Underuse of glucose-lowering medications associated with cardiorenal protection in type 2 diabetes: from delayed initiation to untimely discontinuation

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Two pharmacological classes of antihyperglycaemic agents have demonstrated improved cardiorenal prognosis in patients with type 2 diabetes mellitus (T2DM).[1,2] Sodium-glucose cotransporter 2 inhibitors (SGLT2is) are associated with a reduction in hospitalisation for heart failure (alone or combined with cardiovascular mortality) together with a protection against deterioration of kidney function.[3] Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have proven a reduction in major cardiovascular events (especially stroke) and macroalbuminuria.[4] Because of these remarkable results, which occurs independently of glucose control,[2] both SGLT2is and GLP-1RAs are currently recommended in patients with T2DM at high risk for cardiovascular and/or renal disease in international guidelines.[5]

Nevertheless, several real-world observational studies reported that both pharmacological classes are not enough prescribed in many at-risk patients.[6] This underprescription may be due to commonly observed clinical inertia when treating T2DM but also explained by the higher cost of these medications, at least in many countries. Furthermore, for SGLT2is, initial concerns regarding safety including warnings have most probably dampened the enthusiasm of some physicians.[3] For GLP-1RAs, some patients may be reluctant regarding needle injection or afraid by possible associated gastrointestinal side-effects. Besides a delay in the initiation, treatment adherence is not always optimal in many patients with T2DM, a failure that may be associated with worse prognosis.[7] Another concern may be a quite high rate of therapy discontinuation in the long-term. The underuse of these two pharmacological classes with proven improved cardiorenal prognosis, whatever the cause, may be associated with a loss of chance among patients with T2DM who should most probably benefit.[2]

In this issue of the Lancet Regional Health - Europe, Malik and colleagues reported the results of a nationwide study performed in Denmark that investigated the risk of discontinuing SGLT2is and GLP-1RAs in patients with T2DM.[8] A total of 77,745 first-time users of SGLT2is and 56,037 first-time users of GLP-1RAs were included and followed from 2013 to 2021. Less than two-thirds of patients were adherent to therapy over the first year (58% for SGLT2is and 60% for GLP-1RAs). The absolute five-year risk of discontinuing therapy was 56% and 45% for SGLT2-i- and GLP1-RA users, respectively. Stratified analyses showed that the risk of discontinuation of both drugs has been declining consistently after 2015, presumably following the publication of the first results from large cardiovascular outcome trials. The subsequent probability of reinitiating therapy during the following year was 24% for SGLT2i users and 26% for GLP-1RA users. Thus, in this study, approximately half of the users of SGLT2is and GLP-1RAs discontinued therapy within five years, yet a quarter of these patients reinitiated therapy during the following year. It is amazing that quite similar results were obtained with the two pharmacological classes despite different modalities of use and tolerance profile. Unfortunately, the design of this retrospective observational study based upon Danish nationwide registers did not allow to analyze the reasons for discontinuation and reinitiation of both pharmacological therapies. Nevertheless, the Authors, pointed out that of those who discontinued therapy, more than one third had been hospitalized shortly before, suggesting that these patients might have fallen out of therapy in relation to the hospitalization. Indeed, consensus guidelines have recommended that SGLT2is should be avoided in cases of serious illness and suggest they are not recommended for routine in-hospital use because of a higher risk of diabetic ketoacidosis.[9] Nevertheless, such restriction is less clear for in-hospital GLP-1RA use.

The reasons for discontinuing a pharmacological therapy, including antidiabetic agents, may be diverse, due to the medication itself or to the patient: higher cost, poor tolerance due to adverse events, insufficient glucose-lowering efficacy or poor compliance. In the Danish population, higher cost should not be considered as an issue as the medications are fully reimbursed (which is not the case in many countries). The most common adverse events associated with SGLT2is are genital mycotic infections and events related to volume

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depletion[3] whereas with GLP-1RA therapy nausea, vomiting and diarrhoea are the most prevalent ones, especially during the first few weeks, which could lead to early therapy interruption. For both therapies, an insufficient glucose control is possible; success may depend on both the initial degree of glucose control and the individualized target glycated haemoglobin level (no such information mentioned in Malik's study). Finally, poor compliance to drug therapy is common in a population with T2DM as most patients have no symptoms.[7] Furthermore, the motivation may be less in a cohort mainly in primary prevention. In the Danish study, the presence of cardiovascular comorbidities was rather low and almost similar in the two cohorts. One possible explanation for the discontinuation is the interruption of the therapy during a hospitalization without reinitiation after discharge. Normally, such silly reason should be easily circumvented if both physicians and patients are aware and better informed of the therapy benefit/risk balance.

One should acknowledge the strength of the study by Malik and colleagues,[8] which is the first to investigate the risk of discontinuing SGLT2-is and GLP1-RAs among new users in a nationwide population. Of additional interest, it also analyzed the rate of reinitiation following treatment interruption. As emphasized by the Authors, given the overwhelming evidence of cardioprotective benefits of SGLT2is and GLP-1RAs (plus a renoprotection for SGLT2is), preventive initiatives should be implemented to avoid untimely therapy interruption, especially for patients recently discharged from hospital. Perhaps the widespread policy of stopping SGLT2is during acute illness should be re-examined.[9] In the meantime, a structured discharge plan tailored to the individual should reduce the risk of inappropriate interruption of effective medications.[10] Home and hospital medications must be cross-checked to ensure that no chronic useful medications are stopped. Obviously such a strategy should involve a better information of both physicians and patients, with a large place reserved to a shared decision-making approach.[5]

Declaration of interests

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