Implementing key therapeutic topics: 3
Type 2 diabetes

The QIPP medicines use and procurement workstream aims to ensure that value for money is further enhanced while quality of care is maintained or improved by optimising the use of medicines. This bulletin is the last in a series of three that focus on several of the key prescribing topics outlined in the current version of the NPC document, Key therapeutic topics — Medicines management options for local implementation.

These bulletins summarise the evidence-base for the therapeutic topics reviewed, and contrast this with the prescribing data available for these topics. They aim to provide a focus for prescribers and prescribing managers on the 'implementation gaps' there may be in some localities between this evidence-base and prescribing, highlighting potential areas for local action.

Topics included in this bulletin are the QIPP topics relating to type 2 diabetes:
- Hypoglycaemic agents in patients with type 2 diabetes
- Long-acting insulin analogues in patients with type 2 diabetes
- Self-monitoring of blood glucose in patients with type 2 diabetes.

Topics included in the first bulletin in this series were non-steroidal anti-inflammatory drugs; antibiotic prescribing; and high dose inhaled corticosteroids in asthma. Topics included in the second bulletin were antipsychotics in dementia; statins and ezetimibe; and hypnotics.

Two earlier bulletins have discussed how people make decisions and how decision-making might be done better (MeReC Bulletin 22:1), and how the adoption of evidence into practice can be supported (MeReC Bulletin 22:2).

Useful resources
- Department of Health. Quality, Innovation, Productivity and Prevention (QIPP) webpage
- NHS Business Services Authority. QIPP prescribing comparators webpage
- NHS Business Services Authority. QIPP charts and data webpage
- NHS Business Services Authority. Prescribing Dispensing and Financial Management (with Prescribing Toolkit)
- NHS Business services Authority. ePACT.net
- National Prescribing Centre. Key therapeutic topics — medicines management options for local implementation
- NHS Evidence. QIPP collection webpage

All information was correct at the time of publication (March 2012)
Type 2 diabetes

What is optimal blood glucose control?

- The management of patients with type 2 diabetes is complex, requiring an individualised multifactorial approach. Controlling blood glucose requires a careful balance. There are no arguments in favour of poor glucose control. However, achieving good blood glucose control, while addressing blood pressure, blood lipids, and lifestyle issues (smoking cessation, exercise, losing weight, healthy diet etc.) seems likely to prevent more complications, than a narrower approach focused on intensive blood glucose control.

- NICE guidance on type 2 diabetes recommends that patients should be involved in setting their individualised HbA1c target level, which may be above the general target of 48 mmol/mol (6.5%). Any reduction in HbA1c towards the agreed target level is advantageous to future health, but pursuing highly intensive management to HbA1c levels below 48 mmol/mol (6.5%) should be avoided.

- A NICE quality standard states that people with diabetes should agree with their healthcare professional a documented, personalised HbA1c target, usually between 48 mmol/mol and 58 mmol/mol (6.5% and 7.5%). They should also receive an ongoing review of treatment to minimise hypoglycaemia.

- The Quality and Outcomes Framework (QOF) allocates points for achieving three levels of glucose control in patients with type 2 diabetes — HbA1c of 59 mmol/mol (7.5%) or less, 64 mmol/mol (8%) or less, and 75 mmol/mol (9%) or less.

- If appropriate and achievable in an individual, reducing blood glucose to HbA1c levels of around 59 mmol/mol (7.5%) would seem optimal based on current evidence. Lower levels may be appropriate in individuals with early disease, or if these levels can be achieved reasonably easily with diet or metformin alone.

- Metformin, a sulfonylurea and human NPH (isophane) insulin are the preferred hypoglycaemic drugs recommended by NICE.

- A retrospective cohort study looked at mortality risk among patients with type 2 diabetes receiving combination oral therapy or insulin to control their blood glucose. It found a U-shaped curve, with the risk of all-cause mortality lowest at an HbA1c level of about 59 mmol/mol (7.5%). An increase in HbA1c above this level was associated with a greater risk of mortality, but importantly, so was a decrease below this level.

- Trial evidence in this area (including the CONTROL meta-analysis of the four key randomised controlled trials [RCTs]) suggests a small absolute benefit of intensive compared with conventional blood glucose control in people with type 2 diabetes. Intensive control reduces coronary heart disease (CHD), but not stroke, death from cardiovascular (CV) disease or death from all causes. However, this needs to be balanced against the significantly increased risk of severe hypoglycaemia with intensive blood glucose control.

- Intensive control to reduce HbA1c by an additional 0.9 percentage points over conventional control significantly reduced the risk of CHD, by approximately six fewer CHD events per 1,000 patients over 4.4 years.

- Intensive blood glucose control increased the risk of severe hypoglycaemia (requiring the assistance of a third party), by approximately 42 extra events per 1000 patients over 4.4 years.

- Other meta-analyses have made similar findings in relation to macrovascular outcomes and hypoglycaemia.

- There appears to be a reduction in certain microvascular events with intensive blood glucose control, although results of meta-analyses are inconsistent, and some endpoints were disease-oriented outcomes, such as microalbuminuria, rather than patient-oriented outcomes, such as advanced renal complications.

- The ADDITION-Europe study looked at the effect of early intensive multifactorial management (of HbA1c, blood pressure, cholesterol, and prescription of aspirin) on five-year CV outcomes in people with type 2 diabetes that had been detected by screening. While some small reductions in disease-oriented outcomes (HbA1c, blood pressure, total and LDL-cholesterol) were seen with intensive management compared with usual care, no statistically significant differences were found in any patient-oriented CV outcomes.

What are the preferred hypoglycaemic drugs?

- Metformin, a sulfonylurea and human NPH (isophane) insulin e.g. Insulatard™, Humulin I® or Insuman® Basal (not a long-acting insulin analogue, see below) are the preferred hypoglycaemic drugs recommended by NICE (see Figure 1 and Table 1).

- RCTs have shown these interventions help patients live longer or healthier lives.

- Newer hypoglycaemic drugs, such as pioglitazone, sitagliptin, vildagliptin, saxagliptin, exenatide or lixisludtide may have a role in some individuals, but usually as third-line options (see Figure 1 and Table 1).

- The long-term safety of these newer drugs is not known and robust evidence that they help patients live longer or healthier lives is not available at the current time.
This summary is intended only as a guide to drug treatment for blood glucose control. It is not a comprehensive guide to all aspects of care. See NICE Clinical Guideline 87, May 2009; NICE Technology Appraisal 203, October 2010; and NICE Technology Appraisal 248, February 2012; and/or the NICE pathway on managing type 2 diabetes.

**Figure 1. Summary of NICE recommended treatment options for blood glucose lowering in type 2 diabetes**

- **First-line**
  - Metformin

- **Second-line**
  - Metformin plus sulfonylurea

- **Third-line alternatives (see Table 1 for details)**
  - Consider only if insulin is unacceptable or inappropriate:
    - Metformin + sulfonylurea + pioglitazone
    - Metformin + sulfonylurea + sitagliptin
  - Consider only if specific BMI criteria are met:
    - Metformin + sulfonylurea + exenatide
    - Metformin + sulfonylurea or pioglitazone + liraglutide 1.2mg
    - Metformin + sulfonylurea or pioglitazone + prolonged-release exenatide

- **Alternatives to metformin + sulfonylurea as second line (dual therapy)**
  - Consider only if either metformin or a sulfonylurea is contraindicated or not tolerated, or there is a significant risk of hypoglycaemia with a sulfonylurea:
    - Metformin or sulfonylurea + pioglitazone
    - Metformin or sulfonylurea + sitagliptin or vildagliptin
  - Consider only if either metformin or a sulfonylurea is contraindicated or not tolerated, and also both pioglitazone and a gliptin are contraindicated or not tolerated:
    - Metformin or sulfonylurea + liraglutide 1.2mg
    - Metformin or sulfonylurea + prolonged-release exenatide

- **Alternative to metformin as first line (monotherapy)**
  - Consider only if the patient is not overweight, or metformin is contraindicated or not tolerated, or a rapid response is needed to control hyperglycaemic symptoms
    - Sulfonylurea

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*a Or other higher agreed level.
*b Long-acting insulin analogues (insulin detemir or insulin glargine) are alternatives to NPH (isophane) insulin only in specific circumstances – see Table 1.
*c Saxagliptin was not included in NICE clinical guideline 87.
Second-line therapy

- Only consider if HbA1c remains **above 48 mmol/mol (6.5%) or other higher agreed level.**
- Pioglitazone, sitagliptin and vildagliptin should be continued only if the person has a beneficial metabolic response (a reduction in HbA1c of at least 5.5 mmol/mol [0.5 percentage points] at six months).
- Liraglutide 1.2mg and prolonged-release exenatide should be continued only if stricter conditions are achieved (a reduction in HbA1c of at least 11 mmol/mol [one percentage point] at six months).

Third-line therapy

- Only consider if HbA1c remains **above 59 mmol/mol (7.5%) or other higher agreed level.**
- Sitagliptin or pioglitazone are an option provided the person has a beneficial metabolic response (see above).
- Liraglutide, exenatide or prolonged-release exenatide should be considered only if BMI ≥35 kg/m² and insulin is unacceptable because of occupational implications or weight loss would benefit comorbidities.
- Liraglutide, exenatide or prolonged-release exenatide should be continued only if stricter metabolic conditions are achieved (a reduction of at least 11 mmol/mol [one percentage point] in HbA1c and a weight loss of at least 3% of initial body weight at six months).
- Long-acting insulin analogues may be considered as an alternative to human NPH (isophane) insulin if the patient needs assistance from a carer or health professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily, or the patient's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, or the patient would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs, or the patient cannot use the device to inject NPH insulin.

### Improvements in disease-oriented outcomes

- Improvements in disease-oriented outcomes (or surrogate markers), e.g. HbA1c levels, do not automatically confer benefits on patient mortality or morbidity\(^2\).
- For all these newer drugs, NICE recommends they should be continued only if there is a beneficial metabolic response. This is defined as a reduction in HbA1c of at least 5.5 mmol/mol (0.5 percentage points) at six months for pioglitazone and the gliptins; and a reduction of at least 11 mmol/mol (one percentage point) in HbA1c and a weight loss of at least 3% of initial body weight at six months for exenatide and liraglutide\(^2,15,16\).

### Rosiglitazone

- Rosiglitazone was withdrawn from clinical use in September 2010 due to increased CV risks\(^4\). The MHRA has highlighted several safety concerns with pioglitazone, which have now been incorporated into the summary of product characteristics (SPC)\(^9\). The SPC includes the following:
  - Pioglitazone is contraindicated in patients with heart failure or a history of heart failure. Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with reduced cardiac reserve and when pioglitazone is used in combination with insulin.
  - Pioglitazone should be discontinued if any deterioration in cardiac status occurs.
  - Pioglitazone is contraindicated in patients with bladder cancer or a history of bladder cancer, or in patients with uninvestigated macroscopic haematuria. Risk factors for bladder cancer (age, smoking history, exposure to some occupational or chemotherapy agents or prior radiation treatment in the pelvic region) should be assessed before initiating pioglitazone, and any macroscopic haematuria investigated.
  - In light of age-related risks (especially bladder cancer, fractures and heart failure), the balance of benefits and risks should be considered carefully both before and during treatment in the elderly.
  - After initiation of pioglitazone, patients should be reviewed after three to six months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained.
  - The MHRA has also given specific safety advice about exenatide and the risk of severe pancreatitis and renal failure\(^20\).

### What about long-acting insulin analogues?

- Human NPH (isophane) insulin, used at bedtime or twice-daily according to need, is the preferred first-choice insulin recommended by NICE\(^2\).
  - Human NPH insulin is preferred based on cost-effectiveness and its well-recognised safety profile\(^1\).
  - For most people with type 2 diabetes, long-acting
insulin analogues offer no significant advantage over human NPH (isophane) insulin and are much more expensive. The main benefits of the long-acting insulin analogues, insulin glargine and insulin detemir, relate to lower rates of hypoglycaemia, and once daily use. However, these potential benefits need to be balanced against their much higher costs and lack of long-term safety and outcome data.

- In terms of HbA1c lowering, there is no difference between long-acting insulin analogues and human NPH insulin. 

- Compared with human NPH insulin, long-acting insulin analogues result in statistically significantly lower rates of nocturnal hypoglycaemia and statistically significantly lower rates of severe hypoglycaemia. However, there is no statistically significant reduction in the rate of severe hypoglycaemia.

- The long-term safety of the long-acting insulin analogues, insulin glargine and insulin detemir, is not known. Robust evidence that they improve patient-orientated outcomes and are cost-effective is not available at the current time.

- A health economic analysis by NICE found that the cost-effectiveness of long-acting insulin analogues was not favourable. The incremental cost per QALY (compared with conventional insulin) was greater than £100,000 in all scenarios, and in some scenarios in excess of £400,000. (This is substantially greater than the £20,000 to £30,000 per QALY threshold usually considered in NICE’s cost-effectiveness evaluation.)

- It is more cost-effective to target use of long-acting insulin analogues to those people with type 2 diabetes who would be most likely to benefit. Hence the guidance outlined below.

- NICE guidance on type 2 diabetes recommends that, when initiating insulin, long-acting insulin analogues can be considered as an alternative to human NPH insulin if:
  - the patient needs assistance from a carer or health professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily, or
  - the patient’s lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, or
  - the patient would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs, or
  - the patient cannot use the device to inject NPH insulin.

- Switching to a long-acting insulin analogue from NPH insulin can also be considered in patients:
  - who do not reach their target HbA1c because of significant hypoglycaemia, or
  - who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached, or
  - who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made, or
  - who need help from a carer or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.

What about self-monitoring blood glucose?

- A Cochrane review found the overall effect of self-monitoring blood glucose (SMBG) on glycaemic control in patients with type 2 diabetes (who were not using insulin) was small up to six months after initiation, and subsided after 12 months.

- SMBG reduced HbA1c by a statistically significant 0.3% (about 3mmol/mol) at up to six months follow-up, but the reduction was not statistically significant at 12 months.

- There was no evidence that SMBG affected patient satisfaction, general well-being or general health-related quality of life.

- A previous HTA report found SMBG reduced HbA1c by a statistically significant 0.2% (about 2 mmol/mol), but this was not considered clinically significant as it was less than 0.5% (5.5 mmol/mol).

- NICE guidance on type 2 diabetes recommends that SMBG should only be used if it is going to be an integral part of the patients’ self-management education. The continued benefit of SMBG should be assessed in a structured way each year, and clinicians should ensure that patients using SMBG are clear about the purpose of the monitoring, how results should be interpreted, and what action to take in response to results.

- NICE recommends that SMBG is appropriate in some people with type 2 diabetes, and should be available:
  - to those on insulin treatment
  - to those on oral glucose-lowering medications to provide information on hypoglycaemia
  - to assess changes in glucose control resulting from medication and lifestyle changes
  - to monitor changes during intercurrent illness
  - to ensure safety during activities, including driving.
Health professionals should be aware of recommendations from the DVLA on driving and the monitoring of blood glucose.

An NHS Diabetes report on SMBG in non-insulin treated patients with type 2 diabetes makes several recommendations, stating that SMBG:
- should be available (with appropriate structured education) to people receiving sulfonylureas to identify hypoglycaemic episodes
- should only be provided routinely to people not treated with insulin or sulfonylureas where there is an agreed purpose
- should be used only within a care package, accompanied by structured education, with regular review.

What do the prescribing data look like for type 2 diabetes?

The prevalence of diabetes in England increased from 3.6% in 2005/6 to 4.3% in 2009/10. An NHS Information Centre Report which looked at primary care prescribing trends for the treatment of diabetes (both type 1 and type 2) from April 2005 to March 2011, found the resources associated with managing patients with type 2 diabetes are increasing year on year.
Insulin glargine and insulin detemir are increasingly being prescribed instead of human NPH (isophane) insulin.

There has been a considerable increase in the prescribing of sitagliptin, exenatide and liraglutide, in particular.

associated with managing these patients are increasing year on year. The net ingredient cost of prescribing for diabetes (see Figures 2 and 3) represented 8.4% of the total cost of prescribing in primary care in England in 2010/11, compared to 6.6% in 2005/6.29

Some of the increased prescribing for diabetes reflects the evidence base; for example, the increased prescribing of metformin. However, some of the other increases seem less justified.

There has been a considerable increase in the prescribing of human analogue insulins for type 1 and type 2 diabetes. As discussed above, the preferred basal insulin for patients with type 2 diabetes who require insulin treatment is human NPH (isophane) insulin. However, Figure 4 suggests that the long-acting insulin analogues, insulin glargine and insulin detemir, are increasingly being prescribed instead of human NPH insulin. In 2010, 1.2 million items of insulin glargine were prescribed at a cost of nearly £74 million, and just under 600,000 items

Figure 4. Net ingredient cost of selected non-biphasic intermediate and long-acting insulins, April 2005 to March 2011.29

Source: ePACT

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Figure 5. Net ingredient cost of ‘other antidiabetic drugs’ (excluding glitazones) 2007/08 to 2010/11.29

Source: ePACT

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of insulin detemir at a cost of nearly £39 million. This compared with 300,000 items of NPH insulin at a cost of just over £11 million\textsuperscript{19}.

Glitazone prescribing was increasing but, following the withdrawal of rosiglitazone and recent safety concerns with pioglitazone, the prescribing of glitazones is now decreasing. However, there is increasing use of the ‘other antidiabetic drugs’, such as the gliptins, exenatide and liraglutide. Figure 5 shows there has been a considerable increase in the prescribing of some of these newer drugs (sitagliptin, exenatide and liraglutide, in particular) in recent years\textsuperscript{19}. As discussed above, the long-term safety of these newer drugs is unknown and robust evidence that they help patients live longer or healthier lives is not currently available.

The number of blood glucose testing items prescribed has increased by about 6% over the period 2005/6 to 2010/11, with an increase in net ingredient cost of about 7%\textsuperscript{29}, and there remains a concern that some patients with type 2 diabetes may be self-monitoring unnecessarily. Figure 2 shows the spend on blood glucose testing strips in England in primary care in 2010 was about £150 million. This compares to about £300 million on insulins and £250 million on antidiabetic drugs\textsuperscript{29}.

**What do the QIPP prescribing comparators show?**

There are currently two QIPP prescribing comparators relating to type 2 diabetes\textsuperscript{31}. The first, ‘hypoglycaemic drugs’ gives the number of prescription items for metformin and sulfonylurea drugs as a percentage...
Progression to triple hypoglycaemic therapy should not be automatic — potential benefits of a further HbA1c reduction should be weighed against risks of adding another drug.

People with glycaemic control problems should be properly assessed for underlying causes before newer more expensive insulins are considered.

of the total number of prescription items for all antidiabetic drugs\textsuperscript{31}. Figure 6 shows at the lowest end, there are PCTs with just 75% of antidiabetic drug item prescribing being for the established first- and second-line drugs, metformin and sulfonylureas. This compares with 94% metformin and sulfonylurea prescribing at the highest end. Put another way, this means that in some PCTs, the prescribing of usually third-line drugs such as pioglitazone, the gliptins, exenatide and liraglutide is 6% of antidiabetic drug item prescribing, whereas in others it is 25%.

Progression to triple hypoglycaemic therapy should not be automatic — clinicians and patients should discuss adherence with existing therapies and carefully weigh the potential benefits of a further reduction in HbA1c, against the risks of adding another drug. Patients being considered for third-line therapy are already likely to be taking a statin, antihypertensives, and, where indicated, aspirin, as well as first- and second-line hypoglycaemic agents\textsuperscript{1}. Clinicians need to consider the law of cumulative benefits (or diminishing returns) and discuss with individual patients what additional improvement in outcomes might be gained from adding in a third hypoglycaemic drug in absolute terms, and how this may affect their quality of life\textsuperscript{1}.

The second QIPP comparator, ‘long/intermediate insulin analogues’ gives the number of prescription items for the long-acting analogue insulins, detemir and glargine, as a percentage of the total number of prescription items for all long-acting and intermediate-acting insulins, excluding biphasic insulins\textsuperscript{31}. Figure 7 shows the wide variation in the percentage of long-acting insulin analogues prescribed across PCTs. At the highest end are PCTs where long-acting insulin analogues make up 98% of the prescribing of all long and intermediate-acting insulins (excluding biphasics). At the lowest end is a PCT with a corresponding figure of 38%. In the majority of PCTs, more than 80% of all intermediate or long-acting insulin items (excluding biphasic insulins) are long-acting insulin analogues and in many PCTs the proportion is more than 90%. This means that, in many PCTs, only 10% of all intermediate or long-acting insulin items prescribed are for human NPH (isophane) insulin, the insulin recommended by NICE as first-choice for people with type 2 diabetes who need insulin.

People with glycaemic control problems should be properly assessed for underlying causes before these newer, more expensive insulins are considered. This includes education and checking understanding around how to manage their disease and treatment. Any decision to start an insulin analogue needs to be balanced carefully against the lack of long-term safety and clinical outcome data for these agents and their high prescribing costs\textsuperscript{1}.

Two further prescribing comparators relating to type 2 diabetes are under development. These will use information from the GP Quality and Outcomes Framework, such as QOF patient registers.

So what?

The management of patients with type 2 diabetes is complex, requiring individualised management of blood glucose, blood lipids, blood pressure, and lifestyle issues. The health and resource burden of managing these patients is huge, making type 2 diabetes a key therapeutic area for local activity to improve the productivity and quality of prescribing.

The NPC document, Key therapeutic topics — Medicines management options for local implementation, outlines several options for local implementation around the management of patients with type 2 diabetes. These relate to reviewing and, where appropriate, revising the prescribing of hypoglycaemic drugs, long-acting insulin analogues and SMBG to ensure that it is in line with NICE guidance for the management of type 2 diabetes\textsuperscript{2,15,16}. 
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