GLP-1 receptor agonists in type 2 diabetes: An underused asset? Updated January 2021

David Morris

As our understanding of the incretin hormones has increased, a number of drugs targeting this system have been developed. The realisation of this potential has developed rapidly, and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are now a standard feature in management guidelines for type 2 diabetes. This article reviews the operation of the incretin system and the mechanism by which GLP-1 RAs act to provide benefit in type 2 diabetes. The availability and indications for use of the GLP-1 RAs, and their clinical benefits and disadvantages, are summarised. The position of GLP-1 RAs in the management of type 2 diabetes is discussed pragmatically, with reference to various key guidelines. This article has been updated in January 2021 to incorporate recent guideline changes and the launch in the UK of an oral formulation of semaglutide.

Just over 50 years ago, experimental evidence demonstrated that an oral glucose load elicits a greater insulin response than an intravenous glucose load (Elrick et al, 1964). Subsequently, it was demonstrated that this effect was generated by hormones located in the small intestine secreted in response to oral intake of food (Creutzfeldt and Ebert, 1985). The so-called "incretin effect" is, in fact, mediated principally by two hormones, glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP; Drucker and Nauck, 2006).

The incretin hormones secreted in response to food stimulate insulin release from pancreatic beta-cells and suppress glucagon release from alpha-cells, both of which reduce postprandial hyperglycaemia. Importantly, the activity of the incretin hormones requires elevated blood glucose levels (i.e. it is glucose-dependent), as well as the presence of food in the gut. In addition, the incretin hormones slow gastric emptying, thereby delaying the absorption of food (and particularly glucose) and reducing appetite (Nauck and Meier, 2016).

Both GLP-1 and GIP are metabolised *in vivo* by the enzyme dipeptidyl peptidase-4 (DPP-4) within 2 minutes. In people with type 2 diabetes, GLP-1 receptor activity is retained, and exogenous GLP-1 administered intravenously has been shown to reduce both fasting and postprandial hyperglycaemia (Drucker and Nauck, 2006). In contrast, GIP receptor activity is much reduced in type 2 diabetes, and so the incretin response is diminished in people with type 2 diabetes compared to those without diabetes, probably reflecting beta-cell dysfunction (Nauck et al, 1986; Knop et al, 2007).

The rationale behind using GLP-1 receptor agonists in type 2 diabetes

The short half-life of human GLP-1 *in vivo* renders it unsuitable for clinical use and has led to the search for GLP-1 receptor agonists (GLP-1 RAs) that mimic the action of endogenous GLP-1 (by binding to and activating the GLP-1 receptor) but which have resistance to breakdown by DPP-4 and thus have more prolonged activity (Meier, 2012). The hope would be that GLP-1 RAs could counter

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Article points

1. GLP-1 RAs are highly effective in treating hyperglycaemia in type 2 diabetes and offer the advantages of weight loss and low risk of hypoglycaemia. Further benefits include cardiovascular protection (in those at high risk of cardiovascular disease) and renoprotection.
2. The principal drawbacks to their use are high cost and gastrointestinal side-effects.
3. Most international guidelines place GLP-1 RAs as a third-line option to improve glycaemic control; however, they are recommended as a second-line option by the ADA/EASD, notably in people with or at high risk of cardiovascular disease, independent of glycaemic control, and, where use of SGLT2 inhibitors is not possible, in renal disease and/or heart failure.

Key words

- Cardiovascular disease
- GLP-1 receptor agonists
- Newer therapies

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raised glucose levels by stimulating insulin secretion, suppressing glucagon secretion, delaying gastric emptying and inducing satiety (Nauck and Meier, 2016). In individuals with type 2 diabetes, this should translate into improved HbA_{1c} levels and weight reduction.

The fact that GLP-1 RA activity is glucose-dependent offers the advantage of glycaemic control with low risk of hypoglycaemia, as GLP-1 RAs do not stimulate insulin secretion or suppress glucagon secretion when glucose levels are not raised (Sharma et al, 2018).

Currently available GLP-1 RAs

Currently there are six injectable GLP-1 RAs available for clinical use in the UK, all administered by subcutaneous injection to circumvent the problem of peptide degradation by gastric acid. They all share the same mechanism of action but the different molecular structures and formulations lead to varying duration of action and, in turn, to varied dosage regimens. Differences between the drugs in glycaemic control, weight reduction, cardiovascular effects and side-effect profiles have been seen in clinical trials.

The first GLP-1 RA that gained approval for use in type 2 diabetes was exenatide, licensed for use in the UK in 2007. Exenatide is a synthetic product reproducing the peptide sequence of exendin-4, which had been isolated from the saliva of the Gila monster, a lizard found in the deserts of Arizona and New Mexico. **Exenatide standard-release (Byetta)** is licensed for twice-daily use before two main meals (at least 6 hours apart).

Liraglutide (Victoza) was the next GLP-1 RA to be developed, becoming available in 2009. In contrast to exenatide, it is 97% homologous to human GLP-1. Liraglutide has a half-life of around 13 hours, enabling it to be injected once daily.

The first once-weekly GLP-1 RA approved for use in type 2 diabetes was **exenatide modified-release (Bydureon)**. In this formulation the exenatide molecules are enclosed within biodegradable polymeric microspheres that slowly break down in the subcutaneous tissue, releasing exenatide into the circulation in a controlled manner (Fineman et al, 2011).

Lixisenatide (Lyxumia), like exenatide, is a derivative of exendin-4. It has a short duration of action and is licensed to be taken within one hour before the first meal of the day or the evening meal.

Further once-weekly GLP-1 RAs based on modified human GLP-1 have followed: **dulaglutide (Trulicity)**, albiglutide (Eperzan; now discontinued and never marketed in the UK) and **semaglutide (Ozempic)**.

The principle mechanism of action of the short-acting exendin-4 derivatives, exenatide and lixisenatide, is to delay gastric emptying and thus lower postprandial glucose levels (Nauck and Meier, 2019). In contrast, the longer-acting GLP-1 RAs exert their effects mainly by stimulating insulin release and inhibiting glucagon secretion, which impacts on both postprandial and fasting glucose levels.

Oral semaglutide

Conventional wisdom would dictate that administering peptides orally is unfeasible because of degradation by gastric acid and proteases. However, an oral formulation of semaglutide **(Rybelsus)** is now licensed for use. It is taken once daily with a small sip of water after an overnight fast, following which no food or medication should be taken for 30 minutes.

Oral semaglutide is co-formulated with SNAC (sodium N-[8-(2-hydroxybenzoyl)amino]-capyrate), which acts as an absorption enhancer, allowing entry of semaglutide into the circulation with a bioavailability of around 1%. The SNAC molecule, as a weak carboxylic acid, effectively buffers the acidity of hydrochloric acid in the stomach, restricting enzymatic degradation of the semaglutide. Then, after binding to the semaglutide, SNAC is able to facilitate transcellular absorption across the lipophilic gastric epithelium into the bloodstream, because it has a hydrophobic alkyl chain (Buckley et al, 2018).

Indications and contraindications

GLP-1 RAs are indicated for the treatment of type 2 diabetes in combination with other glucose-lowering medications except DPP-4 inhibitors, including insulin, when these together with diet and exercise do not provide adequate glycaemic control. Liraglutide, dulaglutide and semaglutide are indicated as monotherapy in situations where metformin is poorly tolerated or contraindicated. All currently licensed GLP-1 RAs are given by subcutaneous injection into the abdomen, thigh

Box 1. Who should not receive a GLP-1 receptor agonist?

- Type 1 diabetes.
- Pregnancy and breastfeeding.
- Severe gastrointestinal disease (e.g. inflammatory bowel disease).
- Diabetic gastroparesis.
- History of pancreatitis.
- Caution if high risk of pancreatitis (e.g. gallstones, alcohol excess, hypertriglyceridaemia).
- History of medullary thyroid cancer or multiple endocrine neoplasia (MEN) type 2.
- Caution in renal impairment – see *Table 1*.

Table 1. Recommended use of GLP-1 receptor agonists in chronic kidney disease.

GLP-1 receptor agonist	Renal function (eGFR in mL/min/1.73 m^2)
Exenatide immediate-release (twice-daily)	Avoid if eGFR <30
Liraglutide	Can use down to eGFR 15
Exenatide modified-release (once-weekly)	Avoid if eGFR <50
Lixisenatide	Avoid if eGFR <30, caution if eGFR 30–50
Dulaglutide	Can use down to eGFR 15
Semaglutide	Can use down to eGFR 15

eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide-1.

or upper arm, rotating the injection sites from one injection to the next.

Combination therapy

When adding a GLP-1 RA to an insulin secretagogue (a sulfonylurea or meglitinide), consideration should be given to lowering the dose of the latter medications to reduce the risk of hypoglycaemia. For similar reasons, if a GLP-1 RA is added to a basal insulin then, unless HbA_{1c} is markedly raised, it is prudent to reduce the dose of insulin by as much as 20–25%, although this can be re-uptitrated later as necessary (Nauck and Meier, 2019).

Pioglitazone and sodium–glucose cotransporter 2 (SGLT2) inhibitors are reasonable combination therapies with GLP-1 RAs.

If a DPP-4 inhibitor is being taken, it should be discontinued on commencement of a GLP-1 RA, as the combination does not provide additional glycaemic control (American Diabetes Association, 2018).

Contraindications

Contraindications (these vary slightly between EU and US labels) and reasons to avoid using GLP-1 RAs are summarised in *Box 1*.

GLP-1 RAs are licensed for use in varying stages of renal impairment depending on the agent (*Table 1*). There are no specific requirements regarding the use of GLP-1 RAs in hepatic impairment, other than liraglutide, which is not recommended in severe hepatic impairment (Child–Pugh score >9).

No dose adjustment is necessary with regard to weight, BMI or, in most cases, age (however, a lower starting dose of dulaglutide 0.75 mg once weekly is recommended in those aged 75 years or more; and caution in increasing the dose of immediate-release exenatide from 5 to 10 µg twice daily is advised in the elderly).

Dose regimens and administration

The properties and dose regimens of the GLP-1 RAs are summarised in *Table 2* and *Box 2* (Lyseng-Willimason, 2019; Nauck and Meier, 2019; Romera et al, 2019). It can be seen that the exendin-4-derived GLP-1 RAs are short-acting (exenatide once-weekly having a longer duration of action because of its microsphere formulation), whilst the modified human GLP-1 derivatives are long-acting.

Selection of a GLP-1 RA for an individual may be influenced by frequency of dosing, ease of dose titration and pen-related factors such as ease of administration, including needle arrangements to minimise the fear of injection. Some of these factors are summarised in *Table 3* (Nauck and Meier, 2019; Romera et al, 2019).

The dosing schedule and requirements of oral semaglutide are summarised in *Box 2*. Because semaglutide is primarily degraded in the circulation by enzymatic proteolytic cleavage and beta-oxidation of the fatty acid side-chain, no dose adjustment is necessary in hepatic or renal failure, and semaglutide is licensed for use down to an estimated glomerular filtration rate (eGFR) of 15 mL/min/1.73 m^2 (Pearson et al, 2019).

"Selection of a GLP-1 RA for an individual may be influenced by frequency of dosing, ease of dose titration and pen-related factors such as ease of administration, including needle arrangements to minimise the fear of injection."

Table 2. Properties and dose regimens of GLP-1 receptor agonists.

GLP-1 receptor agonist	Structural class	Dosage regimen	Dosage instruction
Exenatide immediate-release (twice-daily)	Exendin-4 derivative	5 µg twice daily for first month, then 10 µg twice daily	60 minutes before main meals
Liraglutide	Modified human GLP-1	0.6 mg once daily for first week, then 1.2 mg (1.8 mg if needed) once daily	Any time
Exenatide modified-release (once-weekly)	Exendin-4 derivative	2 mg once weekly	Any time
Lixisenatide	Exendin-4 derivative	10 µg once daily for first 2 weeks, then 20 µg once daily	60 minutes before any main meal
Dulaglutide	Modified human GLP-1	0.75 mg once weekly as monotherapy; 1.5 mg once weekly as add-on therapy	Any time
Semaglutide (subcutaneous)	Modified human GLP-1	0.25 mg once weekly for first month, then 0.5 mg once weekly (can increase to 1 mg once weekly after a further 1 month)	Any time
Semaglutide (oral)	Modified human GLP-1	3 mg once daily for 1 month, then 7 mg once daily for at least 1 month. If necessary, increase dose to 14 mg once daily.	See *Box 2*

GLP-1=glucagon-like peptide-1.

Box 2. Administration of oral semaglutide.

- Take on empty stomach, on waking, with a sip of water (up to 120 mL).
- Wait at least 30 minutes before eating, drinking or taking any other oral medication.
- No dose adjustment is needed for renal or hepatic failure or in the elderly.
- If added to a sulfonylurea or insulin, consider dose reduction of these latter treatments to reduce risk of hypoglycaemia.
- Other medications taken after an overnight fast ahead of food (e.g. levothyroxine, oral bisphosphonates) may need to be rescheduled to another (empty stomach) time. If semaglutide and levothyroxine are taken in close proximity, consider checking thyroid function tests subsequently.

Fixed-dose combination products

GLP-1 RAs are also available in combination with a basal insulin in a fixed dose ratio for a once-daily injection. A basal insulin has greatest impact on fasting glucose levels whilst the GLP-1 RA has an effect on postprandial glucose levels (as well as fasting glucose in the case of a long-acting GLP-1 RA; Kenny and Hall, 2015). The GLP-1 RA mitigates insulin-induced weight gain and does not add to hypoglycaemic burden, and the combination is more effective in lowering HbA_{1c} than either component separately (Gough et al, 2014).

Two products are currently available. **IDegLira (Xultophy)** is formulated with a ratio of 1 unit of insulin degludec to 0.036 mg of liraglutide. The multiple-use, disposable pen can accommodate a top dose of 50 units of degludec plus 1.8 mg of liraglutide once daily, given at any time. A starting dose of 10 "dose steps" (equivalent to 10 units of degludec and 0.36 mg of liraglutide) can be added to oral antidiabetes medications; alternatively, if the

Table 3. Administration characteristics of GLP-1 receptor agonist pen devices.

GLP-1 receptor agonist	Single- or multiple-use pen	Pens available	Reconstitution or mixing required	Needle arrangements
Exenatide twice-daily (Byetta)	Multiple	5 µg or 10 µg	No	Needles not included
Liraglutide (Victoza)	Multiple	One pen with variable dose of 0.6 mg, 1.2 mg or 1.8 mg	No	Needles not included
Lixisenatide (Lyxumia)	Multiple	10 µg or 20 µg	No	Needles not included
Exenatide once-weekly (Bydureon)	Single	2 mg	Yes	Needles included
Exenatide once-weekly (Bydureon BCise prefilled pen)	Single	2 mg	Yes	Pre-attached hidden needle
Dulaglutide (Truclicity)	Single	0.75 mg or 1.0 mg	No	Pre-attached hidden needle
Semaglutide (Ozempic)	Multiple	0.25 mg, 0.5 mg or 1 mg	No	Needles included

GLP-1=glucagon-like peptide-1.

individual was previously receiving a basal insulin, the starting dose would be 16 dose steps.

The second combination product is **IGlarLixi** (**Suliqua**, formerly LixiLan), a combination of insulin glargine and lixisenatide. This is available as two differing concentrations: glargine 100 units/mL plus lixisenatide 50 µg/mL, or glargine 100 units/mL plus lixisenatide 33 µg/mL. In the latter combination, for example, the dose can be titrated up to allow a maximum of 60 units of glargine plus 20 µg of lixisenatide, to be administered an hour before the same main meal once daily.

Side-effects and other issues

The most frequent side-effects from using GLP-1 RAs are gastrointestinal. Individuals need to be warned of the possibility of nausea and vomiting but should also be reassured that these are usually mild to moderate in intensity and dissipate with time (Raccah, 2017). The incidence of nausea is around 20%, with a higher rate for the short-acting GLP-1 RAs (Bettge et al, 2017), which is associated with increased discontinuation. Diarrhoea can also be experienced, and in this case incidence is higher for the long-acting rather than short-acting GLP-1 RAs (Bettge et al, 2017).

Acute pancreatitis has been observed with GLP-1 RA use, and product licenses retain a warning on this. Users should also be informed of the symptoms of acute pancreatitis and to stop the GLP-1 RA should they experience severe upper abdominal pain, and to seek medical advice. If pancreatitis is confirmed then treatment should not be restarted. Reassuringly, the incidence of pancreatitis did not appear to be increased in the cardiovascular outcome trials with GLP-1 RAs (see later), and recent meta-analyses did not find evidence of an increased risk of acute pancreatitis or pancreatic cancer, although an increased risk of gallbladder events was identified (Monami et al, 2017; Storgaard et al, 2017; Bethel et al, 2018).

An association between GLP-1 RA use and medullary thyroid cancer had been suggested from animal studies. However, a meta-analysis of once-weekly GLP-1 RAs showed no increased risk in comparison with other antidiabetes drugs (Bethel et al, 2018).

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There was no evidence of an increased risk of pancreatitis, pancreatic carcinoma or thyroid cancer in studies with oral semaglutide (Husain et al, 2019).

Injection site reactions are rare with GLP-1 RAs but do appear to be significantly more frequent with the microsphere formulation of once-weekly exenatide (Blevins et al, 2011).

In situations of hypovolaemia, such as severe gastrointestinal disturbance, GLP-1 RAs have been linked to acute kidney injury, and measures to counter dehydration and temporary cessation of treatment may be required (Filippatos et al, 2014).

In the cardiovascular outcome trial of semaglutide (SUSTAIN-6), a significant increase in risk of the prespecified retinal outcome (a composite of need for photocoagulation, need for intravitreal agents, vitreous haemorrhage or new-onset blindness) was observed (hazard ratio [HR], 1.76), principally in subjects with pre-existing diabetic retinopathy who were using insulin (Marso et al, 2016a). It has been suggested that this was linked to a rapid improvement in glycaemic control, a phenomenon that has been noted in type 1 diabetes and pregnancy studies. Accordingly, caution is advised when using semaglutide in people with diabetic retinopathy. The LEADER trial also showed a signal for increased retinopathy with liraglutide; however, this did not reach the level of significance (Marso et al, 2016b).

Individuals with maculopathy and proliferative retinopathy were excluded in the PIONEER-6 study of oral semaglutide because of the findings with subcutaneous semaglutide. Nonetheless, retinopathy complications with oral semaglutide were numerically greater than with placebo (7.1% vs 6.3%; Husain et al, 2019). It is recommended that similar cautions are applied to the use of oral semaglutide as with injectable semaglutide in people with diabetic retinopathy until further information is available.

Clinical benefits

The GLP-1 RAs are effective glucose-lowering agents, achieving HbA_{1c} reductions in the order of 11 mmol/mol (1.0%) compared with placebo in practice (Waldrop et al, 2018), although there is some variability in efficacy within the class. Greater reductions are seen with higher starting HbA_{1c} levels (Bihan et al, 2016). The longer-acting GLP-1 RAs appear to be more effective in reducing HbA_{1c} than the shorter-acting agents, although not all clinical trials had the same design. The evidence indicates that semaglutide is the most powerful agent, ahead of liraglutide and dulaglutide, followed by exenatide once-weekly and then exenatide twice-daily and lixisenatide (Htike et al, 2017; Davies et al, 2018; Pearson et al, 2019; Pratley et al, 2019).

As indicated previously, a useful property of GLP-1 RAs is their low propensity to induce hypoglycaemia. The risk of hypoglycaemia is lower than with insulin or sulfonylureas (Levin et al, 2017). If a GLP-1 RA is added to insulin or an insulin secretagogue (sulfonylureas and meglitinides), consideration should be given to reducing the dose of the latter agents to minimise the risk of hypoglycaemia.

An important clinical benefit offered by GLP-1 RAs in type 2 diabetes is that of weight loss associated with reduced appetite (Sun et al, 2015; Bihan et al, 2016). This reaches a plateau after 6 months or so of treatment and varies between members of the class from around 1.5 kg to 6.0 kg, the highest reductions being found with subcutaneous and oral semaglutide (Htike et al, 2017; Andreadis et al, 2018; Nauck and Meier, 2019; Pratley et al, 2019). In fact, there is a relatively high degree of variation in weight loss at the individual level (anything from zero to over 20 kg), much greater than the variation seen in glycaemic control (Nauck and Meier, 2019). The weight loss observed with GLP-1 RA therapy contrasts with the weight gain which can be seen with insulin, pioglitazone and most sulfonylureas.

A small reduction in systolic blood pressure (around 2–5 mmHg) is associated with GLP-1 RA treatment, although this is accompanied by a small increase in pulse rate of 2–5 beats/minute (Holman et al, 2017; Nauck et al, 2017). A slightly beneficial effect on lipid profile is also apparent, with a small reduction in LDL-cholesterol and triglyceride levels.

Cardiovascular benefits

Cardiovascular outcome trials have been performed on all the available GLP-1 RAs except twice-daily exenatide. The participants in these double-blind, randomised, placebo-controlled trials comprised individuals with type 2 diabetes

who had pre-existing cardiovascular disease or cardiovascular risk factors. The primary outcome in the majority of these studies was three-point major adverse cardiac events (MACE): a combination of non-fatal myocardial infarction (MI), non-fatal stroke and cardiovascular death. The ELIXA study of lixisenatide used four-point MACE, which included hospitalisation for angina in the combined primary outcome.

The first GLP-1 RA to show significant benefit in cardiovascular outcomes was liraglutide in the LEADER trial (Marso et al, 2016b), with an absolute risk reduction (ARR) in MACE of 1.9% over 3.8 years compared with placebo, and a significant relative risk reduction of 13% (HR, 0.87). The HR for all-cause mortality was also significantly reduced versus placebo (HR, 0.87).

In SUSTAIN-6, semaglutide was also shown to provide cardiovascular benefit, with an ARR of 2.3% over 2.1 years and an HR of 0.74 for MACE compared with placebo (Marso et al, 2016a). This was driven mainly by a reduction in risk of stroke.

The EXSCEL study compared exenatide modified-release with placebo (Holman et al, 2017). Although the HR for MACE was 0.91 in favour of exenatide, this just missed statistical significance. There was a significant reduction in all-cause mortality. For the other exendin-4 derivative, lixisenatide, cardiovascular safety but not benefit was demonstrated in the ELIXA trial (Pfeffer et al, 2015).

Cardiovascular benefits (significant improvements in MACE compared with placebo) were subsequently identified in the trials of dulaglutide (REWIND; Gerstein et al, 2019), principally driven by a reduction in non-fatal stroke, and albiglutide (HARMONY; Hernandez et al, 2018), largely driven by reductions in fatal and non-fatal MI.

The PIONEER-6 trial of oral semaglutide (which was only designed to show cardiovascular safety rather than superiority) showed a strong trend towards cardiovascular benefit (in MACE versus placebo), but this did not reach the level of significance (Husain et al, 2019). The trial showed significant reductions in cardiovascular death and overall mortality compared with placebo, but not reductions in non-fatal MI and stroke. Thus, the current situation is that cardiovascular safety of oral semaglutide is established but not cardiovascular superiority over placebo. A trial to test for the latter is in progress.

A summary of the GLP-1 RA cardiovascular outcome trials can be found in *Table 4*.

In addition to the individual studies above, systematic reviews of the cardiovascular safety

Table 4. Cardiovascular outcome trial results of GLP-1 receptor agonists versus placebo in type 2 diabetes: primary outcome of 3-point MACE*.

GLP-1 receptor agonist	Number in trial	Trial duration (median)	MACE absolute risk reduction versus placebo	MACE hazard ratio (95% confidence interval) versus placebo	Statistically significant
Liraglutide	9340	3.8 years	1.9%	0.87 (0.78–0.97)	Yes
Semaglutide	3297	2.1 years	2.3%	0.74 (0.58–0.95)	Yes
Exenatide once-weekly	14752	3.2 years	1.2%	0.91 (0.83–1.00)	No
Lixisenatide†	6068	2.1 years	–0.2%	1.02 (0.89–1.17)	No
Dulaglutide	9901	5.4 years	1.4%	0.88 (0.79–0.99)	Yes
Albiglutide	9493	1.6 years	2.0%	0.78 (0.68–0.90)	Yes
Oral semaglutide	3183	1.3 years	1.0%	0.79 (0.57–1.11)	No

*3-point MACE was a composite outcome of non-fatal myocardial infarction, non-fatal stroke or death from cardiovascular causes. †The lixisenatide study had a 4-point MACE endpoint, including hospitalisation for angina.

GLP-1=glucagon-like peptide-1; MACE=major adverse cardiac event.

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Box 3. NICE (2015) guidance on use of GLP-1 receptor agonists in adults with type 2 diabetes.

- Use in combination with metformin and a sulfonylurea when triple oral therapy (including metformin) is ineffective, not tolerated or contraindicated and the individual has:
  - BMI of 35 kg/m^2 or more (adjust for ethnic group) and obesity-related psychological or medical problems.
  - BMI lower than 35 kg/m^2 and where occupation would be affected by insulin therapy or weight loss would benefit obesity-related comorbidities.
- Only continue GLP-1 receptor agonist if HbA_{1c} improves by 11 mmol/mol (1.0%) and weight loss of 3% of body weight is achieved in 6 months.
- Specialist advice for using combination of a GLP-1 receptor agonist and insulin.

Box 4. SIGN (2017) guidance on use of GLP-1 receptor agonists in type 2 diabetes.

- Consider in people with BMI ≥30 kg/m^2 as a third- or fourth-line treatment in combination with other agents (including insulin) when glycaemic control is not achieved.
- Consider as an alternative to insulin when oral agents are insufficient.
- In established cardiovascular disease, consider GLP-1 receptor agonists with proven cardiovascular benefit.

of the GLP-1 RAs as a class indicate that they reduce the risk of cardiovascular events, with an overall 10% reduction in MACE, a 13% reduction in cardiovascular death and a 12% reduction in all-cause mortality (Bethel et al, 2018; Jia et al, 2018; Kristensen et al, 2019).

Thus, it would appear that the longer-acting (rather than short-acting) GLP-1 RAs offer benefit in those with established cardiovascular disease, possibly favouring the agents with a close analogy to the human GLP-1 molecular structure. The strongest evidence lies with semaglutide, liraglutide, dulaglutide and albiglutide, followed by exenatide once-weekly (although these results did not reach significance), with lixisenatide being neutral in terms of cardiovascular outcomes. Unlike certain SGLT2 inhibitors, the GLP-1 RAs do not appear to confer benefits in terms of heart failure.

The mechanisms behind these cardiovascular benefits are probably multifactorial (Nauck et al, 2017; Boyle et al, 2018). Reduced blood pressure, weight loss, lower LDL-cholesterol concentrations and lower blood glucose levels are all conventional risk factors that are positively affected by GLP-1 RAs. Other factors that might retard the progress of atherosclerosis are reduced low-grade inflammation and improved plaque stability.

Renal benefits

In the cardiovascular outcome trials of the GLP-1 RAs, renal effects were a secondary outcome, although the criteria were not uniform between different studies. In the LEADER trial, liraglutide demonstrated a 22% relative risk reduction compared with placebo in the prespecified secondary renal composite outcome of new-onset macroalbuminuria, doubling of serum creatinine, end-stage renal disease or death due to renal disease (Mann et al, 2017). In SUSTAIN-6 (Marso et al, 2016a), semaglutide reduced the same secondary renal outcome versus placebo (relative risk reduction, 36%). In both studies, the most significant factor contributing to the improved renal outcome was reduced progression of albuminuria.

Similarly, reduction in progression to macroalbuminuria was found with exenatide once-weekly, lixisenatide, albiglutide and dulaglutide (Pfeffer et al, 2015; Holman et al, 2017; Hernandez et al, 2018; Gerstein et al, 2019). A recent meta-analysis confirmed that treatment with GLP-1 RAs was associated with a reduction in risk of adverse kidney outcomes and that this was principally due to a reduction in urinary albumin excretion (Kristensen et al, 2019). Thus, it can be seen that a beneficial effect on development of proteinuria is a consistent feature of the GLP-1 RAs, although the response in terms of eGFR and incidence of end-stage renal failure is less clear.

Clinical guidelines

NICE (2015) guidance on GLP-1 RAs is summarised in *Box 3*. In light of subsequent evidence, this guidance, in the opinion of the author, now appears quite restrictive and is behind current practice.

More recent guidelines from SIGN (2017) on glycaemic control in type 2 diabetes acknowledge that GLP-1 RAs are an alternative to insulin initiation and recognise their benefit in people with established cardiovascular disease (*Box 4*).

ADA/EASD guidelines

Both NICE and SIGN place GLP-1 RAs as a third- or fourth-line treatment to improve glycaemic control in type 2 diabetes. The American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD) consensus report took

the advice further, recommending GLP-1 RAs as a possible second-line treatment for glycaemic control in type 2 diabetes depending on individual circumstances (Davies et al, 2018). Specifically, in people with established atherosclerotic cardiovascular disease (ASCVD), a GLP-1 RA with proven cardiovascular benefit is recommended as the first choice (Buse, 2020), an alternative being an SGLT2 inhibitor. If HbA_{1c} is already at target, the guidance suggested to consider switching across to a suitable GLP-1 RA to provide cardiovascular benefit.

More recently, the ADA/EASD consensus report was updated, strengthening the recommendations for use of GLP-1 RA and SGLT2 inhibitor therapy, notably in recommending them in those at high risk of cardiovascular disease, chronic kidney disease and/or heart failure (Buse et al, 2020). These drugs are now recommended for consideration in these situations regardless of whether the individual's HbA_{1c} is at target level. GLP-1 RAs with proven cardiovascular benefit (liraglutide, semaglutide and dulaglutide) are recommended in preference to SGLT2 inhibitors if ASCVD is the key pathology because of their positive impact on MACE.

GLP-1 RAs may be considered as an option for individuals with type 2 diabetes who have risk factors for, but not established, ASCVD (risk factors defined as age 55 years or older with >50% stenosis of coronary, carotid or peripheral arteries, left ventricular hypertrophy, eGFR <60 mL/min/1.73 m^2 or albuminuria). The strongest evidence to support this use of GLP-1 RAs in primary prevention of ASCVD came from the dulaglutide cardiovascular outcome trial, in which nearly 70% of participants had this high risk profile but not established ASCVD (Gerstein et al, 2019).

If chronic kidney disease or heart failure predominates, and if an SGLT2 inhibitor (the first-choice therapy) is contraindicated or not tolerated, or if eGFR is less than adequate for SGLT2 inhibitor use, then a GLP-1 RA becomes the agent of choice to improve glycaemic control.

GLP-1 RAs are also an option to add to metformin if there is a compelling need to lose weight or avoid hypoglycaemia.

The ADA/EASD guideline advocates GLP-1 RAs as the first-choice injectable therapy (ahead of a basal insulin) to maximise glycaemic lowering. The caveat to this recommendation is that, for individuals with a very high HbA_{1c} (>97 mmol/mol [11.0%]), evidence of osmotic symptoms (polyuria, polydipsia, weight loss) or if type 1 diabetes is a possibility, insulin is recommended.

Discussion: When to use GLP-1 RAs in the real world

Lifestyle change focused on diet, exercise and weight loss are the cornerstone of managing type 2 diabetes. Almost all guidelines recommend metformin as the first pharmacological treatment; however, the advice begins to diverge after this.

The key principle in choosing treatment is individualisation of therapy. So alongside effectiveness, safety, tolerability, ease of use, cost of treatment and need for monitoring, patient factors including age, comorbidities (notably cardiovascular and renal status), duration of diabetes, other medications and, importantly, the individuals' circumstances (occupation and domestic situation) and preferences need to be taken into account.

Advantages

GLP-1 RAs exert a significant glucose-lowering effect (generally greater than is seen with oral agents) and are effective in both the early and late stages of type 2 diabetes (Nauck and Meier, 2019). The longer-acting GLP-1 RAs hold the advantage in facilitating HbA_{1c} reduction; they act to lower both postprandial and fasting glucose levels, whereas shorter-acting agents exert their effect mainly on postprandial glucose levels alone (Nauck and Meier, 2019). Semaglutide appears to have the greatest HbA_{1c}-lowering effect, followed by liraglutide and dulaglutide, and then exenatide once-weekly. Oral semaglutide has similar efficacy to liraglutide in terms of glycaemic lowering, with a small but significant advantage seen after 1 year (oral semaglutide 14 mg versus subcutaneous liraglutide 1.8 mg; Pratley et al, 2019).

Important features of GLP-1 RAs are the promotion of weight loss and a low risk of hypoglycaemia, which makes them a useful option for managing hyperglycaemia in obese individuals with type 2 diabetes and in situations where hypoglycaemia must be avoided (Buse et al, 2020). Semaglutide (both subcutaneous and oral preparations) appears to offer the greatest weight loss (Nauck and Meier, 2019; Husain et al, 2019).

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SGLT2 inhibitors – moving on with the evidence

David Morris provides a review of the benefits and difficulties associated with the use of SGLT2 inhibitors in people with type 2 diabetes and, potentially, type 1 diabetes.

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There is now good evidence that several long-acting GLP-1 RAs (liraglutide, dulaglutide and semaglutide) provide cardiovascular protection (*Table 4*), and hence these agents (as do SGLT2 inhibitors) become a logical add-on therapy to metformin for glycaemic lowering in those with established cardiovascular disease (Buse et al, 2020).

Many individuals with type 2 diabetes suffer from renal impairment, and it is therefore of practical importance that GLP-1 RAs are licensed to be used in varying degrees of chronic kidney disease (*Table 1*). As a group, the GLP-1 RAs appear to reduce the progression of albuminuria, so they are a logical choice (behind SGLT2 inhibitors) for glycaemic control in diabetic nephropathy (Buse et al, 2020).

Once-daily and, especially, once-weekly GLP-1 RAs may, because of reduced injection frequency, improve compliance (Romera et al, 2019). This may also be an important factor in those with needle phobia, some of whom may prefer a once-weekly injection with a hidden pre-attached needle (see *Table 3*). Oral semaglutide offers an alternative means of administering a GLP-1 RA that may be more convenient, particularly for individuals with a fear of injections, and may facilitate improved adherence.

If a GLP-1 RA is added to a sulfonylurea or a meglitinide (such as repaglinide) then, unless HbA_{1c} is particularly high, it is wise to reduce the dose of the latter to lower the risk of hypoglycaemia. DPP-4 inhibitors are unlikely to have a complementary effect to GLP-1 RAs and, therefore, are recommended to be discontinued (Lajthia et al, 2019; Buse et al, 2020). In contrast, the combination of a GLP-1 RA and an SGLT2 inhibitor to improve glycaemic control looks particularly attractive as both treatments facilitate weight loss and neither induce hypoglycaemia; furthermore, both treatments appear to offer cardiovascular benefits and renoprotection (Castellana et al, 2019; Guo et al, 2020).

The evidence indicates that GLP-1 RAs are at least as effective as basal insulin in lowering HbA_{1c} in type 2 diabetes (Abd El Aziz et al, 2017; Singh et al, 2017), and this coupled with the benefit of weight reduction and low risk of hypoglycaemia (in contrast to insulin) underpins the ADA/EASD advice to use GLP-1 RAs ahead of insulin (Buse et al, 2020). However, be wary when considering the individual with very high blood glucose levels, osmotic symptoms, a personal or family history of autoimmune disease, or with normal or low BMI; such individuals may well be insulin-deficient, not insulin-resistant, and insulin would be the right choice for them.

For individuals with type 2 diabetes already using a basal insulin, options to further improve glycaemic control include addition of a GLP-1 RA or adding a rapid-acting insulin with meals. There are strong arguments for preferring the former strategy. Compared with a prandial insulin, addition of a GLP-1 RA offers potential weight loss (rather than weight gain), avoidance of hypoglycaemia, less monitoring of blood glucose levels and easier dose titration (Abd El Aziz et al, 2017; Wysham et al, 2017; Buse et al, 2020). When adding a GLP-1 RA to insulin, if HbA_{1c} is <70 mmol/mol (8.5%), it is prudent to reduce the dose of insulin (at least initially) by around 20–25% (Nauck and Meier, 2019).

The combination of a GLP-1 RA and basal insulin is highly effective in improving glycaemic control in type 2 diabetes and logical given their complementary actions. Thus, adding a basal insulin to a GLP-1 RA is also a useful strategy (Buse et al, 2020).

Disadvantages

On the downside, GLP-1 RAs are an expensive treatment and this can restrict their use, particularly in developing countries, where they may be excluded from the national formulary on the grounds of cost.

Gastrointestinal side-effects, particularly nausea, are common with GLP-1 RAs, although generally these are mild to moderate in intensity and usually decline over time (Nauck and Meier, 2019). As the side-effects are dose-dependent, it may be appropriate to reduce the dose of GLP-1 RA. Depending on the agent, a gradual uptitration of dose can minimise these side-effects, and a once-weekly preparation may be preferred.

Upper abdominal pain raises the possibility of acute pancreatitis. Amylase levels may be checked, but if pain is severe, hospital admission will be required. In acute illness where there is a risk of dehydration (e.g. diarrhoea and vomiting), temporary discontinuation of the GLP-1 RA should

be considered to avert the problem of acute kidney injury (follow sick day rules; see Milne, 2020). Treatment can be restarted when the illness is over.

For patients with significant diabetic retinopathy, caution should be exercised in the use of semaglutide, following the finding of worsening retinopathy in the SUSTAIN-6 trial (Marso et al, 2016a), and it would be wise to extend this caution to oral semaglutide at present. In practice, the author would, after discussion with the person with diabetes, be happy to use subcutaneous or oral semaglutide in the situation of background diabetic retinopathy but would be reluctant to use it in retinopathy grades beyond this.

Education

An education session for the person with type 2 diabetes and their family and carers, ideally with the Diabetes Specialist Nurse or Practice Diabetes Nurse, is essential for safe use of GLP-1 RAs. Important issues to be covered for injectable GLP-1 RAs are outlined in *Box 5*. Users need to be aware that GLP-1 RAs are different from insulin. In terms of driving, taking a GLP-1 RA places no restriction on holding a Group 1 licence (car and motorcycle). Those holding a Group 2 licence (bus and lorry) need to inform the DVLA (DVLA, 2016). Whilst education around the use of oral semaglutide will also encompass some of the points in *Box 5*, it is inherently simpler to deliver than with the injectable GLP-1 RAs.

Conclusions

The development of the GLP-1 RAs for managing type 2 diabetes has evolved rapidly since their introduction 12 years ago. They have proved to be highly effective in treating hyperglycaemia and offer the advantages of weight loss and low risk of hypoglycaemia. Further benefits of GLP-1 RAs include cardiovascular protection (in those at high risk of cardiovascular disease) and renoprotection. The principal factors limiting their use are gastrointestinal side-effects and expense.

Subcutaneous GLP-1 RAs have typically been used after several oral agents have been tried, but there are now clear circumstances when they may be considered second-line after metformin. They have been recommended internationally as the first injectable treatment of choice, ahead of insulin.

Box 5. Educational points for individuals starting an injectable GLP-1 receptor agonist.

- Explanation of potential benefits: glycaemic lowering, weight loss, low risk of hypoglycaemia.
- Discussion of potential side-effects: nausea/vomiting, diarrhoea, worsening of gastro-oesophageal reflux disease.
- Warning of symptoms of pancreatitis and action to take.
- Demonstration of device: drawing up and injecting GLP-1 receptor agonist.
- Need for injection site rotation and needle changes.
- Needle safety and disposal.
- Advice on dose titration (if appropriate).
- Blood glucose monitoring (if appropriate).
- Changes in other medication (sulfonylureas, insulin).
- Sick day rules.
- Advice to avoid pregnancy (and stop GLP-1 receptor agonist at least 3 months before any planned conception).
- Follow-up arrangements and point of contact if problems.
- Storage.
- Travel advice.

The positioning in treatment and specific choice of GLP-1 RA should be made according to individual factors. A comprehensive education session is essential before commencing treatment.

Oral semaglutide appears to be an important addition to the GLP-1 RA treatments. It could be considered as a second-line option (after metformin) or third-line option (added to two oral agents) to improve glycaemic control in type 2 diabetes, with the benefits of weight loss and low risk of hypoglycaemia. However, dosing instructions will be key to effectiveness and high cost may restrict use. Oral semaglutide may prove to be an attractive choice in primary care.

In the author's opinion, GLP-1 RAs for the treatment of type 2 diabetes could be more extensively used, taking account of recent evidence and careful patient selection. ■

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