NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 2; Number 14 **September 2008**

NICE CLINICAL GUIDELINE 66: *TYPE 2 DIABETES – THE MANAGEMENT OF TYPE 2 DIABETES* (MAY 2008)

The purpose of this special edition of the *PACE Bulletin* is to summarize the key points of the recent NICE Clinical Guideline on the management of type 2 diabetes and to re-emphasize important aspects of treatment selection and patient safety that have emerged from recent local and national guidance on the subject.

Blood-glucose-lowering therapy

Step One: Metformin

If $HbA_{1C} \geq 6.5\%$ after a trial of lifestyle interventions - initiate **metformin**.

- Metformin should be titrated up over several weeks to minimise gastrointestinal intolerance.

PACEF Recommendation: Metformin
The most common side effects associated with metformin are gastrointestinal (e.g. nausea, vomiting, diarrhoea); they are often transient and can be minimised by taking the drug with meals and slowly titrating the dose up over several weeks. Approximately 5% of patients will be forced to discontinue therapy as a result of gastrointestinal intolerance. Standard *BNF* advice is to initiate on 500mg with breakfast for at least a week, increasing to 500mg with breakfast and evening meal for at least another week and then increasing to 500mg with breakfast, lunch and evening meal. The usual maximum dose is 2g daily in divided doses.

- If gastrointestinal intolerance remains a problem despite careful dose titration, consider modified release metformin (Glucophage SR).

PACEF Recommendation: Metformin
The United Kingdom Prospective Diabetes Study (UKPDS) established metformin as the first line drug of choice for the treatment type 2 diabetes. In the study, metformin was shown to reduce the rates of myocardial infarction, diabetes related death and all-cause mortality. Judicious use of modified release metformin in those experiencing gastric intolerance to standard release metformin can help to maximise the number of patients able to benefit. Modified release metformin (Glucophage SR) is a once daily formulation available in identically priced 500mg and 750mg strengths. Where a daily dose of 1500mg is indicated, the 750mg strength should be prescribed both to reduce the patient's tablet burden and to reduce the cost of treatment.

- Review the metformin dose if serum creatinine >130umol/litre or estimated GFR is <45ml/min/1.73m^2.
- Stop the metformin if serum creatinine > 150umol/litre or eGFR < 30ml/min/1.73m^2.
- Prescribe metformin with caution for those at risk of sudden deterioration in kidney function and those at risk of eGFR falling to <45ml/min/1.73m^2.
- Consider a sulfonylurea first line if the person is not overweight or if metformin is not tolerated or contra-indicated or if a rapid therapeutic response is required because of hyperglycaemic symptoms.

Step Two: Metformin and Sulfonylureas

If HbA_{1c} remains ≥ 6.5% - use **metformin** and **sulfonylurea** combination therapy.

Sulfonylureas

- Agents with a low acquisition cost should be prescribed (eg gliclazide, glipizide).
- Once-daily sulfonylureas are preferred, particularly where concordance is a problem.
- Long-acting sulfonylureas like chlorpropamide and glibenclamide are no longer recommended due to the increased risk of hypoglycaemia.

PACEF Recommendation: Sulfonylureas
The once daily sulfonylurea of lowest acquisition cost is generic gliclazide (with generic glipizide as an alternative). Branded prescribing of any of these agents or use of Diamicron MR is not recommended.

- People should be educated about the risk of hypoglycaemia with sulfonylureas (particularly people with renal impairment).
- If hypoglycaemia is a problem with sulfonylureas, consider substituting a glitazone for the sulfonylurea
- If metformin is not tolerated at Step Two, consider substituting a glitazone for metformin.
- Rapid-acting insulin secretagogues, such as nateglinide and repaglinide, can also be considered at Step Two.

Step Three:

If HbA_{1C} remains ≥ 7.5%

- Consider adding a glitazone or insulin.
- Consider adding a glitazone if human insulin is likely to be unacceptable or ineffective (e.g. due to employment, social, recreational or other personal issues or obesity/metabolic syndrome).

Glitazones

- If prescribing a glitazone, warn about significant oedema and tell the person what to do if this happens.
- Do not start or continue a glitazone if the person has evidence of heart failure or is at higher risk of fracture.

- When selecting a glitazone, take into account the most up-to-date advice from regulatory authorities, cost and safety issues.

PACEF Recommendations: Glitazones

Prescribers are reminded that glitazones are advocated by NICE as third line agents in the treatment of type 2 diabetes. They should only be utilized in patients unable to tolerate metformin and sulfonylurea combination therapy or in those for whom either metformin or a sulfonylurea are contra-indicated or inappropriate.

Where a glitazone is indicated, pioglitazone should be initiated. Local diabetologist advice is that rosiglitazone should no longer be initiated due to rising concerns over cardiovascular safety.

All patients currently taking rosiglitazone and pioglitazone should be reviewed to ensure that they are fully aware of the cardiovascular safety risks and that these risks are minimized. Both pioglitazone and rosiglitazone are contra-indicated in patients with cardiac failure or a history of cardiac failure.

The European Medicines Agency (EMEA) has recommended that, in patients with ischaemic heart disease, rosiglitazone should only be used after careful evaluation of each patient's individual risk.

Fluid retention is well documented with glitazones and may exacerbate or precipitate heart failure, particularly in patients at risk (e.g. those with a prior MI or symptomatic coronary artery disease, the elderly, those with mild to moderate renal failure, those on concurrent NSAID or insulin therapy). Patients should be monitored closely during treatment for signs and symptoms of fluid retention, including weight gain or oedema. Treatment should be stopped if any deterioration in cardiac status occurs. People who are at particular risk of heart failure should start rosiglitazone or pioglitazone at the lowest available dose; any dose increases should be done gradually.

The increased fracture risk with both of the glitazones necessitates the need for caution in those at risk.

Exenatide (Byetta)

- Exenatide may be considered as an option at Step Three only if the person:
    - has a BMI >35kg/m^2 **and**
    - has specific psychological, biochemical or physical problems arising from high body weight **and**
    - has inadequate blood glucose control ($HbA_{1c} \geq 7.5\%$) with conventional oral agents after a trial of metformin and sulfonylurea **and**
    - would otherwise be starting other high cost medication, such as a glitazone or insulin.
- Treatment should be continued only if a beneficial response occurs and is maintained. This is defined as at least a 1.0 percentage point reduction in HbA_{1c} in 6 months and weight loss in excess of 5% at 1 year.

PACEF Recommendations: Exenatide

Prescribers are reminded that exenatide (Byetta) is classified as GREEN. Treatment should primarily be initiated by a diabetologist or a GP with a Specialist Interest in diabetes (GPSI), although the GREEN status allows for broader GP initiation. Exenatide initiation should only be considered at Step Three within the context of the NICE initiation criteria as detailed above. Ongoing treatment should be reviewed and discontinued if the person is not

deemed to be responding sufficiently as defined by the NICE review criteria detailed above.
Prescribers are also reminded of the risk of acute pancreatitis with exenatide. This has resulted in the MHRA issuing the following advice to healthcare professionals:
(1) Patients should be informed of the characteristic symptoms of acute pancreatitis (e.g. persistent severe abdominal pain; back pain may also be present).
(2) If pancreatitis is suspected, exenatide and other potentially suspect medicines should be discontinued.
(3) As with all new medicines, the safety of exenatide remains under close review and all suspected adverse reactions should be reported using the yellow card scheme.

Acarbose (Glucobay)

- Acarbose can be considered at Step Three if a person is unable to use other oral glucose-lowering drugs.

PACEF Recommendations: Gliptins
Prescribers are reminded that NICE excluded gliptins from this Clinical Guideline due to late licensing and the limited evidence base. Both sitagliptin (Januvia) and vildagliptin (Galvus) have been reviewed by PACEF and have been designated as RED-RED due to the variable quality of the trial data and the lack of long term safety and outcome data. Gliptins will be subject to ongoing review by PACEF as further evidence emerges.

Step Four:

If HbA_{1C} remains $\geq$ 7.5%, consider insulin plus metformin plus a sulfonylurea.

Insulin therapy

- Preferably, insulin therapy should be commenced with human NPH taken at bedtime or twice daily according to need. NPH insulin is also known as isophane insulin; brands of human isophane insulin include Insulatard, Humulin I and Insuman Basal.
- Consider a once daily long-acting insulin analogue (i.e. insulin glargine) if:
    - the person requires help with administration of insulin injections.
    - his/her lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes.
    - twice-daily basal insulin injections plus oral glucose-lowering medications would otherwise be needed.
    - NPH insulin causes significant nocturnal hypoglycaemia.
- Consider twice daily biphasic human insulin (pre-mixed) regimens, particularly where HbA_{1C} > 9.0%. A once daily regimen may be an option when starting therapy. Examples of biphasic human insulin pre-mixed include: Mixtard 30, Humulin M3 and Insuman Comb 15, 25 and 50.
- Consider pre-mixed insulin analogue preparations rather than pre-mixed human insulin preparations when: immediate injection before a meal is preferred or; hypoglycaemia is a problem or; there are marked postprandial blood glucose excursions. Insulin aspart (NovoMix 30) and insulin lispro (Humalog Mix 25 and 50) are available in biphasic formulations.

- If hypoglycaemia occurs with an insulin plus sulfonylurea combination, review the sulfonylurea.

Step Five:

If HbA1C remains ≥ 7.5%, increase insulin dose and intensify regimen over time.

- Consider pioglitazone plus insulin if a glitazone has been effective previously or high-dose insulin is providing inadequate control.

PACEF Recommendation: Glitazones and Insulin
The incidence of heart failure is increased when either rosiglitazone or pioglitazone is combined with insulin. Clinical trials have recorded an increased risk of cardiac ischaemia for rosiglitazone combined with insulin. This combination should only be used in exceptional circumstances and under close supervision.

Blood pressure management

Targets and Monitoring

- The recommended BP target in a person with type 2 diabetes mellitus should be < 140/80mmHg; if there is kidney, eye or cerebrovascular damage the target should be < 130/80mmHg.
- If BP reaches and consistently remains at target, monitoring should be every 4 to 6 months.
- If the person is not hypertensive or suffering from renal disease, BP should be measured annually.
- If BP is checked and found to be above 150/90, repeat within one month.
- If BP is checked and found to be above 140/80 or 130/80 in patients with kidney, eye or cerebrovascular damage, repeat within 2 months.
- If BP remains above target, move to Step One.

PACEF Recommendation:
Diabetes DM Indicator 12 in the GMS Contract Quality and Outcomes Framework records the percentage of patients with diabetes in whom the last BP measured is 145/85 or less. Aggressive management of hypertension in diabetes is now well established as a means to reduce the risk of macrovascular and microvascular disease. The QOF makes plain that 145/85 is a minimum audit standard and that 140/80 is the standard target (as endorsed by NICE).

Step One: Advice on lifestyle changes

- Among the lifestyle changes advocated are: increasing physical activity, general advice on healthy eating, encouragement to lose weight where the person is overweight, advice on alcohol consumption and smoking cessation where relevant.
- If BP remains above target despite lifestyle change, move to Step Two.

Step Two: ACE Inhibitor (ACEI)

- ACE inhibitors are recommended as standard first line drug treatment. If the patient is intolerant to an ACEI, change to an Angiotensin 2 Receptor Blocker (A2RB).

PACEF Recommendation:
Where an ACEI is indicated, low cost generically available ACEIs such as ramipril capsules (tablets are more expensive) and lisinopril tablets are recommended. Angiotensin 2 Receptor Blockers should only be considered where the patient has proven intolerance to at least one ACEI.

- For people of African-Caribbean descent, an ACEI plus either a diuretic or a calcium channel blocker (CCB) is indicated.
- If there is a risk of pregnancy, a CCB is preferred as first line drug treatment.
- If BP remains above target despite lifestyle change and Step Two drug treatment move to Step Three.

Step Three: Calcium Channel Blocker (CCB) or Diuretic

- Add either a CCB or diuretic (usually bendroflumethiazide 2.5mg daily).

PACEF Recommendation:
Where a CCB is indicated, generic amlodipine tablets are recommended.

Step Four: Add another drug

- If BP remains above target despite lifestyle change and drug treatment with an ACEI (or A2RB if intolerant) plus either a diuretic or a CCB, add in a third drug (either a diuretic or a CCB dependent upon what has already been selected).
- If BP still remains above target consider the addition of an alpha blocker, beta blocker or potassium sparing diuretic. Exercise caution with the potassium sparing diuretic if the person is already taking and ACEI or A2RB.

The management of blood lipids in type 2 Diabetes Mellitus

- NICE recommend that cardiovascular (CV) risk status should be reviewed annually. Such an assessment should involve an assessment of risk factors (e.g. features of metabolic syndrome and waist circumference), note changes in personal or family history and include a full lipid profile including HDL-C and triglycerides (TG).
- All patients with type 2 DM should be considered at high CV risk except those to which **all** of the following apply:
    - (1) they are not overweight or hypertensive;
    - (2) they have no microalbuminuria;
    - (3) they are a non-smoker;
    - (4) they have no high-risk lipid profile;
    - (4) they have no history of CV disease and
    - (5) they have no family history of CVD.
- If the patient emerges from this assessment as not at high CV risk, their risk should be reviewed annually using the UKPDS risk engine. If the UKPDS risk engine estimates their CV risk as greater than 20% in 10 years utilize simvastatin 40mg or a statin of similar efficacy and cost (pravastatin) first line.
- For patients less than 40 with a poor CV risk factor profile, consider a statin. Simvastatin 40mg or a statin of similar efficacy and cost (pravastatin) is advocated first line

- For patients over 40 with a normal to high CV risk for someone with type 2 DM utilize simvastatin 40mg or a statin of similar efficacy and cost (pravastatin) first line.
- Targets of 4mmol/l (TC) and 2mmol/l (LDL-C are advocated with simvastatin 80mg endorsed second line.

PACEF Recommendations:
Prescribers are reminded of standard advice on Lipid Modification that appeared in *PACE Bulletin* Vol 2, No 11 (July 2008):
Statin treatment should be initiated with simvastatin 40mg. If there are potential drug interactions, or simvastatin 40mg is contraindicated, an alternative low-cost preparation such as pravastatin should be chosen. If simvastatin 40mg is not tolerated, a lower dose or pravastatin should be chosen.
Targets of 4mmol/litre (TC) and 2mmol/litre (LDL-C) have been endorsed by NICE as an aspiration, but achievement is not an absolute necessity.
If the patient does not reach target on simvastatin 40mg, increase the dose to 80mg. If the patient does not reach the 4mmol/l and 2mmol/l targets on simvastatin 80mg (over half of patients will not), reduce aspiration to the minimum audit standard and QOF target of 5mmol/l (TC).
Maintain the patient on the dose of simvastatin that has either reached the 4 and 2mmol/l targets or the minimum audit standard of 5mmol/l (TC). Only consider higher-cost, higher-potency agents in those patients that remain above the minimum audit standard of 5mmol/l (TC) despite taking simvastatin 80mg or who are intolerant to simvastatin and pravastatin or have contra-indications or potential interactions.
Remember that high-cost high-potency statins like atorvastatin and rosuvastatin are effective, but have emerged from NICE cost-effectiveness evaluations as not cost-effective in most patients. As a result of this, their use should be restricted to the exceptional circumstances outlined above.

- More intensive statin therapy or the addition of ezetimibe is advocated if there is existing or newly diagnosed CV disease or increased albumin excretion rate. HDL-C should not exceed 1.4mmol/l.
- Nicotinic acid preparations are not advocated routinely. They may have a role in those intolerant of other therapies with more extreme disorders of blood metabolism.
- Omega 3 fish oils are not recommended for primary prevention of CVD.
- If the patient has a high serum TG assess possible secondary causes (e.g. poor glycaemic control). If TG remains above 4.5mmol/l despite optimised glycaemic control, offer a fibrate. If lifestyle measures and fibrate therapy prove ineffective consider a trial of highly concentrated licensed omega-3 fish oils (i.e. Omacor).

PACEF Recommendations:
Prescribers are reminded that Omacor has been reviewed by PACEF and is classified as RED-RED both for hypertriglyceridaemia and for secondary prevention after myocardial infarction.

Anti-thrombotic therapy

- If the patient is 50+ and has a BP <145/90mmHg low dose aspirin 75mg is advocated (or clopidogrel if there is clear aspirin intolerance).

- If the patient is < 50 and has significant other CV risk factors, low dose aspirin 75mg is advocated (or clopidogrel if there is clear aspirin intolerance).

PACEF Recommendations:
Prescribers are reminded that the use of clopidogrel should be restricted primarily to those with hypersensitivity to aspirin.

Stephen Gibson
Head of Prescribing and Medicines Management
Lincolnshire PCT

September 2008