Access to diabetes drugs in New Zealand is inadequate

Jeremy Krebs, Kirsten Coppell, Pip Cresswell, Michelle Downie, Paul Drury, Ann Gregory, Timothy Kenealy, Catherine McNamara, Steven Miller, Kate Smallman

Type 2 Diabetes (T2DM) is one of the biggest health challenges facing New Zealand and is a stated priority of the Minister and Ministry of Health. The prevalence of diabetes in New Zealand is around 7% of the adult population,[1] with over 250,000 individuals in total at the end of 2014, and consistently rising at 7–10% per annum.[2] T2DM is considerably more common in Māori, Pacific and Indian people. Although the actual attributable cost of diabetes to New Zealand is unknown, it is estimated to be approximately $1.3 Billion.[3] Much of this is related to management of diabetes complications, such as renal failure requiring dialysis, amputations, retinopathy and cardiovascular disease, together with the increased length of stays and excessive number of hospitalisations in people with diabetes.

There is overwhelming evidence that effective management of hyperglycaemia and cardiovascular risk factors dramatically reduces the risk of developing, and the high cost of managing, complications of diabetes. This is particularly supported by early intensive glucose lowering,[4] however, recent evidence shows that very intensive management with aggressive glycaemic targets increases the mortality risk in some individuals who have had T2DM for many years, with suggestive evidence that this is linked with hypoglycaemia.[5] In New Zealand, a HbA_1c target of 50–55 mmol/mol is recommended, or as individually agreed taking into account the benefits and harms, in particular hypoglycaemia and weight gain.[6] Despite the evidence and current New Zealand guidance for good glycaemic control, many of those with diabetes have an HbA_1c higher than the recommended 50–55 mmol/mol.[7,8] Access to pharmaceuticals which can effectively control glucose, with minimal risk of hypoglycaemia especially in the elderly and those with established cardiovascular disease, is therefore essential for the improved management of T2DM.

Over the last 12 years, three new classes of glucose-lowering drugs have come through clinical trials to market. These include two classes, which for the first time specifically target fundamental pathophysiological defects present in T2DM, acting through the incretin mechanism, and specifically through the gut-derived hormone glucagon-like peptide-1 (GLP-1). GLP-1 is released from the lower small bowel in response to food, and has multiple actions including stimulating insulin release, suppressing raised glucagon, slowing gastric emptying and inducing satiety. The first of these classes, the dipeptidyl peptidase 4 (DPP-4) inhibitors (the 'gliptins'), reduce the activity of the enzyme which inactivates GLP-1, increasing endogenous levels and thus allowing improved and more prolonged GLP-1 action. The second class (GLP-1 agonists), are a group of injectable peptides which stimulate the GLP-1 receptor, but are not deactivated by the DPP-4 enzyme, and thus produce a prolonged and pharmacological GLP-1 effect. The third new group of drugs, the sodium-glucose co-transporter 2 (SGLT-2) inhibitors (the 'flozins'), reduce the reabsorption of glucose from the proximal tubules of the kidney, increasing urinary glucose excretion by up to 80g/day. This effect is independent of insulin or other oral agents.

The principal strengths of all three novel classes of medicine are their lack of hypoglycaemia, unless combined with insulin or an insulin secretagogue such as a sulphonylurea, and their frequent acceptability in

patients intolerant of or contraindicated for metformin and/or sulphonylurea. Additional benefits are also striking. While significant weight gain is often associated with sulphonylureas and peroxisome proliferator-activated receptor (PPARγ) agonists, the DPP-4 inhibitors are weight neutral, and GLP-1 agonists encourage progressive weight loss sustained over many years of use. SGLT-2 inhibition also leads to modest weight loss, and slight lowering of blood pressure. With cardiovascular safety now shown for one DPP-4 inhibitor[9] and similar trials close to reporting for GLP-1 agonists and SGLT-2 inhibitors, there has been no concerning safety signal and at least one SGLT-2 inhibitor to date showing cardiovascular benefits.[10] Furthermore, these agents do not necessitate self-monitoring of blood-glucose to the extent that sulphonylurea and insulin therapy requires which in itself is an expensive process.

Despite this, not a single example of any of these three classes has yet been funded in New Zealand, even where conventional treatment is contraindicated, as in chronic kidney disease, or where funded drugs are not tolerated or not effective. Even the inexpensive extended-release metformin, which is better tolerated than its simple counterpart and widely used internationally, remains unfunded.

International guidelines and recommendations

In 2012, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) combined to produce a position statement on the management of hyperglycaemia in individuals with T2DM.[11] In 2015, this has been further updated to reflect the progress made over the last decade in the choice of agents, and large, prospective, randomised controlled clinical trial evidence to help understand the efficacy and safety of existing and new drugs, and their combinations.[12] One of the central themes of these guidelines, and those of other international bodies, is the need for and importance of individualising management, taking into account many modifiable and non-modifiable factors, to derive patient-specific targets. This is especially important when gastrointestinal intolerance of metformin, the drug of first choice, affects between 5 and 15% of patients, and when hypoglycaemia is so dangerous for the frail, the elderly, and those with pre-existing cardiovascular disease.

In the UK, the National Institute for Health and Care Excellence (NICE) has been grappling with the issue of optimal management of glycaemia in T2DM and has recently released a draft guideline.[13] This has been heavily criticised by a wide range of diabetes experts in the UK as being overly influenced by economics and downplaying the clinical value of new agents and the importance of side effects from old agents.[14] From this and the other recommendations, it is clear that there are many perspectives on this controversial issue and there is no easy or single solution. While large, randomised, controlled clinical trials are rightly seen as the 'holy grail' of evidence for efficacy and safety of new drugs, these trials inevitably overlook the inter-individual variability in responses to and tolerability of treatments, the very essence of the patient-centred ADA/EASD guidelines.

The Australian Diabetes Society has recently published a revised position statement and blood glucose management algorithm for T2DM.[15] This is largely aligned with the principles of the ADA/EASD guideline, and incorporates all three new classes of drugs.

Availability and funding of agents

DPP-4 Inhibitors have been available and funded in Australia since 2008 (8 years ago). Two SGLT-2 inhibitors were listed in 2013, and two GLP-1 agonists are also funded under the Pharmaceutical Benefits scheme. Similarly in the UK and most of Western Europe, examples of each class are funded, though often under restrictions for selected patients. The same applies to Canada.

The situation in New Zealand

New Zealand lags behind the rest of the developed world in the availability of funded medication for T2DM. Despite

international evidence-based guidelines, continuing evidence-based advice from local diabetes specialists and New Zealand Society for the Study of Diabetes (NZSSD) over the past 10 years, PHARMAC continues to decline the funding of any of the three new classes of agents, all of which are now extensively used in Australia, the UK, and Western Europe as second- and third-line drugs. Multiple applications for funding, and responses to requests for information, have been submitted to PHARMAC from many pharmaceutical companies, as far back as 2007 for GLP-1 agonists, for DPP-4 inhibitors since 2008, and more recently for SGLT-2 inhibitors (ref PHARMAC website).

These drugs are relatively expensive in comparison with metformin and sulphonyureas, often costing $100–$200 per month retail. Wholesale use for everyone with T2DM is neither justified nor required, but it is clear that there is an important role for these drugs in selected individuals who cannot use, cannot tolerate, or do not respond to the first- or second-choice agent. PHARMAC has a track record of staged introduction of new pharmaceutical classes through special authority criteria to limit access and contain costs. While this is a reasonable approach, repeated delays in the introduction of important new agents is curtailing the recommended individualisation of Type 2 DM management in New Zealand, putting them at risk and ultimately costing the country more in the management of late complications. The Executive Committee of NZSSD urges PHARMAC to review their position and to allow better access to newer diabetes agents in appropriate cases.

Author information:

Jeremy Krebs, Endocrine, Diabetes and Research Centre, Wellington Regional Hospital, Wellington; Kirsten J Coppell, Medicine, University of Otago, Dunedin; Pip Cresswell, Endocrine, Diabetes and Research Centre, Capital and Coast Health, Wellington; Michelle Downie, Department of Medicine, Southland Hospital, Invercargill; Paul Drury, Medicine, University of Otago, Dunedin; Ann Gregory, ORA services, Capital and Coast Health, Wellingotn; Timothy Kenealy, South Auckland Clinical School, University of Auckland, Auckland; Catherine McNamara, Endocrinology, Waitemata DHB, Auckland; Steven CM Miller, Diabetes Centre, North Shore Hospital (WDHB), Auckland; Kate Smallman, Diabetes Projects Trust, Auckland.

Corresponding author:

Jeremy Krebs, Endocrine, Diabetes and Research Centre, Wellington Regional Hospital, Wellington, New Zealand.

jeremy.krebs@ccdhb.org.nz

URL:

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REFERENCES:

1. Coppell KJ, Mann JI, Williams SM, Jo E, Drury PL, Miller JC, et al. Prevalence of diagnosed and undiagnosed diabetes and prediabetes in new zealand: Findings from the 2008/09 adult nutrition survey. The New Zealand medical journal. 2013;126:23-42
2. Health NZMo. 2014 virtual diabetes register results. 2014
3. Health NZMo. Report on new zealand cost-of-illness studies on long-term conditions. Wellington: Ministry of health. 2009;2015
4. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. New England Journal of Medicine. 2008;359:1577-1589
5. Effects of intensive glucose lowering in type 2 diabetes. New England Journal of Medicine. 2008;358:2545-2559
6. Health NZMo. New zealand guidelines group. New zealand primary care handbook 2012. 2012
7. Smith R, Krebs J, Weatherall M, McBain L, Hullah M, Shapleski M. Analysis of a primary care led diabetes annual review programme in a multi ethnic cohort in wellington, new zealand. Diabetes

research and clinical practice. 2011;91:164-170

8. Coppell K.J AK, Williams S, Manning P, Mann J. Evaluation of diabetes care in the otago region using a diabetes register, 1998–2003 Diabetes research and clinical practice. 2006;71:345-352
9. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine. 2015;373:232-242
10. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015;373:1-12
11. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: A patient-centered approach: Position statement of the american diabetes association (ada) and the european association for the study of diabetes (easd). Diabetes care. 2012;35:1364-1379
12. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach: Update to a position statement of the american diabetes association and the european association for the study of diabetes. Diabetes care. 2015;38:140-149
13. NICE. Type 2 diabetes in adults: Management of type 2 diabetes in adults. 2015
14. O'Hare J.P M-JD, Hanif W, Hicks D, Evans M, Leslie D, Bain S.C, Barnett A.H. The new nice guidelines for type 2 diabetes – a critical analysis. The British Journal of Diabetes and Vascular Disease. 2015;15:3-7
15. Gunton J.E CNW, Davis T.M.E, Zoungas S, Colagiuri S. . A new blood glucose management algorithm for type 2 diabetes: A position statement of the australian diabetes society. The Medical Journal of Australia 2014;201:650-653