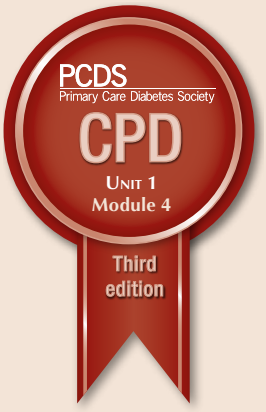

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See page 203

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Learning objectives

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

1. Explain the different mechanisms of action of the older oral blood glucose-lowering agents.
2. Outline the indications and contraindications of each agent.
3. Evaluate the glycaemic and cardiovascular benefits of older oral blood glucose-lowering agents.

Key words

- Acarbose
- Meglitinides
- Metformin
- Pioglitazone
- Sulphonylureas

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Unit 1 Core aspects of care

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

Eugene Hughes

Once type 2 diabetes is diagnosed and beyond the control of lifestyle modifications, glucose-lowering therapy must be initiated, and carefully monitored, using drugs that have been developed based on our understanding of the pathophysiology: impaired insulin secretion and increased insulin resistance. This article focuses on five classes of older oral antidiabetes agent: biguanides (metformin), sulphonylureas, meglitinides, alpha-glucosidase inhibitors (acarbose) and thiazolidinediones (pioglitazone). Modes of action, indications and licences, contraindications and side effects are reviewed, along with key evidence underpinning each drug class.

Type 2 diabetes is a metabolic disorder with multiple causes, characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism. The development of type 2 diabetes is a gradual process. A combination of insulin resistance (the gradual failure of peripheral tissues and the liver to respond to insulin) and reduced pancreatic beta-cell function (reduced ability of beta-cells to secrete insulin in response to hyperglycaemia) is involved, with the contribution of these two major components varying between individuals.

Type 2 diabetes is more common in older individuals, but it is also associated with obesity and a sedentary lifestyle and is increasingly seen at a younger age (Koopman et al, 2005). Prevalence is also increased in certain ethnic groups; in particular, individuals originating from south Asia are around three to six times more likely to develop type 2 diabetes and to develop the condition at a younger age (Barnett et al, 2006). Diabetes UK estimates that one person is diagnosed with diabetes every 3 minutes (Diabetes UK, 2009). Diabetes prevalence rate forecasts indicate that by 2030, the number of people with diabetes over the age of 16 years will increase to 4.6 million (or 9.5% of the English population). Approximately half of this increase is due to the changing age and ethnic group structure of the population and about half is due to the projected increase in obesity (Yorkshire and Humber Public Health Observatory, 2010).

Over time, damage caused by high blood glucose levels affects a number of organs and leads to the long-term complications of diabetes. These can be classified broadly as microvascular complications, such as retinopathy, nephropathy and neuropathy, or macrovascular complications, including myocardial infarction and stroke. Both the duration of diabetes and level of blood glucose control are risk factors for the development of microvascular complications. Epidemiological extrapolation of data from the UK Prospective Diabetes Study (UKPDS) suggests that a 1 percentage point (10.9 mmol/mol) reduction in HbA_{1c} yields relative risk reductions of 14%

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for the incidence of myocardial infarction and 37% for microvascular complications (Stratton et al, 2000).

Compared with people without diabetes, those with the condition have a high risk of morbidity and premature mortality from cardiovascular disease (Haffner et al, 1998; Lotufo et al, 2001; Khaw et al, 2004). Myocardial infarction and stroke are the major causes of premature death in people with diabetes, and the increasing prevalence of diabetes will undoubtedly be closely followed by increases in cardiovascular morbidity and mortality.

Diabetes can be prevented or delayed through lifestyle interventions (Tuomilehto et al, 2001; Knowler et al, 2002). Lifestyle modification has the advantage that it will simultaneously help to reduce other cardiovascular risk factors such as hypertension, obesity and dyslipidaemia. Lifestyle behaviours that should be promoted for optimal management of diabetes include: a healthy, balanced diet; regular physical activity; smoking cessation; and sustained weight loss in overweight people (International Diabetes Federation Clinical Guidelines Task Force, 2006; NICE, 2009). While lifestyle intervention is an integral component of diabetes management, adherence to such regimens is often difficult to achieve and maintain, and most people with type 2 diabetes will require pharmacological intervention for glycaemic control.

In recent years, the range of oral antidiabetes agents available has broadened. This module will summarise the role of the older, or "traditional", oral glucose-lowering agents. These include metformin (*Box 1*), sulphonylureas (*Box 2*), pioglitazone (*Box 3*), meglitinides (*Box 4*) and acarbose (*Box 5*), which differ in mechanism of action (*Figure 1*). The newer agents targeting the incretin system, and the various insulin preparations, will be covered in later modules in this series.

Metformin

History

Metformin was first described in the scientific literature in 1957 (Ungar et al, 1957), but it only received approval from the US Food and Drug Administration (FDA) for type 2 diabetes in 1994 and was first marketed in the US in 1995. Generic formulations are now available. Metformin was an additional option to sulphonylureas or insulin in overweight people in the UKPDS (UKPDS Group, 1998a). In these people, metformin reduced the incidence of any diabetes-related endpoint by 32% compared with people on conventional therapy (diet alone; P=0.0023; UKPDS Group, 1998a). Following publication of these results, metformin use increased and it is now the most widely prescribed oral antidiabetes agent in the world. Metformin is also now available in fixed-dose combinations with many other oral blood glucose-lowering agents.

Mode of action

Metformin belongs to the biguanide class of antidiabetes drugs, which also included phenformin, an agent withdrawn owing to a high incidence of lactic acidosis. Metformin reduces hepatic glucose production, primarily by decreasing gluconeogenesis, thereby reducing fasting plasma glucose. In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake, decreases fatty acid oxidation and decreases absorption of glucose from the gastrointestinal tract (DeFronzo et al, 1991). There has been recent interest in the

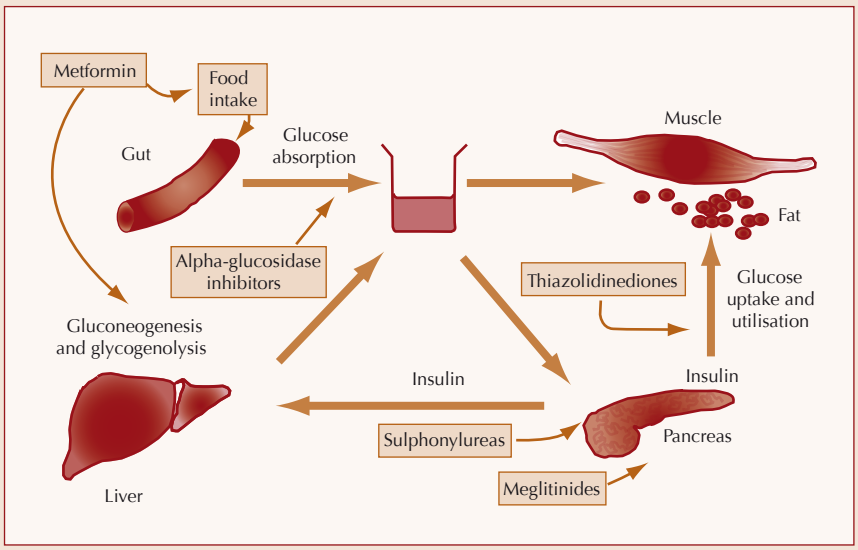

Figure 1. Sites of action of older agents used to treat type 2 diabetes. (Redrawn with kind permission from Springer Science+Business Media: Greich JE and Szoke E (2006) Pathogenesis of type 2 diabetes. In: Skyler JS, ed. Atlas of Diabetes *(3rd edition). Current Medicine Group LLC, Philadelphia, PA, USA.)*

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Box 1. Metformin: Key facts and practical considerations.

- Low cost (representing a cost saving versus conventional treatment [i.e. lifestyle modification] in overweight individuals; Clarke et al, 2001)
- Weight neutral, possibly with some weight reduction as monotherapy (UK Prospective Diabetes Study Group, 1998a)
- Starting dose of 500 mg once daily taken with food, with a slow titration up to 3 g, but the dose–response curve above 2 g is fairly flat and gastrointestinal side effects increase (electronic Medicines Compendium, 2015a)
- Review dose if estimated glomerular filtration rate (eGFR) is <45 mL/min/1.73 m^2 or serum creatinine exceeds 130 µmol/L (NICE, 2009)
- Stop metformin if eGFR is <30 mL/min/1.73 m^2 or if serum creatinine exceeds 150 µmol/L (NICE, 2009)
- Slow-release formulation available
- Fixed-dose combinations available with pioglitazone and vildagliptin
- Reduces HbA_{1c} by approximately 16 mmol/mol (1.5 percentage points; Nathan et al, 2009)
- Does not cause hypoglycaemia

anti-mitogenic properties of metformin (Bo et al, 2012; Bost et al, 2012), and it abolishes most of the increased risk of development of solid tumours which is present in those on insulin and insulin secretagogues (Currie et al, 2009).

Indications and licence

Metformin is indicated for the treatment of type 2 diabetes, particularly in overweight people, when dietary management and physical activity alone does not result in adequate glycaemic control (electronic Medicines Compendium [eMC], 2015a). Across a range of guidelines, metformin is the first-line choice of antidiabetes drug (NICE, 2009; SIGN, 2010; Inzucchi et al, 2015). It may be used as monotherapy or in combination with other diabetes treatments, including sulphonylureas, pioglitazone, acarbose, meglitinides, dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists and insulins.

Contraindications and side-effects

Metformin is excreted in the urine and metformin accumulation can lead to a rare risk of lactic acidosis when renal clearance is limited. As a result, metformin is contraindicated in individuals with renal failure or renal dysfunction (eMC, 2015a). NICE recommends reviewing the dose of metformin if the serum creatinine level exceeds 130 µmol/L or the estimated glomerular filtration rate (eGFR) is below 45 mL/min/1.73 m^2 (NICE, 2009). It should be used with caution in cases of hepatic failure and alcoholism as these conditions may also increase the risk of lactic acidosis. Other conditions that predispose individuals to tissue hypoxaemia or reduced perfusion, such as septicaemia or myocardial infarction, are also contraindications (eMC, 2015a). The H_2 receptor antagonist cimetidine inhibits the renal tubular secretion of metformin, resulting in higher circulating plasma concentrations (Somogyi et al, 1987). It is recommended that metformin be temporarily discontinued prior to the intravascular administration of an iodinated contrast agent in radiological studies (Thomsen and Morcos, 2003; eMC, 2015a), although it is thought that complications are unlikely unless renal function is impaired (Parfrey et al, 1989; Royal College of Radiologists, 2009).

The most common adverse effect of metformin is gastrointestinal upset, including diarrhoea, cramps, nausea, vomiting and increased flatulence; metformin is more commonly associated with gastrointestinal side-effects than most other antidiabetes drugs (Bolen et al, 2007). Gastrointestinal upset can be reduced by careful titration, or by use of a slow-release formulation (now available in 500-, 750- and 1000-mg strengths).

Key evidence

UKPDS

In the UKPDS, metformin was compared with insulin and sulphonylurea therapy to determine the nature of any specific advantages or disadvantages in a subset of overweight people with type 2 diabetes. Metformin was associated with a 39% risk reduction in myocardial infarction after 10 years (P=0.01; UKPDS Group, 1998a). Data from the 10-year post-trial monitoring programme indicate that, in the metformin group, significant risk reductions for myocardial infarction persist (33%; P=0.005; Holman et al, 2008).

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DPP

The Diabetes Prevention Program (DPP) evaluated whether diet and exercise or metformin could prevent or delay the onset of type 2 diabetes in people with impaired glucose tolerance (IGT). Both arms were effective in reducing the progression from IGT to type 2 diabetes. The lifestyle intervention reduced the incidence of diabetes by 58% (95% confidence interval [CI], 48–66%) and metformin reduced it by 31% (95% CI, 17–43%). Metformin was most effective in people aged 25–44 years and in those with a BMI ≥35 kg/m^2 (Knowler et al, 2002).

Box 2. Sulphonylureas: Key facts and practical considerations.

- Low cost, especially if a generic formulation is prescribed
- Reduces HbA_{1c} by approximately 16 mmol/mol (1.5 percentage points; Nathan et al, 2009)
- Effectiveness depends on adequate beta-cell function
- Early rapid reduction in HbA_{1c}, but the action is not sustainable (Kahn et al, 2006)
- Associated with hypoglycaemia and weight gain
- Caution required in people with renal or hepatic impairment
- Start with low dose and titrate slowly
- Slow-release formulation of gliclazide available

Sulphonylureas

History

The sulphonylureas were discovered by researchers studying sulphonamide antibiotics, who observed that they induced hypoglycaemia in animals (Janbon et al, 1942). The sulphonylureas are classified as first-, second- and third-generation agents as follows:

- First generation: tolbutamide; chlorpropamide.
- Second generation: glibenclamide (glyburide in the US and Canada); gliclazide; glipizide.
- Third generation: glimepiride.

Mode of action

The sulphonylureas are pharmacological inhibitors of potassium channels in pancreatic beta-cells and require functioning beta-cells in order to work. As a result of a direct interaction with the SUR1 receptor – the regulatory subunit of the channel – sulphonylureas stimulate insulin secretion by inducing membrane depolarisation even when there is no increase in the metabolic rate (Ashcroft and Gribble, 1999). All sulphonylureas have a similar mode of action, but they differ in their affinity for SUR1. The sulphonylureas reduce both basal and postprandial glucose levels and can cause hypoglycaemia as they stimulate insulin secretion that is not glucose dependent.

Indications and licence

The sulphonylureas are indicated for the treatment of type 2 diabetes. Short- and long-acting sulphonylureas are available and may be prescribed as monotherapy, or in combination with metformin, acarbose, pioglitazone, insulins and the newer incretin-based therapies. As with other older agents discussed in this module, guidelines may restrict the position of classes to certain subgroups.

Contraindications and side effects

In the author's experience, chlorpropamide and glibenclamide are rarely used in practice. Their long duration of action predisposes individuals to hypoglycaemia, particularly older people, in whom they should be avoided. Tolbutamide has a shorter duration of action, but its use in clinical practice is diminishing. The most commonly used agents are gliclazide and glipizide.

The sulphonylureas are associated with both weight gain – typically 1–4 kg in the first 6 months of therapy – and hypoglycaemia, although the risk of the latter is reduced with some of the newer agents.

However, the risks of hypoglycaemia are still significant, as highlighted by the findings from the UK Hypoglycaemia Study Group (2007), which showed that similar levels of hypoglycaemia were experienced by those treated with sulphonylureas compared with people with type 2 diabetes in the first 2–3 years of insulin treatment. The latest guidance from the Driver and Vehicle Licensing Agency draws attention to the risks of hypoglycaemia when driving, and it could be argued that drivers treated with sulphonylureas should be advised to test blood glucose levels before driving (Drivers Medical Group, 2014). They should certainly be provided with written advice concerning these risks.

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Box 3. Pioglitazone: Key facts and practical considerations.

- Useful in people with features of the metabolic syndrome
- Causes weight gain and anaemia
- Increased risk of fractures in post-menopausal women (Spanheimer, 2007; Loke et al, 2009)
- Low risk of hypoglycaemia
- Contraindicated in heart failure and hepatic impairment
- Reduces HbA_{1c} by approximately 5–16 mmol/mol (0.5–1.5 percentage points; Nathan et al, 2009)

The sulphonylureas should be used with caution in people with hepatic or renal disease. The half-life of insulin is extended in these individuals and thus there is an increased risk of hypoglycaemia.

Key evidence

UKPDS

In the UKPDS, intensive blood glucose control with sulphonylureas or insulin, compared with conventional treatment (diet alone), was associated with a 25% reduction in microvascular complications, but no significant benefit was seen in macrovascular complications (UKPDS Group, 1998b). However, during 10 years of post-trial follow-up, a continued reduction in microvascular risk and emerging risk reductions for myocardial infarction and death from any cause were observed (this has been termed the "legacy effect"; Holman et al, 2008).

UGDP

Sulphonylurea therapy was implicated as a potential cause of increased cardiovascular disease mortality in the University Group Diabetes Program (UGDP; Klimt et al, 1970). Concerns raised by the UGDP study have not been substantiated in subsequent landmark trials, including the UKPDS (UKPDS Group, 1998b) and ADOPT (A Diabetes Outcome Progression Trial; Kahn et al, 2006).

However, the debate continues regarding cardiovascular safety and sulphonylurea use, with different meta-analyses reaching different conclusions (Monami et al, 2013; Simpson et al, 2015).

Thiazolidinediones (glitazones)

History

The first member of the thiazolidinedione (TZD) class, introduced in 1997, was troglitazone, but this agent was withdrawn shortly after owing to reports of hepatotoxicity. Two further members of this class, rosiglitazone and pioglitazone, were introduced in 2000. However, rosiglitazone was withdrawn from use in the UK in 2010 following concerns over cardiovascular safety, as described later in this section. Pioglitazone is therefore the only currently licenced TZD in the UK, but rosiglitazone has retained a restricted licence in other parts of the world.

Mode of action

The TZDs work primarily by activating the nuclear transcription factor peroxisome proliferator-activated receptor (PPAR) gamma, thereby turning on and off specific genes for the regulation of glucose, lipids and protein metabolism (Spiegelman, 1998). The effect of PPAR gamma activation is to enhance the action of insulin in insulin-sensitive tissue by increasing glucose uptake in skeletal muscle and adipose tissue and decreasing hepatic glucose production. It is also associated with a transfer of fat from visceral to subcutaneous depots.

In addition, this class of agent has been shown to reduce levels of C-reactive protein (Pfutzner et al, 2005; Goldstein et al, 2006), and, in animal studies, preserve beta-cell function (Diani et al, 2004).

Indications and licence

Pioglitazone is indicated in the treatment of type 2 diabetes as monotherapy in people inadequately controlled by non-pharmacological measures, and in combination with metformin or sulphonylureas as dual or triple therapy (eMC, 2014). In addition, pioglitazone is licensed in combination with insulin: the current insulin dose can be continued upon initiation of pioglitazone therapy (eMC, 2014).

Contraindications and side effects

An important side effect of the TZDs is fluid retention, which usually manifests as peripheral oedema, and this can contribute to weight gain.

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The likelihood of oedema increases when TZDs are used in combination with insulin, and people using this combination should be monitored carefully. In Europe, heart failure at any stage is an absolute contraindication to the use of TZDs as the oedema can be associated with new or worsened heart failure (eMC, 2014).

A decrease in haematocrit and haemoglobin concentration usually occurs during TZD therapy, and this is consistent with a dilutional anaemia.

As mentioned earlier, the first available medication in the TZD class, troglitazone, was withdrawn from the market due to severe liver toxicity. Pioglitazone has not been associated with severe liver toxicity, either as monotherapy or with oral antidiabetes agent or insulin combinations; however, it is recommended that liver enzymes are checked before initiating therapy in all individuals and are monitored periodically thereafter based on clinical judgement (eMC, 2014). TZDs are contraindicated for use in people with hepatic impairment.

Weight gain is a class effect of the TZDs, when prescribed either as monotherapy or in combination with other glucose-lowering agents. Most studies report an average weight gain of 1–4 kg over the first year of TZD treatment.

Long-term use of TZDs has also been associated with an increase in the risk of fractures in women with type 2 diabetes (Loke et al, 2009).

There have been reports of an increased risk of bladder cancer with pioglitazone, and the summary of product characteristics has recently been amended to reflect this (eMC, 2014), although recent observational evidence published in *JAMA* questions the link (Lewis et al, 2015).

An excellent review article relating to both bladder cancer risk and cardiovascular benefits of pioglitazone was published in *Diabetic Medicine* in May 2015 (Ryder, 2015).

Key evidence

PROactive

In the 3-year Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, people with diabetes and cardiovascular disease were randomised to receive pioglitazone or placebo, in addition to conventional antidiabetes therapy (Dormandy et al, 2005). The primary endpoint – a broad composite that included coronary and peripheral vascular events – showed a trend towards benefit from pioglitazone. The main secondary endpoint, consisting of a composite of myocardial infarction, stroke and death from any cause, showed a significant effect favouring pioglitazone. In the PROactive trial, participants randomised to pioglitazone had a reduced need to add insulin to glucose-lowering regimens compared with those on placebo (Dormandy et al, 2005).

The TZD debate

A meta-analysis published in the *New England Journal of Medicine* in May 2007 reported a significant 43% increase in myocardial infarction (P=0.03) and a borderline-significant 64% increase in cardiovascular mortality (P=0.06) for those receiving rosiglitazone as compared with other antidiabetes drugs or placebo (Nissen and Wolski, 2007). An FDA Advisory Committee convened to discuss the meta-analysis and concluded that the use of rosiglitazone for the treatment of type 2 diabetes was associated with a greater risk of myocardial ischaemic events than placebo, metformin or sulphonylureas (Rosen, 2007). The Committee did not recommend that rosiglitazone be removed from the market, but rather that label warnings be added.

In the individual large published trials included in the meta-analysis (specifically the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication [DREAM] trial [DREAM Trial Investigators et al, 2006] and ADOPT [Kahn et al, 2006; 2008]), there were no increases in the rates of myocardial ischaemia or cardiovascular death. The findings have also not been confirmed by studies published subsequent to the meta-analysis, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and the interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial (Home et al, 2007; ACCORD Study Group et al, 2008).

In a consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), group members unanimously advised against

"In the PROactive trial, the main secondary endpoint, consisting of a composite of myocardial infarction, stroke and death from any cause, showed a significant effect favouring pioglitazone."

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Box 4. Meglitinides: Key facts and practical considerations.

- Low cost
- Weight gain can occur
- Less likely to cause hypoglycaemia than some sulphonylureas (Nathan et al, 2009)
- Reduces HbA_{1c} by approximately 5–16 mmol/mol (0.5–1.5 percentage points; Nathan et al, 2009)
- May be useful in people with erratic or variable lifestyles (e.g. shift workers), who may take a dose with a meal but omit doses when meals are skipped, or during religious fasting such as Ramadan

using rosiglitazone (Nathan et al, 2009). In July 2010, the UK Commission on Human Medicines conducted a review into the safety of rosiglitazone and the Chair informed the Medicines and Healthcare products Regulatory Authority (MHRA) that "the benefits no longer outweigh the risks" (NHS Choices, 2010). It was then recommended that all medicines containing rosiglitazone be withdrawn from the UK market (MHRA, 2010).

Meglitinides (glinides)

History

The non-sulphonylurea portion of glibenclamide, a benzamido compound termed meglitinide, was shown in the early 1980s to stimulate insulin secretion (Ribes et al, 1981). Repaglinide was introduced in 1998 and nateglinide in 2001.

Mode of action

The meglitinides bind to potassium channels on the cell membrane of pancreatic beta-cells in a similar manner to sulphonylureas, but at a separate binding site. Known as "prandial insulin releasers", these agents stimulate the first phase of insulin secretion, which is absent or diminished in people with type 2 diabetes. As they are rapidly absorbed and have a fast onset of action, the meglitinides are typically taken 15–30 minutes before main meals. Acting more quickly than the short-acting sulphonylureas, meglitinides have a relatively short duration of action.

Indications and licence

The meglitinides are indicated in combination with metformin in people with type 2 diabetes who are not satisfactorily controlled on metformin alone (eMC, 2015b; 2015c). Repaglinide also has a monotherapy licence.

The initial dose should be low and the drug should be titrated slowly. The recommended starting dose for repaglinide is 0.5 mg, which may be increased to 4 mg (eMC, 2015b). The recommended starting dose for nateglinide is 60 mg three times daily before meals, particularly in people who are near their HbA_{1c} goal. This may be increased to 120 mg three times daily (eMC, 2015c).

Contraindications and side-effects

Like other insulin secretagogues, the meglitinides are capable of causing hypoglycaemia, but because of their short duration of action this may occur less frequently than with the sulphonylureas. The meglitinides have a potential for interaction with drugs that are highly protein bound, such as gemfibrozil. These agents are contraindicated in people with severe hepatic impairment.

In the draft 2015 NICE guidelines, repaglinide was given unexpected prominence in the treatment algorithm for type 2 diabetes (NICE, 2015). However, it only has a dual-therapy licence in combination with metformin; therefore, it would have to be withdrawn and substituted if alternative dual-therapy or triple-therapy regimens were to be considered.

Acarbose

History

Acarbose is the first and only alpha-glucosidase inhibitor and was launched worldwide in 1990, although it is now rarely used in the UK.

Mode of action

Acarbose reduces postprandial glucose levels by inhibiting digestion of polysaccharides from the proximal small intestine and is not associated with hypoglycaemia. It is not as effective as the other oral antidiabetes agents at reducing HbA_{1c}, with typical reductions ranging from approximately 5 mmol/mol (0.5 percentage points) to 9 mmol/mol (0.8 percentage points; Nathan et al, 2009), and it needs to be administered with meals that contain digestible carbohydrates. As carbohydrate absorption occurs distally, no

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malabsorption or weight loss occurs. However, the delayed absorption causes increased flatulence and gastrointestinal symptoms.

Indications and licence

Acarbose is licensed for the treatment of people with type 2 diabetes, either as first-line therapy when dietary measures are insufficient or as an adjunct to conventional oral therapy where glycaemic control is suboptimal (eMC, 2013). It can be used as an add-on therapy in combination with all other antidiabetes agents. Acarbose should be taken with meals starting with a low dose and titrating upwards.

Contraindications and side-effects

Acarbose is contraindicated in people with hepatic impairment and should not be used in those with a creatinine clearance <25 mL/min/1.73 m². The main side effects of acarbose are gastrointestinal, most notably flatulence, which can limit its use. For this reason, a history of chronic intestinal disease can also be a contraindication (eMC, 2013).

Key evidence

STOP-NIDDM

In STOP-NIDDM (the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus), acarbose reduced the relative risk of developing diabetes by 25% in a population with IGT, compared with placebo (Chiasson et al, 2002). Furthermore, the acarbose-treated group experienced a reduction in the risk of cardiovascular events and hypertension (Chiasson et al, 2003).

Treatment algorithms

This article has summarised the mode of action, indications, contraindications and some practical considerations for the five classes of older blood-glucose lowering agents, but where should these therapies be positioned in the treatment algorithm? Guidance exists in abundance at the local, national and international level, and it is constantly being revised.

Comprehensive guidance is available from the ADA and EASD (Inzucchi et al, 2015). At the time of going to print, the 2015 draft NICE guidelines were still at the discussion stage. The first draft drew substantial criticism, not least for the positioning of therapies such as repaglinide and pioglitazone and for the complex algorithms. The subsequent, simplified draft more closely resembled the ADA–EASD consensus statement (NICE, 2015). Finally, SIGN has guidance on the management of type 2 diabetes for Scotland (SIGN, 2010).

Despite the availability of such guidance, treatment choices ultimately need to be tailored to the individual.

Box 5. Acarbose: Key facts and practical considerations.

- Inexpensive
- Caution needed in severe renal or hepatic impairment
- Reduces HbA_{1c} by approximately 5–9 mmol/mol (0.5–0.8 percentage points; Nathan et al, 2009)
- Use may be limited by gastrointestinal side effects
- Start with 50 mg once daily and titrate up to a dose of 100 mg three times daily over 4–8 weeks
- Not associated with weight gain

Concluding remarks

The older blood glucose-lowering therapies remain a mainstay in the management of hyperglycaemia in type 2 diabetes. Their differing mechanisms of action provide the opportunity for combination therapy, targeting both underlying insulin resistance and reduced endogenous insulin secretion. In order to make an appropriate choice of agent for a particular individual, a consideration of a person's lifestyle, history, comorbidities and preferences should be balanced against the key attributes of each drug.

In striving to manage hyperglycaemia in type 2 diabetes, data from the UKPDS (UKPDS Group, 1998a; UKPDS Group, 1998b), the ACCORD study (ACCORD Study Group et al, 2008), the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study (ADVANCE Collaborative Group et al, 2008) and VADT (the Veterans Affairs Diabetes Trial; Duckworth et al, 2009), as well as the UKPDS update (Holman et al, 2008), suggest that early, step-wise treatment, with avoidance of hypoglycaemia, should be our aim. ■

Case examples

A series of case examples can be found in the previous version of this module:

http://bit.ly/1Mkmu7q

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"In striving to manage hyperglycaemia in type 2 diabetes, early, step-wise treatment, with avoidance of hypoglycaemia, should be our aim."

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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. According to Diabetes UK (2009) figures, one person in the UK is diagnosed with new-onset diabetes approximately every *x* minutes.

   How many minutes is represented by *x*? Select ONE option only.

   A. 1
   B. 3
   C. 10
   D. 30
   E. 90

2. Which is the most widely prescribed oral antidiabetic agent worldwide?

   A. Glibenclamide
   B. Gliclazide
   C. Metformin
   D. Repaglinide
   E. Sitagliptin

3. Which one of the following statements most accurately reflects the mode of action of meglitinides?

   Select ONE option only.

   A. Activating the nuclear transcription factor PPAR
   B. Binding to potassium channels on pancreatic beta-cells
   C. Decreasing hepatic gluconeogenesis
   D. Inhibiting alpha-glucosidase
   E. Stimulating the SUR1 receptor

4. According to published research, which oral antidiabetic agent is associated with anti-mitogenic properties?

   Select ONE option only.

   A. Acarbose
   B. Glimepiride
   C. Metformin
   D. Pioglitazone
   E. Repaglinide

5. A 72-year-old man with type 2 diabetes requires an intravenous contrast agent prior to a CT scan.

   According to current recommendations, which of his regular medications should be temporarily discontinued in this situation?

   Select ONE option only.

   A. Aspirin
   B. Metformin
   C. Paracetamol
   D. Pioglitazone
   E. Simvastatin

6. According to the UK Hypoglycaemia Study group, in the first 2 years of treatment, which is the single most appropriate statement regarding the incidence of hypoglycaemia in people with type 2 diabetes taking sulphonylureas compared with those with insulin?

   Select ONE option only.

   A. Less
   B. More
   C. Same
   D. Unknown

7. Which one of the following drug combinations is most likely to be associated with peripheral oedema?

   Select ONE option only.

   A. Acarbose and metformin
   B. Insulin and gliclazide
   C. Metformin and gliclazide
   D. Pioglitazone and insulin
   E. Repaglinide and metformin

8. Which one of the following antidiabetes agents is not licensed in combination with a sulphonlyurea?

   A. Acarbose
   B. Insulin
   C. Metformin
   D. Pioglitazone
   E. Repaglinide

9. According to Nathan et al, which antidiabetes drug class would be expected, on average, to show the LEAST reduction in HbA_{1c} levels?

   Select ONE option only.

   A. Alpha-glucosidase inhibitors
   B. Biguanides
   C. Meglitinides
   D. Sulfonylureas
   E. Thiazolidinediones

10. A 48-year-old man with newly diagnosed, asymptomatic type 2 diabetes cannot tolerate metformin. He has a BMI of 26 kg/m^2 and his HbA_{1c} is elevated despite lifestyle modification.

    According to current guidelines, which is the single most appropriate alternative monotherapy to now recommend?

    Select ONE option only.

    A. Acarbose
    B. Gliclazide
    C. Insulin
    D. Pioglitazone
    E. Repaglinide