COMPASS

Therapeutic Notes on the Management of Type 2 Diabetes Mellitus

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Contents

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Glossary	
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
RBG	Random blood glucose
FBG	Fasting blood glucose
OGTT	Oral glucose tolerance test
PPG	Post-prandial glucose
ACE	Angiotensin-converting enzyme
eGFR	estimated glomerular filtration rate
MHRA	Medicines and Healthcare Regulatory Agency
UTI	Urinary tract infection
UKPDS	UK Prospective Diabetes Study
MCV	Mean corpuscular volume
ALT	Alanine aminotransferase
NYHA	New York Heart Association
NPH insulin	Neutral Protamine Hagedorn insulin
DVLA	Driver and vehicle licensing agency
FDA	Food and Drug Administration (US regulatory body)
SPC	Summary of Product Characteristics
CrCl	Creatinine clearance
SU	Sulfonylurea

Introduction and Background

Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition characterised by insulin resistance (i.e. the body's inability to effectively use insulin) and insufficient pancreatic insulin production, resulting in high blood glucose levels (hyperglycaemia).[1]

Diabetes complications

T2DM is commonly associated with obesity, physical inactivity, raised blood pressure, disturbed lipid levels and a tendency to develop thrombosis. It is therefore recognised to have an increased cardiovascular risk.[1] It is associated with long-term microvascular (neuropathy, retinopathy, nephropathy) and macrovascular complications (e.g. heart attack and stroke), together with reduced quality of life and life expectancy.[1]

What is the prevalence?

More than 3.2 million adults in the UK are diagnosed with diabetes. However many people are thought to be living with diabetes who have not been diagnosed.[2] Prevalence rates in Northern Ireland are currently at 5.3% of the adult population.[2]

It is estimated that about 90% of adults currently diagnosed with diabetes have type 2 diabetes.[1] T2DM diabetes is more common in people of African, African-Caribbean and South Asian family origin than other ethnicities.[1]

A growing trend

The number of people with T2DM is increasing rapidly, both within the UK and worldwide. This rise is thought to be as a result of ageing populations, poor diet, and reduced physical activity.[3] It can occur in all age groups and is increasingly being diagnosed in children.[1]

Correspondingly, costs to society and healthcare are high and escalating.[4] NHS annual spend on diabetes is expected to increase from £9.8 billion (current spend) to £16.9 billion over the next 25 years, and amount to 17% of the overall NHS budget for the UK.[2]

Risk Factors and "Pre-diabetes"

Risk factors for T2DM

Established risk factors for type 2 diabetes are:

- Obesity (fat in the central [truncal] region is more diabetogenic than fat around the hips and thighs).
- Lack of physical activity.
- History of gestational diabetes.
- Impaired glucose tolerance.
- Impaired fasting glucose.
- Drug therapy, e.g. corticosteroid therapy, atypical antipsychotics (e.g. olanzapine, clozapine)
- Cigarette smoking.[12,28]

Can diabetes be prevented?

In light of the large and growing prevalence of T2DM, much research has focussed on ways of preventing the disease in the first place. Diabetes prevention studies have been carried out worldwide. These studies have shown that lifestyle changes can prevent the development of T2DM in high risk individuals. In particular, a legacy effect appears to be emerging, in that *early* intensive lifestyle change appears to result in long-term benefits.[9-11]

There has been much debate around the use of the term "pre-diabetes". It is feared that labelling people with "pre-diabetes" risks medicalising people, bringing with it associated anxiety, issues with insurance, and an added burden on healthcare.
However, being identified as having "pre-diabetes" or being at high risk of developing T2DM should be seen as an opportunity for people to make the necessary lifestyle changes, so that they can prevent progression to T2DM.[2]

Impaired glucose regulation (IGR)

Impaired glucose regulation (IGR) is a risk factor for developing T2DM. It is used to describe both:

- **Impaired fasting glycaemia** (fasting blood glucose 6.1-6.9mmol/l) and
- **Impaired glucose tolerance** (2hr plasma glucose after 75g oral glucose load 7.8-11mmol/l).[8,12]

People with impaired glucose tolerance are at increased risk of diabetes. Although people with impaired fasting glycaemia have been studied less thoroughly than those with impaired glucose tolerance, they also seem to be at increased risk of diabetes.[12]

How to identify those at high risk of T2DM?

In the NICE Public Health guideline on prevention of T2DM in people at high risk, a staged (or stepped) approach is recommended:

Step 1
Use a validated risk-assessment score to estimate the risk of the individual developing T2DM.[8]

Validated risk assessment tools

- The Diabetes Risk Score (or "Leicester score") https://www.diabetes.org.uk/Professionals/Diabetes-Risk-Score-assessment-tool/
- QDiabetes-2015 http://www.qdiabetes.org/)

Step 2
For those who obtain a 'low' or 'intermediate' risk score, NICE recommend advising people on the risks of developing T2DM, the benefits of a healthy lifestyle and modifying risk factors.[8]

For those who obtain a 'high risk' score, NICE recommend offering a blood test (either FPG or HbA1c). Depending on the results of the blood test, people can be risk stratified and given appropriate advice:

Moderate risk of diabetes

HbA1c < 42mmol/mol (6.0%) or FPG < 5.5mmol/l
Offer a brief intervention to:

- Discuss the risks of developing T2DM
- Help modify individual risk factors
- Offer tailored support services

High risk of diabetes

HbA1c 42—47mmol/mol (6.0—6.4%) or FPG 5.5 — 6.9mmol/l
Offer an intensive lifestyle change programme to:

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

Possible diabetes

HbA1c ≥ 48mmol/mol (6.5%) or FPG ≥ 7.0mmol/l
Carry out a further blood test if asymptomatic, to confirm or reject the presence of T2DM.[8]

Diagnosis and Units

Using HbA1c to diagnose

In 2011, the World Health Organisation (WHO) published advice that HbA1c can be used as a diagnostic test for diabetes. An HbA1c of 48mmol/mol (6.5%) is recommended as the cut point for diagnosing diabetes.[7] In asymptomatic patients, a second sample should be taken within 2 weeks to confirm the diagnosis of T2DM.[6] A value less than 48mmol/mol (6.5%) does not exclude diabetes diagnosed using glucose tests.[7]

Can glucose tests still be used to diagnose T2DM?

Diabetes can still be diagnosed using glucose tests:

- RBG ≥ 11.1mmol/l with symptoms
- FBG ≥ 7mmol/l or
- 2-hour blood glucose ≥11.1mmol/l after a 75g glucose load OGTT.[6]

NB – diagnosis should be based on plasma glucose samples measured by the laboratory; capillary samples are not acceptable to base a diagnosis on.[2]

Should both tests be used?

UK guidance does not recommend additional or follow-up glucose measurements as they identify different populations, and may produce conflicting results, confusing the situation.[6]

When not to use HbA1c as a test for diagnosis?

HbA1c does have its drawbacks, HbA1c is a measure of average FBG and PPG levels over the preceding 60 to 90 days and it is affected by conditions that affect red blood cell life span and also haemoglobulinopathies.[6] Do not use HbA1c to diagnose in the following:

- Suspected type 1 diabetes (at any age)
- All children and young people
- Pregnancy — current or within the last two months (use OGTT to diagnose diabetes in pregnancy)
- Short duration of symptoms of diabetes (less than two months)
- Patients at high risk of diabetes who are acutely ill
- Patients newly taking drugs that may cause rapid rise in glucose, e.g. corticosteroids or antipsychotic drugs
- Acute pancreatic damage or pancreatic surgery
- Kidney failure
- Patients being treated for HIV infection
- An abnormal haemoglobin or conditions that may affect red cell survival.[6]

Units for HbA1c

The units for reporting HbA1c changed in 2011 from a percentage (known as DCCT units) to millimoles HbA1c per mol of unglycosylated haemoglobin (mmol/mol) (known as IFCC units).[2] The move was to standardise units internationally. Conversions are shown in **TABLE ONE**.

TABLE ONE: Units for HbA1c

DCCT HbA1c (%)	IFCC HbA1c (mmol/mol)
6	42
6.5	48
7	53
7.5	59
8	64
9	75
10	86

Structured Education

Structured education is an integral part of diabetes care. People with T2DM should be offered structured education at and around the time of diagnosis, and on an ongoing basis, i.e. annual reinforcement and review.[1]

Group education programmes (e.g. DESMOND, X-pert) are the preferred option. However alternative arrangements should be made for those unwilling to participate in group education.[1]

What happens at structured education?

Group education sessions are delivered by trained educators to small groups of people with diabetes. The education sessions are delivered in a way to promote self -management, rather than telling people what they should and shouldn't do. The sessions are supported by specially developed, evidence-based resources.

What does the patient get out of structured education?

The aim of structured education is to improve understanding of diabetes, and to support the patient to set realistic goals and address concerns that they may have with their current lifestyle. Benefits that structured education offers to the patient can include:

- Lowers HbA1c levels
- Lowers blood pressure and cholesterol
- Support to lose weight
- Improves levels of physical activity
- Smoking cessation interventions
- Reduces depression
- Promotes positive behaviour change.[97,98]

Dietary Advice

Adopting a healthy diet is crucial to the management of T2DM, in terms of glycaemic control, weight management and overall health and well being.[88] People with T2DM should be given advice on healthy balanced eating that is applicable to the general population.[1]
Encourage high-fibre, low-glycaemic-index sources of carbohydrate in the diet, such as fruit, vegetables, wholegrains and pulses; include low-fat dairy products and oily fish; and control the intake of foods containing saturated and trans fatty acids.[1]

Discourage the use of foods marketed specifically for people with diabetes.[1]
For recommendations on lifestyle advice, see the NICE guidelines on: preventing excess weight gain, weight management, obesity, physical activity, smoking: brief interventions and referrals, stop smoking services, smoking: harm reduction, and smoking: acute, maternity and mental health services.[1]

T2DM is commonly associated with obesity, physical inactivity, raised blood pressure, disturbed blood lipid levels and a tendency to develop thrombosis. It is therefore recognised to have an increased cardiovascular (CV) risk.[1] Indeed, **CV disease is the leading cause of death in people with T2DM**.

Managing Lipids

Cardiovascular risk and T2DM: new thinking

Previously it was thought that people with T2DM had a similar CV risk as people with coronary heart disease (CHD). However, latest evidence suggests that, for those newly diagnosed or for those who have been living with T2DM for less than 10 years, the risk may not be as high. The risk approaches that of CHD after approximately 10 years.[13]

For this reason, it is recommended to conduct CV risk assessment to determine preventative therapy on an individual basis. This is usually done using QRISK-2-2015® http://www.qrisk.org.[14]

NB — do not use a risk assessment tool to assess CVD risk in people with an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 and/or albuminuria (these people are at increased risk of CVD).[14]

Lipid modification therapy

The NICE guideline on *Cardiovascular disease: risk assessment and reduction, including lipid modification* recommends the following for people with T2DM:

Primary prevention: atorvastatin 20mg if >10% 10 year risk calculated by using QRISK2-2015®.

Secondary prevention: atorvastatin 80mg

Follow-up: The aim of treatment is to achieve at least a 40% reduction in base-line non-HDL-C levels [i.e. total cholesterol (TC) - HDL-C] for both primary and secondary prevention. If this is not achieved, discuss adherence and timing of statin dose, reinforce adherence to diet and lifestyle measures, and consider increasing dose of atorvastatin on an individual basis using clinical judgement.[14] This is a change to previous recommendations for primary prevention.

How to manage triglycerides in T2DM?

Triglycerides should be measured before starting lipid modification therapy for primary prevention (a fasting sample is not needed).[14] If triglycerides are high, recheck fasting triglycerides.

If fasting triglycerides are >1.7mmol/l:

- Optimise diabetic control
- Reduce excess alcohol
- Exclude secondary causes, e.g. hypothyroidism, nephrotic syndrome or cholestasis.

Seek specialist advice in patients with triglycerides > 10mmol/l or if triglycerides are 4 – 9.9mmol/l and non-HDL cholesterol is > 7.5mmol/l (as there is an increased risk of pancreatitis).[14]

Refer to NICE guideline CG181 and Northern Ireland Lipid Management Pathway for an A4 summary of lipid treatment—available on the NI Formulary website / 2.12 Lipid-regulating drugs

Managing Blood Pressure

Blood pressure targets

A risk approach is recommended for blood pressure (BP) targets, aiming for a target BP:

- Less than 140/80 mmHg for most people with T2DM, but
- Less than 130/80 mmHg for those at greater risk (including people with increased albumin excretion rate [microalbuminuria or worse], eGFR less than 60 mL/min/1.73 m^2, retinopathy, or prior stroke or transient ischaemic attack).[12]

What is the antihypertensive of choice in T2DM?

ACE inhibitors have similar blood pressure-lowering effects to other antihypertensive drugs. However, ACE inhibitors provide additional benefit in terms of renal outcomes in people with T2DM compared to other antihypertensive drugs. For this reason, NICE recommend **a generic ACE-inhibitor** as the antihypertensive of choice in T2DM.[1] Refer to the NI Formulary for choices of ACE-inhibitors.

There are exceptions to this:

- People of African or Caribbean family origin: an ACE inhibitor plus either a diuretic or a generic calcium channel blocker (CCB). This is because the BP lowering effect of ACE inhibitors is not as good in this patient group.
- Women who might become pregnant: a CCB.
- People with continuing intolerance to an ACE inhibitor (other than renal deterioration or hyperkalaemia): an angiotensin II receptor antagonist is an alternative.[1]

Do not combine an ACE inhibitor with an angiotensin II receptor antagonist to treat hypertension. Dual therapy is associated with an increased risk of hyperkalaemia, hypotension and impaired renal function (dual therapy has a limited place in therapy for people with heart failure, under specialist recommendation).[1,83]

For further information on *BP management in T2DM*, refer to NICE guideline NG28.

Antiplatelet Therapy

When to offer antiplatelet therapy in T2DM?

Antiplatelet therapy (aspirin or clopidogrel) is no longer recommended for people with T2DM who do not have co-existing cardiovascular disease. This follows advice from the MHRA that the risk/benefit ratio is not considered favorable in primary prevention as the risk of having a major bleed (gastrointestinal bleeding) outweighs any potential vascular benefit.[15]For guidance on the primary and secondary prevention of cardiovascular disease in people with T2DM, see the NICE guidelines on cardiovascular disease and myocardial infarction.

Information prescriptions

A useful resource for patients

Information prescriptions have been designed to provide people with diabetes the information that they need to understand, engage with and improve on their health targets. They are available on the Diabetes UK website for cholesterol, blood pressure and HbA1c.

- They can be downloaded at: www.diabetes.org.uk/info-p-qa.
- They can be linked to the GP clinical system.

Blood Glucose Targets

What target HbA1c should we aim for?

HbA1c targets should be discussed with the patient and a value agreed and set with the person.
For people treated with lifestyle measures alone or who are taking one antidiabetic drug not associated with hypoglycaemia, the usual target HbA1c value is 48 mmol/mol (6.5%). For people on a drug associated with hypoglycaemia, aim for an HbA1c level of 53 mmol/mol (7.0%).[1] For people taking two or more antidiabetic drugs (including insulin), the usual target HbA1c is less than 59 mmol/mol (7.5%).

Consider relaxing the target HbA1c level on a case-by-case basis, especially in those who are older or frail when the person is:

- unlikely to achieve longer-term risk-reduction benefits, e.g. reduced life expectancy.
- a high risk of the consequences of hypoglycaemia, e.g. risk of falling, impaired awareness of hypoglycaemia, driving or operating machinery as part of their job
- intensive management would not be appropriate, e.g. significant comorbidities.[1]

What to take into account when setting a target HbA1c?

The following should be taken into account:

- The person's preference.
- The balance of likely benefits and harms of treatment.
- The risk of microvascular and macrovascular complications.
- The risk and consequences of hypoglycaemia.
- Whether the person will benefit from self-monitoring.
- The intensity of treatment.[12]

HbA1c targets in younger people?

For younger people who are newly diagnosed, or who are early in the course of T2DM, early tight glycaemic control significantly improves microvascular disease in the short term, and macrovascular disease and mortality in the longer-term (the 'legacy effect' or 'metabolic memory'). These individuals may benefit from a HbA1c of < 48mmol/mol (6.5%).[84]

HbA1c targets in older people?

Less stringent HbA1c targets may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with long-standing diabetes in whom HbA1c targets are difficult to achieve despite self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.[85] These individuals may benefit from less stringent glycaemic targets, aiming for a HbA1c of 58 -64mmol/mol (7.5 – 8%) or sometimes higher.[84]

In older people with T2DM, *function* should be considered rather than age when determining optimum HbA1c targets. In frail older patients with diabetes, avoidance of hypoglycaemia, hypotension, and drug interactions due to polypharmacy are of even greater concern than in younger patients with diabetes.[26] Management of co-morbidities is important as this will impact on a person's self-management abilities.[27]

Self-monitoring of Blood Glucose

When should a patient with T2DM carry out self-monitoring of blood glucose?

NICE advise not to routinely offer self-monitoring of blood glucose (SMBG) levels unless:

- The person is on insulin or
- There is evidence of hypoglycaemic episodes or
- The person is on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery or
- The person is pregnant, or is planning to become pregnant.[1]

Short-term SMBG may be considered (with review):

- When starting treatment with corticosteroids or
- To confirm suspected hypoglycaemia.[1]

What medication can increase risk of hypoglycaemia while driving or operating machinery?

- Insulin
- Sulfonlyureas (e.g. gliclazide, glimepiride, tolbutamide, glipizide, glibenclamide)
- Glinides (repaglinide, nateglinide).

What is the advice for SMBG when driving if taking a sulfonylurea or a glinide?

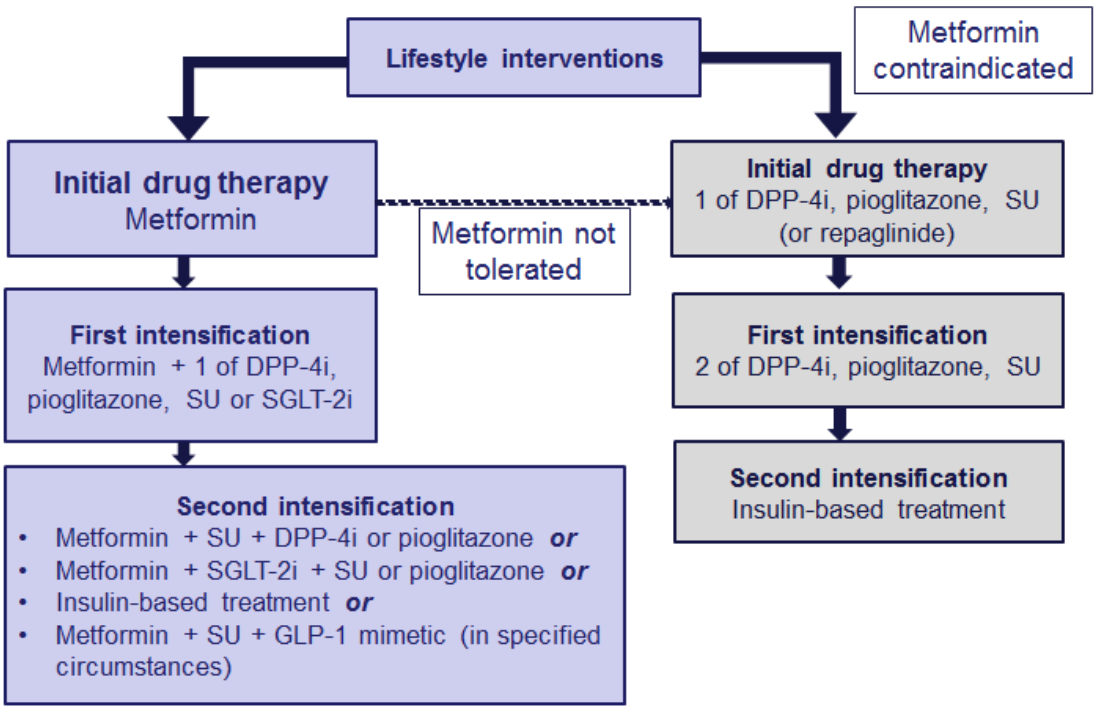
The DVLA provide advice depending on whether the person holds a group 1 (car, motorcycle) or group 2 licence (lorry, bus, taxi driver). This is summarised below, but see DVLA At a Glance Guide for full details.

The Diabetes Team at Belfast Health and Social Care Trust have produced information leaflets for patients and healthcare professionals on driving and diabetes. These have been added to Diabetes UK website (NI news). They aim to supplement the advice provided by the DVLA.

TABLE TWO: DVLA guidelines for SMBG if taking a sulfonylurea or a glinide

Group 1 drivers	• It may be appropriate to monitor blood glucose (depending on clinical factors including frequency of driving) at times relevant to driving to enable the detection of hypoglycaemia. • A meter with a memory is not needed.
Group 2 drivers	• Must regularly monitor blood glucose at least twice daily and at times relevant to driving. • A meter with a memory is needed.[2]

Summary of NICE algorithm for blood glucose lowering pathway (simplified version)



NICE guidance

NICE recommend a stepped process to intensifying blood glucose treatment, as summarised above.

Initial drug treatment

Metformin (standard-release) is the recommended initial drug treatment for adults with T2DM.[1] This is based on UKPDS trial data that showed that metformin lowers blood glucose and reduces the macrovascular complications of diabetes.[12]

If gastrointestinal side effects are experienced with standard-release metformin, a trial of modified-release metformin may be considered.[1]

Initial drug treatment if metformin contraindicated or not tolerated

If metformin is contraindicated or not tolerated, consider initial drug treatment with:

- A dipeptidyl peptidase 4 (DPP-4) inhibitor or
- Pioglitazone or
- A sulfonylurea[1] or
- A sodium glucose co-transporter-2 (SGLT-2) inhibitor.[93]

Rescue therapy at any phase of treatment

If a patient with T2DM is symptomatically hyperglycaemic (e.g. osmotic symptoms), insulin or a sulfonylurea may be used to bring blood glucose under control. Treatment can then be reviewed once blood glucose control has been achieved.[1]

What factors should be considered when choosing blood glucose lowering treatment(s)?

Consider the following when choosing drug treatment(s)

- Effectiveness in terms of metabolic response
- Safety and tolerability
- The person's individual clinical circumstances, e.g. comorbidities, risks from polypharmacy
- The person's preferences and needs
- Licensed indications
- Cost (if two drugs in the same class are appropriate, choose the option with the lowest acquisition cost).[1]

What next after metformin?

NICE recommend adding in a second drug if monotherapy has not continued to control HbA1c to below the person's individually agreed threshold for intensification.[1]

First intensification of drug treatment

Consider dual therapy with metformin plus:

- A DPP-4 inhibitor or
- Pioglitazone or
- A sulfonylurea or
- A sodium glucose co-transporter-2 (SGLT-2) inhibitor.[1]

First intensification if metformin contraindicated or not tolerated

Consider dual therapy with the following combinations:

- A DPP-4 inhibitor and pioglitazone or
- A DPP-4 inhibitor and a sulfonylurea or
- Pioglitazone and a sulfonylurea.[1]

Although not covered in the NICE guidance (outside of the scope), SGLT-2 inhibitors are licensed to be used in combination with other glucose-lowering medicinal products (with the exception of the combination dapagliflozin and pioglitazone).[18-20]

Metformin

How does metformin work?

Metformin works mainly by decreasing gluconeogenesis and by increasing peripheral utilisation of glucose.[12]

What are the main advantages of metformin?

Positive patient-orientated outcome data

The UKPDS study showed that metformin use in overweight people with T2DM improved microvascular complications in the short term and macrovascular complications in the longer term. Therefore metformin is a first line option in all major T2DM guidelines.
NICE recommend that people with T2DM should be prescribed metformin, unless it is contraindicated or not tolerated.[12]

Reduction in HbA1c

Mean HbA1c reduction is 1.5 — 2%.[79,80]

Low risk of hypoglycaemia

Metformin alone does not cause hypoglycaemia.[2]

Weight neutral

Metformin is weight neutral, and may even give rise to minimal weight loss.[102]

What are the main disadvantages of metformin?

GI disturbance

GI disturbance (diarrhoea, abdominal pain, nausea) is the main side effect with metformin. This is common, especially when starting metformin. To minimise this, start at a low dose (500mg with breakfast) and gradually increase by 500mg at intervals of one to two weeks, according to response.[12]

Lactic acidosis

Lactic acidosis has been reported rarely in people taking metformin, although the level of association is debated. To minimise the risk of lactic acidosis, the dose of metformin should be reduced to 500mg twice daily when eGFR is between 30 to 45ml/min, and stopped when eGFR is less than 30ml/min.[12]

Vitamin B_{12} deficiency

Metformin can reduce intestinal absorption of vitamin B_{12}, which can lead to vitamin B_{12} deficiency. However it rarely results in a megaloblastic anaemia.[24, 29]
Measuring of vitamin B_{12} levels is usually only indicated in the presence of symptoms of anaemia, or an elevated MCV as part of a full blood count (FBC).[29]

Sick Day Rules

- Acute kidney injury (AKI) is a sudden and recent reduction in a person's kidney function.
- Renal function is vulnerable to modest reductions in blood pressure or blood volume, including dehydration arising from diarrhoea or vomiting.
- 1 in 5 people admitted to hospital each year as an emergency has acute kidney injury.
- Patients and carers should be educated to **temporarily discontinue selected medications if they develop vomiting, diarrhoea or infections associated with increased fluid losses.**
- Common groups of medications that are associated with increased incidence of AKI:
  - ◊ Metformin
  - ◊ ACE inhibitors and angiotensin II antagonists
  - ◊ Diuretics
  - ◊ NSAIDs
  - ◊ SGLT-2 inhibitors[99]

Prescribing points — Metformin

► Standard-release metformin is the recommended first line drug treatment.
► "Start low and go slow" with the dose of metformin to minimise GI side effects.
► Check renal function. Ensure patient is taking the correct dose of metformin for their renal function — reduce dose to:
- 500mg BD when eGFR < 45ml/min and
- Stop if eGFR < 30ml/min.

► Counsel patients on sick day rules with metformin.
► Continue to prescribe metformin if insulin is started.[1, 12]

Sulfonylureas

There are currently five sulfonylureas on the market: glibenclamide, gliclazide, glimepiride, glipizide, tolbutamide.

How do sulfonylureas work?

Sulfonylureas act by increasing insulin secretion and are therefore only effective when some residual pancreatic beta-cell function is present.[12]

Are all sulfonylureas the same?

Gliclazide, glimepiride, and glipizide are the sulfonylureas of choice [12], with gliclazide being the most commonly prescribed sulfonylurea. Glibenclamide is usually not recommended because it has a prolonged duration of action and therefore increases the risk of hypoglycaemia.[12]

What are the main advantages of sulfonylureas?

Reduction in HbA1c

Mean HbA1c reduction is 1.5 — 2%.[81]

Positive patient-orientated outcome data

There is extensive experience with sulfonylureas. Evidence from the UKPDS33 study showed that sulfonylureas reduce microvascular complications in people with T2DM.

Rapid effect

Sulfonylureas have a rapid response. They are therefore useful if hyperglycaemic symptoms (e.g. osmotic symptoms) are present. Treatment can then be reviewed once HbA1c is under control.[1]

What are the main disadvantages of sulfonylureas?

Risk of hypoglycaemia

Hypoglycaemia is the most common adverse effect with sulfonylureas.[12,43] Consequently there are driving implications for people taking sulfonylureas — see section on 'Self Monitoring of Blood Glucose.'

Caution in elderly patients

Sulfonylureas should be used with caution in the elderly, and avoided if possible in the frail elderly, as this population will be more susceptible to hypoglycaemia.[12]

Caution in renal and liver impairment

The action of sulfonylureas may be prolonged in people with renal and / or liver impairment. Sulfonylureas should therefore be used with caution in renal impairment: a small starting dose should be used with careful patient monitoring.[43,44]

People with irregular meal times

People with irregular meal times will be more susceptible to hypoglycaemia and therefore an alternative glucose -lowering agent should usually be considered.[12]

Weight gain

Sulfonylureas can cause weight gain, usually within the first year of treatment. With monotherapy, mean weight gain is between 1 to 5kg.[12]

Drug-drug interactions

Sulfonylureas can interact with a number of medicines, e.g. antifungals and warfarin.[28] Therefore the possibility of drug interactions should be checked before prescribing other medicines.

Low durability of effect

As residual pancreatic beta-cell function is required for sulfonylureas to work, the glucose-lowering effect of sulfonylureas has been found to wane over time.[31]

Is there an increased cardiovascular risk with sulfonylureas?

A large meta-analysis published in 2016 found that sulfonylureas are not associated with an increased risk of death, myocardial infarction or stroke compared to placebo, diet control or other anti-diabetic drugs.[100] There had been conflicting views on the safety of sulfonylureas: prospective observational studies had highlighted a potential CV risk with sulfonylureas (an increase in risk of CV death and stroke); in contrast many randomised controlled trials (RCTs) included sulfonylureas as active comparators or as part of treatment, and have not indicated that sulfonylureas are associated with increased CV risk (albeit the RCTs were designed to target glycaemic control and were not powered to demonstrate CV risk or benefit). These findings provide reassuring evidence for continued use of sulfonylureas.[89-91,100,101]

NI Formulary choices

For recommended choices of sulfonylureas, see NI Formulary 6.1

Prescribing points — Sulfonylureas

► Discuss the possibility of hypoglycaemia with patients and how to minimise the risk.[12]
► Driving implications — counsel patients as per DVLA guidance.[1]
► Review metabolic response: monitor HbA1c every six months to ensure patient continues to benefit.[12]
► Check renal and liver function to ensure correct dose / appropriateness of therapy.[12]
► Review suitability of treatment in the elderly.[12]

Pioglitazone

How does pioglitazone work?

Pioglitazone binds to the peroxisome proliferator-activated receptor gamma (PPAR gamma) nuclear receptor, affecting insulin-sensitive genes, which regulate various metabolic functions including glucose and lipid metabolism. Pioglitazone therefore increases insulin sensitivity and glucose uptake and reduces hepatic gluconeogenesis. It does not directly stimulate insulin secretion.[12]

What are the main advantages of pioglitazone?

Can be used in renal impairment

No dose adjustment is needed for pioglitazone in patients with renal impairment.[33]

Reduction in HbA1c

Mean HbA1c reduction is 1 — 1.5%.[82]

What are the main disadvantages of pioglitazone?

Whilst NICE place pioglitazone as a second line option after metformin, they stipulate specific criteria of when not to offer or continue pioglitazone — see box 'NICE 'Do not offer or continue pioglitazone' criteria'.

Weight gain

There is an increased risk of both fluid retention and increased adipose tissue with pioglitazone.[33,35] Mean weight gain is 2 to 3kg.[33]

Heart failure

Due to the increased risk of fluid retention with pioglitazone, this can exacerbate or precipitate heart failure.[33,35] Pioglitazone is contraindicated in people with heart failure or a history of heart failure (NYHA stages I to IV).[12]

Caution in macular oedema

Due to the increased risk of fluid retention, pioglitazone has been associated with decreased visual acuity due to worsening or new-onset macular oedema.[35]

NICE 'Do not offer or continue pioglitazone' criteria

If patient has any of the following:

- Heart failure or history of heart failure
- Hepatic impairment
- Diabetic ketoacidosis
- Current, or a history of, bladder cancer
- Uninvestigated macroscopic haematuria.[1]

Hepatic impairment
Pioglitazone is contraindicated in people with hepatic impairment (treatment should not be initiated if baseline ALT > 2.5 times the upper limit of normal, or if there is any other evidence of liver disease).[33]

Bladder cancer
There is a small increased risk of bladder cancer in patients taking pioglitazone. However, the benefits continue to outweigh the risks for those who respond to treatment and in whom there are no identified risk factors for bladder cancer. Careful patient selection is therefore important. Patients with active bladder cancer or with a history of bladder cancer, and those with uninvestigated haematuria, should not receive pioglitazone.[34]

Risk of bone fracture
An increased incidence of bone fractures (bone, hand, or arm) has been observed in women taking pioglitazone. Pioglitazone should probably be avoided in those at high risk of fractures.[33,35]

Prescribing points — Pioglitazone
► Monitor liver function periodically during treatment (expert opinion suggests every 2 to 6 months for the first year).[12]
► Review risk of fracture using FRAX® or QFracture® and consider alternative glucose-lowering agent if patient at high risk of fracture.

DPP-4 inhibitors ('gliptins')

There are currently five DPP-4 inhibitors on the market: alogliptin (Vipidia®▼), linagliptin (Trajenta®), saxagliptin (Onglyza®), sitagliptin (Januvia®), and vildagliptin (Galvus®).

Are all DPP-4 inhibitors the same?
There are differences in licensed indications with respect to combination dual / triple therapy between the DPP-4 inhibitors — licensed indications can be found in the respective SPC http://www.medicines.org.uk/emc/. There is little comparative evidence for efficacy between the gliptins.[46] Relative safety of DPP-4 inhibitors is discussed below.

How do DPP-4 inhibitors work?
The enzyme dipeptidyl peptidase 4 (DPP-4) rapidly degrades the incretin hormones (glucose-dependent insulinotropic polypeptide [GIP] and glucagon-like peptide 1 [GLP-1] which stimulate postprandial insulin secretion and suppress glucagon secretion). DPP-4 inhibitors therefore increase circulating levels of GIP and GLP-1 following the ingestion of food, increase insulin secretion and reduce glucagon secretion.[12]

What are the main advantages of DPP-4 inhibitors?
Weight neutral
DPP-4 inhibitors are weight neutral.

Low risk of hypoglycaemia
DPP-4 inhibitors have a low risk of hypoglycaemia when used alone.[2]

May be used in renal impairment
All DPP-4 inhibitors can be used in renal impairment, albeit with dose titration (with the exception of linagliptin where a dose reduction is not needed in renal impairment).[12]

Cardiovascular outcomes trials for DPP-4 inhibitors

Following safety concerns and subsequent removal from the market of rosiglitazone, the FDA in the USA has requested that newly licensed diabetes drugs are assessed for cardiovascular safety.[45] Cardiovascular outcome trials are underway for DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 agonists.

To date, three trials have been published for DPP-4 inhibitors:
1. SAVOR-TIMI **Saxagliptin** and CV outcomes in T2DM.[37]
2. EXAMINE **Alogliptin** after acute coronary syndrome in patients with T2DM.[39]
3. TECOS Effect of **sitagliptin** on CV outcomes in T2DM.[38]

Results of CV outcome trials for DPP-4 inhibitors:
- The DPP-4 inhibitor trials published to date have shown non-inferiority to placebo in terms of adverse CV outcomes, i.e. the DPP-4 inhibitors have demonstrated CV safety.
- There was however a small but significant increase in hospitalisation for heart failure seen for saxagliptin. An increase in hospitalisation for heart failure was seen for alogliptin, but this did not achieve statistical significance in the CV outcomes trial due to trial size, necessitating further investigation. An increase in hospitalisation for heart failure was not seen in the CV outcomes trials for sitagliptin.[37-39]

What are the main disadvantages of DPP-4 inhibitors?

Reduction in HbA1c

Compared to other anti-diabetic drugs, DPP-4 inhibitors have the lowest reduction in HbA1c — see **TABLE FOUR**. Mean HbA1c reduction is 0.6 — 0.8%.[46,47]

Limited long term data

There is limited long term clinical data with the DPP-4 inhibitors. Furthermore, evidence that DPP-4 inhibitors improve patient-orientated outcomes (i.e. macrovascular or microvascular complications) is lacking.[46]

Pancreatitis

DPP-4 inhibitors have been associated with pancreatitis. The possible mechanism for this is unclear, and people with diabetes have a higher incidence of pancreatitis than non-diabetics. Patients should be counselled on the characteristic symptoms of acute pancreatitis (persistent, severe abdominal pain (sometimes radiating to the back)). If pancreatitis is suspected, the DPP-4 inhibitor should be discontinued. [40,41]

Severe joint pain

Joint pain that can be severe and disabling has been reported rarely with sitagliptin, saxagliptin, linagliptin and alogliptin. Symptoms have been reported from day one to years after starting taking a DPP-4 inhibitor. Symptoms usually resolved in less than a month after stopping the DPP-4 inhibitor. Healthcare professionals should consider DPP-4 inhibitors as a possible cause of severe joint pain and discontinue the drug if appropriate.[36]

NI Formulary choices

For recommended choices of DPP-4 inhibitors, see NI Formulary 6.1

Prescribing points — DPP-4 inhibitors

► Counsel patients on symptoms of acute pancreatitis.

► Monitor renal function: ensure patient is on correct dose of DPP-4 inhibitor for their renal function (with the exception of linagliptin that doesn't require dose adjustment in renal impairment).

► Consider discontinuing medications containing saxagliptin or alogliptin in patients who develop heart failure.

SGLT-2 inhibitors ('gliflozins')

There are currently three SGLT-2 inhibitors on the market: canagliflozin (Invokana®▼), dapagliflozin (Forxiga®▼), and empagliflozin (Jardiance®▼).

Are all SGLT-2 inhibitors the same?

There are differences in relation to administration in renal impairment (see **TABLE THREE**).

No direct head to head studies comparing efficacy or safety within the class currently exist.[49]

How do SGLT-2 inhibitors work?

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule, thereby reducing glucose reabsorption and increasing urinary glucose excretion.[28] The metabolic effects therefore do not depend on an insulin-dependent mechanism.[52]

What are the main advantages of SGLT-2 inhibitors?

Weight loss

SGLT-2 inhibitors promote glycosuria (with urinary loss of approximately 200-300kcal per day for dapagliflozin 10mg). This results in weight loss of around 2 to 3kg.[53-56]

Reduction in blood pressure

SGLT-2 inhibitors have shown a modest reduction in systolic blood pressure of around 5mmHg. The mechanism for this blood pressure lowering effect is not fully understood but proposed mechanisms are:

- Osmotic diuresis
- Weight loss
- Indirect effects due to better glycaemic control.[43]

Reduction in HbA1c

Mean HbA1c reduction is 1%.[55-57]

Cardiovascular outcomes trials for SGLT-2 inhibitors

Cardiovascular outcomes trials are underway for SGLT-2 inhibitors. To date, only one has been published:

1. EMPA-REG **Empagliflozin**, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.[50]

Results of CV outcome trials for empagliflozin:

- Empagliflozin in a population with T2DM and a history of a previous CV event, significantly lowered a composite of CV mortality, hospitalisation for heart failure and all-cause mortality.[50,96]
- It is not clear if the mortality benefits resulted from an effect on weight, blood pressure or cardiovascular load. However, the reduction in mortality does not appear to be due to an effect on atherosclerotic disease. The primary outcome for the pooled empagliflozin doses only just reached statistical significance for superiority and was not statistically significant for individual doses.[96]
- It is unclear at present if this is a class effect or specific to empagliflozin. Further research is therefore required.[50]
- Outcomes relating to myocardial infarction and stroke did not reach statistical significance.[96]
- A secondary end point was microvascular outcomes, in particular progression of kidney disease: empagliflozin was associated with slower progression of kidney disease and lower risk of clinically relevant renal events.[95]

What are the main disadvantages of SGLT-2 inhibitors?

Genitourinary infections
Genitourinary infections, e.g. urinary tract infections and thrush, are a common side effect, particularly in women. This is thought to be due to increased glycosuria.[21-23]

Osmotic symptoms and volume-depleted effects
Osmotic symptoms and a slightly higher rate of volume-depleted effects (dehydration, hypovolaemia, hypotension) are seen with SGLT-2 inhibitors.[21-23] SGLT-2 inhibitors should therefore be used with caution in those on loop diuretics and frail elderly patients.

Rare association with euglycaemic diabetic ketoacidosis (DKA)
There have been reports of DKA with SGLT-2 inhibitors. In some cases, blood glucose levels were only moderately elevated (e.g. <14 mmol/L), which is atypical for DKA. This atypical presentation could delay diagnosis and treatment.

Advice from the MHRA is to:

- Inform patients of the symptoms of DKA (nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness).
- Test for raised ketones in patients with signs and symptoms of DKA.
- If DKA is suspected, stop SGLT-2 inhibitor. [51]

Limited long term data
Longer-term efficacy and safety of the SGLT-2 inhibitors has not been established.[49]

Bone fracture risk
Canagliflozin has been associated with an increased risk of fracture. This has not been shown with either dapagliflozin or empagliflozin so it is unclear currently if this is a class effect or not. It is advised to consider factors that contribute to fracture risk prior to starting patients on canagliflozin.[59]

Increased risk of lower extremity amputations with canagliflozin
An increased risk of lower limb amputation (primarily of the toe) was reported in people taking canagliflozin compared with placebo in a clinical trial in high cardiovascular risk patients. The mechanism behind this adverse effect is unknown, but it is thought that dehydration and volume depletion might increase the risk. Further investigation is ongoing. See MHRA Drug Safety Update June 2016 for further details.[92]

Caution in renal function
SGLT-2 inhibitors require an adequate renal filtration rate in order to remain efficacious (see **TABLE THREE**).

Renal function should therefore be monitored:

- Prior to initiation and then at least annually.
- Prior to initiation of any concomitant drug that may have a negative impact on renal function.
- It is important to reinforce 'Sick day rules' with people taking SGLT-2 inhibitors (see page 7 for further details)
- When renal function is approaching level requiring cessation of SGLT-2 inhibitors, at least 2 to 4 times per year.

TABLE THREE: Renal function required for SGLT-2 inhibitors

Renal Function	Canagliflozin	Dapagliflozin	Empagliflozin
< 60ml/min at initiation	Do not use	Do not use	Do not use
< 60ml/min during treatment	If tolerated, reduce to / maintain at licensed starting dose	Stop	If tolerated, reduce to / maintain at licensed starting dose
< 45ml/min during treatment	Stop	Stop	Stop

NI Formulary choices

For recommended choices of SGLT-2 inhibitors, see NI Formulary 6.1

Prescribing points — SGLT-2 inhibitors
► Monitor renal function and dose reduce or discontinue as appropriate.
► Counsel patients on symptoms of DKA.
► Counsel patients on 'Sick day rules' with SGLT-2 inhibitors.

Patient Review and Decision Aids

Review before second intensification

Drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.[1]

The 'stopping rules' from the previous NICE guideline have been removed for ***oral*** anti-diabetic medicines. However, NICE advise to reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective.[1]

NICE Patient Decision Aid (PDA)

NICE have produced a PDA to compliment their T2DM guideline. The PDA is intended to be used at the first intensification of therapy (i.e. after metformin first line therapy) and aims to support decision-making about:

- Optimal individualised target HbA1c level
- Taking a second medicine for blood glucose control.[86]

Full details can be found at https://www.nice.org.uk/guidance/ng28/resources/patient-decision-aid-1687717

TABLE FOUR: Summary of oral drug treatments for type 2 diabetes

Drug	Mean HbA1c reduction	Risk of hypo-glycaemia	Effect on weight	Advantages	Disadvantages
Metformin	1.5 — 2%	Low	Neutral (or small weight loss)	• Patient-orientated outcome data for improvement in micro– and macro-vascular disease	• GI disturbance • Vitamin B_{12} deficiency and lactic acidosis (rare) • Reduce dose in renal impairment • Remember 'sick day rules'
Sulfonylureas • Glibenclamide • Gliclazide • Glimepiride • Glipizide • Tolbutamide	1.5 — 2%	Yes	1 to 5kg increase	• Rapid response achieved • Patient-orientated outcome data for improvement in microvascular disease	• Risk of hypoglycaemia • Caution in renal and liver impairment • Caution in the elderly • Driving implications • Undetermined cardiovascular risk
Pioglitazone	1 — 1.5%	Low	Increase	• Can be used in renal impairment	• Contraindicated in heart failure • Contraindicated in hepatic impairment • Contraindicated in bladder cancer or uninvestigated macroscopic haematuria • Risk of bone fracture • Caution in macular oedema
DPP-4 inhibitors • Alogliptin▼ • Linagliptin • Saxagliptin • Sitagliptin • Vildagliptin	0.6 — 0.8%	Low	Neutral	• Generally well tolerated • Can be used in renal impairment • Established cardiovascular safety	• Association with pancreatitis (very rare) • Heart failure reported in people taking alogliptin and saxagliptin
SGLT-2 inhibitors • Canagliflozin▼ • Dapagliflozin▼ • Empagliflozin▼	1%	Low	Decrease	• Cardioprotective data for empagliflozin • Weight loss • Decrease in blood pressure	• GU infections • Sufficient renal function needed to maintain efficacy • Remember 'sick day rules' • Hypotension / fainting: caution in frail elderly or people taking loop diuretics • Rare association with euglycaemic diabetic ketoacidosis

NICE guidance
For full details on NICE guidance please refer to the references below:

NICE Type 2 diabetes in adults: management, NG28.
Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes, NICE TA390.
Canagliflozin in combination therapy for treating type 2 diabetes, NICE TA315.
Dapagliflozin in combination therapy for treating type 2 diabetes, NICE TA288.
Empagliflozin in combination therapy for treating type 2 diabetes, NICE TA336.

If dual therapy with metformin and another oral drug has not continued to control HbA1c to target, consider:

- **Triple** therapy with:
  - Metformin + a DPP-4 inhibitor + a sulfonylurea or
  - Metformin + pioglitazone + a sulfonylurea or
  - Metformin + a sulfonylurea + canagliflozin / empagliflozin or
  - Metformin + pioglitazone + canagliflozin / empagliflozin or
- Start **insulin**.

What to use at second intensification if metformin contraindicated or not tolerated?

If dual therapy with two oral drugs has not continued to control HbA1c to target, insulin should be considered.[1]

When to consider a GLP-1 agonist?

NICE advise, if triple therapy with metformin and two oral drugs is not effective / tolerated or is contraindicated, a GLP-1 agonist may be given in combination with metformin and a sulfonylurea if:

- BMI ≥ 35 kg/m^2 (adjusting for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
- BMI < 35 kg/m^2 and:
  - insulin would have significant occupational implications or
  - weight loss would benefit other significant obesity-related comorbidities.[1]

GLP-1 agonists

There are currently five GLP-1 agonists on the market: albiglutide (Eperzan▼®), dulaglutide (Trulicity▼®), exenatide (Byetta®, Bydureon®), liraglutide (Victoza®), and lixisenatide (Lyxumia▼®).

How do GLP-1 agonists work?

The hormone glucagon-like peptide 1 (GLP-1) interacts with pancreatic islet beta cells to stimulate postprandial insulin secretion. GLP-1 also suppresses glucagon secretion. GLP-1 agonists mimic GLP-1, thereby increasing insulin secretion and reducing glucagon secretion.[12]

What are the main advantages of GLP-1 agonists?

Reduction in HbA1c

Mean HbA1c reduction is 1.5%.[59-62]

Weight loss

GLP-1 agonists promote weight loss of approximately 2.5 to 5kg.[59-62]

Low risk of hypoglycaemia

GLP-1 agonists carry a low risk of hypoglycaemia but this is increased when combined with a sulfonylurea or insulin.[63-65]

GLP-1 agonists may be used in moderate renal impairment

GLP-1 agonists, with the exception of exenatide once weekly (Bydureon®), can be used in people with moderate renal impairment (30 to 50ml/min).[66-71] Once weekly exenatide (Bydureon®) is not recommended below a CrCl of 50ml/min.[66]

What are the main disadvantages of GLP-1 agonists?

Gastrointestinal (GI) side effects

GI side effects are very common with GLP-1 agonists, particularly nausea, vomiting and diarrhoea.[59-65]

Risk of pancreatitis

GLP-1 agonists have been associated with pancreatitis and should be discontinued if pancreatitis is suspected. Patients should be counselled on the characteristic symptoms of acute pancreatitis (persistent, severe abdominal pain (sometimes radiating to the back)).[41]

Can a GLP-1 agonist be used with insulin?

NICE advise that a GLP-1 agonist should only be used with insulin under specialist advice with on-going support from a consultant-led multidisciplinary team.[1]

Xultophy® (insulin degludec / liraglutide) is an option for patients with T2DM who are uncontrolled on basal insulin analogues and for whom a GLP-1 agonist is appropriate as an add-on intensification therapy to basal insulin to obtain glucose control.[72]

Stopping rules with GLP-1 agonists

It is important to determine a beneficial metabolic response when a GLP-1 agonist is started. Therefore NICE recommend that GLP-1 agonists should only be continued at 6 months if there is:

- A reduction of at least 11 mmol/mol (1.0%) in HbA1c **and**
- A weight loss of at least 3% of initial body weight in 6 months.[1]

Cardiovascular outcomes trials for GLP-1 agonists

To date, two trials have announced results:

1. ELIXA The Evaluation of **Lixisenatide** in Acute Coronary Syndrome trial.[75]
2. LEADER **Liraglutide** Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results.[94]

Results of CV outcomes trials for GLP-1 agonists:

- Lixisenatide did not show a benefit in CV outcomes. However, lixisenatide did not show any evidence of harm in patients who had recently suffered a coronary event.[75]
- Liraglutide showed lower rates of CV events and death from any cause in patients with T2DM who were at high risk for CV events.[94]

NI Formulary choices

For recommended choices of GLP-1 agonists, see NI Formulary 6.1

Prescribing points — GLP-1 agonists

► Counsel patients on symptoms of acute pancreatitis.
► Stopping rules: review metabolic response after 6 months.
► Monitor renal function and ensure patient continues to receive an appropriate product and dose.

Insulin

If other measures do not keep HbA1c below the person's target, the benefits and risks of insulin should be discussed. Many people with T2DM will ultimately require insulin therapy.[1,12,76-78]

Follow up data from the UKPDS study showed that good glycaemic control early on in the course of T2DM can potentially confer protection against or delay long term diabetes complications. **Therefore insulin therapy should not be delayed if glycaemic control remains suboptimal**.[76-78]

What should be discussed when initiating insulin?

When initiating insulin, a structured programme should be followed, incorporating the following:

- Injection technique
- Continuing telephone support
- Self-monitoring
- Dose titration to target levels
- Dietary understanding
- DVLA guidance ('At a glance guide')
- Management of hypoglycaemia
- Management of acute changes in plasma glucose control
- Support from an appropriately trained and experienced healthcare professional.[1]

Should anti-diabetic drugs be stopped when insulin is started?

Metformin should be continued (provided this is not contraindicated or not tolerated).[1] The continued need for other blood glucose lowering agents should be reviewed.[1]

What is the insulin of choice in T2DM?

NICE recommend NPH insulin (injected once or twice daily according to need) as the first line choice in T2DM.

Combination NPH and a short-acting insulin can be considered, particularly if the person's HbA1c is 75 mmol/mol (9.0%) or higher. This can be administered separately or as a pre-mixed (biphasic) human insulin preparation.[1]

When to consider insulin analogues?

Insulin detemir or insulin glargine (long-acting analogues) are alternatives to NPH insulin if the person:

- Needs assistance to inject insulin, and use of a long-acting would reduce the frequency of injections from twice daily to once daily or
- Has a lifestyle that is restricted by recurrent symptomatic hypoglycaemic episodes or
- Would otherwise need twice daily NPH insulin injections in combination with oral glucose-lowering drugs.[1]

Insulin glargine

There are now three different types of insulin glargine available: the original preparation (Lantus®), a new high strength preparation (Toujeo®) and a biosimilar (Abasaglar▼®). In order to ensure that the patient receives the insulin that is intended for them, it is now even more important that insulin glargine is **prescribed by brand**.

TABLE FIVE: Insulin glargine preparations

Brand name	Strengths available	Administration devices
Lantus®	100 units/ml	SoloStar® prefilled pen, vial, cartridge
Toujeo®	300 units/ml	SoloStar® prefilled pen
Abasaglar▼®	100 units/ml	KwikPen® prefilled pen, cartridge (for use in Lilly reusable pen)

Prescribing points — Insulin in T2DM

► NPH insulin is the first line choice of insulin in T2DM.
► Insulin preparations should always be **prescribed by brand** to avoid confusion and aid product identification.
► Metformin should be continued when insulin is started.

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COMPASS THERAPEUTIC NOTES ASSESSMENT
Therapeutic Notes on the Management of Type 2 Diabetes

COMPASS Therapeutic Notes are circulated to GPs, nurses, pharmacists and others in Northern Ireland. Each issue is compiled following the review of approximately 250 papers, journal articles, guidelines and standards documents. They are written in question and answer format, with summary points and recommendations on each topic. They reflect local, national and international guidelines and standards on current best clinical practice. Each issue is reviewed and updated every three years.
Each issue of the Therapeutic Notes is accompanied by a set of assessment questions. This edition can contribute 3 hours towards your CPD/CME requirements. Submit your completed MCQs to the appropriate address (shown below) or complete online (see below). Assessment forms for each topic can be submitted in **any order** and at **any time**.

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Successful completion of these assessment questions equates with 3 **hours** Continuing Professional Development time. Circle your answer TRUE (T) or FALSE (F) for each question. When completed please post this form to the relevant address shown overleaf. Alternatively, you can submit your answers online:

- **Doctors and nurses** should submit their answers at: **www.medicinesni.com**
- **Pharmacists** should submit their answers at: **www.nicpld.org**

1	**In the management of cardiovascular risk:**			
	a	All patients with type 2 diabetes should be prescribed a statin.	T	F
	b	The aim of statin treatment is to achieve at least a 40% reduction in base-line non-HDL levels.	T	F
	c	A generic ACE inhibitor is the usual antihypertensive of choice in people with type 2 diabetes.	T	F
	d	Aspirin should be prescribed for all people with type 2 diabetes.	T	F
2	**In relation to metformin:**			
	a	Metformin is the recommended initial drug treatment for adults with type 2 diabetes.	T	F
	b	Metformin should be stopped when eGFR falls below 45ml/min.	T	F
	c	Patients taking metformin should be advised to stop metformin temporarily if they develop vomiting or diarrhoea.	T	F
	d	Metformin should be stopped if insulin is started.	T	F
3	**In relation to pioglitazone:**			
	a	The dose of pioglitazone should be reduced when eGFR falls below 45ml/min.	T	F
	b	Pioglitazone is the anti-diabetic drug of choice in patients with osteoporosis.	T	F
	c	Pioglitazone should not be used in patients with heart failure or a history of heart failure.	T	F
	d	Liver function should be monitored periodically during treatment.	T	F
4	**In relation to DPP-4 inhibitors:**			
	a	They produce a moderate reduction in HbA1c, of approximately 0.6-0.8%	T	F
	b	Patients should be counselled on the signs and symptoms of acute pancreatitis, as a possible side effect.	T	F
	c	DPP-4 inhibitors tend to cause weight gain.	T	F
	d	DPP-4 inhibitors carry a high risk of hypoglycaemia.	T	F
5	**In relation to SGLT-2 inhibitors:**			
	a	SGLT-2 inhibitors should be stopped if eGFR falls below 45ml/min.	T	F
	b	SGLT-2 inhibitors are the anti-diabetic of choice in patients taking loop diuretics.	T	F
	c	Euglycaemic diabetic ketoacidosis has been reported in patients taking SGLT-2 inhibitors.	T	F
	d	Patients taking a SGLT-2 inhibitor should be advised to stop the SGLT-2 inhibitor temporarily if they develop vomiting or diarrhoea.	T	F