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

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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 address the current 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. This article updates and replaces the previous version, published in 2009.

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

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 both 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, although the contribution of these two major components varies between individuals.

Type 2 diabetes is more common in older individuals, but is strongly 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 estimate that one person is diagnosed with diabetes every 3 minutes (Diabetes UK, 2009). Diabetes prevalence rate forecasts indicate that by

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Page points

1. Over time, damage caused by high blood glucose levels affects a number of organs and leads to the long-term complications of diabetes.
2. Compared with the healthy population, people with diabetes have a high risk of morbidity and premature mortality from cardiovascular disease.
3. 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 eventually require pharmacological intervention for glycaemic control.

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 UKPDS (UK Prospective Diabetes Study) suggest that a 1 percentage point reduction in HbA_{1c} yields relative risk reductions of 14% for the incidence of myocardial infarction, and 37% for microvascular complications (Stratton et al, 2000).

Compared with the healthy population, people with diabetes 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 (Knowler et al, 2002; Tuomilehto et al, 2001). 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 the overweight (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 alpha-glucosidase inhibitors (*Box 5*), which are differentiated from each other through a variety of mechanisms of action (*Figure 1*). The newer agents targeting the incretin system, and the various insulin preparations are covered in other modules.

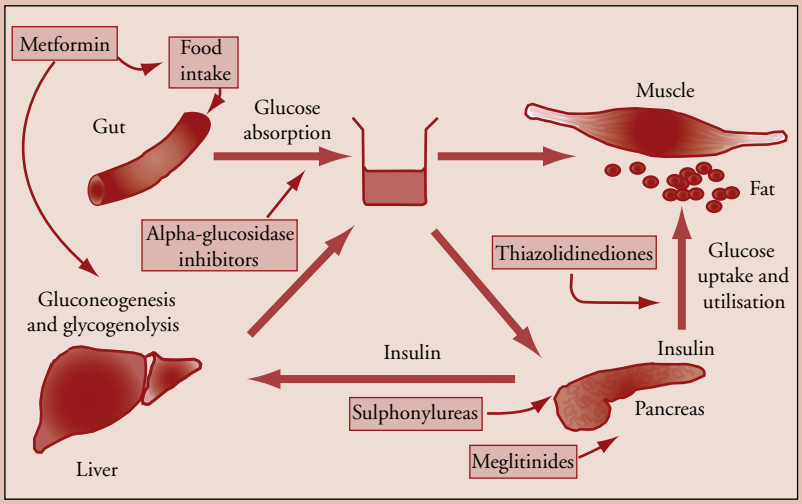

Figure 1. Sites of action of drugs used to treat type 2 diabetes (Reproduced with kind permission from Springer Science+Business Media: Greich JE and Szoke E (2006) Pathogenesis of type 2 diabetes.* In*: Skyler JS ed.* Atlas of Diabetes, *3rd edition. Current Medicine Group LLC, Philadelphia; Figure 8–20)

Metformin

History

Metformin was first described in the scientific literature in 1957 (Ungar et al, 1957), but only received approval by the US Food and

Drug Administration (FDA) for type 2 diabetes in 1994 and was first marketed in the USA 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 due 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 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], 2010). In all guidelines, metformin is the first-line choice of antidiabetes drug (NICE, 2009; Nathan et al, 2009; Scottish Intercollegiate Guidelines Network, 2010). It may be used as monotherapy or in combination with other antidiabetes agents including the sulphonylureas, pioglitazone, acarbose, meglitinides, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists or insulin.

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, 2010). 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/minute/1.73 m^2 (NICE, 2009). It should be used with caution in hepatic failure and alcoholism states as these conditions may also increase the risk of lactic acidosis. Other conditions that predispose to tissue hypoxaemia or reduced perfusion, such as septicaemia or myocardial infarction are also contraindications (EMC, 2010). The H2-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

Page points

1. Metformin reduces hepatic glucose production, primarily by decreasing gluconeogenesis, thereby reducing fasting plasma glucose.
2. Metformin is indicated for the treatment of type 2 diabetes, particularly in overweight people, when dietary management and exercise alone does not result in adequate glycaemic control.
3. Metformin is excreted in the urine and metformin accumulation can lead to a rare risk of lactic acidosis when renal clearance is limited.

Box 1. Metformin: Key facts and practical considerations.

- Low cost (£258 per patient less than conventional treatment, i.e. lifestyle modification; Clarke et al, 2001).
- Weight neutral, possibly some weight reduction as monotherapy (UK Prospective Diabetes Study Group, 1998a).
- Starting dose 500 mg once daily taken with food, 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, 2010).
- Review dose if estimated glomerular filtration rate (eGFR) is <45 mL/minute/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 1.5 percentage points (Nathan et al, 2006).
- Does not cause hypoglycaemia.

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Box 2. Sulphonylureas: Key facts and practical considerations.

- Low cost, especially if a generic formulation is prescribed.
- Approximately 1.5 percentage point reduction in HbA_{1c} (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.

Page points

1. 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.
2. The sulphonylureas were discovered by researchers studying sulphonamide antibiotics who observed that they induced hypoglycaemia in animals.
3. The sulphonylureas are indicated for the treatment of type 2 diabetes and can be considered as an option for first-line glucose lowering-therapy if: the person is not overweight; metformin is not tolerated or is contraindicated; a rapid response to therapy is required because of hyperglycaemic symptoms.

prior to the intravascular administration of an iodinated contrast agent in radiologic studies (EMC, 2010; Thomsen and Morcos, 2003).

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

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).

DPP

The DPP (Diabetes Prevention Program) 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 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).

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 USA 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 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 and can be considered as an option for first-line glucose lowering-therapy if (NICE, 2009):

- The person is not overweight.
- Metformin is not tolerated or is contraindicated.
- A rapid response to therapy is required because of hyperglycaemic symptoms.

Short- and long-acting sulphonylureas are available and may be prescribed as monotherapy, or in combination with

metformin, acarbose, pioglitazone, insulin and the newer incretin system based therapies.

Contraindications and side-effects

In the author's experience, chlorpropamide and glibenclamide are rarely used in practice. Their long duration of action predisposes to hypoglycaemia, particularly in 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 is arguable that drivers treated with sulphonylureas should be advised to test blood glucose levels before driving (Drivers Medical Group, 2011). They should certainly be provided with written advice concerning these risks.

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

Key evidence

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 UGDP (University Group Diabetes Program; Klimt et al, 1970). Concerns raised by the UGDP study have not been substantiated in subsequent landmark studies including the UKPDS (UKPDS Group, 1998b) and ADOPT (A Diabetes Outcome Progression Trial; Kahn et al, 2006).

Thiazolidinediones (glitazones)

History

The first member of the thiazolidinedione (TZD) class, introduced in 1997, was troglitazone, but this agent was withdrawn shortly after due 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. 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

Page points

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2. The UK Hypoglycaemia Study Group 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.
3. 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.

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 0.5–1.5 percentage points (Nathan et al, 2009).

CPD module

Page points

1. 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.
2. An important side-effect of the thiazolidinediones is fluid retention, usually manifested as peripheral oedema, which can contribute to weight gain.
3. There have been recent reports of an increased risk of bladder cancer with pioglitazone, and the summary of product characteristics has recently been amended to reflect this. The risk appears to be greater with higher doses and longer duration of treatment.

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, 2012a). In addition, pioglitazone is licensed in combination with insulin (EMC, 2012a). In combination with insulin, the current insulin dose can be continued upon initiation of pioglitazone therapy (EMC, 2012a).

Contraindications and side-effects

An important side-effect of the TZDs is fluid retention, usually manifested as peripheral oedema, which can contribute to weight gain. 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, 2012a).

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

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 patients and are monitored periodically thereafter based on clinical judgement (EMC, 2012a). TZDs are contraindicated for use in people with hepatic impairment.

Weight gain is a class effect of the TZDs 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 recent reports of an increased risk of bladder cancer with pioglitazone, and the summary of product characteristics has recently been amended to reflect this. The risk appears to be greater with higher doses and longer duration of treatment (EMC, 2012a).

Key evidence

PROactive

In the 3-year PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) 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 toward 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 DREAM [Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; DREAM Trial Investigators, 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 ACCORD (Action to Control Cardiovascular Risk in Diabetes) study and the interim analysis of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) 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 using rosiglitazone (Nathan et al, 2009). In July 2010, the Commission on Human Medicines (CHM) 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, they 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, 2011a; 2011b). Repaglinide also has a monotherapy licence.

The initial dose should be low and titrated slowly. The recommended starting dose for repaglinide is 0.5 mg, which may be increased to 4 mg (EMC, 2011a). The recommended starting dose for nateglinide is 60 mg three-times daily before meals, particularly in people who are near their goal HbA_{1c}. This may be increased to 120 mg three-times daily (EMC, 2011b).

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).
- Reduce HbA_{1c} by 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.

Page points

1. 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. The Committee did not recommend that rosiglitazone be removed from the market, but rather that label warnings be added.
2. In July 2010, the Commission on Human Medicines conducted a review into the safety of rosiglitazone and the Chair informed the Medicines and Healthcare products Regulatory Authority that "the benefits no longer outweigh the risks".

Box 5. Acarbose: Key facts and practical considerations.

- Inexpensive.
- Caution needed in severe renal or hepatic impairment.
- Reduces HbA_{1c} by 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.

Page points

1. Like other insulin secretagogues, the meglitinides are capable of producing hypoglycaemia, but because of their short duration of action this may occur less frequently than with the sulphonylureas.
2. Acarbose is the first and only alpha-glucosidase inhibitor and was launched worldwide in 1990.
3. Acarbose reduces postprandial glucose levels by inhibiting digestion of polysaccharides from the proximal small intestine and is not associated with hypoglycaemia.
4. In the STOP-NIDDM (Study To Prevent Non-Insulin-Dependent Diabetes Mellitus), acarbose reduced the relative risk of developing diabetes by 25% in a population with impaired glucose tolerance, compared with placebo.

Contraindications and side-effects

Like other insulin secretagogues, the meglitinides are capable of producing 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 hepatic disease.

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}, typical reductions range from 0.5 to 0.8 percentage points (Nathan et al, 2009), and needs to be administered with meals that contain digestible carbohydrates. As carbohydrate absorption occurs distally, no 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, 2012b). 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 m^2. 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 is also a relative contraindication (EMC, 2012b).

Key evidence

STOP-NIDDM

In the STOP-NIDDM (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 relative 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 is constantly being revised.

Comprehensive guidance is available from ADA and EASD (Nathan et al, 2009), and NICE updated its guidance in 2009 to include newer therapies for the management of type 2 diabetes for practitioners in England and Wales (NICE, 2009; *Figure 2*). The Scottish Intercollegiate Guidelines Network (2010) published guidance on the management of type 2 diabetes for Scotland.

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

Conclusions

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, diabetes, comorbidities and preferences should be balanced against the key attributes of each drug (*Box 6* provides two exemplar case studies).

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

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Box 6. Case studies.

Narrative

Frank is a 58-year-old HGV driver who presents with thirst and penile thrush. At presentation his BMI is 33 kg/m^2, his fasting blood glucose level is 13.7 mmol/L, his blood pressure is 173/97 mmHg and his cholesterol level is 5.8 mmol/L.

He prefers to try lifestyle change over medication initially. Three months later, his weight is unchanged and he has struggled with changing his diet and increasing his exercise levels due to his on-the-road lifestyle. He commences metformin and this is slowly uptitrated to 1000 mg twice daily.

At review 6 months later, simvastatin 40 mg and lisinopril 10 mg have been added to his diabetes therapy. His BMI is now 32 kg/m^2; HbA_{1c} level is 57 mmol/mol (7.4%); blood pressure is 154/92 mmHg, and his cholesterol level is 4.1 mmol/L.

Discussion

Increasing metformin to 3000 mg/day is unlikely to bring additional benefit and may increase the risk of gastrointestinal side-effects, which is not very welcome given the nature of his profession.

Gliclazide is a possibility but carries the risk of hypoglycaemia and further weight gain. Under the new DVLA regulations, he would have to declare episodes of severe hypoglycaemia and this could threaten his livelihood. It would be important to discuss (and document the discussion) the possibility of weight gain and hypoglycaemia with him, and he is unlikely to agree to this option.

Pioglitazone is not associated with hypoglycaemia, and is a good option, but there is a considerable risk of weight gain and fluid retention. Acarbose would not be suitable due to the side-effect profile.

One of the newer incretin-based therapies would also be a good choice. See the second module in this series for more information (Munro, 2009). An update of this module will be published in May 2012.

Narrative

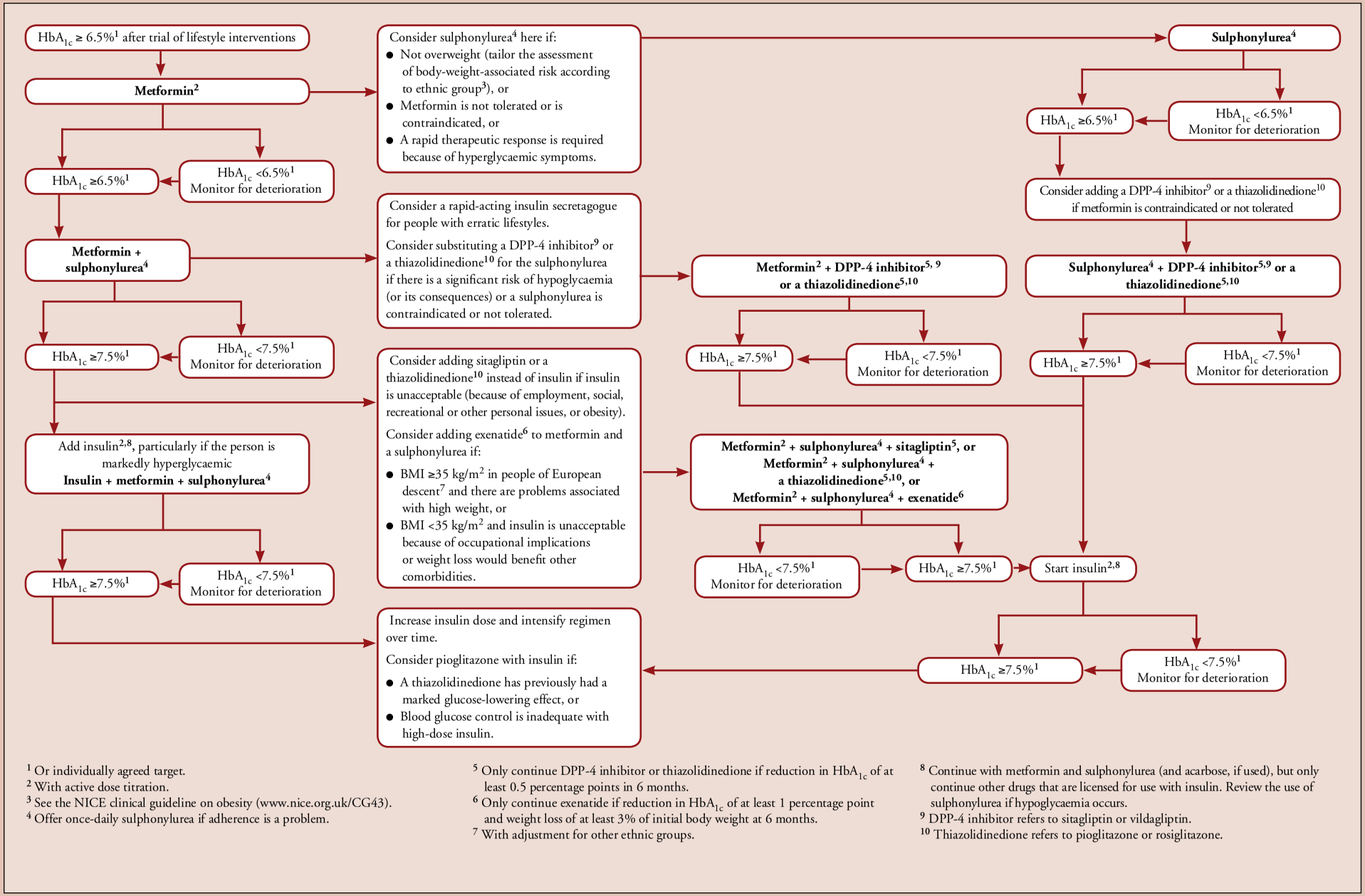
Barbara is a fit 38-year-old physical education teacher who presents with malaise, visual disturbance and increasing urinary frequency. Urine testing in the surgery shows glucose++++, and is negative for ketones. She is keen to commence treatment as soon as possible and starts metformin 500 mg once daily and rapidly titrates up to 500 mg three times daily.

However, she returns to the surgery after 3 weeks. Although tolerating the metformin, she still feels unwell. She has done some random blood glucose measurements using a friend's blood glucose meter and tells you that all the readings are 12–15 mmol/L.

Discussion

Barbara is fit and active with a normal BMI. These factors, together with the rapidity of presentation and progression and poor response to metformin, suggest that insulin resistance is not the major underlying pathophysiological problem. It is likely that beta-cell dysfunction is the predominant factor in her diabetes. Before initiating treatment a fasting blood glucose level and HbA_{1c} level would need to be obtained. She will need a sulphonylurea in the first instance for rapid symptom control, but will need close monitoring including blood glucose monitoring and urine testing for ketones.

Be wary of newly presenting type 2 diabetes in individuals with low or normal BMI. Consider late presenting type 1 diabetes, or LADA (latent autoimmune diabetes of adulthood). These individuals have underlying beta-cell failure as the mechanism for dysglycaemia. Most progress rapidly to insulin therapy. It is also worth checking C-peptide levels if this investigation is available in your laboratory.



[1] Or individually agreed target.
[2] With active dose titration.
[3] See the NICE clinical guideline on obesity (www.nice.org.uk/CG43).
[4] Offer once-daily sulphonylurea if adherence is a problem.
[5] Only continue DPP-4 inhibitor or thiazolidinedione if reduction in HbA_{1c} of at least 0.5 percentage points in 6 months.
[6] Only continue exenatide if reduction in HbA_{1c} of at least 1 percentage point and weight loss of at least 3% of initial body weight at 6 months.
[7] With adjustment for other ethnic groups.
[8] Continue with metformin and sulphonylurea (and acarbose, if used), but only continue other drugs that are licensed for use with insulin. Review the use of sulphonylurea if hypoglycaemia occurs.
[9] DPP-4 inhibitor refers to sitagliptin or vildagliptin.
[10] Thiazolidinedione refers to pioglitazone or rosiglitazone.

Figure 2. NICE (2009) algorithm for blood glucose-lowering therapy in people with type 2 diabetes. From NICE (2009). Adapted from: CG87 Type 2 Diabetes: The Management of Type 2 Diabetes. *NICE, London. Available from: www.nice.org.uk/CG87. Reproduced with permission. DPP-4 = Dipeptidyl peptidase-4.*

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"The older blood glucose-lowering therapies remain a mainstay in the management of hyperglycaemia in type 2 diabetes."

CPD module

CPD module

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 new 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. **Which is the most appropriate statement regarding the development of type 2 diabetes? Select ONE option only.**
   A. The contribution of insulin resistance is significantly more important than reduced pancreatic beta-cell function.
   B. The contribution of insulin resistance is slightly more important than reduced pancreatic beta-cell function.
   C. The contribution of reduced pancreatic beta-cell function is significantly more important than insulin resistance.
   D. The contribution of reduced pancreatic beta-cell function is slightly more important than insulin resistance.
   E. The contribution of insulin resistance and reduced pancreatic beta-cell function varies between individuals.

2. **Which one of the following side-effects is not associated with thiazolidinediones? Select ONE option only.**
   A. Bladder cancer.
   B. Dilutional anaemia.
   C. Fractures in postmenopausal women.
   D. Heart failure.
   E. Pulmonary fibrosis.

3. **According to the relevant SPC (summary of product characteristics), which one of the following can be taken with or without food? Select ONE option only.**
   A. Acarbose.
   B. Gliclazide.
   C. Metformin.
   D. Pioglitazone.
   E. Repaglinide.

4. **Which is the most appropriate description of the mode of action of glimepiride? Select ONE option only.**
   A. Decrease fatty acid oxidation.
   B. Increase glucose uptake in skeletal muscle.
   C. Inhibit digestion of polysaccharides from the small intestine.
   D. Interaction with SUR1 receptor to stimulate insulin secretion.
   E. Suppressing hepatic glucose production.

5. **According to the DVLA, which one of the following oral antidiabetes drugs (OADs) would be most likely to risk inducing hypoglycaemia? Select ONE option only.**
   A. Acarbose
   B. Metformin
   C. Nateglinide
   D. Pioglitazone
   E. None of the above

6. **According to international consensus statements, which one of the following OADs would, on average, lower the HbA_{1c} level the least? Select ONE option only.**
   A. Acarbose.
   B. Gliclazide.
   C. Metformin.
   D. Pioglitazine.
   E. Repaglinide.

7. **Which is the most appropriate OAD to use when a person with type 2 diabetes has coexistent alcoholic liver cirrhosis? Select ONE option only.**
   A. Acarbose.
   B. Glimepiride.
   C. Metformin.
   D. Repaglinide.
   E. None of the above.

8. **An 86-year-old woman has had type 2 diabetes for 8 years, treated with metformin 500 mg twice daily and gliclazide 160 mg once daily. She is living independently with no significant health problems.**
   Her most recent results show:
   - **HbA_{1c}: 41 mmol/mol (5.9%)**
   - **Random blood glucose: 6 mmol/L**
   - **Urine microalbuminuria: negative**
   - **Blood Pressure: 145/85 mmHg**

   Which is the most appropriate next management step? Select ONE option only.
   A. Add aspirin.
   B. Add ramipril.
   C. Stop gliclazide.
   D. Stop metformin.
   E. No medication change.

9. **A 47-year-old Muslim man has poorly controlled type 2 diabetes. He agrees to start medication as lifestyle measures have failed. He intends to strictly observe the rules of Ramadan, fasting during the hours of daylight for 30 days. Which is the most appropriate OAD to recommend during this period of fasting? Select ONE option only.**
   A. Acarbose.
   B. Gliclazide.
   C. Metformin.
   D. Repaglinide.
   E. Pioglitazone.

10. **A 43-year-old woman has poorly controlled type 2 diabetes and is intolerant of metformin. She has previously been reluctant to engage with the healthcare team but seeks advice as she is fatigued and has recurrent intertrigo. Her results are:**
    - **Urine ketones: negative**
    - **Urine glucose: ++++**
    - **Random blood glucose: 16 mmol/L**
    - **HbA_{1c} level: 70 mmol/mol (8.6%)**

    Which is the most appropriate initial OAD to improve her symptoms? Select ONE option only.
    A. Acarbose.
    B. Gliclazide.
    C. Metformin MR.
    D. Pioglitazone.
    E. Repaglinide.