
New international recommendations for type 2 diabetes – consequences for treatment practice in Norway?

PERSPECTIVES

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The author has completed the ICMJE form and declares the following conflicts of interest: He has given talks and chaired meetings for companies that market equipment and medication for the treatment of diabetes, such as Astra Zeneca, Boehringer Ingelheim, Lilly, Merck, Novo Nordisk, Roche and Sanofi, with fees paid to the employer and used for own research. He receives a fee for his role as chair of the Norwegian Diabetes Association's medical committee.

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New international recommendations for the use of anti-hyperglycaemic drugs in patients with type 2 diabetes are at odds with current practice in Norway and the Norwegian Directorate of Health's national clinical guidelines.



Illustration: Andreas Samuelsson

New knowledge indicates that changes are needed in the traditional treatment of patients with type 2 diabetes. Anti-hyperglycaemic drugs that belong to the SGLT2 inhibitor groups (sodium-glucose cotransporter-2 inhibitors) and GLP-1 receptor agonists (glucagon-like peptide-1 receptor agonists) have been shown to reduce cardiovascular events, progression of kidney disease and mortality [\(1–3\)](#). Weight reduction as a result of intensive caloric restriction or bariatric surgery can lead to remission of diabetes in a significant number of patients [\(4, 5\)](#), and is proposed as a new primary treatment goal [\(6\)](#). In addition, new medications will soon be available in Norway which show a documented reduction in blood glucose levels and, in particular, a reduction in body weight that far surpasses previous findings [\(7, 8\)](#).

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Several international clinical guidelines with relevance for doctors and patients in Norway have now been revised based on this knowledge [\(9–12\)](#). The European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) recently published updated consensus recommendations for the management of type 2 diabetes [\(9\)](#). The aim of the treatment is to prevent complications and optimise quality of life. The recommendations emphasise a holistic, person-centred approach to managing

type 2 diabetes and the importance of good communication between healthcare professionals and patients and of using language that is non-stigmatising and based on facts (e.g. not using words such as *diabetic* and *non-compliant*). Emphasis is placed on combating health inequalities and promoting universal access to treatment. The recommendations also have a strong focus on the importance of weight reduction as a cornerstone of treatment, and a summary is given of new knowledge generated from several cardiorenal outcome studies.

The most important changes in the pharmacological treatment of hyperglycaemia include the recommendation that SGLT2 inhibitors or GLP1 receptor agonists 'should' be prescribed for people with established cardiovascular disease and 'could' be prescribed for patients at high risk of such disease, *regardless* of their HbA1c level and of whether they are already using metformin. About one-third of patients with type 2 diabetes have a diagnosed cardiovascular disease. However, the number in the risk group depends on the criteria applied.

For patients with obesity, a weight reduction of 10–15 % is recommended as an important part of the treatment (the current recommendation is 5–10 %). This can normalise blood glucose levels without the need for medication in a significant proportion of patients, but will mean that many patients will require more intensive intervention than they currently receive. The DiRECT study showed that 46 % of patients with established type 2 diabetes were normoglycaemic without medication one year after participating in an intensive low-calorie weight management programme within primary care (4). Several studies, including a randomised controlled trial conducted in Norway (5), have shown remission in 60–70 % of patients after bariatric surgery for morbid obesity. Recently published studies using semaglutide 2.4 mg/week (7) and tirzepatide (8), which are expected to be available in Norway soon, show an average weight reduction of around 10 %, and a large proportion of patients achieved a weight reduction in excess of 15 %. We believe that a broad and open debate is now needed on the use of and funding for such medication, involving users, GPs, specialists and the authorities. It is now three years since the European Society of Cardiology (ESC), in collaboration with the EASD, published its guidelines on diabetes, pre-diabetes and cardiovascular diseases (10). These guidelines obviously have a different and broader approach to cardiovascular diseases than the aforementioned recommendations, but they are largely consistent with them. However, they go further than the EASD and ADA's guidelines in omitting metformin as the medication of first choice for treating hyperglycaemia in people with established or a high risk of cardiovascular disease. They also include more patients in the latter category.

«We believe that a broad and open debate is now needed on the use of and funding for such medication (semaglutide and tirzepatide)»

Heart failure and chronic kidney disease are common major complications of type 2 diabetes and lead to increased mortality and high costs (13, 14). Consequently, the guidelines for these conditions have also been updated (11, 15). Perhaps the most important recommendation in the guidelines for chronic kidney disease is the clear advice to screen for the condition through regular

measurements of the urinary albumin/creatinine ratio (UACR) in addition to estimated glomerular filtration rate (eGFR) in all patients with type 2 diabetes. In relation to pharmacological treatment, the Kidney Disease: Improving Global Outcomes (KDIGO) organisation draws attention to new evidence related to the use of SGLT2 inhibitors and non-steroidal mineralocorticoid receptor antagonists in addition to standard treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists.

Treatment recommendations in Norway

The Norwegian Directorate of Health issued national clinical guidelines for diabetes in 2016 (16), and these were most recently updated in 2019. Chapters 5, 6 and 8 of the guidelines cover treatment with anti-hyperglycaemic drugs and medications aimed at preventing late sequelae of macrovascular disease as well as kidney disease in people with diabetes. Some of these recommendations deviate significantly from what is set out above. This is a major challenge for doctors who want to treat patients based on the best available evidence base. Explaining treatment options to patients who follow international developments can also be difficult.

Can doctors in Norway not just follow the international recommendations? The main challenge is that approved indications for the various medicines are not always in accordance with updated guidelines and current reimbursement rules.

Cost-benefit analysis

The knowledge underlying the recommendations referred to above is based on large-scale, high-quality, randomised controlled trials, where the outcomes tend to be reported in terms of the relative risk reduction for a primary endpoint. The outcomes obviously vary between trials, but a relative risk reduction of 15–40 % is often seen for a serious cardiac, vascular or renal event.

These are impressive figures, but because serious events are (fortunately) relatively rare during the 2–4-year-long trials, it means that the absolute event rate is likely to be reduced by just 1–3 % and that 20–80 patients must therefore be given the relevant treatment for 2–4 years to prevent just one serious event. Some would consider the cost-benefit impact to be too low, representing too great a burden for the individual patient and an unacceptably high cost for society. We also have to consider that these are normally lifelong treatments, not just something that the patient takes for 2–4 years, and that the events are very serious (stroke, heart attack, cardiovascular death, heart failure and terminal kidney failure). Although there is no strong evidence to support this, it is reasonable to assume that the benefit will increase with the duration of treatment.

What is the current practice in Norway?

The Norwegian Medicines Agency's recommendations regarding approved indications and reimbursement rules are constantly changing, and so is the price of pharmacological agents. It is hoped that indications, reimbursement rules and national treatment recommendations will be brought more in line with the frontier of knowledge that the international clinical guidelines represent.

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However, we will have to accept the major discrepancy for the time being, and probably for a long time to come. Some doctors might treat patients without an approved indication, and some patients are already paying for treatment that is not covered by the State. This could lead to a detrimental increase in health inequalities, and we believe it is important that the gap between the updated knowledge base and Norwegian recommendations and actual treatment does not become too wide.

Conclusion

We believe doctors in Norway should be able to prescribe an SGLT2 inhibitor with a demonstrated protective effect on the heart and kidneys to patients with type 2 diabetes and known heart, vascular or kidney disease, regardless of their HbA1c level. The same should probably apply to GLP1 receptor agonists for patients with obesity, although the costs here are higher and the cost-benefit impact more uncertain. Perhaps it should also be possible to prescribe these two drug types to patients with a high risk of heart, vascular or kidney disease, but it may be hard to draw a line between moderate and high risk. Doctors should inform patients with type 2 diabetes that significant weight reduction can lead to remission of diabetes, and they should have access to tools that help them achieve this.

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Publisert: 20 February 2023. *Tidsskr Nor Legeforen*. DOI: 10.4045/tidsskr.22.0672

Received 19.10.2022, first revision submitted 16.11.2022, accepted 21.11.2022.

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