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Improving Equity in Medication Use through Better Kidney Function Measurement

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Racial/ethnic and sex disparities with respect to diabetes prevalence and health outcomes are profound and well recognized. Nationally representative data suggest the prevalence of diagnosed and undiagnosed diabetes among adults in the United States is 38% higher among non-Hispanic Blacks (16.4%; 95% CI, 14.7 to 18.2), 27% higher among non-Hispanic Asians (14.9%; 95% CI, 12.0 to 18.2) and 24% higher among Hispanics (14.7%; 95% CI, 12.5 to 17.3) compared with non-Hispanic Whites (11.9%; 95% CI, 10.9 to 13.0).[1] Additionally, Black and Hispanic patients have been demonstrated to shoulder a greater burden of diabetes complications, such as ESKD, retinopathy, neuropathy, and lower extremity amputations.[2] Diabetes prevalence is similar between the sexes (among men, 14.0%; 95% CI, 12.3 to 15.5; among women, 12.0%; 95% CI, 11.0 to 13.2), but women with diabetes have excess risk of macrovascular complications including stroke and coronary heart disease.[3]

Recent data have not demonstrated substantial differences in diabetes quality of care measures, such as frequent glycosylated hemoglobin testing, yearly foot and dilated eye exams, nephropathy testing, and influenza vaccinations, by race/ethnicity among adults, but have identified some differences by sex.[3,4] Public health interventions that increase access to and use of routine care, such as Medicaid expansion, may thus have the greatest effect on reducing racial (not sex) disparities over time.[5] However, differences in diabetes treatment strategies to attain glycemic control may be another understudied contributor to the poorer health outcomes among racial/ethnic minorities and women with diabetes. Although the number of available oral diabetes medications has proliferated in the past decade, metformin remains the recommended first-line agent for diabetes treatment among individuals with normal renal function as well as those with mild-moderate kidney disease due to its high efficacy and favorable side effect profile.[6] Safely expanding metformin use for racial/ethnic minorities and women with diabetes may be a key strategy to diminish existing disparities in health outcomes.

Until recently, the Food and Drug Administration (FDA) recommendations for the prescription of metformin were based on serum creatinine (sCr), a marker of kidney function that is also influenced by a number of determinants that are independent of GFR. Prior research identified race and sex as two variables that may influence creatinine generation; in research cohorts, sCr tended to be higher among self-reported non-Hispanic Black compared with White patients and among men compared with women. Creatinine-based estimating equations for GFR that include coefficients for both of these factors, in addition to age, closely predict measured GFR.[7] Thus, leveraging these equations rather than sCr to guide metformin prescription might lessen differences in metformin prescription by race and sex.[8]

In this issue, Shin *et al.*[9] move beyond conjecture, tangibly demonstrating the effect of clinicians' use of GFR-estimating equations on metformin prescription.[9] The authors identified two 9-month-period prevalent cohorts of adult Black and White patients with diabetes receiving at least one oral hypoglycemic agent who received care from one healthcare system before and after April 8, 2016—the day on which the FDA changed the metformin label to include a contraindication based on eGFR determined by creatinine ($eGFR_{cr}$; <30 ml/min per 1.73 m^2) rather than one based on sCr (>1.4 mg/dl for women or 1.5 mg/dl for men). Black participants in the cohort defined by the 9 months preceding the label change with an eGFR of 30–44 ml/min per 1.73 m^2 were 35% less likely to be prescribed metformin compared with their White counterparts (adjusted prevalence ratio [aPR], 0.64; 95% CI, 0.52 to 0.82). In the cohort defined by the 9 months after the label

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change, this Black-White disparity in metformin prescription was greatly diminished and likely eliminated (aPR, 0.90; 95% CI, 0.74 to 1.09). Metformin prescription for individuals of either race with an eGFR >45 ml/min per 1.73 m^2 did not change. During the same time periods, attenuation in sex-based disparities in metformin prescription for individuals with an eGFR of 30–44 ml/min per 1.73 m^2 also appeared, although the change was less impressive and nonstatistically significant (aPR before label change, 0.72; 95% CI, 0.58 to 0.88; aPR after label change, 0.79; 95% CI, 0.65 to 0.96). Importantly, these findings were robust to multiple sensitivity analyses and were unique to the prescription of metformin compared with sulfonylureas, which are oral diabetes medications that served as a negative control because their prescribing recommendations did not change during the study time period. Additionally, data from a large healthcare database that included >1 million individuals across 36 different cohorts replicated the results.

The Shin *et al.* study could not ascertain the exact reasoning behind the rapid change in prescription patterns, nor whether changes were consistent among individual clinicians, which would demonstrate uniform application of the new federal recommendations. However, the findings do strongly suggest the sizable effect that federal agencies have in guiding care delivery. An important next step will be to explore whether changes in metformin prescription patterns are associated with undesirable increases in potential adverse events, namely lactic acidosis, or with the anticipated decreases in racial/sex disparities in diabetes complications.

The FDA metformin label change and the subsequent effect constitute a large step forward toward equity in quality of diabetes care delivery. The label change raises other concerns. $eGFR_{cr}$ is an improvement over sCr alone to guide the prescription of medications that are renally cleared; however, the underlying physiologic mechanisms behind purported racial differences in creatinine generation and clearance are not well understood.[7] Application of $eGFR_{cr}$ to guide medication prescription and other clinical decisions based on Black versus non-Black race (a nonbiologic construct) can contribute to racial/ethnic disparities in health outcomes, not only for self-identified Black adults but also for other non-Black, non-White populations. Incorporation of race into clinical algorithms is a subject of increasing debate within the medical community, including but not limited to nephrology.[10] Cystatin C–based GFR estimation is one alternative to $eGFR_{cr}$ that is not influenced by race, and was previously predicted to expand metformin prescription compared with sCr even more than $eGFR_{cr}$ among adults with diabetes.[8] However, there are current pitfalls with widespread use of eGFR based on cystatin C, including lack of a national measurement standard that prevents comparisons across different laboratories and healthcare providers, as well as the relatively high cost.[11]

More investment is needed to identify a reliable, convenient, and cost-favorable eGFR test that is based solely on underlying biologic mechanisms, rather than on social constructs that can be misinterpreted and misapplied. If federal agencies adopt such a test to set recommendations for clinical decision making, the United States healthcare delivery system will make great strides toward the delivery of personalized medicine that maximizes public health while preventing racial/ethnic disparities in health outcomes. The rapid change in patterns of metformin prescribing after the FDA label change that Shin *et al.* documents indicates that clinicians are ready to act upon sound, evidence-based guidance. What are we waiting for?

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