Kidney Medicine

Disparities in the Use of SGLT2 Inhibitors and Glucagon-like Peptide-1 Receptor Agonists in Adults With CKD in the United States

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Disparities in chronic kidney disease (CKD) exist at all CKD stages, particularly in the most vulnerable populations. In the United States, racial and ethnic minority groups tend to have higher prevalence of CKD compared to their White counterparts.[1,2] More specifically, compared to White individuals, African Americans had 3 to 4 times higher rates of kidney failure and are less likely to receive CKD care before developing kidney failure. Although African Americans constitute 13% of the general population, more than a third of individuals awaiting a kidney transplant are African American. African Americans also have the lowest cumulative incidence of living donor kidney transplants irrespective of insurance payer status and the highest mortality risk for individuals with estimated glomerular filtration (eGFR) rates 45 to 95 mL/min/1.73 m^2.[2] Given these statistics, it is of paramount importance to ensure that there is equitable access to guideline-directed medical therapies to reduce risk factors for CKD progression.

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After decades of mainstay glucose-lowering agents, including insulin, metformin, and sulfonylureas, new classes of glucose-lowering medications to optimize diabetes control that also have potential kidney benefits have been introduced. In particular, sodium glucose cotransporter 2 (SGLT2) inhibitors were introduced in 2013 in the United States,[3] whereas the first glucagon-like peptide (GLP)-1 receptor agonist was approved by the Food and Drug Association in 2005 to maximize glucose management.[4,5] The pillars of guideline-directed medical therapies to reduce CKD progression over the past 2 decades focused on risk factor reduction related to glucose lowering and blood pressure optimization, specifically focusing on agents that block the renin angiotensin system.[6-8] However, recent, robust, large-scale cardiovascular and kidney outcomes trials identified SGLT2 inhibitors as having both cardiovascular and kidney protection, and similar studies support the use of GLP-1 receptor agonists for individuals requiring additional glucose lowering beyond baseline therapy and/or at high risk of atherosclerotic disease and for those who are obese and may need further reduction in albuminuria.[7-12]

Between 2013 and 2020, including in 2019 when SGLT2 inhibitors and GLP-1 receptor agonists were included in the American Diabetes Association (ADA) guidelines, general internists and endocrinologists were the most frequent prescribers of these medications, particularly in individuals younger than 65 years compared to those older than 75 years.[13] Since then, guidelines published by the ADA, Kidney Disease: Improving Global Outcomes (KDIGO), and the American Heart Association (AHA) have included SGLT2 inhibitors and GLP-1 receptor agonists, strongly recommending their use in appropriate patients for both cardiovascular and kidney benefit. For example, SGLT2 inhibitors were initially recommended for use in patients with eGFR >30 mL/min/1.73 m^2; however, new indications target eGFR values as low as 20 mL/min/1.73 m^2.[8,14] Unfortunately, despite consensus from KDIGO, the ADA, and the AHA, use of these agents remains consistently and unacceptably low.[15-18] Notably, among 1,375 participants in the National Health and Nutrition Examination Survey (2017-2020) with type 2 diabetes and eGFR >30 mL/min/1.73 m^2, only 5.8% of participants with CKD, congestive heart failure, or atherosclerotic heart disease were using an SGLT2 inhibitor and only 4.4% were using a GLP1 receptor agonist, with substantially less use of SGLT2 inhibitors among the 13% of participants identifying as non-Hispanic Black.[17]

Zhao et al[19] performed a retrospective analysis of 53,029 adult patients who were at least 18 years old with CKD and type 2 diabetes obtained from a 20% random sample of Medicare Part D fee-for-service claims data between 2013 and 2018. The study examined patient data including demographic characteristics, health insurance enrollment, physician visits, and prescription events to assess factors associated with the use of SGLT2 inhibitors or GLP-1 receptor agonists compared to second generation sulfonylureas. The authors used multinomial logistic regression models to examine the elements that contributed to the use of these medications as well as subgroup and sensitivity analyses. At baseline, patients had a mean age of 71 years; approximately 76% identified as White and 14% as Black with CKD stage 3. High proportions of the studied population had cardiovascular disease (66.4%), hypertension (93.1%), and hyperlipidemia (79.6%). At study onset, 10.0% of patients were on an SGLT2 inhibitor, 17.4% were on a GLP-1 receptor agonist, and a much higher proportion (72.6%) were taking a sulfonylurea.

Results from the overall study, as well as sensitivity analyses, demonstrated that more vulnerable patients were less likely to have been initiated on an SGLT2 inhibitor or a GLP-1 receptor agonist. Specifically, patients who were older (greater than or equal to 75 years),

Black compared to White, and with higher Elixhauser comorbid condition scores had lower odds of being prescribed SGLT2 inhibitors or GLP-1 receptor agonists. These results were sustained even after multiple adjustments for clinical factors. In addition, Black patients, regardless of income level (<$60,000 or ≥$60,000), had lower odds of receiving both SGLT2 inhibitors and GLP-1 receptor agonists. Not surprisingly, given the KDIGO guidelines following the time of the current study period, patients with CKD 4-5 (eGFR <30 mL/min/1.73 m^2) were less likely to be initiated on SGLT2 inhibitors.[7] The newest guidelines recommend initiation at an eGFR as low as 20 mL/min/1.73 m^2. Notably, there were lower odds for racial and ethnic minority Hispanic and Asian individuals to be initiated on GLP-1 receptor agonists, whereas the odds were higher for individuals who were female, with higher income, cardiovascular disease, or hyperlipidemia.

One important limitation of the study is the lack of CKD diagnosis by laboratory values. It is known that identification of patients with CKD according to laboratory values (eGFR <60 mL/min/1.73 m^2) typically exceeds CKD diagnosis data based on *International Classification of Diseases Ninth/Tenth Revision* (ICD-9/10) administrative codes, including data extracted from the Medicare database.[20,21] Therefore, the study population may likely have been underestimated. In addition, household median income was based on zip code association that could not be verified, and patients with insurance coverage outside of Medicare Part D were not included in the analyses. Although coverage of SGLT2 inhibitors and GLP-1 receptor agonists on Medicare Part D plans is relatively high, Medicare beneficiaries who are not eligible for subsidies, based on low income levels, often are challenged with high out-of-pocket costs for these newer antidiabetic medications.[22] As such, the study does not encompass assessment of another important group of individuals who would otherwise greatly benefit from these medications. Another critical limitation is that the study included data only on first prescriptions filled following the index date of diagnosis. An important observation of the long-term cardiovascular and kidney benefit from SGLT2 inhibitors and GLP-1 receptor agonists is that primary gains from their use are not recognized for at least 8-12 months following initiation. As a result, the inability to assess persistence of prescribing guideline-directed medical therapies beyond the primary prescription significantly limits the lasting advantage of their use.

This study has important significance because it highlights several aspects related to new therapies that hearken back to the persistently low use of renin angiotensin system blockers, particularly in patients who are considered to be at the highest risk for poorer clinical outcomes. In addition to the relevant racial and ethnic characteristics, these susceptible individuals may subsist at lower socioeconomic positions. As a result, they are more likely to be either uninsured or underinsured, further reducing their ability to afford the high out-of-pocket prices for newer therapies, with subsequent, enormous, enduring costs to not only their individual overall health but also to the general society. A study by O'Brien et al[23] demonstrated that compared with initiation of therapies, such as SGLT2 inhibitors and GLP-1 receptor agonists, use of sulfonylureas and basal insulin is directly associated with poor cardiovascular outcomes. To address the pharmaco-inequity demonstrated in this study, further work needs to be done to understand the mechanisms behind the gaps in care. It is important to understand whether finances are the primary barrier to filling these prescriptions; or whether racial and ethnic differences; equitable access to appropriate medical care; larger, deficient prescribing patterns; or even institutional or regional prescribing practices are at play. For instance, vulnerable patients may be more likely to be cared for by nonspecialists who are less likely to prescribe these drugs. Better understanding of the processes contributing to these inequities is critical to designing effective interventions.

In conclusion, the study by Zhao et al[19] is a well-designed study, albeit with several limitations that preclude generalizability, that expands on existing disparities in CKD. The study strongly supports the need to target populations at greatest risk of CKD progression, especially Black and older patients.

ARTICLE INFORMATION

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