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PERSPECTIVE

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New way, new recommendation: Individualized treatment of novel antidiabetic drugs for people living with type 2 diabetes based on the cardiorenal risks

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Accumulating evidence illustrates the continuous growing prevalence of type 2 diabetes mellitus (T2DM) worldwide. In China, the prevalence of diabetes diagnosed by WHO criteria in adults is rising, with 9.7% in 2007 and 2010, to 10.4% in 2013, and 11.2% in 2017.[1] Cardiovascular disease (CVD), one of the complications of diabetes, is the predominant cause of death among diabetic patients worldwide, which affects 32.2% of all patients with T2DM globally[2] and causes about 50 % of all deaths in the patients with T2DM.[2,3] Therefore, the heavy economic burden of CVD in T2DM has become a major public health problem.[4]

In the past two decades, global fashion guidelines for diabetes shifted from the glucocentric approaches to the prevention of cardiovascular and renal diseases, which are of importance to people who live with type 2 diabetes. This shift owes to the two main reasons. One is the development of cardiovascular outcomes trials (CVOTs) required by the US Food and Drug Administration (FDA) to estimate the cardiovascular safety of antidiabetic drugs; the other reason is the limited effect of intensive glycemic control on CVD which was verified in ADVANCE[5] and Action to Control Cardiovascular Risk in Diabetes (ACCORD)[6] study.

Up to now, most antidiabetic drugs have been proven to be beneficial or at least harmless to the heart and kidney. Much to our excitement, the CVOTs demonstrated that two novel antidiabetic agents, say sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, reduce the occurrence of cardiovascular events and improve the renal damage in people living with type 2 diabetes.[7–11]

It cannot be more exciting to introduce these antidiabetic drugs to help people with type 2 diabetes at risks, but the current situation of their use is not satisfactory. To assess the prevalence of cardiovascular disease in T2DM patients, CAPTURE, the world first noninterventional study, recruited 9823 T2DM patients from 13 countries and regions in 5 continents and found that only 21.9% of T2DM patients had received GLP-1 receptor agonists and/or SGLT2 inhibitors, which was similar in diabetic patients with CVD (21.5%), arteriosclerotic cardiovascular disease (ASCVD) (21.4%), and those without CVD (22.2%).[12] However, this situation is worse in Chinese diabetic patients with ASCVD, only 1.5% of whom received GLP-1 receptor agonists and 5.4% received SGLT-2 inhibitors.[13] The latest reports suggested similar conditions in Chinese people living with diabetes.[14] The available consensuses of ADA and EASD reports, suggest that GLP-1 receptor agonists or SGLT-2 inhibitors should be considered in the appropriate proportion of high-risk patients with T2DM, instead of according to baseline HbA1c or individualized HbA1c.[15] Although a series of cardiovascular risk factors are listed, these consensuses do not clarify how to identify "high-risk" (T2DM patients along with CVD), nor do they give suggestions on how to balance the advantages and disadvantages of the two drugs. Therefore, these consensuses are difficult to promote and apply in individualized comprehensive treatment, which is partly due to the low utilization rate of SGLT-2 inhibitors or GLP-1 receptor agonists.

To improve this situation, an international multidisciplinary team led by Chinese and US experts worked out a new clinical practice guideline for the application of SGLT-2 inhibitors and GLP-1 receptor agonists in T2DM patients[16] based on the integration of the existing articles on systematic review and meta-analysis (including 764 randomized controlled trials, a total of 21,346 patients with type 2 diabetes).[17] Unlike the existing guidelines, this guideline is risk-based, patient

preference-centered for the systematic balancing of risks, benefits, hazards, and preferences of the patients. Furthermore, this guideline provides an approach for individualized diagnosis and therapy of diabetic patients because it calculates the risks and benefits mentioned in the guideline for each patient through the Risk Equations for Complications of Type 2 Diabetes (RECODe). An associated systematic review suggested that RECODe may be the best calibration for risks and benefits and the most ideal comprehensive identification index for CVD, chronic kidney disease (CKD), and heart failure when the localized risk calculator is unapplicable.[18] Finally, this international guideline panel includes the active participation of the patient partners. In general, the guideline suggests that the treatment decisions should be made from the perspective of the patients, with special consideration of the patients' values and preferences, encouraging well-informed treatment choices, and sharing decisions between doctors and patients. Briefly, these recommendations suggest patients with type 2 diabetes were divided into four categories for these drugs based on the cardiovascular risk factors: (1) without established CVD or CKD and ≤ three cardiovascular risk factors, (2) without established CVD or CKD but with >three risk factors, (3) with either CVD or CKD, and (4) with both CVD and CKD. The last recommendation suggests SGLT-2 inhibitors rather than GLP-1 receptor agonists to further reducing patients' risks for cardiovascular and renal disease outcomes. All these considerations fit the clinical scenarios for Chinese endocrinologists in hospitals and family medicine doctors in the primary care.

Although this guideline is glucose-independent, patients with blood glucose levels > 16.7 mmol/L or HbA1c > 9% do not fall in the target population of the guideline for their excess risks of acute complication of diabetes. Insufficient evidence hardly supports the use of SGLT-2 inhibitors and GLP-1 receptor agonists in people with HbA1c ≤6.5%. Besides, considering patient preferences may increase patient compliance, but it is not clear whether patient preferences will affect the long-term efficacy of these drugs. Since the RECODe model used to calculate cardiovascular and renal risk was developed from the North American ACCORD study,[19] the model warrant validation when the different ethnic population is considered. This guideline considers only the effects of cardiovascular and renal damage on diabetes medication decisions, but not other diabetic complications. Given the above limitations in this new guideline, other guidelines are still necessary at the hands of clinicians in their practice.

In summary, the novel recommendations from the guideline provide novel ways for patients and clinicians in the management of type 2 diabetes, especially in China. More importantly, the involvement of patients in the guideline panel serves as a guiding light for future individualized treatment of diabetes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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