South East London Area Prescribing Committee:

South East London Blood Glucose Control Management Pathway for Adults with Type 2 Diabetes Mellitus (T2DM)

Developed by the SEL Diabetes Medicines Working Group on behalf of the SEL APC. If you have any queries or comments on this guideline please contact: LAMCCG.medicinesoptimisation@nhs.net

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South East London Area Prescribing Committee. A partnership between NHS organisations in South East London: Bexley/ Bromley/ Greenwich/ Lambeth/ Lewisham & Southwark Clinical Commissioning Groups (CCGs) & GSTFT/KCH/SLAM/Oxleas NHS Foundation Trusts and Lewisham & Greenwich NHS Trust

South East London Blood Glucose Control Management Pathway for Adults with Type 2 Diabetes Mellitus (T2DM)

After diagnosis discuss lifestyle changes, refer to structured education programme i.e. DESMOND, Xpert or locally provided service.
At ALL appointments reinforce lifestyle messages, check medication adherence and develop a collaborative care plan with the person who has diabetes.

First and second line therapy

Start therapy after 3 months of lifestyle changes if HbA1c ≥48mmol/mol (6.5%). Support the person to aim for a HbA1c of 48mmol/mol (6.5%). Some require a different *individualised* HbA1c target level based on: the person's needs and circumstances including preferences, comorbidities, risks from polypharmacy and tight blood glucose control and ability to achieve longer-term risk-reduction benefits.

NOTE: If adults with T2DM achieve an HbA1c level below their target and they are not experiencing hypoglycaemia, encourage them to maintain it. Consider other reasons for low HbA1c levels.

Metformin standard release

- Start at a dose of 500mg daily. Increase by 500mg every 2 weeks to reach a dose of 1g twice daily.
- Before starting metformin check corrected eGFR and remember renal precautions (see box overleaf).
- Doses should be taken with meals to minimise GI side effects. If GI intolerance occurs, try metformin modified release or reduce dose to previously tolerated dose.
- **Aim for HbA1c level of 48mmol/mol (6.5%). Check HbA1c after patient has been on maximum tolerated dose for 3 months.**

THINK INSULIN if BMI<22 or symptomatically hyperglycaemic – see immediate treatment box

if metformin contra-indicated (C/I) or not tolerated
Consider SU or pioglitazone or gliptin.
NB: SU is preferred option locally.
Gliclazide is the preferred SU locally
Consider alternative if: Group 2 driver or BMI≥35. **NOTE:** caution in frail elderly
A SGLT2 inhibitor can be considered if:
- A gliptin would otherwise be prescribed AND
- A SU or pioglitazone are not appropriate

Aim for HbA1c level of 48mmol/mol* (6.5%) if on pioglitazone, gliptin or SGLT2 inhibitor or 53mmol/mol* (7%) if on a SU

Immediate Treatment
If BMI < 22 or person symptomatically hyperglycaemic, seek advice from diabetes team as early insulin initiation or sulfonylurea (SU) therapy may be required. *See early/urgent insulin initiation guideline.* Insulin should be initiated by accredited health professional
NB: Insulin may be initiated at any step based on clinical need

Remember: Sick day rules (guidance under development)

FIRST INTENSIFICATION: If HbA1c rises to 58mmol/mol* (7.5%) after 3 months
(* or other individualised target)

Patient decision aids are available to support prescribing via the NICE website.

Add sulfonylurea (SU)
Gliclazide is the preferred SU locally
This combination is the preferred option locally due to evidence base and cost effectiveness. Consider alternative if: Group 2 driver or BMI≥35.
NOTE: caution in frail elderly

Add DPP4 inhibitor
(referred to as "gliptin" hereafter)

Add pioglitazone

Add SGLT2 inhibitor
Only use if SU not tolerated /contra-indicated or person at significant risk of hypo or consequences.

Other options for 2nd line therapy:
Support the person to aim for an HBA1c level of 53mmol/mol (7%).
- Gliptin and pioglitazone
- Gliptin and gliclazide
- Pioglitazone and gliclazide

See overleaf for further information on individual agents, such as doses, cautions and contra-indications and drug interactions.

Info on 2nd agent				
Efficacy (↓HbA1c)	High	Mid	High	Mid
Hypoglycaemia	moderate	Low	Low	Low
Weight gain	Possible increase but amount not certain	Neutral	↑2–3 kg over 12 months	↓2–3 kg over 6–12 months
Side effects	Hypoglycaemia	Pancreatitis	Oedema, HF, fractures, ↑bladder cancer risk	GU infections, ↓BP, dehydration
Cost (£)	Low	High	Low	High

SECOND INTENSIFICATION: If HbA1c rises to 58mmol/mol (7.5%), or other individualised target, after 3 months

Remember: Review effectiveness of new treatment after 3 months. Stop if no benefit and consider alternative options.

Add in either:
- Gliptin or
- Pioglitazone or
- SGLT2 inhibitor

Add in:
- Gliclazide or
- SGLT2 inhibitor

Add in either:
- Gliclazide or
- SGLT2 inhibitor

Add in:
- Gliclazide or
- Pioglitazone

NOTE: Dapagliflozin is not recommended to be used in combination with pioglitazone. NICE recommend use of dapagliflozin in triple therapy regimen with metformin and SU only; use of canagliflozin and empagliflozin in triple therapy regimen with metformin and SU or metformin and pioglitazone only; ertugliflozin in triple therapy with metformin and gliptin only if SU or pioglitazone are not appropriate.

If triple therapy with metformin and 2 other oral agents is not effective, not tolerated or contraindicated, consider following options:
1. Referral as per local pathway for insulin initiation or
2. Referral as per local pathway for GLP-1 initiation (see overleaf for starting and stopping criteria) **NOTE: NICE only support use of a GLP-1 agent with metformin and a SU OR a GLP-1 agent in combination with insulin** (see box to right).

Insulin initiation

If HBA1c is >11mmol/mol (1%) above individualised HbA1c target insulin is the preferred option at this stage.

Refer to **accredited health professional e.g.** community diabetes team, specialist GP/nurse for insulin initiation through a structured programme. Advice will also be given regarding continuation of existing oral therapies.

NB: In line with NICE, human isophane (NPH) insulin is recommended as first line basal insulin in T2DM. Long acting insulin analogues should be reserved for patients meeting criteria defined by NICE.

NOTE: Combination use of insulin and a GLP-1 agent can only be initiated by specialist diabetes teams. Prescribing responsibility may be transferred to the GP at 3 months under Transfer of Care arrangements.

Check HbA1c 3 months after any therapy change. Move to next step of therapy if target is not achieved. Discuss/refer to diabetes team if clinical concern at any stage

ADDITIONAL INFORMATION – this information is not exhaustive. Please refer to product literature for full list of doses, cautions and contra-indication and drug interactions – available via www.medicines.org.uk

Metformin (biguanide): (Also refer to sick day rules guidance once this has been developed and is available)
Metformin reduces cardiovascular events in overweight and obese patients to a greater extent than predicted by its glucose lowering effects

Modified release (M/R)dose: Initially 500mg once daily, increased every 10-15 days, max. 2g once daily with evening meal. If control not achieved use 1g twice daily with meals

Standard release- the usual dose is 2g -2.5g daily (max. dose 3g daily in 3 divided doses can be used in exceptional circumstances)

- Patients taking less than 2g daily of standard release can start on same daily dose of M/R

Metformin and the kidney** ("corrected eGFR" refers to eGFR that is corrected for ethnicity)

- Do not start metformin if corrected eGFR <45mL/min. Use under specialist advice only. Review metformin dose if corrected eGFR <45mL/min. Stop/avoid if corrected eGFR <30mL/min**.** Caution in those at risk of sudden deterioration in kidney function and those at risk of corrected eGFR falling below 45/mL/min

**Different dose recommendations exist in renal impairment dependent on preparation. The recommendations here may be outside the product's licence but are in line with NICE NG28. See NICE guideline and www.medicines.org.uk for further information

Pioglitazone

- Start at 15-30mg once daily, increased to 45mg once daily according to response. Start with lowest possible dose in the elderly and increase gradually. Where applicable, dose of concurrent sulfonylurea or insulin may need to be reduced
- Pioglitazone is contraindicated in people with a history of heart failure, uninvestigated macroscopic haematuria and previous or active bladder cancer
- Caution is advised when considering use in cardiovascular disease or in combination with insulin, or in those with an increased risk of bone fractures or risk factors for bladder cancer
- Consider pioglitazone in preference to a gliptin if there is a contraindication or poor response to the gliptin

Pioglitazone and the liver

- Avoid in hepatic impairment
- Monitor liver function before treatment and periodically thereafter. Advise patients to seek immediate medical attention if symptoms such as nausea, vomiting, abdominal pain, fatigue and dark urine develop. Discontinue if jaundice occurs

The safety and efficacy of pioglitazone should be reviewed after 3-6 months. It should be stopped in patients not responding adequately. Efficacy and safety should be reviewed (e.g. 3-6 monthly) in patients continuing therapy. See MHRA advice (Aug 2011) for further details and the summary of product characteristics (SPC)

SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin). Also see sick day rules guidance.

- Prior to initiation take into consideration risk factors for ketoacidosis (**note**: can occur at normoglycemia) as outlined by MHRA. Risk factors include: a low beta cell function reserve and conditions leading to restricted food intake or severe dehydration. Inform patients of the signs and symptoms of metabolic acidosis (such as rapid weight loss, excessive thirst, nausea, vomiting, anorexia, abdominal pain, difficulty breathing or fast and deep breathing, confusion, unusual fatigue and sleepiness, sweet smelling breath, sweet or metallic taste in the mouth or a different odour to urine or sweat). Advise to immediately seek medical advice.
- Monitor renal function prior to initiation and then 6 monthly to annually thereafter.
- Avoid initiating canagliflozin, empagliflozin or ertugliflozin if corrected eGFR <60mL/min. In patients tolerating canagliflozin or empagliflozin whose corrected eGFR falls persistently below 60 mL/min, adjust or maintain dose at: 100 mg once daily for canagliflozin and 10mg once daily for empagliflozin. Discontinue canagliflozin, empagliflozin or ertugliflozin if corrected eGFR is persistently <45 mL/min. Avoid dapagliflozin if corrected eGFR <60mL/min.
- Can cause diuresis and therefore volume depletion and hypotension. They should be used in caution when given with diuretics (do NOT use with loop diuretics) or in those who are volume depleted (e.g. in acute illness).
- Common adverse reactions include genital and urinary tract infections.
- Be aware of EMA information on SGLT2 inhibitors and potential risk of toe amputations. Follow EMA advice. bb
- Be aware of MHRA information on the risks of Fournier's gangrene

Use this guideline in conjunction with discussion and education of the patient. Treatment should be individualised to patient need e.g. in relation to weight gain, hypos, tolerability of medicines and rate of titration

Sulfonylureas - NB gliclazide is the local SU of choice

- Always reassess the patient and emphasise lifestyle issues before prescribing
- For gliclazide, start at a dose of 40-80mg daily with meals (higher doses divided). Titrate dose every 2 weeks according to pre-meal blood glucose levels. Target pre-meal blood glucose level is 4- 6mmol/l (or individualised target). If the patient is not self testing, titrate dose according to HbA1c level every 3 months. It is recommended that patients taking SUs self-monitor their blood glucose in line with DVLA regulations and NICE guideline NG28
- Caution use of SU in patients who are elderly, housebound and in certain occupations (e.g. operating heavy machinery)
- A SU should be used as first line therapy if rapid response is required due to symptomatic hyperglycaemia, if a person is not overweight (BMI < 25) or where metformin is contraindicated
- Check HbA1c after patient has been on maximum tolerated dose for 3 months
- Patients should be educated about risks of hypoglycaemia with sulfonylureas, particularly if renally impaired.

Sulfonylureas and the kidney

- SUs should be used with care in those with mild to moderate renal impairment (corrected eGFR 30-60 mL/min) due to the increased risk of hypoglycaemia. **Avoid** in severe renal impairment (corrected eGFR <30mL/min) unless under specialist guidance

Sulfonylureas and the liver

- Avoid in severe hepatic impairment due to an increased risk of hypoglycaemia

Gliptins

- Locally sitagliptin is **1st line** gliptin of choice. Linagliptin is reserved for patients with severe renal impairment.
- For sitagliptin the dosing is 100mg once daily, reduced to 50mg once daily if corrected eGFR is between 30-50mL/min or 25mg once daily if corrected eGFR <30mL/min. Monitor renal function before treatment and periodically thereafter
- Linagliptin should **ONLY** be considered as a treatment option in patients with severe renal impairment (corrected eGFR <30 mL/min)
- The MHRA has warned that an increased risk of acute pancreatitis has been identified for **all** approved gliptins. Patients should be informed of the characteristic symptoms of acute pancreatitis and encouraged to report these to their healthcare provider. If pancreatitis is suspected, the gliptin and other potentially suspect medicines should be discontinued
- Consider a gliptin in preference to pioglitazone if there is a contraindication, previous poor response or pioglitazone is not tolerated or if further weight gain would cause significant problems
- The FDA has requested changes to the labelling for the gliptins alogliptin and saxagliptin because of a potential increased risk of heart failure (HF). Whilst these agents aren't on the local formulary, health care professionals should consider the risk and benefits prior to initiating treatment in patients at a higher risk for HF. Risk factors include a history of HF or renal impairment. Consider discontinuing saxagliptin and alogliptin in patients who develop HF and monitor their diabetes control. At time of writing it is unclear if this is a class effect for all gliptins

- **GLP-1 analogues**
- Consider if BMI ≥ 35 (adjust accordingly for ethnicity) and specific psychological or other medical problems associated with obesity OR if BMI < 35 and where insulin would have significant occupational implications or weight loss would benefit other significant obesity related co-morbidities
- ONLY continue GLP-1 treatment if there is an HbA1c reduction of at least 11mmol/mol (1%) and a weight loss of at least 3% of initial body weight at 6 months
- Please refer to the South East London GLP-1 analogue pathway for further details

References
(1)NICE clinical guideline 28 – type 2 diabetes, (Last accessed 04.05.16) (2)MHRA Drug Safety Update September 2012, vol 6, issue 2: A3 (3) MHRA Drug Safety Update, April 2016 (4) BNF Online (5) SPCs for all agents, available via www.medicines.org.uk (accessed 20.04.16) (6)Expert opinions of local diabetes clinicians and specialists (7) MHRA Drug Safety Update August 2011 (8) MHRA Drug Safety Update January 2011 (9) FDA Communication April 2016 (10) NICE TAGs for the SGLT2 inhibitors: 288, 315, 336, 390, 418, 572 and 583 (11) MHRA Drug Safety Update June 2016 (12) EMA review SGLT2 inhibitors Feb 2017. See South East London Area Prescribing Committee website for resources