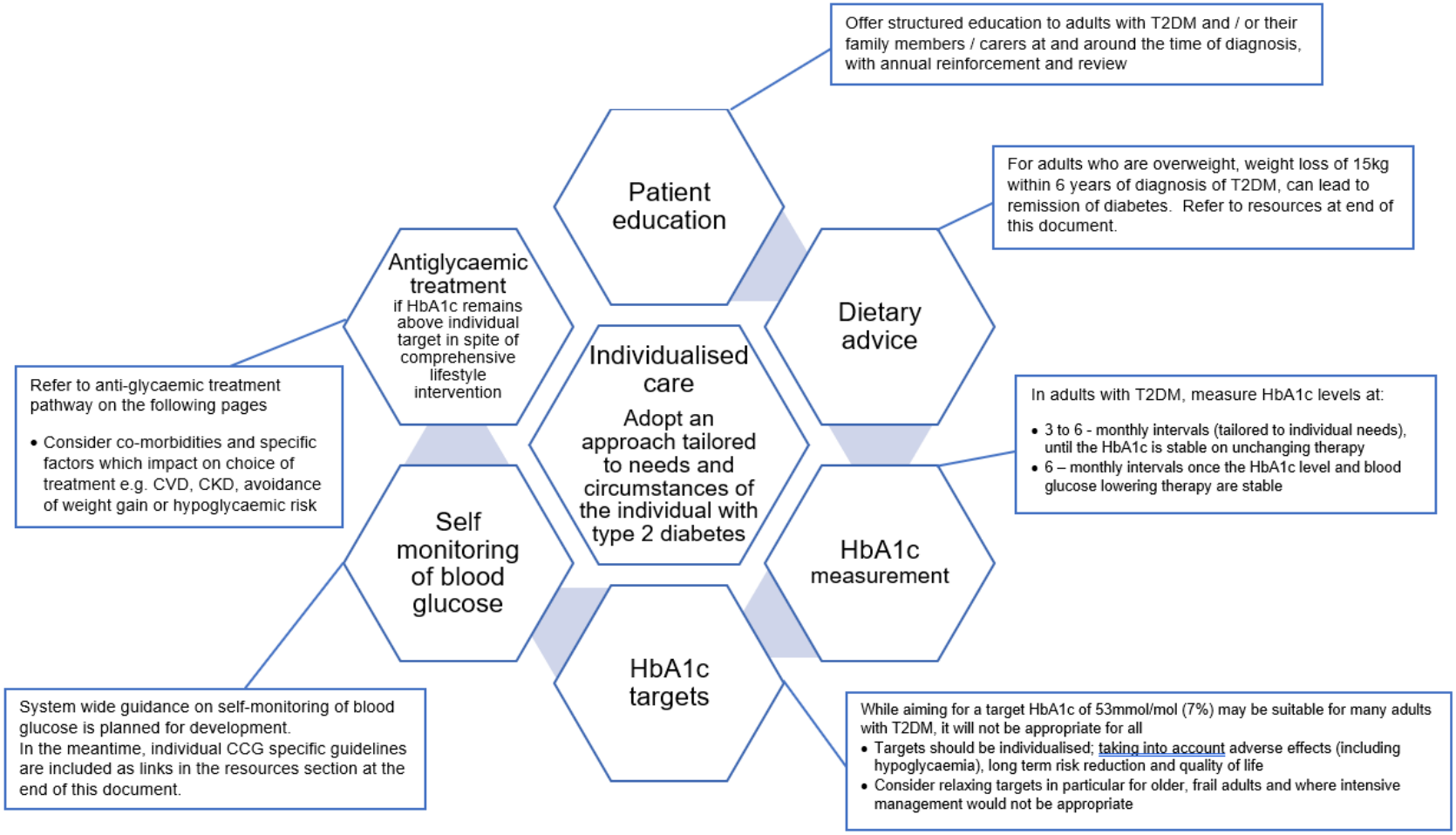
Mid and South Essex Health and Care Partnership

NHS

Type 2 Diabetes Mellitus – Anti-Hyperglycaemic Treatment Pathway

Adopt an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes. **Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective.**



This MSEMOC recommendation is based upon the evidence available at the time of publication. The recommendation will be reviewed upon request in the light of new evidence becoming available.

Antihyperglycaemic treatment options for adults with type 2 diabetes

Review HbA1c every 3-6 months. If not to target, reassess adherence, doses, lifestyle interventions and treatment effectiveness before each treatment intensification.

If an adult with type 2 diabetes is symptomatically hyperglycaemic at any stage of treatment, consider insulin or a sulfonylurea (AVOID SU in elderly or if need to avoid hypoglycaemia), and review/re-assess when blood glucose control has been achieved.

At diagnosis	**Intensive lifestyle intervention:** • Refer to validated structured education programme • Offer dietetic healthy eating advice including weight loss goal for those who are over-weight • Encourage physical activity

Monotherapy After 3/12 intensive lifestyle intervention HbA1c > individualised target	**Lifestyle / education + metformin** Initiate at 500mg OD (with breakfast) for 1 week, increase by 500mg daily per week to max 2g/day in 2-3 divided doses. **Patients unable to tolerate standard release despite slow titration and dosing with meals:** Metformin modified release (prescribed as locally recommended branded generic) Initially 500 mg once daily with evening meal, increased if necessary every 10-15 days up to max 2 g once daily. Alternatively increased to 1 g twice daily, with meals.	**If metformin is contraindicated / not tolerated:** • SGLT2i OR • DPP4i (e.g. alogliptin) OR • Pioglitazone OR • Sulphonylurea (gliclazide) • *GLP1 – reserved at this stage for patients with cardiovascular risk in whom SGLT2i is contraindicated and whom meet criteria in GLP1 box on page 3)* Refer to first intensification table below to guide most suitable choice of agent for individual patient.

First intensification HbA1c > individualised target Continue intensive lifestyle intervention + metformin (unless CI) *If any therapy option is not tolerated or ineffective, <u>stop and replace</u> with an alternative prior to 2nd intensification*	**Add ONE agent based on individual patient history (refer to page 7 for prescribing info)**	
	Patient with atherosclerotic cardiovascular disease (CVD) or heart failure (HF) or CKD[$] [$]At the time of writing, canagliflozin is the only SGLT2i licensed for initiation when eGFR is <60. Refer to SPC for dosing in renal impairment and any license changes.	Add an SGLT2i with strongest vascular outcome data: Dapagliflozin, empagliflozin or canagliflozin [Alternatively, GLP1 may be considered where SGLT2i is contraindicated AND in patients who meet the NICE BMI criteria (refer to GLP1 box on page 3)]
	Patient with no history of CVD / HF /CKD Consider other pt factors e.g. avoidance of hypo, weight neutral, degree of glycaemic reduction and refer to appendix 1 to guide choice.	• Pioglitazone (avoid in frail elderly) • DPP4i (alogliptin) (or linogliptin if impaired renal function as per appendix 1) • SGLT2i (ertugliflozin may be used for this cohort) • Sulphonylureas (gliclazide), avoid in frail, elderly

Key to abbreviations: SU = sulphonylurea; **SGLT2i** = sodium/glucose co-transporter-2 inhibitor; **DPP4i** = Dipeptidyl peptidase-4 inhibitor ('gliptins); **GLP1** = Glucagon-like peptide 1 analogue

Review HbA1c every 3-6 months. If not to target, reassess adherence, doses, lifestyle interventions and treatment effectiveness before treatment intensification.

If an adult with type 2 diabetes is symptomatically hyperglycaemic at any stage of treatment, consider insulin or a sulfonylurea (AVOID SU in elderly or if need to avoid hypoglycaemia), and review/re-assess when blood glucose control has been achieved.

Second intensification

HbA1c > individualised target.

Continue intensive lifestyle intervention + metformin (unless CI) + second agent (if effective but HbA1c remains above target)

If any therapy option is not tolerated or ineffective, stop and replace with an alternative prior to intensification

Add 3rd agent based on current therapy and individual patient factors (refer to page 7/8 for prescribing info)

Currently taking:	**Consider adding one of:** (refer to appendix 1 for consideration of patient factors) (*see additional prescribing information below)
DPP4i + metformin	Pioglitazone OR SGLT2i OR SU OR insulin*
SGLT2i + metformin	Pioglitazone OR DPP4i OR SU OR GLP1* OR insulin*
Pioglitazone + metformin	DPP4i OR SGLT2i OR SU OR GLP1* OR insulin*
SU + metformin	Pioglitazone OR DPP4i OR SGLT2i OR GLP1* or insulin*
Pioglitazone + SU	Metformin OR DPP4i OR SGLT2i OR GLP1* OR insulin*
SU + DPP4i	Metformin OR pioglitazone OR SGLT2i OR insulin*
Pioglitazone + DPP4i	Metformin OR SU OR SGLT2i OR insulin*

GLP1 receptor agonists

If indicated in the pathway above, consider use of a GLP-1 mimetic for adults with type 2 diabetes who additionally:

- have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
- have a BMI lower than 35 kg/m^2, and for whom insulin or alternative ant-glycaemic therapy options would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities
- **Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol [1.0%] and a weight loss of at least 3% of initial body weight in 6 months)**

Insulin-based treatment

If triple therapy is not effective, not tolerated or contraindicated and the patient does not meet NICE criteria for a GLP1, or where rapid glycaemic control is indicated

- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance
- Review the continued need for other blood glucose lowering therapies

Refer to Insulin Prescribing Information (Appendix 2) for further information.

Key to abbreviations:

SU = sulphonylurea; **SGLT2i** = sodium/glucose co-transporter-2 inhibitor; **DPP4i** = Dipeptidyl peptidase-4 inhibitor (‘gliptins); **GLP1** = Glucagon-like peptide 1 analogue

Appendix 1: Prescribing information – summary table (part 1)

DRUG CLASS	FORMULARY CHOICE	Glycaemic efficacy	CV benefit	Hypo risk	Weight	ADDITIONAL INFORMATION (including advice in CKD)
Biguanides	Metformin	Moderate	Yes	Low	Neutral / loss	• Start low dose, with gradual dose escalation, best taken with/after a meal/evening meal. • GI side effects often improve after a few days of continued therapy, or with a small dose reduction. • eGFR <45 ml/min/1.73 m^2: Doses should be lower than licensed maximum and prescribed with increased frequency of monitoring. • Discontinue if eGFR falls below 30 ml/min/1.73 m^2 • Modified release: reserved for those who suffer with persistent GI side effects only after gradual titration with standard release metformin (prescribe as locally agreed branded generic).
SUs	Gliclazide	High	No	High	Gain	• Holders of group 2 licenses (bus and lorry drivers) taking sulphonylureas must be able to provide evidence of checking blood glucose at least twice per day and at times relevant to driving. • Holders of group 1 licenses (car drivers and motorcyclists) taking sulphonylureas need not notify the DVLA provided they have experienced no more than one episode of severe hypoglycaemia in the last 12 months and, if needed, check blood glucose at times relevant to driving and are under regular review. • Safety in renal impairment varies by agent (based on duration of action and site of elimination) • Gliclazide: less than 5% renally eliminated. If eGFR <30, initiate at half dose (40mg OD) and titrate to target avoiding hypos • Avoid renally eliminated and longer acting SUs in renal impairment. E.g. glibenclamide
DPP-4i	Alogliptin Linagliptin	Low / moderate	No	Low	Neutral	• Recommended dose of alogliptin is 25mg once daily. -Dose reduction in moderate renal impairment (eGFR 30-50ml/min): 12.5 mg once daily. -Dose reduction in severe renal impairment (eGFR < 30 ml/min): 6.25 mg once daily. • *Consider linagliptin in patients with end stage/deteriorating renal function, or if trial of lower dose alogliptin in moderate/severe renal impairment does not achieve expected glycaemic reduction.*

DRUG CLASS	FORMULARY CHOICE	Glycaemic efficacy	CV benefit	Hypo risk	Weight	ADDITIONAL INFORMATION (including advice in CKD)
SGLT2i	Empagliflozin Dapagliflozin Canagliflozin Ertugliflozin[$]	Moderate	Yes [$]no data	Low	Loss	• In individuals with type 2 diabetes and established cardiovascular disease, SGLT2 inhibitors with proven cardiovascular benefit should be considered after and in addition to metformin. • Risk of diabetic ketoacidosis (DKA) and lower limb amputation. DKA may present atypically, with relatively normal glucose levels. MHRA guidance advises testing for raised ketone levels in people with symptoms of DKA, even if plasma glucose levels are near normal. • Small risk of developing a genital yeast or fungal infection (most commonly thrush in women) due to more glucose being excreted in the urine. • The mechanism of action of this class is dependent on renal function. Avoid initiation in eGFR <60, discontinue if eGFR <45 (with the exception of canagliflozin which may be initiated in patients with an eGFR >30 at a maximum dose of 100mg)
Thiazolidine dione	Pioglitazone	Moderate	Probable (but fluid retention)	Low	Gain	• When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. • Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. • Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. • No dose adjustment is required in renal impairment (CrCl >4mL/min), however, suggest caution in stage 4/5 renal impairment due to risk of renal bone disease. • Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated
GLP-1 AGONIST	Dulaglutide, Liraglutide, Semaglutide*	Moderate	Yes (semagl. / liragl./ dulagl.)	Low	Loss	• Injectable forms of GLP1-RA should be the first line choice where this class Is indicated, due to their better bioavailability and better vascular outcome data • * Oral semaglutide should only be used (i) after a trial of injectable forms has been considered/ attempted and (ii) for patients with established severe needle-phobia or marked limitations on manual dexterity AND (iii) pt has no access to support partners or carers. • When a GLP-1 receptor agonist is added to a sulphonylurea, a reduction in sulphonylurea dose should be considered. • People taking GLP-1 receptor agonists may hold a regular (Group 1) driving licence without restriction, but must notify the DVLA if they hold a Group 2 licence. • Dose reduction required in eGFR < 45, stop if eGFR <30 • Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol [1.0%] and a weight loss of at least 3% of initial body weight in 6 months)

Appendix 2: Insulin Prescribing information

If triple therapy is not effective, not tolerated or contraindicated and the patient does not meet NICE criteria for a GLP1, or where rapid glycaemic control is indicated

- When starting insulin, use a structured education programme and continue metformin for people without contraindications or intolerance
- Review the continued need for other blood glucose lowering therapies
- Specialist advice or referral is available for insulin selection/initiation
- First line choice in T2DM is NPH insulin once or twice daily according to need.
- Consider starting both NPH and short-acting insulin either separately or as pre-mixed (biphasic) human insulin (particularly if HbA1c is 75 mmol/mol (9.0%) or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargine if the person:
    - needs assistance to inject insulin,
    - lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or
    - would otherwise need twice-daily NPH insulin in combination with oral blood glucose lowering drugs.
- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short- acting human insulin preparations, if:
    - the person prefers injecting insulin immediately before a meal,
    - hypoglycaemia is a problem or
    - blood glucose levels rise markedly after meals
- If initiating new patients on insulin glargine, biosimilar insulin is preferred local choice, prescribed by brand
- Insulin brands are linked with specific devices in which the patient will have been trained and there are now several biosimilar insulins available. To avoid confusion and reduce the risk of prescribing/dispensing errors, insulins should always be prescribed by brand.

Appendix 3: Resources and links:

Dietary advice:
The NHS (and Diabetes UK) recommend a healthy, balanced diet that is low in fat, sugar and salt and contain a high level of fresh fruit and vegetables.
NHS Eating a balanced diet: https://www.nhs.uk/live-well/eat-well/
NHS 9 tips for healthy eating: https://www.nhs.uk/live-well/eat-well/eight-tips-for-healthy-eating/
Diabetes UK NHS Diet Advice for Diabetes: https://www.diabetes.co.uk/diet/nhs-diet-advice.html
Freshwell Low Carb Project: https://lowcarbfreshwell.co.uk/
Freshwell Time restricted eating: https://lowcarbfreshwell.co.uk/time-restricted-eating/

As with all aspects of diabetes care, dietary advice should be individualised to a person's individual risk factors and lifestyle. The most successful weight loss is likely to be with a diet that they can stick to!

Self-monitoring of blood glucose:
A system wide guidance on self-monitoring of blood glucose is planned for development; in the meantime, individual CCGs currently have specific guidance on this available through the following links:

For Basildon & Brentwood and Thurrock CCGs: https://thurrockccg.nhs.uk/about-us/document-library/medicines-management/formulary-and-prescribing-guidelines/chapter-06-endocrine-system/4131-guidelines-for-self-monitoring-of-blood-glucose-in-adults-and-children-april-2020/file

For Mid Essex CCG: https://midessexccg.nhs.uk/medicines-optimisation/clinical-pathways-and-medication-guidelines/chapter-6-endocrine-system-2/1605-diabetes-blood-glucose-meters-test-strips-lancets-guidelines-nov-19/file

For Southend and Castle Point and Rochford CCGs: https://southendccg.nhs.uk/your-health-services/healthcare-professionals/medicines-management/bnf-chapter-6-endocrine/endocrine-diabetes/2449-blood-glucose-test-strips-quick-reference-guide/file

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	• NICE Evidence reviews for SGLT" inhibitors and GLP1 mimetics 2018 https://www.nice.org.uk/guidance/ng28/evidence/march-2018-evidence-reviews-for-sglt2-inhibitors-and-glp1-mimetics-pdf-4783687597 • Zhang X-L, Zhu Q-Q, Chen Y-H, et al. Cardiovascular safety, long-term non-cardiovascular safety, and efficacy of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus: a systemic review and meta-analysis with trial sequential analysis. J Am Heart Assoc 2018;7:e007165 • Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128 • Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–657 • Storgaard H, Gluud LL, Bennett C, et al. Benefits and harms of sodium-glucose co-transporter 2 inhibitors in patients with type 2 diabetes: a systematic review and meta-analysis. PLoS One 2016;11:e0166125 • Summary of Product Characteristics – Invokana (canagliflozin). Napp Pharmaceuticals Ltd. Accessed via https://www.medicines.org.uk/emc/medicine/28400 on 02/07/21 [date of revision 06 Jul 2020]. • Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128 • Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–657 • Esposito K, Chiodini P, Maiorino MI, Bellastella G, Capuano A, Giugliano D. Glycaemic durability with dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a systematic review and meta-analysis of long-term randomised controlled trials. BMJ Open 2014;4:e005442 • Wiviott SD, Raz I, Bonaca MP et al. "Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes" N Engl J Med 2019; 380: 347-357
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