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Original Research

Clinical Outcomes Associated With Rates of Sulfonylurea Use Among Physicians

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Over the past 2 decades, the prevalence of diabetes mellitus has rapidly increased in the United States[1] and globally.[2] Estimates indicate that in 2010, nearly 19 million Americans had diagnosed diabetes, with 7 million more presumably undiagnosed.[3] Type 2 diabetes mellitus (T2DM) accounts for over 90% of new cases of diabetes in adults.[3] The wide range of available treatments has mitigated the impact of this growth[4] but has increased the complexity of T2DM management.

Metformin, a biguanide, is widely accepted and used as first-line treatment for T2DM.[4-6] Unlike many other agents, metformin causes neither acute hypoglycemia nor significant weight gain. Metformin use is usually only limited by gastrointestinal adverse events and is contraindicated in patients with impaired renal clearance. Although T2DM management guidelines do not name a preferred second-line agent,[4] sulfonylureas are prescribed as if they were the favored choice. After metformin, sulfonylureas are the second-most popular T2DM medication, prescribed to approximately one-third of patients.[7,8] Although sulfonylureas achieve glycemic control effectively,[9] their long-term effects on diabetes-related complications are not well established.[10] Widespread sulfonylurea use continues despite the availability of several newer T2DM agents, presumably because sulfonylureas are inexpensive and well established.[11-14]

With the passage of the 2010 Affordable Care Act (ACA), the Centers for Medicare & Medicaid Services (CMS) is required to report performance data on physicians billing Medicare through the Physician Quality Reporting System.[15] Currently, physicians voluntarily report performance data to CMS, but by 2015, the ACA will make it mandatory.[15] This system is intended to reward quality of care and reflects a movement toward physician assessments such as doctor report cards.[16] Because physician performance will be a key metric in determining US healthcare quality, it seems reasonable that physicians and stakeholders should have greater access to quality "physician-level" data to inform healthcare decisions. Specific performance measures are still being defined; the study presented here offers 1 possible measure.

In this retrospective, commercial, claims-based study, we examined the association between T2DM medication prescription patterns and physician performance. We measured physician performance using the occurrence of T2DM-related complications, including hypoglycemic and cardiovascular events, neuropathy, and lower-extremity, vision, and renal complications. We then determined whether T2DM medication prescription patterns were associated with physician performance rank. Our study takes the first steps toward assessing physician prescribing patterns as one simple and easily measurable tool for predicting physician performance. Moreover, we provide payers with a broader context to evaluate sulfonylureas and other T2DM therapies.

METHODS

Data

Humana is a large provider of commercial and Medicare Advantage health insurance plans. We examined patient claims data aggregated at the physician level using the 2007-2011 Humana database. To acquire the physician-level data, we first identified the patient cohorts that would be aggregated to the physician level by examining all commercially insured patient claims data and extracting incident and prevalent cohorts of T2DM patients. To reduce potential bias,[17] the incident cohort was used for base case analyses, while the prevalent cohort and 2 incident subcohorts were reserved for sensitivity analyses (reported in **eAppendix A**, www.ajmc.com). T2DM patients were identified as those with at least 1 claim with the *International Classification of Diseases, Ninth Revision* (*ICD*-9) code 250.x0 or 250.x2 and at least 1 claim for an anti-diabetic medication following the first observed claim with a T2DM diagnosis. Based on published results, these search criteria have a specificity range of 0.93 to 0.99 and sensitivity of 0.44 to 0.91.[18,19] Patients with claims for pregnancy (*ICD*-9 codes 630-79, V22.x–V24.x, V27.x, V29.x, V61.6, V61.7) were excluded during pregnancy and for 6 months thereafter. The cohort includes only working-age patients (aged 18-64 years).

For the prevalent cohort, the first-observed claim with a T2DM diagnosis provided the index date. Patients with less than 1 year of follow-up from the index date were excluded. The incident sample included all patients from the prevalent sample with at least 1 year of continuous enrollment prior to the index date, with no T2DM-related medical or pharmacy claims. We considered all available follow-up months of these patients. We also identified 2 incident subcohorts for sensitivity analyses: the second-line subcohort and the long-run therapy subcohort. In the second-line subcohort, we excluded patients from the incident sample if they did not require a second-line agent during the study period, and we considered all available follow-up months of the remaining patients. A *first-line therapy* was defined as the first anti-diabetic drug used after diagnosis. A second-line therapy was added to or replaced the first agent. For the long-run therapy subcohort, we selected follow-up months for incident patients in which patients used at least 1 drug class they also had used continuously for at least 6 months prior. The study selection criteria are detailed in **Figure 1**.

We collected patient characteristics including age and gender, and tracked monthly comorbidities, medication use, and complications. The Elixhauser Comorbidity Index (ECI) was calculated each month for each patient using comorbid diagnoses over the previous 12 months.[20,21]

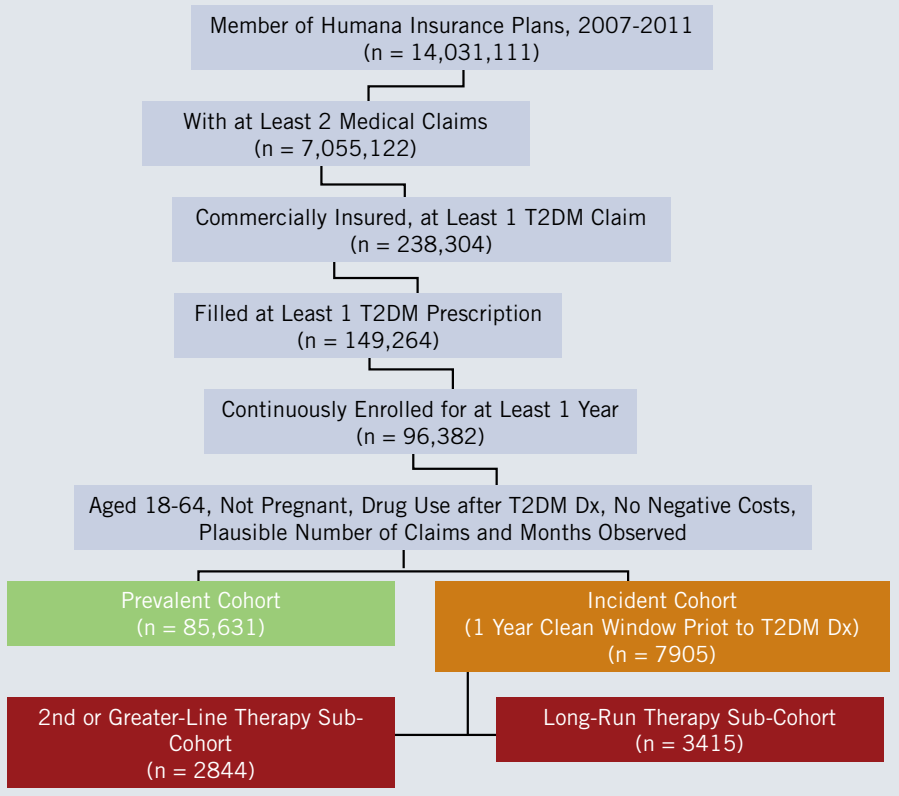
For each patient, we identified anti-diabetic drug use using the National Drug Code (NDC) Directory. We grouped T2DM medications by mechanistic class; specifically, biguanides (metformin), sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, insulins, and "other" (including alpha-glucosidase inhibitors, amylinomimetics, and meglitinides). For each patient, we identified T2DM-related adverse events (cardiovascular, lower-extremity, renal, ophthalmic, neurological, and severe hypoglycemic events) using *ICD*-9 and Current Procedural Terminology (CPT) codes (listed in **eAppendix B**, www.ajmc.com), consistent with previous literature.[22-27]

For each patient cohort (incident, prevalent, second-line, or long-run), we used physician identifiers from the pharmacy claims to link physicians prescribing T2DM medicines to each patient and compile an associated cohort of physicians. Once a patient received T2DM prescriptions from a provider, the patient was considered that provider's patient for the next 6 months. A patient receiving prescriptions from multiple providers was considered the patient of each. For each physician in each month, we calculated complication rates, average patient characteristics (age, sex, ECI), and average T2DM drug usage (fraction of patients using each class) among the physician's T2DM patients.

Statistical Analysis

After tabulating drug use and complication rates for the patient cohort, we created for each month in the study period a case-mix-adjusted measure of physician performance. Specifically, we calculated the fraction of a physician's patients experiencing any of the study complications in a given month. We then used a linear regression model to predict the monthly rate of any T2DM-related complication as a function of average age, gender, and ECI among patients in the practice in a given month, as well as a monthly time trend. This model provided a measure of physicians' performance as relative success at avoiding T2DM-related complications, after adjusting for their patients' age, sex, and comorbidities.

Figure 1. Study Cohort Selection



T2DM indicates type 2 diabetes mellitus.

After deriving this measure of physician performance, we sought to determine whether it was related to T2DM prescription patterns. To do this, we compared each physician's actual performance to the "risk-adjusted" performance predicted by patient characteristics alone (**Figure 2).** Those doctors with lower complication rates than predicted based on patient characteristics were considered "high performers," whereas those with higher complication rates than predicted were considered "low performers." We ranked physicians in each month based on their performance that month, and then sorted doctor-months into 10 ordered and equally sized groups (deciles). After establishing the 10-group ranking of physician performance, we analyzed whether the prescribing patterns in the month prior of highest performing doctors were different than those of the lowest performing doctors for each of the drug classes.

Finally, to quantify the impact of physicians' prescribing decisions, we expanded the previous regression model of physicians' T2DM complication rates on practice characteristics to include rates of use for each of the T2DM drug classes in the month prior. We used this model to predict the change in T2DM complications when switching from "low performer" (bottom decile) prescribing patterns to those of "high performers" (top decile). We performed sensitivity analyses on the prevalent, second-line, and long-run samples.

RESULTS

We identified an incident T2DM cohort of 7905 patients. Demographic descriptions are provided in **Table 1**. A majority of patients were men (n = 4418; 55.90%), and the most frequent age category was 46-55 years (n = 3155, 39.91%). The average age was 50.1 years.

Rates of T2DM drug use are summarized in **Table 2**. The biguanide (metformin) was used during 80,244 patient-months (37.46% of the total patient-months). Sulfonylureas were the second most commonly used (21,429 patient-months; 10.00%). TZDs were the third-most commonly used (8835; 4.12%). Every other drug class was filled less than 3% of the total patient-months. All insulin classes combined (bolus, basal, premixed) totaled 9709 patient-months (4.53%). Because metformin is widely accepted as the first-line T2DM medication,[4] these data suggest that sulfonylureas are the most commonly prescribed second-line agent in this cohort.

We compared baseline ECIs among all patients newly initiating each class of diabetes medication (**Table 3**). Patients newly initiating the biguanide had an average ECI of 2.38 in the year prior to initiation, the lowest score of any T2DM drug class. Sulfonylureas were prescribed to patients who had the second-fewest comorbidities at initiation (average ECI: 2.75). Patients who

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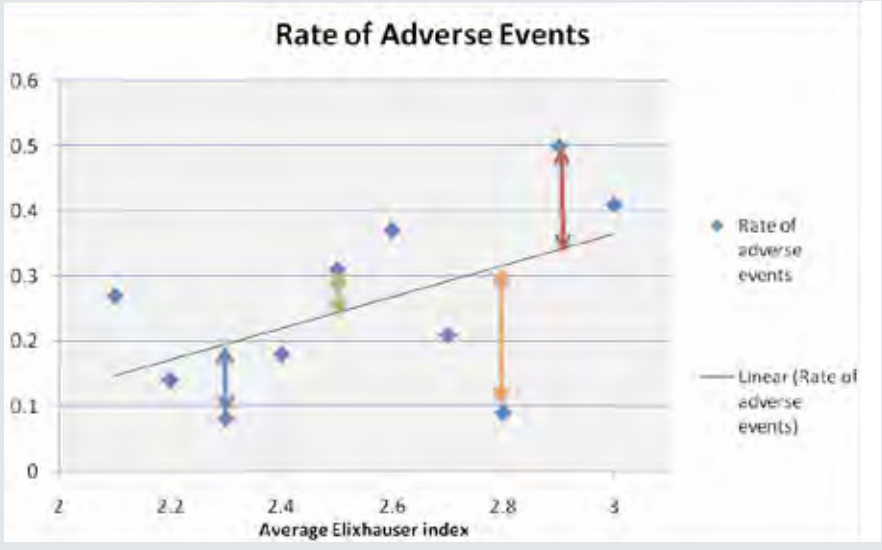
Figure 2. Schematic Illustration of Doctor Performance Assessment



This figure presents a conceptual illustration of the measurement of case-mix–adjusted physician performance. The line represents the regression of complication rates at each physician's practice on the average Elixhauser index of the physician's patients, as well as other patient characteristics (omitted for ease of illustration). The assessment assumes that the adverse-event rate after T2DM medication initiation is proportional to comorbidities at the time of T2DM diagnosis. A physician with performance above or below the regression line has a higher or lower complication rate than others with similar case mix, respectively. The farther away the performance is from the regression line (increasing residual), the less it conforms to the expected performance for a given case mix (either better or worse).

received amylinomimetics had the most comorbidities, on average (4.00).

Rates of complications are summarized in **Table 4**. Cardiovascular complications were the most common, in 6378 patient-months (2.98% of the total patient-months), and neuropathy complications the least common, in 804 patient-months (0.38% of the total patient-months). Overall, 15,492 patient-months (7.23% of the total patient-months) involved any diabetes-related complication.

Table 1. Demographic Characteristics of Incident T2DM Patients

Patient Characteristic	Frequency N = 7905
Age, years, mean (SD)	50.1 (9.2)
Age category, n (%)	
18-25	95 (1.2)
26-35	501 (6.34)
36-45	1652 (20.90)
46-55	3155 (39.91)
56-64	2502 (31.65)
Gender, n (%)	
Men	4418 (55.90)
Women	3486 (44.10)

SD indicates standard deviation; T2DM, type 2 diabetes mellitus.

Among the incident cohort, we identified 10,457 distinct prescribing physicians. The average number of distinct prescribing physicians per incident T2DM patient was 1.7 (range, 1-9), whereas the average number of distinct incident T2DM patients (covered by Humana insurance) per prescribing physician was 1.3 (range, 1-18).

Figure 3 relates prescribing patterns to patient outcomes. Low-performing physicians (ie, those exhibiting higher complication rates for a given patient case-mix) were more likely than high-performing peers to prescribe metformin, sulfonylureas, and insulin. By contrast, high-performing physicians were more likely than peers to prescribe DPP-4 inhibitors, TZDs, GLP-1 agonists, or other classes of diabetes medications. The strongest correlation of drug use to performance was for DPP-4 inhibitors (R^2 = 0.1662), with increasing use of this drug class positively associated with fewer T2DM complications. Sulfonylureas (R^2 = 0.0857) and insulin (R^2 = 0.0166) were more commonly prescribed by low performers. The insulin relationship appeared nonlinear, with high prescription rates among both high and low performers, and lower rates among average performers.

After expanding the regression model to incorporate prescriptions of T2DM drug classes, we were able to predict the number of complications that would be avoided by moving from the prescribing patterns of bottom-decile to top-decile performers. In a population of 100,000 incident T2DM patients, such a change in prescribing patterns would amount to 924 avoided complications per year (95% CI, 597-1251).

DISCUSSION

Our analysis suggests that physicians prescribing sulfonylureas more frequently have a greater proportion of patients with long-term complications than those prescribing other second-line T2DM medications. After accounting for the prior-year health of patients, and other covariates such as age and gender, physicians prescribing sulfonylureas more frequently did worse than expected in preventing T2DM-related complications. Those using DPP-4 inhibitors at higher rates did better than expected, given the observed health of their patients. Physicians prescribing TZDs, GLP-1 agonists, or other newer agents at higher rates also performed better than expected. The amount of variance in prescribing a given drug class explained by physician performance is in the range of 1.7% to 16.6%—consistent with similar models using administrative claims data for various disease states including diabetes.[28-33]

Sulfonylureas are the most commonly prescribed T2DM medication after metformin. It is thus notable that physician tendencies to prescribe sulfonylureas more often are associated with poorer risk-adjusted outcomes. This finding is consistent with related findings in the clinical literature. Sulfonylurea or sulfonylurea-plus-metformin use may be associated with higher mortality rates than metformin alone.[34-37] Sulfonylureas are associated with a 4-fold increased risk for mild/moderate hypoglycemia compared with metformin alone.[9] When sulfonylureas were used as monotherapy, patients had higher blood pressure a year later than when they were prescribed metformin, an effect likely explained by increased body mass index (BMI) with sulfonylureas.[38] Likewise, adjusting for cardiovascular risk factors, the incidence of cardiovascular events such as myocardial infarction or stroke is higher in patients taking sulfonylureas versus metformin.[39,40] Compared with metformin, sulfonylurea use increased the risk of worsening glomerular filtration rate, progression to end-stage renal disease, and death.[41]

The American Diabetes Association (ADA) has estimated that the cost of diagnosed diabetes in 2012 was $245 billion; $176 billion for direct medical costs and $69 billion in reduced productivity.[42] The largest portion of this (43%) was due to inpatient care costs incurred due to diabetes complications. A greater portion of the total estimated cost of diabetes was spent on medications to treat the diabetes complications (18%) than on diabetes medications and supplies themselves (12%).[42] A 2007-2009 survey estimated that insulins and oral hypoglycemic

Table 2. Monthly Drug Use Among Incident T2DM Patients

T2DM Drug Class	Patient-Months in Use, Total (%)
Biguanides	80,244 (37.46)
Sulfonylureas	21,429 (10.00)
Thiazolidinediones	8835 (4.12)
Basal insulin	5917 (2.76)
DPP-4 inhibitors	4023 (1.88)
Bolus insulin	2806 (1.31)
GLP-1 agonists	1066 (0.50)
Premixed insulin	986 (0.46)
Meglitinides	493 (0.23)
Alpha-glucosidase inhibitors	44 (0.02)
Amylinomimetics	27 (0.01)
No drug use	115,694 (54.01)
Total patient-months	214,230

DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; T2DM, type 2 diabetes mellitus.

Table 3. Baseline Elixhauser Comorbidity Index Among T2DM Patients Initiating Drug Therapy

T2DM Drug Class	Elixhauser Comorbidity Index
Biguanides	2.38
Sulfonylureas	2.75
Thiazolidinediones	2.80
DPP-4 inhibitors	3.18
GLP-1 agonists	3.33
Basal insulin	3.48
Meglitinides	3.63
Premixed insulin	3.76
Bolus insulin	3.93
Alpha-glucosidase inhibitors	3.95
Amylinomimetics	4.00

Scores calculated using the Elixhauser Comorbidity Index.[20,21]
DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

agents were the second- and fourth most-common causes of emergency admission, together accounting for 1 in 4 emergent medication-related admissions.[43] Given the high cost of diabetes complications, future research should investigate whether the cost savings of using an inexpensive drug class (sulfonylureas) actually represents an overall cost savings when complication rates are high and may outweigh initial savings.

Our study did have limitations. The relationship between physician prescription patterns and patient complications may be confounded by the patients' diabetes severity level and other health characteristics. Although we accounted for age, sex, and comorbidities in our analyses, data limitations prevented us from controlling for a fuller set of characteristics. Because sulfonylureas are a common therapy and patients initiating them are relatively healthy **(Table 3)**, we find it noteworthy that a strong positive association between sulfonylurea prescription and T2DM complications remains. Further research is needed to shed light on this issue.

As ours and other studies have shown, sulfonylureas are a popular second-line agent in the treatment of T2DM. However, our physician-level study design suggests a potential pitfall associated with their use. Physicians who prescribe sulfonylureas more frequently than their peers have patients with higher complication rates than would be expected from their age, sex, and preexisting comorbidities. This could be due to the properties of the drugs themselves; it could also be due to the skills and characteristics of the physicians who choose to use these drugs more often, or the unmeasured characteristics of their patients. Further investigation is needed to assess whether physician prescribing choices accurately predict patient outcomes, and whether they can serve as an additional metric of quality in today's changing healthcare reimbursement landscape. **EBDM**

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Table 4. Average Complication Rates Among Incident T2DM Patients

Complication Type, n (%)	Rate per Patient per Month
Cardiovascular disease	6378 (2.98)
Lower-extremity complications	4577 (2.14)
Ophthalmic disease	1019 (0.48)
Renal disease	4586 (2.14)
Neuropathy	804 (0.38)
Hypoglycemic emergencies	857 (0.40)
Any diabetes-related complication	15,492 (7.23)

T2DM indicates type 2 diabetes mellitus.
Based on *International Classification of Diseases, Ninth Revision* and Current Procedural Terminology codes. (For specific codes, see eAppendix B, www.ajmc.com.) Cardiovascular events include myocardial infarction, congestive heart failure, ischemic heart disease, and stroke. Lower-extremity complications include arterial occlusion, Charcot foot, claudication, gangrene, lymphangitis, osteomyelitis, paresthesia, ulcer, and amputation. Ophthalmic disease includes diabetic retinopathy, diabetic macular edema, microaneurysms, and blindness. Renal disease includes chronic renal failure, diabetic nephropathy, end-stage renal disease, and proteinuria.

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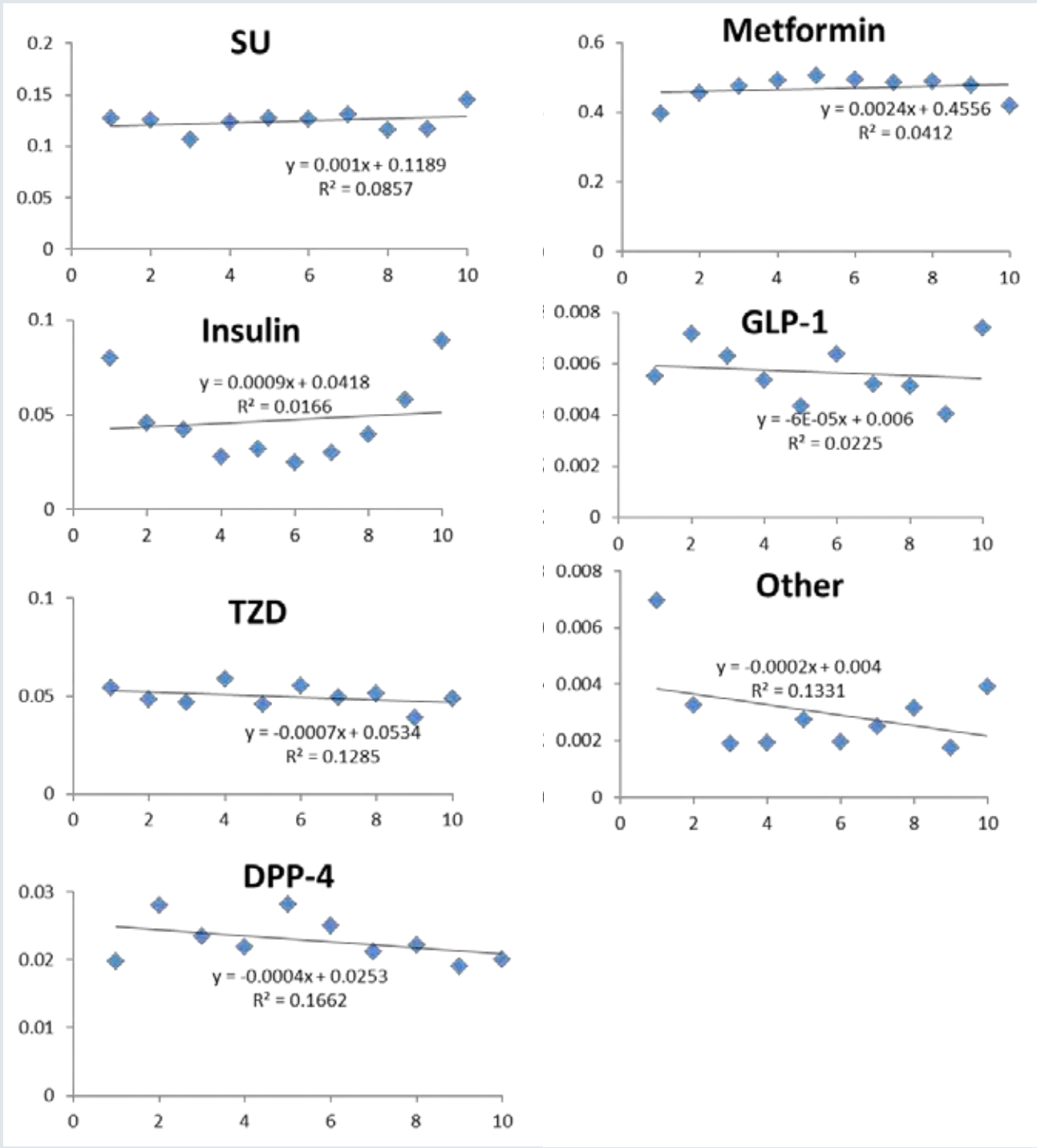
Figure 3. Drug Use Patterns Among the High- and Low-Performing Doctors of Incident Patients



DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SU, sulfonylurea; TZD, thiazolidinedione.
The units on the abscissa correspond to the 10 physician performance deciles; 1 = highest performing; 10 = lowest performing. The ordinate shows the fraction of patients in a physician's practice using the given drug class. Each diamond represents the average rate of drug class prescribing among physicians in the given performance decile.