BRIGHTON AND HOVE, AND HIGH WEALD LEWES HAVENS CCG
Management of Type 2 Diabetes in adults

This guideline has been adapted from the Derbyshire Joint Area Prescribing Committee with permission from the authors

Key messages:

- This guideline primarily considers drug treatments used in type 2 diabetes. It does not address the management of impaired glucose tolerance, impaired fasting glucose, type 1 diabetes or diabetes in pregnancy.

- Education and lifestyle advice are fundamental to patient management, as is overall consideration to the patient's risk of macrovascular and microvascular complications (e.g. glycaemic control, blood pressure management, smoking status, and cholesterol). Diet and exercise should be discussed at every opportunity.

- A structured education programme for adults with type 2 diabetes is an integral part of diabetes care and should be offered to patients and family members/carers. Locally this is offered through Diabetes Care For You (DCFY).

- An individualised approach to diabetes care should be tailored to the needs and circumstances of the adult with type 2 diabetes in association with the individual themselves (considerations include life expectancy, risks from polypharmacy, comorbidities etc.). An adult with type 2 diabetes should be involved in the discussion about target setting, ensuring that they have the right information to make an informed decision. Record the target HbA1c in the patient's record and care plan.

- NICE recommends that if 2 drugs in the same class are appropriate, to choose the option with the lowest acquisition cost.

- Metformin therapy is suitable for most adults with type 2 diabetes; its use is contraindicated or not tolerated in approximately 15% of individuals (NICE NG28). Metformin is the most cost effective of the initial therapy treatments and should **always** be used as the first line agent where indicated.

- There is evidence emerging in relation to the long-term effects of blood glucose lowering therapies, particularly newer agents in terms of efficacy and adverse events in patients with pre-existing cardiovascular disease. There is data to suggest that SGLT2 inhibitors reduce death from cardiovascular disease and all-cause mortality (NEJM 2015: 373:2117-2128), along with reduction in symptoms of heart failure (NEJM 2017; 377:644-657). There is data for reduction in cardiovascular events with some GLP receptor agonists (NEJM2016; 375:311-322). These agents are being reviewed by NICE for the next iteration of its guidelines.

- An HbA1c reduction of 5mmol/mol (0.5%) is considered clinically important. At each review re-assess the person's needs and circumstances and think about stopping any medicines that are not effective at 6 months. Communication regarding the overcoming of the phenomenon of clinical inertia is especially important.

- NICE limits the use of self-monitoring of blood glucose for particular circumstances. E.g. 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. Consider short-term self-monitoring of blood glucose levels in adults when starting treatment with oral or intravenous corticosteroids or to confirm suspected hypoglycaemia. Also consider in patients who have acute intercurrent illness are at risk of worsening hyperglycaemia.

- Do not offer antiplatelet therapy for adults with type 2 diabetes mellitus without cardiovascular disease. Review the ongoing need for these medications in those with no previous history of ischaemic heart disease.

- Driving advice: this should be an individualised decision by the clinician, using the DVLA guidance (https://www.gov.uk/government/publications/at-a-glance) and advice from diabetes.org.uk. For those patients on insulin therapy and medication that may cause hypoglycaemia an understanding of the requirements regarding blood glucose testing and driving is essential, and notes of any discussion between clinician and people with diabetes about driving should be clearly documented.

NICE define

Interventions that should be used - strong recommendation

- **'Offer'** as an intervention which will do more good than harm and be cost effective, for the vast majority of patients.

Interventions that could be used:

- **'Consider'** as an intervention which will do more good than harm for most patients and be cost effective, but other options may be similarly cost effective

Key

ACEI –angiotensin converting enzyme inhibitor
ARB - Angiotensin receptor blockers
BMI – body mass index
CCB –calcium channel blocker
DVLA – Driver and Vehicle Licensing Agency
GI – gastro-intestinal
GLP -1 - Glucagon-like peptide-1 mimetic
Glic – Gliclazide
Gliptin – (DPP4 inhibitors)
HbA1c- Glycated haemoglobin
HF – heart failure
Met - metformin
NG – National guidance
PDE5 inhibitors - phosphodiesterase type 5 inhibitor
Pio – pioglitazone
SGLT2i – sodium-glucose co-transporter 2 inhibitor

Antihypertensive drug treatment –Type 2 Diabetes

Measure BP annually if not hypertensive or renal disease
If >140/90 mmHg confirm consistently raised
Use a threshold of >150/90 and aged >80

Targets
People with CKD and diabetes or ACR >70, or cerebrovascular disease: follow algorithm with target <130/80mmHg
Others: follow algorithm with target <140/90mmHg

Above target

Trial **lifestyle measures alone**
unless >140/90 mmHg (or >135/85 Average home readings)

Women with possibility of pregnancy:
Avoid use of ACEi or ARB drugs
Begin with CCB (Amlodipine)

In people with continuing intolerance to an ACEi (other than renal deterioration or hyperkalaemia):
Substitute Ramipril with Irbesartan

Above target

ACEi: Ramipril*
If African-Caribbean: ARB (Irbesartan) or CCB (Amlodipine)
If possibility of pregnancy: CCB (Amlodipine)

People with microalbuminuria:
Aim for maximum dose of Ramipril (or Irbesartan if not tolerated). Then follow algorithm with target <130/80mmHg

Above target

Add **CCB** (Amlodipine) or
diuretic (Indapamide 2.5mg)

Above target

Add **diuretic** (Indapamide 2.5mg) or **CCB** (Amlodipine)

Above target

Add a potassium-sparing diuretic (Spironolactone**) first or α-blocker (Doxazosin), β-blocker (Bisoprolol)

Above target

Add α-blocker (Doxazosin), β-blocker (Bisoprolol), or potassium-sparing diuretic (Spironolactone**), or refer to specialist

BP targets for people with diabetes

People with diabetes:	< 140/90mmHg (NICE 2019)
People with CKD and diabetes or ACR >70, or cerebrovascular disease	<130/80mmHg ***

BP monitoring
Annual BP measurement for adults with T2DM without previously diagnosed hypertension or renal disease.

Repeat BP measurements (adding or intensifying treatment as appropriate):
- Within 1 month if BP> 150/90
- Within 2 months if BP>140/90
- Within 2 months if BP>130/80 and there is kidney or cerebrovascular disease.

Reinforce preventative lifestyle advice, at every given opportunity

* If intolerant to ACEi e.g. cough (other than renal deterioration or hyperkalaemia) use Irbesartan instead of Ramipril
** If using Spironolactone with ACEi or ARB, monitor potassium carefully
*** The BP targets for hypertension for diabetes were revised in NICE NG136 August 2019 and did not find sufficient evidence for lower target for patients with retinopathy, but RCP guideline for Cerebrovascular disease 2016 still suggests the need for lower thresholds. This is being reviewed as part of the new NICE diabetes guideline due in the next 2 years.

Treatment algorithm for type 2 diabetes in adults

Adopt an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preference.

Initiation of lifestyle and diet intervention. Refer to structured education programme.
Aim for HbA1c – 48mmol/mol (6.5%)

Reinforce dietary and lifestyle advice and adherence to drug treatment at each step and consider discontinuing any medicines that are not effective.

It is recommended to use the most cost-effective treatment as listed in order.

MONOTHERAPY

Move to this step if HbA1c rises above 48mmom/mol (6.5%) with lifestyle alone

Monotherapy:

START metformin

Slow titration over several weeks
(if intolerance develops due to side effects consider the modified release formulation)

(Preferred cost effective modified release brand – Sukkarto)

Aim for HbA1c - 48mmol/mol (6.5%) (or individualised target not met)

FIRST INTENSIFICATION

(dual therapy)

Consider moving to this step if HbA1c ≥58mmol/mol (7.5%), (or individualised target not met)

Dual therapy options:

Metformin + Gliclazide

Metformin + Alogliptin**

Metformin + Empagliflozin[2]

Metformin + [1]Pioglitazone**

Aim for HbA1c - 53mmol/mol (7%) (or individualised target not met)

SECOND INTENSIFICATION

(triple therapy or insulin)

Consider moving to this step if HbA1c ≥58mmol/mol (7.5%) (or individualised target not met)

Triple therapy options:

Met + Glic + Sitagliptin**

Met + Glic + Empagliflozin

Met + Glic + [1]Pio**

Met + [1]Pio + Empagliflozin[2]**

Met + [1]Pio + Alogliptin****

Insulin therapy

Insulin-based treatment

- Continue metformin if tolerated. Review continued need for other hypoglycaemics.
- **Offer NPH insulin first line once or twice daily according to need.**
- Consider starting both NPH + short-acting insulin separately or as biphasic human insulin (particularly if HbA1c ≥75mmol/mol (9%); consider biphasic preparations containing a short-acting insulin analogue if persons prefer injecting immediately before a meal, hypoglycaemia is a problem or blood glucose levels rise markedly after meals)

Aim for HbA1c - 53mmol/mol (7%) (or individualised target not met)

FURTHER INTENSIFICATION

If triple therapy contraindicated, not tolerated or not effective
AND
meet strict criteria for use, (see below) consider:

Met + Glic + GLP-1* if

BMI≥35kg/m² AND specific psychological or other medical problems associated with obesity

or

BMI<35kg/m² AND insulin therapy would have significant occupational implications OR weight loss would benefit other significant obesity-related co-morbidities.

*Only continue GLP-1 if there is a reduction of HbA1c by ≥ 11 mmol/mol (1.0%)] and a weight loss ≥3% of initial body weight in 6 months).

GLP-1 + insulin

Only offer GLP1 in combination with insulin with specialist care advice and on-going support from a consultant-led service.

For continued therapy, Alogliptin (gliptins) /Pioglitazone /Empagliflozin (SGLT2i) must show HbA1c reduction ≥5.5 mmol/mol (0.5%) in 6 months. **Use Linagliptin in patients with renal impairment

[1]Do not offer Pioglitazone if the patient has any of the following: HF or history of HF, hepatic impairment, diabetic ketoacidosis, current, or a history of, bladder cancer and uninvestigated macroscopic haematuria. Use with care in the elderly. An increased risk of bone fractures has been reported in women.

*[2] Offer Empagliflozin if Gliclazide is not appropriate. Do not offer if the patient has a history of diabetic ketoacidosis. Ketoacidosis with normal plasma has been reported. Signs and symptoms include nausea, vomiting, abdominal pain, excessive thirst. Caution with low eGFR- do not initiate if eGFR <60- **see SPC***

NICE recognise that Repaglinide is both clinically effective and cost effective in adults with type 2 diabetes.

Comparison of efficacy, hypoglycaemia, weight, side effects and cost for metformin- based combinations.

	Efficacy (↓HbA1c)	Hypoglycaemia	Weight	Side effects	Costs
Metformin	High	Low risk	Neutral /loss (~ -0.5kg)	GI, lactic acidosis	Low
Met + Gli	High	Moderate risk	Gain (~ 1.5 -2kg)	Hypoglycaemia	Low
Met + Pio	High	Low risk	Gain (~ 4- 5kg)	Oedema, HF, fractures	Low
Met + Gliptin	Intermediate	Low risk	Neutral	Rare	High
Met + SGLT2	Intermediate	Low risk	Loss (~ 2kg)	GU infections, dehydration	High
Met + GLP1	High	Low risk	Loss (~1 - 3kg)	GI	High
Met + insulin	Highest	High risk	Gain (~ 4 - 5kg)	Hypoglycaemia	Variable

†

Treatment algorithm for type 2 diabetes if metformin is contra-indicated or not tolerated

Adopt an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preference.

Initiation of lifestyle and diet intervention. Refer the patient to structured education programme.
Aim for HbA1c – 48mmol/mol (6.5%)

JAPC recommend using the most cost effective treatment.

Reinforce dietary and lifestyle advice and adherence to drug treatment at each step and consider discontinuing any medicines that are not effective.

If metformin contra - indicated or not tolerated

MONOTHERAPY

(without metformin)

Move to this step if HbA1c rises above 48mmol/mol (6.5%) with lifestyle alone

Monotherapy:

Consider:

Gliclazide

Sitagliptin

[1]Pioglitazone

Empagliflozin

Aim for HbA1c :-
- 48mmol/mol (6.5%) if on Sitagliptin or Pioglitazone
- 53mmol/mol (7%)if on Gliclazide
(or individualised target not met)

FIRST INTENSIFICATION

(dual therapy without metformin)

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

Consider dual therapy options:

Gliclazide + Alogliptin**

Gliclazide + [1]Pioglitazone

Alogliptin+ [1]Pioglitazone**

Empagliflozin + Sitagliptin/Pio/ Glic

Aim for HbA1c to 53mmol/mol (7%) (or individualised target not met)

SECOND INTENSIFICATION

(without metformin)

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

Consider Insulin based treatment

Insulin-based treatment

- Review continued need for other hypoglycaemics.
- **Offer NPH insulin once or twice daily first line** according to need.
- Consider starting both NPH + short-acting insulin separately or as biphasic human insulin (particularly if HbA1c ≥75mmol/mol (9%); consider biphasic preparations containing a short-acting insulin analogue if persons prefer injecting immediately before a meal, hypoglycaemia is a problem or blood glucose levels rise markedly after meals)

Aim for HbA1c to 53mmol/mol (7%) (or individualised target not met)

For continued therapy, Alogliptin/Sitagliptin (gliptins) /Pioglitazone must show HbA1c reduction ≥5.5 mmol/mol (0.5%) in 6 months.* ***Use Linagliptin in patients with renal impairment

[1]Do not offer Pioglitazone if the patient has any of the following: HF or history of HF, hepatic impairment, diabetic ketoacidosis, current, or a history of, bladder cancer and uninvestigated macroscopic haematuria. Use with care in the elderly. An increased risk of bone fractures has been reported in women.

SGLT2i (Empagliflozin) as monotherapies are recommended as options for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if:

- *a gliptin would otherwise be prescribed and*
- *a sulfonylurea or pioglitazone is not appropriate.*

SGLT2 may be used with insulin as per NICE TA315, TA288, TA336 Caution with low eGFR- do not initiate if eGFR <60- ***see SPC***

If Metformin is CI or not tolerated, Repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However discuss with any person for whom Repaglinide is being considered, that there is no licensed non-metformin-based combination containing Repaglinide that can be offered at first intensification. (Maybe appropriate for people who have irregular meals or if mealtimes are unpredictable. Use should be limited mainly to early diabetes when the patient is still producing a reasonable amount of endogenous insulin).

	Efficacy (↓HbA1c)	Hypoglycaemia	Weight	Side effects	Costs
Gliclazide	High	Moderate risk	Gain (~1.5 – 2kg)	Hypoglycaemia	Low
Glic + met	High	Moderate risk	Gain (~ 1.5 -2kg)	Hypoglycaemia	Low
Glic + gliptin	Mid	Moderate risk	Neutral	Rare	High
Glic + pio	High	Moderate risk	Gain (~ 4- 5kg)	Oedema, HF, fractures	Low
Glic + GLP1	High	Moderate risk	Loss (~1 - 3kg)	GI	High
Glic + insulin	Highest	High risk	Gain (~ 4 - 5kg)	Hypoglycaemia	Variable

Alternative to NPH insulin:

- Insulin detemir or glargine if person needs assistance to inject insulin, lifestyle restricted by recurrent symptomatic hypoglycaemia or would otherwise need twice daily NPH insulin + oral hypoglycaemics.
- Offer insulin + GLP1 agonist only with specialist advice and consultant-led multidisciplinary support.
- An SGLT2 inhibitor + insulin +/- other antidiabetic drugs is an option after consultant/specialist initiation and assessment.

†

Scope of guideline

This guideline primarily considers drug treatments used in type 2 diabetes. It does not address the management of impaired glucose tolerance, impaired fasting glucose, type 1 diabetes or diabetes in pregnancy.

Management of diabetes requires a multifactorial approach in its management
Diabetes is a complex condition which requires regular monitoring. NICE recommend that patients with diabetes should receive the following nine key tests/processes done at least once a year:

- Weight (aim: health weight between a BMI of 18.5 – 24.9kg/m^2). Overweight patients should aim for a 5-10% target loss.
- Blood pressure (aim: <140/80mmHg or <130/80mmHg with evidence of kidney, eye or CV damage)
- Smoking status
- HbA1c (tailored to individual needs)
- Urinary albumin, or Albumin: Creatinine Ratio- ACR (Aim: <2.5mg/mol for men, <3.5mg/mmol for women)
- Serum Creatinine (>150 micromol/L – discontinue metformin)
- Cholesterol
- Eye examination
- Foot examination (Risk scored as low, moderate and high)

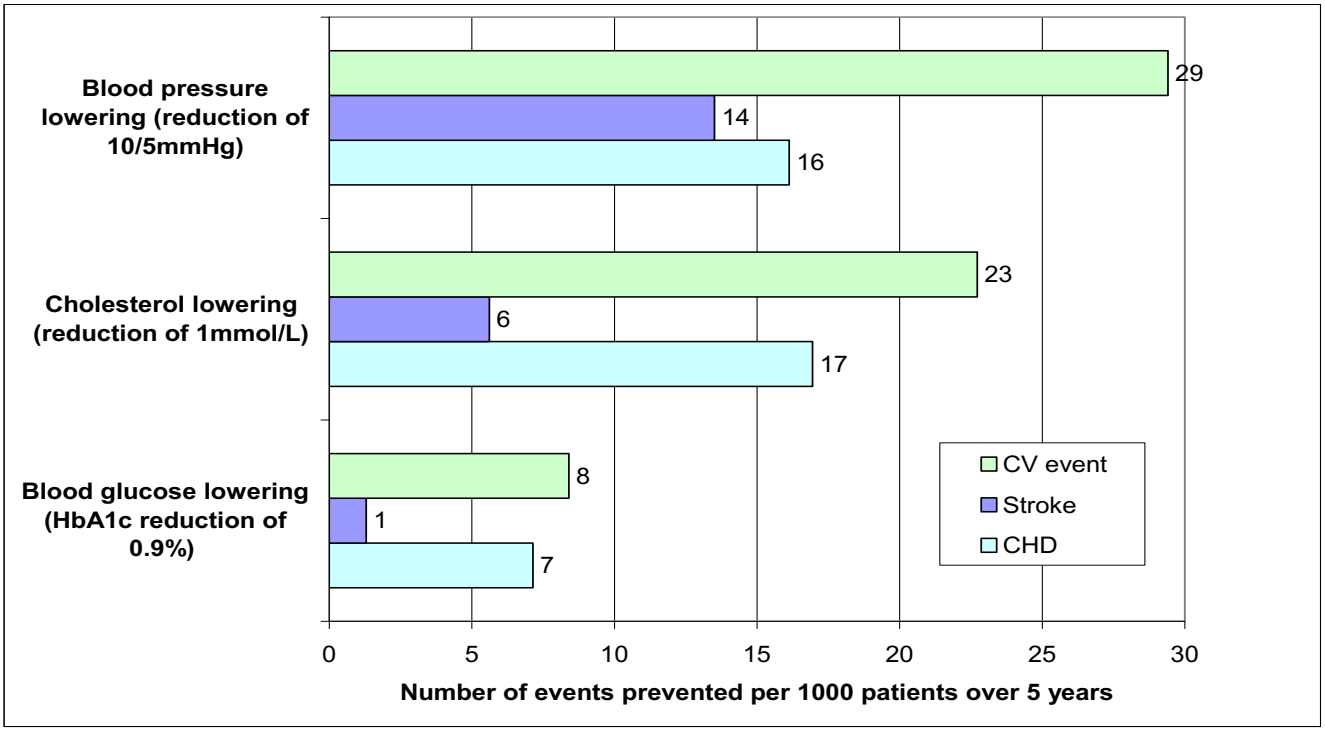
The relative benefit of different treatments.
People with diabetes have a greater chance of developing a variety of complications and health problems, especially if their blood glucose is not well managed. Good glycaemic control will reduce the incidence of micro and macrovascular complications such as blindness, kidney failure and lower limb amputation.

However lifestyle advice, blood pressure monitoring and control of cholesterol level are essential components in the management of type 2 diabetes; blood glucose control is less effective in reducing cardiovascular disease when compared to blood pressure or cholesterol lowering, as demonstrated in the chart below.

The table/chart below shows for every 1000 people (similar to those recruited to major trials) treated with more intensive blood glucose control (HbA1c reduction of 0.9 percentage points) only about eight would avoid a cardiovascular event, compared with 23 in every 1000 whose cholesterol is reduced by 1mmol/L and about 29 in every 1000 whose blood pressure is reduced by 10/5mmHg.

Intervention	Number of cardiovascular events prevented for every 1000 people treated over 5 years
Lowering blood sugar by 0.9%	**8**
Lowering cholesterol by 1mmol/L	**23**
Reducing BP by 10/5	**29**

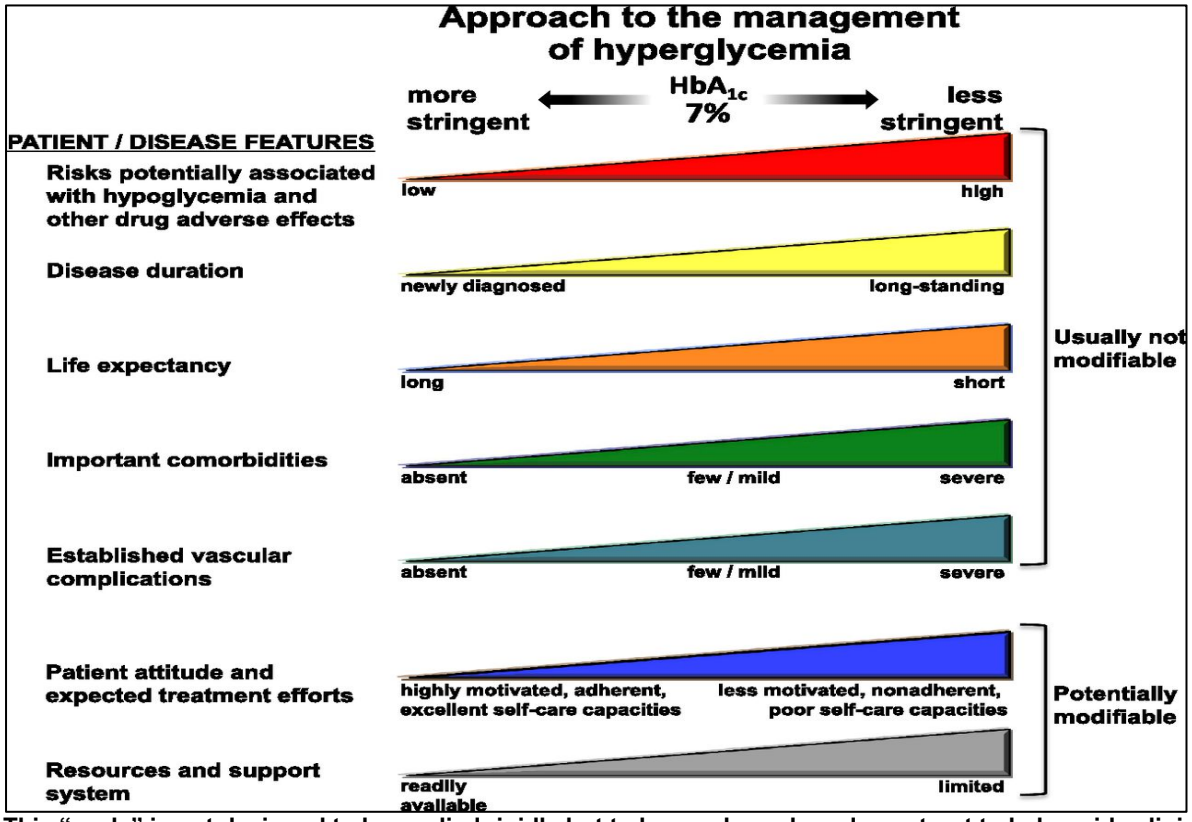
Young adults
It should be noted that young adults who develop type 2 diabetes have significantly elevated mortality, up to six times higher than age matched controls and double that of age matched peers with type 1 diabetes.



Relationship of reductions in cholesterol, blood pressure and HbA1c with improvements in CHD and CV outcomes
Yudkin JS, et al. Diabetologia 2010;53:2079–85, MeReC Bulletin Vol. 21, No. 5, June 2011.

Factors to consider when setting a HbA1c target between the clinician and patient

The diagram below is a depiction of the elements of decision making used to determine appropriate efforts to achieve glycaemic targets. Greater concerns about a particular domain are represented by increasing height of the ramp. Thus characteristics /predicaments towards the left justify more stringent efforts to lower HbA1c, whereas those towards the right are compatible with less stringent efforts. Where possible such decisions should be made in conjunction with the patient, reflecting his or her preferences, needs and values.



This "scale" is not designed to be applied rigidly but to be used as a broad construct to help guide clinical decisions. (Adapted from Silvio E. Inzucchi et al. Dia Care 2015; 38:140-149).

Targets
When setting a target HbA1c level, NICE recommends to:

- Involve patients with type 2 diabetes in the decision regarding individual HbA1c targets. Encourage them to achieve and maintain their targets unless any resulting adverse effects or their efforts to achieve their target impair their quality of life. Record the target HbA1c in the patient's record and care plan.
- Consider relaxing target HbA1c level on a case-by-case basis, with particular consideration for patients who are older or frail.
- Inform a person with a higher HbA1c that any reduction in HbA1c towards the agreed target is advantageous to future health.
- If adults achieve a HbA1c level below target and if you are certain that the patient is not experiencing hypoglycaemia, encourage them to maintain it.
- Avoid pursuing highly intensive management to levels below 42mmol/mol (6.0%).

Patient decision aids can help adults with type 2 diabetes think about their options for controlling their blood glucose to try to reduce the long-term risks of diabetes. NICE patient decision aids can be found here. (NICE NG28 resources)

Management strategies

Individualised care
Adopt an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences. An example of individualised treatment options is to consider the ABCD approach –

Reassess the person's needs and circumstances at each review and consider discontinuing any medicines that are not effective.

The table below is based on targets suggested by the American Diabetes Association and the American Geriatrics Society. They suggest the following targets, based on frailty and co-morbidity (Diabetes Care 2012;35:2650). It should be noted that this is for guidance only and has not yet been adopted by NICE. QOF targets are included for comparison.

Health status	**Target HbA1c** (adapted from ADA)	**QOF Target threshold**	**Target BP**	**Lipid modification for primary prevention**
Healthy • reasonable life expectancy	≤58	≤58	≤140/90 (NICE 2019) ** ≤140/80 (QOF) ≤130/80 if renal disease or stroke	Statins indicated if Qrisk2 score >10%
Moderate Frailty • Several co-morbidities • Limited functional ability • Mild to moderate cognitive impairment	≤64	≤75	≤140/90 (no target set for QOF)	Benefits of statins uncertain
Severe Frailty • End-stage chronic disease • In long-term care/ limited functional ability • Moderate to severe cognitive impairment	≤69	≤75	≤150/90 (no target set for QOF)	Statins not indicated
End of life care	No Target Avoid symptomatic hyperglycaemia	No target	No target	Statins not indicated

Patient education

- Offer therapy (lifestyle and medication) to help achieve and maintain the HbA1c target level.
- Offer structured education to adults with type 2 diabetes and/or their family members/carers (as appropriate) at diagnosis, with annual reinforcement and review. Explain that structured education is an integral part of diabetes care.

Dietary advice

- Provide individualised and on-going nutritional advice from a healthcare professional.
- Sustained weight loss has been shown to reverse type 2 diabetes in nearly 50% of people with diabetes who are not on insulin, and up to 86% of patients who lost 15kg or more (DiRECT trial. Lancet, 2017).
- Integrate dietary advice with a personalised diabetes management plan, including other aspects of lifestyle modification, such as increasing physical activity and losing weight.
- For recommendations on lifestyle advice see 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.

Physical Activity

- Exercise is associated with improved glucose control and lower cardiovascular mortality. Individuals should be encouraged to perform at least 150 minutes (2.5 hours) of moderate intensity physical activity in bouts of 10 minutes or more over a week.
- Individuals should be encouraged to minimise the amount of time spent being sedentary (sitting) for extended periods. (NICE PH44).

Bariatric surgery

Consider bariatric surgery as an option for people with a BMI ≥35 and significant co-morbidities as long as they are also receiving assessment through a tier 3 service (or equivalent).

Blood Pressure (BP) management (See p4 for treatment algorithm of BP)

- Measure blood pressure at least annually in adults with T2DM without previously diagnosed hypertension or renal disease. Consider measuring BP using ambulatory BP monitoring.
- Repeat BP measurements (adding or intensifying treatment as appropriate):
  - Within 1 month if BP> 150/90
  - Within 2 months if BP>140/90
  - Within 2 months if BP>130/80 and there is CKD or ACR >70, or stroke/ TIA
  - Reinforce preventative lifestyle advice, at every given opportunity.
- Reinforce lifestyle/dietary advice for the management of blood pressure.
- Add medications if lifestyle advice does not reduce blood pressure to<140/90mmHg (<130/80mmHg if there is kidney disease, ore cerebrovascular disease)
- Monitor the blood pressure of a person who has attained and consistently remained at his or her blood pressure target every 4–6 months. Check for possible adverse effects of antihypertensive drug treatment – including the risks from unnecessarily low blood pressure.

Be aware of AKI, diabetes and sick day rules.

Lipid management

Patients with Type 2 diabetes are considered to be at high risk of cardiovascular disease, requiring prevention therapies. Risk assess the patient for eligibility for statin therapy using QRISK 2. See Lipid modification guidance for further details.

Anti-platelet therapy

- **Do not** offer antiplatelet therapy (aspirin or clopidogrel) for adults with type 2 diabetes without cardiovascular disease.

HbA1c measurement

NICE recommends the following frequencies for the measurement of HbA1c, however local advice is to tailor measurements according to the individual's needs.

In adults with type 2 diabetes measure $HbA1_c$ levels at:	
• **3-6 monthly intervals**	until the $HbA1_c$ is stable on unchanging therapy
• **6 monthly interval**	Once the $HbA1_c$ level and blood glucose lowering therapy are stable

If HbA1c remains above target levels, but pre-meal self-monitored glucose levels are well controlled, consider self-monitoring to detect postprandial hyperglycaemia and manage this if detected.

If HbA1c monitoring is suspected to be inaccurate (because of disturbed erythrocyte turnover or abnormal haemoglobin type), seek advice from a diabetologist, clinical biochemistry or appropriate specialist if required.

Self-monitoring of blood glucose (SMBG)

NICE recommendations
Do not routinely offer SMBG for adults with type 2 diabetes 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.

Consider short-term SMBG levels (and review treatment as necessary):
- When starting treatment with oral or intravenous corticosteroids or
- To confirm suspected hypoglycaemia

Be aware that adults with type 2 diabetes who have acute intercurrent illness are at risk of worsening hyperglycaemia and review their treatment as necessary.

Preferred formulary choices are:
WaveSense Jazz, Contour TS, MyLife Pura, Omintest 3, Glucomen Areo, Supercheck 2, CareSens PRO and Accu-Chek Performa. GlucoRx Nexus Voice is suitable for the visually impaired

In patients where these testing strips are unsuitable consider any blood glucose testing strips under £10 (per 50 strips), which meet the patient's needs and meet current ISO 15197-2013 standards.

FreeStyle Libre© Specialist initiation. See NHS England's guidance on Flash Glucose Monitoring: National arrangements for funding of relevant diabetes patients. Annex A: Criteria for NHS England Flash Glucose Monitoring Reimbursement for patient criteria.

Blood glucose testing for people with diabetes who drive
See chapter 3 of the document "Assessing fitness to drive - guide for medical professionals" for further guidance.

Preconception advice
NICE recommend all women of child bearing age should regularly be informed that establishing good glycaemic control before conception and continuing this throughout pregnancy will reduce the risk of miscarriage, congenital malformation, stillbirth and neonatal death. It is important to explain that risks can be reduced but not eliminated. www.nice.org.uk/diabetes and pregnancy
For HBA1c targets for women with T2DM who are pregnant or planning to be pregnant see NICE guideline on diabetes in pregnancy.

Oral hypoglycaemic agents.

Please check full specific product characteristics for more detailed and current information. http://www.medicines.org.uk/emc/

BIGUANIDES – METFORMIN Decreases gluconeogenesis and increases peripheral utilisation of glucose			
Drug	**Notes**	**Traffic light status / formulary position**	**Precautions / contra-indications / less desirable patients groups**
Metformin Standard release	**First line choice for all patients** **Long-term safety data - s**trong evidence for the beneficial cardiovascular effect of metformin. **Risk of hypoglycaemia** - low **Weight change** - loss **Dosage:** Take with meals and **start low and go slow.** Start metformin at 500mg OD with main meal for at least one week, then increase to 500mg BD for at least one week. Then increase in 500mg steps at weekly intervals to highest dose tolerated or maximum dose reached. Maximum dose in BNF is 2g/day, but doses up to 3g/day are commonly used in clinical practice. There is additional glucose lowering benefit by increasing doses from 2 to 3g/day, although the UKPDS used a dose of metformin of 1700mg in the morning and 850mg in the evening. Titrate dose over several weeks to minimise risk of gastro-intestinal side effects. N.B. often side effects settle after approximately one week.	**GREEN** **1st line** **(Non-specialist drug)**	As metformin is excreted by the kidneys, serum creatinine levels should be determined before initiating treatment and regularly thereafter: • At least annually in patients with normal renal function. • At least 2 - 4 times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects. **RENAL IMPAIRMENT:** • Review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73-m^2. • Stop the metformin if the eGFR is below 30 ml/minute/1.73-m^2. • Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45ml/minute/1.73-m^2. **LIVER OR CARDIAC IMPAIRMENT:** The benefits of metformin therapy should be discussed with a person with mild to moderate liver dysfunction or cardiac impairment so that: • due consideration can be given to the cardiovascular-protective effects of the drug • an informed decision can be made on whether to continue or stop the metformin (NICE CG87) Lactic acidosis is a **rare**, but serious (high mortality in the absence of prompt treatment) metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure.
Metformin MR	If standard-release metformin is not tolerated due to GI side effects consider a trial of modified-release metformin tablets (***Sukkarto SR is the preferred, cost-effective choice)***	**GREEN** **2nd line** ***(intolerant to standard release formulation)***	

SULFONYLUREAS Augments insulin secretion and consequently is only effective when some residual pancreatic beta-cell activity is present			
Drug	**Notes**	**Traffic light status /formulary position**	**Precautions / contra-indications / less desirable patients groups**
Gliclazide	**Long-term safety data - no significant concerns identified** **Risk of hypoglycaemia** - yes **Weight change** - gain **Prescribe gliclazide when a sulfonylurea is indicated.** Consider a sulfonylurea as an option for first-line glucose lowering therapy if: • the person is underweight • the person does not tolerate metformin (or it is contraindicated) **or** • a rapid response to therapy is required because of hyperglycaemic symptoms. **Dosage:** Initially, 40-80mg daily, adjusted according to response; up to 160mg as a single dose with breakfast. Maximum dose 320mg daily. Consider adding a sulfonylurea at the first intensification when blood glucose control remains or becomes inadequate with metformin. Continue with a sulfonylurea if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added. Increase the dose every 4-6 weeks to achieve glycaemic target or maximal dose is reached. (*Gliclazide MR is more costly than the immediate release preparation. The MR preparation may be beneficial for patients with compliance problems requiring once daily dosing.* ***Not for first line use****)*	**GREEN** **1st line** **(Non-specialist drug)**	Educate the person about the risk of hypoglycaemia, particularly if they have renal impairment. **Gliclazide can cause weight gain (a few kilograms).** **Advice for drivers:** Drivers need to be particularly careful to avoid hypoglycaemia and should be warned of the problems. Key points for drivers taking a sulfonylurea are presented below; please check Fitness to drive document and http://www.diabetes.org.uk/ website for the latest recommendations. For Group 1 drivers (car/motorcycle) it may be appropriate to monitor blood glucose at times relevant to driving to enable the detection of hypoglycaemia. Group 2 drivers (bus/lorry) on sulfonylureas are required to monitor glucose level at least twice daily and at times relevant to driving Gliclazide should be used with care in those with mild to moderate renal impairment, because of the hazard of hypoglycaemia. Avoid in severe renal impairment and hepatic insufficiency.

THIAZOLIDINEDIONE (GLITAZONES) Reduces peripheral insulin resistance, leading to a reduction of blood glucose concentration			
Drug	**Notes**	**Traffic light status /formulary position**	**Precautions / contra-indications / less desirable patients groups**
Pioglitazone	**Long-term safety data -** concerns about bladder cancer, heart failure and fractures (use with caution in elderly where these issues are all more common) **Risk of hypoglycaemia** – rare **Weight change** - gain **NICE NG28** Recommends use of pioglitazone in patients as an option: • initial drug treatment (if metformin is contraindicated or not tolerated) • at first intensification in combination with metformin or • at first intensification with a gliptin or SU (if metformin is CI or not tolerated) • at second intensification if dual therapy has achieved desired HbA1c, in combination with metformin and SU **Lack of outcome data** Discuss the potential benefits and risks of treatment with pioglitazone with the person to enable them to make an informed decision. Warn a person prescribed pioglitazone about the possibility of significant oedema and advise on what action to take if it develops. Pioglitazone should be used in patients at significant risk of hypoglycaemia or who are intolerant or contra-indicated to metformin or a sulfonylurea when used in combination. **Continue pioglitazone therapy only if there is a reduction of ≥ 5.5mmol/mol (0.5% points) in HbA1c in 6 months**	**GREEN (Non-specialist drug)**	Do NOT start or continue pioglitazone in people who: • have heart failure (NYHA class I-IV) or a history of heart failure • diabetic ketoacidosis • are at a higher risk of fracture • macula oedema • hepatic impairment • current bladder cancer or a history of **bladder cancer.** See MHRA safety update • patients with uninvestigated macroscopic or microscopic haematuria • The risk of fractures should be considered, especially long bone fracture in women Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain, and oedema. See MHRA risk of cardiac failure when combined with insulin. **RENAL IMPAIRMENT:** No dosage adjustment is necessary in patients with impaired renal function (CrCL >4ml/min) **Baseline monitoring (UKMI Drug monitoring in primary care): Weight and LFTs.**

DPP-4 INHIBITORS (GLIPTINS) Inhibit dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion					
	Alogliptin	**Linagliptin**	**Sitagliptin**	**Saxagliptin**	**Vildagliptin**
Traffic light status	**GREEN** ***Preferred first line DPP-4 inhibitor when used in combination with the following:*** ***Dual therapy with metformin, sulphonylurea or pioglitazone*** ***As triple therapy with metformin and pioglitazone*** ***Not licenced for monotherapy***	**GREEN** ***Alternative 1st line choice in renal and hepatic impairment*** ***Monotherapy, when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment*** ***Combination therapy, in combination with insulin with or without metformin, or in combination with metformin and a sulphonylurea***	**GREEN** ***Preferred 1st Line Gliptin when used as monotherapy*** ***Or as triple therapy with metformin and a sulphonylurea***	**Non formulary** ***Not routinely commissioned***	**Non formulary** ***Not routinely commissioned***
Regimen	25mg od	5mg od	100mg od	5mg od	50mg bd
Place in therapy	NICE NG28 recommends gliptins as monotherapy, dual therapy (Gliptin + met or SU or Pio) and triple therapy (Gliptin +Met + SU). **ADVICE:** There is a lack of outcome data for these drugs; circumstances for use of gliptins should follow as per diabetes management flowchart on page 5 and 6. Potential exceptions include: • When the aim of treatment is to control symptoms of hyperglycaemia in the short term and in whom prevention of long term diabetes complications is not an issue (e.g. a symptomatic elderly patient, for whom hypoglycaemia is a problem and where insulin is impracticable) • Treatment with a thiazolidinedione is not ideal due to: risk of further weight gain; thiazolidinedione contraindicated or not tolerated. • **Gliptins should only be continued if there is a reduction of ≥5.5mmol/mol (0.5% points) in HbA1c in 6 months.**				
Advantages	Low risk of hypoglycaemia, (however hypoglycaemia may occur when used in combination with sulfonylurea therapy), generally gliptins are weight neutral and similar HbA1c reduction to pioglitazone. Long-term safety data – risk of pancreatitis (see warning section). 3 year CVD safety data for Sitagliptin is reassuring.				
Contraindications/warnings	Ketoacidosis Heart Failure- FDA recommends stopping Alogliptin if patient develops heart failure. SPC states avoid in class III and IV heart failure	Not for treatment of ketoacidosis	Not for treatment of ketoacidosis	Not for treatment of ketoacidosis FDA states stop if patient develops heart failure	Not for treatment of ketoacidosis Avoid in severe heart failure

	Alogliptin	Linagliptin	Sitagliptin	Saxagliptin	Vildagliptin
Renal function	Reduce dose - 12.5mg od if eGFR 30 - 50ml/min/1.73m^2 Reduce dose to 6.25mg od if eGFR <30ml/min/1.73m^2.	In renal impairment**, no dose adjustment** is required	Reduce dose - 50 mg od if eGFR 30-50 mL/min/1.73m^2 Reduce dose 25mg od if eGFR<30ml/min/1.73m^2	Reduce dose – 2.5mg od in moderate to severe renal impairment	Reduce dose – 50mg od if eGFR<50ml/min/1.73m^2
Adverse effects	Abdominal pain, gastro-oesophageal reflux and upper respiratory tract infection. Gliptins may precipitate acute pancreatitis- use with caution if there is a previous history	Nasopharyngitis and cough Gliptins may precipitate acute pancreatitis- use with caution if there is a previous history	GI disturbances, pain, peripheral oedema and upper respiratory tract infection Gliptins may precipitate acute pancreatitis- use with caution if there is a previous history	Dizziness, dyspepsia, gastroenteritis, upper respiratory tract infection and UTI Gliptins may precipitate acute pancreatitis- use with caution if there is a previous history	Rare reports of liver dysfunction discontinue if jaundice or other signs of liver dysfunction occur. Gliptins may precipitate acute pancreatitis- use with caution if there is a previous history
Monitoring	Baseline renal function before commencing treatment and periodically thereafter is recommended.	NA	Baseline renal before commencing treatment and periodically thereafter is recommended.	Baseline renal before commencing treatment and periodically thereafter is recommended.	Monitor liver function before treatment and every 3months for the first year and periodically thereafter.
Warning	The FDA, August 2015 have issued a warning that DPP- 4 inhibitors may cause joint pain that can be severe and disabling. Health care professionals should consider discontinuation of therapy with this class of drugs if severe and persistent joint pain occurs. The MHRA, (Sept 2012) have issued a warning that DPP-4 inhibitors and risk of acute pancreatitis. Discontinue treatment if symptoms of acute pancreatitis occur (persistent, severe abdominal pain) The FDA, April 2016 has added warnings about heart failure risk to labels of medicines containing Saxagliptin and Alogliptin as a safety review they conducted found that they may increase the risk in patients with heart/kidney disease.				

SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITOR

Reversibly inhibits sodium-glucose co-transporter-2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion

Dapagliflozin, canagliflozin, empagliflozin and ertugliflozin are licensed for monotherapy and in combination with other glucose-lowering agents.

Canagliflozin, dapagliflozin and empagliflozin as monotherapies are recommended as options for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if:

- a DPP-4 inhibitor would otherwise be prescribed and
- a sulfonylurea or pioglitazone is not appropriate.

	Canagliflozin	**Dapagliflozin**	**Empagliflozin**	**Ertugliflozin**
NICE guidance	NICE TA315- Canagliflozin in combination therapy for treating type 2 diabetes. (June 2014).	NICE TA288 - Dapagliflozin in combination therapy for treating type 2 diabetes. (updated November 2016) & NICE TA418 – triple therapy for treating type 2 diabetes	NICE TA336 - Empagliflozin in combination therapy for treating type 2 diabetes. (March 2015)	NICE TA572- Ertugliflozin as monotherapy or with metformin for treating type 2 diabetes
Monotherapy as per NICE	Canagliflozin, dapagliflozin, empagliflozin or ertugliflozin as monotherapies are recommended as options for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if: • a gliptin would otherwise be prescribed and • a sulfonylurea or prioglitzone is not appropriate.			
Dual therapy (+Met) as per NICE	Y	Y	Y	Y
Triple therapy (+ met & SU or +met & glitazone) as per NICE	Y	Y (+ met & SU only)	Y	
With insulin (± other antidiabetics) As per NICE	Y	Y	Y	
Traffic light status	**GREEN** as per NICE TA315 & TA390	**GREEN** as per NICE TA288, TA390 & TA418	**GREEN 1st line** as per NICE TA336 & TA390	**GREEN** as per NICE TA572
Regimen	Starting dose : **100mg od** Can be increased to: **300mg od*** (*if eGFR ≥ 60 mL/min/1.73m^2 or CrCl ≥ 60 mL/min and tighter glycaemic control is needed)	Recommended dose:**10mg od**	Starting dose: **10mg od** Can be increased to: **25mg od*** (*if eGFR ≥60 ml/min/1.73m^2 and tighter glycaemic control is needed)	Starting dose: **5mg od** Can be increased to: **15mg od*** (*if eGFR ≥60 ml/min/1.73m^2 and tighter glycaemic control is needed)

Advantages	No hypoglycaemia, weight loss (~2kg stabilising over 6-12 months) and lowering of systolic and diastolic blood pressure in the order of ~ 2-4 / ~ 1-2mmgHg. (Silvio E. Inzucchi et al. Dia Care 2015; 38:140-149)			
	Canagliflozin	**Dapagliflozin**	**Empagliflozin**	**Ertugliflozin**
Renal function	Canagliflozin should **not be initiated** in patients with an eGFR < 60mL/min/1.73 m^2 or CrCl < 60 mL/min. In patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m^2 or CrCl 60 mL/min, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when eGFR is persistently below 45 mL/min/1.73m^2.	Dapagliflozin should **not be initiated** in patients with an eGFR<60 ml/min/ 1.73 m^2 Dapagliflozin should be discontinued when eGFR is persistently below 45 mL/min/1.73m^2.	**No dose adjustment** is required for patients with an eGFR ≥60ml/min/1.73m^2 or CrCl ≥60ml/min. Do not initiate if eGFR <60 ml/min In patients tolerating empagliflozin whose eGFR falls persistently below 60 ml/min/1.73m^2, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73m^2	Initiation is not recommended in patients with an eGFR < 60 ml/min/1.73 m^2 or CrCl less than 60 ml/min. Ertugliflozin should be discontinued when eGFR is persistently less than 45 ml/min/1.73 m^2 or CrCl is persistently less than 45 ml/min.
Hepatic function	Avoid use in severe hepatic impairment	Initial dose 5mg daily in severe impairment, increased according to response.	Avoid use in severe hepatic impairment	Ertugliflozin has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients
Adverse effects	Hypoglycaemia in combination with insulin or a sulfonylurea, vulvovaginal candidiasis, UTI, polyuria, genital infections and nausea. Fournier's gangrene (necrotising fasciitis of peritoneum)	Hypoglycaemia (when used with a sulfonylurea or insulin), urinary tract and genital infection, back pain, dysuria, polyuria, dyslipidaemia and elevated haematocrit.	Hypoglycaemia in combination with insulin or a sulfonylurea, vulvovaginal candidiasis, urinary tract infection and polyuria or pollakiuria, genital infection	Vulvovaginal candidiasis, urinary tract infection and polyuria or pollakiuria, genital infection, balanitis, increased haemoglobin and urea In an ongoing clinical study of ertugliflozin added to existing therapy in type 2 diabetes patients with a history of established cardiovascular disease, an approximately 1.2-1.6-fold increase in cases of lower limb amputation (primarily

				of the toe) has been observed in patients treated with ertugliflozin
Long-term data	Long-term safety data – concerns about diabetic ketoacidosis at only moderately elevated blood sugars, limited long-term data.			
Monitoring	SPC advice for monitoring: • Monitor renal function prior to initiation of canagliflozin and at least annually, thereafter • Monitor renal function prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter. • For renal function approaching moderate renal impairment, at least 2 times to 4 times per year.	SPC advice for monitoring: • Monitor renal function prior to initiation of dapagliflozin and at least yearly, thereafter. • Monitor renal function prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter • For renal function approaching moderate renal impairment, at least 2 to 4 times per year.	SPC advice for monitoring of renal function • Prior to empagliflozin initiation and periodically during treatment, i.e. at least yearly. • Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function.	SPC advice for monitoring of renal function • Prior to ertugliflozin initiation and periodically during treatment, i.e. at least yearly, more frequently if eGFR <60 • Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function
Warning	The MHRA, April 2016 issued a drug safety update warning that the SGLT2 inhibitors used in type 2 diabetes, may lead to ketoacidosis, that may require hospitalisation. When treating patients who are taking an SGLT2 inhibitors: • Test for raised blood ketones in patients with symptoms of diabetic ketoacidosis (DKA); omitting this test could delay diagnosis of DKA. • If you suspect DKA, stop SGLT2 inhibitor treatment. • Do not restart treatment with any SGLT2 inhibitor in patients who experienced DKA during use, unless another cause for DKA was identified and resolved. • If DKA is confirmed, take appropriate measures to correct the DKA and to monitor glucose levels. • Inform patients of the symptoms and signs of DKA (e.g. nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness); advise them to get immediate medical help if these occur • Interrupt treatment with the SGLT2 inhibitor in patients who are hospitalised for major surgery or acute serious illnesses; treatment may be restarted once the patient's condition has stabilised. **Canagliflozin and limb amputation** The MHRA, June 2016 issued a drug safety update warning regarding increased lower limb amputation (primarily of the toe) in people taking canagliflozin compared with placebo. Advice for healthcare professionals • As a precaution, consider stopping canagliflozin if a patient develops a significant lower limb complication (e.g., skin ulcer, osteomyelitis, or gangrene), at least until the condition has resolved, and continue to monitor the patient closely. • carefully monitor patients receiving canagliflozin who have risk factors for amputation (e.g., previous amputations, existing peripheral vascular disease, or neuropathy)			

	• monitor all patients for signs and symptoms of water or salt loss; ensure patients stay sufficiently hydrated to prevent volume depletion in line with recommendations in the product information; note that diuretics can exacerbate dehydration
	• advise patients to:
	  ○ stay well hydrated
	  ○ carry out routine preventive foot care
	  ○ seek medical advice promptly if they develop skin ulceration, discolouration, or new pain or tenderness
	start treatment for foot problems (e.g. ulceration, infection, or new pain or tenderness) as early as possible.
	
	The SPC for ertugliflozin suggests similar precautions for people at risk of lower limb ampuation

GLP-1 (Glucagon-like peptide-1) AGONISTS Increase insulin secretion, suppress glucagon secretion, slow gastric emptying and reducing appetite and food intake			
	Lixisenatide	**Liraglutide**	**Exenatide**

NICE guidance	**NICE NG28 recommends GLP-1s as an option with metformin and gliclazide when triple therapy is not effective/ not tolerated/ contra-indicated for adults who**:
	• Have a BMI of ≥35kg/m^2 or higher in those of European decent with appropriate adjustment in tailoring this advice for other ethnic groups and specific psychological or other medical problems associated with obesity or
	• Have a BMI <35kg/m^2 and
	  ○ For whom insulin therapy would have significant occupational implications or
	  ○ Weight loss would benefit other significant obesity-related co-morbidities.
	Therapy must be reviewed at 6 and 12 months.
	Criteria for continuing therapy:
	• a weight reduction of ≥3% (of initial body weight) in those with a BMI≥ 35kg/m^2 and
	• a reduction of ≥11mmol/mol (1%) by 6 months, with stable renal function.
	NICE NG28 also recommends GLP-1 in combination with insulin with specialist care advice and on-going support from a consultant-led multidisciplinary team.		

Traffic light status	**GREEN**	**GREEN**	**GREEN**
Regimen	Dosage: 10mcg od for 14 days and increased to 20mcg od thereafter, administered by subcut injection, within 1 hour before a meal.	Dosage: initially 0.6mg od for at least 7 days, then increased to 1.2mg od for at least 7 days, administered by subcut injection. SPC states that doses up to 1.8 mg can be used, not specifically endorsed by NICE Patients who fail trial with Lixisenatide can be considered for Liraglutide.	Dosage: 5mcg BD for at least 1 month, then increased if necessary up to 10mcg BD, administered subcut injection within 1 hour before morning and evening meals.
Advantages	Weight loss - which can be modest in most patients, but significant in some, no hypoglycaemia and decrease in some cardiovascular risk factors.		
Contra - indications	Pregnancy and lactation. Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis	Pregnancy and lactation. Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis	Pregnancy and lactation. Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis
Renal function	Not recommended for use in patients with a CrCl<30ml/min and end stage renal disease.	No dose adjustment is required for patients with mild, moderate or severe renal impairment. There is no therapeutic experience in patients with end-stage renal disease, not recommended	Not recommended for use in patients with eGFR < 30ml/min

	Lixisenatide	Liraglutide	Exenatide
Adverse effects	Nausea, vomiting, diarrhoea and headache are common adverse effects Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis	Nausea and diarrhoea ,vomiting, constipation, abdominal pain, and dyspepsia. Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis	Nausea and injection site reaction. Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis
Monitoring	Criteria for continuing therapy: • a weight reduction of ≥3% (of initial body weight) in those with a BMI≥ 35kg/m2 and • a reduction of ≥11mmol/mol (1%) by 6 months, with stable renal function.		
Warnings	• There have been reports of **necrotising and haemorrhagic pancreatitis** with GLP-1 agonists, some of which were fatal. If pancreatitis is suspected, treatment with the GLP-1 agonist should be suspended immediately; if pancreatitis is diagnosed, the GLP-1 agonist should be permanently discontinued. (MHRA warning) 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. This has implications for drivers holding Group 2 (LCV or PCV) licences. These people will require individual DVLA assessment.		

Weekly GLP-1 (Glucagon-like peptide-1) AGONISTS Increase insulin secretion, suppress glucagon secretion, slow gastric emptying and reducing appetite and food intake			
	Dulaglutide prolonged release	**Exenatide prolonged release**	**Semaglutide**
NICE guidance	**Not included in NG28. (ESNM59: June 2015)**	As per NICE NG28 Exenatide modified release can be considered if tolerability and compliance remains a major issue with conventional GLP-1 agonist therapy among patients whose HbA1c remains >59 mmol/mol (7.5%) and BMI>35kg/m^2.	**Not included in NG28. (ESNM59: June 2015)**
Traffic light status	**GREEN (When initiated without insulin)** **BLUE (Specialist initiation only when co-prescribed with insulin)**	**GREEN**	**GREEN** **Preferred 1st line weekly GLP-1**
Product	Pre-filled pen available as: • 750mcg/0.5ml pre-filled pen • 1.5mg/0.5ml pre-filled pen	Dual chamber pre-filled pen, which requires mixing before injection: • 2mg pre-filled pen	Pre-filled pen available as: • 0.25mg/0.19ml pre-filled pen • 0.5mg/0.37ml pre-filled pen • 1mg/0.74ml pre-filled pen
Regimen	Dosage: 750 microgram by subcut injection once weekly. Add on therapy: 1.5mg by subcut injection once weekly.	Dosage: 2mg by subcut injection once weekly.	Dosage: Start 0.25mg by subcut injection increasing to 0.5mg after 4 weeks Can be increased to 1mg weekly if needed
Advantages	As per GLP1s above. Advantage of a weekly preparation • if compliance is an issue or • the patient requires regular visits from a nursing team to administer the drug.		
Contra - indications	Type 1 diabetes, pregnancy and breastfeeding	Type 1 diabetes, pregnancy and breastfeeding	Type 1 diabetes, pregnancy and breastfeeding
Renal function	Not recommended for use in patients with an eGFR <30ml/min	Not recommended for use in patients with an eGFR <30ml/min	No dose adjustment is required for mild, moderate or sever renal impairment. Not recommended for use in end-stage renal disease
Hepatic function	No dosage adjustment is recommended for patients with hepatic impairment	No dosage adjustment is recommended for patients with hepatic impairment	No dosage adjustment is recommended for patients with hepatic impairment
Adverse effects	Acute pancreatitis serious but rare Nausea, vomiting, diarrhoea.	Acute pancreatitis – serious but rare Common AE include diarrhoea, nausea, and injection site rash.	Acute pancreatitis serious but rare Nausea, vomiting, diarrhoea
Monitoring	Criteria for continuing therapy: • a weight reduction of ≥3% (of initial body weight) in those with a BMI≥ 35kg/m2 and • a reduction of ≥11mmol/mol (1%) by 6 months, with stable renal function.		
Warning	See warning in GLP1 section above		

Drug therapy and renal and hepatic impairment

Worsening renal function (eGFR in ml/min)						Hepatic impairment		
Drug	**CKD 1 & 2 eGFR >60**	**3a (59-45)**	**3b (44-30)**	**4 (29-15**	**5 (< 15)**	**Mild**	**Moderate**	**Severe**
Metformin / Metformin MR	✓	✓	✓ (review regularly)	x	x	x Contraindicated in hepatic insufficiency		
Gliclazide	✓	✓	✓	✓ (use lowest effective dose)	x	✓	✓	x contraindicated
Pioglitazone	✓	✓	✓	✓	✓ (but not with dialysis)	x contraindicated	x contraindicated	x contraindicated
Dapagliflozin	✓	x (do not initiate - 60ml/min)	x (discontinue if GFR falls below 45ml/min)	x	x	✓	✓	✓ starting dose 5mg, increase to 10mg if well tolerated
Canagliflozin	✓	x (do not initiate - GFR<60ml/min) Reduce dose to 100mg if taking	x (discontinue if GFR falls below 45ml/min)	x	x	✓	✓	x not recommended
Empagliflozin	✓	x (do not initiate - GFR<60ml/min) Reduce dose to 10mg	x (discontinue if GFR falls below 45ml/min)	x	x	✓	✓	x not recommended
Lixisenatide	✓	✓ (use with caution if GFR<50ml/min)	✓ (use with caution)	x	x	✓	✓	✓
Liraglutide	✓	✓	✓	x No experience	x No experience	✓	✓	x not recommended
Exenatide	✓	✓	✓ (conservative dose escalation)	x	x	✓	✓	✓

Worsening renal function (eGFR in ml/min) →						Hepatic impairment		
Drug	**CKD 1 & 2 eGFR >60**	**3a (59-45)**	**3b (44-30)**	**4 (29-15**	**5 (< 15)**	**Mild**	**Moderate**	**Severe**
Exenatide MR	✓	x (not recommended if GFR between 30-50ml/min)	x	x	x	✓	✓	✓
Dulaglutide	✓	✓	✓	x	x	✓	✓	✓
Semaglutide	✓	✓	✓		x	✓	✓	✓
Insulin	✓	✓	✓	dose adjustment required	dose adjustment required	✓ requirements may be altered in hepatic impairment - monitor and adjust dose accordingly.		
Sitagliptin	100mg	50mg (GFR<50ml/min)	50mg	25mg	25mg	✓	✓	x no studies in severe hepatic impairment
Linagliptin	✓	✓	✓	✓	✓	✓	✓	✓
Saxagliptin	✓	2.5mg	2.5mg	2.5mg (use with caution)	x (not recommended)	✓	use with caution	x not recommended
Vildagliptin	✓	50mg (GFR<50ml/min)	50mg (GFR<50ml/min)	50mg (GFR<50ml/min)	50mg (limited experience)	x not recommended	x not recommended	x not recommended
Alogliptin	✓	12.5mg	12.5mg	6.25mg (limited experience)	6.25mg (limited experience)	✓	✓	x not recommended
Repaglinide	✓	✓	✓	✓ use with caution	✓ use with caution	no studies in hepatic insufficiency	no studies in hepatic insufficiency	x contraindicated

Table 1 lists the various insulins available and their properties. There is a significant difference in costs between insulin analogues and NPH insulin and between different devices such as vials, cartridges and disposable pens. At the present time the CCG recommends that all insulin products are classified as **Blue- specialist initiation only**

	Insulin (all preparations are 100iu/ml unless stated)	**Timing of injection**	**Onset of action**	**Peak**	**Duration of action**
Mealtime insulins	**Short acting human insulins**				
	Soluble insulin (**Actrapid**)	Within 30 mins before meal	Within 30 mins	1.5-3.5 hrs	7-8 hrs
	Soluble insulin (**Humulin S)**	Within 30 mins before meal	30 60 mins	1-6 hrs	6-12 hrs
	Soluble insulin (**Insuman rapid**)	Within 30 mins before meal	Within 30 mins	1 – 4 hrs	7 – 9 hrs
	Rapid-acting analogues				
	Insulin aspart (**Fiasp, Novo Rapid**)	Immediately before meal	10-20 mins	1-3 hrs.	3-5 hrs
	Insulin glulisine (**Apidra**)	Within 0-15 mins of meal	10-20 mins	About 1 hr	3-5 hrs
	Insulin lispro (**Humalog**)	Within 0-15 mins of meal	About 15 mins	1.5 hr	2-5 hrs
Basal insulins	**Intermediate (NPH) human insulin**				
	Isophane (NPH) insulin (**Insulatard**)	At bedtime/12 hrly	Within 1.5 hrs	4 -12 hrs	About 24 hrs
	Isophane (NPH) insulin (**Humulin I**)	At bedtime/12 hrly	30 – 60 mins	1 – 8 hrs	22 hrs
	Isophane (NPH) insulin (**Insuman Basal**)	At bedtime/12 hrly	Less than 60 mins	3 – 4 hrs	11-20 hrs
	Long-acting analogues				
	Insulin detemir (**Levemir**)	Once/twice daily	30 – 60 mins	3-14 hrs	Up to 24 hrs
	Insulin glargine (**Abasaglar**)	Once daily	30 – 60 mins	No peak	Up to 24 hrs
	Insulin glargine (**Lantus**)	Once daily	30 – 60 mins	No peak	Up to 24 hrs
	Insulin glargine **300 units/ml** (**Toujeo**)	Once daily	30 – 60 mins	No peak	24-36 hrs
	Insulin degludec (**Tresiba** 100iu and 200iu/ml)	Once daily			
Biphasic insulins	**Pre-mixed human insulin**				
	Biphasic isophane insulin (soluble insulin 30%+isophane insulin 70%; **Humulin M3**) **Insuman Comb 15** (15% soluble/85% Isophane) **Insuman Comb 25** (25%soluble/75% Isophane) **Insuman Comb 50** (50% soluble/50% Isophane)	Within 30 mins before meal	Within 30 mins	2 and 4hrs	Up to 24hrs

	Pre-mixed analogues				
	Biphasic aspart (insulin aspart 30%+ insulin aspart protamine 70%; N**ovomix 30**)	Within 0-10 mins of meal	Within 10-20 mins	1-4 hrs	Up to 24hrs
	Biphasic insulin lispro (insulin lispro 25%+ insulin lispro protamine 75%; **Humalog Mix 25)**	Within 0-15 mins of meal	About 15 mins	About 2 hrs	Up to 24hrs
	Biphasic insulin lispro (insulin lispro 50%+insulin lispro protamine 50%; **Humalog Mix 50**)	Within 0-15 mins	About 15 mins	About 2 hrs	Up to 24hrs

Formulary products in bold (All times accessed from MIMs online - accessed June 2016) †

Timings of action of insulins are approximate as they vary between individuals, and with injection sites, blood supply, temperature and physical activity.
Long acting insulin analogues, are designed not to have a peak action as such but to release insulin consistently over their duration of activity.

Table 2: Traffic light classification for high strength insulins

Insulin/strength	Traffic light status
Insulin glargine 300iu/ml (Toujeo)	**BLUE** after consultant/specialist initiation: •for patients on insulin Degludec or •for patients being considered for insulin pump therapy or •for patients currently on high dose of insulin (>150units/day) who would otherwise have been started with Humulin R U-500 or degludec.
Insulin degludec 200iu/ml (Tresiba)	**BLUE** after consultant/specialist initiation for patients currently on high dose of insulin (>150units/day) after consideration of Toujeo.
Humulin R U500 500iu/ml	**RED** specialist drug only

Table 3: Insulin cost comparison chart

Active substance	Brand name	Strength	Cost 5 x 3ml cartridge	Cost of 5 x 3ml pre-filled pen	Vial x 10ml
Isophane (NPH) insulin	Insuman Basal	100units/ml	£17.50	£19.80	£5.61
	Humulin I	100units/ml	£19.08	£21.70	£15.68
	Insulatard	100units/ml	£22.90	£20.40	£7.48
Insulin glargine	Lantus	100units/ml	£37.77	£37.77	£27.92
	Abasaglar	100units/ml	£35.28	£35.28	--
Insulin detemir	Levemir	100units/ml	£42	£42 £44.85 (InnoLet device)	--
Insulin degludec	Tresiba	200units/ml	3 x 3ml prefilled pen £55.92		
		100units/ml	5 x 3ml prefilled pen or cartridges £46.60		
Insulin glargine	Toujeo	300units/ml	3 x 1.5ml pre-filled pen £33.13		

Needles: All pen needles ≤ £3/100 are on the joint formulary, see https://www.gp.brightonandhoveccg.nhs.uk/file/18551

Table 4: NPH and insulin analogue products and cost comparisons (MIMS 2019)
Please note that drug costs vary regularly, this table is for comparison only †

Insulin product	Insulin type	Cost and pack size	Cost / ml of insulin (100 units/ml)
Vials			
Insulatard® 10ml vial	Intermediate (NPH) human insulin	£7.48 per 10ml vial	£0.75
Insuman ® basal 5ml vial	Intermediate (NPH) human insulin	£5.61 per 5ml vial	£1.12
Humulin I® 10ml vial	Intermediate (NPH) human insulin	£15.68 per 10ml vial	£1.57
Lantus ® (insulin glargine) 10ml vial	Long-acting analogues	£27.92 per 10ml vial	£2.79
Cartridges			
Insuman® Basal 5 x 3ml cartridge for ClickSTAR®, Autopen® 24	Intermediate (NPH) human insulin	£17.50 for 5 x 3ml cartridge	£1.17
Humulin I® 5 x 3ml cartridge for autopen® classic / HumaPen®	Intermediate (NPH) human insulin	£19.08 per 5 x 3ml cartridge	£1.27
Insulatard penfill® 5 x 3ml cartridge for Novopen®	Intermediate (NPH) human insulin	£22.90 for 5 x 3ml cartridge	£1.53
Lantus® (insulin glargine) 5 x 3ml cartridge for autopen®	Long-acting analogues	£37.77 per 5 x 3ml cartridge	£2.52
Abasaglar (insulin glargine) 5 x 3ml cartridge for Savvio Humapen	Long-acting analogues	£35.28 per 5 x 3ml cartridges	£2.35
levemir® (insulin detemir) penfill 5 x 3ml cartridge for novopen®	Long-acting analogues	£42.00 per 5 x 3ml cartridge	£2.80
Prefilled disposable injection			
Insuman® Basal Solostar® 5 x 3ml	Intermediate (NPH) human insulin	£19.80 for 5 x 3ml pre-filled disposable injection device	£1.32
Prefilled disposable pens			
Insulatard InnoLet® prefilled disposable Pen	Intermediate (NPH) human insulin	£20.40 for 5 x 3ml prefilled disposable pen	£1.36
Humulin I KwikPen® prefilled disposable pen	Intermediate (NPH) human insulin	£21.70 for 5 x 3ml prefilled disposable pen	£1.45
Lantus® (insulin glargine) SoloStar® 5 x 3ml prefilled pen	Long-acting analogues	£37.77 per 5 x 3ml prefilled disposable pen	£2.52
Levemir® (insulin detemir) Flexpen® 5 x 3ml prefilled disposable pen	Long-acting analogues	£42.00 per 5 x 3ml prefilled disposable pen	£2.80
Abasaglar® (insulin glargine) KwikPen	Long-acting analogues	£35.28 for 5 x prefilled disposable pen	£2.35

Table 5: Insulin pen price comparisons

Name	Cartridge size	Price (£)
Autopen 24	**3ml**	**16.71**
Autopen classic	**3ml**	**16.96**
HumaPen Luxura HD	**3ml**	**26.82**
HumaPen Savvio	**3ml**	**26.82**
NovoPen 5	**3ml**	**26.86**
NovoPen Echo	**3ml**	**26.86**

Table 6: Licenced and NICE approved insulin combinations.
This list was correct as of 2015, indications vary regularly, please check BNF and SPC for current licenced combinations

Combination	Licenced (SPC)	NICE approved	Comments
Insulin + Metformin	Yes	NICE NG28	As per diabetes guidance and algorithm
Insulin + Gliclazide	Yes		
Insulin + Pioglitazone	Yes		After consultant/specialist initiation and assessment.
Insulin + Alogliptin	Yes		Only on advice of specialist and with on-going support from a consultant-led service
Insulin + Linagliptin*			
Insulin + Sitagliptin*			
Insulin + Saxagliptin*			
Insulin + Vildagliptin*			
Insulin + Empagliflozin	Yes	NICE TA336 - with insulin +/- other antidiabetic drugs	After consultant/specialist initiation and assessment
Insulin + Dapagliflozin		NICE TA288 - with insulin +/- other antidiabetic drugs	
Insulin + Canagliflozin		NICE TA315 - with insulin +/- other antidiabetic drugs	
Insulin + Exenatide	Yes	NICE NG28	Only on advice of specialist and with on-going support from a consultant-led service
Insulin + Liraglutide		NICE NG28	
Insulin + Lixisenatide		NICE NG28	
Insulin + Dulaglutide[1]		No	
Insulin + Albiglutide[1]		No	
Insulin + Exenatide MR	No	NICE NG28	
Insulin +Metformin (& MR) + Gliclazide	Yes		As per diabetes guidance and algorithm
Insulin + Metformin + Pioglitazone	No		As per diabetes guidance and algorithm

*with or without metformin
[1] Albiglutide and Dulaglutide were not included in NICE NG28 review.

Further Information for GLP-1 agonists

Benefit

- Randomized controlled trials have showed a lowering of HbA1c by 1.0-1.5% across the class and weight loss ranging from 1-2.3kg (maintained beyond 12 months)
- The natural hormone glucagon-like peptide-1 (GLP-1) acts by stimulating insulin secretion, suppressing glucagon secretion, inhibiting gastric emptying, and reducing appetite and food intake.

Initiation of therapy

- Only offer GLP1 in combination with insulin with specialist care advice and on-going support from a consultant-led multidisciplinary team.
- Individual DVLA assessment is required for Group 2 license holders who use GLP-1 agonists in combination with a sulfonylurea due to the risk of hypoglycemia.

Review

Therapy must be reviewed at 6 and 12 months. If HbA1c decrease is <11mmol/mol (1.0%) at 6 months and weight loss is <3% at 6 months, then consider stopping GLP1 treatment

- If a patient fails on initial GLP-1 therapy because of side effects or inadequate response, consider the next GLP-1 agonist in line.
- Often a patient loses weight but their HbA1c rises. They should not continue with GLP-1 agonist therapy because this may indicate beta cell failure and uncontrolled diabetes. Insulin should be considered instead.

Side effects

- Side effects include significant nausea (20-26% of patients were affected in trials) and there are rare reports of acute pancreatitis. It should therefore be avoided in those with previous pancreatitis or considered high risk. Other gastrointestinal side effects may occur and commonly settle after a few days or weeks on therapy.
- Existing patients on Exenatide or Liraglutide who stop due to adverse effects/ lack of efficacy can be tried on Lixisenatide.

Remember the following:

- Be alert to the signs and symptoms of acute pancreatitis.
- Instruct patients taking GLP-1 agonists to seek prompt medical care if they experience persistent severe abdominal pain.
- Discontinue the GLP-1 agonist if pancreatitis is suspected.
- If pancreatitis in a patient using a GLP-1 agonist is confirmed, appropriate supportive treatment should be initiated and the patient carefully monitored until recovery. GLP-1 agonist should not be restarted.

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Apologies to anyone I have missed, Dr Dan Jenkinson, July 2017

† Tables and charts adapted from Red Whale, GP Update with permission

Version 2 November 2017
New guidance on DPP-4 Inhibitors to reflect formulary changes
Addition of Tresiba 100
Formulary altered to reflect traffic light status of Saxagliptin, Vildagliptin and Toujeo
Review date: November 2018

Version 3 Nov 2019
Statement to support emerging evidence of SGLT2 and GLP for all-cause mortality
Updated targets for HbA1c and QOF
Addition of Semaglutide
DiRECT trial reference
Dapagliflozin guidance altered to reflect update on eGFR<60
Drug prices updated
Revision of BP targets as per NICE NG136 August 2019

Review date: Nov 2021