[1] Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL, USA

[2] Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL, USA

Correspondence to: S M Smith
ssmith@cop.ufl.edu

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Newer drug treatments for type 2 diabetes

Guidance developed in partnership with patients recommends a risk based approach

Jingchuan Guo, [1] Steven M Smith[1, 2]

Over 463 million adults worldwide live with diabetes today, and the prevalence is projected to rise to 700 million by 2045.[1] Meanwhile, diabetes causes 1.5 million deaths annually—more than 60% attributable to cardiovascular disease[2]—and substantially increases the risk of non-fatal cardiovascular events.[3 4] A decades-long strategy of strict glycaemic control was pursued in an effort to mitigate these risks. Yet, we now know that such glucocentric strategies have, at best, only a tenuous causal effect on reducing diabetes related cardiovascular disease and death. Fortunately, that discovery provided an opportunity to refocus efforts, both clinically and in drug development, directly on the outcomes that tend to matter most to patients.

The development of sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists has created substantial opportunities for reducing death and improving cardiovascular and kidney outcomes in people with type-2 diabetes.[5] Large trials have demonstrated the efficacy of these agents in reducing cardiovascular and kidney events in patients with type 2 diabetes who are at increased cardiovascular risk.[6 7] Most major guidelines from professional societies and organisations in North America, Europe, and Asia have subsequently updated recommendations to include use of these newer agents, including guidelines by the UK National Institute of Health,[8] American Diabetes Association,[9] American College of Cardiology,[5] European Association for the Study of Diabetes,[10] European Society of Cardiology,[11] and Chinese Diabetes Society/Chinese Society of Endocrinology.[12]

However, ambiguities and discrepancies exist across these recommendations regarding how best to identify "high-risk" patients.[10] Furthermore, guidelines have used inconsistent approaches to developing recommendations from available evidence, and many have lacked clear decision-making algorithms for balancing benefits and harms of these therapies across subgroups with varying cardiovascular risk. These inconsistencies may explain, at least in part, the persistently low use of these outcome-improving therapies.[13-15]

Now an international panel of clinicians, methodologists, and patient partners seek to address these limitations through development of practical guidelines on the use of SGLT-2 inhibitors and GLP-1 receptor agonists for patients with type 2 diabetes.[16] The central approach is risk based, with recommendations for both drug classes in four patient categories: (*a*) those without established cardiovascular or chronic kidney disease and three or fewer cardiovascular risk factors, (*b*) those without established disease but with more than three risk factors, (*c*) those with either cardiovascular disease or chronic kidney disease, and (*d*) those with both cardiovascular and chronic kidney disease. A fifth recommendation centres on the preferences for SGLT-2 inhibitors or GLP-1 receptor agonists for patients committed to further reducing their risk for cardiovascular and kidney disease.

SGLT-2 inhibitors are recommended for all but the lowest risk group, for whom there is no clear benefit but potential risks, such as genital infections. GLP-1 agonists are recommended only for those with cardiovascular disease, chronic kidney disease, or both, though there is a preference for SGLT-2 inhibitors in such patients. Almost all recommendations are considered weak, reflecting the panel's consideration of the balance between treatment benefits and harms, and other practical issues such as cost and accessibility. These recommendations are broadly similar to recently updated guidelines for patients with established cardiovascular or chronic kidney disease, but the recommendation to use SGLT-2 inhibitors for patients with multiple risk factors has not been widely adopted by other guidelines.

The new recommendations were informed by a comprehensive network meta-analysis and benefit from a clear and consistent representation of the evidence that informed the panel's decisions. Importantly, the outcomes considered were heavily influenced by patient preferences, gathered through multiple approaches. None of the previously published guidelines reported patient partnership. In contrast, the guideline panel for the new recommendations included four patient panellists with type 2 diabetes, formed a separate focus group to elucidate the values and preferences of individuals living with type 2 diabetes, and incorporated a systematic review of prior research on patient preferences. Of course, these patients may not reflect the values and preferences of every patient with type 2 diabetes. Nevertheless, patients are the ultimate end user of all guidelines, and full patient partnership in guideline development should become the norm.

Several cautions are warranted in the implementation of these risk-stratified recommendations. First, the new guidance focuses on improving cardiorenal outcomes. But lifestyle modification, effective glycaemic control to minimise the risk of microvascular disease and detriments in quality of life, and the full range of strategies to reduce cardiovascular risk (including active management of blood pressure and lipids) remain the cornerstones of care for people with type 2 diabetes. Second, evidence supporting these risk-stratified

recommendations is derived from cardiovascular outcome trials enrolling patients with or at high risk of cardiovascular disease. Whether sufficiently robust evidence exists for low risk patients is debatable. Third, the guidance does not consider selection of individual drugs within each of the two therapeutic classes, although evidence suggests possible variation in benefits and risks.[5 17]

There is an urgent need to provide clear messages to individuals with type 2 diabetes, their families, and their healthcare providers to support shared decision making for individualised therapy to optimise cardiovascular and renal health. Practical guidelines—developed by patients, clinicians, and methodologists and with clear, systematically informed recommendations—provide an actionable roadmap to guide the incorporation of potentially lifesaving therapies into patient care.

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