NHSGGC DIABETES GUIDELINE

PostScRxipt
from the
NHSGGC Area Drug & Therapeutics Committee
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The recent guideline is now available on the 'Clinical Info' section of Staffnet and www.ggcformulary.scot.nhs.uk/Guidelines/Complete%20diabetes%20guidelines.pdf It is split into sections for easier reading. Topics covered by this comprehensive guideline include:

- Annual review and referral to diabetic clinic
- Blood glucose monitoring
- Continuous subcutaneous insulin pumps
- Diagnosis of diabetes
- Enteral nutrition and diabetes
- Identification and treatment of complications of diabetes or treatments
- Insulin: conversions and dosage adjustments
- Ramadan and Type 2 diabetes
- Sliding scale glucose/KCL/insulin
- Type 2 management

A number of new agents have been added to the *Formulary* over the last few years so the flow chart of treatment escalation in Type 2 diabetes now looks quite different. The discovery of GLP-1, a gut hormone that stimulates glucose sensitive insulin secretion, has led to two new classes of agent. The GLP-1 analogues, such as exenatide and liraglutide (recently added to the Total *Formulary*), mimic GLP-1 and the 'gliptin' group of agents potentiate endogenous GLP-1 by inhibiting the enzyme that breaks it down.

First line therapy

All patients with newly diagnosed Type 2 diabetes are advised to make significant lifestyle changes, for example increasing physical activity levels and making appropriate dietary adjustments. If adequate glycaemic control (as defined by an HbA1c <6.5%) is not achieved by a three-month trial of these changes, metformin is the recommended first line treatment.

The principal effect of metformin is to suppress hepatic gluconeogenesis, thus reducing fasting plasma glucose. Unlike the sulphonylureas, it does not stimulate insulin secretion, but rather improves insulin-stimulated glucose metabolism in skeletal muscle, adipose tissue and liver 3. When used as monotherapy, metformin produces a typical HbA1c reduction of 1.5-2% and is weight-neutral. The precise molecular target of metformin has yet to be elucidated, although it has been shown to activate AMP-activated protein kinase (AMPK), an important cellular regulator of lipid and glucose metabolism.

The commonest adverse effects experienced on initiating metformin are gastrointestinal, such as nausea, taste disturbance, abdominal discomfort and diarrhoea. These effects are usually short-lived, and can be minimised by careful dose titration and timing metformin doses with, or after, meals. Lactic acidosis occurs rarely in patients taking metformin, with an incidence of 0.05 cases per 1,000 patient-years. Metformin should be avoided in patients with renal or hepatic dysfunction, and in those with a history of alcohol excess or metabolic acidosis (acute or chronic).

Compliance can be improved, firstly by describing potential adverse effects to the patient, with an emphasis on the fact that these are usually transient (ie lasting for a few days). Patients should also be advised to time medication with meals and metformin should be introduced gradually, starting with a 500mg dose to be taken with the main meal of the day. If this is well tolerated, the dose can be escalated quickly, in increments of 500mg a week up to a total of 2g daily in divided doses, ideally 1g twice daily.

Long-acting preparations of metformin (Glucophage SR, currently non-*Formulary*) are no more effective than standard release metformin. Evidence of improved gastric tolerability is weak. The preparation offers once-daily administration, which may improve compliance, but this comes at significantly increased cost (annual cost £111 compared with £25 for 2g daily). The impact across the Health Board would be over £800k for a 50% shift towards the once-daily branded product. Generic metformin remains the formulation of choice with careful counselling to improve patient acceptability.

Second line treatments

There are now three possible choices for second line agent:

Drug class	Possible advantages	Possible disadvantages
Sulphonylurea, eg gliclazide	Cost	• Hypoglycaemia • Weight gain
Thiazolidinedione, eg pioglitazone	• Positive cardiovascular outcome with pioglitazone • Useful treatment for patients with fatty liver and non-alcoholic steatohepatitis	• Cost (but generic pioglitazone available January 2011) • Weight gain • Fluid retention and increased risk of cardiac failure • Increased risk of fracture in post-menopausal women
'Gliptin', eg sitagliptin	• Hypoglycaemia unlikely • Weight neutral	• Cost • No long term outcome data

Sub-optimal control on dual agent therapy can now be managed by adding a third oral agent or an injectable agent

contd on page 4

Website
http://www.ggcformulary.scot.nhs.uk

Alphabetical list of most recent ADTC decisions
For full details of SMC advice, visit **www.scottishmedicines.org**

Drug	Indication under consideration (There may be other licensed indications)	NHSGGC decision	
Aliskiren (Rasilez®)	Treatment of essential hypertension.	Non-*Formulary*	x
Budesonide nasal spray (ADTC Appeal)	Allergic and perennial rhinitis.	Total *Formulary* Reserved for use in patients in whom beclometasone and mometasone has been ineffective or not tolerated.	✓
Calcium acetate capsules (PhosLo®)	Prevention/treatment of hyperphosphataemia in patients with advanced renal failure on dialysis.	(S) *Formulary* Preferred List Acknowledge new presentation.	✓R
Darunavir (Prezista®)	Co-administered with low dose ritonavir in combination with other antiretroviral medicinal products, for the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated children and adolescents, from the age of 6 years and at least 20kg body weight, who have failed on more than one regimen containing a protease inhibitor (PI).	(S) Total *Formulary* Restricted to use by HIV specialists.	✓R
Epoetin alfa (Binocrit®)	Treatment of symptomatic anaemia associated with chronic renal failure in adult and paediatric patients.	(S) Total *Formulary* Acknowledge new biosimilar.	✓R
Eslicarbazepine acetate (Zebinix®)	Adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation.	Non-*Formulary*	x
Esomeprazole IV (Nexium IV®)	Prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.	Non-*Formulary*	x
Fortisip® Compact	Nutritional supplementation.	*Formulary* Preferred List Acknowledge new formulation.	✓
Mometasone nasal spray (Nasonex®) (ADTC Appeal)	Allergic and perennial rhinitis.	*Formulary* Preferred List Reserved for use in patients in whom beclometasone has been ineffective or not tolerated.	✓
Pegfilgrastim (Neulasta®) (ADTC Appeal)	Reducing the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy.	(S) Total *Formulary* Restricted to use in accordance with regional protocol in patients who would otherwise receive 5 days or more of filgrastim or lenograstim.	✓R
Sildenafil citrate (Revatio®)	Pulmonary arterial hypertension (PAH) classified as WHO functional class II.	(S) Total *Formulary* Acknowledge new indication. Restricted to initiation by specialists working in the Scottish Pulmonary Vascular Unit or similar specialists.	✓R
Somatropin (Omnitrope®)	Growth disturbance in infants, children and adolescents and growth hormone deficiency in adults.	(S) Total *Formulary* Acknowledge new biosimilar. Use in adults is restricted to initiation by consultant endocrinologists. Use in children is restricted to initiation and monitoring by a paediatrician with expertise in managing childhood growth disorders and growth hormone therapy.	✓R
Tipranavir (Aptivus®)	In combination with low-dose ritonavir for the treatment of HIV-1 infection in highly pre-treated children and adolescents with virus resistant to multiple protease inhibitors.	(S) Total *Formulary* Acknowledge new indication. Restricted to use by HIV specialists.	✓R
Tocilizumab (RoActemra®)	Moderate to severe active rheumatoid arthritis in adults.	(S) Total *Formulary* Restricted to use in combination with methotrexate in accordance with the British Society of Rheumatology guidelines. Use as monotherapy remains non-*Formulary*.	✓R

For NICE advice, visit **www.nice.org.uk** For previous ADTC decisions, visit **www.ggcformulary.scot.nhs.uk**

Drug	Indication under consideration (There may be other licensed indications)	NHSGGC decision	
Tolvaptan (Samsca®)	Treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH).	Non-*Formulary*	x
Trospium chloride (Flotros®)	Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder, eg idiopathic or neurologic detrusor overactivity.	Total *Formulary* Acknowledge new preparation.	✓
Ulipristal acetate tablet (EllaOne®)	Emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.	Total *Formulary* Restricted to use by GPs and sexual health services only in women presenting between 72-120 hours after unprotected intercourse for whom the insertion of an IUD is not acceptable. Levonorgestrel remains the oral treatment of choice for women presenting up to 72 hours after unprotected intercourse.	✓R

✓ =*Formulary* ✓R =*Formulary* (restricted) x =non-*Formulary* ? = awaiting final decision (S) =specialist initiation only (S) =specialist use only

New emergency hormonal contraception

Ulipristal (EllaOne®), a new emergency hormonal contraceptive (EHC), has been added to the Total *Formulary* restricted to use 72-120 hours post unprotected intercourse where the insertion of an IUD is not acceptable. It is also restricted to use by GPs and sexual health services only.

EHC is currently available as levonorgestrel (Levonelle® 1500), which is licensed for use up to 72 hours after intercourse. In NHSGGC, this is available from all sexual health clinics, by prescription from GP practices, in A&E departments and under PGD from most community pharmacies. Over 16s can also purchase it commercially from pharmacies.

Levonorgestrel is more effective the sooner after intercourse that it is taken. There is some evidence of efficacy up to 120 hours after intercourse, and there has been some off license use in the period between 72 and 120 hours.

The fitting of an emergency intra-uterine device (IUD) is the most effective method of emergency contraception and can be offered up to 120 hours after intercourse, or up to 5 days after the predicted day of ovulation. The IUD can then be retained as an ongoing method of long-lasting contraception. Standard practice in sexual health clinics is to offer an emergency IUD to all women presenting for emergency contraception. Currently few women take this option.

Ulipristal is a synthetic progesterone receptor modulator which inhibits or delays ovulation. It represents a new treatment option for women presenting up to 120 hours after intercourse. It has been shown to be as effective as levonorgestrel in individual studies and more effective when studies are pooled. However, the cost for ulipristal is three times that of levonorgestrel.

Emergency contraception options
1 **IUD** (up to 120 hours after intercourse, or up to 5 days after the predicted day of ovulation)
2 If declined:
2.1 **Levonorgestrel** (up to 72 hours after unprotected intercourse) **OR**
2.2 **Ulipristal** (72-120 hours post-unprotected intercourse; restricted to prescribing by GPs and sexual health services)

Thalidomide added to Total *Formulary*

Thalidomide is now available as a licensed product and has been accepted by SMC for use in combination with melphalan and prednisone, as first line treatment of patients with untreated multiple myeloma, aged 65 years or over or ineligible for high dose chemotherapy. It has been added to the Total *Formulary*, restricted to use in accordance with the regional protocol. It was previously used in NHSGGC as an unlicensed product on a named-patient basis.

Multiple myeloma is a haematological cancer in which immature malignant plasma cells (myeloma cells) accumulate in, and eventually destroy, the bone marrow. The pathological effect of this accumulation is an increasingly dysfunctional bone marrow, causing cytopenias, which leads to bacterial infections and anaemia, and osteolytic lesions.

Thalidomide is anti-angiogenic with immunomodulatory and anti-inflammatory activity; its mechanism of action has not been fully elucidated. In the pivotal trial in patients aged 65 to 75 years, at 51.5 months median follow-up, the addition of thalidomide to melphalan and prednisone gave an overall survival advantage of 18.4 months.

Thalidomide is a powerful human teratogen, inducing a high frequency of severe and life-threatening birth defects. The results of prescribing thalidomide in the 1960s led to the development of regulation schemes for medicines in the UK and other countries across the world. The strict conditions of the Thalidomide Pregnancy Prevention Programme must now be fulfilled for all male and female patients before prescribing and dispensing occur.

Updated stroke guidelines for Scotland

In December 2008 the Scottish Intercollegiate Guidelines Network (SIGN) released its updated guidance on the management of patients with stroke or transient ischaemic attack (TIA). The guideline is comprehensive, covering the existing evidence base for assessment, investigation, immediate management and secondary prevention. The broad scope and the wealth of new data assessed make this a significant publication for all those involved in the care of patients with stroke.

Several key challenges in stroke management have been targeted. Perhaps the greatest of these is the provision of acute thrombolytic therapy, which is the only treatment proven to reduce disability after stroke. A smaller proportion of UK stroke patients receive this treatment in comparison with many other European countries and the crucial importance of configuration of clinical services to deliver acute care is recognised.

The guideline now recommends that suitable patients should be treated with intravenous thrombolysis within four and a half hours of definite onset of symptoms of ischaemic stroke. Although this is an extension of the time window for allowing treatment, the therapy should be given as close to the onset of symptoms as possible. SIGN recommend that systems are optimised to allow earliest possible administration within the defined time window.

Since the previous guideline in 1997, a number of large secondary preventative trials have reported and these data have informed the new guideline. Clear and strongly evidence-based recommendations with regard to antiplatelet treatment, lipid and blood pressure lowering therapy and carotid surgery have been added.

• Aspirin 75mg daily and dipyridamole 200mg MR twice daily should be prescribed after ischaemic stroke or TIA.
• A statin should be prescribed to patients who have had an ischaemic stroke, irrespective of cholesterol levels.
• Atorvastatin 80mg should be considered for patients with TIA or ischaemic stroke.
• Other statins (such as simvastatin 40mg) may also be considered as they reduce the risk of major vascular events.
• Patients in atrial fibrillation after ischaemic stroke or TIA should be offered warfarin.
• All patients with previous stroke or TIA should be considered for treatment with an ACE inhibitor and a thiazide regardless of blood pressure.
• Patients who have suffered intra-cranial haemorrhage require different treatment.

It has been estimated that broad adoption of the guideline across Scotland should increase provision of acute treatment with thrombolysis (by an estimated 20 patients a week) and of carotid endarterectomy (by 12 patients a week). Approximately 400 patients a year in Scotland should enjoy an improved outcome due to acute treatment and 217 recurrent strokes should be prevented by timely carotid surgery.

NHSGGC Diabetes Guidelines *contd from page 1*

according to patient preference. The GLP-1 analogues are a credible alternative injectable agent. They prevent weight gain and may promote weight loss. This is a great advantage over insulin which usually causes weight gain. However, no long term outcome data are available for the GLP-1 analogues.

The guideline provides clear advice on choosing an additional agent according to characteristics of the patient and the classes of drug available. The process of reviewing the glycaemic pathway for Type 2 diabetes will begin after the new SIGN Diabetes Guideline is launched.

Have you sent a Yellow Card recently?

The MHRA has identified a problem with the Yellow Card postal delivery service. Some Yellow Cards have been returned to the sender due to an error at Royal Mail. The issue with Royal Mail has now been rectified and online reporting through www.yellowcard.gov.uk is unaffected.

Anyone who has posted a Yellow Card report and has either had it returned or not received an acknowledgement should resend the report.

The Yellow Card Scheme is vital in helping the MHRA monitor the safety of the medicines that are on the UK market. They are an important source of information on side effects. Warnings were added to the product information for varenicline after Yellow Cards were received reporting suicidal ideation. Yellow Cards of adverse drug reactions to the former obesity drug rimonabant contributed to this drug being withdrawn - new evidence meant the risks were considered to outweigh any benefits.

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