News

New NICE guidelines on new treatments for type 2 diabetes

The National Institute for Health and Clinical Excellence (NICE) has issued a new guidance on the use of several newer agents for blood glucose control in adults with type 2 diabetes.

These include long-acting insulin analogues, DPP-4 inhibitors, glucagon-like peptide-1 (GLP-1) mimetics and thiazolidinediones.

Summary of therapies and key recommendations are:

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 needs help to inject the insulin 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)

Healthcare professionals should consider the option of adding a DPP-4 inhibitor in patients taking metformin and a sulfonylurea in whom treatment with insulin is inappropriate, including because of employment, social, or recreational problems related to hypoglycaemia. A DPP-4 inhibitor can also be considered in patients who have contraindications to metformin or a sulfonylurea.

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 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. 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)

A thiazolidinedione can be considered in patients taking metformin and/or a sulfonylurea in whom treatment with insulin is inappropriate because of the potential for hypoglycaemia and its consequences. But thiazolidinedione therapy should not be started or continued in any individual who has heart failure or is at high risk of bone fracture.

In a NICE press release, Philip Home (Professor of Diabetes Medicine at Newcastle Primary Care Trust) who was part of the guideline development group, says: "The expansion in new glucose-lowering therapies in diabetes is both exciting and has led to confusion. It is good then to see an evidence- and cost-based approach to these therapies, and to see them accommodated with positive recommendations within the therapeutic pathway".

New meta-analysis confirms statin benefit in primary prevention

A new meta-analysis has confirmed that statins improve survival and reduce the risk of major cardiovascular events in patients who have risk factors but who do not have established cardiovascular disease.

The meta-analysis, published in the *British Medical Journal* (*BMJ* 2009;**338**:b2376) included 10 primary prevention trials of statins versus placebo including a total of 70,388 people. The trials included were: WOSCOPS, AFCAPS/TexCAPS, PROSPER, ALLHAT-LLT, ASCOT-LLA, HPS, CARDS, ASPEN, MEGA, and JUPITER.

Results showed significant reductions in all-cause mortality, major coronary events and major cerebrovascular events with statins versus placebo (see **table 1**), regardless of age, gender, or diabetes status.

Despite these positive findings, the authors say that the absolute overall benefit in the current study population would be less than 1%, and significant numbers of people would need to be treated to prevent one event. They add that while it is not possible to define one group of people who would benefit most from statin use, older men (>65 years) with risk factors or older women with diabetes and risk factors constitute the highest-risk group and that it is likely that a considerable number of such people would benefit from long-term statin use at reasonable costs

Because the occurrence of cancer was increased in the PROSPER trial of statins in elderly patients, the authors of the current meta-analysis examined cancer rates and found no increase in people taking statins.

But they caution that longer follow-up is needed to rule out increases in new cancer events over time, which they say is critical when statins are used in primary prevention. And they add that concerns might remain about a possible higher risk of cancer in elderly patients.

Table 1. Main results from the meta-analysis

Event	Odds ratio with statins
All-cause mortality	0.88
Major coronary events	0.70
Major cerebrovascular events	0.81

EMEA warns of possible interaction between clopidogrel and PPIs

The European Medicines Agency (EMEA) has issued a warning about a possible interaction between clopidogrel and proton-pump inhibitors (PPIs), such as omeprazole, which are taken for gastric problems. The EMEA has recommended that the product information for all clopidogrel-containing medicines be amended to discourage concomitant use of PPIs unless absolutely necessary.

The UK Medicines and Healthcare Products Regulatory Agency (MHRA), has also issued advice to GPs that concomitant use of a PPI with clopidogrel is not recommended unless considered essential, urging a review of the prescribing of PPIs at the next appointment for patients taking clopidogrel.

The EMEA statement points out that, as heartburn and stomach ulcers can occur as side-effects of clopidogrel, patients taking clopidogrel often take PPIs to prevent or ease these symptoms. It is estimated that around 500,000 patients in the UK are currently prescribed clopidogrel and around half are also prescribed PPIs. Many more may be buying omeprazole over the counter. Other PPIs include esomeprazole, lansoprazole, pantoprazole, and rabeprazole.

EMEA says concern about a possible interaction comes from several recently published studies examining clinical outcomes of clopidogrel users. "Taken together, these studies suggest that a significant interaction might occur between clopidogrel and members of the PPI class of medicines, making clopidogrel less effective when given with these medicines", the statement says. "One possible explanation for this observation is that some PPIs prevent the conversion of clopidogrel into its biologically active form in the body, reducing the effectiveness of clopidogrel and increasing the risk of heart attack or other conditions involving harmful clotting (e.g. strokes). However, as different PPIs have different capacity to affect the metabolism of clopidogrel and as the outcome studies have not fully reflected the different effect of PPIs on activation of clopidogrel, there may be more than one explanation for the effect of this class of medicines on clopidogrel," it adds.

Generic clopidogrel imminent

The European Medicines Agency (EMEA) has given a positive recommendation to six generic versions of clopidogrel. Such recommendations are normally endorsed by the European Commission within a few weeks, so generic clopidogrel should be available in most European countries in the very near future.

Four of the six generics are from the Swiss company Acino, one is from the Israeli company Teva, and one from the Greek firm Pharmathen. Generic clopidogrel is already available in Germany.

Clopidogrel, which is sold under the brand name Plavix® by Sanofi-Aventis and Bristol-Myers Squibb, was the second-biggest selling drug worldwide in 2008, with sales of more than US$ 8 billion. The generic competitors have been the subject of a long-term patent dispute, and Sanofi-Aventis said it would contest the new generics and defend its intellectual property rights.

New programme acts as virtual coach and motivator in patient heart health

A new diet and lifestyle support programme has been launched online for patients once they have completed an NHS Health Check. It is hoped that 'activheart' will not only help save healthcare professionals time in providing lifestyle advice to patients but also complement this information.

'Activheart' is a free web-based behavioural intervention programme designed to act as a virtual coach and motivator to support patient diet and lifestyle change. The programme was created by Flora pro.activ, in partnership with HEART UK and the Primary Care Cardiovascular Society (PCCS), with additional help from independent healthcare professionals and behavioural change experts.

Its launch is being timed to coincide with with NHS Health Checks being rolled out by PCTs nationally. The NHS Health Check, launched in April 2009, is inviting everyone between the ages of 40-74 who has not already been diagnosed with a cardiovascular condition to have a check and be offered advice to help reduce or manage their risk.

Michael Livingston, Director of HEART UK, said he hoped 'activheart' would act as a "bridge between surgery and everyday life". It aims to "get people, not just healthcare professionals, to understand their own cardiovascular risk and to support them in making positive diet and lifestyle changes to help reduce their risk", he said.

The key motivator of the programme is the 'heart age calculator', a new tool based on the Framingham risk score, which estimates and expresses patients' preventable cardiovascular disease risk factors as their 'heart age', compared to their chronological age. The heart age calculator is not intended to be a substitute for professional medical advice

and, according to Jan Procter-King, PCCS Chairman, the programme is deliberately "not clinicalising" the information so that it is a more accessible, "individual and user friendly" tool for patients.

The 'activheart' programme concentrates on eight core lifestyle and diet activities that patients can readily add to their daily routines over time including quitting smoking, reducing salt intake and alcohol, losing weight, eating the 'right' fats and five portions of fruit and vegetables a day, taking more exercise, and controlling stress. For further information, contact www.floraheartage.com

Lucy Purcell

New meta-analysis questions use of aspirin in primary prevention

The results of a new meta-analysis question current guidelines recommending use of aspirin for the primary prevention of heart disease in all individuals above a certain level of risk.

The meta-analysis, published in *The Lancet* (*Lancet* 2009;**373**:1849-60), was conducted by the Antithrombotic Trialists' (ATT) Collaboration at the Clinical Trial Service Unit, Oxford University.

They explain that for patients who already have vascular disease (secondary prevention), the benefit of long-term aspirin treatment in reducing vascular events has been clearly shown to be much greater than the risk of bleeding, but for primary prevention, the balance of risk and benefit is less clear. This is because the patients are at lower risk of vascular disease and the absolute benefits of aspirin are therefore an order of magnitude lower than in secondary prevention.

The researchers point out that previous meta-analyses of aspirin primary-prevention trials were not based on individual participant data, so they could not reliably compare the benefits and risks of aspirin in certain groups and could not quantify reliably the extent to which people at increased risk of coronary heart disease might also be at increased risk of bleeding.

The current guidelines therefore largely ignore any differences in bleeding risk and recommend that aspirin be used widely for primary prevention in those at moderately raised risk of heart disease, and, as age is a major determinant of the risk of coronary heart disease, in all people above a specific age, they note.

The Oxford team conducted a new meta-analysis of the six trials of aspirin use in primary prevention using individual participant data. Results showed an absolute reduction in serious vascular events of 0.07% per year with aspirin, but the risk of major bleeds was increased by 0.03%.

But most people in these trials were not taking statins which reduce vascular risk without the bleeding risk seen with aspirin. The researchers suggest because statin use has less downside, these drugs should be used first in primary prevention patients, and the main questions for aspirin in primary prevention should be whether it is worthwhile to add it to a statin.

They write: "If the risk of vascular disease is already approximately halved by statins, then the further absolute benefit of adding aspirin could well be only about half as large as was suggested by these primary-prevention trials, but the main bleeding hazards could well remain. In that case, the benefits and hazards of adding long-term aspirin in people without pre-existing disease might be of approximately similar magnitude".

They also say that their analysis suggests that the same factors that determine risk of heart disease also determine the risk of bleeding with aspirin, so that, even for people at moderately increased risk of coronary heart disease, the major absolute benefits and hazards of adding aspirin to a statin-based primary-prevention regimen could still be approximately evenly balanced.

"Drug safety is of particular importance in public-health recommendations for large, apparently disease-free populations; there should be good evidence that benefits exceed risks by an appropriate margin. Hence, although the currently available trial results could well help inform personally appropriate judgments by individuals about their own use of long-term aspirin, they do not seem to justify general guidelines advocating the routine use of aspirin in all apparently healthy individuals above a moderate level of risk of coronary heart disease," the Oxford researchers conclude.

Everyone over a certain age should take an antihypertensive?

Further support for the idea of giving antihypertensive drugs to everyone over a certain age, regardless of their blood pressure, has come from the largest meta-analysis of randomised trials of blood pressure reduction to date.

The meta-analysis, published in the *British Medical Journal* (*BMJ* 2009;**338**:b1665), was conducted by Drs Malcolm Law, Joan Morris, and Nicholas Wald from the Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine, Queen Mary University of London.

They included 147 trials in the analysis: 108 trials which studied differences in blood pressure between study drug and placebo (or control) and 46 trials comparing different antihypertensive drugs. Seven trials fell into both categories.

Results showed that lowering systolic blood pressure by 10 mmHg or diastolic blood pressure by 5 mmHg using any of the main classes of blood pressure lowering drugs, reduces coronary heart disease (CHD) events (fatal and non-fatal) by about a quarter, stroke by about a third, and heart failure by about a quarter. These reductions occurred regardless of the presence or absence of vascular disease and of blood pressure before treatment, with no increase in non-vascular mortality.

The authors note that with the exception of the special short term effect of beta blockers in acute myocardial infarction, the preventive effect of all classes of blood pressure lowering drugs is the same or similar in people with and without a history of cardiovascular disease, so there is no reason to use these drugs for secondary prevention but not for primary prevention.

They add that reduction in events is also the same in people with and without high blood pressure. "There is benefit in lowering blood pressure in anyone at sufficient cardiovascular risk whatever their blood pressure, so avoiding the need to measure blood pressure routinely," they write.

The researchers comment: "Our results support the view that blood pressure lowering drugs should no longer be regarded as treatment for hypertension in the same way that statins are now no longer regarded as treatment for hypercholesterolaemia. Consideration should be given to replacing current policies that focus on routinely measuring blood pressure with policies that focus on routinely lowering blood pressure".

As cardiovascular risk is known to increase with age, the authors conclude that: "Our results indicate the importance of lowering blood pressure in everyone over a certain age, rather than measuring it in everyone and treating it in some".

Liraglutide: novel drug for type 2 diabetes launched

The first once-daily human glucagon-like peptide 1 (GLP-1) analogue, liraglutide (Victoza®) for the treatment of type 2 diabetes mellitus (T2DM) has been launched in the UK.

Described by the manufacturer, Novo Nordisk as "a revolutionary product", liraglutide works in a unique way - only when glucose levels become too high - to stimulate insulin release and suppress glucagon secretion. A member of the 'incretin' drug family, the drug is administered subcutaneously once-daily in adults with T2DM who do not achieve glycaemic control, in combination with metformin or a sulphonylurea (SA), or a combination of metformin and a sulphonylurea, or metformin and a thiazolidinedione (glitazone).

Incretin-based therapies are a relatively recent innovation. Incretins are produced in the gastrointestinal tract and are secreted in response to a meal. GLP-1 is the most powerful, naturally occurring incretin, which increases insulin secretion in the beta cells of the pancreas. Naturally occurring incretin is limited by its half-life as it is rapidly degraded, whereas liraglutide, an almost identical analogue of human GLP-1 (97% homology), allows for 24-hour effects with once-daily administration.

Liraglutide appears to facilitate normalisation of glucose as well as cause deceleration of gastric emptying, and appetite suppression/ weight loss.

An extensive clinical development programme, LEAD (Liraglutide Effect and Action in Diabetes), involving some 2,500 patients, has shown that the drug substantially lowered fasting and postprandial glucose concentrations, with an overall reduction in glycosylated haemoglobin (HbA1c) of up to 1-2%, and it was associated with weight loss and reduction in systolic blood pressure of about 7 mmHg.

Speaking at the launch meeting, Professor Anthony Barnett (Professor of Medicine and Honorary Consultant Physician, Heart of England NHS Trust, Birmingham) said that liraglutide, works so well, "and ticks so many boxes" that it was "almost too good to be true".

He emphasised the need for early treatment of T2DM to prevent later complications. "Control matters," he said, adding that patients taking liraglutide can be "confident they are controlling their blood sugar, and they may benefit from weight loss". There was the added advantage that, because of its mode of action, there was minimal risk of hypoglycaemia ('hypos') and that, additionally, "the once-daily formula, independent of meals, should improve patient compliance and, in turn, clinical outcomes".

Further clinical trials may determine whether liraglutide will have an effect on diabetes progression and have positive effects in reducing cardiovascular risk, in Professor Barnett's view.

Liraglutide will have a National Institute for Health and Clinical Excellence (NICE) Technology Appraisal next year. Professor Barnett said he thought that it would be "incredibly disappointing" if PCTs were to restrict its use and not have the drug widely prescribed before this time. He hopes the fact that the drug is injectable (via a very fine needle, causing minimal discomfort) will not concern patients. It will be a "big step" to get patients to try it but he believes this will be worthwhile.

Manchester general practitioner, Dr Chris Steele, called for a national screening campaign at the launch meeting, pointing out there are still up to one million people with undiagnosed diabetes in the UK. The condition results in enormous costs, close to £10 million a day, in treating diabetes and its complications.

Dr Steele also said that he believed that the introduction of liraglutide may well "change the lives of many diabetic patients" for the better.