Submission for Stage Three of the Review for Medicines Used in the Treatment of Type 2 Diabetes

Stephen Colagiuri. Professor of Metabolic Health, Boden Institute, University of Sydney

Thank you for the opportunity to make a submission for Stage Three of the Review for Medicines Used in the Treatment of Type 2 Diabetes. My background in this area includes:

1. Lead author of the evidenced-based NHMRC endorsed guideline on Blood Glucose Control in People with Type 2 Diabetes (1).
2. Chair of the International Diabetes Federation (IDF) Clinical Guidelines Taskforce which developed the IDF Guideline on Type 2 Diabetes (2).

Background

Type 2 diabetes is a complex, lifelong and progressive disease. It is associated with considerable morbidity and premature mortality due to its many microvascular and macrovascular complications which diminish quality of life and have a significant personal, family and societal economic impact. Complications can be prevented or delayed through multifactorial intervention including blood glucose control.

The availability of a broad range of blood glucose lowering therapies is needed to

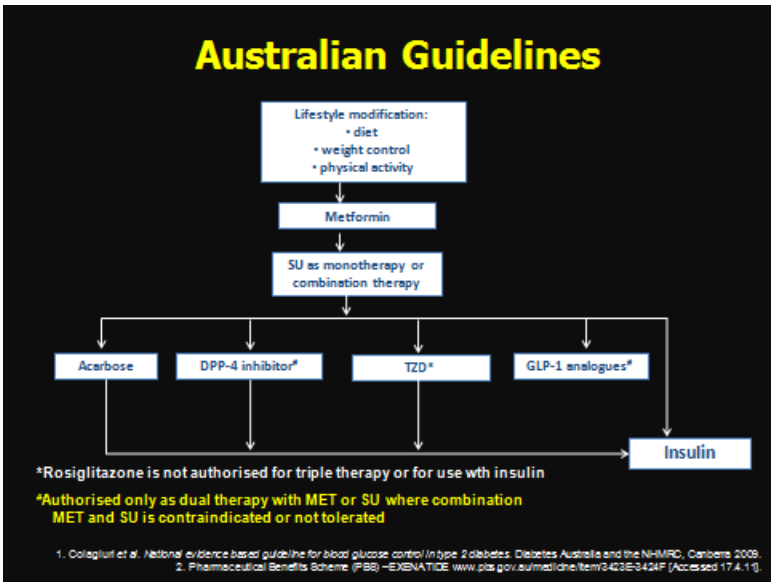
- control blood glucose because of the progressive nature of diabetes and the need for an increasing number of medications as diabetes duration increases
- personalizing therapy to take into account individual variability in efficacy and side effects, and patient preferences.

Current treatment algorithm for type 2 diabetes

Figure 1 illustrates the treatment algorithm contained in the NHMRC guideline on Blood Glucose Control in People with Type 2 Diabetes (1), adapted to include GLP-1 receptor agonists (GLP-1 RA) which were not available in Australia at the time the guideline was published in 2009.

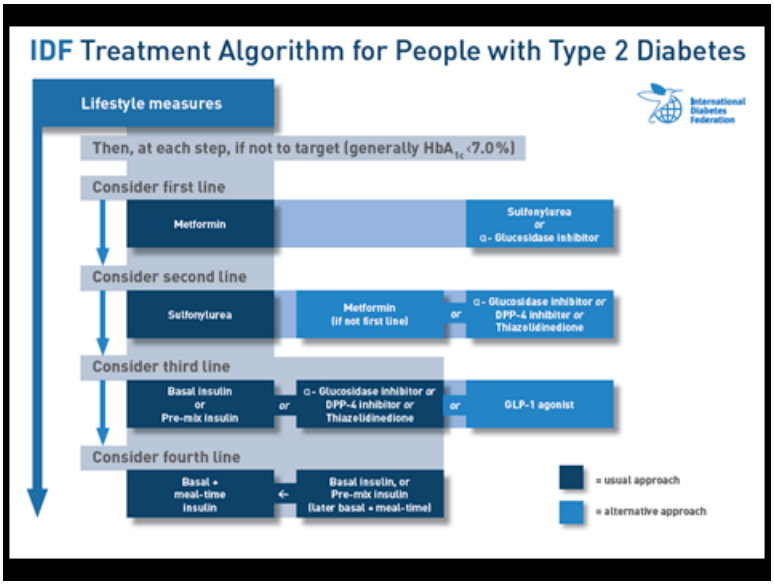
There was considerable discussion during the preparation of the guideline with the Commonwealth Department of Health about the algorithm in relation to whether it should be based on evidence relating to medications and their TGA-approved indications, or evidence relating to medications and their PBS-approved indications. The decision was to use the latter approach as there was concern that to do otherwise may have been confusing for primary care physicians. Therefore the NHMRC guideline included an evidence-based algorithm limited to medications and their PBS-approved indications at the time, not a comprehensive evidence-based algorithm. In retrospect this was an error and the guideline should have included both an algorithm of all medications approved for use in Australia and an algorithm highlighting the PBS restrictions. Consequently the current NHMRC approved algorithm cannot be used to justify the current PBS restriction, but rather is formulated based on the PBS restrictions.

Figure 1:



An alternate approach to formulating a treatment algorithm is the one used by the International Diabetes Federation (Figure 2) which includes options at each step based on a number of considerations including efficacy, side effects, availability and cost and which includes medications which can be considered “usual approach” and those that represent an “alternative approach”.

Figure 2



The limitations of the current Australian treatment algorithm are widely recognized. Consequently Diabetes Australia is currently overseeing a review of the treatment pathways based on available evidence and medications approved for use in Australia (or anticipated to be approved soon) and the development of an updated treatment algorithm. An algorithm based on these criteria would be quite different to the one contained in the current NHMRC guideline and a draft is illustrated below (Figure 3).

Figure 3:

Figure 3 has been removed as requested by submitter.

Clinical Implications

It is well established that development of microvascular and macrovascular complications in people with diabetes is related to blood glucose, as well as other risk factors including blood pressure and lipids. It is also well established that control of blood glucose and other risk factors decrease the risk of the development or progression of these complications, despite the recent challenging of the strength of these findings using an as yet unproven new statistical methodology of time sequence analysis. Improvements in outcomes in people with type 2 diabetes over the past 20-30 years is unequivocal to any clinician who has practiced over this time and today we simply do not see the complications which we used to. However, unfortunately many people with type 2 diabetes still develop potentially preventable complications.

The national level of diabetes control in Australia is not optimal with data from the ANDIAB 2011 survey and the Australian primary care collaborative (3) indicating that only about 30-40% of people with type 2 diabetes achieve the target HbA1c of <7%. Type 2 diabetes is a progressive condition which requires increasing use of medications for its control and the current PBS restrictions on the use of effective evidence-based treatments is a major contributing factor in restricting Australians' access to internationally recognized quality use of medicines.

DUSC Review

The recent DUSC review of use of blood glucose lowering therapies in Australia demonstrated that 72% of usage is in accordance with PBS restrictions but about 28% of usage did not conform with PBS restrictions.

The areas of medication usage outside PBS restrictions are entirely expected based on the evidence-base and on clinical needs. Examples include use of:

- DPP-4 inhibitors (gliptin) in combination with metformin and sulfonylurea (SU) as triple therapy. This is a proven, effective, safe and convenient treatment regimen that is widely used internationally. The current PBS options are restricted to Acarbose and Pioglitazone, both of which are associated with significant side effects
- agents currently not approved as monotherapy reflecting a clinical need in situations where both metformin and SU cannot be used because of contraindications or safety concerns
- DPP-4 inhibitors as second line treatment in combination with metformin where there is concern about over usage because of an apparent failure to try an SU first
- combined use of GLP-1RA and insulin, an emerging and effective treatment combination

Each of the above situations represents good clinical practice, is in accordance with the evidence-base of proven effectiveness and with the locally and internationally recognized need to individualize therapy to suit a particular patient's needs. The NHMRC guideline (1) supports individualizing treatment and contains the following Grade A recommendation "interventions to achieve target glycated haemoglobin should begin with lifestyle modification followed by pharmacological options selected on the basis of individual clinical circumstances, side effects and contraindications".

The importance of personalized / individualized care of people with diabetes is increasingly recognized in the overall management of diabetes and in particular in the selection of therapeutic agents (4). The IDF will soon be publishing guidance on personalizing therapeutic choices for people with type 2 diabetes which emphasizes the importance of personalizing therapeutic choices taking into account patient factors and preferences.

Many surveys of people with type 2 diabetes consistently show that patient concerns focus on medication side effects, fear of hypoglycaemia, weight gain, and taking insulin. The therapeutic choices made outside of the PBS restrictions highlight the use of medications which delay or avoid the use of insulin (eg effective and safe triple oral therapy with DPP4 inhibitors), the use of medications with a low risk of hypoglycaemia or weight gain (DPP4 inhibitors and GLP-1 inhibitors) and insulin and GLP-1 combination which reduces the risk of hypoglycaemia and weigh gain with insulin.

Cost and cost-effectiveness

These are important considerations in choosing a blood glucose lowering medication. However there is a degree of frustration in the diabetes community about an apparent lack of transparency of the PBAC cost-effectiveness model and the omission of important patient valued disutilities such as hypoglycaemia, weight again and the desire to avoid insulin treatment, and how these impact on a person's quality of life. Therefore the calculated cost / QALY ignores important aspects of quality of life.

In addition there seems to be no consideration of costs associated with the longer term social impacts of diabetes and its complications including workforce participation, wealth accumulation, superannuation benefits, and reliance on pensions. Improving blood glucose control and reducing the development of complications would have a significant impact on these personal and societal outcomes.

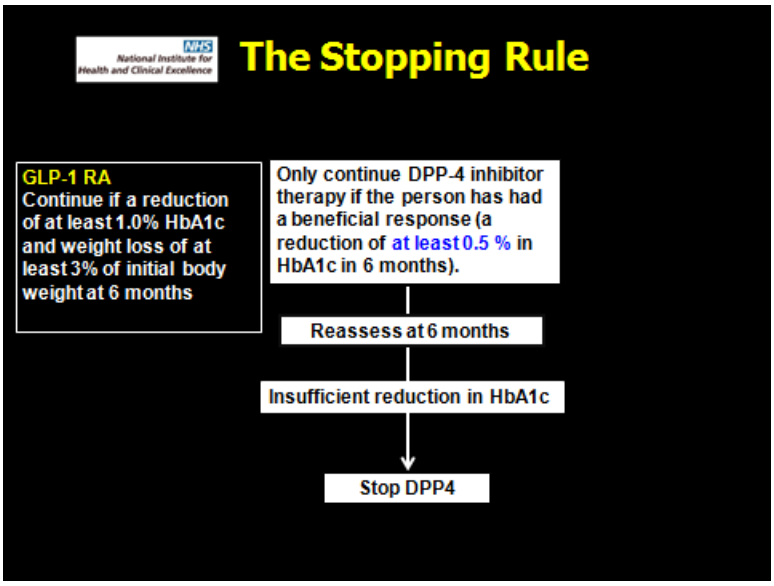
It would seem timely to have an independent review of the approach to the economic modeling used by the PBAC to calculate cost-effectiveness. This should evaluate and review how clinical outcomes, consumer important considerations such as hypoglycaemia, weight gain and avoidance of insulin, and the longer term personal and societal economic impact of diabetes care are incorporated in the model.

Other considerations

The current approach to PBS restrictions for blood glucose lowering therapies is quite different to the approach which clinicians can use for blood pressure lowering therapies, which from a clinical perspective affords the clinician the choice necessary to meet individual patient needs.

It is also puzzling that the indications and recommendations for use of blood glucose lowering treatments, do not include a clinically relevant medication "stop clause" similar to that used in the UK NICE guidelines for newer therapies such as DPP4 inhibitors and GLP-1 RAs (Figure 4).

Figure 4:



Summary:
The current PBS-driven treatment algorithm for the management of people with type 2 diabetes in Australia does not represent best clinical practice and negatively impacts on quality use of medicines and clinical care. The TGA-approved indications align with international standards for best clinical care. This current situation highlights the "evidence-TGA- PBS disconnect".

This review provides an opportunity to reassess this situation. The treatment algorithm and the PBS restrictions should be reviewed to reflect best practice which would largely align with the findings of non-PBS approved usage of medications highlighted in the DUSC review.

There should be an independent external review of the current PBAC economic model for assessing cost-effectiveness and consideration should be given to introducing a treatment stop clause for newer medications when they do not sufficiently improve blood glucose control.

References:

1. Colagiuri S, Dickinson S, Colagiuri, R. Evidence Based Guidelines for Type 2 Diabetes: Blood glucose control. Diabetes Australia & NHMRC, Canberra, 2009.
2. The International Diabetes Federation Global Guideline for Type 2 Diabetes. 2012. http://www.idf.org/guidelines
3. Knight AW, Ford D, Audehm, Colagiuri S, Best J. The Australian Primary Care Collaborative Program: improving diabetes care. *BMJ Qual Saf* 2012; 21: 948-955.
4. Inzucchi SE, Bergenstal RM, Buse JB 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). Diabetologia 2012; 55: 1577-1596