NICE has a place for newer agents for type-2 diabetes

In May, NICE issued updated treatment guidelines for type-2 diabetes. This advice gives doctors the option of using thiazolidinediones or dipeptidyl peptidase-4 inhibitors in patients whose blood-glucose control is inadequate. However, evidence suggests that rosiglitazone may increase the risk of myocardial infarction and heart failure. Pioglitazone has not been shown to have such an effect, but since few data are available to prove pioglitazone's cardiovascular safety, NICE recommends that neither thiazolidinedione should be given to patients with heart failure.

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More than 2 million people have been diagnosed with diabetes in England and Wales, and more than 85% of those have type-2 diabetes. Diabetes is estimated to account for at least 5% of health-care expenditure in the UK, and up to 10% of hospital budgets. Type-2 diabetes usually affects people older than 40 years; however, it can occur earlier, particularly in people of South-Asian or Afro-Caribbean origin.

The recent clinical guidelines from NICE[1] covering the newer drugs for type-2 diabetes emphasise that patients should be treated according to their individual profile and needs. In particular, they recommend that if patients are at significant risk of hypoglycaemia, or its consequences, then glitazones (thiazolidinediones) or gliptins (dipetidyl peptidase-4 [DPP-4] inhibitors) should be used as second line, in preference to a sulphonylurea.

Hypoglycaemia is an important and underestimated problem. Elderly patients are at high risk of hypoglycaemia, and those who live alone are especially vulnerable. Hypoglycaemia is also under-reported because patients often do not want to admit that they have experienced hypoglycaemia for fear of losing their driving license or they may not realise that they have had an episode.

Hypoglycaemia has substantial clinical impact in terms of mortality, morbidity, and quality of life. The cost implications of severe episodes, both direct hospital costs and indirect costs, are considerable. Recent results from the ACCORD study[2] suggested an association between hypoglycaemia and an increased mortality.

Professor Anthony Barnett, professor of medicine at Birmingham University and Heart Of England NHS foundation Trust, says the new quality and outcomes framework target for glycated haemoglobin (HbA1c) of 7% and NICE target of 6·5% for the first two treatment steps are challenging, and he believes that the drive for such strict glycaemic control could increase the number of hypoglycaemic episodes.

"NICE recommend a target HbA1c for the first two treatment steps of 6·5% but recognises that to achieve this target safely, in other words without increasing the risk of hypoglycaemia, then modern agents may be required which have a low risk of this problem," commented Professor Barnett. "The recommendation that drugs such as glitazones and DPP-4 inhibitors can be used second line where the patient is at significant risk of hypoglycaemia or where hypoglycaemia must be avoided at all costs is sensible and allows for real-life prescribing."

Updating previous guidance

This new clinical guidance from NICE updates the type-2 diabetes guidelines published in 2008. Lifestyle advice on diet and physical activity are the first-line treatment when a patient is newly diagnosed with type-2 diabetes, but most people will need the addition of oral glucose-lowering drugs. And because type-2 diabetes is progressive, with the secretion of insulin decreasing over time,

most people with type-2 diabetes will eventually need insulin. The guidelines emphasise that treatment and care should take into account patients' needs and preferences. People with type-2 diabetes should have the opportunity to make informed decisions about their care in partnership with their health-care professionals.

Metformin remains first-line drug therapy, but if blood-glucose control remains or becomes inadequate (HBA1c greater than 6·5%), then a second-line treatment is needed. One option is a sulphonylurea but these drugs have a substantial risk of hypoglycaemia. The new guidance states that a thiazolidinedione (pioglitazone or rosiglitazone) or DPP-4 inhibitor (sitagliptin or vildagliptin) should be prescribed if a patient is at high risk of hypoglycaemia, for example, older people, those who work at heights or with heavy machinery, or people living alone. A thiazolidinedione or DPP-4 inhibitor should also be considered if the patient does not tolerate or has a contraindication to sulphonylureas.

Professor Richard Donnelly, professor of vascular medicine at the University of Nottingham said: "I am pleased to see that glitazones have been recommended by NICE for second-line use in certain circumstances, and I have no doubt that the magnitude and durability of glitazones' HbA1c-lowering effect will help general practitioners get more patients to target glycaemic control for longer"

Using thiazolidinediones

The thiazolidinediones should be prescribed in preference to a DPP-4 inhibitor if the patient exhibits marked insulin insensitivity. A lack of insulin sensitivity, or insulin resistance, is also the dominant feature of the metabolic syndrome, a cluster of disorders that carry an increased risk of cardiovascular complications through atherogenic dyslipidaemia. The thiazolidinediones increase insulin sensitivity so that a person's own insulin is more effective in reducing and maintaining blood-glucose levels. A thiazolidinedione should also be chosen if a patient is contraindicated to DPP-4 inhibitors or has previously had a poor response to, or did not tolerate a DPP-4 inhibitor.

Thiazolidinediones may cause weight gain and the guidance states that a DPP-4 inhibitor may be preferable if further weight gain would cause or exacerbate serious problems associated with a high bodyweight. Thiazolidinediones are also associated with fluid retention (including peripheral oedema) and distal bone fractures in women. As a result, NICE recommends that these drugs should not be used in patients who have heart failure or who are at high risk of fracture. In some patients either drug type may be suitable and then the choice should be based on patients' preference. However, a DPP-4 inhibitor or a thiazolidinedione should only continued if a beneficial metabolic response occurs—ie, a reduction in HbA1c of at least 0·5% in 6 months

A thiazolidinedione can also be used third line in combination with metformin and a sulphonylurea if blood glucose control remains inadequate or if insulin is unacceptable or inappropriate. Of the two thazolidinediones, only pioglitazone is licensed for use with insulin and it can be considered in combination in patients who have previously had a marked glucose-lowering response to thiazolidinedione therapy.

Other treatment options

A glucagon like peptide-1 (GLP-1) mimetic (exenatide) can be considered for third line treatment (with metformin and a sulphonylurea) when control of blood glucose remains or becomes inadequate and the patient is severely obese (body-mass index 35 kg/m^2 or higher) and has specific psychological or medical problems associated with high bodyweight. Exenatide can be considered in patients with a body-mass index of less than 35 kg/m^2 if therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. Treatment with exenatide should be continued only if a beneficial metabolic response occurs; defined as a reduction of at least 1·0% in HbA1c and a weight loss of at least 3% of initial bodyweight over 6 months.

Since NICE published its treatment guideline on the newer agents, liraglutide, another human GLP-1) analogue has been launched in the UK. Liraglutide is a once daily injection, whereas exenatide is administered twice daily. A randomised open label trial showed that liraglutide delivered better glucose control than did exenatide over a 26 week period.[3] Both drugs produced similar weight loss in patients.

If blood glucose remains uncontrolled (HBA1c greater than 7·5%), then the doctor should discuss with the patient the pros and cons of insulin therapy. For a person on dual therapy who is markedly hyperglycaemic, then insulin should be considered in preference to adding another drug.

The guidance also reinforces the practice that human insulin should be first choice for most patients who need insulin, unless severe hypoglycaemia occurs or the patient has practical difficulties in using human insulin. A long-acting insulin analogue should be considered if the patient would need help from a carer or health-care professional to administer insulin injections or if use of long-acting insulin analogues would reduce injections from twice to once daily.

A long-acting insulin analogue such as insulin demetir or insulin glargine, should also be considered if a person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or if the person would otherwise need twice-daily human insulin injections in combination with oral glucose-lowering drugs or the person cannot use the device to inject insulin.

The glitazone controversy

Health-care professionals had hoped that NICE would end the ongoing controversy about the cardiovascular safety of rosiglitazone and give clear guidance to prescribers. Although the draft guidelines clearly differentiated between the two thiazolidinediones, the final recommendations are less definitive. NICE states that for rosiglitazone there is a potentially increased risk of myocardial ischaemia based on a meta-analysis of interventional trials, including a study published in the NewEnglandJournalofMedicine in 2007.[4] The risks of myocardial ischaemia and heart failure increase with concomitant insulin and, as a result, rosiglitazone is not licensed for use with insulin.

The controversy surrounds whether the observed risks of rosiglitazone represent a class effect of thiazolidinediones. NICE states that "the available studies for pioglitazone including published meta-analyses of trials and the completed long-term PROactive study do not raise similar concerns about an increased risk of myocardial infarction in association with pioglitazone treatment." PROactive was a prospective randomised trial; the secondary endpoint consisting of myocardial infarction, stroke, or death from any cause showed a significant effect favouring pioglitazone.[5]

Despite this, NICE still groups the two drugs together stating that doctors should not commence or continue any thiazolidinedione in people who have a history of cardiac failure. NICE does state that "although there are few head to head trials of rosiglitazone and pioglitazone, it appears that, given the current evidence, rosiglitazone offers no clear benefit over pioglitazone. Moreover, pioglitazone is licensed for use with insulin."

NICE also states that when selecting either pioglitazone or rosiglitazone, prescribers should take into account up-to-date advice from the European Medicines Agency. Additionally, the doctor should discuss all potential benefits and risks with the patient to allow an informed decision to be made.

Since publication of the NICE guidelines, results from the RECORD study have been reported.[6] This randomised, open-label trial confirms that the addition of rosiglitazone to glucose-lowering therapy in people with type-2 diabetes does increase the risk of heart failure and of some fractures, mainly in women. An excess of eight cases of myocardial infarction (both fatal and non-fatal) occurred in the rosiglitazone group but the result was not significant. The authors stated that the data are inconclusive about any possible effect on myocardial infarction but that rosiglitazone does not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs.

References

1. NICE. Type 2 Diabetes—newer agents (partial update of CG66). May 2009. http://guidance.nice.org.uk/CG87
2. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545–59
3. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 2009; **374**: 39–47
4. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356**: 2457–71
5. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; **366**:1279–89
6. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009; **373**: 2125–35