City and Hackney
Clinical Commissioning Group

Blood Glucose Management Pathway for Adults with Type 2 Diabetes Mellitus in Primary Care

THE MANAGEMENT OF PREGNANT DIABETIC PATEINTS IS NOT WITHIN THE SCOPE OF THIS PATHWAY. THEY SHOULD BE MANAGED BY DIABETES MATERNITY DEPARTMENT. CONTACT DIABETES CENTRE AT HOMERTON HOSPITAL, TEL 020 85105920.

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Individualised HbA1c targets

Agree an individualised HbA1c target 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.

Support the person to aim for the agreed HbA1c target, measure HbA1c levels at:

- 3-6 monthly intervals (tailored to individual needs), until the HbA1c is stable on unchanging therapy
- 6 monthly intervals once the HbA1c level and blood glucose lowering therapy are stable

Patients group	**Target HbA1c (or individualised)**
Patients managed by lifestyle interventions	< 48 mmol/mol (6.5%)
Taking a single oral agent which is NOT associated with risk of hypoglycaemia (metformin, DPP4 inhibitor, SGLT2 inhibitor, pioglitazone)	48 mmol/mol (6.5%)
Taking a single oral agent which is associated with risk of hypoglycaemia (sulfonylurea, repaglinide)	53 mmol/mol (7.0%)
On dual therapy	53 mmol/mol (7.0%)
On triple therapy	53 mmol/mol (7.0%)
Mild to moderate frail older patients	53-64 mmol/mol (7.0-8.0%)
Patients with severe frailty	58–69 mmol/mol (7.5–8.5%)
Patients with CKD 4 or 5 or on dialysis	58–69 mmol/mol (7.5–8.5%)
Patients with life expectancy < 10 years	69 mmol/mol (8.5%)

Note:

- Fructosamine may be more appropriate for monitoring of diabetes if the following apply: Sickle cell anaemia, other anaemia, homozygous haemoglobin variant disease, or increased red cell turnover.
- In these situations fructosamine provides an alternate means of assessing glucose control. It gives an estimate of glucose control in the preceding 2-3 weeks.
- A corrected fructosamine level of 340 µmol/L indicates exceedingly good diabetes control and a level below 380 µmol/L indicates good control. Seek advice from the diabetes team.

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Discuss diet and lifestyle changes after diagnosis. Refer to structured education programme.

Adopt an individual approach based on the person's needs and circumstances, taking into account their personal preferences, comorbidities, risks from polypharmacy and tight blood glucose control, and ability to achieve longer-term risk-reduction benefits.

MONOTHERAPY: If HbA1c rises to 48mmol/mol (6.5%) on lifestyle interventions

- Start metformin standard release 500mg daily with food for 1 week, increase by 500mg every 1 to 2 weeks to a max dose of 1g twice a day
- DO NOT initiate if eGFR < 30ml/min/1.73m² and use a max dose of 500mg twice a day if eGFR 30ml/min/1.73m² to 45ml/min/1.73m²
- Consider metformin modified release if unable to tolerate standard release tablets due to GI side-effects
- Aim for HbA1c level of 48mmol/mol (6.5%) or other individualised target

If metformin contraindicated or not tolerated, consider

Sulfonylurea or DPP4 inhibitor or SGLT2 inhibitor or pioglitazone

FIRST INTENSIFICATION: If HbA1c rises to 58mmol/mol (7.5%) or other individualised target after 3 months, consider dual therapy (Refer to ADA/EASD recommendation for patients with established ASCVD, CKD or HF; discuss with diabetes team if patients might benefit from GLP-1 agonists)

Metformin + Sulfonylurea (1st choice gliclazide*) OR
Metformin + DPP4 inhibitor (1st choice sitagliptin**) OR
Metformin + SGLT2 inhibitor*** OR
Metformin + Pioglitazone

FIRST INTENSIFICATION
Sulfonylurea + DPP4 inhibitor OR
Sulfonylurea + SGLT2 inhibitor OR
Sulfonylurea + pioglitazone OR
DPP4 inhibitor + SGLT2 inhibitor OR
DPP4 inhibitor + pioglitazone

*Repaglinide can be used if irregular meals or eGFR < 45ml/min/1.73m²
**Linagliptin can be used if renal function unstable or worsening; sitagliptin dose needs to be reduced in renal impairment
***SGLT2 inhibitors on formulary: canagliflozin, empagliflozin, dapagliflozin and ertugliflozin; DO NOT initiate SGLT2 inhibitors if eGFR < 60ml/min/1.73m² except canagliflozin (see additional information). SGLT2 inhibitors might be a suitable option if weight loss beneficial; evidence of CV/renal benefits for patients with established ASCVD, CKD or HF (benefit in HF only for ertugliflozin)

NOTE: Patient decision aids available to support prescribing via NICE website

- Aim for HbA1c level of 53mmol/mol (7%) or individualised target

SECOND INTENSIFICATION
Consider insulin-based treatment (see below)

SECOND INTENSIFICATION: If HbA1c rises to 58mmol/mol (7.5%) or other individualised target after 3 months, consider (Refer to ADA/EASD recommendation for patients with established ASCVD, CKD or HF; discuss with diabetes team if patients might benefit from GLP-1 agonists) :

Triple therapy
Metformin + Sulfonylurea (1st choice gliclazide*) + DPP4 inhibitor (1st choice sitagliptin**) OR
Metformin + Pioglitazone or Sulfonylurea (1st choice gliclazide*) + SGLT2 inhibitor*** OR
Metformin + Sulfonylurea (1st choice gliclazide*) + Pioglitazone
OR Insulin-based treatment (see box to the right)

If triple therapy not effective, not tolerated or contraindicated, consider combination therapy with GLP-1 agonist – only initiated by diabetes team and see additional information for NICE recommendation

Insulin-based treatment
Refer to diabetes specialist nurse for insulin initiation and regular review.
Human isophane (NPH) insulin (eg. Humulin I) is recommended as first line basal insulin in type 2 diabetes. Long acting insulin analogues (eg. Abasaglar, Lantus, Levemir) can be considered if patients meet criteria as per NICE.

*Repaglinide can be used if irregular meals or eGFR < 45ml/min/1.73m²
**Linagliptin can be used if renal function unstable or worsening; sitagliptin dose needs to be reduced in renal impairment
***SGLT2 inhibitors on formulary: canagliflozin, empagliflozin, dapagliflozin and ertugliflozin; DO NOT initiate SGLT2 inhibitors if eGFR < 60ml/min/1.73m² except canagliflozin (see additional information). SGLT2 inhibitors might be a suitable option if weight loss beneficial; evidence of CV/renal benefits for patients with established ASCVD, CKD or HF (benefit in HF only for ertugliflozin)

- Aim for HbA1c level of 53mmol/mol (7%) or individualised target

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Additional information – please refer to the Electronic Medicines Compendium (https://www.medicines.org.uk/emc) for full list of doses, cautions, contraindications and drug interactions

Metformin (biguanide)

- Standard release – 500mg daily with breakfast for 1 week, increased by 500mg every 1 to 2 weeks to a max dose of 1g twice daily with meals
- Modified release – 500mg once daily, increased every 10-15 days up to 2g once daily with evening meal. If control not achieved, use 1g twice daily with meals
- Use a max dose of 500mg twice a day if eGFR 30ml/min/1.73m² to 45ml/min/1.73m² and stop if eGFR < 30ml/min/1.73m²
- Monotherapy does not usually cause hypoglycaemia

Sulfonylureas (formulary choice – gliclazide) and Meglitinides (formulary choice – repaglinide)

- Gliclazide – 40-80mg daily with breakfast, can be increased if necessary up to a max dose of 320mg a day in divided doses
- Repaglinide – 500mcg within 30mins before main meals and increased if necessary up to a max dose of 16mg a day in divided doses; dose can be omitted if skipping a meal
- Sulfonylureas should be used with caution in elderly and moderate renal impairment, and avoided in severe renal impairment
- Repaglinide can be used in severe renal impairment with caution and in patients with erratic eating pattern
- Educate patients about risk of hypoglycaemia and treatment
- Self-monitoring of blood glucose is recommended for drivers, see DVLA website for details
- Avoid in pregnancy and breast-feeding

DPP4 inhibitors (formulary choices – sitagliptin and linagliptin)

- Sitagliptin – 100mg once daily, reduce dose to 50mg once daily if eGFR 30-45ml/min/1.73m² and to 25mg once daily if eGFR < 30ml/min/1.73m²
- Linagliptin can be considered in patients with renal impairment or worsening renal function, dose 5mg once daily
- Refer to MHRA advice for further details for risk of acute pancreatitis and counsel patients on the symptoms
- Low risk of hypoglycaemia
- Avoid in pregnancy and breast-feeding

Pioglitazone

- Initially 15-30mg once daily, can be increased to a max dose of 45mg once daily according to response
- Contraindications include hepatic impairment, history of heart failure, previous or active bladder cancer and uninvestigated macroscopic haematuria
- Use with caution in CVD or in combination with insulin (risk of heart failure), elderly, patients with increased risk of bone fractures or risk factors for bladder cancer
- Monitor liver function before treatment and periodically thereafter
- Refer to MHRA advice for further details for risk of cardiac failure and risk of bladder cancer
- Low risk of hypoglycaemia
- Avoid in pregnancy and breast-feeding

SGLT2 inhibitors (canagliflozin, empagliflozin, dapagliflozin and ertugliflozin)

- Canagliflozin – 100mg once daily preferably before breakfast, increased if tolerated to 300mg once daily if required; reduce dose to 100mg once daily if eGFR falls persistently < 60ml/min/1.73m². For treatment of diabetic kidney disease, 100mg once daily can be continued until dialysis or renal transplantation
- Empagliflozin – 10mg once daily, increased if tolerated to 25mg once daily if required; reduce dose to 10mg once daily if eGFR falls persistently < 60ml/min/1.73m²
- Dapagliflozin – 10mg once daily
- Ertugliflozin – 5mg once daily, increased if tolerated to 15mg once daily if required
- **DO NOT initiate if eGFR < 60ml/min/1.73m² and discontinue if eGFR persistently <45ml/min/1.73m² for empagliflozin, dapagliflozin and ertugliflozin**
- **DO NOT initiate canagliflozin if eGFR < 30ml/min/1.73m²**
- Monitor renal function before treatment, then at 6 to 8 weeks after initiation and then at least annually thereafter; increase monitoring frequency to at least 2 to 4 times per year if eGFR < 60ml/min/1.73m². Closer monitoring may be appropriate for patients on medications such as diuretics
- Counsel patients on common adverse effects such as genital infection and UTI, also symptoms of DKA which is rare
- Increased risk of volume depletion, especially if used with diuretics, counsel patients on sick day rules
- Refer to MHRA advice for further details for risk of DKA, increased risk of lower-limb amputation and Fournier's gangrene
- Low risk of hypoglycaemia
- Avoid in pregnancy and breast-feeding
- **See Appendix 1 checklist for initiation**

GLP-1 agonists (formulary choices – lixisenatide, liraglutide and dulaglutide)
These should be initiated by diabetes team

- Lixisenatide – 10mcg SC once a day for 14 days, then increased to 20mcg SC once a day, use within 1 hour before the first meal or the evening meal
- Liraglutide – 0.6mg SC once a day for at least 1 week, then increased to 1.2mg SC once a day for at least 1 week, then increased if necessary to 1.8mg SC once a day
- Dulaglutide – 1.5mg SC once weekly for add-on therapy
- Consider if BMI ≥ 35 kg/m² (adjusted for ethnicity accordingly) and specific psychological or other medical problems associated with obesity OR if BMI < 35 kg/m² and for whom insulin would have significant occupational implications or weight loss would benefit other significant obesity related comorbidities
- Only continue if there is a reduction of HbA1c by at least 11mmol/mol (1%) and a weight loss of at least 3% of initial body weight in 6 months
- Patients should be counselled on symptoms of acute pancreatitis
- Refer to MHRA advice for further details for reports of DKA when concomitant insulin was rapidly reduced or discontinued
- Risk of hypoglycaemia when used with sulfonylurea/repaglinide or insulin
- Remember to stop DDP4 inhibitors when GLP-1 agonists are initiated
- Avoid in pregnancy and breast-feeding

Drug profiles

Drug	Efficacy	CV benefit	Hypoglycaemic risk	Weight	Main adverse effects
Metformin	Moderate	Yes	Low	Reduction	Gastrointestinal
Sulfonylureas	High	No	High	Gain	Hypoglycaemia
DPP4 inhibitors	Low/moderate	No	Low	Neutral	Few
Pioglitazone	Moderate	Probable (but fluid retention)	Low	Gain	Oedema/fractures
SGLT2 inhibitors	Moderate	Yes (specific agents)	Low	Loss	Genital mycotic
GLP-1 agonists	High	Yes (specific agents)	Low	Loss	Gastrointestinal
Basal insulin	High	No	Highest	Gain	Hypoglycaemia

Adapted from Scottish Intercollegiate Guidelines Network SIGN guideline 154. Pharmacological management of glycaemic control in people with type 2 diabetes.

Abbreviations

ADA	American Diabetes Association
ASCVD	Atherosclerotic cardiovascular disease
CKD	Chronic kidney disease
CV	Cardiovascular disease
DKA	Diabetic ketoacidosis
DPP4	Dipeptidyl peptidase-4
EASD	European Association for the Study of Diabetes
GLP-1	Glucagon-like peptide 1
HF	Heart failure
SGLT2	Sodium glucose co-transporter 2

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Drug treatment - Renal and hepatic impairment

Drug	Renal function (eGFR ml/min/1.73m^2)					Hepatic impairment		
	CKD 1& 2 (≥ 60)	CKD 3a (45 - 59)	CKD 3b (30 - 44)	CKD 4 (15 – 29)	CKD 5 (< 15)	Mild	Moderate	Severe
Metformin	√	√	Max 500mg bd	x	x	Withdraw if tissue hypoxia likely		
Gliclazide	√	√	√	Use lowest effective dose	x	√	√	x
Repaglinide	√	√	√	Use with caution)	Use with caution	√	√	x
Sitagliptin	√	√	50mg od (if eGFR 30-45 ml/min/1.73m²)	25mg od	25mg od	√	√	Use with caution, not been studied
Linagliptin	√	√	√	√	√	√	√	√
Pioglitazone	√	√	√	√	√ (for CrCl>4ml/min) Avoid in dialysis	x	x	x
Canagliflozin	√	**Can initiate** (reduce dose to 100mg od if already on it)	**Can initiate** 100mg od	**Do not initiate** 100mg od if already on it until dialysis or renal transplantation	**Do not initiate** 100mg od if already on it until dialysis or renal transplantation	√	√	x
Empagliflozin	√	**Do not initiate** (reduce dose to 10mg od if already on it)	X (discontinue)	x	x	√	√	x
Dapagliflozin	√	**Do not initiate**	X (discontinue)	x	x	√	√	Start at 5mg od, increase to 10mg od if tolerated
Ertugliflozin	√	**Do not initiate**	X (discontinue)	x	x	√	√	x
Dulaglutide	√	√	√	√	x	√	√	√
Liraglutide	√	√	√	√	x	√	√	x
Lixisenatide	√	√	√	x	x	√	√	√
Insulin	√	√	√	Requirement may be reduced	Requirement may be reduced	Requirement may be reduced		

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NICE Patient Decision Aid https://www.nice.org.uk/guidance/ng28/resources/patient-decision-aid-pdf-2187281197

The Patient Decision Aid is available to help patients with type 2 diabetes make informed decision about taking a second agent for blood glucose control (ie. first intensification). It summarises information for patients to consider and discuss with their healthcare team:

- What new target HbA1c level is best for them, and
- Which medicines they might try to achieve this target

Your target blood glucose (HbA1c) level: weighing it up

Make a mark on the lines to show how you feel about these statements. The more you agree with the statement on the left, the further to the left you should put the mark. The more you agree with the statement on the right, the further to the right you should put the mark. You and your healthcare professional can use this to help decide the best target HbA1c level for you.

*Hypos might also be a problem for you for other reasons, such as if you operate machinery, if you are at risk of falling, or if you find it difficult to recognise the warning symptoms of a hypo.

NICE Patient Decision Aid for choice of therapy

Issue	How important is this to me?			
	Very important	Important	Unimportant	Very unimportant
Getting to a lower target blood glucose (HbA1c) level				
How many tablets I would have to take and how often				
The possibility of getting hypos				
The possibility of gaining weight				
The possibility of other side effects				
Other concerns or questions I want to discuss with my healthcare professional				

References

1. NICE guideline NG 28 – Type 2 diabetes in adults: management https://www.nice.org.uk/Guidance/NG28
2. MHRA Drug Safety Update https://www.gov.uk/drug-safety-update
3. eBNF May 2020
4. Electronic Medicines Compendium https://www.medicines.org.uk/emc
5. South East London Blood Glucose Control Management Pathway for Adults with Type 2 Diabetes Mellitus May 2017
6. North Central London Antihyperglycaemic Agents for Type 2 Diabetes August 2019
7. Scottish Intercollegiate Guidelines Network SIGN guideline 154 - Pharmacological management of glycaemic control in people with type 2 diabetes https://www.sign.ac.uk/assets/sign154.pdf
8. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) https://link.springer.com/content/pdf/10.1007/s00125-019-05039-w.pdf
9. Managing frailty and associated comorbidities in older adults with diabetes: Position Statement on behalf of the Association of British Clinical Diabetologists (ABCD) https://abcd.care/sites/abcd.care/files/site_uploads/Resources/Position-Papers/ABCD-Position-Paper-Frailty.pdf

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Appendix 1

Checklist for initiating SGLT2 inhibitors (canagliflozin, empagliflozin, dapagliflozin and ertugliflozin)

Contraindications:

- Type 1 diabetes (except dapagliflozin 5mg od, licensed for type 1 diabetes)
- Patients <18 years and ≥85 years
- Pregnancy and breast-feeding
- Empagliflozin, dapagliflozin and ertugliflozin - eGFR < 60ml/min/1.73m²**
- Canagliflozin – DO NOT initiate if eGFR < 30ml/min/1.73m² but can continue on 100mg once daily if already on it until dialysis or renal transplantation
- Severe hepatic impairment (except dapagliflozin, start at 5mg od)
- Previous DKA on SGLT2 inhibitors
- Lactose intolerance

Cautions:

- Risk of volume depletion, especially in elderly patients, review diuretics
- Risk of hypotension, especially in elderly patients, review anti-hypertensives
- Consider adjusting dose of sulfonylurea/repaglinide/insulin or seek specialist advice
- Complicated or recurrent UTI

DKA risk factors:

- Low beta cell function reserve (eg. low C-peptide levels, latent autoimmune diabetes in adults [LADA], or history of pancreatitis)
- Restricted food intake or severe dehydration
- Sudden reduction in insulin
- Increased insulin requirement due to acute illness
- Surgery
- Alcohol abuse

Seek specialist advice or consider alternative option if the patient is at risk of DKA.

****Only initiate empagliflozin, dapagliflozin and ertugliflozin if eGFR ≥60ml/min/1.73m² and discontinue if eGFR persistently <45ml/min/1.73m²**

Monitoring requirement:

- Check HbA1c, weight and BP before initiation
- Assess liver function before initiation
- Assess renal function before treatment, then at 6 to 8 weeks after initiation and then at least annually thereafter, increase monitoring frequency to 2 to 4 times per year if eGFR < 60ml/min/1.73m² or if on medications which may increase risk of renal impairment such as diuretics

Initial increases in creatinine and initial decreases in eGFR are generally transient during continuous treatment or reversible after discontinuation

Patient advice:

☐ SGLT2 inhibitors reduce blood glucose by preventing the kidneys from reabsorbing glucose back into the blood so excess glucose is passed out in the urine

☐ Risk of DKA and symptoms (vomiting, nausea, abdominal pain, a sweet smell to the breath, confusion, etc), and seek urgent medical help

☐ Sick day rules – stop drug temporarily during acute illness, vomiting and diarrhoea

☐ Common adverse reactions such as polyuria, genital infection and UTI; advise to use clotrimazole 1% cream (can be bought OTC) if symptoms of genital candida infection develop

☐ Importance of foot care and amputation prevention

☐ Risk of hypotension and volume depletion

☐ Increase fluid intake (at least 500ml/day) to compensate for increased urinary fluid loss and to avoid dehydration

☐ If Fournier's gangrene is suspected, stop the SGLT2 inhibitor and seek urgent medical help

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