Coventry and Warwickshire APC Type 2 Diabetes Algorithm for Glucose-lowering Treatment in Adults

(excluding patients who are pregnant)

Coventry & Warwickshire Area Prescribing Committee

Clinical Guideline

New diagnosis

Lifestyle optimisation: Offer patient education. If relevant: diet, activity advice. Weight loss can lead to remission if overweight.
Agree individualised target HbA1c.
Comprehensive CVD risk reduction must be a major focus of therapy including BP and lipid management, smoking cessation, limit alcohol intake.

Offer DESMOND + **Offer** IAPT

Metformin 500mg once daily, increasing gradually to 1g bd.
Allow at least one week between dose increases, advise patients that GI effects are usually transient.
If persistent GI side effects, offer metformin MR. If higher doses not tolerated, reduce to last tolerated dose.

Very high HbA1c at diagnosis (>85mmol/mol) and/or osmotic symptoms, consider adding short-term sulfonylurea.
Or
Consider early insulin: if significant symptoms, weight loss, hyperglycaemia > 13 -15 mmol/L or blood ketones > 0.6 mmol/L
See Appendix 1 - insulin

At every review reinforce lifestyle advice and check medication adherence.
Consider referral to diabetes specialist dietitian. Community pharmacy NMS can support adherence.

Subsequent additions to therapy should be individualised, taking into account patient preference, co-morbidities, CV risk, recent weight change, frailty, HbA1c, employment, driving, eGFR and medication adverse effect profile.
Additional treatment should be added in a stepwise manner if HbA1c remains above 53 mmol/L (or individualised target), except in patients with CVD/high CV risk/CKD where early addition of SGLT2i may be indicated.

Evidence-based choices (see BNF, SPC and notes below for prescribing info.)

ASCVD*	Heart Failure**	CKD	High CV Risk#	Frail/ Elderly	Obesity
Irrespective of HbA1c, consider adding:				If HbA1c remains above 53 (or individualised target) add:	
SGLT2i Empagliflozin 10-25mg od	**SGLT2i** Dapagliflozin10mg od	**SGLT2i** Canagliflozin 100mg od† Glycaemic effect reduced.	**SGLT2i** Canagliflozin 100-300mg od Dapagliflozin 10mg od Empagliflozin 10-25mg od	**DPP4i** Alogliptin 6.25-25mg od, depending on CrCl	**GLP1-RA**^ Semaglutide 0.5-1mg ow sc Liraglutide 1.2mg od sc Dulaglutide 1.5-4.5mg ow sc Or **SGLT2i** Choice based on CV risk
If HbA1c remains above 53 (or individualised target) add:					If HbA1c above target, add SGLT2i to GLP1-RA/ GLP1-RA to SGLT2i
GLP1-RA^ Semaglutide 0.5-1mg ow sc Dulaglutide 1.5-4.5mg ow sc Liraglutide 1.2mg od sc	**GLP1-RA**^ Semaglutide 0.5-1mg ow sc Liraglutide 1.2mg od sc	**GLP1-RA**^ Semaglutide 0.5-1mg ow sc Dulaglutide 1.5-4.5mg ow sc Liraglutide 1.2mg od sc	**GLP1-RA**^ Dulaglutide 1.5-4.5mg ow sc Semaglutide 0.5-1mg ow sc		
If HbA1c remains above 53 (or individualised target) consider other options					
Avoid	Pioglitazone, saxagliptin	Caution with SUs		SGLT2i, GLP1-RA. Caution with SUs	Sulfonylureas, pioglitazone

Review therapy and lifestyle every 3-6 months until stable control achieved

Other options:

Sulfonylurea: (gliclazide, glimepiride) if rapid glucose lowering needed and hypos are not a concern

Pioglitazone: can improve lipids, useful for insulin resistance if no C/Is

Repaglinide: can be useful in shift workers/ irregular meal patterns

Insulin: see Appendix 1

Consider referral to Specialist

od once daily, ow once weekly, sc subcutaneous, CrCl creatinine clearance, SU sulfonylurea, C/I contraindication

^*Maintenance dose range shown; for initiation doses/dose titration information see individual SPCs*

*Patients with a diagnosis of atherosclerotic cardiovascular disease ** Particularly heart failure with reduced ejection fraction <45% †eGFR 45-60 mL/min/1.73m^2 or 30-44 and uACR >300mg/g; **do not initiate if eGFR<30**

#Patients with LVH or retinopathy, or patients with diabetes for more than 10 years with one or more cardiovascular risk factor (age, smoking, hyperlipidaemia, obesity)

Lifestyle advice:

- **Stress lifestyle measures at every clinical review and at each stage of intensification of therapies**
- Increasing physical activity, and optimising weight and diet, especially with specialist dietetic support, can reduce HbA1c by up to 22 mmol/mol.[1]
- Dietary advice specific to diabetes should be offered regularly. The leaflets 'Diabetes: How to Take Control' and 'Eating well with Diabetes' are available to print from Coventry GP gateway.
- Offer links to PocketMedic information videos.
- Consider referral to diabetes specialist dietitian.
- Consider referral to IAPT to support behaviour change. The IAPT leaflet 'Living Well with Diabetes' is available on GP gateway.

Target HbA1c:

- In general aim for HbA1c of 48 mmol/mol for patients managed on diet/metformin alone, 53 mmol/mol if on two or more medicines or on a medicine which can cause hypoglycaemia.[2]
- Consider relaxing HbA1c targets in *older people* depending on their functional status & comorbidities[1,2,4,5], *e.g.*
    - Independent/ healthy: HbA1c 53-59 mmol/mol
    - Functionally dependent: 53 – 64 mmol/mol, up to 70 mmol/mol in those with multiple comorbidities and severe frailty/dementia
- In frail elderly at risk of malnutrition and sarcopenia, consider effects of medication on weight; avoid SGLT2s and GLP-1s for this reason. Strict dietary restrictions should be avoided.[5]
- Consider higher target HbA1c in those who drive or operate machinery, those at risk of falls, or patients who have impaired awareness of hypoglycaemia. [1,2]
- Exercise caution with insulin use in the above-mentioned groups of people as it can increase risk of hypoglycaemia and offsets any benefits of improved glycaemic control.
- Consider reducing doses or deprescribing sulfonylureas/insulin in patients experiencing recurrent hypoglycaemia, particularly if HbA1c is below target.

Remission of diabetes

Remission of diabetes is possible through diet and lifestyle changes, as demonstrated in the DiRECT trial. In the first 12 months, there was a remission rate of 86% in those that lost 15kg of weight or more and 57% in those that lost 10-15 kg of weight.[6]

Patients achieving an HBA1c below 48 without any medication for at least 6 months can be described as having diabetes in remission[7] and coded as such, but annual reviews, including foot checks and retinal screening, should continue.

Sick day rules

It is important that patients with diabetes know what to do with their medicines when unwell.

During an acute dehydrating illness, patients should be advised to stop the SADMAN drugs, and restart once they have been eating and drinking normally for 24-48 hours[8]:

S	A	D	M	A	N
SGLT2 inhibitors (risk of DKA)	ACE inhibitors (risk of AKI)	Diuretics (risk of AKI)	Metformin (risk of lactic acidosis)	ARBs (risk of AKI)	NSAIDs (risk of AKI)

Consideration should also be given to stopping **GLP1-RAs** temporarily as the GI effects may increase risk of dehydration and AKI. This is especially in those with vomiting, diarrhoea and reduced food and fluid intake.

Patients should usually continue all other diabetes medicines, including insulin (dosage may need to be adjusted up or down). Increase blood glucose monitoring for those who use this. Advise the patient to maintain regular fluid intake and have small high carbohydrate snacks if unable to eat meals.

A useful summary for clinicians is available from the PCDS here.[8]

TREND diabetes have a patient information leaflet available here. There is also information available on the Diabetes UK site in English and in different languages.

Blood Glucose Self-Monitoring : see APC RD003 for guidance

Driving: DVLA guidance for patients with diabetes should be explained to patients. The DVLA has produced several guides for patients, available here.

Notes on medication classes: (see also SPCs and BNF monograph for individual medicines)

The community pharmacy **New Medicines Service** can support patients when starting a new glucose-lowering medicine. The pharmacist can provide the patient with information about their new medicine and follow them up at 2 and 4 weeks after initiation to answer any further questions and identify any issues. Suitable patients can be highlighted to the pharmacy via a note on the prescription.

Metformin

Used in most cases at or within days of diagnosis of Type 2 Diabetes. Ensure that glucose levels are < 13 mmol/l and there is no evidence of elevated blood ketones. *Insulin must be used at diagnosis for all Type 1 patients.*

To reduce incidence of GI side effects, use low dose of Metformin initially - 500mg OD - then increase gradually to 1g BD or 850mg TDS over several weeks.[2] Take with main meals to reduce side effects. Consider Metformin SR if poorly tolerability[2] – either as single daily dose of 2g or as 1g bd. Use highest tolerated dose (maximum 2g SR daily). 500mg od is still beneficial.
Metformin combination products may be helpful for patients who have been stabilised on the individual components, particularly if high tablet burden or adherence issues.
Metformin has been linked to B12 deficiency, B12 levels should be tested if symptoms of neuropathy develop/worsen, but annual B12 testing is not necessary.[9]

HbA1c efficacy	Weight	Hypos	Lipids	CV Safety	CKD	Renal benefit
Moderate[3]	Neutral/loss[3]	Low risk[3]	Improved[11]	Likely benefit[1,3,10]	Max 1g daily if GFR < 45, STOP if GFR < 30.[2]	No

SGLT2 inhibitors

Empagliflozin may be preferentially used in people with established ASCVD[12]; dapagliflozin and canagliflozin have evidence of benefit in high CV risk patients.[13,14] Canagliflozin is licensed in CKD at low dose – see notes below.[15] Dapagliflozin has evidence of benefit in CKD but is not yet licensed for this.[16]

Dapagliflozin is licensed for treatment of symptomatic heart failure with reduced ejection fraction in patients with or without diabetes.[17] Empagliflozin also has evidence of benefit in HF.[18]
In low CV risk patients, ertugliflozin is a cost-effective choice.
An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with canagliflozin. [13,15] It is unknown whether this constitutes a class effect. Caution is advised for all drugs in this class. As for all patients with diabetes, it is important to counsel patients on routine preventative foot-care.
Advise patients on the risks/signs of DKA.[20] Sick day rules should be explained (see above). Patients should ensure they maintain adequate hydration.
Counsel patients on risk of UTI/ genital infections, and also potential risks/signs of Fournier's gangrene.

- SGLT2 inhibitors should not be initiated in patients with eGFR<60ml/min, apart from canagliflozin which can be initiated down to eGFR 45 at low dose (eGFR 30 if ACR>300mg/g).[15,17,21]
- SGLT2 inhibitors other than canagliflozin should be discontinued if eGFR falls below 45ml/min.[17, 21]
- SGLT2 inhibitors may cause a small drop in eGFR on initiation but in the long term reduce decline in eGFR.[22]

Caution in combination with loop diuretics due to risk of volume depletion – diuretic dose may need to be reduced.
Avoid in patients at high risk of dehydration e.g. elderly, binge alcohol drinking. Avoid in ketogenic diets.

HbA1c efficacy	Weight	Hypos	Lipids	CV Safety	CKD	Renal benefit
Moderate[3]	Loss[3]	Low risk[3]	Increase HDL, LDL-C[11]	Proven benefit[10]– see notes above.	See notes above	Yes[1]

GLP1 receptor agonists (sc)

Semaglutide, Dulaglutide and Liraglutide have positive outcomes in established ASCVD.[1] Dulaglutide has best evidence in patients with high CV risk.[23] Once weekly GLP1-RA can be very convenient for many patients especially those in the 'care' environment.

If one GLP1-RA is not tolerated or there is suboptimal response, an alternative GLP1-RA can be tried.[24] Treatment with GLP1-RAs has been shown to be more effective when combined with specialist dietitian advice.[25] The weight loss benefits of a GLP1-RA may be enhanced if the patient is aware of the expected reduction in appetite, and proactively aims to reduce their food intake. Advise patients to stop eating when they feel full, which may be after a smaller portion than they are used to eating. Adverse effects such as nausea are more likely if this is ignored. Smaller meals with lower fat content may help reduce GI side effects, which will usually settle with continued use.[26] Patients should ensure they maintain adequate hydration.

GLP1 receptor agonists (po): Oral semaglutide is only fully effective if patients are able to follow the very specific administration instructions (swallow whole on an empty stomach with a sip of water only - max 120ml).[27] It is designated as 'Specialist Advised' by the APC and should only be used by patients with a contraindication to injectable therapy or needle phobia.[28]

Warn patients of the risks/ signs of pancreatitis. Avoid in patients with a history of/risk factors for pancreatitis.
If a patient is prescribed a DPP4, stop this when initiating a GLP1-RA – there is no additional benefit.

Caution – semaglutide may worsen pre-existing retinopathy; additional monitoring may be needed

HbA1c efficacy	Weight	Hypos	Lipids	CV Safety	CKD	Renal benefit
High[3]	Loss[3]	Low risk[3]	Improved[11]	Proven benefit[10] - see notes above	Avoid in ESRD	Yes[1]

DPP4 inhibitors

Alogliptin is the cost-effective formulary choice, dosage must be adjusted according to CrCl.
If renal function unstable use linagliptin (no dosage adjustment needed).
May be beneficial in combination with basal insulin to improve post-prandial sugars. Warn patients of the risks/ signs of pancreatitis.
Consider deprescribing if no significant response after 3-6 months or if patient would benefit from change to alternative glucose-lowering medicine with proven cardiovascular benefit.
Do not use in combination with GLP1-RA – no additional benefit.

HbA1c efficacy	Weight	Hypos	Lipids	CV Safety	CKD	Renal benefit
Low/moderate[3]	Neutral[3]	Low risk[3]	Improved TGs, alogliptin may reduce LDL-C[11]	No benefit shown.[3,10] Avoid saxagliptin in heart failure.[1,10]	Adjust dosage as per SPC.	No

Sulfonylureas

Use low dose initially (*e.g.* Gliclazide 40mg OD or BD and titrate it up to 80 mg BD if needed to maximum 160mg BD).
Gliclazide MR useful if adherence an issue but must have regular food intake (max dose 120mg OD – 30mg MR is equivalent to 80mg standard tablets).
If patient is obese and actively trying to lose weight, consider other options – patients may need to eat more to maintain blood glucose levels when on sulfonylureas.
DVLA guidance must be followed.
Stop or reduce dose if initiating insulin.
Taking sulfonylureas up to 30 minutes before a meal may be beneficial so that peak effect is achieved post-prandially. However, for some patients it may be safer to take with the meal.
Risk of hypoglycaemia is greater when there could be a disconnect between dosing and mealtimes (e.g. in care homes, hospital settings). Care is also needed when added to monitored dosage systems, for the same reason. If prescribed twice a day, ensure the second dose is not taken at bedtime.

HbA1c efficacy	Weight	Hypos	Lipids	CV Safety	CKD	Renal benefit
High[3]	Gain[3]	High risk[3]	Small improvement in TGs[11]	Caution in intensive control[10]	Caution – increased risk of hypoglycaemia	No

Pioglitazone

Of most benefit for initial 5 years or so after diagnosis, beneficial in fatty liver disease.
Discontinue if no significant response after 3-6 months treatment.
Monitor for and counsel on early signs of potential adverse effects: heart failure (check cardiac status at each review and consider BNP), bladder cancer (dysuria, haematuria) and liver toxicity (vomiting, abdominal pain). Contraindicated in any patients diagnosed with these conditions.
Caution in elderly, post-menopausal women, osteoporosis due to increased risk of fractures.

HbA1c efficacy	Weight	Hypos	Lipids	CV Safety	CKD	Renal benefit
Moderate[3]	Gain[3]	Low risk[3]	Improved HDL-C & TGs[11]	Can cause oedema, heart failure. May have some benefit in ASCVD[10]	No dosage adjustment needed	No

Repaglinide

is only licensed as monotherapy or in combination with metformin. Take within 30 minutes before main meals.
DVLA guidance must be followed.

HbA1c efficacy	Weight	Hypos	Lipids	CV Safety	CKD	Renal benefit
Moderate[29]	Gain	High risk	Unknown	Unknown	Caution – increased risk of hypoglycaemia	No

Referral for specialist care:

Consider referral to specialist clinic in the following situations:

- Patients with significant complications of diabetes – nephropathy, retinopathy, foot problems, autonomic neuropathy
- Patients with complex hyperlipidaemia
- Patients with poor glycaemic control despite 3 or more glucose-lowering therapies
- For help with initiation or adjustment of insulin
- Patients experiencing significant hypoglycaemia or hypoglycaemia unawareness
- Patients planning a pregnancy
- Patients where diagnosis is unclear – e.g. suspected LADA, MODY

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APPENDIX 1: Insulin

The ADA has a useful algorithm for insulin in Type 2 Diabetes, which can be found here.

When to consider insulin:

- **At diagnosis if Type 1 diabetes suspected**: marked polyuria, polydipsia, weight loss, thrush. Especially if glucose > 14 mmol/l and ketones > 1.5 mmol/l.
- **For rapid glucose control where initial suspicion Type 2 diabetes but significant hyperglycaemia (>13-15) and osmotic symptoms or poor response to initial treatment:** Useful to use glucose monitoring in patient with glucose levels > 14 mmol/l at diagnosis that do not respond to the immediate diet measures (no sugar, lower carbs). Once sugars controlled, review and consider oral agents with diet, weight control and physical activity.
- **Inadequate response to non-insulin therapies:** if poor response to any intensification stage consider insulin.

Safe Insulin prescribing and monitoring:

The RCN have produced guidance on initiating injectable therapies in primary care, available here.

- Ensure that the HCP is adequately trained in safe insulin prescribing, dose calculation and adjustment, glucose monitoring, driving safety and employment issues.
- Check understanding and ability to carry out blood glucose monitoring.
- Consider dexterity when choosing injection devices.
- Explain dosage and timing, particularly with regards to meals. Explain any changes needed to other medicines.
- Discuss storage of insulin and expiry dates.
- Explain device assembly, air shot and demonstrate good injection technique (guidance and supporting materials available on the Trend Diabetes: Injection Technique Matters website, including videos for patients).
- Provide education on safe sharps disposal. Information on prescribing and disposal of sharps can be found on Coventry GP Gateway here.
- Counsel patient on the signs and symptoms of hypoglycaemia and how to treat a hypo.
- Discuss driving regulations.
- Provide insulin passport or safety card and contact numbers for support.

NHS Diabetes has an insulin safety leaflet available here, and TREND also have a leaflet on 'Keeping Safe with Insulin Therapy', available here.

Regimes to consider: (prescribe insulin by brand to reduce risk of errors)

- **Basal insulin**: Isophane nocte as first choice (NICE). If nocturnal hypoglycaemia or high-risk consequences (e.g. lives alone) then consider long acting analogue *e.g.* glargine (as Semglee®) or detemir (Levemir®). Tresiba® (insulin degludec) is recommended only if advised by a specialist.[30] Toujeo® (glargine 300 units/ml) useful if erratic control, nocturnal hypoglycaemia or those requiring high dose insulin.
  Initial dose 10 units or 0.2 units per kg nocte. Titrate upwards 2 units or 10% dose every 2-3 days until target sugars achieved. Once basal dose >0.5 units per kg, consider adding prandial insulin:

- **Basal plus**: consider adding a single bolus (4 units or 10% basal dose) of quick acting insulin with main meal of the day - usually the evening meal if blood glucose levels before meals are within target range but HbA1c is still above target (4 units or 10% basal dose).

- **Biphasic Pre-mix Insulins**: consider in patients with "stable lifestyles". Convert to same total daily units but may need adjustment. Use two thirds of the total daily dose at breakfast and the remaining third with evening meal.
- **Basal-bolus regime**: Typical regime: 50% of total daily dose of insulin as basal insulin; the remaining 50% dose divided equally in 3 doses and each dose given before main meals (breakfast, lunch and evening meal).