NICE and SIGN guidelines for type 2 diabetes

Diabetic retinopathy is covered in the online handbook in the Ophthalmology chapter

Diabetic neuropathic pain is covered in the Neurology chapter

Only available online (www.gp-handbook.co.uk):
- HbA1c targets: a summary of the evidence
- Self-monitoring in type 2 diabetes
- Managing diabetes during Ramadan
- Managing diabetic foot complications

Diagnostic criteria for type 2 diabetes and pre-diabetes

WHO diagnostic criteria

The World Health Organisation (WHO) set the following criteria for the diagnosis of type 2 diabetes. They are designed for developed and undeveloped settings. In the UK, I would suggest that it would be most unusual to make a diagnosis based on a single test result alone, or to use random glucose as a diagnostic test.
TYPE 2 DIABETES
(units are mmol/l)

<table>
<thead>
<tr>
<th>SYMPTOMATIC (e.g. polyuria, polydipsia, unexplained weight loss)</th>
<th>ASYMPOMATIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A single fasting plasma glucose ≥7 OR A single random plasma glucose ≥11.1.</td>
<td>A fasting glucose ≥7 on two separate occasions OR A random glucose ≥11.1 on two separate occasions OR An HbA1c ≥6.5% (48mmol/mol) on two separate occasions OR An HbA1c ≥6.5% AND a single elevated plasma glucose (fasting ≥7 or random ≥11.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IMPAIRED FASTING GLUCOSE</th>
<th>PRE-DIABETES</th>
<th>IMPAIRED GLUCOSE TOLERANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose 6.1–6.9mmol/l (WHO criteria)</td>
<td>HbA1c 6–6.4% (42–47mmol/mol) (NICE) The American Diabetes Association uses wider criteria (HbA1c 5.7–6.4% (39–47mmol/mol))</td>
<td>Fasting plasma glucose &lt;7.0mmol/l AND 2h plasma glucose (after 75g oral glucose load) 7.8–11mmol/l (WHO criteria)</td>
</tr>
</tbody>
</table>

Do note that although impaired fasting glucose/pre-diabetes/impaired glucose tolerance are all distinct entities based on which diagnostic test you use, the clinical management is sufficiently similar that, in primary care, we can consider them to be one condition.

HbA1c in the diagnosis of diabetes

Some cautions with HbA1c and diagnosis:

- Do NOT use HbA1c for the diagnosis of type 1 diabetes.
- An HbA1c of <6.5%/48mmol/mol does not exclude type 2 diabetes. The HbA1c test is less sensitive than fasting glucose measurements, but this disadvantage may be offset, at a population level, by doing more testing overall, because of wider acceptability and greater convenience (Diabetes Care 2010(33):S1).
- You can’t use HbA1c if:
  - Increased red cell turnover (including pregnancy!), anaemia and haemoglobinopathies (Diabetes Care 2010(33):S1).
  - Blood sugar levels have risen rapidly (type 1 diabetes, acute illness, drugs that raise blood sugar such as oral steroids and antipsychotics) (Practical Diabetes 2012;29(1):12).
- The American Diabetes Association defines a group with ‘pre-diabetes’; an HbA1c of 5.7–6.4% (39–47mmol/mol). However, a UK expert consensus statement suggests those at most risk are those with an HbA1c of 6–6.4 (42–47mmol/mol).

What does this mean in practice?

Neither NICE nor the American Diabetes Association recommend one test over another (NICE Public Health Guidance on Diabetes Prevention 2012, 38 Diabetes Care 2010(33) S1).

The important thing to remember is that you should follow the WHO diagnostic criteria (above).

It is up to individual practices to make a decision as to which of these criteria to use. In our practice we are moving towards basing the diagnosis on the combination of a single raised fasting glucose and a single raised HbA1c, taken on the same day, to reduce patient inconvenience and to speed up the diagnostic process.
New units for HbA1c

Remember that in the UK we are moving from using percentages as the units for HbA1c to mmol/mol. I’ve put a conversion table in the Appendix (there is no simple sum you can do!), which you can photocopy to pin up in your room once your lab switches off dual reporting, or use the conversion calculator on the Diabetes UK website (see Useful website box, below).

The two I remember are:

\[
\begin{align*}
6.5\% & \Rightarrow 48\text{mmol/mol} \\
7.5\% & \Rightarrow 58\text{mmol/mol}
\end{align*}
\]

Diagnosing diabetes

- Pick a WHO criterion and follow it! It probably doesn’t matter which you choose!
- What are you going to use as your new diagnostic criteria? Is it time to sit down as a practice and think this through?
- There is a conversion calculator on the Diabetes UK website, or use the table in the Appendix.
- www.diabetes.org.uk/Professionals/Publications-reports-and-resources/Tools/Changes-to-HbA1c-values/ or http://tinyurl.com/percentageconversion if you are typing this manually.

Personal learning points/actions:

Preventing type 2 diabetes

Over 8% of the NHS budget is spent on type 2 diabetes.

In 2012 NICE produced public health guidance on identifying and managing those at high risk of diabetes (NICE 2012, PHG38). What are the implications for primary care?

The recommendations focus on:

- Identifying those at risk of developing type 2 diabetes through risk assessment scoring (a bit like we do with CVD risk scoring with QRISK and Framingham) and a blood test (HbA1c or fasting blood glucose) if indicated.
- Offering intensive lifestyle-based change programmes to those at risk.

Although I focus here on the aspects of this strategy from the point of view of primary care, risk assessment is encouraged from community pharmacists, dentists, opticians, community leaders, occupational health teams and those working in prisons, as well as those providing services for those with learning disabilities.

NICE on identifying and managing those at high risk of diabetes

NICE 2012, PHG38

Assess risk of diabetes for all aged over 25.

25–39y at high risk of diabetes

- South Asian, Chinese, African–Caribbean origin
- CVD, PCOS
- PMH of gestational diabetes (although see next section, as other NICE guidance recommends annual screening for these people)
- Mental illness/learning disabilities
- Those on oral steroids, anti-retrovirals, some antipsychotics

Use risk assessment tool to stratify risk

(see below for the tools available)

If South Asian/Chinese & BMI >23 consider blood test without further risk assessment

40–74y

Risk assess via NHS Health Check

≥75y

Use risk assessment tool to stratify risk (see below for the tools available)
### Risk assessment tools

There are a variety of risk assessment tools:

- **NICE** suggest the Diabetes Risk Score which assesses risk based on:
  - Age
  - Sex
  - Ethnicity
  - Family history of diabetes in a first degree relative
  - BMI & waist circumference
  - PMH of hypertension.

- Other scores are also available including the Cambridge diabetes risk score, the Leicester practice score and QDiabetes risk.

The Diabetes Risk Score is available from the Diabetes UK website, but unfortunately you have to email them and then they send it to you, as a paper based tool rather than an online tool! I have put a link to the request form in the Useful website box at the end of this section. I have asked NICE and Diabetes UK to make it more accessible, and have asked for permission to reproduce the tool in this Handbook, but so far my requests have fallen on deaf ears!

- After risk assessment using the Diabetes Risk Score (available from Diabetes UK, see Useful websites box) people will fall into one of two groups.

#### Outcome of risk stratification using the Diabetes Risk Score

**Low–moderate risk score**
- Diabetes Risk Score <25
  - Offer brief advice on:
    - Risks of developing diabetes
    - Healthy lifestyle
    - Modification of any risk factors
  - Reassess risk every 5y

**High risk score**
- Diabetes Risk Score ≥25
  - Blood test
    - (HbA1c or fasting plasma glucose; NICE do not suggest both)
  - Reassess risk every 3y

- **HbA1c <6% (42mmol/mol) OR fasting plasma glucose <5.5mmol/l**
  - Moderate risk of diabetes
  - Offer brief interventions:
    - Discuss risks of developing diabetes
    - Help modify any risk factors
    - Offer tailored support to achieve this
  - Reassess risk every 3y

- **HbA1c 6–6.4% (42–47mmol/mol) OR fasting plasma glucose 5.5–6.9mmol/l**
  - Offer intensive lifestyle change programme to:
    - Increase physical activity
    - Achieve & maintain weight loss
    - Increase dietary fibre, reduce dietary fat intake
    - Consider metformin and orlistat (see below for criteria)
  - Reassess BMI annually
  - Offer annual blood test

- **HbA1c ≥6.5 (48mmol/mol) OR fasting plasma glucose ≥ 7mmol/l**
  - Possible diabetes
  - Perform diagnostic tests (see WHO diagnostic criteria).
    - Basically either 2 fasting plasma glucose tests separated in time or an HbA1c & a single fasting plasma glucose test.
  - If not diabetic offer quality assured intensive lifestyle change programme
  - Offer annual blood test
  - Reassess BMI annually
Drugs in those at high risk of diabetes:

NICE suggest the following may be used. Obviously you need to think about CV risk and the role for statins too, although this isn’t covered by this NICE guideline.

- **Offer metformin to those who are at high risk of diabetes and:**
  - Despite intensive lifestyle intervention their HbA1c is not falling
  - OR they can’t undertake intensive lifestyle programmes because of illness or disability.

Start metformin at 500mg once daily and increase to 1500–2000mg/day if tolerated. Review HbA1c at 3m, and stop if there has been no fall in HbA1c. Review prescribing and risk 6–12months after starting, but warn patients that treatment is likely to be lifelong.

- **Offer orlistat if at high risk of diabetes and BMI ≥28 and:**
  - HbA1c not falling despite intensive lifestyle interventions
  - Or unable to take part in physical activity programme because of illness or disability.

If prescribed, review after 12w. If 5% weight loss has not been achieved consider stopping orlistat, although remember that weight loss can be slower in those with diabetes/pre-diabetes and so you don’t have to be too strict about this. Do not continue orlistat beyond 12m.

### What if you stop being pre-diabetic?

I’d like to say that many of my patients listen to my ‘Now, you’ve got pre-diabetes and if you don’t do something about it now, you are going to get diabetes’ talk and take all my messages to heart, radically changing their diet and lifestyle, losing weight and becoming normoglycaemic. Sadly, only a few actually do (perhaps there is a lesson in there for me!). But very occasionally people do make significant changes and do become normoglycaemic. What of them?

The DPPOS is a long term observational study of people with pre-diabetes (6 year follow-up).

- Those who reverted from pre-diabetes to normoglycaemia had a significantly reduced risk of developing diabetes (about half) compared to those who remained in the pre-diabetes state. The absolute risk cannot be calculated from the paper, but in the first 3 years of the cohort trial from which the DPPOS patients were recruited, the risk of diabetes was around 33%. Halving that would be a significant benefit!
- Interestingly, even if participants reverted to normoglycaemia for only a limited period of time (and about 25% of people managed this), they still had a significantly reduced risk of diabetes.
- **It really is worth persevering with this group!**

### So what does this mean in practice?

This latest NICE public health guidance summarises what we have known for some time; that we should intervene in those at risk of diabetes. What the NICE guidance does is to give us a systematic approach to identifying those at greatest risk of diabetes within our populations and gives clear advice on what interventions and what follow-up is indicated.

Our challenge now is to do this!

Tools are currently being developed that will integrate this risk stratification approach into clinical computer systems so that high risk patients can be flagged and then screened.

In the meantime we should start thinking about how we will deliver such care, both to those we have already identified as being at high risk of diabetes, and those who we will identify once systematic approaches are integrated into our clinical systems.

### Lifestyle or social class as a cause of diabetes?

We know that lifestyle and, in particular, obesity increase your risk of developing diabetes, but what about social class and deprivation? Do they affect your risk of diabetes?

The Whitehall study is a prospective cohort study following civil servants over time. It looks at a whole variety of different outcomes. In this cohort they followed 7000 people without diabetes and regularly assessed their health behaviours (diet, exercise, etc.) and vital statistics (BP, BMI, cholesterol, etc.). Follow-up was over 14 years, and both men and women were included (BMJ 2012;345:e5452).
Over the 14 years of follow-up:
- Those in the lowest social groups were at increased risk of diabetes (1.86x more likely to develop diabetes, CI 1.48–2.32).
- Health behaviours and BMI accounted for almost half of this difference.

From our perspective this is important because it gives an estimate of how much the risk of diabetes comes from socioeconomic factors and how much from lifestyle: it’s about 50/50. Modifying health behaviours (hard though this is to achieve) could have a potential impact on the risk of developing diabetes in the most deprived communities, when factors such as deprivation may be harder to change at an individual patient level.

This study is important because it is one of the first studies to be able to estimate this risk accurately because it is based on multiple snapshots of behaviour over time and not just a single snapshot.

### Preventing type 2 diabetes

- A systematic approach to identify those at risk of type 2 diabetes is now advocated by NICE.
- This involves stratifying risk using the Diabetes Risk Score and then offering a blood test to those at high risk.
- Tools that help us to identify those most at risk are being developed to integrate with our clinical systems to make this process easier!
- For those at increased risk of diabetes, lifestyle modification is recommended with re-screening every few years according to risk.
- For those with pre-diabetes, more intensive management is required, possibly using metformin and/or orlistat with annual re-screening for diabetes.
- Returning to normoglycaemia for a period after being in the pre-diabetic state is beneficial, even if this return to normoglycaemia is only transient.
- Health behaviours contribute about half of the increased risk of diabetes seen in deprived populations.

### Personal learning points/actions:

- Lifestyle and bariatric surgery

In this chapter I focus a lot on the drugs used in diabetes, because that is what clinicians struggle with. However, the role of lifestyle, and particularly weight management, cannot be over-emphasized.

### Long term DESMOND follow-up

DESMOND attracted a lot of attention a few years ago. It is a 6h education programme for people with newly diagnosed type 2 diabetes; you may have courses running in your area. Early trials showed that not only was DESMOND cost-effective but it also improved weight, smoking, CV risk, depression scores and illness beliefs 12m later. Not bad for a 6h programme! Now an analysis looks at impact of the course 3 years later.

Three years on both the intervention group (who attended a DESMOND education programme) and the usual care group had no significant differences in biomedical data (HbA1c, cholesterol, depression scores, etc.) or lifestyle data (smoking rates, exercise, etc.) or depression scores, although those who had received DESMOND had a better understanding of their illness and their ability to influence the course of the disease. A rather disappointing finding!
**Bariatric surgery for diabetes**

Clearly one of the big issues is access to surgery, although across the NHS this is improving. The Lancet reviewed some of the evidence (Lancet 2012;379:2300).

**Risk depends in part on the procedure done.** For laparoscopic adjustable gastric band (the most likely procedure for diabetics), the evidence suggests:

- Average weight loss: 20–30%
- 30d post-op mortality: 0.05–0.1%
- 30d post-op major morbidity: 1%
- Maximum weight loss: 2–3 years after surgery
- Evidence of improved long-term survival?: Yes
- Nutritional concerns: Minor compared to other procedures (iron, B12 and folate deficiencies)

What is lacking is long-term follow-up data after bariatric surgery to look at outcomes 10–20y down the line.

**Who is eligible?**

NICE and SIGN both set their criteria for diabetics to be considered for bariatric surgery at a BMI >35 with one weight-loss responsive co-morbidity.

- Something to seriously consider in those with a BMI over 35, if patients are willing and motivated and after other options to modify diet and lifestyle have failed.

A case-control study in Sweden looked at 1600 obese individuals without diabetes who underwent bariatric surgery and compared them with obese patients not undergoing bariatric surgery and then followed them up for 15y (NEJM 2012;367:695).

- The incidence of diabetes in those not having surgery was 28/1000 person years.
- The incidence of diabetes in those having bariatric surgery was 7/1000 person years.
- Unsurprisingly, those with abnormal glycaemic control (pre-diabetes) had most benefit in terms of diabetes prevention.

Studies have also shown that the costs of bariatric surgery is fully offset by the reduced costs in terms of other medications within 26m of surgery (BMJ 2012;345:e4552).

**Is bariatric surgery associated with a risk of fracture?**

No... a trial has suggested a non-significant trend towards an increased risk of fracture over 3–5y. The study was a cohort study of 2000 patients undergoing bariatric surgery, matched with 10 000 controls. Although no increased risk of osteoporotic and non-osteoporotic fractures was demonstrated, the non-significant trend towards an increased risk of fracture suggests this is something that should be investigated further (BMJ 2012;345:e5085).

**The newer diabetes drugs**

Before we start, let’s remember two important things:

- Metformin gives you a cardiovascular hug: that is, it offers you cardiovascular protection over and above its blood sugar lowering effect (see below).
- The newer drugs do not offer significant benefits in terms of glycaemic control compared with other oral hypoglycaemic agents (DTB 2008;46:7).
- For the newer drugs we have limited evidence on (DTB 2008;46:7):
  - Impact on mortality.
  - Impact on diabetic complications.
  - Safety of long term use.

**Don’t forget metformin!**

Metformin is increasingly being used soon after diagnosis because of its ability to offer cardiovascular protection over and above its blood sugar lowering mechanism.

A systematic review and meta-analysis looked at all oral hypoglycaemic drug trials to see which show benefit in terms of reducing cardiovascular events (Arch. Int. Med. 2008;168:2070–80). The authors identified 40 studies that reported data on cardiovascular events. Notably, however, only 6 of the trials went on for more than 12m and almost half ran for 6m or less. The best data, unsurprisingly, came from the UKPDS studies. They concluded that:
- Metformin reduces cardiovascular mortality compared with any other oral hypoglycaemic agents or placebos (odds ratio 0.74, CI 0.62–0.89) (sorry we can’t calculate NNTs from published paper).
- Metformin reduces cardiovascular morbidity and all-cause mortality by a similar amount, but the results were not statistically significant.

A further large review of over 91 000 people on the UK GP Research Database looked at all hypoglycaemic agents (BMJ 2009;339:b4731).

- Once again, the benefits of using metformin were confirmed. Metformin, compared to the sulphonylureas, was associated with a reduced incidence of congestive cardiac failure, MI and all-cause mortality.

What about metformin and lactic acidosis?
A case report in the BMJ reminds us that lactic acidosis is a rare but serious complication with metformin (BMJ 2009;339:b3660). But is this true? A Cochrane systematic review of over 70 000 patient years showed no cases of lactic acidosis in those on metformin, when used according to trial protocols (although remember that not all our patients are as closely monitored or as compliant as trial populations) (Cochrane 2010, CD 002967).

So what do we need to know about lactic acidosis?
- It is incredibly rare (incidence is 1–5/100,000), but mortality is 30–50%.
- It presents with non-specific symptoms (anorexia, nausea, vomiting, abdominal pain, altered consciousness, thirst).
- The BMJ clinical review reminds us that dehydration is a trigger for this and that we should consider stopping metformin during intercurrent illness, especially if associated with dehydration (as in diarrhoea and vomiting).
- We should also be particularly aware of the risks of lactic acidosis in those taking nephrotoxic drugs, especially during intercurrent illness/dehydration.

The BMJ clinical review recommends that we should
- Review the dose of metformin if creatinine >130 or eGFR <45.
- Stop metformin if creatinine >150 or eGFR <30.
- Temporarily withdraw metformin:
  - During periods of suspected tissue hypoxia (e.g. sepsis, MI)
  - For 3d after the use of contrast medium containing iodine
  - 2d before general anaesthesia.

What does this mean in practice?
- All these data add weight to the use of metformin soon after diagnosis.
- Metformin may be associated with lactic acidosis. Although very rare, it is associated with substantial mortality.
- Use metformin with care in renal impairment (creatinine >130 or eGFR <45).
- Stop metformin if creatinine >150 or eGFR <30.
- Have a low threshold for checking creatinine/eGFR when those taking metformin are unwell.

Overview of newer drugs
If, like me, you find all the new names and classes a little confusing, here is a quick guide. Insulins are covered in the next section.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Generic examples</th>
<th>Trade names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones = glitazones</td>
<td>Pioglitazone</td>
<td>Actos</td>
</tr>
<tr>
<td>DPP-4 inhibitors = gliptins</td>
<td>Sitagliptin</td>
<td>Januvia</td>
</tr>
<tr>
<td></td>
<td>Vildagliptin</td>
<td>Galvus</td>
</tr>
<tr>
<td>GLP-1 mimetics/agonists/analogues</td>
<td>Exenatide</td>
<td>Byetta</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>Victoza</td>
</tr>
<tr>
<td>Insulin secretagogues</td>
<td>Repaglinide</td>
<td>Prandin</td>
</tr>
<tr>
<td>(not included in NICE guidelines)</td>
<td>Nateglinide</td>
<td>Starlix</td>
</tr>
</tbody>
</table>
Combination therapies involving newer drugs:
- Pioglitazone with metformin = Competact
- Vildagliptin with metformin = Eucreas.

How the newer drugs work

First the macro-physiology...
There are two main components of hyperglycaemia in diabetes: insulin resistance and reduced insulin production.

Insulin resistance comes, in part, from obesity, so optimising weight is a crucial part of diabetes control at all stages of the disease.

Reduced insulin production occurs with time in diabetes, as pancreatic beta-cell function fails. As the cells fail, any drug that tries to flog the pancreas into making more insulin will no longer be effective. At this stage insulin is required.

In a patient who is using their medication correctly, and is eating sensibly, but still has persistent hyperglycaemia, ask yourself: has this person’s pancreas reached the point of no return? Am I flogging a dead donkey (or in this case a dead beta-cell?!).

No drug that ultimately acts on the beta cells, no matter how flashy and wonderful it sounds, will be effective at this stage.

Now the micro-physiology...
- In the body a gut based hormone GLP-1 (glucagon-like peptide-1) increases insulin secretion.
- Another gut hormone, DPP-4 (dipeptidyl peptase-4) breaks down GLP-1, thus lowering insulin levels.
- The drugs act by:
  - DPP-4 inhibitors (the gliptins), inhibit DPP-4, thus stopping the breakdown of GLP-1 and allowing ongoing insulin secretion.
  - GLP-1 mimetics/analogues (exenatide, liraglutide) mimic GLP-1, increasing insulin secretion.
  - GLP-1 analogues (liraglutide) but not the GLP-1 mimetics, resist breakdown by DPP-4 allowing ongoing insulin secretion. How clinically important this is isn’t clear.
- Glitazones work by increasing insulin sensitivity in peripheral tissues.
- Repaglinide and nateglinide stimulate insulin release via action on the pancreatic beta-cell (but through different receptors to the sulphonylureas). They are excreted via bile and faeces so theoretically can be used in renal impairment (but see later!). They have a rapid onset and short duration of action.

Or if you prefer that pictorially...read the GREY boxes and arrows first – these show normal physiological control. Then read the white boxes, which show how the drugs work.
Gut hormone GLP-1

GLP-1 mimetics/analogues (exenatide/liraglutide)
Act like GLP-1, stimulating insulin secretion

Gut hormone DPP-4

Reduces insulin secretion by breaking down GLP-1

Repaglinide/nateglinide
Stimulate pancreatic beta cells causing insulin release (but NOT like sulphonylureas)

Glitazones
Increase sensitivity of peripheral tissues to insulin

Gliptins
Inhibit DPP-4, so GLP-1 persists, allowing on-going insulin secretion

Do note that all drugs acting on the GLP-1 pathway may increase the risk of pancreatitis. Persistent or severe nausea or vomiting may be an early manifestation and should be investigated (NEJM 2010;362:776). The MHRA has said that all patients on gliptins (as well as those on exenatide) should be warned about the symptoms and signs of pancreatitis (persistent severe abdominal pain sometimes radiating to the back) and told to report symptoms early (Drug Safety Update 2012;6(2);A3).

Pancreatic cancer risk: a new study has also shown an increased risk of pancreatic cancer with both exenatide and sitagliptin (DTB 2011;49(11):124). The increased risk was in the order of 2.5x (but remember pancreatic cancer is not that common – it is the 10th commonest cancer, with around 8000 cases /year compared with 50,000 breast cancers and 40,000 lung cancers a year (Cancer Stats UK, latest data, www.info.cancerresearchuk.org/cancerstats/incidence/commoncancers/#Twenty)

NICE guidance on the newer drugs

NICE guidelines, summarised in the Appendix, create a complex flow chart of which drug to use when. But try thinking about them in a stepwise approach (like the BTS asthma guidelines), with first and second choice drugs at each step.

Please note, NICE do not talk about steps or present their guidance in a stepwise approach, this is simply my way of interpreting their rather complex flow diagrams.

So, I would see the NICE guidance like this:
### A framework for the newer diabetes drugs

New drugs appear on the market from time to time, but it is unusual for so many new classes of drugs to appear in such a short space of time for one condition, as has happened in diabetes. No wonder most of us are a little confused about how the new drugs fit in. The aim of this section is to give you an overview of the new drugs and a framework on which to hang them so you have an idea of which could be used in certain situations.

All the new drugs are currently being used in secondary care, and GPs are starting to use them in primary care. As with any new drug we each need to build up our competence and confidence using them over a period of time, often learning from our secondary care colleagues or the diabetes nurse specialists.

And remember:

- **If you are new to prescribing these drugs please take advice from secondary care/the diabetes nurse specialists and read the BNF.** The licensing criteria (particularly which combination of drugs they can be used with) change frequently.
- **Remember that for all the new drugs, they are as effective as insulin but no better (lower HbA1c by <1%/11mmol/mol).** So always ask yourself ‘Why would this drug be better than insulin in this patient?’
- **Long-term evidence on impact of the newer drugs on important endpoints such as diabetic complications, morbidity and mortality is lacking.**
- **Rarely would you use these agents as monotherapy.** Most would be added to metformin/sulphonylurea (i.e. in triple therapy).
- **To compare costs, remember metformin costs <£17/y, gliclazide <£35/y and insulin £35–195/y.**

#### Note:

- The target HbA1c is <6.5%/48mmol/mol at steps 1–3 but rises to 7.5%/58mmol/mol at steps 4 & 5. Given the discussion in the section above, most would now set this at 7%/53mmol/mol or 7.5%/58mmol/mol.
- Insulin is ADDED to current oral therapy, and does not replace it.
- Don’t forget the importance of lifestyle at all stages of care!
### Gliptins

If you remember nothing else about gliptins... **remember that they may be your first choice after metformin/sulphonylureas if you can’t use insulin.**

**THINK:** 1st 2nd LINE CHOICE

- **FORMULATION:** tablets. Usually used in combination with other oral agents.
- **ACTION:** DPP-4 inhibitors. By inhibiting DPP-4, gliptins stop the breakdown of GLP-1, and allow ongoing insulin secretion. Not as effective as metformin in reducing HbA1c, but when used in combination with metformin as effective as sulphonylureas and glitazones in reducing HbA1c, but less effective than liraglutide/exenatide (BMJ 2012;344:e1369).
- **RISK OF HYPOS:** minimal increased risk (but may need to reduce sulphonylurea/insulin dose when starting therapy).
- **NICE RECOMMENDATIONS:**
  - **Stop after the first 6m if HbA1c has not dropped by 0.5% (5–6mmol/l).**

**SIDE-EFFECTS:**
- Main side-effect is headache: in clinical trials few stopped treatment because of this.
- Weight neutral or small weight gain. Probably less weight gain than sulphonylureas or glitazones (BMJ 2012;344:e1369).
- Caution in renal disease (see specific guidance in BNF as varies from drug to drug)
- **COSTS:** £207–434/y.

### GLP-1 mimetics (exenatide & liraglutide)

**THINK:** OBESITY

If you remember nothing else about exenatide and liraglutide... **remember that they tend to result in weight loss and use should be targeted at those who are significantly overweight.**

- **FORMULATION:** Given by subcut injection, with meals.
- **ACTION:** as GLP-1 mimetics/analogues gliptins mimic GLP-1, increasing insulin secretion. Increased risk of pancreatitis because of action on GLP-1 pathway.
- **RISK OF HYPOS:** may be lower than insulin. When starting liraglutide you may need to reduce dose of sulphonylurea to reduce the risk of hypos (not necessary with exenatide).
- **NICE RECOMMENDATIONS:**
  - **Stop after the first 6m if HbA1c has not dropped by ≥1% (11mmol/mol) AND weight has not fallen by ≥3%**. (In a recent meta-analysis weight loss averaged around 2kg in placebo-controlled trials. Interestingly the study showed similar weight loss in non-diabetics. Don’t start using it for this though! (BMJ 2012;344:d7771 & editorial d7282.))
  - **Remember:** tend to result in weight loss, so use where:
    - BMI≥35 and problems likely with further weight gain
    - BMI<35 and weight loss would be beneficial to other co-morbidities
    - BMI<35 and if insulin unacceptable because of occupational implications.
- **SIDE-EFFECTS:**
  - Nausea (over 50% in exenatide trials) and vomiting (<20% in exenatide trials). Most side-effects settle within 8w. However, in clinical trials 16% stopped using exenatide because of side-effects.
  - Caution in renal disease. Exenatide: avoid if eGFR<30, caution if eGFR 30–50. Liraglutide: avoid if eGFR<60. Liraglutide should also be avoided if impaired liver function.
  - Both may delay gastric emptying. Do not use either in those with gastroparesis. With exenatide some drugs must be avoided in the hour before and 4h afterwards (see SPC for details).
- **COSTS:** £830/y for exenatide. Up to £1400/y for liraglutide.
Glitazones

**DTB 2008;46:7, NICE 87, 2009, BNF 59, 2010**

*If you remember nothing else about glitazones...remember that they increase sensitivity of peripheral tissues to insulin so their use should be targeted towards those with significant insulin resistance.*

**THINK: INSULIN RESISTER?**

**THINK: DO THE BENEFITS OUTWEIGH THE HARMS?**

- **FORMULATION:** tablets.
- **ACTION:** increase sensitivity of peripheral tissues to insulin.
- **RISK OF HYPOS:** hypos are rare (possibly lowest risk of all the ‘new’ drugs (BMJ 2012;344:e1213)).
- **NICE RECOMMENDATIONS:**
  - Step 3 or 4, particularly if marked insulin insensitivity.
  - If metformin and sulphonylureas are not achieving adequate control, adding insulin will result in better control than adding a glitazone.
  - **Stop after the first 6m if HbA1c has not dropped by 0.5% (5–6mmol/l).**
- **SIDE-EFFECTS:**
  - Reasonably well tolerated. Main side-effects are GI disturbance.
  - Weight gain common.
  - Rarely cause liver toxicity: monitor LFTs before and during treatment.
  - Do not use in heart failure or in those at increased risk of fractures (and see below for more on harms).
- **COSTS:** £290–440/y.

Concerns about (details overleaf):

- **Bladder cancer**
- **Increased risk of heart failure**
- **Cardiovascular risk**
- **Risk of fractures**

The MHRA suggests we should be reviewing all our patients on glitazones to see if an alternative drug is more suitable (Drug Safety Update, Aug 2010).

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Insulin secretagogues (repaglinide & nateglinide)


*If you remember nothing else about the insulin secretagogues...remember that they are not widely used, are not included in the NICE review of drugs and are excreted in bile.*

**THINK: NOT LOVED, NOT NICED, NOT LIVER**

- **FORMULATION:** tablets.
  - **ACTION:** insulin secretagogues. Act on the pancreatic beta cells, but through different receptors to the sulphonylureas. Rapid onset and short duration of action and so are given immediately before food.
- **RISK OF HYPOS:** they can cause hypoglycaemia.
- **NICE RECOMMENDATIONS:** not covered by NICE guidance.
- **SIDE-EFFECTS:**
  - Main side-effects are rashes and urticaria (allergic hypersensitivity reactions are not uncommon) and abdominal symptoms (pain, diarrhoea, vomiting).
  - Excreted via bile and faeces so should not be used in hepatic impairment.
  - Nateglinide can be used in renal impairment but repaglinide should be used with care in renal impairment.
- **COSTS:** approximately £300/y.

**Concerns about glitazones:**

- **Bladder cancer.** The MHRA, in the light of a review by the European Medicines Agency, noted an association (not a proven causation) between pioglitazone and bladder cancer. The absolute risk increase is small. Current recommendations are (MeReC Monthly 2011, no. 43):
○ Do not use if a past history of bladder cancer or with uninvestigated haematuria.
○ Assess known risk factors for bladder cancer before use: smoking, occupational chemicals, some chemotherapies, previous pelvic irradiation.
○ Investigate any bladder symptoms promptly in those on glitazones.
○ In the elderly, be particularly cautious of using glitazones because of the increased risk of bladder cancer and heart failure with age.
○ A nested case–control study confirms the increased risk, which appears to be associated with pioglitazones only (BMJ 2012;344:e3645). This showed an increased risk that was related to duration of use and total dose exposure. After 2 years use the risk was doubled (rate ratio 1.99; CI 1.14–3.45, but remember that baseline incidence is low). Some risk factors for bladder cancer, such as chemical exposure, were not adjusted for which means confounding may be present.
○ Why? Glitazones are related to glitazars, which lower blood sugar and lipid profiles but were withdrawn from use after it was recognised they were carcinogenic in animals (BMJ 2012;344:e3500).

- **Pneumonia.** The National Prescribing Committee reminds us that glitazones are associated with a small increased risk of pneumonia (one extra case for every 239 people treated over 3.9 years) (MeReC Monthly 2011, number 43). This won’t hugely impact on the way we use them.

- **Increased risk of heart failure.** Why? Some have suggested that this may be related to fluid retention (open label RCT of 4000 people, Lancet 2009;373:2125; meta-analysis of 20 000 people, Lancet 2005;370:1129).

- **Cardiovascular risk.** Trials have painted a mixed picture.
  ○ Some trials have shown an increased risk of MI (retrospective cohort study of >91 000 people from UK Research Database, BMJ 2009;339:b4731; meta-analysis of >15 000 people, BMJ 2007;334:1233).
  ○ Some have shown no significant change in CV endpoints (meta-analysis of 20 000 people, Lancet 2007;370:1129).
  ○ One study has shown a reduction in all-cause mortality (UK research database cohort, above, BMJ 2009;339:b47312).

- **Risk of fractures.** This may only be in women and seems to be the arms or distal leg fractures rather than hips or vertebral fractures (Lancet 2009;373:2125, BMJ 2009;339:b4731).

**What about my patients who are taking pioglitazone?**

- The MHRA suggests we should be reviewing all our patients on glitazones to see if an alternative drug is more suitable (Drug Safety Update, Aug 2010).
- We should be particularly mindful of the new concerns about the association with bladder cancer (MHRA July 2011).

**Which agent after metformin?**

A Lancet Comment looks at the evidence around which drug to use after metformin (Lancet 2012;379:2220). It points out that at present long-term data are sorely lacking for any of the new drugs, and so sulphonylureas are widely used at this stage. In the future, however, this may change and the two most likely possibilities were discussed: the use of gliptins or insulin in place of sulphonylureas. The authors accepted the hurdles to overcome in adopting an ‘early insulin’ approach however (patient and clinician reluctance, cost).

The Comment was triggered by two trials of the next agent to add after metformin, one of exenatide vs. glimepiride (a sulphonylurea), and the other a trial of insulin glargine vs. a gliptin (sitagliptin). I’ve summarised the key features here.

**Trial of exenatide vs. sulphonylurea** (Lancet 2012;379:2270)
Sponsored and run by the makers of exenatide, 1000 patients were randomised to either exenatide or glimepiride and followed over 3 years. All were already on metformin but no other hypoglycaemics. Average starting HbA1c was about 7.5%. The trial showed that:
- 44% of those in the exenatide group achieved an Hba1c of <7% compared with 31% in the glimepiride group. This difference is statistically significant. Cardiovascular endpoints were not reported.
- Over the 3 years discontinuation rates were similar between the two groups.
- Average weight loss in the exenatide group was 3.3kg compared with a 1.1kg gain in the glimepiride group.
Rates of severe hypos and other significant adverse events were similar, although there were fewer symptomatic but not severe episodes of hypos in the exenatide group.

**Glargine insulin vs. gliptins** (Lancet 2012;379:2270)
500 patients were randomised to insulin (in this case the long-acting insulin glargine) or gliptins (in this case sitagliptin). The trial was short at just 24 weeks.
- Insulin glargine was superior to gliptins in terms of glycaemic control.
- Severe hypos were more common in the insulin group, although numbers were too small to analyse the difference statistically.

Neither of these trials should yet make us change our practice or deviate from the NICE guidance as set out in the ‘staircase’ above.

**The new diabetes drugs**
- Lifestyle is central to blood sugar control.
- Add oral hypoglycaemics in a stepwise approach starting with metformin, then sulphonylureas. Consider adding insulin if HbA1c ≥ 7.5/58mmol/mol on metformin and a sulphonylurea.
- Metformin should be used first line because of its cardiovascular benefits. Be aware of the possible risks of lactic acidosis with metformin, particularly in renal impairment or dehydration.
- The newer drugs have a limited role: when other drugs have failed, or in specific circumstances such as morbid obesity.
- None of the newer drugs have been shown to reduce mortality or morbidity and none are better at controlling blood sugar than conventional therapies.

If you remember nothing else…
- Gliptins are an alternative to insulin if insulin is not tolerated or is undesirable for occupational reasons.
- Exenatide and liraglutide tend to result in weight loss and are targeted towards those who are significantly overweight.
- Glitazones work by increasing sensitivity of peripheral tissues to insulin: main use is in insulin-insensitive patients. Beware of the harms!
- The insulin secretagogues repaglinide and nateglinide are not covered by NICE guidance but are tablets with a rapid onset and short duration of action. They are excreted in bile so cannot be used in liver disease.

Are you using metformin first line? What about reviewing your diabetes protocol in the light of the new NICE guidelines? And are you using the new drugs in line with NICE and SIGN guidance?

Have you reviewed all your patients on glitazones to ensure it really is the best drug for them?

**Personal learning points/actions:**

**Insulin in type 2 diabetics**

NICE place insulin at step 4. But if we are to use insulin, which regimen should we use? This DTB article very helpfully looks at the evidence and makes some simple recommendations (DTB 2010;48:134).

- Remember, NICE suggest we add in insulin to maximum tolerated oral medication rather than stopping/reducing current oral therapies.
- Remember that here we are talking about insulin in type 2 diabetes.
- The different sorts of insulins, their speed of onset and duration of action are summarised in a table in the Appendix.
- None of the newer drugs are better than insulin.

**Before starting insulin**
- Optimise diet, exercise and weight.
- Review adherence to current therapies.
Review barriers to insulin therapy (impact on driving (especially LGV/PSV drivers), fear of weight gain, occupation, etc.).

Which insulin?

- Traditionally there are 3 main groups of insulin: short-, intermediate- and long-acting. However, if you look at the duration of action of the insulins (see table in Appendix) you will see that there are only really two sorts of insulins, short-acting and long-acting (which includes the intermediate acting insulins).
- Here I will refer to insulins as short-acting (e.g. Actrapid, Humulin S) and long (intermediate) acting (e.g. Insulatard, Humulin I).
- Insulin analogues are available for both the short and long (intermediate) insulins. Long-acting insulin analogues are in many ways similar to long (intermediate) acting insulins. However, short-acting insulin analogues are quicker in their onset of action than short-acting ordinary insulins (inject and eat, rather than wait 30 mins). See below for a review of their uses.
- Pre-mixed insulin preparations are also available, combining short-acting and long-acting insulins.

Insulin analogues

- The benefit of short-acting insulin analogues is the ability to ‘inject and eat’, without waiting the 20–30 minutes usually recommended for the ordinary short-acting insulins.
- The benefit of longer acting insulin analogues particularly relate to a reduction in nocturnal hypos, but the authors argue that this benefit may have been exaggerated by the types of studies used (driving to tight glycaemic control which inevitably increases night time hypos). When analogues are compared with ordinary insulins there is no difference in rates of severe hypoglycaemia (BMJ 2012;345:e4611).
- In addition, they are costly (see the Appendix): short-acting analogues cost at least 30% more than ordinary insulins, and the long-acting insulin analogues are around 50% more (BMJ 2012;345:e4611).
- Insulin analogues account for 8.4% of all NHS prescribing in the UK! If no analogues were used, over £600 million could be saved each year by the NHS.
- The DTB concluded that insulin analogues have only minor advantages over ordinary insulins (no better glycaemic control, no difference in hypos or other adverse events) and are significantly more expensive. They should be reserved for specific situations (DTB 2010;48:134).

How many injections a day?

- The commonest insulin regimens are:
  - Basal: once daily dose of a long (intermediate) acting insulin.
  - Basal/bolus: once daily long (intermediate) acting insulin, with the addition of prandial short-acting insulin.
  - Biphasic regimens: using pre-mixed insulin (a combination of long- and short-acting insulins), 2 or 3x daily.
- The DTB suggests that for most, a basal regimen (single daily dose of a long (intermediate) acting insulin) in addition to oral therapy is most appropriate. If this needs to be intensified then a basal/bolus regimen can be used.

Why? Because an RCT of 700 patients with type 2 diabetes showed that whether they were allocated to:

basal insulin or
basal +2x daily prandial boluses or
basal +3x daily prandial boluses

after 3y it showed that glycaemic control between the three groups was similar and there were fewer hypos and less weight gain in those on basal insulin (NEJM 2009;361;1736).

The DTB concludes (DTB 2010;48:134):

- Most patients should be started on a basal insulin regimen: a single daily dose of a long (intermediate) acting ordinary insulin (e.g. Insulatard, Humulin I).
The next step would be to add short-acting ordinary insulin (e.g. Actrapid, Humulin S). For most, insulin analogues have no significant clinical advantage and are much more expensive. These recommendations from the DTB are in line with the guidance from NICE and SIGN. Having said all that, the DTB does acknowledge that other factors (patient factors such as lifestyle, device usability (e.g. if poor vision), patient choice) may make you follow a different route, although for most the above approach will be acceptable and efficacious.

What does this mean in practice?

- For most we should ADD insulin to maximum tolerated oral therapies.
- Most patients should be started on a single daily dose of a long (intermediate) acting ordinary insulin (e.g. Insulatard, Humulin I).
- If intensification of insulin regimen is required then a basal/bolus regimen should be considered.
- The newer insulin analogues (rapid-acting insulins and long-acting insulin analogues) have few clinical advantages in most patients and are significantly more expensive. Use the newer insulins only if there is a good indication in that specific patient.

Using insulin and metformin together?

Metformin is widely recognised to offer cardiovascular protection in type 2 diabetes, although most of the evidence for this is based on data from obese patients.

The editorial accompanying this paper suggests that (BMJ 2009;339:b4227):

- About 40% of the favourable effect of metformin is attributable to weight reduction.
- About 35% can be attributable to the intrinsic effect of metformin on endothelial function.

It also points out that metformin might act a bit like GLP-1 (an intestinal hormone that stimulates post-prandial secretion of insulin), as well as increasing the sensitivity of peripheral tissues to insulin. This might explain why metformin also works in non-obese individuals, in whom insulin resistance is much less common.

This study looked at the use of metformin with insulin or an insulin secretagogue (repaglinide) in non-obese people with type 2 diabetes (BMI ≤27).

Patients were randomised to biphasic insulin aspart (a mixture of short- and intermediate-acting insulins) plus either repaglinide or metformin. Insulin doses were adjusted to keep fasting sugars in the range of 4–6. The study was small – only 97/102 completed the trial.

- At the end of the trial HbA1cs were similar as were total daily insulin doses and episodes of hypos.
- However, weight gain was significantly less in the metformin group (average 2.5kg less, range 1–4) compared with the repaglinide group.

The accompanying editorial concludes that:

- When insulin is started in non-obese patients we should continue metformin, because this study suggests it may have beneficial effects on both weight and cardiovascular risk.
- If metformin is contraindicated, the authors suggest repaglinide may be an alternative (although long-term data on repaglinide are lacking and it is not included in the NICE guidelines).

Insulin alone in type 2 diabetes

Insulin is traditionally used in combination with other oral hypoglycaemics in type 2 diabetes, and all guidelines recommend continuing metformin when commencing insulin. However, the evidence to continue metformin when starting insulin is limited.

This meta-analysis of 23 trials (just over 2000 patients) looked at the different outcomes when insulin is used alone (outside guidelines) compared with when insulin is used with metformin (BMJ 2012;344:e1771). The researchers found that:

- Using insulin alone had no impact on all-cause or CV-related mortality (i.e. it was neither beneficial nor harmful, although confidence intervals were wide). This is interesting given previous evidence suggesting metformin reduces CV endpoints.
Depending on how the data were analysed, metformin + insulin may have resulted in more hypos (demonstrated in one analysis, but not in another!).

Metformin + insulin resulted in a lower HbA1c (HbA1c 0.5% lower), less weight gain (1kg difference) and lower insulin dosing (5U/day fewer) compared with insulin use alone.

The authors concluded that current guidance of using metformin with insulin has some benefits (lower HbA1c, less weight gain) but no benefit in terms of CV mortality or all-cause mortality. They also remind us that metformin has not been shown to reduce microvascular endpoints (unlike insulins and sulphonylureas).

What does this mean in practice?

Don’t change your practice! More evidence is needed, but we should continue metformin when starting insulin, until better evidence is available.

**Insulins in type 2 diabetes**

- When initiating insulin, in most, we should ADD insulin to oral therapies, and metformin in particular, because it reduces weight gain and offers CV protection.
- Most patients should be started on a single daily dose of a long (intermediate) acting ordinary insulin (e.g. Insulatard).
- If intensification of insulin regimen is required then a basal/bolus regimen should be considered.
- The newer insulins (rapid-acting insulins and insulin analogues) have few clinical advantages in most patients and are significantly more expensive. Use the newer insulins only if there is a good indication in that specific patient.

**Personal learning points/actions:**

**Lipids, BP, aspirin, cardiovascular risk and diabetes**

*We all know that people who have had an MI are at increased risk of further coronary events. But did you know that people with diabetes who have not had an MI, are at the same risk of having a coronary event as non-diabetics who have had an MI? (NEJM 2010;362:1628).*

There are two key guidelines: NICE & SIGN. SIGN is much easier!

The full NICE guidelines say ‘Nearly all people with type 2 diabetes are at high risk of cardiovascular disease – high enough to justify statin therapy without further assessment’. This made me think that NICE would recommend statins for all, or at least all over a certain age. However, they managed to come up with guidelines so much more complicated that I am going to struggle to remember them in the consultation!

As a practice, therefore, we have taken the more pragmatic approach as recommended by SIGN (SIGN 2010, 116):

**SIGN on cardiovascular risk in diabetes**

<table>
<thead>
<tr>
<th>SIGN 2012, 116</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle advice for all (smoking, diet, exercise, etc.).</strong></td>
</tr>
<tr>
<td><strong>Statins for all over the age of 40y</strong> (40mg simvastatin or 10mg of atorvastatin), treat more intensively if established CVD.</td>
</tr>
<tr>
<td>Consider statins in those &lt;40y if significant other risk factors (e.g. microalbuminuria).</td>
</tr>
<tr>
<td><strong>Target BP &lt;130/80</strong> (but see below for more on whether really tight BP control is beneficial). Strictly speaking this target is &lt;130/81 as SIGN say &lt;130 and ≤80, but who’s going to remember that!</td>
</tr>
<tr>
<td><strong>Do NOT offer aspirin in primary prevention for CVD in diabetics</strong> (more on this below).</td>
</tr>
</tbody>
</table>

**Tight blood pressure control in diabetes**

Back in the 1990s UKPDS showed us that tight blood pressure control was more important than tight blood sugar control to reduce cardiovascular risk.

In the Online Handbook I have summarised the evidence around tight blood sugar control, and how we are shifting away from really tight control. Might this also be true for blood pressure?
This trial, based on the UK General Practice Research Database (now called the Clinical Practice Research Datalink) followed over 125,000 people with newly diagnosed type 2 diabetes, about 10% of whom had established CVD when the diabetes was diagnosed. Follow-up was for a median of 3.5y, during which 20% of the cohort died (!) (BMJ 2012;345:e5567).

In those with diabetes:
- Tight blood pressure control (<130/80) was not associated with improved survival when other risk factors were controlled for.
- Low blood pressure was associated with an increased risk of death. The figures below are for those with CVD and diabetes, but are similar to those with diabetes without CVD.
  - A systolic BP <110 was associated with an almost 3x increased risk of death compared with a systolic BP of 130–140 (HR 2.79, CI 1.74–4.48).
  - A diastolic BP of 70 was associated with almost 2x increased risk of death compared with a diastolic BP of 80–84 (HR 1.89, CI 1.4–2.56).

This fits with the results of the ACCORD trial (4700 patients with diabetes at high risk of CVD), which showed that aiming for a BP tighter than 130–140 did not reduce the risk of CV events over 5y (NEJM 2010;362:1575).

**What do the guidelines say?**
NICE suggests target BP of <140/80. If renal, eye or CV damage: target is <130/80 (NICE 2009, CG 87).

SIGN suggests target BP of <130/80 (SIGN 2010, 116).

QOF incentivises us to aim for a BP below 140/80.

**What does this mean in practice?**
- **Do not get the wrong message here!** The studies are NOT saying that blood pressure control doesn’t matter: lots of evidence tells us that it does!
- What these trials show is that really tight blood pressure control may be harmful (<110/70) and that aiming for blood pressures <130/80 may not be beneficial in diabetes, whether with or without CVD.
- Given this, it seems reasonable to follow NICE guidance (which is the same as QOF) and aim for a BP target of systolic 130–140 and a diastolic of 80 but not much below.
- Now we know what to aim for, we just have the challenging task of trying to reach these targets!!!

**Aspirin in diabetes**
Let’s be clear, in someone who has had stroke or heart attack we would use anti-platelets as SECONDARY PREVENTION (but probably clopidogrel, not aspirin, as discussed in the Cardiovascular chapter). This is true whether or not they had diabetes.

In PRIMARY PREVENTION in non-diabetics, there is now a significant body of evidence that using aspirin is not indicated, because the benefits are minute. We have always assumed that some populations at higher risk of CVD (such as diabetics), may still benefit from aspirin. The latest evidence suggests not!

Two high quality trials have now confirmed that aspirin should NOT be used in PRIMARY prevention (POPADAD, BMJ 2008;337:a1840; Japanese RCT, JAMA 2008;300:2134).

A further meta-analysis of primary prevention of CVD in diabetics also concluded that aspirin was either of very low efficacy or not efficacious at all (relative risk 0.9, CI 0.81–1) (BMJ 2009;339:b4531). This meta-analysis included 157 trials (over 10,000 patients), although the authors did point out that many of the trials have been of poor quality. The accompanying editorial rightly points out that the confidence intervals reach 1, suggesting there may be some benefit (BMJ 2009;339:b4596). Indeed, we know from primary prevention trials in non-diabetics that aspirin offers some benefit, but that the benefit is too small to be worth taking a tablet every day for (NNT 1666/y to prevent 1 CV event).

**What does this mean in practice?**
- Aspirin is no longer recommended for PRIMARY prevention of CVD in diabetics.
Lipids, BP, aspirin and cardiovascular risk

- Review cardiovascular risk annually in diabetics.
- You can then follow the NICE guidance, or take the simpler approach offered by SIGN and offer statins to all over 40y.
- Although we have assumed aspirin is helpful in primary prevention in diabetes, evidence suggests this is not true.

For professionals:
UKPDS risk engine is at www.dtu.ox.ac.uk/index.php?maindoc=/riskengine

Personal learning points/actions: