Rosiglitazone Is Associated with Mortality in Chronic Hemodialysis Patients

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ABSTRACT

Recent studies have associated rosiglitazone, a thiazolidinedione drug, with adverse cardiovascular outcomes in the general population with diabetes. Using data from the Dialysis Outcomes and Practice Patterns Study in the United States, we examined cardiovascular hospitalization and mortality associated with prescription of rosiglitazone, compared with other oral hypoglycemic agents, among 2393 long-term hemodialysis patients who were followed for a median of 1.1 yr. We assessed mortality risk using Cox models in patient-level and dialysis facility–level analyses that used the facility proportion of patients on rosiglitazone as the predictor (instrumental variable approach) and adjusted the models for demographics, comorbid conditions, laboratory values, and achieved dialysis dosage. Compared with patients prescribed other oral hypoglycemic agents, patients prescribed rosiglitazone had significantly higher all-cause (hazard ratio \([HR]\) 1.38; 95% confidence interval \([CI]\) 1.05 to 1.82) and cardiovascular (HR 1.59; 95% CI 1.14 to 2.22) mortality, and their adjusted HR for hospitalization with myocardial infarction was 3.5-fold higher (\(P = 0.02\)). We did not observe similar associations in a secondary analysis evaluating pioglitazone. By the instrumental variable approach, facilities with more than the median adjusted percentage (6.2%) of patients who had diabetes and were prescribed rosiglitazone had significantly higher all-cause mortality (HR 1.36; 95% CI 1.15 to 1.62) and cardiovascular mortality (HR 1.42; 95% CI 1.07 to 1.88) than facilities with less than the median expected percentage prescribed rosiglitazone. Our practice-based findings suggest significant associations of rosiglitazone use with higher cardiovascular and all-cause mortality among hemodialysis patients with diabetes.


Thiazolidinedione (TZD) use is increasing in patients with diabetes. For example, its reported use rose from 7.2% in 1998 to 16.2% in 2001 in a population of Medicare patients who were hospitalized for diabetes; however, concern exists that the TZD rosiglitazone may increase the risk for adverse outcomes. A meta-analysis of 42 randomized, controlled trials comparing rosiglitazone with other oral hypoglycemic agents (OHAIs), insulin, or placebo in the general population suggested a significantly higher risk for myocardial infarction (MI) and a borderline increased risk for death from cardiovascular causes. Another meta-analysis of four randomized, controlled clinical trials demonstrated a 42% significantly increased risk for MI and a two-fold significantly increased risk for congestive heart failure (CHF). Whether rosiglitazone results in adverse clinical outcomes remains uncertain, given the limitations of meta-analysis design and literature demonstrating rosiglitazone’s favorable influence on glycemic control.

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The association of rosiglitazone with cardiovascular outcomes in patients with diabetes and chronic kidney disease (CKD) is unknown. The recent Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for managing diabetes in patients with CKD and ESRD6 suggested the need for further study of TZDs in this population, given that (1) diabetes is the leading cause of ESRD in the United States,7 (2) rosiglitazone use has increased since its introduction in 1999,1 and (3) ESRD is associated with markedly increased risks for CHF8 and cardiovascular mortality.9 We evaluated the relationship between rosiglitazone use and, as a secondary analysis, pioglitazone use with cardiovascular outcomes in the US population of the Dialysis Outcomes and Practice Patterns Study (DOPPS), a multinational prospective cohort study designed to evaluate practice patterns and clinical outcomes among hemodialysis patients.

RESULTS

Of 29,838 patients enrolled in DOPPS I and II, 12,984 were enrolled in the United States. Limiting this US sample to patients who were taking an OHA and on dialysis as of or after July 1, 1999, yielded 2393 patients. Among them, 177 (7%) were prescribed rosiglitazone and 118 (5%) were prescribed pioglitazone (Table 1).

The number of patients who had diabetes and were prescribed an OHA ranged from 1 to 32 (median 11) per facility; the facility percentage of such patients prescribed rosiglitazone ranged from 0 to 53%. Rosiglitazone was prescribed to fewer than 10% of patients on OHAs at 60% of facilities; only 3% of facilities prescribed rosiglitazone to at least 30% of their patients on OHAs.

Table 1 shows baseline characteristics of patients prescribed rosiglitazone, pioglitazone, or a non-TZD OHA. Years with ESRD was significantly shorter in those who were treated with rosiglitazone compared with a non-TZD OHA (1.3 versus 1.8 yr; \( P < 0.004 \)). Patients of black race were less likely to be treated with a TZD (\( P < 0.001 \)). Other differences with \( P < 0.01 \) may be chance observations as a result of multiple comparisons. Plasma glucose was significantly higher among rosiglitazone patients.

Facilities were divided into quartiles on the basis of frequency of rosiglitazone use. Patient demographic and clinical
characteristics at each quartile revealed statistically significant trends for fewer black patients, a higher percentage of patients achieving a Kt/V >1.2, and a higher percentage of patients with a serum phosphorus concentration >5.5 mg/dl (P < 0.01 for trend) at the upper quartiles. Facilities that prescribed rosiglitazone had more patients achieving a hemoglobin level >11 g/dl, although the trend was inconsistent (Table 2).

Median time at risk was 1.1 yr (interquartile range 0.5 to 1.9 yr). We found 58 deaths (29 cardiovascular related) among patients taking rosiglitazone and 626 deaths (273 cardiovascular related) among those taking non-TZD OHAs. For patients prescribed rosiglitazone and those prescribed non-TZD OHAs, respectively, the all-cause mortality rates were 30.7 versus 25.1 deaths per 100 patient-years; the cardiovascular mortality rates were 15.3 versus 10.9 deaths per 100 patient-years.

**Patient-Level Analyses**

In multivariable Cox models, the risk for all-cause mortality was 33 to 38% higher for the rosiglitazone group than for patients on a non-TZD OHA (model 1 [adjusted for insulin use]: hazard ratio [HR] 1.33 [95% confidence interval (CI) 1.02 to 1.73; P = 0.03]; model 2 [added adjustments include demographic factors including body mass index (BMI), comorbidities, and laboratory values]: HR 1.38 [95% CI 1.05 to 1.82; P = 0.02]; Table 3). Patients prescribed rosiglitazone, starting after 0.25 to 0.50 yr of study follow-up, had higher mortality risk, seen in the adjusted cumulative mortality curves (Figure 1). Similar analyses for pioglitazone yielded inconsistent results. The risk for cardiovascular mortality was particularly elevated, 52 to 59% higher, among patients prescribed rosiglitazone compared with patients prescribed non-TZD OHAs.

A 3.5-fold higher risk for hospitalization for acute MI was found for patients prescribed rosiglitazone (model 2: HR 3.49; 95% CI 1.21 to 10.04; P = 0.02) versus patients prescribed non-TZD-OHAs in the adjusted model. Risk for hospitalization for causes related to CHF were not significantly higher for patients prescribed rosiglitazone (model 2: HR 1.21; 95% CI 0.72 to 2.05; P = 0.47).

**Sensitivity Analyses**

We found no significant difference in rosiglitazone-treated patients on insulin versus those not using insulin (interaction P = 0.27, model 2 adjustments). Because 94% of patients prescribed OHAs and 96% of patients prescribed rosiglitazone were older than 40 yr at ESRD onset, this study is reflective of hemodialysis patients with type 2 diabetes. To minimize a potential inclusion of patients with type 1 diabetes, we performed a sensitivity analysis excluding those whose age at

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**Table 2.** Descriptive characteristics of patients by facility quartile of rosiglitazone use

| Characteristic                | Q1  
|------------------------------|-----
| Age (yr)                     | 62.6
| Male (%)                     | 51.1
| Black race (%)               | 32.4
| BMI                          | 22.2
| Years with ESRD              | 1.6
| Coronary artery disease (%)  | 62.1
| CHF (%)                      | 49.7
| Cerebrovascular disease (%)  | 23.9
| Other cardiovascular disease (%) | 30.3
| Hypertension (%)             | 91.1
| Diabetes (%)                 | 98.1
| Peripheral vascular disease (%) | 38.3
| Lung disease (%)             | 12.3
| Gastrointestinal bleeding (%) | 7.8
| Neurologic disease (%)       | 12.9
| Psychological disorder (%)   | 31.2
| Cancer (%)                   | 9.4
| Recurrent cellulitis (%)     | 15.2
| HIV (%)                      | 1.5
| Hospital-based facilities (%) | 12.3
| Facility Hb >11 g/dl (%)     | 49.2
| Facility Kt/V >1.2 (%)       | 48.5
| Facility Ca >9.5 mg/dl (%)   | 4.5
| Facility PO4 >5.5 mg/dl (%)  | 35.4

<table>
<thead>
<tr>
<th>% Patients on Rosiglitazone in Facility</th>
</tr>
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<tbody>
<tr>
<td>Q1 ≤4.8</td>
</tr>
<tr>
<td>Q2 4.9 to 6.2</td>
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<tr>
<td>Q3 6.3 to 9.3</td>
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<tr>
<td>Q4 &gt;9.3</td>
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Data from US DOPPS I (1999 through 2001) and II (2002 through 2004), among patients reportedly on an OHA (n = 2393). Q1 through 4 are quartiles from the distribution of facility percentage of patients on rosiglitazone.  

<table>
<thead>
<tr>
<th>P &lt; 0.01 for trend.</th>
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<td>P &lt; 0.05 for trend.</td>
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Table 3. Patient-level and facility-level mortality models

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mortality Models versus Non-TZD OHAs</th>
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<tbody>
<tr>
<td></td>
<td>All-Cause Mortality</td>
</tr>
<tr>
<td></td>
<td>Model 1</td>
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<tr>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Patient-level: Medications</td>
<td></td>
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<tr>
<td>Rosiglitazone</td>
<td>1.33 (1.02 to 1.73)</td>
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<tr>
<td>Pioglitazone</td>
<td>1.11 (0.76 to 1.61)</td>
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<tr>
<td>Facility-level: Prescribing</td>
<td></td>
</tr>
<tr>
<td>Adjusted facility percentage</td>
<td>1.14 (1.07 to 1.21)</td>
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<tr>
<td>of patients prescribed</td>
<td></td>
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<tr>
<td>rosiglitazone, 75th versus</td>
<td></td>
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<tr>
<td>25th percentile (9.4% versus 4.9%)</td>
<td></td>
</tr>
<tr>
<td>Above versus below overall</td>
<td>1.36 (1.14 to 1.61)</td>
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</table>

*aData from US DOPPS I (1999 through 2001) and II (2002 through 2004), among patients reportedly on an OHA (n = 2393). Shown are HRs for the two TZDs, versus the reference category of all other (non-TZD) OHAs (HR = 1; data not shown). Models were stratified by study phase and controlled for the effects of facility clustering. Each facility measure was evaluated as a separate set of the two models. Model 1 covariate adjustments included the two TZD types and insulin; model 2 added covariates for age, gender, race (black versus nonblack), BMI, years with ESRD, comorbid conditions, hemoglobin, serum glucose, total cholesterol concentration, serum albumin, and delivered single-pool Kt/V. Cardiovascular deaths were those caused by the following: Acute MI, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, CHF, stroke/cerebrovascular accident, and ischemic brain damage/anoxic encephalopathy.

Figure 1. Adjusted cumulative all-cause mortality by medication type. Data from US DOPPS I (1999 through 2001) and II (2002 through 2004) among patients reported on an OHA (n = 2393). A Cox model was used to calculate the proportions of patients surviving through observed follow-up according to respective stratiﬁcation classes; the model adjusted for demographic factors, years with ESRD, comorbid conditions, serum glucose, total cholesterol concentration, and insulin use. Shown on the y axis is cumulative mortality (i.e., the cumulative proportion of deaths occurring up to a respective study time point). Study years at risk and (parenthetically) the number of patients remaining in the risk set at a given study time are shown on the x axis. Mortality curve for patients prescribed rosiglitazone versus non-TZD OHA is significantly different (P = 0.03); pioglitazone versus non-TZD OHA is nonsignificantly different.

ESRD onset was <40 yr; findings (model 2: HR 1.36 [95% CI 1.03 to 1.79, P = 0.03] for all-cause mortality; model 2: HR 1.59 [95% CI 1.13 to 2.23; P < 0.008] for cardiovascular mortality) were consistent with rosiglitazone use and mortality risk in Table 3. In another sensitivity analysis, when hemoglobin A1c (HbA1c) measurements were included with model 2 covariates for 1012 DOPPS II patients for whom HbA1c results were available, the mortality risk associated with rosiglitazone was consistent with the models that did not include HbA1c adjustment, although this did not achieve statistical significance (model 2: HR 1.34 [95% CI 0.96 to 1.86; P = 0.09] for all-cause mortality; HR 1.30 [95% CI 0.81 to 2.08, P = 0.03] for cardiovascular mortality).

Facility-Based Analyses

Relationships between the facility practice–based measure of rosiglitazone prescription and all-cause and cardiovascular mortality were studied. The adjusted percentage of patients who were taking an OHA within a facility and were prescribed rosiglitazone ranged from 0.2 to 30.2%. Parameter estimates were scaled to the interquartile range of facility rosiglitazone use, comparing the adjusted HR for facilities prescribing rosiglitazone at the 75th percentile (9.4% adjusted rosiglitazone use) versus those at the 25th percentile (4.9% adjusted rosiglitazone use) in Table 3. In another sensitivity analysis, when hemoglobin A1c (HbA1c) measurements were included with model 2 covariates for 1012 DOPPS II patients for whom HbA1c results were available, the mortality risk associated with rosiglitazone was consistent with the models that did not include HbA1c adjustment, although this did not achieve statistical significance (model 2: HR 1.34 [95% CI 0.96 to 1.86; P = 0.09] for all-cause mortality; HR 1.30 [95% CI 0.81 to 2.08, P = 0.03] for cardiovascular mortality).

To determine whether the facility percentage of rosiglitazone use and higher mortality risk depended on the number of patients receiving an OHA per facility, we restricted analyses to facilities with ≥10 patients prescribed an OHA. Comparing
those above the median facility-level rosiglitazone prescription with those below, we found significant all-cause mortality risk (HR 1.42; 95% CI 1.17 to 1.69; \( P = 0.0001 \)). Analysis of the facility measure by quartiles clarified that excess mortality exists primarily in the upper two quartiles (Figure 2).

Facility-level rosiglitazone prescription was similarly associated with a significantly higher risk for cardiovascular mortality despite the smaller number of events (\( n = 328 \)). Comparing those above the median facility-level rosiglitazone prescription with those below, we found significant cardiovascular mortality risk (HR 1.42; 95% CI 1.07 to 1.88; \( P = 0.01 \)).

**DISCUSSION**

Our patient analyses show strong (>38% higher), consistent (across age groups), and statistically significant (\( P = 0.02 \)) higher all-cause and cardiovascular mortality risks among those prescribed rosiglitazone versus non-TZD OHAs in a prevalent sample of hemodialysis patients in the United States. These results persisted after adjusting for potential confounding variables (clinical and demographic characteristics) that may influence patient outcomes, including BMI.

Findings were corroborated by facility-level analysis, which reduces the potential for confounding by indication. These observations are important, given that >50% of long-term dialysis patients in the United States have diabetes.\(^7\) On entry into the DOPPS in 2002, approximately 10% of long-term hemodialysis patients on an OHA were prescribed rosiglitazone.

Our patient-level analyses are consistent with a recently published meta-analysis that found rosiglitazone to be associated with an increased risk for MI (odds ratio [OR] 1.43; \( P = 0.03 \)) and for cardiovascular death (OR 1.68; \( P = 0.06 \)) in the general type 2 diabetes population.\(^2\) We observed a similar magnitude of effect among hemodialysis patients, with an HR of 1.59 (\( P = 0.0002 \)) for cardiovascular mortality and an even stronger association with MI (HR 3.49; \( P = 0.002 \)).

Published studies show no consistent association between rosiglitazone and adverse cardiovascular outcomes. In the Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial, rosiglitazone was not associated with increased risk for cardiovascular events, although an increased number of patients developed CHF.\(^11\) The ADOPT (Analysis from a Diabetes Outcome Progression Trial) trial showed no greater risk for cardiovascular events with use of rosiglitazone compared with metformin, although the rate of CHF was higher than with glyburide.\(^12\) An unplanned interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) Study revealed no increased risk for the end point of hospitalization or death from cardiovascular causes; however, the authors considered this analysis inconclusive.\(^13\) These previous studies focused on patients without ESRD, which may explain the differences with our findings.

Substantially increased risk for cardiovascular mortality is a clinical characteristic of the population with ESRD.\(^9\) We observed that rates of death and MI across our study groups were much higher than those in the general population groups reported in the meta-analysis by Nissen and Wolski.\(^2\)

Potential biologic mechanisms for our observations may include the effect of rosiglitazone on lipid profile.\(^14\) We attempted to account for this by adjusting for predialytic serum lipid levels, although our analysis was limited because fasting levels were unavailable. Another potential explanation is the reported risk for CHF associated with rosiglitazone,\(^8\) which evidence suggests may be related to an increase in distal tubular nephron sodium retention\(^15\); however, this may be irrelevant in patients with ESRD. Emerging evidence of the proinflammatory activities of TZDs suggests another potential biologic mechanism,\(^16–18\) given the widely recognized ongoing low-grade inflammation observed in the population with ESRD.\(^19\)

We evaluated outcomes associated with pioglitazone use as a secondary analysis. A recent meta-analysis demonstrated a significant 18% risk reduction in the combined end points of death, MI, and stroke associated with its use.\(^20\) Our findings were inconsistent, with trends toward lower all-cause yet higher cardiovascular mortality but lower cardiovascular hospitalization and cardiovascular events. The inconsistent results

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**Figure 2.** Adjusted all-cause mortality by facility-practice quartile of patients prescribed rosiglitazone among OHA-treated patients. Data from US DOPPS I (1999 through 2001) and II (2002 through 2004) among patients reported on an oral hypoglycemic agent (\( n = 2393 \)). The Cox model adjusted for age, gender, race (black versus nonblack), BMI, years with ESRD, comorbid conditions, serum glucose, total cholesterol concentration, serum hemoglobin and albumin, delivered single-pool Kt/V, and insulin use. Shown on the y axis is the HR for all-cause mortality for each quartile of the facility measure versus the referent category (adjusted facility percentage of patients prescribed rosiglitazone 4.9 to 6.2%). Respective HRs for each quartile, along with respective 95% CIs (whiskers) and \( P \) values, are plotted across the x axis. The inset text describes the results of modeling the facility measure as a continuous variable, expressing the HR as the risk among patients at facilities at the 75th percentile of use relative to those at facilities at the 25th percentile.
may reflect the relatively small number of patients on pioglitazone; however, previous studies suggest beneficial effects.\textsuperscript{21–26} Its use in patients with ESRD and diabetes will be the subject of future DOPPS analyses once additional data become available.

The DOPPS collects an extensive list of comorbidities, laboratory values, medication use, facility practice data, and hospitalization and outpatient events longitudinally, allowing adjustment for potential confounders in multivariable analyses, as well as time-to-event analyses. The consistency of our results, in patient- and facility-level analyses, is an important strength. We used an instrumental variable approach, which can substantially reduce confounding by indication. This mimics a clinical trial in which patients are randomly assigned to different practices at different facilities—in this case, the fraction of patients prescribed rosiglitazone at each facility.\textsuperscript{27} Published literature has similarly used physician prescribing patterns as an instrumental variable for evaluating the effects of cyclooxygenase-2 inhibitors on gastrointestinal bleeding.\textsuperscript{28}

Our analyses used an ecological treatment variable (the facility percentage of patients prescribed a TZD adjusted for the case mix of patients at the facility) while evaluating patient-level outcome. This approach uses the ability of instrumental variables to reduce treatment-by-indication bias while taking into account possible confounders at the individual level.\textsuperscript{29}

The following limitations should be considered. As with any observational study, it is possible that associations are not causally linked. Incomplete HbA\textsubscript{1c} data allowed for adjustment for glycemic control only in a subset of patients. It is possible that patients who have poor glycemic control and are at higher risk for cardiovascular disease are more likely to be prescribed rosiglitazone, as suggested by the higher plasma glucose. The instrumental variable analyses address these issues by reducing the potential for confounding by indication. Complete data on type of OHA used was missing for 47% of patients; they were included in the reference group. This approach would only have biased our association toward the null value; there may have been patients on TZD who were misclassified to the non-TZD comparison group. Our medication data do not measure duration of therapy, changing treatments, or whether a dose-response relationship exists between TZD use and clinical outcomes. Our data do not capture physician-level practice patterns; within-facility practice pattern variations may exist if multiple nephrologists staff the facility. Finally, although the \textit{a priori} hypotheses of the DOPPS included evaluating the impact of prescribing patterns on patient outcomes, we did not specifically identify rosiglitazone as a medication of interest before data collection.

In summary, our findings demonstrate a significant association between rosiglitazone use and cardiovascular morbidity and mortality among hemodialysis patients. Whether pioglitazone is associated with similar effects cannot be ascertained on the basis of limited sample size. Most studies, including the RECORD trial, have not included patients with ESRD.\textsuperscript{30} We believe that additional study of risks associated with rosiglitazone use in the vulnerable ESRD population, including a randomized clinical trial, are warranted.

**CONCISE METHODS**

This study analyzed data from 2393 patients participating in the US DOPPS I (data collected 1999 through 2001) and DOPPS II (data collected 2002 through 2004), in which a representative sample of US hemodialysis facilities participated (142 and 80 facilities, respectively). A random sample of patients who were aged $\geq 18$ yr and receiving long-term hemodialysis was enrolled in each facility. Details of the study design have been described previously.\textsuperscript{31,32} One aim of the DOPPS is to evaluate prescribing patterns and their impact on patient outcomes; a comprehensive medication list is completed during enrollment. This analysis was limited to US DOPPS facilities because TZD use in other countries was infrequent ($<1\%$). We further restricted our analysis to patients who were prescribed any OHA at entry into this study.

Because rosiglitazone was not on the US market until late May 1999, patients who were enrolled in the DOPPS before July 1, 1999, were assigned to OHA treatment based on the first available follow-up data after that date. OHAs were classified into three types—rosiglitazone, pioglitazone, and non-TZD OHAs—regardless of the duration of or subsequent change in medication use. Thus, our analysis seeks to evaluate the impact of baseline exposure to rosiglitazone, with non-TZD OHAs serving as the comparison group, as in a recent meta-analysis.\textsuperscript{2} In a secondary analysis, we similarly evaluated the other currently available TZD, pioglitazone, \textit{versus} all non-TZD OHAs. Patients who were treated with troglitazone were excluded, because it was withdrawn from the market in 2000.

**Statistical Analysis**

Patient characteristics were reported for each OHA group and for each quartile of facility frequency of rosiglitazone use. These included age; gender; race (black \textit{versus} nonblack); BMI; years since ESRD onset; 12 summary comorbid conditions (coronary artery disease, cerebrovascular disease, CHF, other cardiovascular disease, cancer other than skin, gastrointestinal bleeding in previous year, hypertension, lung disease, psychiatric disorder, neurologic disorder, peripheral vascular disease, cellulitis/gangrene); hemoglobin; and serum concentrations of albumin, glucose, and total cholesterol; and delivered single-pool K\textsubscript{i}/V. Information on comorbid conditions was obtained at patient entry into the study. Patient data regarding longitudinal laboratory values, treatment characteristics, and cause and date of hospitalization mortality were obtained by medical record abstraction and reported at 4-mo intervals using a standardized questionnaire. The missing indicator method was used to account for patients with missing covariate values\textsuperscript{33}; patients with $<1$ d of follow-up time were excluded from the analysis ($n = 48$).

For patient-level analyses, multivariable Cox proportional hazards models were used to estimate adjusted relative mortality rates among OHA treatment groups. Cardiovascular mortality—defined as death from acute MI, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, CHF, cerebrovascular accident, or ischemic brain damage/anoxic encephalopathy—was similarly analyzed. Patients who were enrolled before July 1, 1999, began accruing time at risk at the end of the first data collection interval after that date. Patients who were enrolled on or subsequent to July 1, 1999, accrued
time at risk from the date of enrollment. All patients were considered at risk and accrued follow-up time until the earliest occurrence of any of the following events: Death, loss to follow-up, or study end. Patients prescribed a non-TZD OHA served as the reference group for both patient-level models.

Model 1 compared patients prescribed rosiglitazone with the reference group, adjusting only for concomitant use of insulin; model 2 also adjusted for age, gender, race (black versus nonblack), years with ESRD, BMI, comorbid conditions, serum glucose, total cholesterol concentration, hemoglobin, serum albumin, and delivered single-pool Kt/V, because these factors are independently associated with patient outcomes. Because HbA1c levels were available for fewer than 50% of DOPPS II patients and not available in DOPPS I, predialysis glucose level was used as a surrogate measure of glycemic control. All models were stratified by DOPPS study phase and accounted for effects of facility clustering using robust SE estimation techniques based on the sandwich estimator. A secondary analysis for pioglitazone was performed using a similar method.

Because the potential for confounding by indication (i.e., patients prescribed rosiglitazone may have diabetes that is more difficult to control and carries a higher mortality risk), we analyzed facility-based treatment practices to evaluate the relationship between facility prescribing patterns for rosiglitazone and patient-level clinical outcomes using an instrumental variable approach. The facility was chosen as the instrument because (1) patient characteristics across treatment groups displayed balance when patients were categorized by facility use of TZDs (Table 3) rather than by their individual TZD prescription (Table 1) and (2) because a smaller proportion of variance in TZD could be attributed to patient case-mix variable alone ($R^2 = 0.031$) than variance attributed to both case mix and the facility ($R^2 = 0.166$). The facility practice–based measure is an adjusted instrumental variable measuring observed level of rosiglitazone use among facility OHA-treated patients relative to the expected level of use based on the facility’s case mix of OHA-treated patients; it was calculated for each facility at the start of each study phase. The instrumental variable method involves two stages. First, for each facility, the adjusted fraction of patients treated was estimated as a random intercept in a patient-level mixed linear model for rosiglitazone treatment, adjusting for patient-level covariates listed in model 2. Each facility intercept estimated the fraction of patients treated by that facility that was above or below the “expected” fraction, given patient case mix and other factors likely to influence rosiglitazone prescription. For yielding a more interpretable scale, the difference above or below the expected fraction was added to overall national prevalence of rosiglitazone prescription (7.4% [177 of 2393] on OHAs), generating an adjusted percentage treated with rosiglitazone at each facility. Thus, the variable represented a rosiglitazone treatment pattern for each facility, and all patients at a facility were assigned the corresponding level of treatment. In the second stage, Cox models were used to estimate the relative mortality rates associated with different levels of the fraction treated, adjusted for the covariates in models 1 and 2.

All statistical analyses were performed with SAS 9.1 (SAS Institute, Cary, NC). For all analyses, $P < 0.05$ was considered statistically significant. The statistical calculations ($P$ values) were not adjusted for multiple comparisons. Two sided $P$ values were reported. Institutional review boards approved the study; informed patient consent was obtained.

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DISCLOSURES

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REFERENCES

11. The DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or


