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Therapeutic Brief

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Reducing the impact of cardiovascular and renal disease in type 2 diabetes: what medicines and when?

Diabetes is the fastest growing chronic condition in Australia, increasing at a faster rate than other chronic diseases such as heart disease and cancer. All types of diabetes are increasing in prevalence.[1]

65% of all cardiovascular deaths in Australia occur in people with diabetes.[2]

Diabetes is the most common cause of chronic kidney disease (CKD).[3] 20% of people with diabetes in Australia have CKD.[4]

Prevention, early detection, and continuing care with regular monitoring and ongoing evaluation for complications are key elements in reducing the growing burden of diabetes.[5]

This therapeutic brief considers the role of two classes of medicines (SGLT2i and GLP-1A) in the management of your veteran patients with type 2 diabetes mellitus (T2DM) who have established cardiovascular or renal disease or are at risk of developing these complications.

Patients with established disease are likely to achieve the greatest benefit from aggressive management of modifiable risk factors and newer glucose-lowering agents.[6]

Enrol your veteran patient in the Coordinated Veterans' Care (CVC) program. This is a proactive coordinated care program for veterans who are living in the community, have a chronic condition and at risk of unplanned hospitalisation, and hold a Veteran Gold Card. www.dva.gov.au/providers/health-programs-and-services-our-clients/coordinated-veterans-care/coordinated-veterans-0#cvc-program-information-for-providers

INSIDE

Key points

- Early and continuing lifestyle interventions are the foundation of diabetes management. Metformin is the preferred first line medicine in type 2 diabetes.
- Cardiovascular disease is the leading cause of death in people with diabetes - intensive management of cardiovascular risk factors is a priority.
- Consider early use of SGLT2 inhibitors and GLP-1 analogues – they provide extra benefit.
- Review patients on other regimens (e.g. DPP4i, sulfonylureas, acarbose) that do not have cardiovascular benefits.

A type 2 diabetes refresher

T2DM is a heterogeneous disorder with many genetic and lifestyle influences.[5] Key organs in the body become resistant to the effects of insulin and insulin production by the pancreas may eventually reduce.

In the past, type 2 diabetes was typically diagnosed after 50 years of age, but now is increasingly diagnosed in younger adults, adolescents and even children.[1] This concerning trend sees a longer lifetime exposure to hyperglycaemia and its complications. Emerging evidence suggests that early-onset T2DM is a more aggressive disease than later-onset T2DM, and is associated with more rapid progression of macrovascular and microvascular complications.[1]

Cellular and organ changes lead to serious complications such as heart disease, stroke, eye disease (including retinopathy), kidney disease, peripheral vascular disease, nerve damage, foot problems, increased infection risk, poor wound healing and gum disease. Diabetes is also associated with serious mental health challenges including treatment-related distress, anxiety and depressive symptoms.

The most common cause of death in people with diabetes is cardiovascular disease. Assess absolute cardiovascular risk (Australian cardiovascular risk calculator at: www.cvdcheck.org.au/calculator) and renal disease risk (check eGFR and urinary albumin to creatinine ratio) for all your diabetic patients.[6]

Intensive management of cardiovascular risk factors is a priority in patients with T2DM. Ensure patients with diabetes and established CVD or high absolute cardiovascular risk (> 15%) are on lipid lowering therapy and blood pressure therapy. These medicines are underused in this high-risk population.[7, 8]

Prevention is better than cure – public health interventions are important and beneficial (see box 1). There is increasing evidence for, and interest in, the concept of 'diabetes remission' using intensive lifestyle interventions early after diagnosis.[9]

Always reinforce the benefits of lifestyle intervention and the need for exercise and diet modification throughout the course of the disease.[10, 11, 12]

Abbreviations:

ASCVD – atherosclerotic cardiovascular disease

CKD – chronic kidney disease

CVD – cardiovascular disease

SU – sulfonylureas

eGFR – estimated glomerular filtration rate

DPP4i – dipeptidylpeptidase-4 inhibitors (also called 'gliptins')

GLP-1A – glucagon-like peptide-1 analogues

HbA1c – glycated haemoglobin

SGLT2i – sodium glucose cotransporter 2 inhibitors (also called 'flozins')

T2DM – type 2 diabetes mellitus

Box 1: Supporting patients to achieve best outcomes

- Organise a GP management plan and team care arrangements* (or multidisciplinary care plan for a resident in an aged care facility) to facilitate lifestyle management: e.g. refer to a dietitian, physiotherapist and/or exercise physiologist.
- Credentialled diabetes educators can be accessed via these plans and are a valuable resource helping patients understand their medicines and reinforcing lifestyle interventions.
- Refer patients for a Home Medicines Review (HMR – MBS item 900) or Residential Medication Management Review (RMMR – MBS item 903) to check patients' understanding of diabetes medicines, side effects and adherence to current therapies.
- Complete a diabetes annual cycle of care (MBS item 2517).
- If eligible, enrol your veteran patient living in the community and at risk of unplanned hospitalisation in the CVC program (see above).

DVA pays for all Gold Card holders and some White Card holders to receive services from a range of healthcare providers as clinically required.

*Items 721, 723, 729, 731 and 732 provide rebates to manage chronic conditions such as diabetes by preparing, coordinating, reviewing or contributing to chronic disease management (CDM) plans.

Use metformin first

Metformin remains the preferred first line medicine to use in treating patients with T2DM who are not reaching glycaemic targets with lifestyle modification alone. It is mostly very well tolerated and provides effective HbA1c reduction and improves cardiovascular outcomes.[4, 7, 9, 10, 11, 12] Metformin is entirely cleared by renal excretion. It can be safely used in chronic kidney disease but the maximum daily dose should be reduced according to eGFR. See table 1 below - Dosing of selected diabetes medicines in renal impairment.

What if my patient does not tolerate metformin? This is fortunately uncommon. Gastrointestinal adverse effects are often dose dependent; start with a low dose and gradually increase (e.g. over several weeks). It is also worth encouraging your patients to take the medication with meals or trying a slow-release formulation.[9, 10]

The only other approved PBS options for monotherapy in type 2 diabetes are SU, acarbose and insulin.[9]

What comes next?

The Australian Type 2 diabetes glycaemic management algorithm provides stepwise guidance to managing patients that are not meeting HbA1c targets.[9]

www.diabetessociety.com.au/downloads/20210412%20T2D%20Management%20Algorithm%2001032021.pdf

It acknowledges the importance of individualising treatment according to the presence of cardiovascular risk and comorbidities (especially heart failure and

CKD) and gives a broad choice of options for dual or triple therapy.[9]

SGLT2i and GLP-1A medicines have cardiovascular and renal benefits that are independent of their glycaemic lowering benefits.[9]

These diabetes medicines are potentially underused in patients who would benefit from them. A growing body of evidence suggests that treatment should be started without delay in people at high risk who meet PBS criteria.[13]

Sodium-glucose co-transporter 2 inhibitors

Inhibit sodium-glucose co-transporter 2, thereby reducing glucose reabsorption in the kidney thus increasing its urinary excretion.[14]

These are available as oral formulations; dapagliflozin, empagliflozin (which have proven CVS benefit) and ertugliflozin (which, at present, has a lack of data for cardiovascular benefit).

For PBS listing see www.pbs.gov.au/browse/body-system?depth=4&codes=a10bk#a10bk

SGLT2i appear to be better than GLP-1A for heart failure (and are now PBS listed for this indication in people without diabetes).[13, 14, 15, 16] Dapagliflozin has been listed on the PBS for CKD with macroalbuminuria.

The SGLT2i rely on adequate glomerular filtration for their glycaemic benefit and are not as effective at glycaemic control in patients with CKD. However, they still should be strongly considered in these patients for their renal benefit. Check renal function before starting treatment and initially every month. You may see an initial decrease in eGFR but this should stabilise.[17] See table 1 - Dosing of selected diabetes medicines in renal impairment.

Polyuria is common and there is an approximate 3 to 5 fold increase in genital candidiasis.[18] This usually improves with topical antifungals (which are available on the RPBS) without the need for medicine cessation. An increase in urinary tract infections was seen in some studies.[19]

Warning!

There is a potential risk for patients with diabetes using a SGLT2i to develop euglycaemic ketoacidosis. The risk is increased in patients:

- with vomiting or diarrhoea
- fasting for a prolonged time
- who have a low carbohydrate diet
- with severe dehydration
- who have excessive alcohol intake
- in whom perioperative guidelines require fasting or reduced fluid intake.

SGLT2i may need to be withheld or dose reduced in these circumstances.[20]

Glucagon-Like Peptide 1 Receptor analogues

Act as agonists on glucagon like peptide 1 (GLP-1) receptors in the pancreas enhancing insulin release and reducing glucagon secretion. Effects on GLP-1 receptors in the CNS and the gastrointestinal tract delay gastric emptying leading to reduced appetite and delayed glucose absorption.[21]

For PBS listing see www.pbs.gov.au/browse/body-system?depth=4&codes=a10bj#a10bj

In Australia only injectable forms of this drug class are available: dulaglutide, semaglutide (liraglutide is non-PBS).

Dulaglutide and semaglutide are usually preferred as they have demonstrated benefit on cardiovascular outcomes, they are given once weekly and they are PBS-listed. Liraglutide (non-PBS) requires daily dosing. Despite initial hesitancy, most patients cope well and can self-inject without problems given clear advice and education.

This class may help weight loss in obesity and reduce non-alcoholic fatty liver disease (NAFLD) so may provide additional treatment options in diabetic patients with these issues. Liraglutide and semaglutide have a separate TGA indication for overweight (exclusive of diabetes); this is not PBS listed and is expensive.

GLP-1A have a high incidence of gastrointestinal (GI) adverse effects – these may reduce over time so reassure your patient and encourage small meals and avoidance of fatty foods. Semaglutide may need slow dose escalation to reduce adverse effects. Many patients who experience initial GI adverse effects often find these can settle with ongoing therapy.[22]

Recent changes to the PBS criteria allow them to be co-prescribed with metformin, SU and/or insulin.[23]

Consider adding GLP-1A before using insulin or as an insulin sparing agent in patients already on insulin, particularly in those at high ASCVD risk.

Different members of this class are impacted in different ways by reduced kidney function. See table 1 - Dosing of selected diabetes medicines in renal impairment.

In general, consider adding a SGLT2i if there is known ASCVD, heart failure or CKD (eGFR > 25).

Consider adding a GLP-1A in ASCVD or if there is obesity.

Specific considerations

Heart Failure

It is widely recognised that the risk of developing HF in T2DM is substantially increased even in the absence of overt myocardial ischaemia.[15]

SGLT2i reduce the risk of heart failure-related hospitalisation for people with CVD and type 2 diabetes.[14]

The SGLT2i medicines dapagliflozin and empagliflozin are now PBS listed for add on therapy for heart failure with reduced ejection fraction (HFrEF) without the presence of diabetes.

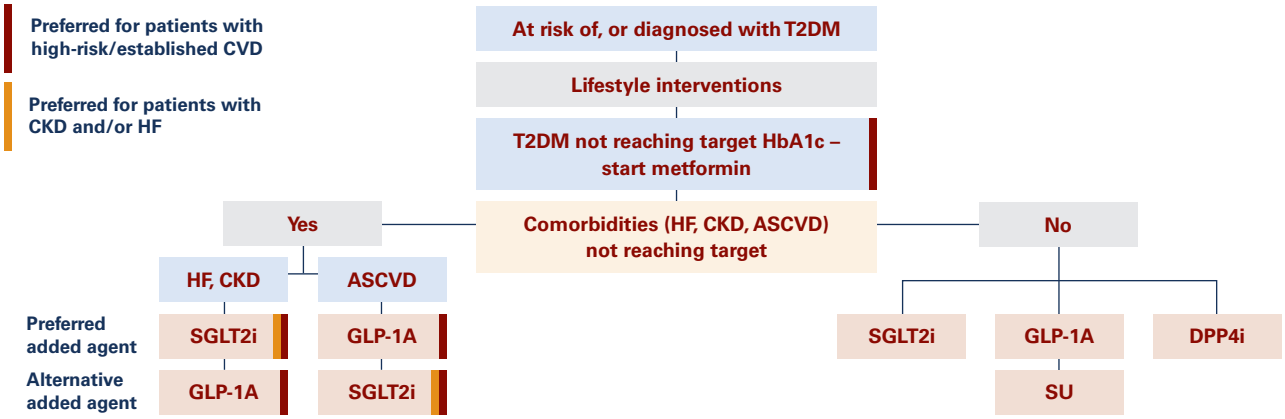
The PBS listing is for symptomatic (New York Heart Association (NYHA) class II–IV) heart failure with LVEF ≤ 40%.
The treatment must be an add-on therapy to optimal standard treatment, which must include, unless contraindicated or cannot be tolerated, a beta blocker and angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker or angiotensin receptor-neprilysin inhibitor.

What is the role of older classes of medicines?

DPP4i (the 'gliptins') i.e.: alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin or SU–gliclazide, glimepiride, glipizide and glibenclamide can continue if HbA1c is at target and there are no comorbidities of concern and you are not particularly concerned about side effects or hypoglycaemia.[9]

DPP4i do not improve cardiovascular

Simplifying treatment for type 2 diabetes *(adapted from guide developed by Associate Professor Gary Kilov.[24])*



Insulin can be considered at any stage in treatment - if HbA1C is above 9%. Consider referral to an endocrinologist if you are dealing with significant clinical complexity, if the patient is not meeting targets after trying different therapies or where the diagnosis is unclear.

outcomes and are only modestly effective at reducing HbA1c. SU increase the risk of hypoglycaemia and weight gain and do not improve cardiovascular outcomes.

If your patients with diabetes are on the above medicine classes and are not reaching glycaemic targets, and have cardiovascular or renal comorbidities, switch to SGLT2i or GLP-1A.[9, 10]

Acarbose, TZD or pioglitazone are used infrequently due to adverse effects and availability of better options. Do not use them if there is coexisting ASCVD or CKD.

Insulin still has a significant role in managing type 2 diabetes especially if the HbA1C remains high despite lifestyle and medical therapy. It remains the most effective agent at rapidly achieving glycaemic control when there is poor glucose control or if the patient is symptomatic of hyperglycaemia. If uncertain seek specialist advice.

Table 1. Dosing of selected diabetes medicines in renal impairment

(adapted from NPS[25] and AMH[26])

Class	Medicine	Dose advice according to eGFR (mL/min/1.73m2)
Biguanide	*Metformin*	60 to 90: up to 2 g daily 30 to 60: no more than 1 g daily 15 to 30: 500 mg daily and monitor renal function closely Less than 15 – not recommended
SGLT2i	*Dapagliflozin*	25 to less than 45 – reduced glucose lowering effect, but can be used Less than 25 – do not initiate treatment but can be continued with monitoring
	Empagliflozin	Less than 30 – contraindicated
	Ertugliflozin	Less than 45 – contraindicated
GLP-1A	*Dulaglutide*	Less than 15 – limited data thus not recommended
	Semaglutide	Less than 30 – limited data thus not recommended
	Liraglutide	Less than 30 – not recommended due to increased risk of gastrointestinal side effects

Practice Points

- If HbA1c levels are not dropping to target, the Australian Type 2 diabetes glycaemic management algorithm suggests substitution, the addition of other therapy such as SGLT2i or GLP-1A, or advancement to insulin therapy.
- Check response to any change in therapy after 3 months. Stop any medicine that has not reduced HbA1c by ≥ 0.5% unless indicated for non-glycaemic benefits.
- Consider the non-glycaemic benefits of SGLT2i and GLP-1A in patients at high cardiovascular risk, with existing ASCVD, in heart failure or with CKD.[7, 8, 10]
- Advise your patients about possible adverse effects and how to manage them including making sick day plans and preparing for elective surgery.
- Treat to target but be flexible depending on patients' circumstances – you may need to accept a higher target depending on age, frailty, preferences.[27]
- Refer patients for a HMR, create a GPMP and remember to complete an annual diabetes cycle of care.
- This is a constantly evolving area - evidence is rapidly accumulating and guidelines frequently changing.

Full reference list available at: www.veteransmates.net.au

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