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New diabetes drugs – beneficial for many, harmful for some

EDITORIAL

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New anti-hyperglycaemic drugs in patients with type 2 diabetes can prevent heart and kidney disease, but costs and adverse effects make it difficult to know where to place them in the treatment protocol.

Good blood glucose control has traditionally been the primary treatment goal in type 2 diabetes, and it prevents late microvascular complications in the kidneys, eyes and nerves (1). Prevention of cardiovascular disease requires a broader approach, including good lipid and blood pressure control. We have now learned that the choice of anti-hyperglycaemic drugs also has an impact on the risk of cardiovascular disease. Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) and glucagon-like peptide-1 (GLP-1) receptor agonists can reduce total mortality, the risk of cardiovascular events and the progression of kidney disease via mechanisms that are at least partially independent of the effect on blood glucose (1–3).

When using SGLT2 inhibitors, ketoacidosis is sometimes seen, which is a potentially life-threatening condition that is most often found in patients with type 1 diabetes and an insulin deficiency. Ketoacidosis in patients using SGLT2 inhibitors differs from other diabetic ketoacidosis in that the blood glucose

does not need to be substantially elevated (euglycaemic diabetic ketoacidosis, often defined by blood glucose < 14 mmol/L), as illustrated by the patient series from Haukeland University Hospital presented by Lejlic et al. in this edition of the Journal of the Norwegian Medical Association (4). The non-specific symptoms, such as nausea, vomiting and abdominal pain, can make ketoacidosis difficult to detect.

In randomised trials, 1–5 per 1000 SGLT2 inhibitor users with type 2 diabetes developed ketoacidosis (3). In a Canadian-British cohort study, the incidence was almost three times as high with the use of SGLT2 inhibitors compared to dipeptidyl peptidase-4 (DPP-4) inhibitors, with an incidence rate of 2.0 vs. 0.75 per 1000 person-years (5). By comparison, it is estimated that the use of SGLT2 inhibitors in 1000 people for five years would save three deaths among those with few cardiovascular risk factors and 40 deaths among those who have the combination of type 2 diabetes, cardiovascular disease and chronic kidney disease (2).

> ***«The expected benefits, adverse effects and costs of SGLT2 inhibitors and GLP-1 receptor agonists will determine their place in the treatment protocol»***

We have insufficient knowledge about the incidence of ketoacidosis associated with the current, more widespread use of SGLT2 inhibitors in diabetes as well as in heart failure and chronic kidney disease without diabetes. Should ketoacidosis lead to permanent discontinuation, as we now recommend (6), or should we dare to reintroduce the medication provided that it is paused during vulnerable situations? It is now recommended that SGLT2 inhibitors are temporarily discontinued in cases of intercurrent illness, symptoms of ketoacidosis, hospitalisation and before planned major surgery or fasting (6) – situations which are considered to put patients at risk of developing ketoacidosis. This is also reflected in the patient series from Haukeland University Hospital (4).

The expected benefits, adverse effects and costs of SGLT2 inhibitors and GLP-1 receptor agonists will determine their place in the treatment protocol. As described by Birkeland et al. (7), there is currently a discrepancy between new international consensus recommendations (1) and Norwegian guidelines and reimbursement rules. This may partly be due to a natural delay between the international research front and national implementation, but differing cost-benefit considerations are also likely to play a role.

New recommendations also highlight the importance of weight reduction in the early phase of type 2 diabetes (1). In the DiRECT study, patients with type 2 diabetes of few years duration followed an intensive low-calorie weight management programme. Among those who had lost at least 10 kilos after two years, 64 % achieved diabetes remission, and 24 % of participants in the intervention group achieved this weight loss (8). For a significant proportion, early weight-loss interventions to address one of the disease's main causes may be one path to type 2 diabetes remission, at least for a lengthy period of time.

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