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REVIEW

Managing Cardiovascular Risk in Type 2 Diabetes: What Do the Cardiovascular Outcome Trials Mean for Australian Practice?

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ABSTRACT

Understanding the implications of cardiovascular (CV) outcomes data of glucose-lowering agents on the management of type 2 diabetes mellitus can be challenging for many primary practitioners. Amongst different classes of diabetes medications assessed for CV safety, several agents within the sodium-glucose transport protein-2 inhibitor and glucagon-like peptide-1 receptor agonists classes have demonstrated CV risk reduction. Applying the trial findings to patients typically seen in clinical practice, such as those with established CV disease and those with multiple CV risk factors without established CV disease, requires further clarity. To bridge this gap in our current knowledge, the aim of this review was to utilise expert-driven opinions on common case scenarios and practical recommendations on the most appropriate choice of agents, according to an individual patient's clinical risk profile (CV and kidney disease), treatment preference and reimbursement environment from an Australian perspective.

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Keywords: Cardiovascular; DPP-IV inhibitor; GLP-1RAs; Hospitalisation; Kidney; MACE; Management; Outcome; Risk; SGLT-2 inhibitors; Type 2 diabetes

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CLINICAL BURDEN OF DIABETES IN AUSTRALIA

As the worldwide prevalence of type 2 diabetes mellitus (T2DM) increases, with approximately 8.8% of the adult population (20–79 years of age) affected, 1.5 million Australians are currently estimated to have T2DM [1, 2]; it remains one of the most common chronic conditions managed in primary care and the number of

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patients with T2DM is estimated to continue to rise. Indeed, > 1 in 10 patients aged 45–64 years who present to primary practice have been diagnosed with T2DM and typically have 9 primary practitioner visits a year, 4 of which are related to diabetes [3]. Most of these individuals are also diagnosed with other chronic conditions, such as arthritis, depression and notably cardiovascular disease (CVD), including heart failure [4], and have associated risk factors of hypertension and dyslipidaemia. Collectively, all serve to increase the clinical burden of T2DM further [5].

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

IDENTIFYING CARDIOVASCULAR RISK IN T2DM IN PRIMARY PRACTICE

In Australia, as many as two in three adults with T2DM have CVD [2]. Indeed, CVD is a major cause of death in these individuals [6]. This clinical burden makes it imperative that primary practitioners attempt to reduce the CV risk of patients with T2DM with agents that have evidence to improve CV outcomes.

The risk of CV morbidity and mortality is disproportionately higher in those with T2DM than in those without [7]. While T2DM was considered to be "cardiovascular risk equivalent" to those without T2DM but who had experienced a prior coronary event [8], a more contemporary view is that there is large heterogeneity in CV risk among T2DM populations [9, 10]. Special populations such as smokers, the elderly, Aboriginal and Torres Strait Islanders, those of Asian and Pacific descent and those with chronic kidney disease (CKD) have a higher absolute risk of CVD. Women and younger adults with diabetes have a disproportionately higher relative risk of CVD compared with those without diabetes; furthermore, those who have T2DM and pre-existing CVD have a much higher risk of CV death compared with those with T2DM who do not already have CVD [11].

Consequently, guidelines recommend CV risk stratification of patients into one of three categories—low (< 10%), moderate (10–15%) and high (> 15%)—to better identify those who would benefit from a more or less intensive prevention and management strategy [12]. For Australian clinicians, for information on how to calculate the absolute CV risk, refer to the National Vascular Disease Prevention Alliance initiative at: https://www.cvdcheck.org.au where you can access the calculator and supporting resources.

MODIFYING CARDIOVASCULAR RISK IN T2DM

Is Glycaemic Control Important in CV Risk?

There are compelling and established data supporting the benefit of long-term glycaemic control in reducing the risk of microvascular complications in T2DM. Whether lowering blood glucose translates into similar macrovascular CV benefits has been a major focus in the past decade. Studies, such as the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC), suggested a 'legacy effect' in newly diagnosed individuals with diabetes, whereby good glycaemic management improved longer-term CV outcomes [13, 14]. However, other studies, such as Action in Diabetes and Vascular Disease (ADVANCE), Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Veterans Affairs Diabetes Trial (VADT) found that intensive glycaemic lowering did not result in favourable CV outcomes and rather, in some cases, increased the risk of both total mortality and CV death [15–17].

The potential risks of intensive glucose-lowering are further supported by two separate meta-analyses of CV outcome trials (CVOT) in T2DM [18, 19]. While both report a modest and significant reduction in major CV events, such

as MI, following tighter glycaemic control, they found that the CV benefit was at the expense of a significant increase in hypoglycaemia events and no mortality benefit. Collectively, these data present a reminder that patient characteristics, particularly duration of diabetes, and the 'legacy effect' may influence the choice of an individual's glycated haemoglobin (HbA_{1c}) target and that this target in turn may change with long-term, optimal glycaemic control in advancing diabetes.

Australian Diabetes Society guidelines recommend an HbA_{1c} target of 7% (53 mmol/mol) for most T2DM patients [20]. A more stringent HbA_{1c} target of 6.5% (48 mmol/mol) may be considered if it can be achieved without hypoglycaemia except where contraindications exist such as known CVD, long duration of T2DM and if having existing episodes of severe hypoglycaemia. For women planning pregnancy, the goal is to achieve an HbA_{1c} target of 6.0% (42 mmol/mol). Less ambitious targets are recommended for elderly patients and those with lowered awareness of hypoglycaemia or major comorbidities (HbA_{1c} of 8.0%; 64 mmol/mol) [20]. For patients with limited life expectancy or at a palliative care stage, there are no targets and the goal is to keep them 'safe' and relatively asymptomatic.

Can the Choice of Glucose-Lowering Medication Impact CV Outcome?

Metformin has been established as baseline therapy for type 2 diabetes, based on evidence for a role in the reduction of microvascular complications from the seminal UKPDS study and an emergent macrovascular benefit on long-term analysis [21]. Unlike newer agents, funded CV outcome trails of similar quality do not exist, however, as it has been used for $\geq$ 60 years in clinical practice, confidence exists that it certainly does not increase CV risk and, based upon on the extended data from UKPDS (in a small cohort of obese patients), is likely to benefit CVD outcomes [22].

In the case of sulphonylureas, their association with CV risk factors, hypoglycaemia and weight gain is widely recognised [23]. However, controversy exists with respect to their association with CV outcomes and mortality, especially in patients with an elevated risk of CVD or established CVD. While observations of increased CVD events and raised mortality have questioned the use of sulphonylureas either as monotherapy or in combination with metformin vs. other glucose-lowering agents [24–27], some meta-analyses and systematic reviews have provided reassurance on the CV safety of this drug class [28, 29], alongside the ADVANCE study [15], and the recent announcement of the non-inferiority results of the CAROLINA study [30]. Despite this, with more favourable CV profiles of newer agents emerging, ADA/EASD guidelines have shifted away from recommending the early use of sulphonylureas in patients with established CVD [31].

The impact of more recent glucose-lowering agents on CVD risk had, until recently, been less well known [32, 33]. There is now increasing evidence from CVOTs that demonstrates CV benefits with certain diabetes medications, in particular the sodium-glucose transport protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) [34]. In recognition of these findings, there has been a contemporary shift in the recommended strategy for CV risk reduction in managing T2DM that extends beyond glucose control.

A summary of recommendations from Australian as well as several international guidelines is outlined in BOX 1 [31, 34–38].

Box 1: Multifactorial approach to CV risk reduction in T2DM

Approach	Guideline target/individualised goal recommendations
HbA_{1c} control	$HbA_{1c} \leq 7\%$ (53 mmol/mol)*
	*Target customised according to age and comorbidities
Blood pressure control	< 140/90 mmHg for patients with T2DM and hypertension
	< 130/80 mmHg for patients with albuminuria/proteinuria
	Measure at every routine visit and on separate days to diagnose and confirm hypertension
Cholesterol management	Total cholesterol < 4.0 mmol/l
	HDL-C ≥1.0 mmol/l
	LDL-C < 2.0 mmol/l (< 1.8 mmol/l if CVD is present)
	Triglycerides < 2.0 mmol/l*
	Assess cholesterol levels at time of T2DM diagnosis, at initial review and every 5 years if < 40 years or more frequently if indicated
	Assess cholesterol levels at time of statin or initiation of other cholesterol-lowering therapy at 4–12 weeks after initiation or a change in dose and then annually to help monitor response and adherence to medication
	*Note: Canadian guidelines on dyslipidaemia in T2DM stipulate a target of triglyceride < 1.5 mmol/l [35]
Therapies with proven CV benefit	Blood pressure medications (ACEi/ARB favoured if evidence of CKD)
	Cholesterol-lowering agents—statin, ezetimibe, PCSK9 inhibitors
	Antiplatelet agents—low-dose aspirin (in established CVD)
	Glucose-lowering therapies—SGLT-2 inhibitors and GLP-1RAs
Screening for complications	Cardiac—ECG, longer term monitoring or opportunistic screening may be needed if a patient is > 65 years or has a detectable dysrhythmia or is symptomatic [38]
	Kidney—assess eGFR and ACR annually, or more frequently if indicated
	Eye disease—refer for retinal examination every 2 years (once a year if T2DM > 15 years or $HBA_{1c} > 8\%$, presence of diabetes complications or poorly controlled BP and lipids)
	Foot—assess monofilament/vibration annually or more frequently if indicated
Lifestyle interventions	Smoking cessation—0 cigarettes/day
	Exercise—approximately 30 min of moderate physical activity on most if not all days of the week (total ≥150 min/week)
	Alcohol consumption—≤ 2 standard drinks (20 g) per day for men and women

A REVIEW OF THE EVIDENCE

In 2008, the FDA issued a mandate requiring all new glucose-lowering medications to demonstrate CV safety prior to approval [32]. Consequently, there are now a multitude of completed and ongoing CVOTs (Table 1) [34], particularly for the dipeptidyl peptidase-IV

Table 1 CVOTs of glucose-lowering medications. Adapted from Cefalu et al. [34]

Drug class	Cardiovascular outcome trial	Completed	Ongoing
α-Glucosidase inhibitor			
Acarbose	Acarbose Cardiovascular Evaluation (ACE)	✔	
DPP-IV Inhibitor			
Alogliptin	Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE)	✔	
Linagliptin	Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA)	✔	
	Cardiovascular Outcome Trial of Linagliptin versus Glimepiride in Type 2 Diabetes (CAROLINA)	✔	
Saxagliptin	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53)	✔	
Sitagliptin	Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)	✔	
GLP-1 receptor agonist			
Albiglutide	Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus (HARMONY)	✔	
Exenatide	Exenatide Study of Cardiovascular Event Lowering (EXSCEL)	✔	
Dulaglutide	Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND)	✔	
Liraglutide	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)	✔	
Lixisenatide	Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA)	✔	
Semaglutide	Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6)	✔	
Insulin			
Insulin degludec	A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE)	✔	

Table 1 continued

Drug class	Cardiovascular outcome trial	Completed	Ongoing
Insulin glargine	Outcome Reduction with an Initial Glargine Intervention (ORIGIN)	✔	
SGLT-2 inhibitor			
Canagliflozin	Canagliflozin Cardiovascular Assessment Study (CANVAS)	✔	
	Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE)		✔
Dapagliflozin	Multicenter trial to evaluate the effect of dapagliflozin on the incidence of cardiovascular events (DECLARE-TIMI 58)	✔	
	A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (DAPA-CKD)		✔
	DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure)		✔
Empagliflozin	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)	✔	
	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved)		✔
	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced)		✔
Ertugliflozin	Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (VERTIS CV)		✔
TZD			
Pioglitazone	Insulin Resistance Intervention After Stroke (IRIS)	✔	

(DPP-IV) inhibitors, GLP-1RAs and SGLT-2 inhibitors. These trials have informed our approach as to which glucose-lowering medications may be safe in the context of T2DM and CVD.

Which Glucose-Lowering Medications Offer CV Protection?

DPP-IV inhibitors Collectively, these appear to have a neutral effect on CV outcomes (Table 2).

Table 2 Summary of DPP-IV inhibitors CVOTs

DPP-IV inhibitors			
TGA-approved	**Reimbursed**	**CVOT**	**CV effect**
Alogliptin [41, 42] (Nesina)	✔	*EXAMINE (n = 5380)*	Neutral for MACE
		High CV risk population	HR 0.96 (95% CI < 1.16); $p = 0.32$
		ACS requiring hospitalisation within 15–90 days before randomisation	
		Primary end point: 3-point MACE	
		Non-inferiority design	
		Alogliptin vs. PBO	
Linagliptin [30, 61] (Trajenta)	✔	*CAROLINA (n = 6033)* [29]	Not yet published
		High risk CV and/or CKD population	
		Established CVD or increased risk of CVD	
		Primary end point: 3-point MACE	
		Non-inferiority design	
		Linagliptin vs. glimepiride	
		CARMELINA (n = 6979) [61]	Neutral for MACE
		High CV risk population	HR 1.02 (95% CI 0.89–1.17); $p < 0$ .001
		Existing CKD, established CVD or both	
		Primary end point: 3-point MACE	
		Non-inferiority design	
		Linagliptin vs.PBO	
Saxagliptin [39, 40] (Onglyza)	✔	*SAVOR-TIMI (n=16,492)*	Neutral for MACE
		High CV risk population	HR 1.0 (95% CI 0.89–1.12); $p = 0.99$
		History of established CVD or multiple risk factors for vascular disease	
		Primary end point: 3-point MACE	
		Superiority and non-inferiority design	
		Saxagliptin vs. PBO	
Sitagliptin [60] (Januvia)	✔	*TECOS (n = 14,671)*	Neutral for MACE
		High CV risk population	HR 0.98 (95% CI 0.88–1.09); $p < 0.001$
		Pre-existing CVD	
		Primary end point: 4-point MACE	
		Superiority and non-inferiority design	
		Sitagliptin vs.PBO	

Table 2 continued

DPP-IV inhibitors			
TGA-approved	**Reimbursed**	**CVOT**	**CV effect**
Vildagliptin (Galvus)	✔	*NO CVOT reported*	Unknown

3-point MACE: *CI* confidence interval; CV death, nonfatal MI or nonfatal stroke; 4-point MACE: CV death, nonfatal MI, nonfatal stroke or hospitalisation for unstable angina; *ACS* acute coronary syndrome, *CVD* cardiovascular disease, *HF* heart failure, *HR* hazard ratio, *MACE* major adverse CV effect, *PBO* placebo

None of the trials demonstrated an increase in the primary composite end point of major adverse cardiovascular events (MACE), which included CV death, nonfatal MI, nonfatal stroke with or without hospitalisation for unstable angina. There was a very small absolute increase in cases of hospitalisation for heart failure (0.7%) associated with the use of saxagliptin [39]. The increase in risk was highest in patients at the highest absolute risk of heart failure, i.e., those with established CVD or multiple CVD risk factors [40]. A similar trend was seen with alogliptin but not with the other DPP-IV inhibitors [41, 42]. Overall, DPP-IV inhibitors satisfied the regulatory CV safety criteria for T2DM but appear to have no positive impact on CV outcomes.

GLP-1RAs CVOT data are available for three of the five GLP-1RAs approved in Australia (Table 3). While not yet registered in Australia, semaglutide also has published CV data [43]. The SUSTAIN-6 study reported a protective effect on 3-point MACE, driven by a significant reduction in nonfatal stroke [HR 0.61; (95% CI 0.38–0.99; $p = 0.04$)] and a nonsignificant reduction in nonfatal MI [HR: 0.74; (95% CI 0.51–1.08; $p = 0.12$)]. No difference in the risk of CV death was noted [43]. In contrast, lixisenatide (ELIXA study) had a neutral effect on CV outcomes [44], whereas the EXSCEL study assessing the once-weekly exenatide preparation just failed to reach significance for CV benefit with a 9% reduction in events (CI 0.83–1.00; $p = 0.06$) although a significant reduction in cardiovascular mortality was observed (Table 3) [45]. With liraglutide in the LEADER study, fewer patients experienced CV-related death, nonfatal MI or nonfatal stroke compared with placebo: 13% (608 of 4668 patients) vs. 14.9% (694 of 4672 patients), respectively (Table 3) [46]. The CVOT of dulaglutide is yet to be published [47], although the full data set is anticipated in 2019 [48].

The heterogenous effects on MACE within this drug class may reflect differences in the patient populations and designs of the CVOTs as well as being potentially related to the pharmacokinetic and structural differences between the individual GLP-1RAs. Nevertheless, CV safety for all the approved agents in this class has been demonstrated in high-risk T2DM patients [43–46]. In terms of safety and tolerability, transient nausea and vomiting are common side effects among patients initiated on GLP-1RAs yet are usually self-limiting with the longer acting agents. Retinopathy was seen in small numbers with semaglutide in cardiac safety trials [43].

SGLT-2 inhibitors Three out of four TGA-approved agents in this class have CVOT data (Table 4). Both canagliflozin and empagliflozin demonstrated a CV benefit in terms of reducing the primary end point of MACE, while dapagliflozin was found to have a non-significant reduction in this end point [49–51]. Ertugliflozin is yet to report CV outcome data (Table 1). In the EMPA-REG OUTCOME study, participants had established CVD (76% with coronary artery disease; 47% with a history of MI). The primary composite end point of death from CV causes, nonfatal MI or nonfatal stroke occurred in 10.5% (490 of 4687) receiving empagliflozin (pooled doses of 10 mg and 25 mg) vs. 12.1% (282 of 2333) in the placebo group, translating into a 14% relative risk reduction in these events (Table 4). This reduction was primarily driven by a 38% relative risk reduction in CV-related death [50].

Table 3 Summary of GLP-1RA CVOTs

GLP-1RAs			
TGA-approved	**Reimbursed**	**CVOT**	**CV effect**
Dulaglutide [47] (Trulicity)	✔	*REWIND (n = 9901)* High CV risk population Prior CV event, evidence of CVD or ≥ 2 CV risk factors Primary end point: 3-point MACE Dulaglutide vs. PBO	Just published
Exenatide BD (Byetta)	✔	*NO CVOT reported*	Unknown
Exenatide QW [45] (Bydureon)	✔	*EXSCEL (n = 14,752)* High CV risk population Pre-existing CVD Primary end point: 3-point MACE Non-inferiority design Exenatide QW vs. PBO	Neutral for MACE HR 0.91 (95% CI 0.83–1.00) $p < 0.001$ for noninferiority
Liraglutide [46] (Victoza)	✗	*LEADER (n = 9340)* High CV risk population Pre-existing CVD; kidney disease; HF; or ≥ 1 CV risk factor Primary end point: 3-point MACE Superiority and non-inferiority design Liraglutide vs. PBO	Benefit for MACE HR 0.87 (95% CI 0.78–0.97) $p < 0.001$ for noninferiority, $p = 0.01$ for superiority
Lixisenatide [44] (Lyxumia)	✗	*ELIXA (n = 6068)* High CV risk population Pre-existing CVD Primary end point: 4-point MACE Superiority and non-inferiority design Lixisenatide vs. PBO	Neutral for MACE HR 1.02 (95% CI 0.89–1.17) $p < 0.001$ for noninferiority

Table 3 continued

GLP-1RAs			
TGA-approved	**Reimbursed**	**CVOT**	**CV effect**
Semaglutide[a] [43]	✔	*SUSTAIN-6 (n = 3297)* High CV risk population Established CVD, chronic heart failure or CKD ≥ stage 3 or ≥ 60 years of age with at least one CV risk factor Primary end point Non-inferiority design Semaglutide vs.PBO	Benefit for MACE HR 0.74 (95% CI 0.58–0.95) $p < 0.001$ for noninferiority

BD twice daily, *CKD* chronic kidney disease, *HR* hazard ratio, *MACE* major adverse CV events, *PBO* placebo, *QW* once weekly

[a] Not available as of March 2019, pending TGA approval

Although no longer government-reimbursed in Australia, canagliflozin also led to a 14% reduction in MACE compared with placebo in the CANVAS programme study (Table 4) [49]. The DECLARE-TIMI 58 study supported the CV safety of dapagliflozin in patients with T2DM and established CVD or those with T2DM and CV risk factors (differing from the more homogenous EMPA-REG OUTCOME cohort) and, unlike canagliflozin and empagliflozin, resulted in a non-significant reduction in the co-primary end point of MACE (Table 4) [51]. Dapagliflozin did result in a lower rate of CV death or hospitalisation for heart failure vs. placebo (4.9% vs. 5.8%, respectively; $p = 0.005$), principally driven by a reduction in admission for heart failure [51]. A meta-analysis of these major trials released, at the same time as DECLARE-TIMI 58 concluded that "SGLT-2 inhibitors have moderate benefits on atherosclerotic MACE that seem confined to patients with established atherosclerotic CVD. However, they have robust benefits on reducing hospitalisation for heart failure and progression of renal disease regardless of existing atherosclerotic CVD or a history of heart failure" [52].

Aside from CV safety, it is important to note that SGLT-2 inhibitors as a class have shown an increased risk of mycotic genital infections and rarely euglycaemic diabetic ketoacidosis [49–51]. The class generally has low rates of hypoglycaemia unless prescribed in conjunction with sulphonylureas or insulin. The risk can be minimised through appropriate patient education and monitoring, such as temporarily ceasing the medication when a patient has an intercurrent illness or dehydration or to stop the medication 3 days before elective surgery/procedures.

To summarise, unlike DPP-IV inhibitors, specific agents in the GLP-1RAs and SGLT-2 inhibitor classes have been found to confer CV benefits in variable populations of T2DM patients with established CVD or who are at high risk of a CV event.

SGLT-2 Inhibitors or GLP-1RAs for At-Risk CV Individuals with T2DM?

With their demonstrable CV safety, combined with their favourable effects on weight and low potential of hypoglycaemia, the recent ADA/EASD guidelines have recommended GLP-1RAs and SGLT-2 inhibitors as preferred treatment

Table 4 Summary of SGLT-2 inhibitor CVOTs

SGLT-2 inhibitors			
TGA-approved	**Reimbursed**	**CVOT**	**CV effect**
Canagliflozin [49] (Invokana)	✗	*CANVAS programme (n = 9901)*	Benefit for MACE
		High CV risk population	Primary end point MACE
		Prior CV event, evidence of CVD or ≥ 2 CV risk factors	HR: 0.86 (95% CI 0.75–0.97)
		Primary end point: 3-point MACE	$p < 0.001$ for noninferiority
		Canagliflozin vs. PBO	$p = 0.02$ for superiority
		Superiority and non-inferiority design	
Dapagliflozin [51] (Forxiga)	✔	*DECLARE-TIMI 58 (n = 17,160)*	Neutral for MACE
		High CV risk population	HR: 0.93 (95% CI 0.84–1.03); $p = 0.17$
		History of established CVD or multiple CVD risk factors	Benefit for composite of CV death or hospitalisation for heart failure
		Co primary end points	HR 0.83; (95% CI 0.73–0.95); $p = 0.005$ for superiority
		1. 3-point MACE	
		2. Composite of CV death or hospitalisation for heart failure	
		Dapagliflozin vs. PBO	
Empagliflozin [50] (Jardiance)	✔	*EMPA-REG OUTCOME (n = 7020)*	Benefit for MACE
		High CV risk population	HR 0.86 (95% CI 0.74–0.99)
		Pre-existing CVD	$p = 0.04$ for superiority
		Primary end point: 3-point MACE	
		Empagliflozin vs. PBO	
		Superiority and non-inferiority design	
Ertugliflozin (Steglatro)	✔	*NO CVOT reported*	Unknown

options in addition to metformin for those with established CVD (e.g., patients who had experienced an MI or stroke or had undergone a revascularisation procedure) [30]. In those patients with T2DM and established CVD with co-existing heart failure, or those with T2DM and CKD (with or without CVD), SGLT-2 inhibitors are considered the most appropriate choice unless contraindicated, in which case GLP-1RAs with proven CV benefits are recommended [34, 53]. It is worth noting that there are limited data highlighting the glycaemic benefit of combining SGLT-2 inhibitors and GLP-1RA therapies [54, 55]; moreover, the impact of such a combination on CV outcomes is unknown. From an Australian government reimbursement perspective, such combined use is not approved for subsidy at the present time.

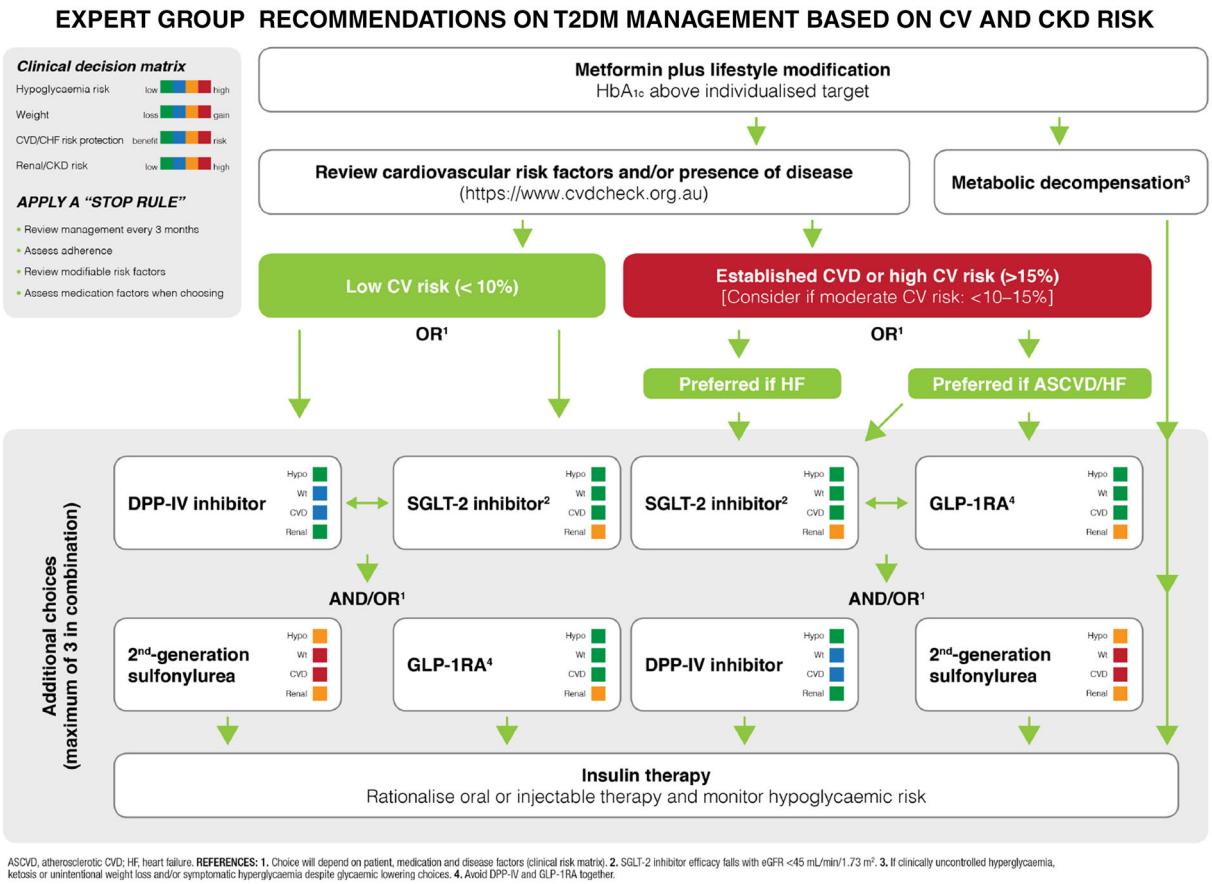

Fig. 1 Treatment algorithm according to CV and CKD risk

NAVIGATING COMMON AND COMPLICATED CASE SCENARIOS IN T2DM: EXPERT PERSPECTIVES

So how should primary practitioners interpret the CVOT data and recent guidelines to inform management of T2DM in primary practice? As informative as these guidelines are, a major gap is understanding how to treat T2DM with multiple CV risk factors but without established CVD. To address this, a local expert committee that included primary practitioners, a cardiologist and an endocrinologist was convened to identify and discuss case studies of T2DM patients commonly seen in clinical practice who could be stratified according to high, moderate and low CV risk as well as by additional complications such as the presence of CKD. The key objective was to provide a clinical narrative alongside an algorithm (Fig. 1) that goes beyond glucose-lowering to help guide the treatment decision-making process for each situation.

CASE SCENARIO: HIGH CV RISK PATIENT

James: a 64-year-old male (ex-smoker) with a 4-year history of T2DM. This was diagnosed when he had documented triple-vessel disease and underwent coronary artery bypass graft surgery 4 years ago. He recently moved into the area and needed prescriptions. This visit provided an opportunity to review his current medication and management.

Clinical Assessments HbA_{1c} 7.3% (56 mmol/mol); eGFR 60 ml/min/1.73 m^2;

weight 92.5 kg; height 1.83 m; BMI 27.6 kg/m^2; total cholesterol 3.9 (LDL 1.82; triglycerides 2.0; HDL 1.03); blood pressure 130/80 mmHg; urine ACR 7.5 mg/mmol.

Existing Medications Aspirin 100 mg once daily; insulin glargine (40 U) and insulin aspart (6 U at his main meal); rosuvastatin 10 mg once daily; perindopril 5 mg once daily.

Clinical Considerations for James

James has presented with T2DM with established CVD, which significantly increases his immediate risk of heart failure several-fold as well as premature mortality [56]. Diabetes management needs to focus on optimising ways to reduce these risks. He also has microalbuminuria, which contributes to a greater CV event rate.

Primary Considerations To prevent future risk of CVD-associated death and heart failure. To achieve an appropriate HbA_{1c} target (< 7%; 53 mmol/mol) and optimise his glucose management to prevent the progression of microalbuminuria and renal complications without increasing hypoglycaemia.

How to Manage? To consider where change in therapy may provide additional benefit, e.g., consideration should be focussed on the established CV benefit from newer glucose-lowering agents as well as optimising blood pressure control to further lower risk of heart failure [57].

Which Glucose-Lowering Agent? An agent that may optimise glycaemia, has a low hypoglycaemic profile and a low-to-acceptable clinical risk with proven CVD risk reduction in a patient such as James with a high risk of a CV event. Based on current evidence, an SGLT-2 inhibitor (dapagliflozin, empagliflozin) or GLP-1RA (liraglutide) may be appropriate alternative options as they have demonstrated CV benefits. To note, in clinical trials with patients with a similar presentation, empagliflozin showed a CV mortality benefit while both empagliflozin and dapagliflozin reduced HF hospitalisation [50, 51]. When selecting SGLT-2 inhibitors, baseline eGFR and the need for ongoing monitoring need to be carefully considered. Of note, dapagliflozin is not indicated for patients with an eGFR < 60 ml/min/1.73 m^2, while empagliflozin is not appropriate for patients with an eGFR < 45 ml/min/1.73 m^2.

Other Considerations To consider patient profile (lifestyle/adherence), patient preference (oral versus injectable therapy) as well as cost implications (reimbursement criteria) and specific side effect profiles (risks for genitourinary infections).

Following an informed discussion with James and the fact that he is at risk of heart failure and CV death, he expressed a preference for an oral medication. An SGLT-2 inhibitor was therefore prescribed in addition to his existing glucose-lowering medications, and we ceased his prandial (rapid-acting) insulin. He was instructed to monitor his blood glucose and report any hypoglycaemia. The perindopril was increased to 10 mg daily.

Review

There was no reported hypoglycaemia after an initial monthly review, and then after 3 months, James presented to review his blood investigation result. His HbA_{1c} was now at 6.8% (51 mmol/mol), and his weight had dropped to 90.5 kg. He was happy as he was able to cease his meal-time insulin. Home-monitoring of blood pressure showed a reduction to 110/70. He also felt motivated to make some lifestyle changes and had started to do more daily walking.

CASE SCENARIO: MODERATE CV RISK PATIENT

Chris, a 59-year-old male non-smoker with a 10-year history of T2DM and prior diagnosis of hypertension, presented to his primary practitioner for a routine visit, which provided an opportunity to review his current medication and management of T2DM.

Clinical Assessments HbA_{1c} 7.6% (60 mmol/mol); eGFR 61 ml/min/1.73 m^2; weight 101.4 kg; height 1.78 m; BMI 32.0 kg/m^2; total cholesterol 3.8 (LDL 1.99; triglycerides 0.7; HDL 1.11); blood pressure 145/90 mmHg. Urine ACR < 2.5 mg/mmol.

Existing Medications Atorvastatin 10 mg; sitagliptin/metformin 50/850 mg BD; ramipril 5 mg once daily.

Clinical Considerations for Chris

While Chris has not presented with established CVD, he has several high-risk factors that predispose him to future risk of CVD. The question arises as to how to modify CV risk in a patient like Chris.

Primary Considerations To optimise glycaemic control for microvascular risk reduction and address any weight issues by optimally assisting with weight loss.

How to Manage? Review self-management and lifestyle modification to assist with weight loss and improved glycaemia. Consider the addition of a glucose-lowering agent with proven CVD safety or positive CVD benefit that also has weight-loss potential.

Which Glucose-Lowering Agent? Based on new research and guidelines [30, 34, 53, 57], an SGLT-2 inhibitor (oral once-daily dapagliflozin, empagliflozin) or a GLP-1RA (once-daily liraglutide, once-weekly dulaglutide) is an appropriate add-on therapy to Chris's current standard-of-care treatment. When selecting SGLT-2 inhibitors, baseline eGFR and the need for ongoing monitoring need to be carefully considered and the risk of euglycaemic diabetes ketoacidosis and uncommon risks such as mild diuresis and mycotic genital infections discussed. When selecting a GLP-1RA, the frequency of injections may alter choice.

Other Considerations To consider patient profile (lifestyle/adherence), patient preference (oral versus injectable therapy) as well as cost implications (reimbursement criteria).

Following an informed discussion with Chris, he expressed preference for an oral, daily medication (dapagliflozin, empagliflozin) as he felt he may forget taking an injection once a week (exenatide QW; dulaglutide). He was not prepared to be out of pocket for the once-daily GLP-1RA option (liraglutide) but was open to using a weekly injection in the future. An SGLT-2 inhibitor was therefore prescribed. In addition, his existing medications were optimised with the dose of sitagliptin/metformin increased to 50/1000 mg BD. The dose of ramipril was also increased to 10 mg and it was recommended to be taken at night.

Review

After 3 months, Chris presented for review. He felt happy as he had managed to get his weight down to below 100 kg. This has spurred him on to set a weight goal of 90 kg. His HbA_{1c} was now 7.1% (54 mmol/mol) and he had tolerated the SGLT-2 inhibitor well, with some manageable increased urinary frequency. As he was tolerating the SGLT-2 inhibitor, for cost reasons he was switched to a combination SGLT-2 inhibitor and DPP-IV inhibitor and continued on metformin.

CASE SCENARIO: LOW CV RISK PATIENT

Gabrielle, a 56-year old female non-smoker with a 7-year history of T2DM, presented to her primary practitioner for a routine visit, which provided an opportunity to review her current medication and management of T2DM.

Clinical Assessments HbA_{1c} 7.2% (55 mmol/mol); eGFR 90 ml/min/1.73 m^2; weight 78 kg; height 1.66 m; BMI 28.3 kg/m^2; total cholesterol 5.8 (LDL 3.2; triglycerides 1.4; HDL 1.2); blood pressure 110/70 mmHg; ACR normal. Absolute CVD risk score reveals Gabrielle to have a low risk of CV (6%).

Clinical Considerations for Gabrielle

In a younger patient with T2DM there is a need to focus on long-term complication prevention. "Tight" glycaemic control may assist in reducing microvascular risk, but macrovascular risk reduction is equally important. Women with diabetes may in fact have higher long-term risks of ischaemic heart disease compared with aged-

matched males [58] and a 50% greater risk of a CV-related fatal outcome [59]. Specific attention to modifiable risk factor reduction is therefore imperative.

Existing Medications Metformin 850 mg BD.

Primary Consideration To proactively manage long-term modifiable CV risk while managing glycaemia.

How to Manage? To consider individualising "tight' glycaemic management without increasing hypoglycaemia risk and addressing lipid control.

Other Considerations To consider patient profile (lifestyle/adherence), patient preference (formulation) as well as cost implications (reimbursement criteria).

Following an informed discussion and reinforcing the importance of lifestyle modifications, Gabrielle agreed the first step would be to optimise her current medications to improve her glycaemic and lipid levels. We should be concerned about her long-term CVD risk as this is often underestimated in women. Her CVD risk should continue to be monitored and will fall into a high-risk group as she turns 60. For the time being, changes to her glucose-lowering medications are not considered necessary and she will continue to be monitored.

Review

After 3 months, Gabrielle presented for review. She was commenced on a DPP-IV inhibitor and achieved a reduction of HbA_{1c} to 6.9% (52 mmol/mol). By maintaining a healthier lifestyle, she has also experienced some 2 kg weight loss and has understood the importance of assessing her cholesterol on an ongoing basis.

CONCLUSIONS

Individuals with T2DM and who are at an increased risk of CV and/or CKD can be optimally managed through the addition of selective SGLT-2 inhibitors or GLP-1RAs to their existing standard of care. Treatment choice should be guided by clinical criteria, including the level of CV or CKD risk, as well as individual goals, patient preference for oral or injectable therapies and cost implications of a given treatment for the patient.

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