The FDA Metformin Label Change and Racial and Sex Disparities in Metformin Prescription among Patients with CKD

Jung-Im Shin,1 Yingying Sang,1,6 Alex R. Chang,3 Stephan C. Dunning,2 Josef Coresh,1,4 Lesley A. Inker,5 Elizabeth Selvin,1,4 Shoshana H. Ballew,1 and Morgan E. Grams1,4

1Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
2OptumLabs, Cambridge, Massachusetts
3Kidney Health Research Institute, Geisinger, Danville, Pennsylvania
4Department of Medicine, Johns Hopkins University, Baltimore, Maryland
5Division of Nephrology, Tufts Medical Center, Boston, Massachusetts
6OptumLabs Visiting Fellow, OptumLabs, Cambridge, Massachusetts

ABSTRACT

Background In 2016, the Food and Drug Administration (FDA) changed labeling regarding metformin contraindications in patients with diabetes and CKD from using serum creatinine–based thresholds to using eGFR-based thresholds. Because race and sex affect serum creatinine levels independently of GFR, the earlier creatinine-based contraindication may have inadvertently caused racial and sex disparities in metformin prescription among patients with low eGFR.

Methods In an analysis of 15,946 Black and White primary care patients with diabetes and eGFR 30 ml/min per 1.73 m² in a large health system (the primary cohort), we assessed the association of race and sex with metformin prescription across eGFR level before and after the FDA label change. For a replication cohort, we meta-analyzed data from 36 cohorts with 1,051,723 patients from OptumLabs Data Warehouse.

Results In the primary cohort, before the label change, Black patients with eGFR of 30–44 ml/min per 1.73 m² were prescribed metformin less often than White counterparts (adjusted prevalence ratio [aPR], 0.65; 95% confidence interval [95% CI], 0.52 to 0.82); this disparity was significantly attenuated after the label change (aPR, 0.90; 95% CI, 0.74 to 1.09; P value for interaction by period = 0.04). Results were consistent in the replication cohorts. Men with eGFR of 30–44 ml/min per 1.73 m² received metformin prescriptions less often than women counterparts before the label change; this was nonsignificantly attenuated after the label change, but we found significant attenuation in the replication cohorts (aPRpre-label change, 0.76; 95% CI, 0.73 to 0.79; aPRpost-label change, 0.85; 95% CI, 0.83 to 0.88; P value for interaction by period <0.001).

Conclusions The metformin label change to an eGFR-based contraindication may have reduced racial and sex disparities in metformin prescription in moderate kidney dysfunction.

JASN 31: 1847–1858, 2020. doi: https://doi.org/10.1681/ASN.2019101119
Diabetes is a major public health challenge, afflicting >30 million adults in the United States. Diabetes leads to macrovascular and microvascular complications, including two to four times the risk of cardiovascular disease and two to three times the risk of CKD compared with the general population. Metformin is the first-line glucose-lowering medication for patients with type 2 diabetes, and it is recommended in major national and international guidelines because of its favorable adverse effect profiles, low cost, and effectiveness.

Metformin use has been controversial in the approximately 10%–20% of patients with diabetes who have CKD. Metformin is cleared primarily by the kidneys, and it is frequently avoided in patients with CKD due to concerns of drug accumulation and case reports of lactic acidosis. Until 2016, the US Food and Drug Administration (FDA) prescribing guidelines stated that metformin was contraindicated when serum creatinine levels were at or above 1.5 mg/dl (≥132 μmol/L) in men and at or above 1.4 mg/dl (123 μmol/L) in women. Relying on observational evidence, the FDA revised the metformin label on April 8, 2016, guiding prescriptions on the basis of the eGFR. The revised metformin label relaxed the kidney contraindications, allowing for continued metformin use in patients with mild to moderate CKD, defined as an eGFR of 30–60 ml/min per 1.73 m², but not in those with eGFR<30 ml/min per 1.73 m².

The previous FDA label on the basis of serum creatinine may have inadvertently introduced disparities in metformin prescription among patients with CKD. Creatinine has a number of non-GFR determinants, including race and sex. Thus, creatinine-based estimating equations for GFR include coefficients for race and sex to mitigate these influences: serum creatinine levels are higher in Black individuals than in White individuals and in men than in women at the same level of GFR. A contraindication solely on the basis of sex-specific thresholds of creatinine might cause underprescription of metformin in Black patients compared with White patients. The objective of this study was to investigate racial differences in metformin prescription in the population with CKD pre- and post-revision of the FDA label for metformin. We evaluated the association between race and metformin prescription by the level of eGFR in period prevalent cohorts, analyzing data from a single health system with a high proportion of Black patients. As a secondary objective, we also evaluated whether there were disparities in metformin prescription by sex. We then sought to replicate findings in a separate geographically diverse set of United States health system cohorts.

**Methods**

**Study Population and Design**

Johns Hopkins Medicine (primary cohort) is a large health system in Maryland, with a heterogeneous patient population. To study the change in metformin prescription before and after the FDA label change (April 8, 2016), we created two 9-month period prevalent cohorts. The pre-label change period prevalent cohort was selected between July 15, 2015 and April 8, 2016, and the post-label change period prevalent cohort was selected between April 9, 2016 and January 1, 2017. Each cohort contained Black and White primary care patients older than 18 years with diabetes taking at least one glucose-lowering medication and having at least one outpatient measure of serum creatinine during the 9-month period. We excluded patients with eGFR<30 ml/min per 1.73 m² as they had contraindications against metformin use in both the previous and revised FDA labels. Diabetes was identified using the Health Plan Employer Data and Information Set criteria: one inpatient or two outpatient diagnostic codes (i.e., International Classification of Disease, Ninth and Tenth Revisions, Clinical Modification) or a prescription for a medication to treat diabetes other than metformin monotherapy.

The total study population was 15,946.

**Definitions of Variables**

The exposures race (Black or White) and sex were abstracted from the electronic health record. The outcome, metformin prescription, was electronic health record documentation of at least one outpatient medication prescription containing metformin (i.e., including combination medications) at any time during the cohort period. We defined off-label prescription before the FDA label change as metformin prescription when serum creatinine ≥1.5 mg/dl in men and ≥1.4 mg/dl in women.

Covariates included age, sex, eGFR, hemoglobin A1c (HbA1c), body mass index (BMI), history of comorbid conditions (i.e., hypertension, congestive heart failure, hypoglycemia, acidosis, myocardial infarction, liver disease, and AKI), and antidiabetic medication prescription other than metformin (i.e., insulins, sulfonylureas, and all other hypoglycemic agents). In each period, we used the first measured outpatient serum creatinine value and eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation. We categorized eGFR into four groups (≥90 [G1],...
60–89 [G2], 45–59 [G3a], and 30–44 [G3b]) according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines.23 We used the first HbA1c and BMI values in each 9-month cohort period. In each cohort, the baseline date was considered the first serum creatinine measurement date during the 9-month period. Comorbid conditions were identified by the presence of relevant diagnostic codes at any time prior to the baseline date. Glucose-lowering medication prescription other than metformin was captured in the same way of defining metformin prescription.

Negative Control Outcome
To evaluate for temporal trends not specific to metformin, we selected sulfonylurea prescription as a negative control outcome because the prescription of this medication was expected to be independent of the FDA metformin label change (i.e., the metformin–related policy change is irrelevant to the frequency of sulfonylurea prescription).

Statistical Analyses
We described baseline characteristics of the study population by race in each period prevalent cohort. We compared the prevalence of metformin prescription before and after the FDA label change, stratified by eGFR within each race. We assessed the proportion of off-label metformin prescription by race. We used Poisson regression with a robust variance clustered by individual to calculate the prevalence ratio (PR) for metformin prescription in Black patients compared with White patients across eGFR categories in each cohort. We formally tested whether the PR in each eGFR category after the label change was different from corresponding PR before the label change using three-way interaction terms (race × eGFR category × period). We performed a complete data analysis as a primary analysis.

For a secondary objective, we examined sex differences in metformin prescription in the same manner as our primary objective of racial differences. For an analysis with a negative control outcome, we assessed both racial and sex differences in sulfonylurea prescription in the same way.

Sensitivity Analyses
First, we performed analyses after imputing missing values of HbA1c and BMI using multiple imputation by chained equations.24 Second, we repeated analyses using average serum creatinine values if patients had at least two serum creatinine measurements available within a 9-month period. Third, we created four additional 9-month period prevalent cohorts before the FDA metformin label change (i.e., baseline comparison periods: [1] August 7, 2012 to May 1, 2013; [2] May 2, 2013 to January 24, 2014; [3] January 25, 2014 to October 19, 2014; and [4] October 20, 2014 to July 14, 2015) to compare with the 9-month period prevalent cohort after the label change, and then, we assessed racial and sex differences in metformin prescription as well as sulfonylurea prescription.

Replication in Nationwide Health System Data with Three Years of Post-Label Change Period
We replicated the analysis in 36 cohorts selected from the OptumLabs Data Warehouse (OLDW). The OLDW contains deidentified administrative claims and electronic health record data, representing a diverse mixture of ages, ethnicities, and geographic regions across the United States.25 After excluding 7 cohorts from a total of 62 cohorts in electronic health record data due to insufficient serum creatinine testing (<5% tested among all patients), we included all cohorts having at least three metformin prescriptions in all categories of race and eGFR. We created one 1-year period prevalent cohort (April 9, 2015 to April 8, 2016) before the FDA label change (i.e., baseline period) and three 1-year period prevalent cohorts after the FDA label change (April 9, 2016 to April 8, 2017; April 9, 2017 to April 8, 2018; and April 9, 2018 to April 8, 2019). Exposure, medication prescription, covariates, and laboratory values were determined in the same manner to Johns Hopkins Medicine. In each of the 36 cohorts, we estimated the adjusted PR for metformin prescription by race and sex across eGFR categories using Poisson regression with a robust variance clustered by individual and three-way interaction terms (race × eGFR category × period). Then, we estimated pooled adjusted PR using random effects meta-analysis. We conducted all analyses using Stata/MP 14.2 (StataCorp, College Station, TX) and considered P values of <0.05 statistically significant. This study was reviewed and approved by the Johns Hopkins School of Medicine Institutional Review Board.

RESULTS
Baseline Characteristics of the Johns Hopkins Medicine Study Population
There were 15,946 patients with diabetes included at least once in the two period prevalent cohorts in the Johns Hopkins Medicine analyses (6579 [41.3%] were in both cohorts). Black patients comprised 4937 (43.4%) and 4784 (42.9%) patients of the pre- and post-period prevalent cohorts, respectively. Black patients were younger, were more often women, had higher eGFR, and had slightly higher HbA1c compared with White patients (all P<0.05) (Table 1). Black patients also had more hypertension, congestive heart failure, acidosis, hypoglycemia, and AKI but less liver disease compared with White patients (all P<0.05).

Racial Differences in Metformin Prescription across eGFR Levels before the FDA Label Change
Low eGFR was associated with a lower prevalence of metformin prescription in both races (all P<0.001). Before the label change, there was a steeper reduction in metformin prescription at eGFR<60 ml/min per 1.73 m² in Black patients (G1, 79.1%; G2, 75.2%; G3a, 57.2%; and G3b, 26.1%) than in
Table 1. Baseline characteristics of the Johns Hopkins Medicine study population (n=15,946)a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before FDA Metformin Label Change</th>
<th>After FDA Metformin Label Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Black</td>
<td>White</td>
</tr>
<tr>
<td>N (%)</td>
<td>4937 (43.4)</td>
<td>6448 (56.6)</td>
</tr>
<tr>
<td>Age, yr, mean (SD)</td>
<td>59.3 (12.7)</td>
<td>62.6 (12.3)</td>
</tr>
<tr>
<td>Women</td>
<td>2948 (59.7)</td>
<td>2990 (46.4)</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m², mean (SD)</td>
<td>83.8 (26.2)</td>
<td>76.9 (21.3)</td>
</tr>
<tr>
<td>eGFR category, ml/min per 1.73 m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1: eGFR ≥ 90</td>
<td>2031 (41.1)</td>
<td>1979 (30.7)</td>
</tr>
<tr>
<td>G2: eGFR of 60–89</td>
<td>1908 (38.7)</td>
<td>2951 (45.8)</td>
</tr>
<tr>
<td>G3a: eGFR of 45–59</td>
<td>607 (12.3)</td>
<td>977 (15.1)</td>
</tr>
<tr>
<td>G3b: eGFR of 30–44</td>
<td>391 (7.9)</td>
<td>541 (8.4)</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)b</td>
<td>34.1 (8.0)</td>
<td>33.9 (7.5)</td>
</tr>
<tr>
<td>Missing BMI</td>
<td>232 (4.7)</td>
<td>331 (5.1)</td>
</tr>
<tr>
<td>HbA1c, %, mean (SD)c</td>
<td>7.92 (1.85)</td>
<td>7.61 (1.58)</td>
</tr>
<tr>
<td>History of comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3973 (80.5)</td>
<td>4909 (76.1)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>434 (8.8)</td>
<td>435 (6.8)</td>
</tr>
<tr>
<td>Acidosis</td>
<td>164 (3.3)</td>
<td>125 (1.9)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>238 (4.8)</td>
<td>273 (4.2)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>213 (4.3)</td>
<td>335 (5.2)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>261 (5.3)</td>
<td>647 (10.0)</td>
</tr>
<tr>
<td>AKI</td>
<td>334 (6.8)</td>
<td>263 (4.1)</td>
</tr>
<tr>
<td>Median day (IQI) between the first eGFR measurement and the first antidiabetes prescription</td>
<td>0 (−51 to 47)</td>
<td>0 (−51 to 54)</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, data are reported as number (percentage) of patients. IQI, interquartile interval.

aOnly for patients with BMI values (n=15,286).
bOnly for patients with HbA1c values (n=15,946).
cOnly for patients with HbA1c values (n=10,966).

Racial Differences in Metformin Prescription across eGFR Levels after the FDA Label Change

Post-label change, there was a significant increase in metformin prescription in Black patients with eGFR of 30–44 ml/min per 1.73 m² from 26.1% to 32.6%; P=0.02 (Figure 1A). There was no change among White patients within the same eGFR category (P=0.29). There was no significant difference in metformin prescription before and after the label change in either race at eGFR=45 ml/min per 1.73 m². There was also no apparent difference by sex (Supplemental Figure 1).

The racial disparity in metformin prescription at eGFR of 30–44 ml/min per 1.73 m² before the label change (adjusted PRGFR of 30–44 = 0.65; 95% CI, 0.52 to 0.82) was significantly attenuated and no longer significant after the label change (adjusted PRGFR of 30–44 = 0.90; 95% CI, 0.74 to 1.09; P value for interaction by period = 0.04) (Table 2). Similar to the period before the label change, there was no racial difference in metformin prescription among patients with eGFR=45 ml/min per 1.73 m² in the period after the label change.

Sex Differences in Metformin Prescription across eGFR Levels

Baseline characteristics of the Johns Hopkins Medicine study population by sex and period are shown in Supplemental Table 1. Men were 28% less likely to be prescribed metformin compared with women at eGFR of 30–44 ml/min per 1.73 m² before the label change (adjusted PRGFR of 30–44 = 0.72; 95% CI, 0.58 to 0.88) (Table 3). This difference was slightly attenuated after the label change (adjusted PRGFR of 30–44 = 0.79; 95% CI, 0.65 to 0.96), but the difference in PRs pre- and post-label change was not statistically significant.
Analyses with a Negative Control Outcome:
Sulfonylurea Prescription
There was no signifi-
cant difference in sulfonylurea prescrip-
tion by race nor was there a difference in sulfonylurea pre-
scription between the two period prevalent cohorts in all
eGFR categories (Figure 1B, Table 4). In both periods, men
were more likely to receive sulfonylurea prescription com-
pared with women except for at eGFR of 30–44 ml/min per
1.73 m², where sulfonylurea prescription was similar be-
tween men and women (Table 4).

Sensitivity Analyses
Across all of the analyses of metformin and sulfonyl-
urea prescription by race and sex, results were materi-
ally unchanged in analyses with multiple imputations
of missing HbA1c and BMI or in analyses using average

Figure 1. Under the FDA’s serum creatinine-based metformin label, there was a steeper reduction in metformin prescription at
eGFR<60 ml/min per 1.73 m² in Black patients than in White patients. After FDA’s revision to an eGFR-based label, there was a
significant increase in metformin prescription only in Black patients with eGFR of 30-44 ml/min per 1.73 m² (A). There was no difference
in sulfonylurea prescription (the negative control outcome) by race, nor was there a change in sulfonylurea prescription after the label
change in all eGFR categories (B).
Table 2. Association of race (Black versus White) with metformin prescription across eGFR levels among patients with diabetes in Johns Hopkins Medicine

<table>
<thead>
<tr>
<th>Statistics</th>
<th>eGFR Category, ml/min per 1.73 m²</th>
<th>eGFR ≥90</th>
<th>eGFR of 60–89</th>
<th>eGFR of 45–59</th>
<th>eGFR of 30–44</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Black</td>
<td>White</td>
<td>Black</td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>Metformin prescription, %</td>
<td>Before the FDA label change, n=11,385</td>
<td>79.1</td>
<td>78.4</td>
<td>75.2</td>
<td>76.2</td>
</tr>
<tr>
<td></td>
<td>After the FDA label change, n=11,140</td>
<td>78.5</td>
<td>78.5</td>
<td>74.2</td>
<td>76.8</td>
</tr>
</tbody>
</table>

Adjusted PR (95% CI), Black versus White

Complete case analysis

| Before the FDA label change, n=6913 | 1.02 (0.99 to 1.05) | 0.98 (0.95 to 1.01) | 0.97 (0.89 to 1.05) | 0.90 (0.74 to 1.09) |
| After the FDA label change, n=6705 | 1.02 (0.99 to 1.05) | 0.99 (0.96 to 1.02) | 0.92 (0.85 to 1.01) | 0.90 (0.74 to 1.09) |

Analysis with MICE

| Before the FDA label change, n=11,385 | 1.02 (0.95 to 1.10) | 1.01 (0.95 to 1.09) | 0.93 (0.82 to 1.07) | 0.66 (0.52 to 0.84) |
| After the FDA label change, n=11,140 | 1.01 (0.94 to 1.09) | 1.00 (0.94 to 1.08) | 0.90 (0.79 to 1.04) | 0.91 (0.73 to 1.13) |

Analysis with average serum creatinine values

| Before the FDA label change, n=6913 | 1.02 (0.99 to 1.06) | 0.98 (0.95 to 1.02) | 0.95 (0.86 to 1.04) | 0.68 (0.54 to 0.87) |
| After the FDA label change, n=6705 | 1.02 (0.99 to 1.05) | 0.99 (0.96 to 1.02) | 0.93 (0.86 to 1.01) | 0.85 (0.68 to 1.07) |

MICE, multiple imputation by chained equations.

aAdjusted for age, race, eGFR, HbA1c, BMI, history of comorbidities (i.e., hypertension, myocardial infarction, congestive heart failure, liver disease, acidosis, hypoglycemia, and AKI), insulin use, sulfonylurea use, and other glucose-lowering agent use.

bAdjusted for age, sex, eGFR, HbA1c, BMI, history of comorbidities (i.e., hypertension, myocardial infarction, congestive heart failure, liver disease, acidosis, hypoglycemia, and AKI), insulin use, sulfonylurea use, and other glucose-lowering agent use.

cAdjusted PR after the label change was significantly different from corresponding PR before the label change (P value for interaction by period: complete case analysis =0.04, analysis with MICE =0.01, and analysis with average serum creatinine values =0.06).

Metformin prescription was consistently lower in Black patients compared with White patients at eGFR of 30–44 ml/min per 1.73 m² in all five baseline comparison periods before the label change (Figure 2A), whereas sulfonylurea prescription was consistently similar between Black patients and White patients in the same eGFR category and time period (Figure 2B).

Similarly, metformin prescription was consistently lower in men compared with women at eGFR of 30–44 ml/min per 1.73 m² in all five baseline comparison periods before the label change (Figure 2C), whereas sulfonylurea prescription was consistently similar between men and women in the same eGFR category and time period (Figure 2D).

Replication Analyses: Race and Sex Differences in Metformin Prescription

There were 1,051,723 patients with diabetes during the 4-year study period of the replication cohorts. Baseline characteristics of patients in the 36 individual cohorts by race and period were similar, with the exception of a slightly higher prevalence of diabetes among women compared to men (Table 3).

Table 3. Association of sex (men versus women) with metformin prescription across eGFR levels among patients with diabetes in Johns Hopkins Medicine

<table>
<thead>
<tr>
<th>Statistics</th>
<th>eGFR Category, ml/min per 1.73 m²</th>
<th>eGFR ≥90</th>
<th>eGFR of 60–89</th>
<th>eGFR of 45–59</th>
<th>eGFR of 30–44</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>Metformin prescription, %</td>
<td>Before the FDA label change, n=11,385</td>
<td>81.2</td>
<td>76.6</td>
<td>77.3</td>
<td>74.2</td>
</tr>
<tr>
<td></td>
<td>After the FDA label change, n=11,140</td>
<td>79.7</td>
<td>77.5</td>
<td>76.9</td>
<td>74.7</td>
</tr>
</tbody>
</table>

Adjusted PR (95% CI), men versus women

Complete case analysis

| Before the FDA label change, n=6913 | 1.07 (1.04 to 1.10) | 1.05 (1.02 to 1.08) | 0.93 (0.86 to 1.01) | 0.72 (0.58 to 0.88) |
| After the FDA label change, n=6705 | 1.04 (1.01 to 1.07) | 1.01 (0.98 to 1.04) | 0.94 (0.86 to 1.02) | 0.79 (0.65 to 0.96) |

Analysis with MICE

| Before the FDA label change, n=11,385 | 1.07 (1.04 to 1.10) | 1.04 (1.01 to 1.08) | 0.95 (0.89 to 1.03) | 0.80 (0.67 to 0.95) |
| After the FDA label change, n=11,140 | 1.04 (1.01 to 1.07) | 1.04 (1.01 to 1.07) | 0.96 (0.89 to 1.03) | 0.90 (0.76 to 1.05) |

Analysis with average serum creatinine values

| Before the FDA label change, n=6913 | 1.08 (1.04 to 1.12) | 1.06 (1.03 to 1.10) | 0.90 (0.82 to 0.99) | 0.69 (0.55 to 0.87) |
| After the FDA label change, n=6705 | 1.05 (1.01 to 1.09) | 1.03 (1.00 to 1.07) | 0.93 (0.85 to 1.02) | 0.74 (0.59 to 0.93) |

MICE, multiple imputation by chained equations.

aAdjusted for age, race, eGFR, HbA1c, BMI, history of comorbidities (i.e., hypertension, myocardial infarction, congestive heart failure, liver disease, acidosis, hypoglycemia, and AKI), insulin use, sulfonylurea use, and other glucose-lowering agent use.
are shown in Supplemental Table 2, and those by sex and period are shown in Supplemental Table 3.

Before the label change, Black patients were 31% less likely to be prescribed metformin compared with White patients at eGFR of 30–44 ml/min per 1.73 m² (adjusted \( \text{PR}_{\text{eGFR \geq 30–44}} = 0.69; \) 95% CI, 0.66 to 0.73) (Table 5). Metformin prescription increased at eGFR of 30–44 ml/min per 1.73 m² in both races over time after the label change (Black: 24.6%–29.9% and White: 38.5%–42.1%; all \( P<0.001 \)). Racial disparities in metformin prescription were significantly attenuated by the third year after the label change but still existed (adjusted \( \text{PR}_{\text{eGFR \geq 30–44}} = 0.77; \) 95% CI, 0.72 to 0.83; \( P \) value for interaction by period =0.003). There were no changes in PRs for metformin prescription (Black versus White) between the periods before and after the label change at eGFR>45 ml/min per 1.73 m².

Before the label change, men were 24% less likely to be prescribed metformin compared with women at eGFR of 30–44 ml/min per 1.73 m² (adjusted \( \text{PR}_{\text{eGFR \geq 30–44}} = 0.76; \) 95% CI, 0.73 to 0.79) (Table 5). This difference was significantly attenuated by the third year after the label change (adjusted \( \text{PR}_{\text{eGFR \geq 30–44}} = 0.85; \) 95% CI, 0.83 to 0.88; \( P \) value for interaction by period <0.001). Similarly, men were 6% less likely to be prescribed metformin compared with women at eGFR of 45–59 ml/min per 1.73 m² before the label change (adjusted \( \text{PR}_{\text{eGFR \geq 45–59}} = 0.94; \) 95% CI, 0.92 to 0.96), a difference that was no longer observed by the third year after the label change (adjusted \( \text{PR}_{\text{eGFR \geq 45–59}} = 1.00; \) 95% CI, 0.99 to 1.02; \( P \) value for interaction by period <0.001).

**DISCUSSION**

In this study spanning multiple United States health systems, moving from a serum creatinine–based to an eGFR-based indication for metformin reduced racial disparities in the prescription of metformin among patients with diabetes and moderate...
CKD. Our findings were specific to metformin prescription, showing no racial difference in sulfonylurea prescription (the negative control outcome) either before or after the metformin label change. Interestingly, we also saw attenuation in sex disparities in metformin prescription among patients with mild to moderate CKD after the label change, with men with mild CKD achieving parity in the 3 years after the change to an eGFR-based label. These results are the first, to the best of our knowledge, to quantify the effect of the FDA’s revision from a serum creatinine–based to an eGFR-based metformin label on disparities in prescribing metformin using real-world clinical data.

The Institute of Medicine states that reducing racial disparities in health care is one of the top strategic priorities for United States health care.26 There are racial disparities in both the burden and outcomes of diabetes. The prevalence of diabetes is almost two times as high in Black individuals compared with White individuals,1 and Black patients have a disproportionately high burden of diabetic CKD compared with White patients.27,28 Metformin, the first-line therapy for diabetes, is at least equally effective in Black patients compared with White patients.29,30 Moreover, metformin use is associated with a lower risk of mortality compared with nonuse in
Table 5. Association of race (Black versus White) and sex (men versus women) with metformin prescription across eGFR levels among patients with diabetes in replicating cohorts

<table>
<thead>
<tr>
<th>Statistics</th>
<th>eGFR Category, ml/min per 1.73 m²</th>
<th>Black</th>
<th>White</th>
<th>Black</th>
<th>White</th>
<th>Black</th>
<th>White</th>
<th>Black</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eGFR ≥ 90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>before the FDA label change</td>
<td>87.5</td>
<td>85.5</td>
<td>87.5</td>
<td>85.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>after the label change—first year</td>
<td>87.5</td>
<td>85.5</td>
<td>87.5</td>
<td>85.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>after the label change—second year</td>
<td>87.5</td>
<td>85.5</td>
<td>87.5</td>
<td>85.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>after the label change—third year</td>
<td>87.5</td>
<td>85.5</td>
<td>87.5</td>
<td>85.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted PR (95% CI), men versus women</td>
<td>1.04 (1.03 to 1.05)</td>
<td>0.96 (0.95 to 0.97)</td>
<td>0.89 (0.88 to 0.90)</td>
<td>0.78 (0.76 to 0.80)</td>
<td>35.6%</td>
<td>34.5%</td>
<td>34.6%</td>
<td>33.5%</td>
<td></td>
</tr>
</tbody>
</table>

Association of race with metformin prescription

Metformin prescription, %

<table>
<thead>
<tr>
<th></th>
<th>Black</th>
<th>White</th>
<th>Black</th>
<th>White</th>
<th>Black</th>
<th>White</th>
<th>Black</th>
<th>White</th>
<th>Black</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>before the FDA label change</td>
<td>80.0</td>
<td>78.0</td>
<td>78.0</td>
<td>79.0</td>
<td>51.4</td>
<td>64.5</td>
<td>24.6</td>
<td>35.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after the label change—first year</td>
<td>80.0</td>
<td>78.0</td>
<td>78.0</td>
<td>79.0</td>
<td>52.9</td>
<td>64.9</td>
<td>25.1</td>
<td>38.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after the label change—second year</td>
<td>80.0</td>
<td>78.0</td>
<td>78.0</td>
<td>79.0</td>
<td>53.6</td>
<td>65.4</td>
<td>28.1*</td>
<td>39.6*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after the label change—third year</td>
<td>80.0</td>
<td>78.0</td>
<td>78.0</td>
<td>79.0</td>
<td>56.5a</td>
<td>67.0a</td>
<td>29.9a</td>
<td>42.1a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Prevalence of metformin use was significantly different from corresponding prevalence before the label change (P < 0.05).

Adjusted PR after the label change was significantly different from corresponding prevalence before the label change (P < 0.05).

Adjusted PR after the label change was significantly different from corresponding prevalence before the label change (P < 0.05).

Adjusted PR after the label change was significantly different from corresponding prevalence before the label change (P < 0.05).

Adjusted PR after the label change was significantly different from corresponding prevalence before the label change (P < 0.05).

Adjusted PR after the label change was significantly different from corresponding prevalence before the label change (P < 0.05).

Adjusted PR after the label change was significantly different from corresponding prevalence before the label change (P < 0.05).

mild to moderate CKD,31 without increasing the risk of acidosis.32 Despite these facts, we found a lower prevalence of metformin prescription in Black patients with mild to moderate CKD compared with White counterparts, particularly prior to the change in the FDA label.

A previous study reported low use of metformin in low eGFR under the creatinine-based label.12 Our work expands on this literature by demonstrating a more prominent reduction in metformin prescription with low eGFR in Black patients than in White patients and in men than in women. These findings were predicted by a previous study suggesting a larger effect by the use of eGFR rather than serum creatinine on expanding metformin indications in Blacks compared with Whites and in men compared with women.16

Similar to a previous study in which off-label metformin use was reported in 4.5% of patients,33 we found that, pre-label change, metformin was prescribed off label in 5.9% of Black patients and 4.1% of White patients. Despite the FDA's restriction on metformin use in CKD according to serum creatinine in the past, the American Diabetes Association, KDIGO, the European Association for the Study of Diabetes, and United Kingdom National Institute of for Health and Care Excellence all previously suggested the use of metformin at GFR of 45–59 ml/min per 1.73 m² and cautious use of metformin at GFR of 30–44 ml/min per 1.73 m².23,34,35 These societies' recommendation may have affected metformin prescription even prior to the FDA label change.

Our study highlights the potential benefit of eGFR-based labels for optimizing medication prescription. How best to estimate GFR has been studied extensively. The KDIGO guidelines recommend estimating GFR using creatinine and the CKD-EPI 2009 equation, with eGFR on the basis of both creatinine and cystatin as generally the most accurate.23 Because of differences in serum creatinine by race and sex, the CKD-EPI equation contains a coefficient for each as well as age; cystatin-based eGFR contains age and sex only. There exist some concerns regarding the use of race to estimate GFR.36

The potential benefit of removing race in creatinine-based eGFR computation should be balanced with potential harms (e.g., underdosing medications or falsely labeling a patient as having CKD). Our study suggests medication dosing regimens that rely on serum creatinine alone without accounting for race may cause racial disparities in medication use.

The National Kidney Disease Education Program suggests using eGFR or estimated creatinine clearance (eClcr) by the Cockcroft–Gault Equation37 for drug indication/dosing...
guidance. Of note, eClcr may also result in misclassification by race because there is no accounting for the differential creatinine production by race in the Cockcroft–Gault formula. For most drugs, FDA labels were developed prior to the uniform reporting of eGFR calculated from standardized serum creatinine values. Therefore, eClcr is the most commonly used guidance on FDA labels for drug prescribing guidance. However, the FDA also occasionally provides drug labels on the basis of serum creatinine. For example, the FDA-approved label for apixaban in 2012 states that dose reduction is indicated not on a specific eGFR or eClcr but rather, when two of the following three criteria are met: age ≥80 years, body weight ≤60 kg, and serum creatinine ≥1.5 mg/dl. This label may inadvertently cause underdosing in Black patients compared with White patients, which might lead to worse clinical outcomes. Going forward, the FDA may want to avoid serum creatinine–based dosing recommendations in the label of newly approved drugs.

There are several limitations in this study. First, each analysis covered different periods. In Johns Hopkins Medicine, we evaluated only 9 months before and after the label change, which might introduce bias if there was seasonality in metformin prescription or might be too short to see the true effect of the label change. However, results were consistent in the replication cohorts with data that extended 3 years after the label change. Second, we could not adjust for socioeconomic status, an important factor for providers to consider in prescribing medications. However, metformin is relatively inexpensive, and our study population consisted of insured patients who were taking at least one glucose-lowering medication; thus, the effect of socioeconomic status may be minimal. Third, comorbidities were ascertained by diagnostic codes, which may be insensitive. Fourth, medication prescription may not be a true reflection of use. Nonetheless, a prescription is the necessary first step for medication use, and our study focused on differences in providers’ prescription patterns by race and sex. Fifth, creatinine measurement and prescription were not necessarily concomitant, although they were within 9 months of each other. Approximately half of serum creatinine measurements were after the metformin prescription in a given 9-month period. However, metformin does not have an acute effect on GFR. Sixth, we were unable to quantify the effect of education campaigns to increase provider awareness after the label change, particularly in the replication cohorts, where such campaigns are likely to be diverse and heterogeneous. Seventh, we evaluated metformin prescription without regard to whether it was a new or continued prescription. It is worth noting that the FDA revised label allowed the continuation of metformin but did not recommend initiation of metformin at eGFR of 30–44 ml/min per 1.73 m². Eighth, we could not examine whether metformin prescribing patterns differed by provider types.

Despite these limitations, our study is the first to evaluate racial and sex differences in metformin prescription across the range of eGFR using real-world data from multiple health systems under both the FDA serum creatinine– and eGFR-based metformin labels. We used rigorous methods to ensure the validity of our findings, including a negative control outcome, multiple baseline comparison periods, and analysis with multiple imputation. We found consistent results between primary analyses with a single health system and meta-analyses of 36 large replication cohorts.

In conclusion, our study shows that Black patients with diabetes and moderate CKD were significantly less likely to receive metformin prescription compared with White counterparts under the FDA serum creatinine–based metformin label. This disparity was also present by sex and improved following the introduction of the FDA eGFR-based metformin label. This study suggests that drug dosing recommendations solely on the basis of serum creatinine may inadvertently cause racial and sex disparities in medication use.

ACKNOWLEDGMENTS

M. Grams and J.-I. Shin designed the study; Y. Sang and J.-I. Shin analyzed data; S. Ballew, A. Chang, J. Coresh, S. Dunning, L. Inker, and E. Selvin interpreted data; M. Grams supervised the analysis; J.-I. Shin drafted the manuscript; S. Ballew, A. Chang, J. Coresh, S. Dunning, L. Inker, and E. Selvin provided critical comments on the manuscript; M. Grams and J.-I. Shin revised the manuscript; S. Ballew, A. Chang, J. Coresh, S. Dunning, M. Grams, L. Inker, Y. Sang, E. Selvin, and J.-I. Shin approved the final version of the manuscript; and M. Grams and J.-I. Shin take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

J. Coresh reports grants from the National Kidney Foundation and the National Institutes of Health, outside the submitted work. M. Grams reports grants from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases, grants from the National Kidney Foundation, and nonfinancial support from DCI, outside the submitted work. L. Inker reports grants from Reata Pharmaceuticals, grants from Omeros Corporation, grants from Retrophin, grants from Otsuka, and other from Tricida, outside the submitted work. J.-I. Shin reports grants from Merck, outside the submitted work.

DISCLOSURES

All authors have nothing to disclose.

FUNDING

The project described was supported by National Institute of Diabetes and Digestive and Kidney Diseases grants R01DK115534 (principal investigators:...
M. Grams and L. Inker) and K01DK121825 (principal investigator: J.-I. Shin).
J. Coresh reports grants from the National Institutes of Health and grants from
the National Kidney Foundation during the conduct of the study. L. Inker
reports grants from the National Institute of Diabetes and Digestive and Kid-
ney Diseases during the conduct of the study. E. Selvin reports grants from
the National Institutes of Health during the conduct of the study. J.-I. Shin reports
grants from the National Institutes of Health during the conduct of the study.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at
DCSupplemental.
Supplemental Figure 1. Prevalence of metformin prescription
across eGFR levels among patients with diabetes in Johns Hopkins
Medicine stratified by race and sex.
Supplemental Table 1. Baseline characteristics of the Johns Hop-
skins Medicine study population by sex and period.
Supplemental Table 2. Baseline characteristics of the study pop-
ulation in replicating cohorts from OptumLabs Database Warehouse
by race and period.
Supplemental Table 3. Baseline characteristics of the study pop-
ulation in replicating cohorts from OptumLabs Database Warehouse
by sex and period.

REFERENCES

1. Centers for Disease Control and Prevention: National Diabetes Statis-
tics Report, 2017, Atlanta, GA, Centers for Disease Control and
Prevention, US Department of Health and Human Services, 2017
2. Campbell PT, Newton CC, Patel AV, Jacobs EJ, Gaspurt SM: Diabetes
and cause-specific mortality in a prospective cohort of one million U.S.
of new-onset kidney disease in a community-based population. JAMA
291: 844–850, 2004 14970063
Association Task Force on Practice Guidelines: 2013 ACC/AHA
guideline on the assessment of cardiovascular risk: A report of the
American College of Cardiology/American Heart Association task force
on practice guidelines [published correction appears in Circulation 129
24222018
as a risk factor for incident chronic kidney disease and end-stage renal
disease in women compared with men: A systematic review and meta-
analyses. Endocrine 55: 66–76, 2017 27477292
6. Qaseem A, Barry MJ, Humphrey LL, Forciea MA; Clinical Guidelines
Committee of the American College of Physicians: Oral pharmacologic
treatment of type 2 diabetes mellitus: A clinical practice guideline
update from the American College of physicians. Ann Intern Med 166:
279–290, 2017 28055075
of Clinical Endocrinologists and American College of Endocrinolo-
y on the comprehensive type 2 diabetes management algorithm
30742570
8. American Diabetes Association: 9. Pharmacologic approaches to gly-
Care 42(Suppl 1): S90–S102, 2019 30559235
9. International Diabetes Federation: Recommendations for managing
type 2 diabetes in primary care, 2017. Available at: www.idf.org/
PJ, Tuttle K, et al.: Diabetes and CKD in the United States pop-
29054846
11. Thomas MC, Cooper ME, Zimet P: Changing epidemiology of type 2
diabetes mellitus and associated chronic kidney disease. Nat Rev
Nephrol 12: 73–81, 2016 26553517
12. Flory JH, Hennessy S: Metformin use reduction in mild to moderate
renal impairment: Possible inappropriate curbing of use based on Food
and Drug Administration contraindications. JAMA Intern Med 175:
458–459, 2015 25561419
13. Lipska KJ, Bailey CJ, Inzucchi SE: Use of metformin in the setting of
mild-to-moderate renal insufficiency. Diabetes Care 34: 1431–1437,
2011 21617112
food and drug administration to change prescribing guidelines: The
15. Food and Drug Administration: Drug Safety Communication (4-8-
2016): FDA revises warnings regarding use of the diabetes medicine
metformin in certain patients with reduced kidney function, 2016.
Available at: https://www.fda.gov/media/96771/download. Accessed
September 20, 2019
Surveillance Team: Potential impact of prescribing metformin accord-
ing to eGFR rather than serum creatinine. Diabetes Care 38:
2059–2067, 2015 26307607
17. Jones CA, McQuillan GM, Kusek JW, Eberhardt MS, Herman WH,
Coresh J, et al.: Serum creatinine levels in the US population: Third
national health and nutrition examination survey. Am J Kidney Dis 32:
992–999, 1998 9856515
cociation of african ancestry and elevated creatinine in the coronary
artery risk development in young adults (CARDIA) study. Am J Nephrol
31: 202–208, 2010 20029176
19. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modifi-
cation of Diet in Renal Disease Study Group: A more accurate
method to estimate glomerular filtration rate from serum creatinine:
10075613
20. Heymsfield SB, Artega C, McManus C, Smith J, Moffitt S: Measure-
ment of muscle mass in humans: Validity of the 24-hour urinary creati-
21. National Committee for Quality Assurance (NCQA): HEDIS measures and
technical resources, 2018. Available at: https://www.ncqa.org/
hedis/measures/. Accessed October 20, 2019
HI, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collab-
oration): A new equation to estimate glomerular filtration rate [published
150: 604–612, 2009 19414839
23. Kidney Disease Improving Global Outcomes: KDIGO 2012 clinical
practice guideline for the evaluation and management of chronic kid-
24. White IR, Royston P, Wood AM: Multiple imputation using chained
2011 21225900
25. OptumLabs: OptumLabs and OptumLabs Data Warehouse (OLDW)
Descriptions and Citation. 2019


