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REVIEW ARTICLE

Early type 2 diabetes treatment intensification with glucagon-like peptide-1 receptor agonists in primary care: An Australian perspective on guidelines and the global evidence

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Abstract

Early and intensive management of type 2 diabetes has been shown to delay disease progression, reduce the risk of cardiorenal complications and prolong time to treatment failure. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are being increasingly recognized for their potential in early disease management, with recent guideline updates recommending second-line use of this injectable drug class alongside oral glucose-lowering drugs. GLP-1RAs target at least six of the eight core defects implicated in the pathogenesis of type 2 diabetes and offer significant glycaemic and weight-related improvements over other second-line agents in head-to-head trials. In addition, placebo-controlled clinical trials have shown cardiovascular protection with GLP-1RA use. Even so, this therapeutic class is underused in primary care, largely owing to clinical inertia and patient-related barriers to early intensification with GLP-1RAs. Fortunately, clinicians can overcome barriers to treatment acceptance through patient education and training, and management of treatment expectations. In this review we comment on global and Australian guideline updates and evidence in support of early intensification with this therapeutic class, and provide clinicians with practical advice for GLP-1RA use in primary care.

KEYWORDS
early intensification, early treatment, GLP-1RA, guidelines, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes (T2D) is a complex, chronic and progressive disease characterized by uncontrolled hyperglycaemia, arising as a consequence of peripheral insulin resistance and declining insulin production from pancreatic β-cells.[1] A multidisciplinary approach to patient care is often required, owing to the prevalence of co-morbidities such as obesity, cardiovascular disease (CVD) and renal disease,[2] which have strong pathological links to T2D; for example, prolonged hyperglycaemia can increase the risks of macrovascular and microvascular complications such as myocardial infarction and renal damage.[3,4] Given these complications, it is concerning that one in two patients with T2D in Australia does not achieve glycaemic targets recommended by local guidelines.[5]

Early intensive management of T2D is understood to have a beneficial impact on disease progression, risk of complications and time to treatment failure.[6-10] The first-line pharmacological intervention for hyperglycaemia is metformin,[11] which can be initiated at diagnosis alongside diet and lifestyle modification.[1,12] However, more than one-half of patients need the addition of a second glucose-lowering agent within 3 years of diagnosis.[13,14] As T2D progresses, patients often require further intensification of pharmacotherapy using multiple agents as well as insulin.[15-17]

An algorithmic subclassification approach for T2D was proposed in 2018 by Leif Groop (also referred to as the Ahlqvist classification), in which patients are clustered into five phenotypically similar groups based on important risk factors and aspects of diabetes pathogenesis (presence of glutamic acid decarboxylase 65 autoantibodies, age at T2D diagnosis, body mass index, HbA1c at diagnosis and homeostatic model assessment estimates of insulin secretion capacity).[18] The stability of these clusters has since been validated across three large, independent cohorts from Sweden and Finland.[19] Importantly, these clusters differ substantially in terms of the speed of progression towards insulin requirement and risk of diabetes complications,[18,19] highlighting the need for a range of second-line treatment options to address the diverse clinical characteristics and treatment requirements of patients with T2D.

Fortunately, in the last 5-10 years, a number of additional second-line treatment options for T2D have become available to help meet these needs, including oral glucose-lowering drugs (sodium-glucose co-transporter-2 inhibitors [SGLT2is], dipeptidyl peptidase-4 inhibitors [DPP4is]) and, most recently, glucagon-like peptide-1 receptor agonists (GLP-1RAs).[1,12] However, obstacles remain to the second-line use of GLP-1RAs in primary care. Clinical inertia is a common barrier to patients receiving treatments such as GLP-1RAs that may help them to achieve HbA1c targets,[20] and patients may be reluctant to initiate GLP-1RAs owing to a fear of needles or negative associations with injectable T2D treatments.[21-23]

In this review, we comment on recent guideline updates and clinical data in support of the early use of GLP-1RAs, and provide clinicians with practical advice to reduce barriers to the use of GLP-1RAs as second-line agents in primary care. Although developed from an Australian perspective, this review is based on international evidence, and the lessons and conclusions thus derived are applicable to diabetes care globally.

2 | EARLY INTERVENTION WITH GLP-1RAS

2.1 | General evidence supporting early and intensive T2D treatment

Early treatment intensification has been shown to delay treatment failure in patients newly diagnosed with T2D.[8] For patients assigned to oral vildagliptin 2 years after diagnosis, in addition to their existing metformin regimen, time to treatment failure was almost double that of patients who received metformin alone (61.9 vs. 36.1 months). Additionally, early treatment intensification with vildagliptin resulted in consistently lower HbA1c values for more than 5 years and greater proportions of patients with HbA1c values below 6.5% (< 48 mmol/mol) and 6.0% (< 42 mmol/mol).[8]

Early intensification has been shown to have a beneficial impact on long-term T2D complications. In the UK Prospective Diabetes Study, initiation of sulphonylureas or insulin immediately after diagnosis was shown to reduce HbA1c by 11% and microvascular complication risk by 12% after 10 years, compared with a lack of intensification.[9] A 10-year follow-up of this study showed that early intensification also resulted in lower rates of microvascular disease, myocardial infarction and diabetes-related mortality in the long term, even if intensive treatment of hyperglycaemia was not continued.[10] These and other data[7,24] suggest that early and intensive management of hyperglycaemia has a 'legacy' effect of long-term protection from both microvascular and macrovascular disease.[7,10,24]

2.2 | Evidence supporting early T2D treatment with GLP-1RAs

In a 104-week randomized controlled trial, the GLP-1RA liraglutide was compared with other second-line oral glucose-lowering drugs (SGLT2is, DPP4is, sulphonylureas, alpha-glucosidase inhibitors, thiazolidinediones and meglitinides) with regard to efficacy in patients with uncontrolled hyperglycaemia despite metformin use.[25] Median time to loss of glycaemic control was 44 weeks longer with liraglutide than with the pooled group of other agents (109 vs. 65 weeks, $P < .0001$); changes in HbA1c and body weight at week 104 or at premature treatment discontinuation also significantly favoured liraglutide. Furthermore, median time to premature treatment discontinuation, for any reason, was longer with liraglutide than with other agents (80 vs. 52 weeks, $P < .0001$). Rates of hypoglycaemia were comparable between the two groups (11.5% for liraglutide vs. 10.3% for the pooled comparator group). However, fewer patients discontinued because of adverse events with the pooled comparator group than with liraglutide (4.1% vs. 7.9%).[25] Findings from a recent retrospective study provide further support for early-line initiation of GLP-1RAs. Use of GLP-1RAs as a first- or second-line therapy was associated with significantly greater reductions in HbA1c percentage from baseline and an increased likelihood of achieving an HbA1c value of less than 7% (< 53 mmol/mol), compared with initiation as a third- or fourth-line therapy.[26]

The effects of second-line combination therapies with metformin on weight and HbA1c were compared in the prospective, observational, global DISCOVER study. At 36 months, all second-line combinations (GLP-1RAs, SGLT2is, DPP4is and sulphonylureas) with metformin showed similar mean reductions in HbA1c values of between −0.8% and −1.0%, with the largest reduction of around −1.4% observed at 6 months with metformin + GLP-1RA, compared with between −0.75% and −0.95% for the other combinations at this time point.[27] All combinations were associated with significantly

greater weight loss compared with metformin + sulphonylurea, with the largest reductions observed at 36 months, particularly with metformin + GLP-1RA (~5 kg mean weight reduction vs. between 1 and 3 kg for the other combinations).[27] The cumulative risk of hypoglycaemia at 36 months was also significantly lower with all combinations versus metformin + sulphonylurea (HR range: 0.28-0.47).[27]

The GRADE trial was designed to compare the effectiveness of four agents—glimepiride, sitagliptin, insulin glargine and liraglutide—when used as second-line therapy in combination with metformin in patients diagnosed with T2D of less than 10 years' duration and with a low risk of CVD. Results indicate that maintenance of glycaemic control with second-line liraglutide is on a par with insulin, and greater than the efficacy of glimepiride and sitagliptin.[28] Rates of serious adverse events were comparable across the four groups.[28] As expected, the lowest hypoglycaemia rates were seen with liraglutide and sitagliptin.[28]

In a retrospective, observational database study (PATHWAY 2-OADs), outcomes were compared between propensity score-matched cohorts of patients with T2D receiving two oral glucose-lowering drugs at baseline for whom treatment was intensified with the addition of a GLP-1RA, an oral glucose-lowering drug or insulin.[29] In this study, significantly more patients intensifying treatment with a GLP-1RA achieved an HbA1c value of less than 7% (< 53 mmol/mol) than with oral glucose-lowering drugs (38.3% vs. 32.1%) or insulin (32.7% vs. 22.9%).[29] GLP-1RAs were also associated with significantly greater reductions in weight than with oral glucose-lowering drugs (−2.2% vs. −0.6%) or insulin (−2.3% vs. +0.3%).[29] Although T2D duration at baseline was not reported, the low mean rates of CVD (2.8% to 4.5%) and diabetes complications (Adapted Diabetes Complications Severity Index scores: 0.52 to 0.65) across the cohorts suggest a population with comparatively early T2D progression.

It is well recognized that β-cell function decline begins early in the course of disease, probably even before T2D is diagnosed.[30] The decline in β-cell function continues with T2D progression and ultimately necessitates treatment intensification.[16] Thus it is conceivable that the progression of T2D could be delayed if β-cell function or mass is increased. Preclinical evidence suggests that GLP-1RAs may stimulate β-cell proliferation and neogenesis and suppress apoptosis.[31-33] In addition, clinical evidence indicates that GLP-1RAs may improve both β-cell function and glucose sensitivity from 8 hours after dosing and for up to 3 years.[34-38] However, further research on the impact of GLP-1RAs on β-cell function and the implications for T2D progression are needed before any specific recommendations can be made.

Two in three Australians are overweight or obese,[39] with comparable rates reported in the United States (74%) and Europe (59%),[40,41] and excess body weight is a key driver of T2D pathogenesis.[42,43] Elevated serum levels of non-esterified fatty acids (NEFAs), glycerol, hormones and pro-inflammatory cytokines released by adipose tissue in people with obesity (PwO) can contribute to insulin resistance. This, in combination with β-cell dysfunction related to either elevated NEFA levels or genetic predisposition, can lead to T2D.[42] Indeed, more than 90% of adults with T2D are overweight or PwO.[44]

Given the relationship between body weight and T2D pathogenesis, it is perhaps not surprising that intensive weight loss interventions may slow T2D progression, if implemented early in the course of disease. A study at the general practice level found that 68 (46%) of 149 patients who participated in a weight management programme were in 'diabetes remission' at 12 months, defined as HbA1c less than 6.5% (< 48 mmol/mol) after at least 2 months without glucose-lowering agents, compared with only six (23%) of 26 patients in the control group. The intervention was initiated within 6 years of diagnosis for all patients and diabetes remission was more frequent in those who had lost 10-15 kg or more during the study.[6] Even modest targets of 5% to 10% weight loss are associated with significant improvements in CVD risk factors after 1 year.[45] Given the considerable weight loss effected by second-line treatments such as GLP-1RAs (as described later), early treatment intensification could help patients to attain key weight loss targets to potentially slow T2D progression.

2.3 | Guideline updates supporting early T2D treatment with GLP-1RAs

Glycaemic control, together with weight management and cardiorenal protection, are crucial goals of T2D management. Clinical guidelines have evolved to recommend that pharmacotherapy be selected on the basis of the cardiorenal benefits conferred, alongside considerations such as glucose-lowering efficacy, patient preferences, impact on body weight, contraindications and tolerability.[12,30,46,47]

In parallel, there has been a key change in the positioning of GLP-1RAs in treatment algorithms.[48] No longer categorized as the 'final' option before insulin initiation,[49] GLP-1RAs are now recommended as a second-line treatment option alongside oral glucose-lowering drugs such as SGLT2is and DPP4is.[1,12,30,47] Some Australian guidelines go further to identify GLP-1RAs and SGLT2is as second-line agents of choice for patients with CVD, or who are at high risk of CVD.[1,12] The Australian Diabetes Society treatment algorithm is presented in Figure S1.

The American Association of Clinical Endocrinologists and American College of Endocrinology recommend GLP-1RAs ahead of SGLT2is as second-line therapy for patients who do not reach glycaemic control with metformin treatment alone.[30] SGLT2is with shown efficacy and long-acting GLP-1RAs are equally recommended for patients with, or at high risk of, atherosclerotic CVD, stage 3 chronic kidney disease or heart failure with reduced ejection fraction, independent of HbA1c status, highlighting the importance of cardiorenal protection in T2D management.[30] The American Diabetes Association and the European Association for the Study of Diabetes have made similar recommendations, stating that CVD and renal disease risks should be 'considered independently of baseline HbA1c or individualized HbA1c target'.[47] Furthermore, these guidelines recommend the addition of GLP-1RAs to metformin in patients with a high risk of CVD or established atherosclerotic CVD with a 'grave' threat of major adverse cardiovascular events (MACEs).[47] Conversely, the Living Evidence for Diabetes Consortium recommends the addition of a GLP-

1RA when patients with established CVD are unable to be prescribed an SGLT2i owing to either intolerance or contraindication.[50] However, unlike other guidelines, these recommendations do not distinguish between different CVD types[30,47,50]; this information would be potentially useful for selecting optimal T2D treatment for patients with atherosclerotic disease versus heart failure. Some examples of clinical scenarios where early initiation of GLP-1RAs may be considered are outlined in Figure 1.

3 | CLINICAL EFFICACY AND SAFETY OF GLP-1RAS

3.1 | Hyperglycaemia

GLP-1RAs improve glycaemic control by mimicking the effects of endogenous GLP-1,[51] triggering glucose-dependent insulin secretion by stimulating GLP-1 receptors on pancreatic β-cells[46] and inhibiting glucagon secretion through glucose-dependent suppression of pancreatic α-cells.[52] Additionally, GLP-1RAs reduce hepatic glucose output through suppression of glucagon secretion and delayed gastric emptying, and increase satiety.[53] Overall, GLP-1RAs target at least six of the eight core defects (described as the ominous octet) implicated in T2D pathogenesis (Figure 2).[54]

Studies have shown that GLP-1RAs can reduce fasting blood glucose by 1.1 to 2.8 mmol/L and reduce HbA1c by 0.8% to 1.8%,[55-57] with larger HbA1c reductions observed in patients with higher baseline values.[58,59] Greater insulin sensitivity has also been associated with larger reductions in HbA1c with GLP-1RA treatment in patients with T2D.[60] GLP-1RAs are associated with greater reductions in HbA1c than other second-line treatment classes[61]; the magnitude of effect of GLP-1RAs appears to be closer to that of insulin.[61] The degree of HbA1c reduction required to meet patient-specific targets is thus an important factor when choosing between second-line treatments (see the Patient B example in Figure 1). The glucose-lowering efficacy values of individual GLP-1RAs indicated for the management of T2D in Australia (and similarly indicated elsewhere) are presented in Table 1.

3.2 | Body weight

GLP-1RAs have been shown to reduce calorie intake, mediated by central regulation of appetite (improving eating habits, increasing satiety and reducing hunger and food 'cravings').[55,62,63] Consequently, GLP-1RA treatment is associated with substantial weight loss: up to 6.5 kg from baseline (not placebo adjusted) with once-weekly semaglutide 1.0 mg in patients with T2D,[55-57] primarily through a loss of fat mass.[64] Clinical trials of higher GLP-1RA doses in patients with T2D have shown reductions in body weight versus placebo (as add-on to lifestyle intervention) of −4.0% to −4.3% with liraglutide 3.0 mg, and −6.2% with semaglutide 2.4 mg.[65] Weight loss with dulaglutide at higher doses has also recently been assessed in patients with T2D in the AWARD-11 trial, with greater effects observed with dulaglutide 3.0 and 4.5 mg (−4.0 and −4.7 kg vs. baseline, respectively [not placebo adjusted]) than with dulaglutide 1.5 mg (−3.1 kg vs. baseline).[66] The potential for weight loss with these drugs is thus an important factor to consider when contemplating their use (see the Patient A, C and D examples in Figure 1).

GLP-1RAs have also been observed to reduce body weight in the absence of T2D, indicating that weight loss is facilitated by a mechanism independent of that which controls blood glucose levels (Figure 2).[67] Clinical trials of higher GLP-1RA doses in patients without T2D have shown reductions in body weight versus placebo (as add-on to lifestyle intervention) of −3.4% to −6.1% with liraglutide 3.0 mg and −10.3% to −13.9% with semaglutide 2.4 mg.[65] Consequently, these drugs also have indications for weight management in a number of countries at higher doses (3.0 mg/day [liraglutide] and 2.4 mg/week [semaglutide]) than those used for T2D management (1.2-1.8 mg/day [liraglutide] and 0.5-1.0 mg/week [semaglutide]).[68-72]

3.3 | Cardiovascular disease

People with T2D are at greater risk of dying from CVD than any other cause.[73] Unfortunately, one in three individuals with T2D has CVD; of these, more than 80% have atherosclerotic CVD (e.g. coronary artery disease, or a history of myocardial infarction or ischaemic stroke).[73,74] Consequently, many glucose-lowering agents have been investigated in clinical trials to ensure that cardiovascular (CV) risk is not 'unacceptably' increased with their use.[75] Results of cardiovascular outcome trials (CVOTs) of GLP-1RAs are presented in Figure 3 and Table **S1**. In a meta-analysis of these and other trials, GLP-1RA treatment led to a 14% reduction in three-point MACEs, a composite of CV death, stroke and myocardial infarction; a 12% reduction in all-cause mortality; an 11% reduction in hospital admission for heart failure; and a 21% reduction in a composite renal outcome that included progression to end-stage kidney disease or death attributable to kidney-related causes.[76] GLP-1RAs have also been shown to reduce systolic blood pressure (2-3 mmHg [placebo controlled]); the mechanism for this is unclear, but may be related to promotion of natriuresis and vasodilation.[77] Mechanisms behind the antiatherosclerotic effects of GLP-1RAs are also unclear, although preclinical studies suggest that these effects may result from reductions in inflammation, oxidative stress and postprandial lipid deposition.[78,79]

Benefits observed with GLP-1RAs have led to a greater appreciation of their potential in patients with both T2D and CVD, evident in recent guideline recommendations, and risk factors for CVD should be part of decisions around GLP-1RA use (Figure 1).[12,30,47,80,81] However, less than one-quarter of adults with T2D and CVD currently take a glucose-lowering agent that has been shown to have a CV benefit,[74] and only 6.8% of Australian adults with T2D and CVD are receiving a GLP-1RA.[82] Evidence from the global DISCOVER study suggests a similarly low uptake of GLP-1RAs in other countries, with initiation as second-line therapy occurring in only 3.3% of patients (GLP-1RA only:

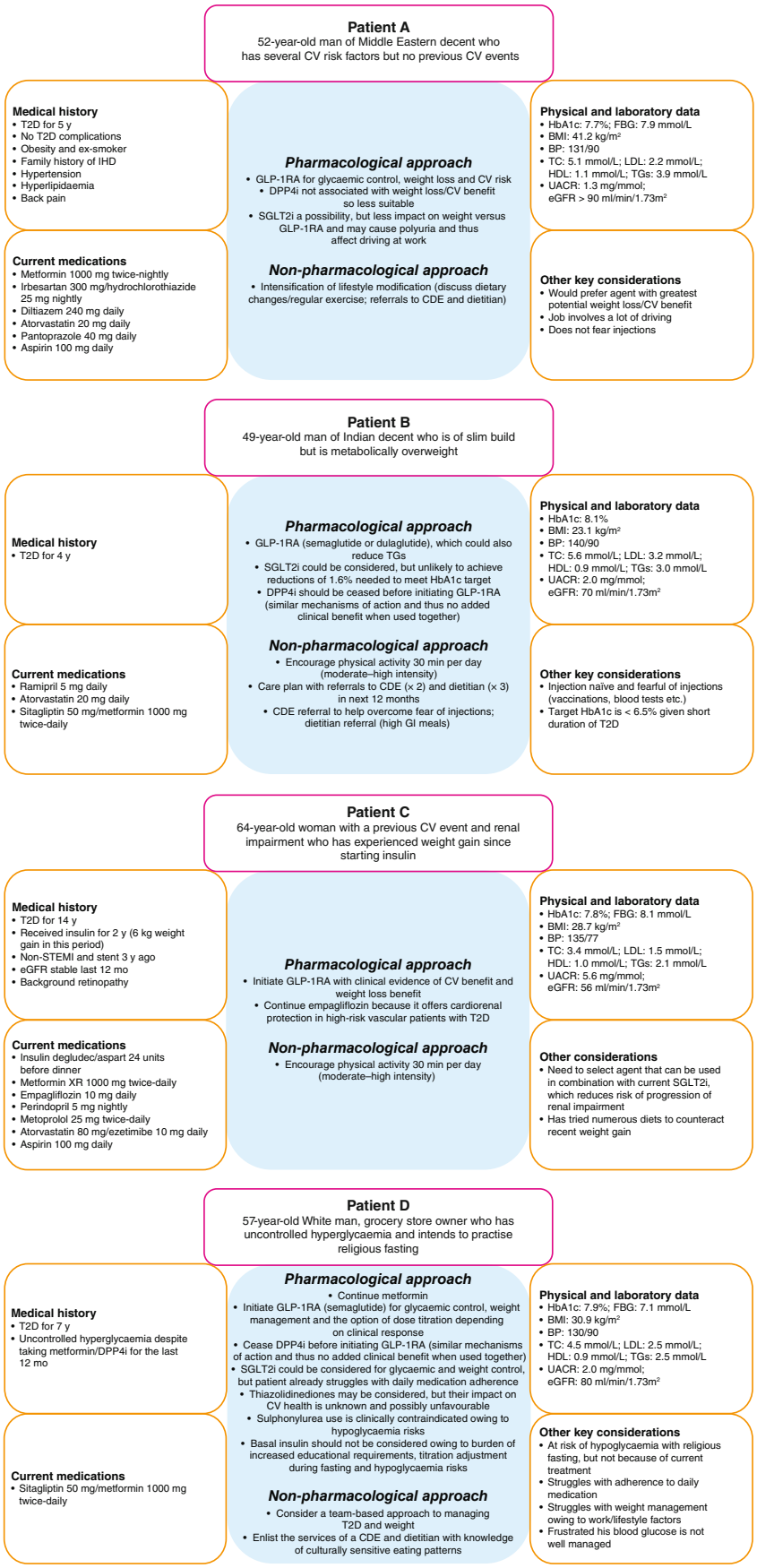

FIGURE 1 Examples of clinical scenarios in which early use of GLP-1RAs may be considered for patients with T2D. BMI, body mass index; BP, blood pressure; CV, cardiovascular; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; GI, glycaemic index; GLP-1RA, glucagon-like peptide-1 receptor agonist; HDL, high density lipoprotein; IHD, ischaemic heart disease; LDL, low density lipoprotein; SGLT2i, sodium–glucose co-transporter 2 inhibitor; STEMI, ST-elevation myocardial infarction; T2D, type 2 diabetes; TC, total cholesterol; TG, triglycerides; UACR, urine albumin-to-creatinine ratio. XR, extended release[95,144,145]

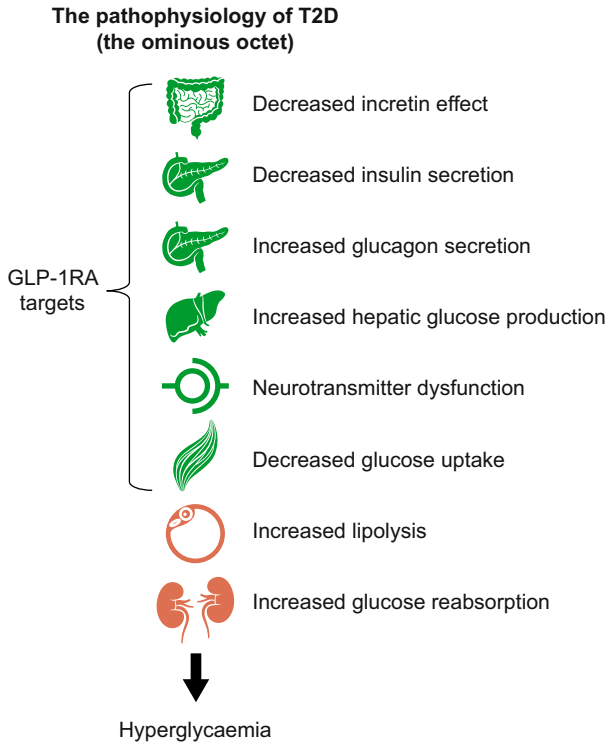

FIGURE 2 T2D pathophysiological factors targeted by GLP-1RAs. Adapted from DeFronzo.[54] GLP-1RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes

2.6%; GLP-1RA + SGLT2i: 0.7%) at the 36-month follow-up point in this study, although this had increased from 2.2% at initial study enrolment (GLP-1RA only: 2.1%; GLP-1RA + SGLT2i: 0.1%).[83] The authors of this study concluded that global use of GLP-1RAs and SGLT2is is suboptimal, particularly in subgroups of patients with the greatest potential to benefit from these drugs.[83] Similarly, an observational study conducted in the United States found that only a small fraction of patients (6.0%) who were potentially eligible to receive a GLP-1RA had been prescribed one of these agents.[84] Prescription of GLP-1RAs appears to be particularly low in primary care,[85,86] although once again there are trends towards increased uptake.

3.4 | Safety profile

Gastrointestinal side effects such as nausea, vomiting and diarrhoea are considered 'very common' with GLP-1RAs (experienced by ≥ 10% of patients).[48] The timing of onset of nausea and vomiting typically corresponds to the time at which the peak plasma concentration is achieved after dose administration, which is shortest for twice-daily exenatide (< 6 hours after injection).[55] These side effects are generally mild to moderate and transient in duration; for example, the severity of nausea usually peaks within 8 weeks of starting twice-daily exenatide and 4-8 weeks after starting liraglutide,[87] then generally subsides without the need to discontinue treatment.[55,88,89]

There has been speculation that weight loss associated with GLP-1RA use may be caused by associated gastrointestinal side effects.[90] This theory was examined in analyses of the SUSTAIN trials (head-to-head trials of long-acting GLP-1RAs), which found that gastrointestinal adverse events may play an insignificant role, but that central nervous system effects on appetite are largely responsible for weight loss.[90,91]

Stimulation of insulin release and inhibition of glucagon suppression with GLP-1RA use is dependent on blood glucose concentration.[92] As such, GLP-1RAs are associated with a low risk of hypoglycaemia (an important consideration in patients at higher risk of these events, such as those practising religious fasting—see the Patient D example in Figure 1), similar to DPP4i and SGLT2i use.[69,93-100] GLP-1RAs also pose a comparatively low risk of hypoglycaemia compared with agents such as insulin and sulphonylureas.[101] However, hypoglycaemia is a 'very common' side effect when GLP-1RAs are used in combination with sulphonylureas or insulin (or metformin, in the case of dulaglutide) in combination therapy.[69,98-100,102] Guidelines therefore recommend self-monitoring of glucose levels and review of medication dosages for reducing or managing hypoglycaemia risk with such combination therapies.[1]

Cases of acute pancreatitis and malignancies have been observed in preclinical trials and clinical practice with incretin-based glucose-lowering medications. Subsequently, pancreatitis and malignancy risks were investigated by way of CVOTs involving patients who did not have a history of pancreatitis; the rate of adverse events with GLP-1RAs was similar to that seen for placebo across CVOTs.[103] A meta-analysis of CVOTs further confirmed that GLP-1RAs were not associated with an elevated risk of developing pancreatic cancer, or any malignant neoplasm.[66-68] Similarly, GLP-1RAs do not appear to substantially elevate the risk of acute pancreatitis.[103,104]

3.5 | Comparison with other key second-line treatments

Numerous head-to-head trials, systematic reviews and meta-analyses have compared the safety and efficacy of GLP-1RAs with other second-line treatments.[12,93,94,96,105-108]

DPP4is are incretin-based agents that inhibit GLP-1 degradation, thereby increasing endogenous GLP-1 levels and receptor stimulation, acting via a similar mechanism to GLP-1RAs.[46,109] Of the DPP4is, only sitagliptin has been directly compared with GLP-1RAs. In these trials, once-weekly use of GLP-1RAs provided additional reductions compared with sitagliptin in HbA1c (treatment differences: −0.38% to −1.06%) and body weight (−1.07 to −4.20 kg), with semaglutide (0.5 and 1.0 mg) associated with the greatest additional improvements in HbA1c (−0.77% and −1.06%) and body weight (−2.35 and −4.20 kg).[110] Meta-analyses have provided further evidence to suggest that GLP-1RAs provide greater reductions in HbA1c, fasting blood glucose concentrations and weight than DPP4is.[61,105,111] Given that GLP-1RAs and DPP4is act through the

TABLE 1 Overview of GLP-1RAs indicated for the management of T2D in Australia

TGA-approved GLP-1RAs[a]	Description[55]	Glucose-lowering effect[56,57]	Effect on body weight[56,57]	Indications[69,98-100]	Dosing and administration[69,92,98-100]
Dulaglutide	Long acting	40-wk trial HbA1c: −1.4% vs. baseline with 1.5 mg dose FBG: −2.2 mmol/L vs. baseline with 1.5 mg dose	40-wk trial −3.0 kg vs. baseline with 1.5 mg dose	Treatment of adults with T2D; reduction in risk of MACEs in those at high CV risk or with established CVD	1.5 mg once-weekly, SC administration. Single-use device with preattached hidden needle and fixed-dose delivery
Exenatide	Short acting	26-wk trial HbA1c: −0.8% vs. baseline with 10 µg dose FBG: −0.6 mmol/L vs. baseline with 10 µg dose	26-wk trial −2.9 kg vs. baseline with 10 µg dose	Treatment of adults with T2D	5-10 µg twice-daily, SC administration Needle to be attached and primed and patient to select appropriate dose. Multiuse device Needles to be provided separately
Liraglutide[b]	Long acting	26-wk trial HbA1c: −1.1% vs. baseline with 1.8 mg dose FBG: −1.6 mmol/L vs. baseline with 1.8 mg dose	26-wk trial −3.2 kg vs. baseline with 1.8 mg dose	Treatment of adults with T2D; reduction in risk of CV events in those at high CV risk	1.2 to 1.8 mg once-daily, SC administration (maintenance) Needle to be attached and primed and patient to select appropriate dose. Multiuse device Needles to be provided separately
Semaglutide	Long acting	40-wk trial HbA1c: −1.5% and −1.8% vs. baseline with 0.5 and 1.0 mg dose, respectively FBG: −2.2 and −2.8 mmol/L vs. baseline with 0.5 and 1.0 mg dose, respectively	40-wk trial −4.6 and −6.5 kg vs. baseline with 0.5 and 1.0 mg dose, respectively	Treatment of adults with T2D	0.5 to 1.0 mg once-weekly, SC administration (maintenance) Needle to be attached and primed once per device, and patient to select appropriate dose. Multiuse device Needles included with medication

Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; FBG, fasting blood glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular event; PBS, Pharmaceutical Benefits Scheme; SC, subcutaneous; T2D, type 2 diabetes; TGA, Therapeutic Goods Administration.

[a]See www.pbs.gov.au for list of PBS restrictions for reimbursed use in Australia.

[b]Liraglutide is not PBS-reimbursed in Australia.

same pathway, the use of these agents in combination offers limited additional benefit and is not recommended (see the Patient B and D examples in Figure 1).[112] As a class, DPP4is are well tolerated and have an acceptable safety profile.[113] Common side effects (experienced by ≥ 5% of patients in pooled analyses) associated with some DPP4is (sitagliptin, saxagliptin and linagliptin) include nasopharyngitis, upper respiratory tract infection, urinary tract infection and headache.[114-116]

SGLT2is prevent the reabsorption of glucose from the filtrate in the kidney, and are associated with glycaemic control, weight loss and cardiorenal protection for patients with heart failure and chronic kidney disease.[107,110] Common side effects related to SGLT2 inhibition include genital infections (empagliflozin, dapagliflozin and ertugliflozin) and increased serum lipids (empagliflozin).[117-120] It is also important to be aware of signs and symptoms of euglycaemic diabetic ketoacidosis (e.g. nausea, vomiting, abdominal pain, malaise, shortness of breath) that have been reported, albeit infrequently, in patients with T2D taking SGLT2is.[117-119,121]

To date, there have been no head-to-head clinical trials comparing SGLT2i and GLP-1RA agents with respect to CV protection, although two trials have directly compared glucose-lowering efficacy. In DURATION-8, in which patients had a mean baseline HbA1c of approximately 9.0% (75 mmol/mol), the change from baseline in HbA1c at week 28 was −1.6% with once-weekly exenatide and −1.4% with daily dapagliflozin.[95] In SUSTAIN 8, semaglutide 1.0 mg administered once-weekly was more effective than daily canagliflozin

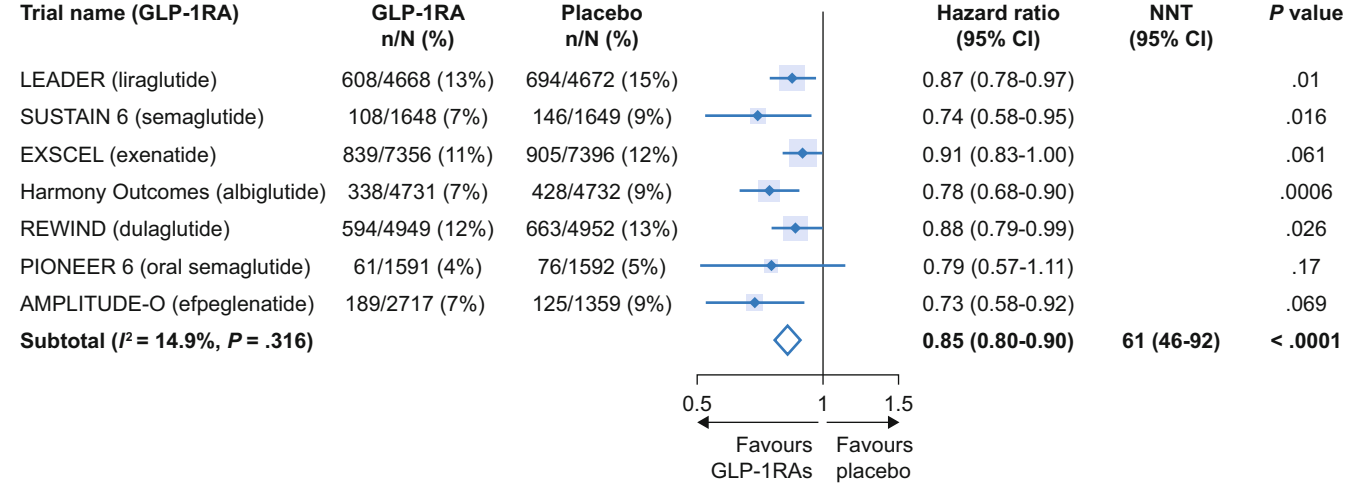

FIGURE 3 Risk of three-point MACE[a] with GLP-1RA treatment[b] in cardiovascular outcomes trials. Adapted from Sattar et al.[76] [a]Three-point MACE is a composite outcome comprising death from cardiovascular causes (undetermined causes of death were also included in AMPLITUDE-O), non-fatal myocardial infarction and non-fatal stroke. [b]Administered via subcutaneous injection unless otherwise specified. CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular event; NNT, number needed to treat

300 mg in terms of reducing HbA1c (difference of −0.49%) and body weight (difference of −1.06 kg) at week 52.[94]

While expensive relative to other agents, second-line use of SGLT2is and GLP-1RAs is generally considered cost-effective in patients with T2D.[122] Data comparing the cost-effectiveness of early SGLT2i use with that of early GLP1RA use are, however, extremely limited. A recent analysis compared the cost-effectiveness, from the perspective of the US healthcare system, of second-line addition of empagliflozin (followed by liraglutide then insulin) to metformin with second-line addition of liraglutide (followed by empagliflozin then insulin) to metformin. This study reported that empagliflozin as second-line therapy was less expensive and more effective than liraglutide in patients with T2D with or without CVD.[123] However, data on the cost-effectiveness of early semaglutide use versus early SGLT2i use are not yet available. This is important in light of real-word data indicating greater improvements with semaglutide treatment in terms of weight loss (vs. liraglutide and exendin-based [exenatide and lixisenatide] GLP-1RAs) and reduced HbA1c levels (vs. dulaglutide, lirаglutide and exendin-based GLP-1RAs),[124] which are broadly consistent with previous findings from clinical trials.[56,125-127]

Given that SGLT2is and GLP-1RAs act by different mechanisms, it may follow that dual therapy could offer additive benefits to either agent alone. Indeed, clinical trial and real-world data are promising, showing additive improvements in glycaemic measures and reductions in body weight and CV risk with dual therapy compared with either agent alone.[95,128-130] Although such combinations may be limited by cost or reimbursement restrictions in some markets, targeting multiple components of T2D pathology, and cardiorenal risk, is probably the future of diabetes care (see the Patient C example in Figure 1).[131,132] In the same vein, dual glucose-dependent insulinotropic polypeptide and GLP1 receptor agonists, also known as 'twincretins', are another emerging therapy with the potential to further enhance the treatment of T2D.[133] As always, other patient-specific circumstances will also play a role in determining the suitability of using a SGLT2i versus (or in addition to) a GLP-1RA (see the Patient A, B and D examples in Figure 1), as well as future therapies.

4 | CLINICAL PROFILES OF DIFFERENT GLP-1RAS

Although GLP-1RAs share the same core mechanism of action,[55,92] structural differences (relating to the degree of homology to human GLP-1) between agents translate into some variations in clinical characteristics. Individual GLP-1RAs may differ in terms of duration of action, glycaemic control and effects on body weight (Table 1).[134,135] 'Long-acting' agents (once-weekly) are associated with larger reductions in fasting blood glucose concentrations than 'short-acting' agents (taken daily).[55,134] Additionally, there are smaller fluctuations in plasma drug concentrations during the day with long-acting agents, possibly because of differences in the predominant mechanisms by which short-acting and long-acting GLP-1RAs reduce postprandial glucose 'spikes'.[55,134] Short-acting GLP-1RAs delay gastric emptying, leading to a reduced rate of nutrient absorption by the gut; consequently, glucose-lowering effects are primarily observed with the meal that follows dose administration.[55] Long-acting agents reduce postprandial glucose spikes by increasing insulin secretion while inhibiting glucagon secretion; as such, postprandial effects are largely independent of the timing of dose administration.[55]

No head-to-head trials of short- versus long-acting GLP-1RAs have been conducted. However, two randomized, open-label, phase 3, head-to-head trials comparing GLP-1RAs within these categories have been performed. In the LEAD-6 trial, the short-acting GLP-1RAs liraglutide (1.8 mg once-daily) and exenatide (10 μg twice-daily) were compared in patients with uncontrolled T2D, despite maximally tolerated doses of metformin, sulphonylurea, or both.[57] Liraglutide was found to be superior to exenatide in terms of glycaemic control, and

was better tolerated in general. More recently, the SUSTAIN 7 trial compared the long-acting GLP-1RAs semaglutide and dulaglutide in adults with T2D and HbA1c 7.0% to 10.5% (53 mmol/mol to 91 mmol/mol) while receiving metformin monotherapy. Semaglutide was superior to dulaglutide in terms of reducing HbA1c and body weight after 40 weeks of once-weekly treatment at both low (0.5 and 0.75 mg, respectively) and high (1.0 and 1.5 mg, respectively) doses, with similar adverse event profiles reported for both drugs.[56]

With regard to tolerability, evidence from a large analysis of more than 32 phase 3 trials of GLP-1RAs suggests that nausea and vomiting may be less frequent, and diarrhoea more common, with long-acting versus short-acting GLP-1RAs.[89]

5 | PRACTICAL CONSIDERATIONS FOR GLP-1RA USE

A key barrier to therapeutic success in many disease areas is the failure of clinicians to initiate/cease or intensify/de-intensify therapy where appropriate, commonly referred to as 'clinical inertia'. This highly complex issue has been well described elsewhere in relation to suboptimal achievement of metabolic control in patients with T2D.[20] Thus, in the following section, we instead focus on practical tips for clinicians who have already made an informed decision to treat patient(s) with a GLP-1RA, with the goal of helping them overcome potential patient-related barriers to GLP-1RA initiation. It is worth noting, however, that a recent systematic review and meta-analysis found that the most effective approach to reducing inertia and improving HbA1c levels in individuals with T2D was to empower non-physician healthcare providers (e.g. nurses, pharmacists and diabetes educators) to initiate and intensify treatments as per guidelines.[136]

5.1 | Overcoming barriers to initiation

Patient education is critical for treatment acceptance. Some patients may view injectable therapy as a 'threat' or a 'failure' on their part to control their diabetes with oral glucose-lowering drugs, stemming from a lack of awareness of the progressive nature of T2D.[137,138] Other patients may simply prefer oral glucose-lowering medications over injectable options, probably being more accustomed to oral medications.[21] Clinicians may improve treatment acceptance by

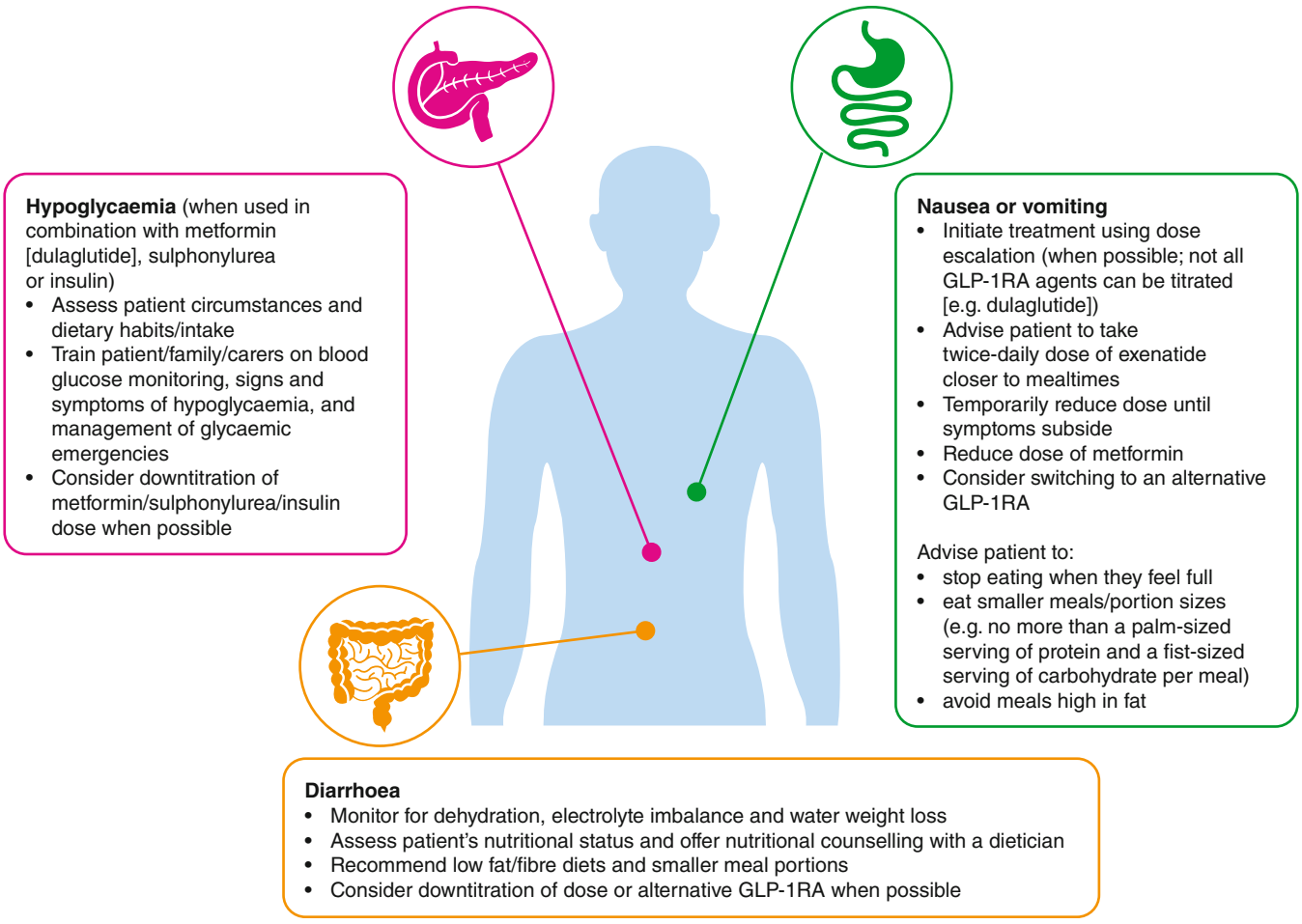

FIGURE 4 Very common side effects associated with GLP-1RAs[a] (as monotherapy or in combination with other glucose-lowering agents) and suggestions[b] for risk mitigation and management. [a]Experienced by ≥ 10% of patients in phase 3 clinical trials.[69,98-100,102] [b]Based on literature[1,48,92,99,109] and the opinions of the authors. GLP-1RA, glucagon-like peptide-1 receptor agonist

communicating the potential benefits of GLP-1RAs for these patients, emphasizing that injectable GLP-1RAs are not the same as insulin, but are simply another 'early' treatment option alongside oral glucose-lowering drugs, and highlighting the convenient features of GLP-1RAs such as once-weekly dose administration. Depression has been associated with negative attitudes towards initiating insulin therapy,[138] and is at least twice as prevalent in patients with T2D compared with the general population.[139] Therefore, patients who are reluctant to intensify therapy may benefit from having a mental health assessment.

Patients may have a fear of needles or lack confidence in completing the steps involved in administering injectable therapy.[137] For patients who are apprehensive about handling or viewing needles, autoinjector devices may be useful.[140] Patients who fear the pain of injections may also benefit from practical tips for reducing pain; for example, avoiding the use of an alcohol wipe on the needle, which may remove factory coatings that are designed to reduce injection pain by easing skin penetration.[21] Performing a dummy injection in the clinic may help a patient to understand what to expect in terms of pain levels, ahead of prescribing a particular T2D treatment.

Training is critical for correct dose administration and to reduce the risk of side effects associated with self-injection (e.g. needle-stick injury, injection site reaction).[1] Patients may become more confident with administration if they are able to inject their first dose of medication in the consultation room, in the presence of a doctor, nurse or diabetes educator.[48]

5.2 | Management of side effects

Concerns about side effects and, to a lesser extent, actual experiences with side effects, can lead to poor adherence to a treatment regimen.[1,48,141] It is helpful to manage patient expectations at initiation. The clinician could draw on their own experience to frame the likelihood of side effects in terms of the number of patients (e.g. of every 10 patients receiving the drug) who have experienced the side effect of concern.[141] Patients reluctant to initiate treatment may accept titratable GLP-1RA agents; a slow increase in dose could potentially minimize discomfort from side effects.[55]

For very common side effects associated with GLP-1RAs, clinicians should be prepared to discuss the probable duration or time of onset, and provide simple practical management tips at initiation (Figure 4).[142] For example, it may be helpful to counsel patients on the mild to moderate, transient nature of gastrointestinal side effects associated with GLP-1RAs,[48] and proactively manage side effects that may affect treatment adherence.[143]

6 | CONCLUSIONS

GLP-1RAs are becoming increasingly recognized for their potential in the early management of T2D, with recent guideline updates influenced by numerous trials outlining the glycaemic, CV and weight-related benefits of this drug class. However, implementation of these guidelines may be below par in practice and hinder clinical uptake of GLP-1RAs. Clinicians may play a key role in overcoming patient-related barriers to treatment intensification and numerous strategies are available to help to achieve this goal.

AUTHOR CONTRIBUTIONS

All authors contributed to the study concept, contributed relevant literature, reviewed and revised the manuscript for important intellectual content, and approved the final manuscript version for submission. The authors did not receive compensation for their involvement in this manuscript.

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CONFLICT OF INTEREST

RR has received honoraria and been on advisory boards or provided educational consultancy for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi. SA has received speaker fees from Novo Nordisk, AstraZeneca, Eli Lily and Boehringer. GD has received advisory board and speaker fees from Boehringer Ingelheim, Novo Nordisk, Eli Lily, AstraZeneca, MSD, Novartis, Abbot and Sanofi. RO has received advisory board and speaker fees from Abbot, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lily, MSD, Mylan, Novartis, Novo Nordisk, Pfizer and Sanofi. JO has received speaker fees from Novo Nordisk, Eli Lily and AstraZeneca.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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REFERENCES

1. The Royal Australian College of General Practitioners. *Management of type 2 diabetes: a handbook for general practice*. East Melbourne: RACGP; 2020 Available at: https://www.racgp.org.au/getattachment/41fee8dc-7f97-4f87-9d90-b7af337af778/Management-of-type-2-diabetes-A-handbook-for-general-practice.aspx. Accessed July 8, 2022
2. White S. *Chronic Kidney Disease, Diabetes & Cardiovascular Disease: Evidence Report 2021*. Melbourne, Australia: Kidney Health Australia. Available at: https://kidney.org.au/uploads/resources/Make-the-link-kidneys-diabetes-heart-report.pdf; 2020 Accessed July 8, 2022.
3. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD). *Diabetes Care*. 2018;41:2669-2701.
4. van Wijngaarden RPT, Overbeek JA, Heintjes EM, et al. Relation between different measures of glycemic exposure and microvascular and macrovascular complications in patients with type 2 diabetes mellitus: An observational cohort study. *Diabetes Ther*. 2017;8:1097-1109.
5. Sainsbury E, Shi Y, Flack J, Colagiuri C. Burden of diabetes in Australia: it's time for more action. 2018. Available at: https://www.sydney.edu.au/content/dam/corporate/documents/faculty-of-medicine-and-health/research/centres-institutes-groups/burden-of-diabetes-its-time-for-more-action-report.pdf. Accessed July 8, 2022.
6. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet*. 2018;391:541-551.
7. Lind M, Imberg H, Coleman RL, Nerman O, Holman RR. Historical HbA1c values may explain the type 2 diabetes legacy effect: UKPDS 88. *Diabetes Care*. 2021;44:2231-2237.
8. Matthews DR, Paldánius PM, Proot P, et al. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. *Lancet*. 2019;394:1519-1529.
9. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-853.
10. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577-1589.
11. American Diabetes Association. Standards of medical care in diabetes – 2017. *Clin Diabetes*. 2017;40:S1-S134.
12. Australian Diabetes Society. 2021. Australian type 2 diabetes glycaemic management algorithm. Available at: http://t2d.diabetessociety.com.au/documents/BD92rkh5.pdf. Accessed July 8, 2022.
13. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK prospective diabetes study (UKPDS) group. *JAMA*. 1999;281:2005-2012.
14. Ross SA. A multiplicity of targets: evaluating composite endpoint studies of the GLP-1 receptor agonists in type 2 diabetes. *Curr Med Res Opin*. 2015;31:125-135.
15. Group UPDSU. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes*. 1995;44:1249-1258.
16. Saisho Y. β-Cell dysfunction: its critical role in prevention and management of type 2 diabetes. *World J Diabetes*. 2015;6:109-124.
17. Home P, Riddle M, Cefalu WT, et al. Insulin therapy in people with type 2 diabetes: opportunities and challenges? *Diabetes Care*. 2014;37:1499-1508.
18. Ahlqvist E, Storm P, Karajamaki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol*. 2018;6:361-369.
19. Slieker RC, Donnelly LA, Fitipaldi H, et al. Replication and cross-validation of type 2 diabetes subtypes based on clinical variables: an IMI-RHAPSODY study. *Diabetologia*. 2021;64:1982-1989.
20. Andreozzi F, Candido R, Corrao S, et al. Clinical inertia is the enemy of therapeutic success in the management of diabetes and its complications: a narrative literature review. *Diabetol Metab Syndr*. 2020;12:52. 10.1186/s13098-020-00559-7
21. Kruger DF, LaRue S, Estepa P. Recognition of and steps to mitigate anxiety and fear of pain in injectable diabetes treatment. *Diabetes Metab Syndr Obes*. 2015;8:49-56.
22. Blonde L, Aschner P, Bailey C, et al. Gaps and barriers in the control of blood glucose in people with type 2 diabetes. *Diab Vasc Dis Res*. 2017;14:172-183.
23. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. *Diabetes Care*. 2013;36:3411-3417.
24. Chalmers J, Cooper ME. UKPDS and the legacy effect. *N Engl J Med*. 2008;359:1618-1620.
25. Unger J, Allison DC, Kaltoft M, et al. Maintenance of glycaemic control with liraglutide versus oral antidiabetic drugs as add-on therapies in patients with type 2 diabetes uncontrolled with metformin alone: a randomized clinical trial in primary care (LIRA-PRIME). *Diabetes Obes Metab*. 2021;242:204-211.
26. Boye KS, Mody R, Lage MJ, Malik RE. The relationship between timing of initiation on a glucagon-like peptide-1 receptor agonist and glycosylated hemoglobin values among patients with type 2 diabetes. *Clin Ther*. 2020;42:1812-1817.e2.
27. Khunti K, Charbonnel B, Cooper A, et al. Associations between second-line glucose-lowering combination therapies with metformin and HbA1c, body weight, quality of life, hypoglycaemic events and glucose-lowering treatment intensification: the DISCOVER study. *Diabetes Obes Metab*. 2021;23:1823-1833.
28. GRADE Study Research Group, Nathan DM, Lachin JM, et al. Glycemia reduction in type 2 diabetes - glycemic outcomes. *N Engl J Med*. 2022;387:1063-1074.
29. Desouza C, Kirk AR, Mangla KK, Wolden ML, Lingvay I. Real-world clinical outcomes following treatment intensification with GLP-1 RA, OADs or insulin in patients with type 2 diabetes on two oral agents (PATHWAY 2-OADs). *BMJ Open Diabetes Res Care*. 2020;8:e001830.
30. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of endocrinology on the comprehensive type 2 diabetes management algorithm – 2020 executive summary. *Endocr Pract*. 2020;26:107-139.
31. Vilsbøll T. The effects of glucagon-like peptide-1 on the beta cell. *Diabetes Obes Metab*. 2009;11((Suppl 3)):11-18.
32. Farilla L, Hui H, Bertolotto C, et al. Glucagon-like peptide-1 promotes islet cell growth and inhibits apoptosis in Zucker diabetic rats. *Endocrinology*. 2002;143:4397-4408.
33. Xu G, Stoffers DA, Habener JF, Bonner-Weir S. Exendin-4 stimulates both beta-cell replication and neogenesis, resulting in increased beta-cell mass and improved glucose tolerance in diabetic rats. *Diabetes*. 1999;48:2270-2276.
34. Retnakaran R, Kramer CK, Choi H, Swaminathan B, Zinman B. Liraglutide and the preservation of pancreatic β-cell function in early type 2 diabetes: the LIBRA trial. *Diabetes Care*. 2014;37:3270-3278.
35. Santilli F, Simeone PG, Guagnano MT, et al. Effects of liraglutide on weight loss, fat distribution, and β-cell function in obese subjects with prediabetes or early type 2 diabetes. *Diabetes Care*. 2017;40:1556-1564.

36. Bunck MC, Cornér A, Eliasson B, et al. Effects of exenatide on measures of β-cell function after 3 years in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 2011;34:2041-2047.
37. Chang AM, Jakobsen G, Sturis J, et al. The GLP-1 derivative NN2211 restores beta-cell sensitivity to glucose in type 2 diabetic patients after a single dose. *Diabetes*. 2003;52:1786-1791.
38. Kapitza C, Dahl K, Jacobsen JB, Axelsen MB, Flint A. Effects of semaglutide on beta cell function and glycaemic control in participants with type 2 diabetes: a randomised, double-blind, placebo-controlled trial. *Diabetologia*. 2017;60:1390-1399.
39. Australian Institute of Health and Welfare. 2020. Overweight and obesity. Available at: https://www.aihw.gov.au/reports/australias-health/overweight-and-obesity. Accessed July 8, 2022.
40. Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among adults aged 20 and over: United States, 1960–1962 through 2017–2018. NCHS Health E-Stats 2020. Available at: https://www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/obesity-adult.htm. Accessed September 9, 2022.
41. World Health Organization. WHO European regional obesity report. 2022. Available at: https://apps.who.int/iris/bitstream/handle/10665/353747/9789289057738-eng.pdf. Accessed September 9, 2022.
42. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*. 2006;444:840-846.
43. Apovian CM, Okemah J, O'Neil PM. Body weight considerations in the management of type 2 diabetes. *Adv Ther*. 2019;36:44-58.
44. Centers for Disease Control and Prevention. 2020. National diabetes statistics report: Estimates of diabetes and its burden in the United States. Available at: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed July 8, 2022.
45. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care*. 2011;34:1481-1486.
46. Davies MJ, Bianchi C, Del Prato S. Use of incretin-based medications: what do current international recommendations suggest with respect to GLP-1 receptor agonists and DPP-4 inhibitors? *Metabolism*. 2020;107:154242.
47. Buse JB, Wexler DJ, Tsapas A, et al. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD). *Diabetes Care*. 2018;2020(43):487-493.
48. Kalra S, Das AK, Sahay RK, et al. Consensus recommendations on GLP-1 RA use in the management of type 2 diabetes mellitus: south Asian task force. *Diabetes Ther*. 2019;10:1645-1717.
49. Australian Diabetes Society. A new blood glucose management algorithm for type 2 diabetes. 2016. Available at: https://diabetessociety.com.au/documents/ADS_POSITIONSTATEMENT_v2.4.pdf. Accessed July 8, 2022.
50. Living Evidence for Diabetes Consortium. Australian evidence-based clinical guidelines for diabetes. 2020. Available at: https://app.magicapp.org/#/guideline/E5AbPE. Accessed July 8, 2022.
51. Caparrotta TM, Templeton JB, Clay TA, et al. Glucagon-like peptide 1 receptor agonist (GLP1RA) exposure and outcomes in type 2 diabetes: a systematic review of population-based observational studies. *Diabetes Ther*. 2021;12:969-989.
52. Nauck MA, Heimesaat MM, Behle K, et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. *J Clin Endocrinol Metab*. 2002;87:1239-1246.
53. Rasalam R, Barlow J, Kennedy M, Phillips P, Wright A. GLP-1 receptor agonists for type 2 diabetes and their role in primary care: an Australian perspective. *Diabetes Ther*. 2019;10:1205-1217.
54. Defronzo RA. Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58:773-795.
55. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. *Mol Metab*. 2021;46:101102.
56. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol*. 2018;6:275-286.
57. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet*. 2009;374:39-47.
58. Aroda VR, Capehorn MS, Chaykin L, et al. Impact of baseline characteristics and beta-cell function on the efficacy and safety of subcutaneous once-weekly semaglutide: a patient-level, pooled analysis of the SUSTAIN 1-5 trials. *Diabetes Obes Metab*. 2020;22:303-314.
59. Harris KB, McCarty DJ. Efficacy and tolerability of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes mellitus. *Ther Adv Endocrinol Metab*. 2015;6:3-18.
60. Heald AH, Narayanan RP, Lowes D, et al. HOMA-S is associated with greater HbA1c reduction with a GLP-1 analogue in patients with type 2 diabetes. *Exp Clin Endocrinol Diabetes*. 2012;120:420-423.
61. Tsapas A, Avgerinos I, Karagiannis T, et al. Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review and network meta-analysis. *Ann Intern Med*. 2020;173:278-286.
62. Ten Kulve JS, Veltman DJ, van Bloemendaal L, et al. Liraglutide reduces CNS activation in response to visual food cues only after short-term treatment in patients with type 2 diabetes. *Diabetes Care*. 2016;39:214-221.
63. Blundell J, Finlayson G, Axelsen M, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. *Diabetes Obes Metab*. 2017;19:1242-1251.
64. Sargeant JA, Henson J, King JA, Yates T, Khunti K, Davies MJ. A review of the effects of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors on lean body mass in humans. *Endocrinol Metab*. 2019;34:247-262.
65. Jensterle M, Rizzo M, Haluzik M, Janez A. Efficacy of GLP-1 RA approved for weight management in patients with or without diabetes: a narrative review. *Adv Ther*. 2022;39:2452-2467.
66. Bonora E, Frias JP, Tinahones FJ, et al. Effect of dulaglutide 3.0 and 4.5 mg on weight in patients with type 2 diabetes: exploratory analyses of AWARD-11. *Diabetes Obes Metab*. 2021;23:2242-2250.
67. Zhang F, Tong Y, Su N, et al. Weight loss effect of glucagon-like peptide-1 mimetics on obese/overweight adults without diabetes: a systematic review and meta-analysis of randomized controlled trials. *J Diabetes*. 2015;7:329-339.
68. Therapeutic Goods Administration. Liraglutide (SAXENDA) Product Information. August 24, 2022. Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2016-PI-01008-1. Accessed October 19, 2022.
69. Therapeutic Goods Administration. Liraglutide (VICTOZA) Product Information. August 24, 2022. Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2012-PI-02302-3. Accessed October 19, 2022.
70. US Food and Drug Administration. FDA Prescribing Information for WEGOVY (semaglutide). 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215256s000lbl.pdf. Accessed July 9, 2022.
71. European Medicines Agency. European public assessment report on WEGOVY (semaglutide). March 10, 2022. Available at: https://

www.ema.europa.eu/en/documents/overview/wegovy-epar-medicine-overview_en.pdf. Accessed October 19, 2022.
72. Therapeutic Goods Administration. Semaglutide (WEGOVY) Product Information. September 1, 2022. Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2022-PI-01930-1. Accessed October 19, 2022.
73. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovasc Diabetol*. 2018;17:83. 10.1186/s12933-018-0728-6
74. Mosenzon O, Alguwaihes A, Leon JLA, et al. CAPTURE: a multinational, cross-sectional study of cardiovascular disease prevalence in adults with type 2 diabetes across 13 countries. *Cardiovasc Diabetol*. 2021;20:154. 10.1186/s12933-021-01344-0
75. US Food and Drug Administration. Guidance for industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. 2008. Available at: https://www.fda.gov/media/71297/download. Accessed July 8, 2022.
76. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol*. 2021;9:653-662.
77. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Circulation*. 2017;136:849-870.
78. Rakipovski G, Rolin B, Nøhr J, et al. The GLP-1 analogs liraglutide and semaglutide reduce atherosclerosis in ApoE−/− and LDLr−/− mice by a mechanism that includes inflammatory pathways. *JACC Basic Transl Sci*. 2018;3:844-857.
79. Sanada J, Obata A, Obata Y, et al. Dulaglutide exerts beneficial anti atherosclerotic effects in ApoE knockout mice with diabetes: the earlier, the better. *Sci Rep*. 2021;11:1425. 10.1038/s41598-020-80894-x
80. Goldman JD. Cardiovascular safety outcomes of once-weekly GLP-1 receptor agonists in people with type 2 diabetes. *J Clin Pharm Ther*. 2020;45(Suppl 1):61-72.
81. Schernthaner G, Shehadeh N, Ametov AS, et al. Worldwide inertia to the use of cardiorenal protective glucose-lowering drugs (SGLT2i and GLP-1 RA) in high-risk patients with type 2 diabetes. *Cardiovasc Diabetol*. 2020;19:185. 10.1186/s12933-020-01154-w
82. Marson A, Raffoul N, Osman R, Deed G. Management of patients with type 2 diabetes and cardiovascular disease in primary care. *Aust J Gen Pract*. 2021;50:238-245.
83. Arnold SV, Tang F, Cooper A, et al. Global use of SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes. Results from DISCOVER. *BMC Endocr Disord*. 2022;22:111.
84. Arnold SV, Inzucchi SE, Tang F, et al. Real-world use and modeled impact of glucose-lowering therapies evaluated in recent cardiovascular outcomes trials: an NCDR(R) research to practice project. *Eur J Prev Cardiol*. 2017;24:1637-1645.
85. Greiver M, Havard A, Bowles JK, et al. Trends in diabetes medication use in Australia, Canada, England, and Scotland: a repeated cross-sectional analysis in primary care. *Br J Gen Pract*. 2021;71:e209-e218.
86. Heald AH, Livingston M, Bien Z, Moreno GYC, Laing I, Stedman M. The pattern of prescribing of glucose modulating agents for type 2 diabetes in general practices in England 2016/17. *Int J Clin Pract*. 2018;72:e13080.
87. Reid TS. Practical use of glucagon-like peptide-1 receptor agonist therapy in primary care. *Clin Diabetes*. 2013;31:148-157.
88. Nauck MA, Petrie JR, Sesti G, et al. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label liraglutide in patients with type 2 diabetes. *Diabetes Care*. 2016;39:231-241.
89. Bettge K, Kahle M, Abd El Aziz MS, Meier JJ, Nauck MA. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: a systematic analysis of published clinical trials. *Diabetes Obes Metab*. 2017;19:336-347.
90. Ahrén B, Atkin SL, Charpentier G, et al. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials. *Diabetes Obes Metab*. 2018;20:2210-2219.
91. Lingvay I, Hansen T, Macura S, et al. Superior weight loss with once-weekly semaglutide versus other glucagon-like peptide-1 receptor agonists is independent of gastrointestinal adverse events. *BMJ Open Diabetes Res Care*. 2020;8:e001706.
92. Romera I, Cebrián-Cuenca A, Álvarez-Guisasola F, Gomez-Peralta F, Reviriego J. A review of practical issues on the use of glucagon-like peptide-1 receptor agonists for the management of type 2 diabetes. *Diabetes Ther*. 2019;10:5-19.
93. Ahrén B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol*. 2017;5:341-354.
94. Lingvay I, Catarig AM, Frias JP, et al. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2019;7:834-844.
95. Frías JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2016;4:1004-1016.
96. Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). *Diabetes Care*. 2014;37:2149-2158.
97. Russell-Jones D, Cuddihy RM, Hanefeld M, et al. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. *Diabetes Care*. 2012;35:252-258.
98. Therapeutic Goods Administration. Exenatide (BYETTA) Product Information. September 12, 2022. Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01780-1. Accessed October 19, 2022.
99. Therapeutic Goods Administration. Dulaglutide (TRULICITY) Product Information. July 14, 2020. Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2015-PI-01412-1. Accessed October 19, 2022.
100. Therapeutic Goods Administration. Semaglutide (OZEMPIC) Product Information. March 25, 2022. Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2019-PI-01881-1. Accessed October 19, 2022.
101. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes a meta-analysis. *JAMA*. 2016;316:313-324.
102. Therapeutic Goods Administration. Exenatide (BYDUREON) Product Information. November 3, 2020. Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2017-PI-01224-1. Accessed October 19, 2022.

103. Abd El Aziz M, Cahyadi O, Meier JJ, Schmidt WE, Nauck MA. Incretin-based glucose-lowering medications and the risk of acute pancreatitis and malignancies: a meta-analysis based on cardiovascular outcomes trials. *Diabetes Obes Metab*. 2020;22:699-704.
104. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7:776-785.
105. Aroda VR, Henry RR, Han J, et al. Efficacy of GLP-1 receptor agonists and DPP-4 inhibitors: meta-analysis and systematic review. *Clin Ther*. 2012;34:1247-1258.e22.
106. Wei XB, Wei W, Ding LL, Liu SY. Comparison of the effects of 10 GLP-1 RA and SGLT2 inhibitor interventions on cardiovascular, mortality, and kidney outcomes in type 2 diabetes: a network meta-analysis of large randomized trials. *Prim Care Diabetes*. 2021;15:208-211.
107. Hussein H, Zaccardi F, Khunti K, Seidu S, Davies MJ, Gray LJ. Cardiovascular efficacy and safety of sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 receptor agonists: a systematic review and network meta-analysis. *Diabet Med*. 2019;36:444-452.
108. Wysham C, Bergenstal R, Malloy J, et al. DURATION-2: efficacy and safety of switching from maximum daily sitagliptin or pioglitazone to once-weekly exenatide. *Diabet Med*. 2011;28:705-714.
109. Shomali M. Optimizing the care of patients with type 2 diabetes using incretin-based therapy: focus on GLP-1 receptor agonists. *Clin Diabetes*. 2014;32:32-43.
110. Patel D. Glycaemic and non-glycaemic efficacy of once-weekly GLP-1 receptor agonists in people with type 2 diabetes. *J Clin Pharm Ther*. 2020;45((Suppl 1)):28-42.
111. Tsapas A, Karagiannis T, Kakotrichi P, et al. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetes Obes Metab*. 2021;23:2116-2124.
112. Nauck MA, Kahle M, Baranov O, Deacon CF, Holst JJ. Addition of a dipeptidyl peptidase-4 inhibitor, sitagliptin, to ongoing therapy with the glucagon-like peptide-1 receptor agonist liraglutide: a randomized controlled trial in patients with type 2 diabetes. *Diabetes Obes Metab*. 2017;19:200-207.
113. Deacon CF. Dipeptidyl peptidase 4 inhibitors in the treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2020;16:642-653.
114. Therapeutic Goods Administration. Linagliptin (TRAJENTA) Product Information. 2020. Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-03485-3. Accessed October 19, 2022.
115. Therapeutic Goods Administration. Sitagliptin (JANUVIA) Product Information. October 22, 2021. Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-03937-3&d=20211014172310101. Accessed October 19, 2022.
116. Therapeutic Goods Administration. Saxagliptin (ONGLYZA) Product Information. February 25, 2019. Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-02123-3. Accessed October 19, 2022.
117. Therapeutic Goods Administration. Empagliflozin (JARDIANCE) Product Information. September 9, 2022. Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2014-PI-01783-1. Accessed October 19, 2022.
118. Therapeutic Goods Administration. Dapagliflozin (FORXIGA) Product Information. August 30, 2022. Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2012-PI-02861-1. Accessed October 19, 2022.
119. Therapeutic Goods Administration. Ertugliflozin (STEGLATRO) Product Information. April 6, 2022. Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01724-1. Accessed October 19, 2022.
120. Basu D, Huggins LA, Scerbo D, et al. Mechanism of increased LDL (low-density lipoprotein) and decreased triglycerides with SGLT2 (sodium-glucose cotransporter 2) inhibition. *Arterioscler Thromb Vasc Biol*. 2018;38:2207-2216.
121. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. *Diabetes Care*. 2015;38:1638-1642.
122. Gurgle HE, White K, McAdam-Marx C. SGLT2 inhibitors or GLP-1 receptor agonists as second-line therapy in type 2 diabetes: patient selection and perspectives. *Vasc Health Risk Manag*. 2016;12:239-249.
123. Reifsnider OS, Pimple P, Brand S, Bergrath Washington E, Shetty S, Desai NR. Cost-effectiveness of second-line empagliflozin versus liraglutide for type 2 diabetes in the United States. *Diabetes Obes Metab*. 2022;24:652-661.
124. Crabtree TSJ, Adamson K, Reid H, et al. Injectable semaglutide and reductions in HbA1c and weight in the real world in people switched from alternative glucagon-like peptide-1 receptor agonists. *Diabetes Obes Metab*. 2022;24:1398-1401.
125. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care*. 2018;41:258-266.
126. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet*. 2018;392:637-649.
127. Rubino DM, Greenway FL, Khalid U, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. *JAMA*. 2022;327:138-150.
128. Dave CV, Kim SC, Goldfine AB, Glynn RJ, Tong A, Patorno E. Risk of cardiovascular outcomes in patients with type 2 diabetes after addition of SGLT2 inhibitors versus sulfonylureas to baseline GLP-1RA therapy. *Circulation*. 2021;143:770-779.
129. Ludvik B, Frías JP, Tinahones FJ, et al. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2018;6:370-381.
130. Zinman B, Bhosekar V, Busch R, et al. Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2019;7:356-367.
131. van Baar MJB, van Ruiten CC, Muskiet MHA, et al. SGLT2 inhibitors in combination therapy: from mechanisms to clinical considerations in type 2 diabetes management. *Diabetes Care*. 2018;41:1543-1556.
132. DeFronzo RA. Combination therapy with GLP-1 receptor agonist and SGLT2 inhibitor. *Diabetes Obes Metab*. 2017;19:1353-1362.
133. Chow E, Chan JCN. The emerging role of incretins and twincretins. *Nat Rev Endocrinol*. 2022;18:73-74.
134. Gentilella R, Pechtner V, Corcos A, Consoli A. Glucagon-like peptide-1 receptor agonists in type 2 diabetes treatment: are they all the same? *Diabetes Metab Res Rev*. 2019;35:e3070.
135. Sposito AC, Berwanger O, de Carvalho LSF, Saraiva JFK. GLP-1RAs in type 2 diabetes: mechanisms that underlie cardiovascular effects and overview of cardiovascular outcome data. *Cardiovasc Diabetol*. 2018;17:157. 10.1186/s12933-018-0800-2
136. Powell RE, Zaccardi F, Beebe C, et al. Strategies for overcoming therapeutic inertia in type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2021;23:2137-2154.

137. Hendrieckx C, Halliday JA, Beeney LJ, Speight J. Diabetes and emotional health: a practical guide for health professionals supporting adults with type 1 or type 2 diabetes. Canberra: National Diabetes Services Scheme, 2nd edition. 2020. Available at: https://www.ndss.com.au/wp-content/uploads/resources/diabetes-emotional-health-handbook.pdf. Accessed July 8, 2022.
138. Holmes-Truscott E, Skinner TC, Pouwer F, Speight J. Negative appraisals of insulin therapy are common among adults with type 2 diabetes using insulin: results from diabetes MILES - Australia cross-sectional survey. *Diabet Med*. 2015;32:1297-1303.
139. van Dooren FE, Nefs G, Schram MT, et al. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. *PLoS One*. 2013;8:e57058.
140. Iwanaga M, Kamoi K. Patient perceptions of injection pain and anxiety: a comparison of NovoFine 32-gauge tip 6mm and micro fine plus 31-gauge 5mm needles. *Diabetes Technol Ther*. 2009;11:81-86.
141. Devine F, Edwards T, Feldman SR. Barriers to treatment: describing them from a different perspective. *Patient Prefer Adherence*. 2018;12:129-133.
142. Jimmy B, Jose J. Patient medication adherence: measures in daily practice. *Oman Med J*. 2011;26:155-159.
143. Sav A, Kendall E, McMillan SS, et al. 'You say treatment, I say hard work': treatment burden among people with chronic illness and their carers in Australia. *Health Soc Care Community*. 2013;21:665-674.
144. Lipska K, Inzucchi SE. Cardiovascular risk-benefit ratio of thiazolidinediones. *Curr Cardiovasc Risk Rep*. 2009;3:42-50.
145. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes Obes Metab*. 2016;18:783-794.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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