Nottinghamshire Health Community Treatment Guideline for the Management of Type 2 Diabetes (T2D) in Adults

These guidelines are intended to support prescribing for T2D in adults. Please refer to the BNF or Summary of Product Characteristics for further information on contraindications, precautions, adverse effects and interactions for any named medicine. This most recent update takes into account recommendations from NICE in NG28. Currently the use of SGLT2 inhibitors as first line therapy for people with diabetes and at high risk of CVD, but without established CVD or Heart Failure is not endorsed locally. Therefore, treatment choices for this group should follow the options given in this guideline.

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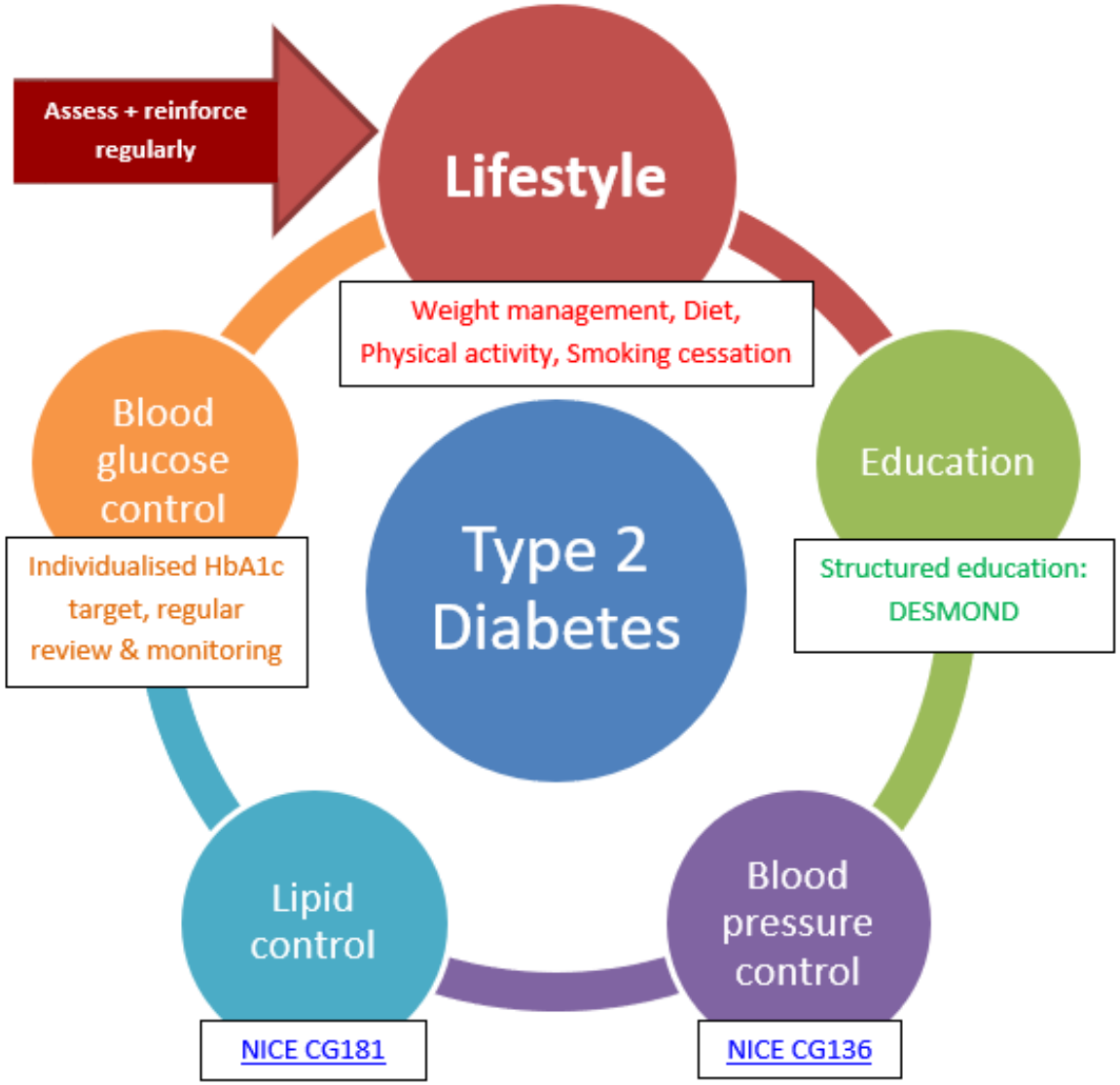
Summary of patient centred approach in T2D

Lifestyle improvements, BP control & cholesterol control are important for macrovascular and microvascular protection.

Assess and reinforce at every review and when considering intensification of medication.



Lifestyle

Weight

- For adults with T2D who are overweight, discuss and agree an initial body weight loss target of 5% to 10%. Remember that a small amount of weight loss may still be beneficial, and a larger amount will have advantageous metabolic impact in the long term (NICE).
- Weight loss can offer greater potential benefits than any medication or combination of medications.
- Support available from Nottinghamshire's Wellbeing Service
- **Low calorie diet service:** Clinicians can refer eligible patients to nottslowcaloriediet

Physical Activity

Physical activity benefits both mental and physical health. There are several resources available to promote physical activity. Consider signposting to the following:

- Nottinghamshire Move More
- We are undefeatable
- Active 10 website and app
- Parkrun

Smoking cessation

- Nottingham City: Stub It!
- Nottinghamshire: Stop Smoking

Patient education

- All adults with type 2 diabetes (and/or their carer) should be offered structured education (DESMOND).
- Explain that this is an integral part of diabetes care.
- If a group setting is unsuitable for an individual, an alternative can be offered. Please refer to DESMOND and state on the referral why they require an alternative. Following structured education (DESMOND), individuals may be referred to a dietitian if they require additional dietary support. Please state clearly the reason why further support is needed.

Nottingham City: https://www.nottinghamcitycare.nhs.uk/our-services/desmond-diabetes-education-and-self-management-going-and-newly-diagnosed

Nottinghamshire: https://www.nottinghamshirehealthcare.nhs.uk/desmond-programme-for-type-2-diabetes

Hypertension

- The treatment thresholds are the same as for the general population, as per NICE 2019 hypertension guidelines
- However, if the person has chronic kidney disease (CKD) and albumin-to-creatinine ratio (ACR) ≥70, aim for a clinic systolic blood pressure below 130 mmHg (target range 120 to 129 mmHg) and a clinic diastolic blood pressure below 80 mmHg.

Lipids

Manage in line with NICE lipids guidance

Blood glucose control

Treatment of Hyperglycaemia
If an adult with T2D is symptomatically hyperglycaemic, consider insulin or a sulfonylurea, and review treatment when blood glucose control has been achieved (NICE).

Glycaemic Target
Adopt an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with T2D, taking into account:

- The person's preference.
- The balance of likely benefits and harms of treatment.
- The risk of microvascular and macrovascular complications - consider age, duration of diabetes and current complication status.
- The risk and consequences of hypoglycaemia - consider employment or driving issues.
- Whether the person will benefit from self-monitoring.
- The intensity of treatment.

- The individualised target should be reviewed every 3-6 months. Reassess the person's needs and circumstances at each review and consider whether to stop any medicines that are not effective.
- HbA1c should be measured at 3-6 monthly intervals until stable on unchanging therapy and 6 monthly thereafter.
- Lifestyle should be reviewed before every treatment escalation.
- Avoid the use of highly intensive management strategies to achieve an HbA1c level less than 48 mmol/mol (6.5%).

Blood glucose control (continued)

Suggested target HbA1c, taking into account patient factors listed on the previous page:

Target level	
48mmol/mol (6.5%)	For people treated with lifestyle measures alone or who are taking one antidiabetic medicine not associated with hypoglycaemia.
53mmol/mol (7.0%)	People taking two or more antidiabetic medicines (including insulin), or a single agent associated with hypoglycaemia.
53-70mmol/mol (7.0%-8.5%)	People with frailty Limited life expectancy Recurrent severe hypoglycaemia/or unawareness of hypoglycaemia

Falls

Having diabetes may increase the risk of falls. Various non-diabetic medications are associated with an increased risk of falls- see here for further details.

Pre-diabetes

Offer intensive lifestyle-change programme for people with pre-diabetes (HbA1c 42-47mmol/mol). The Healthier You NHS Diabetes Prevention Programme is a nine-month programme available both as a face-to-face group service and as a digital service: https://www.lwtcsupport.co.uk/

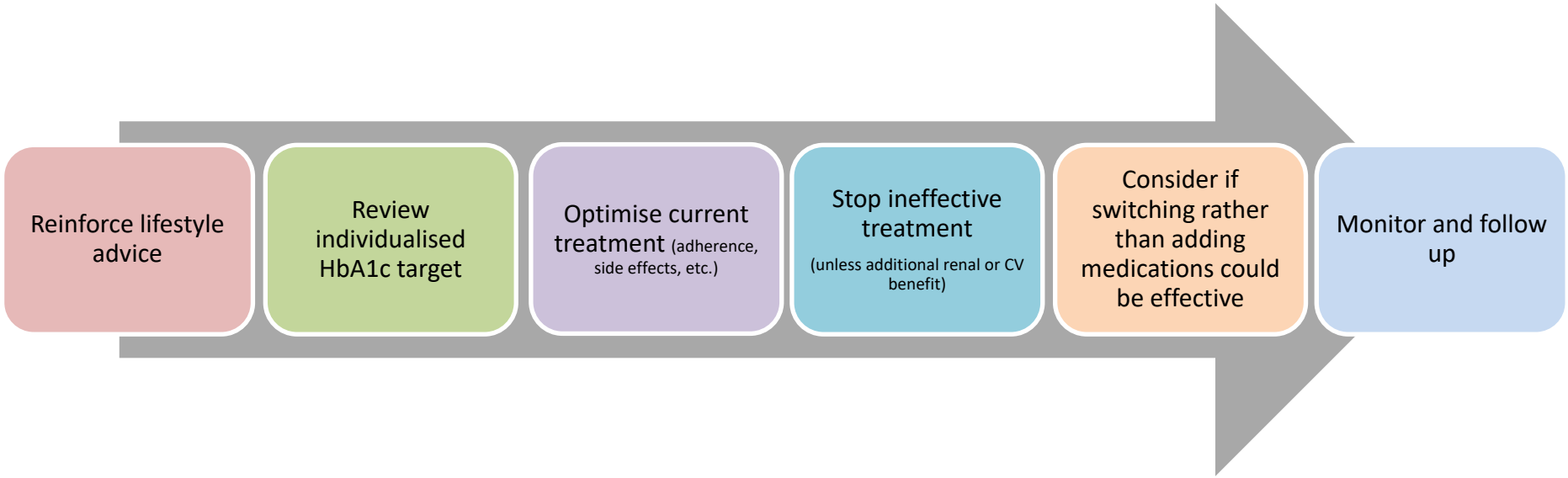
NICE PHG38 Type 2 diabetes: prevention in people at high risk contains information on identifying and assessing risk, lifestyle advice and discusses when metformin might be considered.

Reviewing Medications

When reviewing or considering a change to treatment for adults with T2D, discuss the following:

- how to optimise current treatment regimen taking into account factors such as:
  - the need to revisit advice about diet and lifestyle
  - adverse effects
  - adherence to existing medicines
  - prescribed doses and formulations
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment.
- whether switching rather than adding medicines could be effective.
  (NICE 2022)

Summary of considerations when reviewing medications:



How to choose first-line medicines

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or gliclazide and review when blood glucose control has been achieved

Assess HbA1c, cardiovascular risk and kidney function

Chronic heart failure or established atherosclerotic CVD*

Offer

Metformin

or if GI disturbance

Metformin MR

Once metformin tolerability confirmed offer

SGLT2 inhibitor ('flozin')

with proven cardiovascular benefit

If metformin contraindicated

Offer

SGLT2 inhibitor alone ('flozin')

No established CVD* or heart failure

Offer

Metformin

or if GI disturbance

Metformin MR

Start metformin alone to assess tolerability before adding an SGLT2

If metformin contraindicated

Choose from:

Gliclazide or

DPP-4 inhibitor ('gliptin') or

Pioglitazone or

An SGLT2 inhibitor ('flozin') for some people:

- gliclazide or pioglitazone is not appropriate and

-a DPP-4 inhibitor ('gliptin') would otherwise be prescribed

For information on using SGLT2 inhibitors for people with T2D and CKD see pg. 9.

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD*

See treatment options if further interventions are needed below

*Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

This treatment pathway is adapted from NICE NG28. Currently the use of SGLT2 inhibitors as first line therapy for people with diabetes and at high risk of CVD, but without established CVD or Heart Failure is not endorsed locally. Therefore, treatment choices for this group should follow the options given for those without established CVD or Heart Failure.

How to choose medicines for further treatment

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or gliclazide and review when blood glucose control has been achieved

Treatment options if further interventions are needed

At any point

HBA1c not controlled below individually agreed threshold

Switching or adding treatments

Choose from:

Gliclazide | Or | DPP-4 inhibitor ('gliptin') | Or | Pioglitazone | Or

An SGLT2 inhibitor ('flozin')

-In *dual therapy* if gliclazide is contraindicated or not tolerated or the person is at significant risk of hypoglycaemia or its consequences.

-In *triple therapy*: (see links below or pg 12)

- TA315 Canagliflozin
- TA418 Dapagliflozin
- TA336 Empagliflozin
- TA583 Ertugliflozin

At any point

Cardiovascular status change

If the person has or develops chronic heart failure or established atherosclerotic CVD*

Switching or adding treatments

Offer:

An SGLT2 inhibitor ('flozin') (if not already prescribed)

*Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance. Switch or add treatments from different medicine classes up to triple therapy (dual therapy if metformin is contraindicated).

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other medicines).

GLP-1 mimetic treatments (GLP1s)

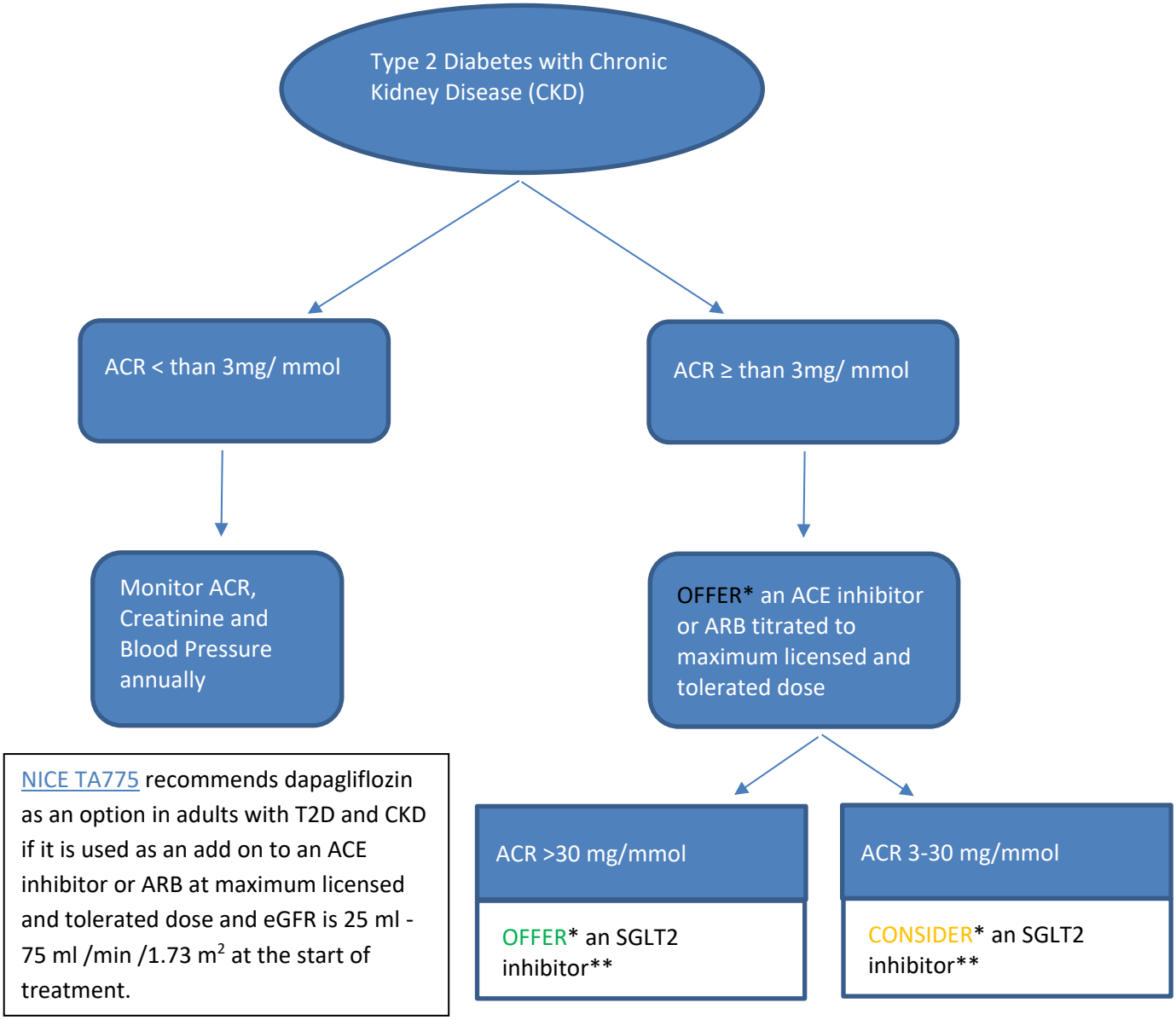
If triple therapy with metformin and two other oral medicines is not effective, not tolerated or contraindicated, consider triple therapy by switching one medicine for a GLP-1 mimetic ('GLP1') for adults with T2D who:

- have a body mass index (BMI) of 35 kg/m2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m2 **and:**

– for whom insulin therapy would have significant occupational implications **or**

– weight loss would benefit other significant obesity related comorbidities.

Managing Chronic Kidney Disease in T2D



*OFFER= strong recommendation CONSIDER= recommendation for which evidence of benefit is less certain.

- Strong evidence shows SGLT2 inhibitors reduce the risk of CKD progression, mortality and CV events.
- People with ACR>30mg/mmol have a higher risk of events than those with lower ACR values.

As the absolute risk reduction depends on the baseline risk of events there is more uncertainty about the clinical and cost effectiveness of SGLT2 inhibitors at lower ACR values.

- When deciding on whether to initiate a SGLT2 inhibitors at lower ACRs consider additional risk factors, likely benefits for individual, patient preference etc.

**Dapagliflozin and canagliflozin are the only SGLT2 inhibitors that are currently licensed for CKD.

NB. The glycaemic lowering effect of SGLT2 inhibitors will be reduced at GFR <45 ml/min. Therefore, additional hypoglycaemic therapy may be required when being used for cardiorenal protection or Heart Failure treatment at lower GFRs.

ACR= Urine albumin to creatinine ratio, ACE inhibitor= Angiotensin- converting enzyme, ARB= Angiotensin receptor blockers

METFORMIN (a BIGUANIDE) Green

Decreases gluconeogenesis and increases peripheral utilisation of glucose.
Cardioprotective.

HbA1c efficacy	Good (reduction in HbA1c of 11–16 mmol/mol)	**Effect on weight**	Loss	**Hypo risk**	None	**Cost per 28 days**	£2.84 – Metformin 1g tablets (1g twice daily) £2.78 – Metformin 1g MR tablets (2g daily) £23.52- Metformin 500mg powder sachets (1g twice daily) £123.16 Metformin 500mg/5ml oral solution sugar free (1g twice daily)

Dosing	• Initially 500mg once daily and gradually increase at weekly intervals to minimise gastrointestinal (GI) side effects. • Titrate to maximum tolerated dose. Usual maximum dose is 1g twice daily or 850mg three times a day. • Review dose and monitor renal function more frequently in moderate renal impairment (CrCl 30-59ml/min) – EMA advice • Metformin MR may be beneficial for people experiencing GI side effects from metformin.
Counselling points	• Take with or after meals. • Sick day rules should be explained. More detailed advice for clinicians is available here. Explain the importance of maintaining adequate hydration and pause metformin if vomiting, diarrhoea or fever occur due to a risk of lactic acidosis. • As for all people with diabetes, it is important to counsel on routine preventative foot-care and periodontitis.
Contraindications and cautions	• Contraindicated in severely reduced renal function (CrCl <30ml/min) – EMA advice • Contraindicated in acute and unstable heart failure. • Caution required in moderate renal impairment. • Medicines that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution. • Hepatic insufficiency.
Monitoring	• Renal function – check before treatment and annually if renal function is normal. Monitor 3-6 monthly if additional risk factors or deterioration in renal function and in the elderly. • Consider vitamin B12 levels for those with symptoms of / risk factors for B12 deficiency (MHRA). • HbA1c 3-6 monthly.

- **First line treatment**: Offer standard-release metformin as the initial medicine treatment for adults with T2D - NICE guidance (NG28).
- If considering SGLT2 as part of first line therapy for those with established CVD or heart failure, only start the SGLT2 once established on metformin.

SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS (also known as 'flozins') Amb3

Reversibly inhibits sodium-glucose co-transporter-2 (SGLT2) to reduce glucose reabsorption and increase urinary glucose excretion.

HbA1c efficacy	Moderate (reduction in HbA1c of up to 11 mmol/mol)	**Effect on weight**	Loss	**Hypo risk**	Low	**Cost per 28 days**	£36.59- Dapagliflozin, empagliflozin, canagliflozin £29.40- Ertugliflozin

Dosing	• Once daily dosing • Dose reductions may be required in renal impairment- see below and appendix 1.
Counselling points	• Advise on the risks/signs of Diabetic Ketoacidosis (DKA) and to seek medical advice if unwell. Medical advice should be sought before undertaking very low carbohydrate diets (see below). • Sick day rules should be explained. More detailed advice for clinicians is available here. Explain the importance of maintaining adequate hydration. • Explain the risk of UTI/ genital infections (TREND diabetes information), and also potential risks/signs of Fournier's gangrene. • As for all people with diabetes, it is important to counsel on routine preventative foot-care and periodontitis
Contraindications and cautions	• The glycaemic lowering effect of SGLT2 inhibitors will be reduced at GFRs <45 ml/min. Although these medicines may be used for their cardiovascular and reno-protective properties in renal impairment (see appendix 1), additional hypoglycaemic therapy may be required. • An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with canagliflozin. It is unknown whether this constitutes a class effect. Carefully monitor those who have risk factors for amputation and consider stopping SGLT2 inhibitor if foot complications develop. See MHRA warning for more information. • Caution in combination with loop diuretics due to risk of volume depletion – diuretic dose may need to be reduced. • Rare cases of DKA have been reported in those taking SGLT-2 inhibitors. Presentation can be atypical with only a moderate rise in blood glucose levels, below 14mmol/L. If DKA is suspected or diagnosed SGLT2 inhibitors should be discontinued. See MHRA warning for more information. • Avoid in those at high risk of dehydration e.g. elderly, binge alcohol drinking. Avoid in very low carbohydrate or ketogenic diets. • Due to the mechanism of action, people taking SGLT2 inhibitors are at increased risk of urinary tract infection and will test positive for glucose in their urine. • Pregnancy/ breastfeeding
Monitoring	HbA1c 3-6 monthly Renal function – prior to initiation and at least annually thereafter
Established cardiovascular disease	

SGLT2 inhibitors with evidence of cardiovascular benefit (dapagliflozin, empagliflozin, canagliflozin) should be offered to those with **Chronic Heart failure or established atherosclerotic cardiovascular disease*** as first line hypoglycaemic therapy **alongside metformin** once tolerability of metformin has been confirmed.
*established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (stroke and transient ischaemic attack) and peripheral arterial disease.

Chronic Kidney Disease
SGLT2 inhibitors have been shown to reduce the risk of chronic kidney disease (CKD) progression, mortality and cardiovascular events when used in people with CKD. Dapagliflozin should be considered for people with **T2D and CKD** in line with NICE TA 775. Prior to initiation, treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) should be optimised to the highest tolerated licensed dose unless these are contraindicated. NG28 recommends that an SGLT2 inhibitor is *offered* if the albumin-to-creatinine ratio (ACR) is over 30 mg/mmol and *considered* if the ACR is 3 mg/mmol or more. Currently only dapagliflozin and canagliflozin are licensed for CKD. See flowchart for managing Chronic Kidney Disease in T2D (pg. 9).

T2D without CVD or CKD
SGLT2 inhibitors may be used *as an option for monotherapy* in line with NICE TA390 and NICE TA572 if metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, if:

- a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and
- a sulfonylurea or pioglitazone is not appropriate

as an option for dual therapy in line with NICE TA315, TA336, TA288, TA572 in combination with metformin if:

- a sulfonylurea is contraindicated or not tolerated or
- the person is at significant risk of hypoglycaemia or its consequences.

as an option for triple therapy in line with NICE TA315, TA418, TA336, TA572 as an option for treating T2D in combination with:

- metformin and a sulfonylurea or
- metformin and a thiazolidinedione (empagliflozin and canagliflozin only) or
- metformin and a DPP4 inhibitor (ertugliflozin only if the disease is uncontrolled with metformin and a DPP-4 inhibitor, and a sulfonylurea or pioglitazone is not appropriate.

In combination with insulin with or without other antidiabetic medicines (empagliflozin, dapagliflozin and canagliflozin only) in line with NICE TA288, TA336, TA315.
Treatment of Chronic Heart Failure with reduced ejection fraction (HFrEF)
Dapagliflozin and empagliflozin may also be used on Specialist advice for the treatment of HFrEF in line with NICE TA679 and TA773. Use for this indication is outside the scope of this guidance- for further information see Nottinghamshire Heart Failure Guidelines.

GLICLAZIDE (a SULFONYLUREA) Amb3

Augments insulin secretion and consequently is only effective when some residual pancreatic beta-call activity is present.

HbA1c efficacy	Very Good (reduction in HbA1c of 11-22 mmol/mol)	**Effect on weight**	Gain	**Hypo risk**	High	**Cost per 28 days**	£0.91 - £3.64 - Gliclazide 80mg daily - 160mg twice daily £2.81 - £11.24 - Gliclazide MR 30mg -120mg daily

Dosing	• Initially 40mg to 80mg daily with breakfast. Maximum dose is 160mg twice daily. • Increase dose every 4-6 weeks. Check blood glucose (finger prick) before each titration to reduce hypoglycaemia. • If adding additional diabetes medicine to gliclazide, it may be appropriate to decrease the gliclazide dose. • Modified release tablets (once daily dose) can be considered if compliance is poor.
Counselling points	• Hypoglycaemia risk, particularly in renal impairment. Patient information leaflet: TREND • Gliclazide can cause weight gain (a few kilograms). • Self-monitoring of blood glucose- see guidance on Frequency of Blood Glucose Self-Monitoring. • Dietary advice e.g. regular meals, avoid alcohol What is a healthy, balanced diet for diabetes? | Diabetes UK • Sick day rules should be explained. More detailed advice for clinicians is available here. • As for all people with diabetes, it is important to counsel on routine preventative foot-care and periodontitis
Contraindications and cautions	• HbA1c <53mmol/ml should prompt a review of therapy due to a risk of symptomatic hypoglycaemia. • Severe renal or hepatic insufficiency • Pregnancy / breast feeding
Monitoring	• HbA1c 3-6 monthly and renal function at least annually • Blood glucose monitoring advice for drivers (see guidance on Frequency of Blood Glucose Self-Monitoring): o Group 1 drivers (car/motorcycle) - it may be appropriate to monitor blood glucose regularly and at times relevant to driving to enable the detection of hypoglycaemia. o Group 2 drivers (bus/lorry) – must notify DVLA and are required by law to monitor glucose level at least twice daily and at times relevant to driving (within two hours before driving and two hourly once driving). o Guidance for professionals o Patient advice: Government guidance for drivers and Diabetes UK

- Consider gliclazide or insulin as rescue therapy if an adult with type 2 diabetes is symptomatically hyperglycaemic, and review treatment when blood glucose control has been achieved.

- HbA1c target for those on metformin plus gliclazide should not be lower than 53mmol/ml.

DPP-4 INHIBITORS (also known as 'gliptins') Amb3

Augments insulin secretion and consequently is only effective when some residual pancreatic beta-call activity is present.

HbA1c efficacy	Low (reduction in HbA1c of 6-9 mmol/ mol)	**Effect on weight**	Neutral	**Hypo risk**	Low	**Cost per 28 days**	£26.60 Alogliptin, alogliptin/metformin £33.26 Sitagliptin, sitagliptin/metformin, linagliptin, linagliptin/metformin

Dosing	• Once daily dosing. • Dose reduction required in renal impairment, except linagliptin- see appendix 1. • Caution required in advanced age (limited safety data). • Switch to the DPP-4/metformin combination tablet if currently on both medications as separate tablets (more cost effective) and if GFR is ≥45ml/min.
Counselling points	• Acute pancreatitis risk and symptoms: persistent, severe abdominal pain (sometimes radiating to the back). Any symptoms should be reported to their healthcare provider (MHRA). • Sick day rules should be explained. More detailed advice for clinicians is available here. • As for all people with diabetes, it is important to counsel on routine preventative foot-care and periodontitis
Contraindications and cautions	• Acute pancreatitis • Bullous pemphigoid • Hypoglycaemia risk increased in combination with sulfonylurea or insulin • Pregnancy / breast feeding • Hepatic impairment • Heart failure (alogliptin)
Monitoring	• HbA1c 3-6 monthly and renal function at least annually • LFTs – prior to initiation, then 3 monthly for the first year for vildagliptin then periodically thereafter See manufacturers information

NICE guidance (NG28):

Consider initial treatment with a DPP-4 inhibitor OR pioglitazone OR a sulfonylurea if metformin is contraindicated or not tolerated.

Can be used as part of dual or triple therapy if initial treatment does not control HbA1c to the person's individually agreed target in combination with:

- metformin
- pioglitazone
- sulfonylurea
- metformin and a sulfonylurea

Saxagliptin is not recommended locally because of an association with an increased risk of heart failure.
In line with local specialist opinion, combination use of a DPP-4 inhibitor and a GLP-1 agonist is not recommended.

PIOGLITAZONE (a THIAZOLIDINEDIONE, also known as a 'GLITAZONE')

Reduces peripheral insulin resistance, leading to a reduction of blood glucose concentration.
Useful for insulin resistance (central obesity / high insulin requirement)

HbA1c efficacy	Good (reduction in HbA1c of 11-16 mmol/mol)	**Effect on weight**	Gain	**Hypo risk**	Low	**Cost per 28 days**	£1.50 - £2.61 Pioglitazone 15mg – 45mg daily

Dosing	• Once daily dosing • In older people or frailty start with the lowest dose and increase gradually

Counselling points	• Advise people to report any signs of:
	  o heart failure (shortness of breath, oedema, rapid increase in weight)
	  o bladder cancer (blood in urine, pain when urinating, sudden need to urinate)
	• Sick day rules should be explained. More detailed advice for clinicians is available here.
	• As for all people with diabetes, it is important to counsel on routine preventative foot-care and periodontitis

Contraindications and cautions	• Heart failure / history of heart failure • Hepatic impairment • Current / history of bladder cancer (MHRA) • Uninvestigated macroscopic haematuria • DKA • Pregnancy / breast feeding • Macular oedema • Caution in combination with insulin - observe for signs and symptoms of heart failure, weight gain and oedema (MHRA) • Caution in elderly (age related risks of heart failure, bladder cancer and fractures) • The risk of fractures should be considered in the long-term care of patients treated with pioglitazone
Monitoring	• Liver function – test before treatment initiation and then periodically based on clinical judgement • Weight • HbA1c 3-6 monthly

NICE guidance (NG28):

Consider initial treatment with a DPP-4 inhibitor OR pioglitazone OR a sulfonylurea if metformin is contraindicated or not tolerated.

Can be used as part of dual or triple therapy if initial treatment does not control HbA1c to the person's individually agreed target in combination with:

- metformin
- sulfonylurea
- metformin and a sulfonylurea
- insulin (if metformin not appropriate)

Particularly useful where there is insulin resistance (central obesity / high insulin requirement).

GLP-1 (Glucagon-like peptide-1) AGONISTS (also known as 'GLP1s') Amb2

Increase insulin secretion, suppress glucagon secretion, and slow gastric emptying

HbA1c efficacy	Very Good (reduction in HbA1c of 11-22 mmol/mol)	**Effect on weight**	Loss	**Hypo risk**	Low	**Cost per 28 days**	£81.89 Exenatide (Byetta®) £73.36 Exenatide prolonged release (Bydureon® BCise) £73.25 Dulaglutide (Trulicity), Semaglutide (Ozempic®▼) £78.48 Liraglutide (Victoza®)- **1.2mg daily dose only**. 1.8mg dose is classified Grey £73.25 Oral semaglutide (Rybelsus®▼)

Dosing	• Subcutaneous injection: Exenatide (Byetta®) twice daily; Liraglutide: once daily; other injectable products are once weekly. • Oral: Semaglutide (Rybelsus®) once daily (at least 30 minutes before eating, drinking or taking other oral medicines). • Dose reduction in renal impairment (see appendix 1).
Counselling points	• Sick day rules should be explained. More detailed advice for clinicians is available here. • Oral semaglutide (Rybelsus®) must be taken on an empty stomach with a small amount of water at least 30 minutes before eating, drinking or taking other oral medicines. • Empty pens of semaglutide (Ozempic®) or liraglutide (Victoza®) may be recycled via Pencycle. • As for all people with diabetes, it is important to counsel on routine preventative foot-care and periodontitis.
Contraindications and cautions	• Pancreatitis: Necrotising and haemorrhagic pancreatitis with GLP-1 agonists. If pancreatitis is suspected, suspend treatment immediately; if pancreatitis is diagnosed, the GLP-1 agonist should be permanently discontinued (MHRA warning). • Diabetic ketoacidosis has been reported in people with T2D on a combination of a GLP-1 receptor agonist and insulin who had doses of concomitant insulin rapidly reduced or discontinued (MHRA warning). • For adults with T2D, only offer combination therapy with a GLP-1 mimetic and insulin along with specialist care advice and ongoing support from a consultant-led multidisciplinary team (NICE).
Monitoring	• **Weight - Only continue GLP-1 mimetic therapy if there is a HbA1c reduction of at least 11 mmol/mol and weight loss of at least 3% of initial body weight in 6 months.** • Routine monitoring of blood glucose levels is only required if the GLP-1 agonist is given in combination with another agent likely to cause hypoglycaemia e.g. sulfonylurea. • HbA1c 3-6 monthly.

NICE guidance (NG28):

Not recommended by NICE as a cost-effective option for CVD prevention. GLP1s may be considered if triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated. One medicine may be switched for a GLP-1 mimetic for adults with T2D who:

• have a body mass index (BMI) of 35 kg/m2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or

• have a BMI lower than 35 kg/m2 and:

— for whom insulin therapy would have significant occupational implications **or**

— weight loss would benefit other significant obesity-related comorbidities.

If all other patient factors are equal prescribe the GLP-1 agonist with the lowest acquisition cost.

Oral semaglutide (Rybelsus®) is reserved only for adults with T2D if:

- They are unsuitable for the SC injection e.g. difficulty in injection, needle phobia, recurrent local complications due to injection **and**
- The administration guidance can be followed: Taken daily with a sip of water on an empty stomach at least 30 minutes before eating, drinking or taking other medicines.

Combination use of a DPP-4 inhibitor and a GLP-1 agonist is not recommended.

Insulin treatment

- If other measures do not keep HbA1c to <59 mmol/mol (or other agreed target), discuss benefits and risk of insulin treatment.
- **Initiate with a structured programme including patient education and management plan.** Insulin therapy should be initiated from a choice of a number of insulin types and regimens by a practitioner with the appropriate knowledge, competencies and experience to choose the most appropriate starting regimen tailored to each patient.
- Sick day rules should be explained. A more detailed guide for clinicians is available here.

Blood Glucose Monitoring

- Advise on self-monitoring of blood glucose- see guidance on Frequency of Blood Glucose Self-Monitoring.
- See Blood Glucose Test Meters Formulary for the Blood Glucose Test Meters and Test Strips currently recommended locally.
- Blood glucose monitoring using Freestyle Libre2 may be appropriate in some circumstances - see inclusion criteria
- Drivers with diabetes treated with insulin must inform the DVLA and monitor blood glucose no more than two hours before a journey and every two hours after driving has started- DVLA advice.
- Group 2 drivers (bus/lorry) must continue to use fingerprick testing for the purposes of driving.

Choice of insulin

- Begin with human NPH insulin (Isophane insulin e.g. Insulatard®, Humulin I®) taken at bedtime or twice daily according to need. **There is no evidence of a clinical benefit of analogue insulins over human insulins in T2D.**
- Consider starting both NPH and short-acting insulin, particularly where HbA1c >75mmol/mol administered either separately or as a pre-mixed (biphasic) human insulin preparation. **Pre-mixed (biphasic) preparations that include short-acting human insulin preparations (e.g. Humulin M3) should be used rather than pre-mixed (biphasic) preparations that include rapid acting insulin analogues, unless:**
    - A person prefers injecting insulin immediately before a meal, or
    - Hypoglycaemia is a problem, or
    - Blood glucose levels rise markedly after meals
- Insulin analogues (insulin detemir or insulin glargine) rather than NPH insulin preparations should only be considered when:
    - The person needs assistance from a carer or healthcare professional to inject insulin, and the use of insulin detemir or insulin glargine would reduce the frequency of injections from twice daily to once daily, or
    - The person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, or

  - People cannot use the device needed to inject NPH but could administer their own insulin safely and accurately if switched to a long-acting analogue, or
  - The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering medicines.
- Recurrent symptomatic hypoglycaemia should prompt a re-examination of the current insulin regimen, injection sites, a search for other co-morbidities (such as liver or renal disease) and a review of the agreed HbA1c target. If tight control is still required, then consider a trial of analogue insulin.
- When starting an insulin for which a biosimilar is available (e.g. insulin glargine, insulin aspart), use the product with the lowest acquisition cost. See formulary for the recommended brand. **This should be prescribed by brand.**
- Ensure the risk of medication errors with insulins is minimised by following the MHRA guidance on minimising the risk of medication error with high strength, fixed combination and biosimilar insulin products, which includes advice for healthcare professionals when starting treatment with a biosimilar.
- When people are already using an insulin for which a lower cost biosimilar is available, consider switching to the biosimilar. This should only be done as a shared decision with the person after discussing their preferences. For further information on biosimilars see Biosimilars FAQs.

Intensifying the insulin regimen

- Monitor those using basal insulin regimens for the need for short acting insulin before meals or pre-mixed insulin.
- Monitor those using premixed insulin once or twice daily for need for further injections of short acting insulin before meals or change to mealtime plus basal regimen.

Oral agent combination therapy with insulin

- When starting insulin therapy:
  - Continue with metformin for people without contraindications or intolerance. Review the need for other blood glucose lowering therapies.
  - SGLT2 inhibitors should be continued if being used for people with established cardiovascular disease, heart failure or chronic kidney disease.

Use of GLP1 analogues in combination with insulin

- Use of GLP1 analogues with insulin has been approved for use locally only when patients fulfill the following criteria; morbidly obese (BMI >35) **and** HbA1c >75mmol/mol **and** currently using insulin.
- This regimen must be initiated by a specialist and only prescribed when there is ongoing support from a consultant-led multidisciplinary team.

- Serious and life-threatening cases of DKA have been reported in patients on a combination of insulin and GLP1 agonists, particularly after discontinuation or rapid dose reduction of concomitant insulin. Any dose reduction of insulin should be done in a stepwise manner with careful blood glucose monitoring, especially when the GLP-1 agonist is initiated. See MHRA for more information.
- **Continue the GLP1 in combination with insulin only if the person has a reduction in HbA1c of ≥11mmol/mol and a 3% loss of initial bodyweight in 6 months**.

Insulin delivery devices

- Offer education to a person who requires insulin on using an injection device (usually a pen injector and cartridge or a disposable pen) to ensure that that they and/or their carer find it easy to use.
- If a person has a manual or visual disability and requires insulin, offer a device or adaptation that:
  - takes into account their individual needs
  - they can use successfully.
- Appropriate local arrangements should be in place for the disposal of sharps.
- Advise users of disposable pen devices of recycling schemes such as Pencycle. This currently accepts Novomix 30®, Levemir®, Novorapid®, Fiasp® and Tresiba® pre-filled pens for recycling.
- In use shelf life of reusable pen devices is usually several years but depends on product used- refer to individual manufacturer's websites for further guidance. These should be issued as acute prescriptions rather than added to repeat templates.

References

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Version Control- **Type 2 Diabetes Treatment Guideline**			
Version	Author(s)	Date	Changes
V5	Lynne Kennell/ Michelle Haigh	Nov 22	Full review- updated treatment flowcharts, added CKD flowchart in line with NG28. Updated medication tables, table of commonly used insulins, renal/ hepatic impairment tables. Removed licensing/ NICE approval tables.
V5.1	Lynne Kennell	Feb 23	Amended Rybelsus & canagliflozin prices, removed Insuman products due to discontinuation, amended exenatide formulation to include Bydureon BCise. Added link to NottsAPC guidance on Frequency of Blood Glucose Self-Monitoring and Medicines and Falls Chart.
V5.2	Lynne Kennell	July 23	Pregnancy/ breastfeeding added as a contraindication to SGLT2i's. Link to biosimilar FAQs added. Clarity added to recommendation to avoid concomitant use of gliptin and GLP-1. Clarity added to hepatic impairment table about definitions of hepatic impairment. Highlighted liraglutide 1.8mg is classified grey.

Appendix 1- Dosing in renal impairment

	Worsening renal function (GFR range in ml/min)				
MEDICINE	**1 & 2 (>60)**	**3a (59-45)**	**3b (44-30)**	**4 (29-15)**	**5 (< 15 or RRT)**
Metformin	✓	Review dose and monitor		✗	✗
Gliclazide	Monitor			Use lowest effective dose	✗
Sitagliptin	✓	✓	**50mg OD**	**25mg OD**	
Alogliptin	✓	**12.5mg OD** if CrCl <50ml/min		**6.25mg OD**	
Linagliptin	✓	✓	✓	✓	✓
Pioglitazone	✓	✓	✓	✓	If CrCl >4ml/min
Exenatide	✓	✓	Conservative dose escalation if CrCl 30-50ml/min	✗	✗
Exenatide MR	✓	✓	✓	✗	✗
Lixisenatide	✓	✓	✓	✗	✗
Liraglutide	✓	✓	✓	✓	✗
Dulaglutide	✓	✓	✓	✓	✗
Semaglutide	✓	✓	✓	✓	✗
Dapagliflozin	✓	✓	Glycaemic lowering efficacy reduced *		✗
Canagliflozin	✓	**100mg OD**	Glycaemic lowering efficacy reduced *	Do not initiate. Continue existing treatment until dialysis or renal transplant	
Empagliflozin	✓	**10mg OD**	Glycaemic lowering efficacy reduced *	Unless for heart failure & CrCl ≥20ml/min	✗
Ertugliflozin	✓	✓	Do not initiate	✗	✗
Insulin	✓	✓	✓	Requirements may be reduced– monitor and adjust dose accordingly	

*Glycaemic lowering efficacy reduced with canagliflozin, dapagliflozin and empagliflozin where CrCl <45ml/min. Although these medications may be continued for cardiorenal protection and treatment of Heart Failure, additional glucose lowering treatment should be considered.

N.B. In patients at extremes of weight (BMI <18.5 kg/m^2 or >30 kg/m^2) or age (>70yr), calculate renal function using Cockcroft and Gault equation (see calculator available here).
Data is from manufacturers' recommendations and local consensus. The Renal Drug Database (password required) may recommend lower thresholds for dose reductions.

Appendix 2- Dosing in hepatic impairment

Hepatic Impairment		
MEDICINE	**Mild / Moderate**	**Severe**
Metformin	Review dose / use with caution if there are risks of lactic acid producing events e.g. active alcohol consumption, dehydration, hypotension, sepsis, reduced cardiac function, reduced kidney function.	× Contraindicated
Gliclazide	✓	× Contraindicated
Sitagliptin	✓	× Not studied in severe hepatic impairment
Alogliptin	✓	× Not studied in severe hepatic impairment
Linagliptin	No dose adjustment required, but clinical experience is lacking	
Pioglitazone	× Contraindicated	
Exenatide	✓	✓
Exenatide MR	✓	✓
Lixisenatide	✓	✓
Liraglutide	✓	× Not recommended
Dulaglutide	✓	✓
Semaglutide	✓	Caution required, limited experience
Dapagliflozin	✓	Start at 5mg, increase to 10mg if well tolerated
Canagliflozin	✓	× Not studied in severe hepatic impairment
Empagliflozin	✓	× Not recommended
Ertugliflozin	✓	× Not recommended
Insulin	Requirements may be altered in hepatic impairment – monitor and adjust dose accordingly	

Definitions of hepatic impairment are based on the Child-Pugh Score (A-C).
Please seek specialist advice if the degree of hepatic impairment or the need to review treatment is uncertain.

Appendix 3- Commonly used insulins – Note this table is not comprehensive; see Nottinghamshire formulary for details of all insulins.

Type of insulin	Name of Insulin (v=vial, c=cartridge, i= innolet, pf= pre-filled pen *=recyclable via Pencycle)	Traffic light classification	Price (for 5 x 3ml cartridges/ pre-filled pens)	Patient Group
NPH (Human, intermediate acting)	**Humulin I** (v, c, pf) **Insulatard** (v, c, i)	Green	£19.08-£21.70 £19.08-£21.70	Preferred first choice insulin if HbA1c <75 mmol/mol • Once or twice daily • Innolet device may be preferred by those with visual impairment/ dexterity issues
Biphasic (human)	**Humulin M3** (v, c, pf)	Green	£19.08-£21.70	Preferred first choice insulin if HbA1c >75 mmol/mol or if there is significant postprandial hyperglycaemia on NPH • Twice daily at mealtimes
Biphasic (analogue)	**NovoMix 30** (c, pf*) **Humalog Mix 25** (v, c, pf) **Humalog Mix 50** (c, pf)	Amb2	£28.79- £29.89 £29.46- £30.98 £29.46- £30.98	Second line to human biphasic insulins if: • A person prefers injecting insulin immediately before a meal • Problematic hypoglycaemia or postprandial hyperglycaemia with human biphasic insulin
Long acting (analogue)	**Semglee** (insulin glargine 100units/ml biosimilar) (pf) **Lantus** (insulin glargine 100units/ml) (v, c, pf) **Levemir** (v, pf*, i)	Amb2	£29.99 £34.75 £42-£44.85	Second line to NPH if: • Carer administration of insulin is needed and twice daily insulin otherwise required • Symptomatic hypoglycaemia on NPH • The person would otherwise require twice daily NPH plus oral glucose lowering medications

Rapid acting (analogue)	**Trurapi** (insulin aspart biosimilar) (v, c, pf) **Novorapid** (v, c, pf*) **Admelog** (insulin lispro biosimilar) (v, c, pf) **Humalog** (100 units/ml) (v, c, pf) **Humalog** (200 units/ml) (pf)	Amb2	£19.82-£21.42 £28.31-£32.13 £21.23-£22.10 £28.31- £29.46 £58.92	• To be used if additional mealtime insulin or basal bolus regime required because of inadequate glucose control on biphasic insulin. • Trurapi is first line option for new users of rapid acting insulin. • Humalog 200units/ml reserved for those who require higher doses of insulin because of insulin resistance.
Very rapid acting (analogue)	**Fiasp** (v, c, pf*) **Lyumjev** (100 units/ml) (v, c, pf)	Amb2	£28.31-£30.60 £28.31- £29.46	• See formulary for prescribing restrictions.