Absolute Benefits From Glucagon-Like Peptide 1 Receptor Agonists and Sodium–Glucose Cotransporter 2 Inhibitors

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Glucagon-like peptide 1 receptor agonists (GLP-1RA) and sodium–glucose cotransporter-2 inhibitors (SGLT2i) are newer prescription medications developed for glucose lowering for individuals with type 2 diabetes (T2D). Both drug classes have been shown to be effective among individuals with T2D for prevention of major adverse cardiovascular events (MACE), heart failure, and adverse renal outcomes (1–3). Accumulating evidence supports that the effectiveness of these drugs for prevention of complications extends to individuals without T2D and with established or increased risk for cardiovascular disease (CVD) or chronic kidney disease (4–6). Recently, these medications were approved for clinical use in the U.S. among individuals without T2D but with obesity, chronic kidney disease, or heart failure (7–9). The baseline cardiovascular risk profiles of these patient populations differ substantially, as does their risk for atherosclerotic CVD, heart failure, and adverse renal outcomes. Summarizing the effect of GLP-1RA and SGLT2i on risk of cardiovascular and renal outcomes across the spectrum of baseline cardiovascular risk will advance our understanding of the efficacy of the different drug classes across heterogenous patient populations. With this understanding, clinicians can better target use of these medications to patients who are more likely to receive clinical benefit and consider alternative therapies where benefit from GLP-1RA or SGLT2i may be minimal.

In this issue of *Diabetes Care*, Rodriguez-Valadez et al. (10) investigated the effect of GLP-1RA and SGLT2i with risk for cardiovascular mortality, MACE, heart failure, and a composite renal outcome. Investigators included published summary data from 22 randomized trials among individuals with and without T2D (totaling over 150,000 participants), 9 trials assessing GLP-1RA, and 13 trials assessing SGLT2i. Investigators used meta-analysis methods to estimate relative and absolute risk for each outcome associated with randomization to addition of GLP-1RA or SGLT2i compared with current therapy or standard of care. Meta-regression was used to assess heterogeneity of each association across background cardiovascular risk, defined by the cardiovascular mortality rate of each trial's control arm. Randomization to GLP-1RA was associated with lower hazard cardiovascular mortality (hazard ratio 0.87; 95% CI 0.80, 0.96), MACE (0.87; 0.79, 0.97), hospitalization for heart failure (0.89; 0.81, 0.99), and composite renal outcome (0.84; 0.73, 0.97). Similar and stronger magnitudes of associations were observed for randomization to SGLT2i, with lower risk for cardiovascular mortality (0.86; 0.81, 0.92), MACE (0.88; 0.82, 0.95), hospitalization for heart failure (0.70; 0.67, 0.74), and composite renal outcome (0.65; 0.58, 0.74). Five-year absolute risk differences for each outcome and drug class association favored randomization to GLP-1RA or SGLT2i, ranging from 0.98% to 4.25% lower absolute risk. Greater absolute risk differences in cardiovascular mortality, MACE, hospitalization for heart failure, and the composite renal outcome comparing the SGLT2i arm with the control arm were observed with higher trial control arm cardiovascular mortality rate, but this heterogeneity was not observed on the relative risk scale. Absolute and relative associations for GLP-1RA versus the control for each outcome did not appear to differ by trial control arm cardiovascular mortality.

The strengths of the study by Rodriguez-Valadez et al. (10) include the large number of international trials and overall sample size, randomized treatment assignment, use of random-effects meta-analysis methods, assessment of bias, and robustness of findings across several sensitivity analyses. By including clinically heterogenous trial study populations, the results of this study can be generalized to broader patient populations than those of the individual studies included in the meta-analysis. Further, this allowed investigators to assess the impact of GLP-1RA and SGLT2i with risk of cardiovascular mortality, MACE, hospitalization for heart failure, and a composite renal outcome across the spectrum of background cardiovascular risk of each trial population (i.e., control arm mortality rate). Investigators did not have access to individual-level data and were limited to using published summary data from each trial, which may

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be susceptible to ecological, publication (selection), and information bias (11). This limits the ability of investigators to standardize definitions of critical variables and study design parameters, such as follow-up time. There were differences in end point definitions across the different trials, particularly for the composite renal outcome. This methodological issue can be thought of as nondifferential misclassification of the outcome (i.e., information bias) and likely contributes to greater imprecision of association summary estimates, which, in addition to the larger variance accompanying use of random-effects meta-analysis methods, will result in more conservative estimates. The investigators did conduct an assessment for risk of bias across studies using the Cochrane Collaboration's methodology (12) and concluded low risk of bias.

The major importance of this work is the quantification of absolute risk reduction for each drug class–outcome association across the spectrum of background cardiovascular risk. Relative risk is helpful for understanding the strength of association when treated (exposed) but has the limitation of being inherently linked to the background risk in the population. In contrast, absolute risk quantifies the amount of disease prevented in the population that is associated with being treated (i.e., cases prevented in the population due to treatment). The greater absolute risk reduction of SGLT2i use with risk of cardiovascular mortality, MACE, hospitalization for heart failure, and the composite renal outcome with higher background cardiovascular risk demonstrates the potential clinical impact of these drugs. The trial populations included in this meta-analysis were enriched with older adults with established CVD risk factors, and results cannot be generalized to younger populations or those with lower background CVD risk. There was substantially greater variance in control arm cardiovascular mortality rate among the trials that assessed SGLT2i use than among the trials of GLP-1RA use. This limits the generalizability and clinical guidance that the GLP-1RA results provide for higher-risk populations. These considerations on generalizability of the study results raise additional potential avenues of research. Because aggregate-level data were used for this study, interrogation of risk reduction for each of these drug classes among specific patient subgroups was not feasible (e.g., sex, race/ethnicity, age, and obesity status). Addressing this gap would advance the authors' mission to develop baseline risk assessment tools to improve clinical decision-making and cost-effectiveness of these drug classes. Fundamental to this discussion and noted by the study authors are the high out-of-pocket costs for patients for these medications on the U.S. market (13,14). Two recent studies that included insured populations of U.S. adults with T2D report lower GLP-1RA and SGLT2i use among individuals with higher atherosclerotic CVD risk and for Asian, Black, and Hispanic U.S. adults of lower socioeconomic status (15,16). Without consideration of the high cost of these medications and removing this economic barrier, inequities in T2D, CVD, and kidney outcomes are sure to be exacerbated.

In conclusion, this study by Rodriguez-Valadez et al. (10) adds to the evidence that GLP-1RA and SGLT2i medications are effective for prevention of cardiovascular mortality, MACE, hospitalization for heart failure, and adverse renal outcomes across higher-risk, clinically heterogeneous patient populations.

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