GP-Update
Red Whale

The GP Update Handbook

Autumn 2015/Winter 2016

www.gp-update.co.uk

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:

Ann. Int. Med.	Annals of Internal Medicine
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.

Cochrane 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**

Copyright

Registered in England and Wales no. 7135974.

Registered Office: Prospect House, 58 Queens Road, Reading, RG1 4RP.

You can contact us at: GP Update, Science & Technology Centre, The University of Reading, Earley Gate, Whiteknights Road, Reading RG6 6BZ.

Red Whale is a registered trademark of GP Update Limited.

Type 2 Diabetes and Pre-diabetes

51 Pre-diabetes

54 NICE guidelines on type 2 diabetes

67 Insulins in type 2 diabetes

The following topics are available on the website www.gpCPD.com

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.

PRE-DIABETES	IMPAIRED FASTING GLUCOSE	IMPAIRED GLUCOSE TOLERANCE
HbA1c 42–47mmol/mol or 6–6.4%	Fasting plasma glucose 6.1–6.9mmol/L (NICE)	Fasting plasma glucose <7.0mmol/L AND 2h plasma glucose 7.8–11mmol/L

- **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?

NICE on managing pre-diabetes NICE 2012, PHG38

Lifestyle modification

Offer intensive lifestyle change programme to:

- Increase physical activity
- Achieve and maintain weight loss
- Increase dietary fibre, reduce dietary fat intake

Drug therapy in pre-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 1500–2000 mg/day if tolerated. Review HbA1c at 3 m, 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.

- **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.

- **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 & NICE DRAFT lipids guidance 2014).

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.

Added to this, in the section on NICE guidance on the diabetes drugs, we discuss the evidence emerging suggesting that metformin in type 2 diabetes may not offer the cardiovascular protection we previously thought it did (see the section 'NICE guidance on drugs for glycaemic control').

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

NICE guidelines on type 2 diabetes

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).

Intervention (MeReC 2011:21(5))	**Number of cardiovascular events prevented for every 1000 people treated over 5y**	**Microvascular benefits**
Lowering blood sugar by 0.9%	8	Less clear! Glycaemic control is important, although BP control may be more important.
Lowering cholesterol by 1mmol/L	23	
Reducing BP by 10/5	29	

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 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.

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:

Health status (for those over 65y)	Target HbA1c		Target BP	Lipid modification
	%	mmol/mol		
Healthy *Rationale: reasonable life expectancy*	<7.5	<58	<140/80	Statins indicated
Intermediate health • Several co-morbidities • Limited functional ability • Mild to moderate cognitive impairment *Rationale: intermediate life expectancy, high treatment burden (polypharmacy), vulnerable to hypoglycaemia and falls*	<8	<64	<140/80	Statins indicated
Poor health • End-stage chronic disease • In long-term care/limited functional ability • Moderate to severe cognitive impairment *Rationale: limited life expectancy: benefits of treatment uncertain*	<8.5	<69	<140/90	Benefits less certain: greater benefit in secondary prevention

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.

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!).

- **A BMJ editorial reminds us 'Treat the patient, not the HbA1c' (BMJ 2013;346:f2625).**

NICE guidelines: key changes in the DRAFT NICE guidance (2015)

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!). Do note that these guidelines are DRAFT as we go to press (September 2015) and are due to be published in October 2015.

- **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: 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 are some data showing short term benefits. However, long term data to look at outcomes in people with diabetes 10–20y later, are lacking (Lancet 2012;379:2300, BMJ 2013;347:f5934).
  - 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 and 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.
  - **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. I've ranked them by cost, starting with the cheapest.

Remember 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).

Risk of hypos, impact on weight, renal function and important safety data

This table is based on the drug SPCs, BNF, NICE guidance, MHRA data, DTB 2013;51(9):98, NEJM 2015;373:232 and BMJ 2012;344:e1213

Drug	Risk of hypos	Weight change	Long term safety data	Use in renal impairment	Costs (1m at maximum dose)
Metformin	None	Loss	CV benefits	eGFR <45: review dose eGFR <30: stop	<£2 (modified release £17)
Pioglitazone	Rare	Gain	Concerns about (see later): • Heart failure • Bladder cancer • Facture	Safe	<£2
Sulphonylurea (gliclazide)	Yes	Gain	No significant concerns identified	Increased risk of hypoglycaemia	<£5
Repaglinide	Yes	Gain	No significant concerns identified	Safe NB. excreted in bile: avoid in liver disease	<£6
Gliptins (DPP4 inhbitors)	Rare	Neutral	• Risk of pancreatitis • Rarely cause liver toxicity: monitor LFTs • 3y safety data for sitagliptin in those with CVD shows no increased CVD risk	Linagliptin safe in renal impairment For others reduce dose in renal impairment (eGFR <50 or <30 depending on gliptin)	£31–34
Gliflozins (SGLT-2 inhibitors)	Rare	Loss	Limited long term data Concerns about DKA at only moderately elevated blood sugars (see Drug dilemma, below)	Dapagliflozin: eGFR <60: do not use Cana and empagliflozin: do not start if eGFR <60 but if already on drug and eGFR falls below 60, reduce dose; stop if eGFR falls below 45	Around £36
GLP-1 mimetics (incretins) (NICE set strict criteria for use, see below)	Rare	Loss	No significant concerns identified	Liraglutide: eGFR <30: do not use Exenatide and lixisenatide: eGFR 30–50: use with caution eGFR <30 do not use	£50–70

Acarbose was not recommended by NICE for use in diabetes due to insufficient evidence or evidence of ineffectiveness.

NICE DRAFT type 2 diabetes guidelines

Summary of DRAFT NICE type 2 diabetes guidelines (2015)

Diagnosis

Fasting glucose ≥7 on <u>two</u> separate occasions

OR

HbA1c ≥48mmol/mol (6.5%) on <u>two</u> separate occasions <u>two</u> 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

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

Lifestyle	• Refer to structured education programme at diagnosis. Reinforce diet/lifestyle annually. • **If overweight aim to reduce weight by 5–10% (but any weight loss is beneficial).** • **Erectile dysfunction:** ask men about this annually. Review and optimise CVD risk factors including lifestyle. Offer PDE5 inhibitor (e.g. sildenafil) & other treatments if this is ineffective.	
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/gliptin/piogitazone. 53/7% for those on other treatments.
	BUT tailor targets to individual's needs. Beware consequences of hypos especially if drives/at risk of falls. Relax targets if patient unlikely to live long enough to gain benefit. ***Lifestyle crucial!*** **Self-monitoring:** only if on insulin or good indication (such as driving/occupation).	
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 join, often painful). **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 recommendations for glycaemic control in type 2 diabetes (2015)

TOP STAIRCASE: FIRST LINE THERAPY FOR THE MAJORITY

HbA1c trigger to step up varies (*'Move to this step if…'):* 48/6.5% initially, then 58/7.5%.
HbA1c target once stepped up varies (***'Aim to get HbA1c to…'***): 48/6.5% initially, then 53/7%.

MONOTHERAPY

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

START metformin

(if not tolerated try modified release metformin)

Aim to get HbA1c to 48/6.5%

FIRST INTENSIFICATION

(dual therapy)

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

ADD second drug:

Metformin + sulphonylurea (SU)

Metformin + gliptin

Metformin + pioglitazone

(note contraindications, see below)

Aim to get HbA1c to 53/7%

SECOND INTENSIFICATION

(triple therapy or insulin)

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

ADD third drug

Metformin + SU + gliptin

Metformin + SU + pio

OR

Consider insulin therapy

(see separate article on insulins)

Aim to get HbA1c to 53/7%

FURTHER INTENSIFICATION

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

If metformin 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 (SU)
Gliptin
Pioglitazone
Repaglinide

If using pio beware of contraindications (see below)

Aim to get HbA1c to:

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

FIRST INTENSIFICATION

(dual therapy without metformin)

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

Stop repaglinide, if using

(licensed only as monotherapy or with metformin)

ADD second DRUG

SU + gliptin
SU + pio
Gliptin + pio

If using pio beware of contraindications (see below)

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)

Contraindications for pioglitazone (more on this in drug dilemma below)

- Heart failure/risk of failure
- Fractures
- Risk of/PMH of bladder cancer
- Elderly (because of above)

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 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.**

What role for SGLT2 inhibitors/gliflozins?

NICE refer to their existing guidance (references below) which basically says can be used:

- As dual therapy with metformin if sulphonylureas contraindicated or not tolerated.
- In triple therapy with either metformin + sulphonylurea or metformin + pioglitazone.
- With insulin with or without other agents.

Why did NICE make these suggestions?

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 tolbutamide 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.

What role for modified release sulphonylureas?

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

Drug dilemma: cautions with gliptins

NICE refer to the long term safety concerns of gliptins.

If treating people with gliptins warn them about the symptoms of acute pancreatitis: persistent severe abdominal pain (sometimes radiating to the back) and encourage them to report such symptoms . Frequency not known but reported to be between 1 in 100 and 1 in 1000. Usually resolves on discontinuation (Drug Safety Update September 2012;6(2):A3).

Drug dilemma: cautions with pioglitazones

NICE reminds us of the issues with pioglitazones (more info below):

- Association with bladder cancer.
- Increased risk of heart failure.
- Increased risk of fractures (women only).
- Care to be taken in the elderly (in whom heart disease and bladder cancer are more common).

NICE suggests we follow MHRA advice and therefore we should review the effectiveness of pioglitazone 3–6m into therapy and stop in those who do not get sufficient control (Drug Safety Update 2011;5(1):A1).

Bladder cancer risks

This is an association rather than proven causation. The absolute risk increase is small. Why? Glitazones are related to glitazars, which lower blood sugar and lipid profiles, but which were withdrawn from use after it was recognised they were carcinogenic in animals (BMJ 2012;344:e3500).

MHRA advice is (Drug Safety Update 2011;5(1):A1):

- Do not use in those with uninvestigated haematuria, history of or active bladder cancer.
- Before starting assess for known risks for bladder cancer: age, smoking history, exposure to some occupational or chemotherapeutic agents (including cyclophosphamide) and pelvic irradiation.
- Use with care in the elderly because the risk of bladder cancer increases with age.

Heart failure

- Absolutely contraindicated in heart failure.
- Care should be taken in those at risk of heart failure, and for this reason it is recommended that in older people start at the lowest possible dose and monitor regularly.

- When used in combination with insulin, patients should be observed for signs of heart failure, weight gain and oedema (Drug Safety Update 2011;4(6):A2).

Risk of fractures

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

Pioglitazone doses

15–30mg daily increased to 45mg once daily if needed.

In elderly (because of concerns about heart failure) start lowest possible dose and increase gradually. Review effectiveness 3–6m into treatment and regularly thereafter (BNF/SPC).

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

OR

- 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).

What role for SGLT2 inhibitors/gliflozins?

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

The NICE diabetes guidelines include brief reference to the SGLT2 inhibitors – they suggest they should be used in line with pre-existing NICE guidance (although they are currently reviewing their role – due to be published in 2016) (NICE 2013, TA288; 2014, TA315; 2015, TA336):

- As dual therapy with metformin if sulphonylureas contraindicated or not tolerated.
- In triple therapy with either metformin + sulphonylurea or metformin + pioglitazone.
- With insulin with or without other agents.

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 carcinogencity. 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.)

Drug dilemma: gliflozins (SGLT2 inhibitors) and diabetic ketoacidosis

Cases of serious and life threatening diabetic ketoacidosis (DKA) have occurred in those on gliflozins (canagliflozin, dapagliflozin and empagliflozin). Importantly these cases occurred when blood sugars were only moderately elevated (<14mmol/L, which is very uncommon for DKA). Half of the cases occurred in the first 2m of treatment. One-third of cases occurred when the drugs were used for type 1 diabetes (an off-label use – and the MHRA remind us that they should not be used in these patients). The reason for the DKA at such low sugars is not known (Drug Safety Update June 2015). The MHRA advise:

- **All patients on gliflozins (canagliflozin, dapagliflozin and empagliflozin) should be informed of the symptoms and signs of DKA (nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue, sleepiness).**
- **Clinicians should test for ketones in patients presenting with these features on these drugs, even if the blood sugar is only mildly elevated.**

Diabetic ketoacidosis 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), glycogenolysis (breakdown of glycogen) and lipolysis. It is the lipolysis that results in fatty acids that are metabolised into ketone bodies. Traditionally it has 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!

Please note the Drug dilemma (above) related to the gliflozins and DKA, highlighting the fact that cases of serious and life threatening diabetic ketoacidosis (DKA) have occurred in those on gliflozins (canagliflozin, dapagliflozin and empagliflozin). Importantly these cases occurred when blood sugars were only moderately elevated (<14mmol/L). for more details, and the related MHRA advice, please read the Drug dilemma (above).

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.

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.

Hypoglycaemia and cardiovascular disease

This important meta-analysis showed that severe **hypog**lycaemia 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, something patients perhaps need reminding of.

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	
Group 1 licence (ordinary drivers)	**Group 2 licence (PSV/LGV)**
Must have awareness of hypoglycaemia. Must not have had more than one episode of hypoglycaemia requiring the assistance of another person in the preceding 12m. There must be appropriate blood glucose monitoring (at least in the 2h before setting off and 2-hourly whilst driving).	There have been no episodes of hypoglycaemia requiring the assistance of another person in the preceding 12m. They have full awareness of hypoglycaemia. 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). The DVLA will arrange an examination by an independent consultant diabetologist every 12m, at which 3m of blood glucose readings must be available.

Hypo-inducing agents (sulphonylureas, repaglinide)	
Group 1 licence (ordinary drivers)	**Group 2 licence (PSV/LGV)**
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: • Must not have had more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12m. It may be appropriate to monitor blood glucose regularly and at times relevant to driving to enable the detection of hypoglycaemia.	No episode of hypoglycaemia requiring the assistance of another person has occurred in the preceding 12m. Has full awareness of hypoglycaemia. **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).
Non-hypo-inducing agents (everything else?)	
Group 1 licence (ordinary drivers)	**Group 2 licence (PSV/LGV)**
Can usually continue to drive providing all other standards (such as vision) are met.	Drivers will be licensed unless they develop relevant disabilities. They must be under regular medical review.

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 new DRAFT 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 hypos, 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!
- 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?

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

DVLA at a glance guide: http://tinyurl.com/GPU-DVLA

My notes

Insulins in type 2 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.

Insulin	Trade names/examples	Timing of injection	Onset of action	Peak action	Duration of action	Cost for 15ml*
SHORT-ACTING INSULINS						
Short-acting ordinary insulins						
Soluble insulin	Actrapid Humulin S	Up to 30min before meal	Within 30min	1.5–3.5h	7–8h	– £19
Rapid-acting analogues						
Aspart	NovoRapid	Immediately before meal	10–20min	1–3h	3–5h	£28
Glulisine	Apidra	Within 15min of meal	10–20min	About 1h	3–5h	
Lispro	Humalog	Within 15min of meal	About 15min	30–70min	2–5h	
LONGER ACTING INSULINS						
Intermediate (NPH) ordinary insulin						
Isophane (NPH) insulin	Insulatard Humulin I	At bedtime/12-hrly	Within 1.5h	4–12h	About 24h	£23 £19
Long-acting analogues						
Glargine	Lantus (came off patent in 2014)	Once daily	About 1h	No peak	Up to 24h	£42
Detemir	Levemir	Once/twice daily	0.8–2h	3–14h	Up to 24h	
Ultra-long acting analogue						
Degludec	Tresiba (do not muddle the 2 strengths!)	Once daily (although half-life 25h)	30–90min	None	Up to 42h	£58
PRE-MIXED INSULINS						
Pre-mixed ordinary insulin						
Biphasic isophane insulin	Humulin M3 = 30% soluble insulin + 70% isophane insulin	Up to 30min before meal	Within 30min	2–8h	Up to 24h	£20
Pre-mixed analogues						
Biphasic aspart	NovoMix 30 = 30% aspart + 70% aspart protamine	Within 10min of meal	Within 10–20min	1–4h	Up to 24h	£29
Biphasic lispro	Humalog Mix 25 = 25% lispro + 75% lispro protamine	Within 15min of meal	About 15min	About 2h	Up to 24h	
Biphasic lispro	Humalog Mix 50 = 50% lispro + 50% lispro protamine	Within 15min of meal	About 15min	About 2h	Up to 24h	

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

Understanding insulins

- 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 above) 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 (= NPH insulin, e.g. Insulatard, Humulin I).**

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

NICE recommendation for type of insulin in type 2 diabetes

The role of insulin in type 2 diabetes is outlined in the step diagram in the article on NICE guidelines on 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).

Insulin type and examples	NICE recommendations for use in type 2 diabetes
LONGER ACTING INSULINS	
Intermediate (NPH) ordinary insulin Isophane insulin (e.g. Insulatard, Humulin I)	• **Probably first line for most with type 2 diabetes, unless any of the issues below apply**
Long-acting analogues Glargine (Lantus), detemir (Levemir)	• Use if carer/health professional needed to inject insulin • 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 Biphasic isophane insulin (Humulin M3)	• Consider particularly if HbA1c ≥75mmol/mol / 9% • 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.

(Short-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 insulins 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).)

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.

Insulins and insulin analogues	
Group 1 licence (ordinary drivers)	**Group 2 licence (PSV/LGV)**
Must have awareness of hypoglycaemia. Must not have had more than one episode of hypoglycaemia requiring the assistance of another person in the preceding 12m. There must be appropriate blood glucose monitoring (at least in the 2h before setting off and 2-hourly whilst driving).	There have been no episodes of hypoglycaemia requiring the assistance of another person in the preceding 12m. They have full awareness of hypoglycaemia. 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). The DVLA will arrange an examination by an independent consultant diabetologist every 12m, at which 3m of blood glucose readings must be available.

Insulins in type 2 diabetes

- There are 2 main sorts of insulins: short- and long-acting.
- There are analogue versions of both short- and long-acting insulins, but they are more expensive than ordinary insulins.
  - Long-acting insulin analogues are very similar to long-acting ordinary insulins.
  - Short-acting insulin analogues have a quicker onset of action (you can inject and eat) than short-acting ordinary insulins.
- NICE recommends a single daily dose of a long-acting ordinary insulin is suitable for most type 2 diabetics, but remember to optimise diet and lifestyle first.
- Use insulins with metformin in type 2 diabetes.
- Beware the risks of hypoglycaemia (both short- 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

My notes