Statistics explained

In the online handbook (www.gpCPD.com) you will find a simple summary of all the statistics used in this book. It's written by us GPs, none of whom are great statisticians, so it should make sense in a way that some statistics books might not! It should also help registrars preparing for the AKT!

Abbreviations used in the GP Update Handbook

We try to avoid using abbreviations except where they are universally recognised (MI, COPD). Statistical abbreviations are listed and explained in the Statistics chapter (www.gpCPD.com). We do abbreviate journal references:

- Arch. Int. Med. - Archives of Internal Medicine
- BJGP - British Journal of General Practice
- BMJ - British Medical Journal
- DTB - Drugs and Therapeutics Bulletin
- JAMA - Journal of the American Medical Association
- MeReC - National Prescribing Centre Bulletins (not exactly an abbreviation!)
- NEJM - New England Journal of Medicine
- NICE - National Institute for Health and Care Excellence
- SIGN - Scottish Intercollegiate Guidelines Network
- UKMI - UK Medicines Information

References

Most references are given in standard format (Journal, year;volume:page) with a few exceptions. Cochran reviews are referenced as: Cochrane 2005;CD002946. Go to www.cochrane.org (NOT cochrane.co.uk) and type the ‘article number’ without the date (e.g. CD002946) into the search engine.

UKMI question and answer references are given as UKMI 55.6 (the question number), followed by the year. To access the original article go to www.evidence.nhs.uk and type UKMI followed by the question number (i.e. UKMI 55.6) and this will take you to the article.

Icons used in this book

At the end of each section in the Handbook you will find a summary box, which include the key take home messages, some ideas to help you apply your learning and some useful websites.

- This icon occurs where we list Take home messages
- This icon occurs where we list possible ideas for CPD actions
- This icon occurs where we list Useful websites
- This icon shows where you can add your own Notes

We make every effort to ensure the information in these pages is accurate and correct at the date of publication, but it is of necessity of a brief and general nature, and this should not replace your own good clinical judgement, or be regarded as a substitute for taking professional advice in appropriate circumstances. In particular check drug doses, side-effects and interactions with the British National Formulary. Save insofar as any such liability cannot be excluded at law, we do not accept any liability for loss of any type caused by reliance on the information in these pages.

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Diabetes and Pre-diabetes

Take a look at our Online Handbook, at www.gpCPD.com (access code on the inside front cover of this Handbook), for more than 450 articles, in addition to those listed here!

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Pre-diabetes

Diagnostic criteria

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.

<table>
<thead>
<tr>
<th>PRE-DIABETES</th>
<th>IMPAIRED FASTING GLUCOSE</th>
<th>IMPAIRED GLUCOSE TOLERANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c 42–47mmol/mol or 6–6.4%</td>
<td>Fasting plasma glucose 6.1–6.9mmol/L (NICE)</td>
<td>Fasting plasma glucose &lt;7.0mmol/L AND 2h plasma glucose 7.8–11mmol/L</td>
</tr>
</tbody>
</table>

- **HbA1c is NOT suitable** if rapid rise in blood sugar (type 1, acute illness, drugs such as steroids) or if increased red cell turnover, pregnancy, anaemia, haemoglobinopathies. HbA1c less sensitive but more acceptable and convenient (DM Care 2010;33:S1).

- **Oral glucose tolerance test**: used in pregnancy but limited role in other situations because complex, expensive, and less reproducible (NEJM 2012;367:542). Do note that in pregnancy (but not other conditions) NICE have changed the thresholds for the diagnosis of gestational diabetes: fasting glucose ≥5.6mmol/L (previously 7) and 2h glucose of ≥7.8mmol/L (NICE 2015, NG3).

Is screening and treating pre-diabetes worth it?

The DPPOS was a long-term observational study of people with pre-diabetes (6y follow-up) and looked at the benefits of returning to normoglycaemia through lifestyle modification (Lancet 2012;379:2243). Of those recruited in the first 3y of the trial, 33% developed diabetes:

- 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 (ARR 16%).

- 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.

However, the long-term benefits are less clear (Lancet 2012;379:2279).

- In a Chinese study of pre-diabetes, treatment resulted in a 3.6y delay in developing diabetes and a 50% reduction in severe retinopathy, but no change in other microvascular events.

- Results on the impact of pre-diabetes management on macrovascular outcomes have been equivocal, although this may be in part because of the relatively short duration of some of the trials.

So treating pre-diabetes reduces the progression to diabetes, which seems like a good thing, however, whether this actually reduces long-term morbidity and mortality is less clear.

And of note, a large cohort trial (ADDITION) showed that screening for diabetes with intensive post-diagnosis care showed no benefit after 10y in terms of all-cause mortality, diabetes-related mortality or cardiovascular mortality compared with no screening at all (Lancet 2012;380:1741).

Which pre-diabetics benefit most from an intervention?

This trial looked at 3000 US patients enrolled in the Diabetes Prevention Program which was a large trial for those with pre-diabetes (actual criteria were more complex involving raised BMI (defined for each ethnicity) and impaired fasting glucose, but I think it is reasonable to say these patients roughly equated to people we see with pre-diabetes). Those in the trial were randomised to usual lifestyle advice + metformin, usual lifestyle + placebo, or an intensive lifestyle programme without metformin (BMJ 2015;350:h454).

In the original trial, after almost 3y follow-up, the progression to diabetes (compared with the lifestyle + placebo arm) was reduced by:

- 58% in the intensive lifestyle arm (CI 47–66%)
- 31% in the metformin + usual lifestyle arm (CI 17–43%).

The researchers then developed a way of stratifying people’s risk of progression to diabetes based on 17 variables (including BMI, waist circumference, BP, lipids, HbA1c). Using this model they then stratified all the patients into quartiles from highest to lowest risk.

- Regardless of whether their risk of diabetes was high or low, all gained benefit in terms of absolute risk of progression to diabetes.

- Those stratified as higher risk got more benefit than those at lower risk. NNT to prevent one case of diabetes over almost 3y were:
  - NNT 3.5 in the highest risk quartile
NNT 20.4 in the lowest risk quartile.

- However, the benefit from metformin was really only seen in those at highest risk of diabetes (NNT 4.6 to prevent one case of diabetes over almost 3y) compared with no benefit in the lowest risk group.

The authors comment that this suggests we should be able to move towards more effective targeting of pre-diabetes interventions. The downside: we can’t, at the moment, easily stratify our pre-diabetics to identify those in the highest risk groups who would most benefit from metformin (or identify those least likely to benefit).

In summary:
- Regardless of risk, intensive lifestyle intervention reduces progression to diabetes (at least in the short term), with those at highest risk gaining most.
- Metformin is beneficial in those at highest risk of progression to diabetes, but has no benefit in those with pre-diabetes who are at low risk of progression.
- We don’t yet have the tools used in this study to stratify risk.
- The impact of detecting and treating pre-diabetes on long term outcomes is, as we discussed above, still unclear.

Management: NICE guidance

Once diagnosed, what treatment does NICE recommend for pre-diabetes?

<table>
<thead>
<tr>
<th>NICE on managing pre-diabetes</th>
<th>NICE 2012, PHG38</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle modification</strong></td>
<td></td>
</tr>
<tr>
<td>Offer intensive lifestyle change programme to:</td>
<td></td>
</tr>
<tr>
<td>• Increase physical activity</td>
<td></td>
</tr>
<tr>
<td>• Achieve and maintain weight loss</td>
<td></td>
</tr>
<tr>
<td>• Increase dietary fibre, reduce dietary fat intake</td>
<td></td>
</tr>
<tr>
<td><strong>Drug therapy in pre-diabetes</strong></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>• Offer metformin to those who are at high risk of diabetes and:</td>
<td></td>
</tr>
<tr>
<td>† Despite intensive lifestyle intervention their HbA1c is not falling</td>
<td></td>
</tr>
<tr>
<td>† OR they can’t undertake intensive lifestyle programmes because of illness or disability.</td>
<td></td>
</tr>
<tr>
<td>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 6–12 m after starting, but warn patients that treatment is likely to be lifelong.</td>
<td></td>
</tr>
<tr>
<td>• Offer orlistat if at high risk of diabetes and BMI ≥28 and:</td>
<td></td>
</tr>
<tr>
<td>† HbA1c not falling despite intensive lifestyle interventions</td>
<td></td>
</tr>
<tr>
<td>† Or unable to take part in physical activity programme because of illness or disability.</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>• NICE say nothing about lipids or blood pressure, but clearly these are important too – for now I would manage them as per the hypertension and lipids guidance (so offer ambulatory BP if BP 140/90 or more and assess CV risk using QRISK2 and offer atorvastatin 20mg if QRISK2 is 10% or more) (NICE 2011, CG127 &amp; NICE DRAFT lipids guidance 2014).</td>
<td></td>
</tr>
</tbody>
</table>

Orlistat: drug dilemma

There have been concerns that orlistat may cause liver damage. A case–control study of over 90,000 UK patients showed that the incidence of acute liver damage was the same in the 3m before starting orlistat as in the first month of use (BMJ 2013;346:f1936). This suggests it is the lifestyle changes and any changes that might precipitate the desire to change weight (such as associated illnesses), rather than the orlistat itself that causes the liver damage. Liver damage was broadly defined as significant change in LFTs, jaundice or worse. LFT monitoring is not recommended in the SPC.

An animal study raised the possibility of orlistat causing colorectal cancer. However, a matched cohort trial of over 33,000 people who had taken orlistat showed no increased risk, after controlling for the important
risk factors and screening. The nature of this trial means it cannot rule out an increased risk in long-term orlistat users, but for most people using it in line with NICE guidance, these are reassuring data (BMJ 2013;346:f5039).

Evidence for metformin

A Lancet review in 2012 discussed this (Lancet 2012;379:2279):
- There is good evidence that metformin in pre-diabetes reduces progression to diabetes (reduces risk by about 45%).
- The benefits are greater in those who are most overweight or who have the higher blood sugar levels.
- The harms are minimal (GI upset being the main problem).
- However, the long term benefits are less clear.

Managing pre-diabetes

- Screening for pre-diabetes reduces risk of progression to diabetes, but impact on long term morbidity and mortality is less certain.
- For those with pre-diabetes, intensive management is recommended, possibly using metformin and/or orlistat with annual re-screening for diabetes.

How do you code and manage those with pre-diabetes?

My notes
Diabetes mellitus: type 2

We run a usual doctor system in our practice, but if I asked our type 2 diabetics who their usual doctor was, most of them would answer, “Alison, the practice nurse”. The good news is that whether you have a GP or a nurse who does most of your diabetic care, a study showed HbA1c levels are no different (BJGP 2015;65:514). But of course diabetes is about much more than glycaemic control...

The role of insulins in type 2 diabetes is discussed in a separate article.

Priorities in type 2 diabetes

Let’s start by reminding ourselves of the relative benefits of glycaemic control vs. cardiovascular risk factor control (BP, cholesterol).

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Number of cardiovascular events prevented for every 1000 people treated over 5y</th>
<th>Microvascular benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowering blood sugar by 0.9%</td>
<td>8</td>
<td>Less clear!</td>
</tr>
<tr>
<td>Lowering cholesterol by 1mmol/L</td>
<td>23</td>
<td>Glycaemic control is important, although BP control may be more important.</td>
</tr>
<tr>
<td>Reducing BP by 10/5</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

This is backed up by data 10y after the ADVANCE trial. This trial randomised people to tight blood sugar control or tight blood pressure control and followed them for almost 5y. After this they went back to usual care. Ten years after the trial started researchers looked at outcomes (NEJM 2014;371:1392).

- Blood pressure control during the 5y of the trial showed benefits in terms of reduced cardiovascular and all-cause mortality. These benefits persisted 5y after completing the trial and returning to usual care.
- Tight blood sugar control during the trial showed a reduction in nephropathy but no other benefits. There were no significant benefits 5y after returning to usual care.
- However, the Veterans Affairs Diabetes trial did show CV benefits from tight blood sugar control (10y follow-up over 1500 diabetics, randomised to 5y of tight control (median HbA1c 6.9%) vs. standard care (median HbA1c 8.4%). After 10y there were 8.6 fewer vascular events/1000 people years in the tight control arm although not overall survival benefit – almost exactly the benefit quoted above – and so significantly fewer benefits than lowering cholesterol or BP.

The challenge of complexity in diabetes

The challenges of diabetes were beautifully summarised in an editorial in the BJGP in July 2015 by Jonathan Sleath, a GP in Hereford (BJGP 2015;65:334). He outlined the following concerns:

- Raised blood glucose is just one component of a complex assortment of metabolic abnormalities.
- Raised blood sugar and type 2 diabetes are risk factors for macro- and microvascular cardiovascular disease.
- Antihypertensives and statins are cheaper and easier to use than hypoglycaemics and do not have the side-effects of weight gain or hypoglycaemia.
- Since statins and antihypertensives are off-patent, the pharmaceutical industry has invested heavily in developing and promoting drugs to lower blood sugar. Do the modest reductions some of these drugs offer actually reduce long term important outcomes? Will they be associated with any long term harms we are not yet aware of (or have only had hints of)?
- Should we focus on young patients and those with very high HbA1c and be less aggressive with older patients where we should focus on established risk factors (BP, cholesterol) rather than bringing the HbA1c down just a little bit further.

As we look at the NICE guidelines, and think about the care we offer to individual patients, bear in mind that although glycaemic control is important, cardiovascular risk reduction (and of course lifestyle is an important part of this) may be more important.

Tight glycaemic control may be harmful

An increasing number of studies have suggested that really tight blood sugar control may offer no additional benefits and may in fact actually be harmful in terms of cardiovascular or all-cause mortality (NEJM 2008;358:2630 & 2633; Lancet Commission 2009;373:1737).
The evidence suggests there may be a U-shaped curve associated with blood sugar control: poor control (raised blood sugars) increases mortality, but so does very tight control. The optimum point seems to be around 53mmol/mol (7%).

Harms of hypoglycaemia

This important meta-analysis showed that severe hypoglycaemia is important to avoid in type 2 diabetes (BMJ 2013;347:f4533).

It was a meta-analysis of trials looking at cardiovascular events and hypoglycaemia. Hypoglycaemia was defined as impaired consciousness or needing medical help, so picked up the more severe end of the spectrum. Importantly, it excluded trials done in acute hospital settings (where co-morbidity may fudge the results). 900,000 people were included, all with type 2 diabetes.

- The study showed that severe hypoglycaemia in type 2 diabetes is strongly associated with a higher risk of CVD.
- The risk of CVD in those with severe hypoglycaemic episodes is about double those who have not had severe hypos (RR 2.05, CI 1.74–2.42).
- This increased risk could not be entirely explained by biasing caused by co-morbidity (i.e. co-morbidity that may have induced the hypo or be a risk factor for CVD).

Why might this be the case?

In response to severe hypoglycaemia there is a sympathetic nervous system response: catecholamines released in this have an adverse effect on the myocardium and vasculature but also increase platelet aggregation and other inflammatory responses that may encourage atherosclerosis development. Added to that, severe hypoglycaemia can also trigger arrhythmias.

So what does this mean in practice?

- The authors suggest this provides more evidence that we should set individualised HbA1c targets in those with type 2 diabetes, and that these should be higher in those at risk of severe hypos.
- The authors suggest this adds weight to the argument to use drugs such as metformin widely in type 2 diabetes (as discussed in the next section).
- They also remind us that many cases of severe hypos are caused by variation in food intake, perhaps something we should remind our patients about.
- Remember that a trial has shown that, when gliptins are added to sulphonylureas, there is a significant increase in the risk of hypoglycaemia, compared with when people are on sulphonylureas alone (1 extra case for every 17 people treated in the first 6 months) (BMJ 2016;353:i2231). The BNF recommends reducing the dose of a sulphonylurea when starting a gliptin, and this study confirms this may be a sensible approach.

Over-testing HbA1c

This study identified over 30,000 diabetic Americans who had had 2 consecutive HbA1c tests in the last 2y, both with an HbA1c of <7%. That is, well controlled and stable diabetics. They then looked at how frequently blood sugars were re-measured, and whether action was taken in the light of that test (BMJ 2015;351:h6138).

- Despite being well-controlled 6% had their HbA1c measured 5 or more times in the next year and 55% had their HbA1c measured 3–4 times over the same time.
- Despite good control 8% of patients had their treatment intensified.
- They did not look at under-testing.
- Interestingly, after 2009 excessive testing rates almost halved

The authors concluded that excessive testing was wasteful and increased patient burden with no clear benefit. The authors suggest the factors that may have contributed to over-testing include:

- Fragmentation of care may have led to over-testing (different providers repeating tests).
- A desire to be thorough.
- A failure to understand the test is an average of the last 3m of control.

Over-testing and over-treating is particularly undesirable in the light of the data showing too tight control may be harmful in established diabetics.
The accompanying editorial reminds us of the law of diminishing returns and reminds us that if we have to obsess over numbers we should make it the absolute risk reduction from any intervention (which would stop much of our meddling!) (BMJ 3015;351:h6549).

**Tight BP control may be harmful**

We’ve just discussed that low blood sugars may be associated with a J-shaped curve. Evidence is emerging that this may also be true for blood pressure control in type 2 diabetes.

A meta-analysis pooled data from over 70,000 people with type 2 diabetes, and showed that reducing baseline systolic blood pressure was not always beneficial (BMJ 2016;352:i717).

- At baseline systolic BP of above 140mmHg, lowering the blood pressure resulted in a reduction in all-cause mortality and some other benefits.
- At a baseline systolic BP of below 140mmHg, lowering the blood pressure increased cardiovascular mortality with no benefits in any other areas.

The details, and relative risk, are shown below. Where no benefit or harm was shown, this is marked ‘–’.

<table>
<thead>
<tr>
<th>Impact of lowering BP</th>
<th>Baseline SBP &gt;150</th>
<th>Baseline SBP 140-150</th>
<th>Baseline SBP&lt;140</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Reduced risk (RR 0.89, CI 0.8-0.99)</td>
<td>Reduced risk (RR 0.87, CI 0.78-0.98)</td>
<td>Trend towards increased risk (RR 1.05, CI 0.95-1.16)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>Reduced risk (RR 0.75, CI 0.57-0.99)</td>
<td>–</td>
<td>Increased risk (RR 1.15, CI 1.03-1.29)</td>
</tr>
<tr>
<td>MI</td>
<td>Reduced risk (RR 0.74, CI 0.63-0.87)</td>
<td>Reduced risk (RR 0.84, CI 0.76-0.93)</td>
<td>–</td>
</tr>
<tr>
<td>CVA</td>
<td>Reduced risk (RR 0.77, CI 0.65-0.91)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>Reduced risk (RR 0.82, CI 0.71-0.94)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Heart failure</td>
<td>–</td>
<td>Reduced risk (RR 0.8, CI 0.66-0.97)</td>
<td>–</td>
</tr>
</tbody>
</table>

- This data contradicts another meta-analysis which showed cardiovascular benefits even when lowering the blood pressure below 130, including in the diabetes sub-group analysis (although the numbers in the subgroup analysis were smaller – around 25,000 vs. 70,000 in the BMJ trial above) (Lancet 2016; 387: 957).

The accompanying editorial pointed out that trials are always full of relatively healthy, younger patients, and so some harms, such as postural hypotension, may be under represented, and that (BMJ 2016;352:i813):

- Benefits of BP lowering may be over represented in trials compared with the ‘average’ (older, less healthy) patient we see.
- We need to be aware of the burden of treatment for patients (side effects, adverse events, the need to take multiple tablets, etc.).
- Individual patients’ priorities may not fit our neat bio-medical model!

**Are ACE inhibitors/ARBs the best drugs for BP control in diabetes?**

NICE guidelines on hypertension in diabetes recommend ACE inhibitors are used first line to control blood pressure.

A meta-analysis of 25,000 people (19 trials) showed no significant benefits in important outcomes (death, cardiovascular death, IHD, CVA, heart failure) compared with other antihypertensives in diabetic patients. It also showed no benefit in terms of the risk of developing end-stage renal disease (BMJ 2016;352:i438).

There is an ongoing debate about whether the benefits of ACE inhibitors/ARB come entirely from their blood pressure lowering effect (in which case any antihypertensive will offer similar benefits), or whether they have benefits through other mechanisms.

The accompanying editorial pointed out that this was a relatively healthy cohort of diabetics: none of the patients had CHD, heart failure, renal failure or proteinuria. In diabetics with these other co-morbidities, there are good reasons why ACE inhibitors/ARBs would be a preferred first line drug (BMJ 2015;352:i560).
What does this mean in practice?

- High blood pressure is damaging in diabetes. Reducing blood pressure is beneficial (to a point, see above!). Which drug is used to do this may be less important in healthy diabetics.
- Interestingly, European and some other national guidance no longer recommends using ACE inhibitors first line in diabetics without other co-morbidities.
- NICE does still recommend using ACE inhibitors first line in diabetics, and this should certainly be the case in those with CHD, heart or renal failure or proteinuria.

Tailoring HbA1c targets based on age/co-morbidity

Given what we have discussed above, it is good to know that although NICE set targets for glycaemic control, they also make clear that targets should be tailored to an individual's needs. The American Diabetes Association and the American Geriatrics Society have issued joint guidance, based on consensus, around treating type 2 diabetes in older age. They suggest the following targets, based on frailty and co-morbidity (Diabetes Care 2012;35:2650).

For those of 65 and over:

<table>
<thead>
<tr>
<th>Health status (for those over 65y)</th>
<th>Target HbA1c %</th>
<th>Target BP mmol/mol</th>
<th>Lipid modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>&lt;7.5</td>
<td>&lt;58</td>
<td>&lt;140/80 Statins indicated</td>
</tr>
<tr>
<td>Intermediate health</td>
<td>&lt;8</td>
<td>&lt;64</td>
<td>&lt;140/80 Statins indicated</td>
</tr>
<tr>
<td>Poor health</td>
<td>&lt;8.5</td>
<td>&lt;69</td>
<td>&lt;140/90 Benefits less certain: greater benefit in secondary prevention</td>
</tr>
</tbody>
</table>

This makes sense, and is what we often do in primary care, but it is good to see it as a consensus statement from a formal organisation. Do bear in mind though that QOF has no adjustment for age.

A BMJ review of diabetes in older people with co-morbidities reminds us (BMJ 2016;535:i2200):

- Of the seriousness of hypoglycaemia in all groups, but especially the elderly.
- The burden of daily tablet taking (and blood sugar measuring).
- The impact of diabetes and complications on quality of life.
- The lack of evidence base for many of the new drugs in older people or those with co-morbidities.

An interesting article tried to assess the benefits of blood sugar control in terms of quality adjusted life years (QALYs). Now, when it comes to QALYs a lot of assumptions are made about how much any benefit or any harm affects quality of life, and you can adjust these assumptions and see what impact it has on QALY. This study looked at how burdensome treatment to lower blood sugar was (both tablets and insulin), and what benefits it gave (JAMA Intern Med doi:10.1001/jamainternmed.2014.2894).

- Not surprisingly they found most benefit in lowering blood sugar in those who were younger.
- The benefit was minimal in those over 75 (unless HbA1c was above 9%). However, it all depends on how burdensome the treatment is to the individual. A reminder that whatever trials show for whole populations, tailoring to an individual's wishes and their perceptions of benefits/burden is crucial – thankfully that is what GPs and practice nurses are good at (even if QOF isn't!).


NICE guidance: key changes

Here I will tell you both what has changed and what hasn’t (because that is equally important as you need to know where your current practice is in line with NICE recommendations) (NICE 2015, NG28).
• **Lifestyle is crucial, as is weight loss if overweight** (sorry to state the obvious but in a section that focuses hugely on drugs, I don’t want you to think I’ve forgotten lifestyle is central to diabetes care!).

• **Bariatric surgery: can be considered in those who have a BMI ≥30 (lower in those of Asian ethnicity), when all other non-surgical measures have been tried** (NICE 2014, CG189). In Scotland the SIGN guidelines suggest surgery may be considered in those with a BMI of 35 or more (SIGN 2010, 115). **What is the evidence?**
  
  ○ There is some evidence of short-term benefits. A small (60 patients) but long-term follow-up (over 5y) of those with diabetes having bariatric surgery showed that many became non-diabetic after surgery and 50% of all those who had surgery remained non-diabetic after 5y, compared with none in the usual care group. However, the surgery was either gastric bypass or diversion, not banding, which is the more common procedure. Relapse was common though, so in those who do lose their diabetic status, regular re-testing is needed to detect early relapse (Lancet 2015;386:964).
  

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

• **The BP targets remain the same: 140/80 (130/80 if renal, eye or cerebrovascular complications).** BP treatment is in line with NICE hypertension guidelines but use an ACE inhibitor first line in everyone regardless of age because of renal benefits.

• **Lipids: in line with NICE lipids guidance:**
  
  ○ In primary prevention if QRISK2 ≥10% offer atorvastatin 20mg. NICE recommends fire and forget but QOF will drive us to get cholesterols <5.
  
  ○ In secondary prevention: atorvastatin 80mg. Aim to reduce non-HDL cholesterol by 40% (see lipids article in Cardiovascular chapter for an explanation of non-HDL cholesterol). QOF will drive us to get cholesterols <5.

• **Glycaemic control:** NICE are keen to emphasise individualised targets, based on the risks of hypos, age, frailty and co-morbidity and life expectancy. However, they do also give us some targets!
  
  ○ Intensify treatment if HbA1c rises above: 48mmol/mol / 6.5% if on lifestyle alone OR 58mmol/mol / 7.5% for those on drug therapy.
  
  ○ Once treatment has been intensified, aim to get HbA1c down to: 48mmol/mol / 6.5% if on monotherapy with metformin, gliptin/pioglitazone OR 53mmol/mol / 7% if on other drugs.

  ○ Self-monitoring is not indicated for most. Use only if on insulin or if hypoglycaemia may cause problems for example with driving/operating machinery.

• **When it comes to drug therapy, in the guidance:**
  
  ○ Metformin remains first line because of cardiovascular benefits. After that it is a bit of a free for all! This is discussed in more detail later in this article.

• **NICE remind us about the features of autonomic neuropathy:** reduced hypo awareness or unexplained bladder emptying or GI tract symptoms: gastroparesis (bloating, vomiting, erratic blood sugars), unexplained diarrhoea, especially at night.

• **Foot, eye and renal care remains unchanged.**

**An overview of the drugs used in diabetes**

Here I have included an overview of the impact each class of drug has on the risk of hypoglycaemia, weight, renal function and important safety data. Understanding this is important, because on the basis of these sorts of factors you will make your choice about which drug to start for which patients. I’ve ranked them by cost, starting with the cheapest.

Remember that, apart from metformin and insulin, there is no good evidence to say any drug, or class of drugs is better at lowering blood sugar than any other (DTB 2013;51(9):98).

When starting a new hypoglycaemic agent, the key factors that will guide your choice will include:

• Does this drug increase the risk of hypos?

• What impact does this drug have on weight?

• What are the harms and cautions for this drug, and how relevant are these to the person sitting in front of me?

• Can this drug be used at the level of renal impairment my patient has?

• Will this drug be cost effective, all other things being equal?

I have summarised these elements in the table below.
Comparing diabetic drugs
Costs are based on 1m at maximum dose.
(Acarbose not included: NICE found insufficient evidence for its use/evidence of ineffectiveness).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Risk of hypos</th>
<th>Weight change</th>
<th>Safety issues (including use in renal impairment)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metformin</strong></td>
<td></td>
<td></td>
<td>• Cardiovascular benefits.</td>
</tr>
<tr>
<td>£2</td>
<td></td>
<td>Loss</td>
<td>• In renal impairment:</td>
</tr>
<tr>
<td>Modified release</td>
<td></td>
<td></td>
<td>o eGFR&lt;45: review dose.</td>
</tr>
<tr>
<td>£17</td>
<td></td>
<td></td>
<td>o eGFR&lt;30: stop.</td>
</tr>
<tr>
<td><strong>Pioglitazone</strong></td>
<td>Rare</td>
<td>Gain</td>
<td>• Use with care in the elderly, where all risks detailed below are more significant.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o Contraindicated if PMH bladder cancer.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o Assess for known risks of bladder cancer before starting: age, smoking, exposure to some occupational chemotherapeutic agents, pelvic irradiation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Large cohort study confirmed this risk. Dose and duration dependent. Absolute risk increase small (32/100,000 person years) (BMJ 2016;352:i541).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Heart failure (Drug Safety Update 2011;4(6):A2):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o Absolutely contraindicated in heart failure.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o Use with care if at risk of heart failure (especially elderly).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Fractures (Lancet 2009;373:2125, BMJ 2009;339:b4731)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o Women only? Arm or distal leg fractures. Cause unclear.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• In renal impairment: safe.</td>
</tr>
<tr>
<td><strong>Sulphonylureas</strong></td>
<td>Yes</td>
<td>Gain</td>
<td>• No significant concerns identified.</td>
</tr>
<tr>
<td>(gliclazide)</td>
<td></td>
<td></td>
<td>• Increased risk of hypos especially in those on warfarin.</td>
</tr>
<tr>
<td>£5</td>
<td></td>
<td></td>
<td>• In renal impairment: increased risk of hypoglycaemia.</td>
</tr>
<tr>
<td><strong>Repaglinide</strong></td>
<td>Yes</td>
<td>Gain</td>
<td>• No significant concerns identified.</td>
</tr>
<tr>
<td>£8</td>
<td></td>
<td></td>
<td>• Avoid in liver disease: excreted in bile.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• In renal impairment: safe.</td>
</tr>
<tr>
<td><strong>Gliptins (DPP4 inhibitors)</strong></td>
<td>Rare</td>
<td>Neutral</td>
<td>• Pancreatitis: warn all patients of symptoms: persistent severe abdominal pain sometimes radiating to the back. Risk 1 in 100 to 1 in 1000 (Drug Safety Update 2012;6(2):A3).</td>
</tr>
<tr>
<td>(also called incretins)</td>
<td></td>
<td></td>
<td>• No increased risk of pancreatic cancer (BMJ 2016;352:i581).</td>
</tr>
<tr>
<td>£31–34</td>
<td></td>
<td></td>
<td>• Liver toxicity: rare.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Heart failure: possible small increased risk of admission with heart failure: around 8/1000 people/5y (confidence intervals mean that could be between 0 and 16 extra cases/1000/5y (meta-analysis BMJ 3016;352:i610). Although another meta-analysis showed no increased risk (NEJM 2016;374:1145).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• In renal impairment: linagliptin safe, reduced dose for other gliptin (see SPC).</td>
</tr>
<tr>
<td><strong>Gliflozins</strong></td>
<td>Rare</td>
<td>Loss</td>
<td>• Life-threatening diabetic ketoacidosis (DKA) AT ONLY MODERATELY RAISED BLOOD SUGARS (&lt;14mmmol/l). MHRA advises:</td>
</tr>
<tr>
<td>(SGLT-2 inhibitors)</td>
<td></td>
<td></td>
<td>o Inform all patients of symptoms and signs of DKA (nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, fatigue, sleepiness).</td>
</tr>
<tr>
<td>Around £36</td>
<td></td>
<td></td>
<td>o Clinicians to test for ketones in patients presenting with these symptoms, even if blood sugar is only mildly elevated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Possible CV and renal benefits and risk of amputation discussed later.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• In renal impairment:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o Dapagliflozin: GFR&lt;60: do not use.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o Cana and empagliflozin: do not start if eGFR&lt;60. If stable on drug and eGFR drops to 45–6, may continue it (see SPC).</td>
</tr>
<tr>
<td><strong>GLP-1 mimetics</strong></td>
<td>Rare</td>
<td>Loss</td>
<td>• No significant concerns identified.</td>
</tr>
<tr>
<td>(also called incretins)</td>
<td></td>
<td></td>
<td>• Because of cost, NICE sets strict criteria for use (see later).</td>
</tr>
<tr>
<td>£50–70</td>
<td></td>
<td></td>
<td>• In renal impairment:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o Liraglutide: eGFR&lt;30: do not use.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o Exenatide and lixisenatide: eGFR 30–50 use with caution. eGFR&lt;30: do not use.</td>
</tr>
</tbody>
</table>

## NICE guidance: summary

### Summary of NICE type 2 diabetes guidelines (2015)

#### Diagnosis

- **Fasting glucose ≥7 on two separate occasions**
- **HbA1c ≥48mmol/mol (6.5%) on two separate occasions two weeks apart**

(Don’t use HbA1c if rapid rise in blood sugar/increased red cell turnover/pregnancy/anaemia/haemoglobinopathies)

**Oral glucose tolerance test?** Limited role except in pregnancy. Complex, expensive, less reproducible (NEJM 2012;367:542)

#### Management

<table>
<thead>
<tr>
<th>BP target</th>
<th>Cholesterol target</th>
<th>HbA1c target</th>
</tr>
</thead>
<tbody>
<tr>
<td>140/80</td>
<td>Primary prevention: fire &amp; forget</td>
<td>Intensify treatment if HbA1c above:</td>
</tr>
<tr>
<td>(130/80 if cerebrovascular/renal/eye complications)</td>
<td>Secondary prevention of CVD:</td>
<td>48/6.5% (lifestyle alone)</td>
</tr>
<tr>
<td></td>
<td>40% fall in non-HDL chol</td>
<td>58/7.5% (all others)</td>
</tr>
<tr>
<td>QOF target 140/80 for max. points</td>
<td>QOF target &lt;5 for all</td>
<td>QOF target 58/7.5 for max. points</td>
</tr>
</tbody>
</table>

**BP**

- **Follow NICE hypertension guidance but use ACE inhibitor first line regardless of age.**
  - 1st line: ACE inhibitor (because of renal benefits). If intolerant of ACE try an ARB.
  - African/Caribbean origin: ACE AND either a thiazide-like diuretic OR CCB.
  - Women who may become pregnant: calcium channel blocker.
  - 2nd line: ADD calcium channel blocker (CCB) OR thiazide-like diuretic (indapamide).
  - 3rd line: ACE + CCB + thiazide-like diuretic (indapamide).
  - 4th line: Add alpha-blocker/beta-blocker/potassium sparing diuretic. If this fails, refer.

**Lipids**

- **Primary prevention:** Atorvastatin 20mg if QRISK2 ≥10%. **NICE target:** fire and forget.
- **Secondary prevention:** Atorva 80mg. **NICE target:** reduce non-HDL cholesterol by 40%.
- **Aspirin/antiplatelets:** Do NOT use unless known cardiovascular disease.

**Glycaemic control**

- **Intensify treatment if HbA1c greater than:**
  - 48/6.5% on lifestyle alone.
  - 58/7.5% on any drug therapy.
- **Target after intensifying treatment:**
  - 48/6.5% if on monotherapy with metformin/glititin/pigolitazone.
  - 53/7% for those on other treatments.

**Foot care**

- **Annual examination for risk factors and stratification of risk:**
  - Neuropathy (use 10g monofilament).
  - Evidence of ischaemia.
  - Ulceration, callouses, infection or gangrene.
  - Deformity, Charcot’s arthropathy (warm, red, swollen, deformed joint, often painful).
  - **Gastroparesis** can be treated with erythromycin (unlicensed).
- **If anything other than low risk (i.e. 1 or more of the above):** refer.

**Autonomic neuropathy**

- **Reduced hypo awareness.**
- **Unexplained bladder emptying.**
- **GI tract symptoms:** gastroparesis (bloating, vomiting, erratic blood sugars), unexplained diarrhoea, especially at night. Gastroparesis can be treated with erythromycin (unlicensed).

**Peripheral neuropathy**

- **Remember tight glycaemic control reduces progression of neuropathy!**
- **Treat as per NICE guidelines on peripheral neuropathy (start with amitriptyline).**

**Renal**

- **Follow NICE CKD guidelines. Remember BP target is lower in renal disease: 130/80.**

**Eyes**

- **Annual eye screening. Remember BP target is lower in those with eye problems: 130/80.**
### NICE guidance: glycaemic control

**NICE recommendations for glycaemic control in type 2 diabetes (NICE 2015, NG 28)**

#### TOP STAIRCASE: FIRST LINE THERAPY FOR THE MAJORITY

<table>
<thead>
<tr>
<th>MONOTHERAPY</th>
<th>START metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Move to this step if HbA1c rises above 48/6.5% with lifestyle alone</strong></td>
<td><strong>(if not tolerated try modified release metformin)</strong></td>
</tr>
</tbody>
</table>

**SU= sulphonylurea (use ordinary release, modified release not recommended)**

**Pio = pioglitazone. If using pioglitazone, note contraindications, below.**

**Aim to get HbA1c to 48/6.5%**

**ADD second drug:**

- Metformin + any TABLET EXCEPT repaglinide

**Options therefore are:**

- Metformin + SU
- Metformin + gliptin
- Metformin + pioglitazone
- Metformin + gliflozin (only if SU not tolerated/contraindicated)

**Aim to get HbA1c to 53/7%**

#### FIRST INTENSIFICATION (dual therapy)

- Move to this step if HbA1c ≥58/7.5% (or individualised target not met)

**SECOND INTENSIFICATION** (triple therapy or insulin)

- Add third drug
  - Metformin + SU + gliptin
  - Metformin + SU + pio
  - Metformin + SU + gliflozin
  - Metformin + pio + gliflozin

OR

- Consider insulin therapy
  - (see separate article on insulins)

**Aim to get HbA1c to 53/7%**

#### FURTHER INTENSIFICATION

- Insulin intensification
  - OR if triple therapy contraindicated, not tolerated or not effective
  - AND meet strict criteria for use, (see below) consider:
    - Metformin + SU + GLP-1 mimetic

### BOTTOM STAIRCASE: USE IF MEFORMIN CONTRAINDICATED OR NOT TOLERATED

**MONOTHERAPY (without metformin)**

- **Move to this step if HbA1c rises above 48/6.5% with lifestyle alone**

**Start ONE of:**

- Sulphonylurea
- Gliptin
- Pioglitazone
- Repaglinide

**Aim to get HbA1c to:**

- 48/6.5% if on gliptin/pio
- 53/7% if on SU/repaglinide

**Use any 2 of the following drugs:**

- Sulphonylurea
- Gliptin
- Pioglitazone

**Stop repaglinide, if using**

- (licensed only as monotherapy or with metformin)

**Aim to get HbA1c to 53/7%**

**SECOND INTENSIFICATION** (without metformin)

- Move to this step if HbA1c ≥58/7.5% (or individualised target not met)

- **Consider INSULIN**
  - (see separate article on insulins)

**Aim to get HbA1c to:**

- 48/6.5% if on gliptin/pio
- 53/7% if on SU/repaglinide

### Contraindications for pioglitazone (more in section ‘An overview of the drugs used in diabetes’)

- Uninvestigated frank haematuria/risk of/PMH of bladder cancer
- Heart failure/risk of failure
- Fractures
- Care in elderly (fracture/failure/cancer risk increased)

**NICE remind about MHRA guidance: review effectiveness of pioglitazone 3–6m into therapy and stop if control not achieved.**

### Criteria for GLP-1 mimetic

- BMI ≥35 AND weight-related co-morbidities/psychological issues.
- BMI <35 AND EITHER insulin would have significant occupational implications OR weight loss would improve other weight-related co-morbidities.
- Continue GLP-1 mimetics only if over first 6m of use 3% fall in weight AND 11mmol/1% fall in HbA1c is achieved.
Evidence base for NICE recommendations

NICE made most of their recommendations based on data from 10,000–20,000 people, aged under 65y in trials running for 2y or less. They themselves ranked the evidence as low or moderate to low. Given this, aside from the use of metformin first line (because of cardiovascular benefits), most of the decision are based on COST rather than CLINICAL effectiveness. This is highlighted by the known unknowns raised by NICE: questions we ought to know the answer to but we don’t!

- What is best first line therapy in those who can’t take metformin?
- What are the long-term effects of gliptins?
- What are the long-term effects of SGLT-2 inhibitors/gliflozins?
- What are the patient characteristics that predict response (or otherwise) to each of the drug groups?
- In a person with type 2 diabetes and multimorbidity (i.e. not the healthy people who are in trials) what are the best drugs to lower blood sugar?

Why start with metformin?

Metformin didn’t perform the best in terms of glycaemic control but it is recommended first line because of:

- Cardiovascular benefits.
- Lack of hypoglycaemia.
- Weight loss.
- Ability to titrate up the dose (and therefore possibly reduce gastrointestinal side-effects).

When using metformin the recommendations are to:

- Increase the dose gradually over several weeks to reduce gastrointestinal side-effects.
- Prescribe with caution in those at risk of sudden falls in eGFR.
- Review the dose if eGFR <45.
- Stop if eGFR <30.

But 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;CD002967).

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).
- Dehydration is a trigger for this and so 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:

- Have a low threshold for checking creatinine/eGFR when those taking metformin are unwell.
- 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 role for modified release metformin?

NICE recommend that modified release metformin should only be tried if ordinary release metformin is not tolerated.

Sulphonylureas: which to use?

Be aware that the different sulphonylureas have different risk profiles. This was highlighted in a DTB review article (DTB 2015;53(3):27). In a meta-analysis of trials involving sulphonylureas, the risk of death was:

- 4% in gliclazide users (and this benefit over glibenclamide is statistically significantly).
- 7% in glibenclamide users.
- 11% in glimepiride users.
- 15% in glipizide users.
- 17% in tolibutamide users.
- 23% in chlorpropamide users.

Although these data aren't without their limitations, we should bear them in mind if using anything other than gliclazide as your sulphonylurea of choice.

Warfarin, sulphonylureas and hypoglycaemia

A US study identified that serious hypoglycaemia was more common in those who took warfarin with glipizide or glimepiride (1.2× increased risk). There was also an increased risk of admissions for fall-related fractures (1.5× increased risk). The increased risk was higher the older you were. Unfortunately, the other sulphonylureas were not included (gliclazide isn’t available in the US) (BMJ 2015;351:h6223).

Two potential mechanisms of action were identified:

- Displaced protein binding: warfarin displaces the sulphonylurea thus increasing the plasma concentration of the sulphonylurea.
- Competition for one of the enzymes in the cytochrome P450 system (CYP2C9): all the drugs are metabolised by this enzyme, and it may be saturated by warfarin, increasing plasma concentrations of the sulphonylureas.

These theories also apply to the other second generation sulphonylureas (the ones that begin with ‘g’) so although they were not included in the study, they may also be implicated.

What role for modified release sulphonylureas?

NICE concluded that there was insufficient evidence to recommend modified release sulphonylureas.

Criteria for GLP-1 mimetic use (exenatide, liraglutide, lixisenatide)

NICE set strict criteria for GLP-1 mimetic (incretin) use. They are:

- BMI ≥35 AND weight related co-morbidities/psychological issues
- BMI <35 AND
  - EITHER insulin would have significant occupational implications
  - OR weight loss would improve weight-related co-morbidities.

Continue GLP-1 mimetics only if over first 6m there is a 3% fall in weight AND 11mmol/mol (1%) fall in HbA1c.

Repaglinide use and dosing

NICE noted that repaglinide is not widely used in the UK, and has the big drawback that it is only licensed for monotherapy or dual therapy with metformin. Therefore if someone is started on it, once they require intensification the repaglinide needs to be stopped and 2 other agents started.

Repaglinide has a rapid onset of action so it is taken 30min before food. Starting dose is 0.5mg (500mcg tablet) 30min before main meals. The BNF and SPC suggest adjusting the dose every 1–2w. The maximum
dose is listed as 4mg as a single dose with each main meal, but also listed as being 16mg/d which suggests at maximum dose we should be inviting our diabetics to have 4 main meals a day! I’m sure that won’t help! ... Importantly, it is NOT recommended over 75y (no data from clinical trials) (BNF/SPC).

**SGLT2 inhibitors/gliflozins**

These are relatively new drugs and include dapagliflozin (Forxiga), canagliflozin (Ivokana) and empagliflozin (Jardiance).

Please see important notes about the risk of diabetic ketoacidosis at relatively low blood sugars in the section ‘An overview of the drugs used in diabetes’ earlier in this document.

**SGLT2 inhibitors/gliflozins: background**

For those not familiar with gliflozins, here is some background information:

- Once daily tablet.
- Work in a completely different way to other hypoglycaemics: they inhibit glucose reabsorption in the kidneys, increasing urinary glucose excretion. Because of this hypo risk very low.
- Very few side-effects: main one is increased risk of UTIs (probably because sugar in urine increases bacterial growth) and genital infections.
- Caution in renal disease: see table at the beginning of this article.
- Caution in liver disease: except with empagliflozin.
- No data on use in over 75s.
- Initial dapagliflozin trials showed an increase in bladder cancers in men, although absolute numbers were small and some had haematuria on entry into the trial (so the disease may have predated the drug). Animal studies did not show any carcinogenicity. The SPC states that a causal relationship is unlikely. However, until more data are available dapagliflozin should not be used with pioglitazone (because of concerns about glitazones and bladder cancer). No increased risk of bladder cancer has been reported with the other gliflozins yet.
- Evidence base is relatively limited (small trials running for relatively short time frames).
- The Scottish Medicines Consortium approved the gliflozins for use with metformin, metformin and a sulphonylurea, or insulin but NOT as monotherapy.

(Information above from: UKMi New drugs briefing 2012, Scottish Medicines Consortium 7/7/14, SPC, DTB 2013;51(9):105; NICE 2013, TA288; 2014, TA315.)

**Risk of amputation**

The MHRA has raised a concern about the possible increased risk of amputation with canagliflozin (MHRA June 2016). Early indications from the CANVAS trial have raised concerns that there might be an increased risk of amputation (mainly toe amputations) in those on canagliflozin compared with those on placebo. This has not been reported in other trials, or for other gliflozins. The absolute risk is small, and causation has NOT been established (risk 3/1000 in placebo group, 5/10 000 in 50mg group, 7/1000 in 100mg group). Until more information is available, and this possible concern has been further evaluated, the MHRA reminds us to:

- Consider stopping canagliflozin in those who develop significant lower limb complications (ulcers, osteomyelitis, gangrene) at least until the condition has resolved.
- Monitor those receiving canagliflozin who have risk factors for amputation. In particular, ensure the patient is aware that hydration should be maintained (it is thought dehydration may contribute to the increased risk) and that patients check their feet regularly and report any changes quickly.

**Cardiovascular benefits of gliflozins?**

A much publicised trial looked at the cardiovascular benefits of empagliflozin in 7000 patients with type 2 diabetes followed for 3y (NEJM 2015;373:2117). What did the trial actually show? Run by the makers of empagliflozin, participants were randomised to one of two empagliflozin arms (10mg or 25mg) or placebo.

The primary outcome was death from CV causes, non-fatal MI and non-fatal stroke (a pooled endpoint). All the patients had known cardiovascular disease. After the initial 12w, other drugs to lower glucose levels were allowed if clinically indicated. Participants and clinicians were encouraged to optimise other CV risk factors including BP and lipids.
• There was NO significance between the placebo group or either of the empagliflozin groups for the primary outcome (death from CV causes, non-fatal MI and non-fatal stroke).

As a result they pooled the 2 empagliflozin groups to create a larger sample size, which then showed statistical significance for a number of endpoints. Using this pooled empagliflozin group vs. placebo:

• There was a reduction in the primary endpoint (death from CV causes, non-fatal MI and non-fatal stroke) in the pooled empagliflozin group (HR 0.86, CI just significant at 0.74–0.99). That is an NNT of 62 over 3y for people with known cardiovascular disease.

• There was also a reduction in (although these were not primary or secondary outcomes on their own) cardiovascular mortality, all-cause mortality and hospitalisations for heart failure (heart failure hospitalisations were not part of the original study criteria).

• There was no difference in non-fatal MI or CVA between the groups.

• The only adverse event noted that differed between the two groups was an increase in genital infections in the empagliflozin group, which is not surprising giving its mechanism of action. There was no difference in DKA rates between the groups.

• The average reduction in blood sugar over the study in the treatment groups was roughly 0.4–0.5% initially reducing to 0.2–0.4% by the end of the trial (so not a massive difference).

• In terms of other cardiovascular risk factors, the empagliflozin group had a slightly lower weight and waist circumference and slightly lower BP, but had a small increase in LDL and HDL compared with the placebo group. These changes, as well as lower blood sugars may have contributed to the reduced CV deaths.

What does this mean?

This was a large trial run over 3y. When analysed according to the original plan of the trial, it showed no CV benefits from empagliflozin. When the two empagliflozin groups were pooled to produce a large sample size, a benefit was seen (NNT 62 over 3y). Do note that this trial ONLY applies to those with established cardiovascular disease. Do also note that there are significant concerns over the risk of DKA with the gliflozins (discussed earlier). A definite case where more data are needed to understand the benefits and risks of these drugs before we rush headlong into using them widely!

Renal benefits of gliflozins?

The same trial was also used to look at impact on renal disease (NEJM 2016;375:323). All 7000 patients had an eGFR of over 30 at entry into the trial, and all had established CVD. Most (over 80%) were on an ACE inhibitor/ARB. The empagliflozin arms were combined, as they were in the CVD trial, above. When the empagliflozin arms were combined, empagliflozin showed some renal benefits, but note the NNTs are small:

• Doubling of serum creatinine: NNT 91 over 3 years (that is, you have to treat 91 people with empagliflozin for 3 years to get one fewer person to double their serum creatinine, compared with placebo).

• Progression to renal replacement: NNT 333 over 3 years. Also note, the total numbers were tiny so confidence intervals would be very wide (13 in the empagliflozin arm and 14 in the placebo arm in a trial of over 7000!).

• Impact on nephropathy: this is tricky because a composite endpoint was used – ‘progression to nephropathy or new onset of nephropathy’.

Digging around, it seems this was made up of a combination of progression to macroalbuminuria, a doubling of serum creatinine, the start of renal-replacement therapy, or renal death, which is quite a big catch all endpoint! And the benefits seen appear to be mainly driven by a reduction in macroalbuminuria. So although a significant benefit was seen (NNT 16 over 3 years to prevent progression to nephropathy or new onset of nephropathy), remember this was a composite endpoint, and the benefits are mainly due to one of those many (and varied!) endpoints (www.medscape.com/viewarticle/864857#vp_3).

Why might the gliflozins offer renal benefits?

The authors suggest the benefits may be multifactorial. This might include direct effects on the kidney (reducing sodium reabsorption and glomerular pressure) and on the vasculature (arterial stiffness, vascular resistance). The average reduction in blood sugar, which was relatively small, is probably not the only or main explanation.

What does this mean?

Empagliflozin offers some renal benefits over placebo in people with established CVD, but the benefits in terms of meaningful outcomes (progression to renal replacement) are small. The authors remind us the results cannot be generalised to those without CVD.
Symptomatic HYPERglycaemia/rescue therapy

If at any stage someone develops symptomatic hyperglycaemia then as ‘rescue therapy’ consider insulin or a sulphonylurea and then review treatment once control achieved.

Insulins in type 2 diabetes

These are covered in a separate article in the diabetes chapter.

Diabetes and driving

Here is a summary of DVLA guidance on diabetes, however, for advice for individual patients you MUST check these recommendations against the latest DVLA ‘At a glance’ guide (see Useful websites, below), as I have only included the key points and these do change intermittently. Obviously the usual visual standards, etc. must also be met.

Insulins and insulin analogues

<table>
<thead>
<tr>
<th>Group 1 licence (ordinary drivers)</th>
<th>Group 2 licence (PSV/LGV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Must have awareness of hypoglycaemia.</td>
<td>There have been no episodes of hypoglycaemia requiring the assistance of another person in the preceding 12m.</td>
</tr>
<tr>
<td>Must not have had more than one episode of hypoglycaemia requiring the assistance of another person in the preceding 12m.</td>
<td>They have full awareness of hypoglycaemia.</td>
</tr>
<tr>
<td>There must be appropriate blood glucose monitoring (at least in the 2h before setting off and 2-hourly whilst driving).</td>
<td>They regularly monitor their condition by checking their blood glucose levels at least twice daily and at times relevant to driving (at least in the 2h before setting off and 2-hourly whilst driving).</td>
</tr>
<tr>
<td>The DVLA will arrange an examination by an independent consultant diabetologist every 12m, at which 3m of blood glucose readings must be available.</td>
<td></td>
</tr>
</tbody>
</table>

Hypo-inducing agents (sulphonylureas, repaglinide)

<table>
<thead>
<tr>
<th>Group 1 licence (ordinary drivers)</th>
<th>Group 2 licence (PSV/LGV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>If all the other DVLA requirements (e.g. vision) are met, for a Group 1 licence, the DVLA do not need to be notified. The most important requirement is:</td>
<td>No episode of hypoglycaemia requiring the assistance of another person has occurred in the preceding 12m.</td>
</tr>
<tr>
<td>• Must not have had more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12m.</td>
<td>Has full awareness of hypoglycaemia.</td>
</tr>
<tr>
<td>It may be appropriate to monitor blood glucose regularly and at times relevant to driving to enable the detection of hypoglycaemia.</td>
<td>Regularly monitors blood glucose at least twice daily and at times relevant to driving (at least in the 2h before setting off and 2-hourly whilst driving).</td>
</tr>
</tbody>
</table>

Non-hypo-inducing agents (everything else?)

<table>
<thead>
<tr>
<th>Group 1 licence (ordinary drivers)</th>
<th>Group 2 licence (PSV/LGV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can usually continue to drive providing all other standards (such as vision) are met.</td>
<td>Drivers will be licensed unless they develop relevant disabilities.</td>
</tr>
<tr>
<td>They must be under regular medical review.</td>
<td></td>
</tr>
</tbody>
</table>

Diabetes that ‘goes away’

Some people, given the diagnosis of diabetes, radically change their lifestyle, lose weight and their HbA1c drops out of the diabetic range. What do you do?

There is little guidance on this, but bear the following in mind:

• They are at high risk of ‘relapsing’ and becoming diabetic again – in our practice we do an annual HbA1c to look for this (and BP, cholesterol, etc.).

• They continue to need retinal screening. In order to ensure they are called for this use the code ‘Diabetes in remission’ (C10P) NOT ‘Diabetes resolved’ (212H) as this latter code doesn’t trigger recall. Do note that ‘Diabetes in remission’ does NOT exempt them from QOF – but should they not be getting QOF-style care anyway? (National Diabetes Retinal Screening Programme, 2014).
**Type 2 diabetes**

- Glycaemic control is important in type 2 diabetes but blood pressure and cholesterol reduction are probably more important, particularly to reduce cardiovascular complications.
- Because most antihypertensives and statins are off-patent the pharmaceutical industry has invested million of pounds into developing new drugs to lower blood sugar. Only time to tell what long-term benefits/harms they bring.

**The NICE guidelines on diabetes**

- Lifestyle is crucial, as is weight loss if overweight.
- Blood pressure guidance is in line with the existing NICE hypertension guidelines, but use an ACE for all regardless of age (because of renal benefits).
- In the primary prevention of CVD in diabetes, offer atorvastatin 20mg if QRISK2 ≥10%. NICE recommends a fire and forget approach.
- In secondary prevention: use atorvastatin 80mg and aim to reduce non-HDL cholesterol by 40%.
- Glycaemic control: NICE are keen to emphasise individualised targets, based on the risks of types, age, frailty and co-morbidity and life expectancy. Use metformin first line because of cardiovascular benefits. After that it is a bit of a free for all! Be aware of the pros and cons of each drug, and choose accordingly.
- Self-monitoring of blood sugar is not indicated for most. Use only if on insulin or if hypoglycaemia may cause problems for example with driving/operating machinery.
- Foot, eye and renal care remains unchanged.

In those on metformin, how many have an eGFR <30? That’s a good quick safety audit! And how many have an eGFR <45 – and when was their dosing last reviewed?

Audit how your diabetics meet lipid, BP and glycaemic targets. Are you getting your priorities right here?

Where do the new drugs have a role in your current practice? Is this in line with NICE guidance?

Can you measure ketones in your practice if you are worried someone has DKA?

How often do you discuss erectile dysfunction with your male patients with diabetes?

DVLA at a glance guide: [http://tinyurl.com/GPU-DVLA](http://tinyurl.com/GPU-DVLA)

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**My notes**
Insulins in diabetes

Insulins: a summary of types/actions

Read this in conjunction with the section ‘Understanding insulins’ below. From DTB 2010;48:134 & BNF 2010, 29.

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Trade names/examples</th>
<th>Timing of injection</th>
<th>Onset of action</th>
<th>Peak action</th>
<th>Duration of action</th>
<th>Cost for 15ml*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SHORT-ACTING INSULINS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-acting ordinary insulins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Soluble insulin</td>
<td>Actrapid, Humulin S</td>
<td>Up to 30min before meal</td>
<td>Within 30min</td>
<td>1.5–3.5h</td>
<td>7–8h</td>
<td>£19</td>
</tr>
<tr>
<td><strong>Rapid-acting analogues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart</td>
<td>NovoRapid</td>
<td>Immediately before meal</td>
<td>10–20min</td>
<td>1–3h</td>
<td>3–5h</td>
<td>£28</td>
</tr>
<tr>
<td>Glulisine</td>
<td>Apidra</td>
<td>Within 15min of meal</td>
<td>10–20min</td>
<td>About 1h</td>
<td>3–5h</td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td>Humalog</td>
<td>Within 15min of meal</td>
<td>About 15min</td>
<td>30–70min</td>
<td>2–5h</td>
<td></td>
</tr>
<tr>
<td><strong>LONGER ACTING INSULINS</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate (NPH) ordinary insulin</td>
<td>Insulatard, Humulin I</td>
<td>At bedtime/12-hrly</td>
<td>Within 1.5h</td>
<td>4–12h</td>
<td>About 24h</td>
<td>£23</td>
</tr>
<tr>
<td><strong>Long-acting analogues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>Lantus (came off patent in 2014)</td>
<td>Once daily</td>
<td>About 1h</td>
<td>No peak</td>
<td>Up to 24h</td>
<td>£42</td>
</tr>
<tr>
<td>Detemir</td>
<td>Levemir</td>
<td>Once/twice daily</td>
<td>0.8–2h</td>
<td>3–14h</td>
<td>Up to 24h</td>
<td></td>
</tr>
<tr>
<td><strong>Ultra-long acting analogue</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Degludec</td>
<td>Tresiba (do not muddle the 2 strengths!)</td>
<td>Once daily (although half-life 25h)</td>
<td>30–90min</td>
<td>None</td>
<td>Up to 42h</td>
<td>£58</td>
</tr>
<tr>
<td><strong>PRE-MIXED INSULINS</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pre-mixed ordinary insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biphasic isophane insulin</td>
<td>Humulin M3</td>
<td>Up to 30min before meal</td>
<td>Within 30min</td>
<td>2–8h</td>
<td>Up to 24h</td>
<td>£20</td>
</tr>
<tr>
<td><strong>Pre-mixed analogues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biphasic aspart</td>
<td>NovoMix 30</td>
<td>Within 10min of meal</td>
<td>Within 10–20min</td>
<td>1–4h</td>
<td>Up to 24h</td>
<td>£29</td>
</tr>
<tr>
<td>Biphasic lispro</td>
<td>Humalog Mix 25</td>
<td>Within 15min of meal</td>
<td>About 15min</td>
<td>About 2h</td>
<td>Up to 24h</td>
<td></td>
</tr>
<tr>
<td>Biphasic lispro</td>
<td>Humalog Mix 50</td>
<td>Within 15min of meal</td>
<td>About 15min</td>
<td>About 2h</td>
<td>Up to 24h</td>
<td></td>
</tr>
</tbody>
</table>

*Costs from BMJ 2012;345:e4611, rounded to the nearest whole pound.

Understanding insulins

- Short-acting insulins are now referred to as rapid-acting insulins.
- Traditionally there are 3 main groups of insulin: rapid-, intermediate- and long-acting. However, if you look at the duration of action of the insulins (see table below) you will see that there are only really two sorts of insulins, rapid-acting and long-acting (which includes the intermediate-acting insulins).
- Insulin analogues are available for both the rapid and long insulins.

---

Red Whale
• Long-acting insulin analogues are in many ways similar to long-acting insulins. Although they have been promoted on the basis of fewer hypos the evidence for this is limited (London Medicines Evaluation Team, 2014).
• Rapid-acting insulin analogues are quicker in their onset of action than rapid-acting ordinary insulins (inject and eat, rather than wait 30min).
• Pre-mixed insulin preparations are also available, combining rapid-acting and long-acting insulins.

Type 2 diabetes: NICE recommendations around insulin

The role of insulin in type 2 diabetes is outlined in the step diagram in the article on type 2 diabetes. The NICE guidance reminds us that before starting insulin we should:
• Optimise diet, exercise and weight and adherence to current therapies.
• Offer: structured education including dietary advice, telephone support, frequent self-monitoring, management of hypoglycaemia, management of acute changes in blood sugar.
• Review barriers to insulin therapy (impact on driving, especially for LGV/PSV drivers, fear of weight gain, occupation, etc.).

When starting insulin in type 2 diabetes:
• Use insulin ALONGSIDE metformin (review and consider need for all other oral agents).
• Use a single daily dose of long-acting insulin because good quality trials have shown this was almost as good as more complex regimens and resulted in fewer hypos and less weight gain (NEJM 2009;361;1736).

<table>
<thead>
<tr>
<th>Insulin type and examples</th>
<th>NICE recommendations for use in type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>LONGER ACTING INSULINS</td>
<td></td>
</tr>
<tr>
<td>Intermediate (NPH) ordinary insulin (e.g. Insulatard, Humulin I)</td>
<td>• Probably first line for most with type 2 diabetes, unless any of the issues below apply</td>
</tr>
<tr>
<td>Long-acting analogues</td>
<td></td>
</tr>
</tbody>
</table>
| Glargine (Lantus, Toujeo), detemir (Levemir) | • Use if carer/health professional needed to inject insulin (because may be given once daily). |• Lifestyle restricted by recurrent symptomatic hypoglycaemic episodes
|                                  | • Would otherwise need twice daily long-acting ordinary insulin AND oral hypoglycaemics                         |
| Ultra-long acting analogue       |                                                                                                               |
| Degludec (Tresiba)               | • Not recommended: not cost-effective.                                                                          |
| PRE-MIXED INSULINS               |                                                                                                               |
| Pre-mixed ordinary insulin       | • Consider particularly if HbA1c ≥75mmol/mol (9%)                                                             |
| Biphasic isophane insulin (Humulin M3) | • Usually twice daily but can be used once daily                                                                 |
| Pre-mixed analogues              |                                                                                                               |
| Biphasic analogues (e.g. NovoMix, Humalog Mix) | • A person prefers to inject insulin immediately before a meal
|                                  | • Blood sugar levels rise markedly after meals                                                                 |
|                                  | • Hypoglycaemia is a problem.                                                                                  |

(Rapid-acting insulins (ordinary and analogues) are not in this table because they are not recommended for use in type 2 diabetes.)

Insulin pumps in type 2 diabetes

We are familiar with type 1 diabetics increasingly using insulin pumps that deliver insulin at a constant rate subcutaneously. This trial (Opt2mise) took those with poorly controlled type 2 diabetes who were already on multiple daily doses of insulin, and randomised them to continue treatment or to swap to an insulin pump (Lancet 2014;384:1265). Five hundred patients were recruited from hospital settings across 4 continents(!) with HbA1cs of 64–108mmol/mol (8–12%). The trial was funded by the pump makers. (Do note that for most type 2 diabetics the preferred insulin regimen is a single daily injection of long-acting insulin, but clearly multiple injections may be warranted in those with poor control.)
• After 6m, those on insulin pumps had significantly lower HbA1cs (average 1.1% lower, which was 0.7% lower than the average in the multiple injection arm).
• Significant events such as hypo- and hyperglycaemia were low and similar in both groups.
Clearly more data are needed, but this could be a potential option in the future for our poorly controlled type 2 diabetics.

(An observational study of people with type 1 diabetes using insulin pumps rather than multiple daily injections showed a reduction in cardiovascular mortality after almost 7y of treatment, however, those opting for a pump may be a different sort of person and so further evidence from RCTs is needed (BMJ 2015;350:h3234)).

**Type 1 diabetes: NICE recommendations around insulin**

In type 1 diabetes, a more complex insulin regimen is indicated. The NICE guidelines on type 1 diabetes recommends (NICE 2015, NG17):

- Use multiple daily injections using a basal–bolus regimen.
  - **For the BASAL insulin:** use twice daily detemir (Levemir) insulin (a long-acting insulin analogue) unless already using an alternative and achieving HbA1c target on this.
  - **For the BOLUS insulin:** rapid-acting insulin analogues are preferred to rapid-acting ordinary insulins. These should be given before, not after, meals (reduces both hyperglycaemia immediately after eating and subsequent hypoglycaemia).
- Twice daily regimens should ONLY be used if basal–bolus regimens are not possible. In which case, use pre-mixed ORDINARY insulin. If significant hypoglycaemia, swap to a pre-mixed insulin analogue.
- Ensure people understand the ‘sick-day’ rules.
- **Optimising insulin therapy:** if erratic and unpredictable blood glucose control, before changing insulin regimen, consider:
  - injection sites and technique
  - lifestyle, skills/knowledge around self-monitoring and self-management, psychological and psychosocial difficulties
  - possible organic causes such as gastroparesis.
- **Insulin pumps** (=continuous subcutaneous insulin infusion) should be used if (this comes from NICE 2008, TA151):
  - HbA1c high (≥69mmol/mol (8.5%)) despite multiple daily insulin injections or multiple injection causing disabling hypos.

**Why the change to insulin analogues in type 1 diabetes?**

NICE recommended insulin analogues should be used in preference to ordinary insulins, and they specifically recommended detemir as the long-acting insulin analogue of choice. Why?

**For the long-acting insulins**

For the long-acting insulins, NICE concluded that when comparing the long-acting insulin analogues, with long-acting ordinary insulins there were:

- No significant differences in glycaemic control.
- No significant differences in the rates of hypoglycaemia.
- BUT detemir had the stronger evidence around cost-effectiveness, which presumably drove their decision.

Most of the evidence used to make this decision was considered by NICE to be of low to very low quality.

**For the rapid-acting insulins**

When it came to the rapid-acting insulins, NICE concluded that analogues are preferred to ordinary insulins. This was based on:

- better glycaemic control
- fewer hypos
- cost-effectiveness.

Although the evidence base was relatively weak.
What about the risks of insulins?

One of the challenges of diabetes (or any disease actually!) is that the treatment can have harms and side-effects. We are acutely aware that for insulins there is a significant risk of hypoglycaemia and that whole ‘injection/blood sugar monitoring’ barrier to overcome, but there are other issues too. Lately concerns have been raised about the cardiovascular and cancer risks of insulins.

A UK GP research database retrospective cohort trial of almost 85,000 people with type 2 diabetes suggests that insulin therapy may increase the cardiovascular and cancer risks slightly (HR 1.3, CI 1.2–1.5 for insulin with metformin compared with metformin alone) (DTB 2013;51(4):41).

A US veterans study of those on metformin also showed that when insulin was added, as opposed to a sulphonylurea, there was also an increase risk in non-fatal cardiovascular events and all-cause mortality (adjusted HR 1.3, CI 1.07–1.58).

However, the downside of these studies was that although they were able to adjust for many risk factors, there was significant confounding that they could not adjust for (e.g. in a retrospective cohort trial those treated with a sulphonylurea are likely to be different to those treated with insulin). They also only followed-up patients for 3y in the first study and 14m in the second study, and so longer duration follow-up is needed to quantify the harms but also to look at the longer term benefits.

The DTB reminds us that choosing those who will benefit from insulin is a challenge!

What place for GLP-1 mimetics WITH insulin?

GLP-1 mimetic should only be offered WITH insulin in specialist settings.

Diabetes and driving

Here is a summary of DVLA guidance on insulins in diabetes, however, for advice for individual patients you MUST check these recommendations against the latest DVLA ‘At a glance’ guide (see Useful websites, below), as I have only included the key points and these do change intermittently. Obviously the usual visual standards, etc. must also be met. The DVLA guidance on other drugs in diabetes is in the article on NICE guidelines on diabetes.

<table>
<thead>
<tr>
<th>Insulins and insulin analogues</th>
<th>Group 1 licence (ordinary drivers)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Must have awareness of hypoglycaemia.</td>
<td>Must not have had more than one episode of hypoglycaemia requiring the assistance of another person in the preceding 12m.</td>
<td>There have been no episodes of hypoglycaemia requiring the assistance of another person in the preceding 12m.</td>
</tr>
<tr>
<td>Must have appropriate blood glucose monitoring (at least in the 2h before setting off and 2-hourly whilst driving).</td>
<td>There have been no episodes of hypoglycaemia requiring the assistance of another person in the preceding 12m.</td>
<td>They have full awareness of hypoglycaemia.</td>
</tr>
<tr>
<td>They regularly monitor their condition by checking their blood glucose levels at least twice daily and at times relevant to driving (at least in the 2h before setting off and 2-hourly whilst driving).</td>
<td>They regularly monitor their condition by checking their blood glucose levels at least twice daily and at times relevant to driving (at least in the 2h before setting off and 2-hourly whilst driving).</td>
<td>The DVLA will arrange an examination by an independent consultant diabetes specialist every 12m, at which 3m of blood glucose readings must be available.</td>
</tr>
</tbody>
</table>

Insulins in diabetes

- There are 2 main sorts of insulins: rapid- and long-acting.
- There are analogue versions of both rapid- and long-acting insulins, but they are more expensive than ordinary insulins.
  - Long-acting insulin analogues are very similar to long-acting ordinary insulins.
  - Rapid-acting insulin analogues have a quicker onset of action (you can inject and eat) than rapid-acting ordinary insulins.
- For type 2 diabetes NICE recommends a single daily dose of a long-acting ordinary insulin, but remember to optimise diet and lifestyle first. Use insulins with metformin in type 2 diabetes.
- For type 1 diabetes NICE recommends using a basal–bolus regimen of detemir (a long-acting insulin analogue) with a rapid-acting insulin analogue.
- Beware the risks of hypoglycaemia (both rapid- and long-term).
- Being on insulin has significant implications for driving and a licence will be withdrawn if hypo awareness is impaired.
How many of your insulin using type 2 diabetics are on metformin?
Audit the use of insulin analogues and pre-mixed insulin in your patients with type 2 diabetes.

DVLA at a glance guide: http://tinyurl.com/GPU-DVLA
Diabetic ketoacidosis in type 1 and 2 diabetes

Diabetes ketoacidosis (DKA) is a relative or absolute lack of insulin which leads to the breakdown of fatty acids (lipolysis). This results in the formation of ketone bodies, which are acidic. When the body can no longer buffer the acid produced, ketosis results. This BMJ Clinical review highlights some important points (BMJ 2015;351:h5660).

If you remember nothing else from this article remember this:

• DKA can occur in type 2 as well as type 1 diabetes, and in those taking gliflozins (cana-, dapa- and empagliflozin, also known as the sodium glucose co-transporter 2 inhibitors) and it can occur at relatively low blood sugars.

• In an unwell person with diabetes (whether type 1 or type 2) ALWAYS check for ketones.

Diagnosis

The Joint British Diabetes Societies recommend a diagnosis of DKA can be made if the following features are present (JBDS, 2013):

• Ketones ≥3mmol/L (or ≥2+ on urine sticks).
• Blood glucose >11mmol/L (or known diabetes mellitus).
• Bicarbonate <15 and/or venous pH <7.3 (clearly not something we can measure in primary care).

Key facts about DKA

• 6% of cases of DKA are in people newly presenting with type 1 diabetes.
• In those with established type 1 diabetes, about 4% will have an episode of DKA each year.
• DKA usually develops rapidly over 24h.
• Presentation is with polyuria and polydipsia, vomiting and dehydration and if severe altered consciousness and coma. Abdominal pain may be a presenting feature or may indicate an underlying abdominal cause that was the trigger.
• Infection is a key trigger and there may be features of this.
• Consider DKA in any unwell person with type 1 or type 2 diabetes.
• Occasionally DKA can occur with relatively normal glucose levels (euglycaemic ketoacidosis) and low levels of blood ketones (<3mmmol/L) do not exclude a diagnosis.

DKA in type 2 diabetes

You thought this never happened? Well it does! Read on… (BMJ 2013;346:f3501).

A reminder of the physiology of DKA...

DKA is a complex disordered metabolic state with hepatic gluconeogenesis (glucose production from non-carbohydrates), glycolysis (breakdown of glycogen) and lipolysis. It is the lipolysis that results in fatty acids that are metabolised into ketone bodies. Traditionally it had been thought that lipolysis would not occur in those with type 2 diabetes because of residual background insulin production. However, this thinking has been challenged. It seems that some people with type 2 diabetes may get an acute reduction in insulin production which can cause DKA. This type of diabetes is referred to as ketosis-prone type 2 diabetes, type 1b diabetes, or Flatbush diabetes (apparently Flatbush is the area in New York where it was first described!). It is a retrospective diagnosis, because it can take months for insulin production to return.

DKA in type 2 diabetes

Ketosis-prone type 2 diabetes seems to be much more common in Afro-Caribbeans and other non-white populations. Management of DKA in type 2 diabetes is initially identical to that of DKA in a type 1 diabetic. Aftercare, however, requires different education – all the usual things around type 2 diabetes management, but most of these patients are discharged on insulin (although this can often be stopped within 3–6m) and they also need education around prevention of future episodes and home ketone testing. Over years, they often eventually end up on insulin. Management is by the hospital diabetes team!

DKA in type 2 diabetes is not to be confused with HONK (hyperosmolar non-ketotic acidosis), where the blood sugar is very high but there are few ketones in the urine (≤2+) and the urine osmolality is very high. Both, however, should be treated with immediate admission.
Management of DKA

- When diagnosed urgent admission is required.
- The mainstay of treatment is fluids and insulin, and watching for and correcting electrolyte imbalances, particularly hypokalaemia.
- On discharge it is important to review precipitants to try to prevent this happening again. Understanding sick day rules is particularly important (see Useful website box).
- Remember the sodium glucose co-transporters/gliflozins (dapa-, cana- and empagliflozin) can occasionally result in DKA but at relatively low glucose levels (<14).

### Diabetic ketoacidosis in type 1 and 2 diabetes

- Possible in both type 1 and type 2 diabetes.
- THINK about it in any unwell diabetic and MEASURE THEIR BLOOD SUGAR AND KETONE LEVELS!
- Admit immediately.
- On discharge, review contributing factors to reduce the risk of recurrence.
- Remember this can occur in those on gliflozins at relatively low blood sugars.

Do you have a ketone meter in your practice? Do you know how to use it?!

### Sick day rules

Leicestershire diabetes.org have sick day rules for both type 1 and type 2 diabetes (quite complex for patients to follow, but I found them very helpful as a GP!). They are both in pdf format at the bottom of the page this link points to: [http://tinyurl.com/GPU2015-sick-day](http://tinyurl.com/GPU2015-sick-day) or [www.leicestershirediabetes.org.uk/438.html](http://www.leicestershirediabetes.org.uk/438.html)


### My notes