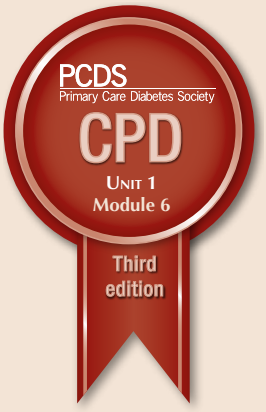

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See page 310

Citation: Kenny C (2015) Hyperglycaemia in type 2 diabetes: Newer blood glucose-lowering therapies. *Diabetes & Primary Care* **17:** 302–10

Learning objectives

After reading this article, the participant should be able to:

1. Understand the incretin effect and how it has been explored therapeutically for the treatment of type 2 diabetes.
2. Explain the mechanism of action of sodium–glucose cotransporter 2 (SGLT2) inhibitors.
3. Prescribe and manage glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors and the SGLT2 inhibitors in practice, referring to national guidance.

Key words

- Blood glucose lowering
- DPP-4 inhibitors
- GLP-1 receptor agonists
- Guidelines
- SGLT2 inhibitors

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Unit 1 Core aspects of care

Hyperglycaemia in type 2 diabetes: Newer blood glucose-lowering therapies

Colin Kenny

Many of the traditional therapies for reducing hyperglycaemia in type 2 diabetes, including biguanides, sulfonylureas, meglitinides, thiazolidinediones and alpha-glucosidase inhibitors, were discovered by serendipity. The majority of the newer agents for the treatment of hyperglycaemia that have been developed by manipulating scientifically discovered enzyme pathways in the body, often by blocking them. Focusing on the mechanism of the incretin effect has enabled development of glucose-lowering therapies – glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors – that overcome some of the unwanted effects of earlier oral agents. GLP-1 receptor agonists and DPP-4 inhibitors may be associated with weight loss or weight neutrality, and they are less likely to cause hypoglycaemia than a number of other therapies currently used in clinical practice as they have a more glucose-dependent mode of action. Another target in the development of pharmaceuticals has been the blocking of renal glucose reabsorption through inhibition of the sodium–glucose transporters located in the proximal renal tubule. This has led to the sodium–glucose cotransporter 2 inhibitor class of drugs. This article explores the expanding evidence base for these agents and updates and replaces the previous version, published in 2012.

Several classes of agents are now available to reduce hyperglycaemia in type 2 diabetes. The purpose of this module is to facilitate decision-making by healthcare professionals as more of these newer therapies with novel modes of action become available for use in routine clinical practice. A previous module explored the utility of established oral therapies, including biguanides, sulfonylureas, meglitinides, thiazolidinediones and alpha-glucosidase inhibitors (Hughes, 2015). This article explores the three newer non-insulin classes: glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium–glucose cotransporter 2 (SGLT2) inhibitors.

The NICE (2015) and SIGN (2010) guidelines both emphasise the need to tailor diabetes care to a person's needs and circumstances, as well as their personal preferences. This is very relevant in selecting newer glucose-lowering therapies, which may offer preferable dosing intervals and fewer adverse events, such as hypoglycaemia or weight gain.

Following on from the withdrawal of rosiglitazone in the UK in 2010, an advisory

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committee meeting of the US Food and Drugs Administration (FDA) mandated that manufacturers of newer antidiabetes agents establish an independent cardiovascular endpoints committee for prospective adjudication of all phase II and III trials, with outcomes of interest to include major adverse cardiovascular events (MACE): cardiovascular death, myocardial infarction (MI) and stroke (Hirshberg and Katz, 2013). This has had a major impact, requiring the manufactures of antidiabetes agents to carry out cardiovascular safety studies (necessitating recruitment of thousands of participants to achieve sufficient statistical power) as part of drug development, and in some cases it has delayed new therapies coming to market.

Drug regulators in Europe and the US have had to draw a fine line between enabling new therapies to become available as quickly as possible and ensuring that these new agents lack significant adverse effects when used in routine clinical practice, especially in the longer term (many trials designed to obtain drug licences have short time horizons).

Further to this, NICE and other guidance-producing bodies in the UK examine practical aspects of treatment – such as frequency of dosing, method of administration, monitoring requirements, and drug interactions – and also emphasise cost-effectiveness (informed by increasingly complex network meta-analyses to determine relative clinical benefits). The process is exemplified by the new NICE guideline for type 2 diabetes in adults, which is discussed later.

The incretin system

Incretin hormones are peptides released from the intestinal tract in response to mixed meals and they contribute to glucose homeostasis by promoting glucose-dependent insulin secretion. The incretin effect is observed experimentally when insulin responses to oral and intravenous glucose loads are compared. Paradoxically, an enhanced response is seen with oral – as opposed to parenteral – glucose, suggesting an underlying active transport mechanism.

Two hormones secreted from the gastrointestinal tract account for over 50% of the incretin effect of a mixed meal. They rapidly stimulate insulin release in the presence of hyperglycaemia. The hormones are GLP-1, with 30 amino acids, and glucose-dependent insulinotropic polypeptide (GIP), with 42 amino acids (McIntyre et al, 1964; Nauck et al, 1986). In type 2 diabetes, the beta-cell response to GIP is largely lost, but GLP-1 receptor sensitivity remains.

In addition to its glucose-dependent action on insulin secretion, GLP-1 has been shown to suppress glucagon secretion, delay gastric emptying and induce satiety and a sense of fullness, with resultant reduction in food intake (Levy, 2006). Elevated glucagon levels are found in people with type 2 diabetes and contribute to background and postprandial hyperglycaemia.

GLP-1 is degraded (and inactivated) in 1–2 minutes by DPP-4, a ubiquitous intracellular enzyme. This rapid degradation reduces the usefulness of human GLP-1 in clinical practice (since it would have to be continually infused in order to retain its biological action) and has led to the development of GLP-1 receptor agonists, which are resistant to degradation by DPP-4 (owing to alterations in their molecular structure), and DPP-4 inhibitors, which lead to increased levels of GLP-1.

Current and future GLP-1 receptor agonists

The GLP-1 receptor agonists available for people with type 2 diabetes in the UK are shown in *Table 1*. As shown in *Table 1*, there

"Incretin hormones are peptides released from the intestinal tract in response to mixed meals and they contribute to glucose homeostasis by promoting glucose-dependent insulin secretion."

Table 1. Glucagon-like peptide-1 receptor agonists available for people with type 2 diabetes in the UK.

Generic name (dosing scheme)	Brand name
Dulaglutide (once-weekly injection)	Trulicity®
Exenatide (once-weekly injection)	Bydureon®
Exenatide (twice-daily injection)	Byetta®
Liraglutide (once-daily injection)	Victoza®
Lixisenatide (once-daily injection)	Lyxumia®

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"Weight loss is not, at the time of writing, a licensed indication of any glucagon-like peptide-1 receptor agonist, but it is a property that is attractive to both clinician and patient."

is some variation in dosing scheme between the agents. In a recent systematic review, Karagiannis et al (2015), concluded that once-weekly GLP-1 receptor agonists are a convenient therapeutic option (for use as add-on to metformin).

The first GLP-1 receptor agonist to be launched was exenatide twice daily in 2007. It is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster (a poisonous North American lizard) that has a 53% homology with human GLP-1. It is administered by subcutaneous injection. Subsequently, exenatide once weekly became the first once-weekly GLP-1 receptor agonist available for clinical use in the UK (Karagiannis et al, 2015). The formulation consists of injectable microspheres of exenatide (2 mg) and poly(D,L-lactide *co*-glycolide), a biodegradable polymer, allowing slow and controlled drug release from the subcutaneous tissue (Tracy et al, 1999). EXSCEL (Exenatide Study of Cardiovascular Event Lowering Trial) is the cardiovascular outcome trial for injectable exenatide and has an estimated completion date of 2018.

Dulaglutide was launched in the UK early in 2015 and is the second once-weekly GLP-1 receptor agonist for people with type 2 diabetes. The cardiovascular outcome study for this agent is REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes), which is due to be completed in 2019.

Liraglutide is an albumin-bound analogue of human GLP-1 that has been in clinical use since 2009. It has a once-daily dosing scheme. The dose regimen starts at 0.6 mg daily and rises to 1.2 mg daily, and potentially 1.8 mg daily. All doses are delivered through a single pen device. The cardiovascular outcome study being conducted for liraglutide, which may report in 2016, is LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation). In 2015, Novo Nordisk, the manufacturer of liraglutide, received a licence for a fixed-dose combination of this agent with insulin degludec. This is marketed as Xultophy® (IDegLira; Kenny and Hall, 2015).

Lixisenatide is a once-daily GLP-1 receptor agonist that was launched in the UK in 2013. ELIXA (Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010), the first cardiovascular outcomes study for GLP-1 receptor agonists to report, found lixisenatide to have a neutral effect on heart failure and other cardiovascular outcomes (Pfeffer et al, 2015).

In addition to the UK-available GLP-1 receptor agonists described above, albiglutide has been approved in Europe and, at the time of writing, has been launched in the Republic of Ireland but not the UK, while semaglutide is currently in phase III.

Across the class, as with other glucose-lowering drugs, there may be responders and non-responders. The ability of the beta-cell to secrete insulin as a result of GLP-1 activation determines the glucose-lowering potential of this class of drug in individual people. It may be difficult to accurately identify those who will respond optimally.

There is some variation in the efficacy of these agents across phase III and post-licensing trials, while weight loss is noted consistently in study populations (e.g. Bailey, 2011). In the SCALE – Obesity and Pre-diabetes (Effect of Liraglutide on Body Weight in Non-diabetic Obese Subjects or Overweight Subjects With Co-morbidities) trial, which examined liraglutide used at a higher dose, early weight loss was found to predict an overall weight loss response (Lau et al, 2015). Weight loss is not, at the time of writing, a licensed indication of any GLP-1 receptor agonist, but it is a property that is attractive to both clinician and patient.

Side effects of GLP-1 receptor agonists are predominantly gastrointestinal and infrequently lead to cessation of therapy. For further details on these – as well as information on the licences, which vary from agent to agent – prescribers are advised to consult the summaries of product characteristics for these agents.

Note

Cardiovascular outcome study timing estimates are based on information from ClinicalTrials.gov (accessed 02.12.15).

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Current and future DPP-4 inhibitors

Five DPP-4 inhibitors are currently available for use in clinical practice in the UK – alogliptin (Vipidia®), linagliptin (Trajenta®), saxagliptin (Onglyza®), sitagliptin (Januvia®) and vildagliptin (Galvus®). All are also available as fixed-dose combinations with metformin:

- Alogliptin plus metformin (Vipdomet™).
- Linagliptin plus metformin (Jentadueto®).
- Saxagliptin plus metformin (Komboglyze®).
- Sitagliptin plus metformin (Janumet®).
- Vildagliptin plus metformin (Eucreas®).

As oral agents that inhibit degradation of endogenous GLP-1 by DPP-4, their glucose-lowering action is less pronounced than that of the GLP-1 receptor agonists, whose pharmacological dosing produces levels of GLP-1 receptor agonism several times greater than those seen with DPP-4 inhibitors (Holst et al, 2008). However, the side-effect profile is also less pronounced (probably as a result of lower levels of GLP-1 receptor agonism) and the class is, in general, well tolerated (Holst et al, 2008). In addition, DPP-4 inhibitors have the advantage of being oral preparations.

Recent developments have seen extensions of licensed use in various levels of renal impairment. Whether there is a need to reduce drug dosage or perform additional monitoring with declining renal function depends on the route of elimination of the agent, and there are differences within the class in this regard. There is some variation in the licence for co-administration with other glucose-lowering agents. For further details on these – as well as more information on adverse events – prescribers are advised to consult the summaries of product characteristics for these agents.

DPP-4 inhibitors have broadly similar modes of action and efficacy. There are few relevant direct comparator studies. Three of the agents have now reported cardiovascular outcome studies (see *Table 2*): EXAMINE, SAVOR-TIMI 53 and TECOS. These studies all showed non-inferiority for the primary MACE analyses and all fulfilled the FDA requirements, as the upper bound of the confidence interval was less than 1.3. Both EXAMINE and SAVOR-TIMI 53 had increased hospitalisations for heart failure (not statistically significant with the former

Table 2. CV outcome studies for dipeptidyl peptidase-4 inhibitors, based on information from ClinicalTrials.gov (accessed 02.12.15). No CV outcome study is planned for vildagliptin.

Trial	Active study drugs	Primary endpoint	*n*	Completion status
EXAMINE	Alogliptin 6.25–25 mg once daily	Composite of CV death, non-fatal MI or non-fatal stroke	5380	Completed (White et al, 2013)
SAVOR-TIMI 53	Saxagliptin 2.5–5 mg once daily	Composite of CV death, non-fatal MI or non-fatal ischaemic stroke	16 492	Completed (Scirica et al, 2013)
TECOS	Sitagliptin 50–100 mg once daily	Composite of CV-related death, non-fatal MI, non-fatal stroke or unstable angina requiring hospitalisation	14 671	Completed (Green et al, 2015)
CARMELINA	Linagliptin 5 mg once daily	Composite of CV-related death, non-fatal MI, non-fatal stroke or unstable angina requiring hospitalisation	~8000	Estimated completion date: January 2018
CAROLINA	Linagliptin 5 mg once daily versus glimepiride 1–4 mg once daily	Composite of CV-related death, non-fatal MI, non-fatal stroke or unstable angina requiring hospitalisation	~6000	Estimated completion date: September 2018

CARMELINA=Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; CAROLINA=Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes; CV=cardiovascular; EXAMINE=Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; MI=myocardial infarction; SAVOR–TIMI 53=Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53; TECOS=Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

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"In EMPA-REG OUTCOME, there was a significant 38% relative risk reduction in the cardiovascular death rate (3.7% versus 5.9%) in those treated with empagliflozin compared with those receiving placebo."

[White and Heller, 2013]), but there was no increase in associated mortality. Previously, concern had arisen about an increased risk of pancreatic cancer and pancreatitis with both this class of agents and GLP-1 receptor agonists (Cohen, 2013), but none of these studies bore out this potential risk.

In addition to the UK-available GLP-1 receptor agonists described above, omarigliptin is in phase III development and may become available as a once-weekly preparation. Development of dutogliptin appears to have been suspended.

Currrent and future SGLT2 inhibitors

Three SGLT2 inhibitors are now available in the UK: canagliflozin (Invokana®), dapagliflozin (Forxiga®) and empagliflozin (Jardiance®). All are also available as fixed-dose combinations with metformin:

- Canagliflozin plus metformin (Vokanamet®).
- Dapagliflozin plus metformin (Xigduo®).
- Empagliflozin plus metformin (Synjardy®).

The agents in this class block the action of SGLT2 in reabsorbing glucose and sodium from the renal tubules, resulting in significant urinary glucose excretion, and thus reduction in blood glucose and weight loss. SGLT2 is expressed in the S1-segment of the proximal renal tubule and is responsible for 90% of glucose reabsorption via the renal tract (Kanai et al, 1994). There was significant glucose lowering observed in phase III trials, as well as a favourable metabolic response (Ferrannini et al, 2014). Adverse events are related to the presence of glucose in the urine, including genital mycotic infection and lower urinary tract infection, and are more often observed in women than in men. There can also be a slight increase in diuresis. SGLT2 inhibitors offer a potentially attractive option for people with type 2 diabetes who are failing with metformin monotherapy, especially if weight is part of the underlying treatment consideration (Nauck, 2014).

Recently, the European Medicines Agency began a review SGLT2 inhibitors to evaluate the risk of diabetic euglycaemic ketoacidosis (Rosenstock and Ferrannini, 2015). Although, by June 2015, 101 cases had been reported (approximately equally among the three available agents), this remains a very rare condition given the wide exposure of the three agents. Nevertheless, prescribers should ensure that people taking the agents have type 2 diabetes and not misdiagnosed type 1 diabetes. A recent warning from the UK government suggested testing for raised ketones in individuals with acidosis symptoms, even if plasma glucose levels are near normal (Medicines and Healthcare products Regulatory Agency, 2015).

For further details on adverse events – as well as information on the licences – prescribers are advised to consult the summaries of product characteristics for these agents.

As with the other classes, cardiovascular outcome studies have been initiated for these agents. The first of these outcome studies to report (Zinman et al, 2015) was EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients). This trial investigated the cardiovascular profile of empagliflozin versus placebo. It showed that there were no differences in the rates of MI or stroke between the empagliflozin and placebo groups, but that there was a significant 38% relative risk reduction in the cardiovascular death rate (3.7% versus 5.9%) in those treated with empagliflozin. There was also a significant 32% relative risk reduction for all-cause death in the empagliflozin group. The mortality rates in the placebo and empagliflozin groups separated very early, within the first 3 months, and the benefits were maintained throughout the study. This perhaps unexpected positive outcome has led to considerable debate about the potential cause or causes of this effect and whether it will be a class effect for the SGLT2 inhibitors.

The cardiovascular outcome studies that have been established for canagliflozin (CANVAS [Canagliflozin Cardiovascular Assessment Study]) and dapagliflozin (DECLARE-TIMI 58 [Dapagliflozin Effect on Cardiovascular Events – Thrombolysis

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in Myocardial Infarction 58]) are currently expected to be completed in June 2017 and April 2019, respectively.

In addition to the UK-available SGLT2 inhibitors described above, ertugliflozin is in phase III trials, but the development of ipragliflozin has been discontinued in Europe.

Selecting agents in practice

There is now an extensive range of glucose-lowering agents licensed for the treatment of type 2 diabetes in the UK. Some are licensed for monotherapy and most have licences for combination use with metformin and other agents. Ideally, decisions should be based on the need to empower people with diabetes through a shared decision-making process that strikes a balance between efficacy, utility and adverse effects. A number of national and international guidelines are available to aid decision-making.

NICE guidance

An update of NICE clinical guideline 87 (NICE, 2009) was published in December 2015 as NICE guideline 28 (NG28; NICE, 2015). This guideline will help healthcare professionals to decide how to use these newer agents and suggests they should be used in a process of step-wise intensification. A case example illustrating the new guideline is presented in *Box 1*, while part of the algorithm for blood glucose-lowering therapy is shown in *Figure 1*.

For the first time, NICE has agreed to the use of sustained-release forms of metformin if standard metformin is not tolerated. If no metformin preparation is tolerated, or is contraindicated, then a DPP-4 inhibitor, pioglitazone or a sulfonylurea may be used as first-line agents.

The guideline also suggests that, at first intensification (to dual therapy), if HbA_{1c} has risen to 58 mmol/mmol (7.5%) then metformin may be combined with a DPP-4 inhibitor, pioglitazone, a sulfonylurea or an SGLT2 inhibitor. The choice of agents then remains broadly the same for a second intensification, although licences for their use in these combinations may vary.

Box 1. Case example.

History

Jean is a 49-year-old community nurse and mother of three teenage children. She drives about 80 miles per week for her work. She is Caucasian and has had type 2 diabetes for 6 years, having struggled with her weight from the birth of her children, and had gestational diabetes in her last pregnancy. Jean feels her family is now complete. She has a family history of both ischaemic heart disease and diabetes. She has had hypertension for 10 years and is on a diuretic and calcium-channel blocker, having not initially tolerated an angiotensin-converting enzyme inhibitor. She has been prescribed a statin.

Her diabetes medication has been metformin 2 g daily from diagnosis with pioglitazone 45 mg daily for 18 months, with her not having been able to tolerate any sulfonylureas owing to hypoglycaemia. She has an understanding of the risks and side effects associated with pioglitazone, and is only moderately tolerant of metformin as it can cause her diarrhoea, which is awkward when she is visiting clients.

Examination

On examination, Jean's weight is 97 kg with a BMI of 34.5 kg/m^2. She has a blood pressure of 159/87 mmHg, a total cholesterol level of 4.8 mmol/L, a random blood glucose level of 9.8 mmol/L, an HbA_{1c} of 66 mmol/mol (8.2%) and an estimated glomerular filtration rate of above 90 mL/min/1.73 m^2.

Jean has a frank discussion with her GP. She knows her diabetes control should be better, as she visits people with type 2 diabetes who require insulin and understands the importance of good control. She is unhappy with her weight, in spite of attending Weight Watchers. She does not want an additional therapy that might interfere with her driving, as she needs to work irregular hours. She knows that she does not qualify for a glucagon-like peptide-1 (GLP-1) receptor agonist under NICE guidance and feels she is not ready for insulin.

Discussion

Healthcare professionals helping Jean with her care will want to adhere to NICE (2015) or SIGN (2010) guidelines, which offer broadly similar guidance for people like Jean. Early tight control of diabetes is recognised as being important, and Jean understands this. She feels that weight is also a concern for her. Her hypertension is not completely controlled. She does not want an injectable and would not fully qualify for a GLP-1 receptor agonist; her main option is triple oral therapy at this stage. We know she is intolerant of a sulfonylurea.

Two products would be potentially useful to Jean: a dipeptidyl peptidase-4 (DPP-4) inhibitor and a sodium–glucose cotransporter 2 (SGLT2) inhibitor. Both could be used in combination with her pioglitazone. A SGLT2 has an insulin-independent mechanism of action and does not cause hypoglycaemia as monotherapy. It may be predicted to improve HbA_{1c}, weight and systolic blood pressure and her normal renal function makes it a suitable agent for her.

A DPP-4 inhibitor may be combined with her other agents to improve HbA_{1c}. Hypoglycaemia is not normally associated with DPP-4 inhibitors unless combined with sulfonylureas. There is no expected effect on blood pressure. Finally, her GP could consider a GLP-1 receptor agonist for her in the circumstances outlined in the new NICE guideline.

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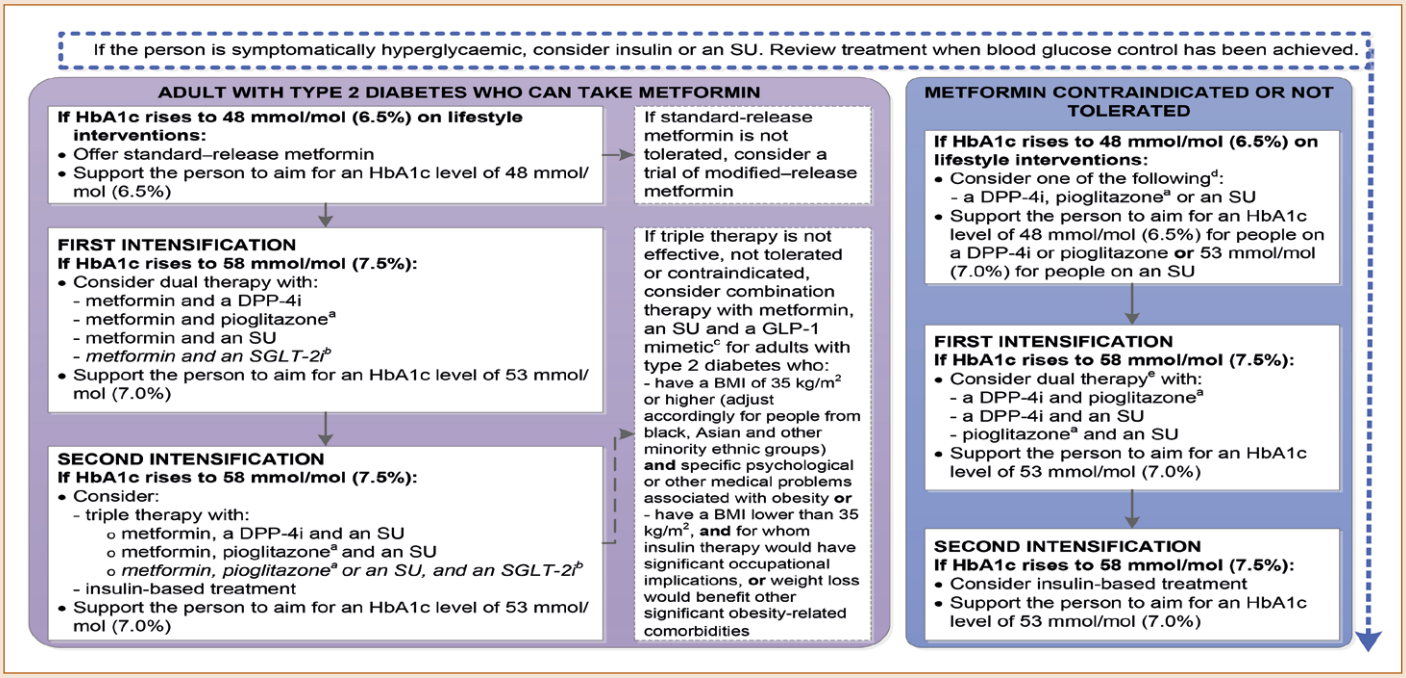

Figure 1. Extract from the algorithm for blood glucose-lowering therapy in adults with type 2 diabetes, reproduced with permission from NICE (2015).

Another suggestion made in the guideline is that a GLP-1 receptor agonist may be used as triple therapy with metformin and a sulfonylurea in people who:

- Have a BMI of 35 kg/m^2 or higher (adjusting accordingly for people from black, Asian and other minority ethnic groups), as well as specific psychological or other medical problems associated with obesity.

OR

- Have a BMI lower than 35 kg/m^2 and are someone for whom insulin therapy would have significant occupational implications or for whom weight loss would benefit other significant obesity-related comorbidities.

The guideline recommends only continuing GLP-1 receptor agonist therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA_{1c} and a weight loss of at least 3% of initial body weight in 6 months).

NICE has also published technology appraisals for canagliflozin (TA315), dapagliflozin (TA288), empagliflozin (TA336), exenatide once weekly (TA248) and liraglutide (TA203), which can be accessed online using the URL http://www.nice.org.uk/ followed by the appraisal abbreviation (e.g. "http://www.nice.org.uk/TA315". These documents enable clinicians to make prescribing decisions with patients based on the characteristics of the agents themselves, as well as taking into account the challenges and aspirations of each individual.

Other guidance

Relevant documents for Scotland have been produced by SIGN and the Scottish Medicines Consortium (see www.scottishmedicines.org.uk). The SIGN (2010) guideline is broadly aligned with the previous NICE guideline (CG87) in its algorithms. It is expected that an update of this guideline will be published over the coming years. In addition to these national guidelines, the American Diabetes Association and the European Association for the Study of Diabetes convened a joint task force to examine the evidence and develop recommendations for glucose-lowering therapy in adults with type 2 diabetes (Inzucchi et al, 2015). This guidance takes a patient-

centred approach and noted that glycaemic targets and glucose-lowering therapies should be individualised. As with other guidance, metformin is presented as the optimal first-line drug. After metformin, it takes the pragmatic approach of allowing combination therapy with an additional one or two oral or injectable agents, as reasonable, aiming to minimise side effects where possible.

Conclusion

We have almost a decade of experience of using these newer classes of agent in the management of type 2 diabetes. Established agents still have utility and many can be used in combination with the newer agents. As with any drug, new or old, constant surveillance is needed if rare long-term complications associated with their use are to be detected. Outcome studies have proved to be very important, releasing much more data into the public domain. The continuing interest of researchers and pharmaceutical companies in elucidating the mechanisms underlying diabetes and developing better treatments is essential if the lives of those with diabetes are to be further improved. ■

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"The continuing interest of researchers and pharmaceutical companies in elucidating the mechanisms underlying diabetes and developing better treatments is essential if the lives of those with diabetes are to be further improved."

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Online CPD activity

Visit www.diabetesonthenet.com/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. A short explanation of the correct answer is provided. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learnt in practice. The CPD centre keeps a record of your CPD activities and provides the option to add items to an action plan, which will help you to collate evidence for your annual appraisal.

1. Pharmaceutical companies are now required to establish independent cardiovascular endpoint data for any new antidiabetes agent.

   Which antidiabetes agent was directly responsible for this change in expectations regarding drug company trials? Select ONE option only.

   A. Albiglutide
   B. Empagliflozin
   C. Glipizide
   D. Linagliptin
   E. Rosiglitazone

2. In addition to GLP-1, which intestinal hormone MOST significantly contributes to the incretin effect after eating a mixed meal? Select ONE option only.

   A. Ghrelin
   B. GIP
   C. GLP-2
   D. Oxyntomodulin
   E. PYY

3. In addition to glucose-dependent actions on insulin secretion, which is the MOST LIKELY clinical effect of GLP-1? Select ONE option only.

   A. Constipation
   B. Delayed gastric emptying
   C. Diarrhoea
   D. Increased appetite
   E. Weight gain

4. Which GLP-1 receptor agonist, if any, is available in BOTH once-daily and once-weekly formulations? Select ONE option only.

   A. Dulaglutide
   B. Exenatide
   C. Liraglutide
   D. Lixisenatide
   E. None available

5. Which GLP-1 receptor agonist, if any, was shown by the ELIXA trial to have neutral effects on heart failure and cardiovascular outcomes? Select ONE option only.

   A. Dulaglutide
   B. Exenatide
   C. Liraglutide
   D. Lixisenatide
   E. None of the above

6. All of the currently available DPP-4 inhibitors are available in a fixed-dose combination preparation with which SINGLE other antidiabetes agent? Select ONE option only.

   A. Dapagliflozin
   B. Glimepiride
   C. Glipizide
   D. Metformin
   E. Repaglinide

7. In addition to glucose, the reabsorption from the renal tubules of which electrolyte is ALSO significantly blocked by SGLT2 inhibitors? Select ONE option only.

   A. Calcium
   B. Magnesium
   C. Potassium
   D. Sodium
   E. Zinc

8. What was the relative risk reduction in all-cause death in the EMPA-REG OUTCOME trial, for the empagliflozin arm compared with the placebo arm? Select ONE option only.

   A. 2.2%
   B. 3.7%
   C. 32%
   D. 38%
   E. 62%

9. A 49-year-old obese man was diagnosed with type 2 diabetes 6 months ago. His BMI has remained at 38 kg/m^2, urinalysis shows glycosuria on most days and a recent HbA_{1c} result is 61 mmol/mol.

   According to current guidance, which is the SINGLE MOST appropriate antidiabetes agent? Select ONE option only.

   A. Canagliflozin
   B. Exenatide
   C. Glipizide
   D. Metformin
   E. Sitagliptin

10. A 62-year-old woman has type 2 diabetes, hypertension and impaired left-ventricular systolic function and is needle-phobic. She has recently been advised to stop her metformin monotherapy due to confirmed stage-4 chronic kidney disease.

    Despite trying to modify diet and exercise, her BMI is 41 kg/m^2 and her HbA_{1c} over the past 18 months has been consistently between 72 and 81 mmol/mol.

    Which ONE of the following is the SINGLE MOST appropriate management option? Select ONE option only.

    A. Actos®
    B. Diamicron®
    C. Januvia®
    D. Victoza®
    E. Xigduo®