# Diabetes: guidance on newer agents

Type 2 diabetes usually develops in people over the age of 40 years, and the risk of getting it increases with age. It is more common in men and hyperglycaemia caused by untreated type 2 diabetes can lead to a number of long-term complications. It confers a two to four-fold greater risk of coronary heart disease among men compared to a three to five-fold increased risk among women. This article looks at the latest guidance from NICE on management.

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Type 2 diabetes is a chronic metabolic disorder caused by insulin insensitivity combined with insufficient insulin secretion from the pancreas. Prolonged high blood glucose levels can result in microvascular and macrovascular damage, with potentially devastating consequences, including coronary, cerebrovascular, ophthalmological and renal disease. It is more common in men, and confers a two to four-fold greater risk of coronary heart disease among men compared to a three to five-fold increased risk among women.[1,2]

The vast majority (more than 85%) of the 2·1 million sufferers from diabetes in England and Wales have type 2 diabetes.[3] Type 2 diabetes usually occurs in people older than 40 years, though it can appear earlier in life, particularly in people of South Asian or Africa-Caribbean origin.[3] The UK healthcare burden of diabetes has been estimated as at least 5% of healthcare expenditure and up to 10% of hospital budgets.[3]

## Management

The improvement of blood glucose levels is the mainstay of treatment for type 2 diabetes.[1] Although lifestyle interventions (diet and exercise) are the first choice of treatment, type 2 diabetes is a progressive disease with a gradual decline in insulin secretion over time. Most patients will therefore require oral glucose-lowering drugs and ultimately insulin. The most widely used first-line oral agent is metformin. Sulphonylurea may be added as a second-line therapy if blood glucose levels remain poor or deteriorate. A number of novel treatments for type 2 diabetes have recently been introduced in the UK, including gliptins (or DPP-4 inhibitors), GLP-1 mimetics, thiazolidinediones, and long-acting insulin analogues.

## NICE guidance

The new NICE clinical guidance aims to improve the care of adults with type 2 diabetes by making evidence-based recommendations on the role of these newer agents and their place in the care pathway.[3] These include recommendations on the use of long-acting insulin analogues, DPP-4 inhibitors, GLP-1 mimetics and thiazolidinediones within their licensed recommendations. Metformin continues to be recommended as standard first line therapy. Sulfonylureas continue to be recommended as first-line therapy if the patient is not overweight, metformin is contraindicated, or rapid response to therapy is required due to hyperglycaemia. It is standard second-line therapy if blood glucose control is inadequate with metformin. Further NICE recommendations[3] are outlined below:

### Insulin therapy (including the long-acting insulin analogues, insulin detemir, insulin glargine)

Insulin detemir and insulin glargine, like NPH insulin, provide slowly-released insulin to meet basal requirements. When the decision to start insulin is made, human NPH insulin should be started; healthcare professionals should consider switching to a long-acting insulin analogue if the patient experiences significant hypoglycaemia, is unable to use the device needed to inject NPH insulin, or who needs help to inject from a carer or healthcare professional, and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.

### DPP-4 inhibitors (sitagliptin, vildagliptin)

Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulfonylurea as second-line therapy to first-

line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6·5%, or other higher level agreed with the individual), if the person is at significant risk of hypoglycaemia or its consequences or people in certain social circumstances (for example, those living alone), or the person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated.

Consider adding a DPP-4 inhibitor as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6·5%, or other higher level agreed with the individual), if the person does not tolerate metformin, or metformin is contraindicated.

Consider adding sitagliptin as third-line therapy to

first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7·5% or other higher level agreed with the individual) and insulin is unacceptable or inappropriate.

A DPP-4 inhibitor may be preferable to a thiazolidinedione if further weight gain would cause or exacerbate significant problems associated with a high body weight, or a thiazolidinedione is contraindicated, or the person has previously had a poor response to, or did not tolerate, a thiazolidinedione.

## GLP-1 mimetic (exenatide)

Exenatide lowers blood glucose and may lead to weight loss; it is licensed for the treatment of elevated blood glucose (but not elevated body weight) in type 2 diabetes. The drug requires twice-daily injection. Healthcare professionals should consider the option of adding the GLP-1 mimetic (exenatide) to metformin and a sulfonylurea in a patient who requires improved control of glucose, has a high body mass index (35 kg/m$^2$ or higher) and experiences problems associated with high body weight.

GLP-1 (exenatide) may also be added to metformin and a sulfonylurea if the patient has a body mass index below 35 kg/m$^2$, who has a medical problem resulting from being overweight, or for whom insulin is not an option.

## Thiazolidinediones (pioglitazone, rosiglitazone)

Healthcare professional should consider adding a thiazolidinedione instead of a sulfonylurea as second-line therapy to first-line metformin when control

### View points

"As the number of people with type 2 diabetes continues to rise, GPs play an increasingly pivotal role in the management of type 2 diabetes, and it is important to ensure that our patients are on a regime which provides optimal glucose control, whilst minimising dangerous and debilitating side effects including hypoglycaemia."
Dr David Haslam GP and Clinical director of the National Obesity Forum, Hertfordshire

"One of the key issues when considering treatment options is striking a balance between achieving optimal glycaemic control while also minimising the risk of hypoglycaemia, and the newer treatments provide us with a wider choice of options. NICE should be applauded for recognising these newer agents, as this represents a significant milestone in the treatment of type 2 diabetes and may have an impact across the rest of Europe. We now have an array of effective treatment options to offer appropriate patients whose blood glucose is not adequately controlled by first-line treatments plus diet and exercise, to help get their blood sugar under control in order to carry on with their everyday lives."
Professor Anthony Barnett, Consultant Physician, Birmingham

"The guideline for type 2 diabetes newer agents is important for healthcare professionals because it helps clarify which patients are appropriate candidates for these newer treatments. With a chronic condition such as diabetes it is essential that patients are educated about their condition, have access to a wide range of treatment options and maintain the best quality of life possible. The guideline for type 2 diabetes newer agents certainly supports these efforts."
Dr Martin Hadley-Brown, chairman of the Primary Care Diabetes Society

"The new NICE Guideline comes at an important time for diabetes management, the prevalence of which is increasing across the UK. In addition to the problems patients face in meeting their blood sugar targets, they also experience unpleasant side effects with current treatments, most notably weight gain and hypoglycaemia. Hypoglycaemia in particular can be extremely dangerous and have a significant impact on patient's quality of life. It is time we made the most of the treatments available to us and put the patients right at the centre of diabetes care."
Professor Jiten Vora Consultant Endocrinologist, Royal Liverpool and Broadgreen University Hospitals

of blood glucose remains or becomes inadequate (HbA1c ≥ 6·5%, or other higher level agreed with the individual), if the person is at significant risk of hypoglycaemia or its consequences or people in certain social circumstances (for example, those living alone), or a person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated. Consider adding a thiazolidinedione as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6·5%, or other higher level agreed with the individual), if the person does not tolerate metformin or metformin is contraindicated.

Consider adding a thiazolidinedione as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7·5%, or other higher level agreed with the individual) and insulin is unacceptable or inappropriate.

Thiazolidinedione therapy should not be started or continued in any individual who has heart failure or is at high risk of bone fracture.

A thiazolidinedione may be preferable to a DPP-4 inhibitor if the person has marked insulin insensitivity, or a DPP-4 inhibitor is contraindicated, or the person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor.

In addition, NICE states that prescribers should be fully aware of the latest data and guidance from the relevant safety agency (in this case, the European Medicines Agency, EMEA).

## Patient centred care

The new NICE guidance updates the type 2 diabetes clinical guideline by NICE published in 2008. It ensures that treatment is patient centred with patients treated according to their particular profile and needs.[3] Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English. If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care. Families and carers should also be given the information and support they need.[3]

## Hypoglycaemia

The new NICE guidance also states that thiazolidinediones and DPP-4s should be used after metformin (in preference to a sulphonylurea) when a patient is at risk of developing hypoglycaemia. Hypoglycaemia occurs when the level of glucose in the blood falls too low, usually under 4 mmol/l. People with diabetes who take insulin and/or certain diabetes tablets are at risk of having hypoglycaemia. It may occur if someone has taken too much diabetes medication, delayed or missed a meal or snack, not eaten enough carbohydrate, taken part in unplanned or more strenuous exercise than usual, and has been drinking alcohol without food. Treatment is usually very simple and requires taking some fast acting carbohydrate, such as a sugary drink or some glucose tablets, and following this up with some longer acting carbohydrate, such as a cereal bar. If left untreated the person might, eventually, become unconscious and would need to be treated with an injection of glucagon (a hormone that raises blood glucose levels). But in the vast majority of cases the body will release its own stores of glucose and raise the blood glucose level to normal, though this may take several hours.[4]

There may be some people for whom either a DPP-4 inhibitor (sitagliptin, vildagliptin) or a thiazolidinedione (pioglitazone, rosiglitazone) may be suitable and, in this case, the choice of treatment should be based on patient preference.

### References


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