Glucagon-like peptide-1 receptor agonist (GLP1-RA) therapy in type 2 diabetes

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Background
Type 2 diabetes (T2D) is a national health priority. Its rising prevalence is accompanied by a high burden of diabetes-related complications, many of which are preventable. Numerous glucose-lowering medications have been developed in recent years with growing evidence relating to their efficacy and safety. These advances have increased the complexity of prescribing decisions in T2D.

Objective
This review provides clinicians with relevant evidence and practical advice concerning glucagon-like peptide-1 receptor agonists (GLP1-RAs) in T2D.

Discussion
The Royal Australian College of General Practitioners recommends GLP1-RAs as an option for second-line therapy in T2D. GLP1-RAs contribute to weight loss and glycated haemoglobin reduction. GLP1-RAs also reduce incidence of cardiovascular events in selected populations, and available evidence suggests renoprotective effects. Common adverse effects include gastrointestinal symptoms, especially in the weeks following treatment initiation. GLP1-RAs should be considered for people with T2D at high cardiovascular risk or where weight loss is a priority.

TYPE 2 DIABETES (T2D) is a national health priority in Australia due to its growing prevalence and the high burden of diabetes-related complications, many of which are preventable.[1] The vast majority of T2D care occurs in general practice, from preventing diabetes in those at risk through to care for those reaching end of life.[2] The landscape of diabetes therapy has seen remarkable changes with recent developments in therapeutic options. This has enabled a shift from predominantly focusing on glucose-lowering, to facilitating selection of glucose-lowering agents on the basis of their ability to reduce cardiovascular and renal risk, side-effect profile, cost and individual patient preferences.

Prescribing of newer classes of glucose-lowering medications, such as sodium–glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP1-RAs), is increasing rapidly due to their favourable effects on cardiovascular and renal disease, as well as metabolic risk profile.[3,4] The ever-expanding treatment options for T2D, accompanied by a growing body of evidence, have increased the complexity of prescribing decisions in general practice. Alongside lifestyle measures targeting diet, physical activity and weight management, Australian guidelines recommend metformin as usual first-line pharmacotherapy unless contraindicated or not tolerated.[4]

Recommendations for second-line dual therapy now include five therapeutic class options: SGLT2 inhibitors, GLP1-RA, dipeptidyl peptidase-4 (DPP-4) inhibitors, sulphonylureas and insulin.[4] Each of these classes includes multiple available agents. While there is added complexity, the benefit is that clinicians are increasingly able to tailor evidence-based therapy to the individual patient. A review of evidence and prescribing advice for SGLT2 inhibitors in T2D has been published in *Australian Journal of General Practice* previously.[5] The aim of this review is to summarise current evidence for GLP1-RA therapy in T2D and offer practical guidance for application in general practice.

Available GLP1-RAs

Six GLP1-RAs have been developed, with four currently available in Australia: dulaglutide 1.5 mg weekly, exenatide 10 µg BD, semaglutide 0.5 or 1.0 mg weekly, and liraglutide 1.2 mg or 1.8 mg daily (all but liraglutide are available via the Pharmaceutical Benefits Scheme with some restrictions). Exenatide 2 mg weekly has been withdrawn from the Australian market for commercial reasons. Currently available GLP1-RAs are all administered subcutaneously due to limited oral bioavailability. Oral semaglutide, which is co-formulated with an absorption enhancer, has been developed but is not yet registered for use in Australia.[6]

Mechanism of action

Glucagon-like peptide-1 (GLP1) is one of two main known incretin hormones triggered by oral nutrient intake. Diminished GLP1 release is a known characteristic of T2D.[7] For individuals with T2D, beneficial effects of exogenous GLP1 include a reduction in glucagon secretion, hepatic gluconeogenesis and appetite and gastric emptying, while stimulating insulin secretion.[8] Promotion of satiety results in reduced caloric intake. While these effects of GLP1 counter hyperglycaemia, exogenous GLP1 does not impair the physiological glucagon response to hypoglycaemia.[9]

Glycaemic and weight-loss benefits

GLP1-RA therapy achieves weight loss through the aforementioned impact on gastric emptying and satiety.[10] These agents have shown benefit in reducing fasting and postprandial glycaemia, thereby reducing glycated hemoglobin (HbA1c).[8] Superior glucose-lowering effects have been demonstrated when compared to established oral agents including sulphonylureas,[11] DPP-4 inhibitors[12] and SGLT2 inhibitors.[13]

Head-to-head studies between different GLP1-RAs are limited but suggest superior weight loss and HbA1c reduction with dulaglutide 1.5 mg compared to twice-daily exenatide 10 µg (AWARD 1),[14] with semaglutide 1 mg weekly compared to weekly exenatide 2 mg (SUSTAIN 3),[15] and with semaglutide 0.5 mg or 1 mg weekly compared to dulaglutide 0.75 mg or 1.5 mg weekly, respectively (SUSTAIN 7).[16]

Cardiovascular risk

In response to concerns about the cardiovascular safety of some glucose-lowering therapies, the United States Food and Drug Administration mandated cardiovascular outcome trials (CVOTs) of new agents. This requirement led to unanticipated results showing not just safety but also cardiovascular benefits of both SGLT2 inhibitors and GLP1-RAs.[17] In large trials involving patients with high cardiovascular risk, GLP1-RAs have shown a consistent modest reduction in risk of major adverse cardiovascular events, a composite outcome including cardiovascular death, myocardial infarction and stroke (Table 1). The secondary outcome results from these trials suggest that GLP1-RAs may be of greater benefit for prevention of stroke than of myocardial infarction.[18,19] The cardiovascular benefits of GLP1-RAs are independent of reductions in glycaemia and weight.[20,21] Meta-analyses have also suggested favourable effects of GLP1-RAs with regard to heart failure hospitalisations and all-cause mortality.[22] Furthermore, GLP1-RA therapy is associated with modest improvements in other cardiovascular risk factors, including lipid profiles and blood pressure.[23]

Renal benefits and safety

There are presently no published trials primarily investigating renal outcomes of GLP1-RA therapy, although some are underway. Secondary and exploratory analyses from CVOTs have suggested renoprotective effects, primarily through reduction in albuminuria, with some data also suggesting protection against reductions in estimated glomerular filtration rate (eGFR).[23,24] The reduction in urinary albumin excretion likely relates directly to improvements in glycaemia. GLP1-RAs are a useful option in the context of renal impairment, with no dose adjustment necessary. Dulaglutide and liraglutide are approved for use

Table 1. Summary of key trials investigating risk of major adverse cardiovascular events (MACE) with GLP1-RA agents available in Australia[18,19,31,32]

GLP1-RA	Trial name, year published	Study population (n)	Pre-existing CVD	Median follow-up (months)	3-point MACE HR compared to placebo (95% CI; *P* value for superiority)	MACE absolute event rate (treatment vs placebo)
Liraglutide	LEADER[31] 2016	9,340	81.3%	46	0.87 (0.78, 0.97; *P* = 0.01)*	13.0% vs 14.9%
Semaglutide	SUSTAIN 6[19] 2016	3,297	83.0%	25	0.74 (0.58, 0.95; *P* = 0.002)*	6.6% vs 8.9%
Exenatide extended release	EXSCEL[32] 2017	14,752	73.1%	38	0.91 (0.83, 1.00; *P* = 0.06)*	11.4% vs 12.2%
Dulaglutide	REWIND[18] 2019	9,901	31.5%	65	0.88 (0.79, 0.99; *P* = 0.0467)*	12.0% vs 13.4%

**Aside from REWIND, the primary hypothesis for each trial was non-inferiority against placebo (ie cardiovascular safety). This endpoint was met in each trial.*
CI, confidence interval; CVD, cardiovascular disease; GLP1-RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio

down to eGFR 15 mL/min/1.73 m^2, while semaglutide is approved down to eGFR 30 mL/min/1.73 m^2.

Safety and tolerability

Gastrointestinal side effects

The main adverse effects of GLP1-RA therapy are gastrointestinal symptoms, in particular nausea and vomiting, which are frequently encountered.[25] These symptoms are dose dependent and usually diminish over time,[26] but may be sufficient to lead to discontinuation of therapy in a small proportion of patients. Diarrhoea may also occur and is more common with longer-acting GLP1-RAs.[27]

Pancreatic and gall bladder events

Early animal studies, case reports and adverse event reporting data raised the possibility that GLP1-RAs could increase risk of acute pancreatitis and possibly chronic pancreatitis and pancreatic cancer.[28] However, these associations have not been confirmed in subsequent meta-analyses of clinical trials.[29] GLP1-RAs do appear to increase serum lipase and amylase levels, but these elevations are not associated with increased risk of acute pancreatitis.[30] Aside from the LEADER trial (liraglutide), major GLP1-RA trials have excluded participants with a history of pancreatitis.[18,19,31,32] Therefore, it is reasonable for clinicians to be cautious using these agents in this situation. GLP1-RA use has additionally been linked to an increased occurrence of cholelithiasis and cholecystitis in some but not all trials.[19,31,33] Rapid weight loss is a plausible mechanism for this association.

Medullary thyroid cancer

Results from animal studies raised concern of an increased risk of thyroid C-cell adenomas and medullary thyroid carcinomas with GLP1-RA use, but this has not been replicated in humans.[34] Nonetheless, the general recommendation is avoidance of these agents in people with a history of medullary thyroid cancer or multiple endocrine neoplasia, and these formed part of the exclusion criteria for major GLP1-RA trials.

Table 2. Potential adverse effects of GLP1-RAs and considerations for clinical practice

Potential effect	Clinical considerations
Nausea and vomiting	• Advise patients of potential effect and that this will likely subside over a few weeks. Offer management strategies, including to eat slowly, reduce portion size, avoid eating beyond satiety and avoid high-fat foods • Delay dose up-titration of semaglutide or twice-daily exenatide if necessary
Gastroparesis	• Take caution if history of gastroparesis or severe gastro-oesophageal reflux disease • Weekly GLP1-RA may have less gastrointestinal side effects than the twice-daily exenatide
Hypoglycaemia	• Minimal risk, but needs to be considered when GLP1-RAs used in combination with insulin or sulphonylureas • Consider dose reduction of insulin or sulphonylurea, depending on baseline HbA1c and glucose levels (in clinical trials a 10–20% insulin dose reduction has been undertaken on commencement of GLP1-RA therapy) • Educate patients at risk about hypoglycaemia management and advise to increase frequency of blood glucose level monitoring initially
Diabetic retinopathy	• If HbA1c well above target or history of retinopathy, ensure patients are up to date with retinal screening before starting GLP1-RA • If patients have proliferative diabetic retinopathy, arrange ophthalmologist consultation and management prior to starting GLP1-RA
Increased heart rate	• GLP1-RAs cause mild reversible elevation in heart rate (average increase 2–3 beats per minute[38]), which does not appear to have clinical implications[39]
Cholelithiasis and cholecystitis	• Advise patients of potential risk • No role for routine ultrasonography unless relevant symptoms/signs appear
Pancreatitis	• If patients have a history of pancreatitis, consider alternative agents and only initiate after advising of possible risks • Discontinue GLP1-RA during acute pancreatitis. Ensure thorough investigation for underlying cause without premature dismissal of the role of future recommencement of GLP1-RA therapy • No role for routine testing of pancreatic enzymes unless pancreatitis is suspected
Pancreatic cancer	• No clinical evidence of increased risk, but advisable to avoid GPL1-RA in context of existing pancreatic cancer or pre-malignant pancreatic lesions
Medullary thyroid carcinoma	• Avoid use of GLP1-RA if there is a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2

GLP1-RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin

Diabetic retinopathy

Diabetic retinopathy (DR) in the context of GLP1-RA use is a safety concern requiring further clarification. The use of semaglutide compared to placebo in individuals at high cardiovascular risk resulted in an increased occurrence of DR.[19] Dulaglutide compared to placebo

resulted in a non-significant increase in DR.[18] This may partly be accounted for by the phenomenon of rapid glycaemic improvement leading to deterioration of pre-existing DR. This is supported by the absence of this adverse event among patients without pre-existing retinopathy treated with semaglutide, and the increased risk of worsening retinopathy seen with greater HbA1c reductions.[10]

Prescribing

GLP1-RAs can be used as an adjunct to oral hypoglycaemic agents and with insulin therapy. Metformin remains the first line of treatment for T2D, and GLP1-RAs can be used as second- or third-line agents, or in combination with insulin.[4]

GLP1-RAs should not be used in combination with DPP-4 inhibitors because there is no additive benefit. Insulin dose reduction should be considered if the patient's HbA1c is close to target.[35] There is limited experience with the use of GLP1-RAs in individuals aged >75 years, and in individuals with severe hepatic or renal impairment (eGFR <15 mL/min/1.73m^2). These agents should be avoided in pregnancy and breastfeeding.

Patients should be counselled on possible adverse effects (Table 2) and strategies to manage common events such as gastrointestinal symptoms. Regular communication and close follow-up to facilitate exploration of patient concerns and experiences will improve adherence.[36]

All eligible people with diabetes in Australia are encouraged to be registered on the National Diabetes Services Scheme (NDSS). Some GLP1-RA preparations require disposable pen needles that can be accessed via the NDSS.

Choosing SGLT2 inhibitors and/or GLP1-RA therapy

With growing efficacy evidence for both SGLT2 inhibitors and GLP1-RAs, clinicians are often faced with a choice between the two classes. Treatment with one or both of these classes should be considered for individuals with T2D and established cardiovascular disease (CVD), multiple cardiovascular risk factors or chronic kidney disease (CKD;

Table 3. Considerations for clinicians when choosing second-line glucose-lowering therapy after metformin for adult patients with type 2 diabetes*[2,4,5,40]

	Clinical scenario where class is recommended	Advantages	Disadvantages	Clinical scenario where caution is warranted or class should be avoided
GLP1-RA	• Established CVD or high CVD risk • Obesity	• Weekly administration • HbA1c and weight-lowering effects stronger than other classes • CVD and renal benefits observed in selected cohorts	• Injectable therapy • Risk of gastrointestinal side effects • Possible risk of cholecystitis • High cost	• History of pancreatitis • Untreated retinopathy • Gastroparesis • eGFR <15 mL/min/1.73m^2
SGLT2 inhibitor	• Heart failure • Stage 1–3 CKD • Established CVD or high CVD risk	• Beneficial effect on weight • CVD and renal benefits observed in selected cohorts	• Increased risk of genitourinary infection • Side effects can include polyuria and polydipsia	• Recurrent or complicated genitourinary infections • Fasting, peri-operative, acute illness (DKA risk) • eGFR <25 mL/min/1.73m^2
DPP-4 inhibitor		• Well tolerated • Neutral effect on weight • Safe at any eGFR (all but linagliptin require dose adjustment)	• Possible increased risk of pancreatitis	• History of pancreatitis
Sulphonylurea		• Low cost	• Hypoglycaemia risk • Weight gain	• Increased hypoglycaemia risk (eg renal impairment, elderly)
Insulin	• Consider early if very high blood glucose levels	• Dose can be titrated to effect	• At least daily injections • High cost • Hypoglycaemia risk • Weight gain	• Limited capacity for self-management (injecting, glucose monitoring etc)

**Other less commonly used but approved second-line therapies include acarbose and thiazolidinediones (not included here).*
CKD, chronic kidney disease; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; SGLT2, sodium–glucose co-transporter-2

Table 3; refer also to relevant approved product information for each individual agent regarding safe use in CKD).[2] Using SGLT2 inhibitors and GLP1-RAs together is safe and has been associated with a greater reduction in HbA1c, weight and systolic blood pressure when compared to SGLT2 inhibitor monotherapy.[37] However, this combination is not currently government subsidised in Australia and patients may incur an unreasonable cost. The decision to introduce GLP1-RA or SGLT2 inhibitor therapy should consider patient preferences, risk of adverse effects and likelihood of benefit according to individual risk factor profiles. Table 3 summarises key prescribing considerations for GLP1-RA and the other four classes of medications recommended as second-line options for adults with T2D. At present, there is stronger evidence for SGLT2 inhibitor use specifically with regard to prevention of hospitalisation for heart failure and delaying CKD progression.[3,23] GLP1-RAs are associated with greater reduction in weight and HbA1c.[13]

Conclusion

The approach to pharmaceutical management of T2D is evolving, with increasing emphasis on personalising therapy according to patient preferences and individual risk of specific diabetes complications. Where indicated, GLP1-RA or SGLT2 inhibitor therapy should be considered for prevention of diabetes complications, not just glucose-lowering. GLP1-RAs favourably impact weight, glycaemia, lipids and blood pressure. Aside from frequent gastrointestinal side effects with treatment initiation, they are relatively safe and the option for once-weekly dosing is convenient. Weekly GLP1-RAs should be considered for people with T2D at high risk of CVD or where weight loss is particularly desired, noting that daily oral SGLT2 inhibitor therapy may be preferable when heart failure risk or delaying CKD progression are priorities.

Key points

- There has been a rapid increase in therapeutic options for T2D.
- Choice of glucose-lowering therapy should be tailored to the individual patient.
- GLP1-RAs are recommended as an option for second- or third-line T2D treatment.
- GLP1-RAs effectively reduce glycaemia and promote weight loss.
- There is a relative cardiovascular risk reduction with GLP1-RA therapy in people at high risk.

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