → TDE=2; DS>60 → TDE=3, where DS= Days Supply.
TDE=0 serves as the reference category.
The coefficients reported are based on a single multinomial logistic regression.
All drugs were classified according to the same TDE metric
The F-test for the joint significance of all the coefficients resulted in p-value < 0.0001.
All standard errors are robust and standard errors are clustered at the individual patient level.
The multivariate regression includes controls for demographics and clinical characteristics of a patient, the charcteristics of the patient's primary care facility, and time dummies.

Appendix Table A6: Odds Ratios (95% CIs) Representing the Odds of a Veteran with Type 2 Diabetes Receiving a Rosiglitazone Prescription as a function of location of patient's primary care facility (urban vs. any).

VISN	All Time Periods Location = All (Urban AND Rural)	All Time Periods Location = Urban ONLY
1 (Reference)	1.00	1.00
2	0.92** (0.86 - 0.98)	0.86*** (0.80 - 0.93)
3	0.87*** (0.83 - 0.92)	0.87*** (0.82 - 0.93)
4	0.84*** (0.80 - 0.89)	0.88*** (0.83 - 0.94)
5	0.82*** (0.77 - 0.88)	0.82*** (0.77 - 0.88)
6	0.68*** (0.65 - 0.72)	0.70*** (0.66 - 0.74)
7	0.93** (0.88 - 0.97)	0.94* (0.89 - 1.00)
8	1.43*** (1.36 - 1.49)	1.45*** (1.38 - 1.53)
9	0.82*** (0.78 - 0.86)	0.83*** (0.78 - 0.88)
10	0.55*** (0.52 - 0.59)	0.55*** (0.51 - 0.59)
11	0.80*** (0.76 - 0.84)	0.86*** (0.81 - 0.91)
12	0.80*** (0.75 - 0.84)	0.75*** (0.71 - 0.81)
15	1.58*** (1.50 - 1.66)	1.60*** (1.51 - 1.70)
16	1.29*** (1.23 - 1.34)	1.38*** (1.31 - 1.46)
17	1.35*** (1.29 - 1.42)	1.41*** (1.33 - 1.49)
18	0.68*** (0.65 - 0.72)	0.61*** (0.57 - 0.65)
19	1.16*** (1.09 - 1.24)	1.23*** (1.14 - 1.32)
20	0.60*** (0.56 - 0.64)	0.59*** (0.55 - 0.63)
21	1.51*** (1.43 - 1.59)	1.58*** (1.49 - 1.68)
22	1.18*** (1.13 - 1.25)	1.21*** (1.15 - 1.28)
23	0.58*** (0.55 - 0.61)	0.56*** (0.52 - 0.60)
Observations	7,626,779	6,735,998
Pseudo R2	0.105	0.106

CI=confidence interval; VISN=veterans integrated services network.
***p<0.001; **p<0.01; *p<0.05
The F-test for the joint significance of all the coefficients resulted in p-value < 0.0001.
All standard errors are robust and standard errors are clustered at the individual patient level.
The multivariate regression includes controls for demographics and clinical characteristics of a patient, the characteristics of the patient's primary care facility, and time dummies.