

Treatment algorithm for glucose-lowering agents in adults with Type 2 diabetes *(Endorsed by ARDEN consultant group)*

Coventry & Warwickshire Area Prescribing Committee

Clinical Guideline – CG014

Lifestyle optimisation: Patient education, diet, weight loss, increase activity/exercise*

Comprehensive CVD risk reduction must be a major focus of therapy including BP and lipid management, smoking cessation, alcohol intake within safe limit^{1,2,3}

Consider individualising the target HbA_{1c} on a case-by-case basis.†

• Aim for HbA_{1c} <53 mmol/mol in younger patients • Consider relaxing HbA_{1c} targets in frail / elderly people† and in specific groups†

See guidance on blood glucose self-monitoring in the notes ‡

Please see associate document on page 4/5 - "Treatment Options - Cost and Clinical Comparisons" for individual drug cost / clinical efficacy and safety information.
NICE recommends lowest acquisition cost treatment for each class²

Please consult APC Net formulary for local formulary and specialist drug choices/positioning

Offer Metformin (MET)^a 500mg OD/BD initially

MET^a contraindicated

SU^{b,c}/DDP^d/PIO^f/#SGLT^e

Optimise MET therapy^a

Intolerant to MET^a

Metformin SR 500mg > 1g >2g

First intensification

If HbA_{1c} is still > 53 mmol/mol, consider dual therapy

The therapy options are Sulfonylurea (SU)^{b,c}, DPP-4 inhibitors (DPP)^d, SGLT2 inhibitors (SGLT)^e, Pioglitazone (PIO)^f & GLP-1^g
Consider individualising therapy based on individual circumstances, recent change in weight, HbA_{1c}, employment, driving and eGFR. †
The following algorithm based on body mass index (BMI) provides an example.

Initial suspicion Type 2 diabetes but significant hyperglycaemia and poor response to diet, consider low dose gliclazide on temporary basis for rapid glucose lowering and then review the treatment (Refer to insulin notes in the Appendix)

Consider early insulin: if significant symptoms, weight loss, hyperglycaemia > 13 -15 or blood ketones > 0.6. (Refer to insulin notes, Appendix)

Seek specialist advice when necessary

Non-obese
(BMI <25, SA <23)

Overweight
(BMI = 25-30, SA= 23-27.5)

Obese
(BMI > 30, SA >27.5)

MET + DDP^d

alternatives are
MET + SU^{b,c}
MET + PIO^f

MET + DPP^d

alternatives are
MET + SGLT^e
MET + low dose SU^{b,c}

MET + SGLT^e

alternatives are
MET + DPP^d

Second intensification

If HbA_{1c} is still > 53 mmol/mol, consider triple therapy

Consider early insulin if: significant symptoms, weight loss, hyperglycaemia > 13 -15 or blood ketones > 0.6.
Seek specialist advice when necessary.

MET + DPP^d + SGLT^e

alternatives are
MET + DPP^d + SU^{b,c}
MET + SGLT^e + SU^{b,c}
MET + SU^{b,c} + PIO^f
MET + SGLT^e + PIO^f

MET + DPP^d + SGLT^e

alternatives are
MET + DPP^d + low dose SU^{b,c}
MET + SGLT^e + low dose SU^{b,c}

MET + SGLT^e + DPP^d

If triple therapy fails and HbA_{1c} >58

MET + SGLT^e + GLP1^g (Refer to specialist dietician** before starting GLP1)

Alternative are MET + low dose SU^{b,c} + GLP1^g

If triple therapy fails and HbA_{1c} >58

Consider insulin therapy after carefully taking into account the balance of benefits versus harm from insulin†, Refer to specialist dietician** before initiation of insulin

Third intensification

Continue MET, review need for other HbA_{1c} lowering agents and start insulin (see Appendix)

In those reluctant to start insulin, consider adding SU^{b,c} or PIO^f to triple therapy (if not tried before). Also consider PIO^f in those with significant insulin resistance. **Seek specialist advice when necessary.**

*** Lifestyle advice:**

- **Stress lifestyle measures at every clinical review and at each stage of intensification of therapies**
 - Increasing physical activity, optimising weight and diet can reduce HbA1c by 11-22 mmol/mol (1-2%)
 - Refer to **DESMOND** when newly diagnosed. In Coventry and Rugby, refer to REFRESH if known diabetes > 1 year duration
- Specialist dietary advice should be offered regularly during the course of the treatment. The sheets 'Diabetes, Taking Control' and 'Healthy Eating in Diabetes' are available to print from the Coventry GP gateway

****In Coventry & Rugby CCG area specialist diabetes dietitians are available as a part of specialist community diabetes service**

† Target HbA1c:

- Use the Inzucchi Diagram and the Table given on page 3 as a guide to individualize HbA1c targets and other clinical goals
- Consider relaxing HbA1c targets in *older people* depending on their functional status & comorbidities^{1,2,3}, e.g.
 - Independent /Healthy: HbA1c 7-7.5% (53-58 mmol/mol)
 - Functionally dependent/frail/ dementia/moderate comorbidities: 7.5 - 8.5% (58 – 69 mmol/mol) upto 9% (75 mmol/mol) in those with multiple comorbidities and severe frailty/dementia
 - End of Life: glycaemic target is to avoid symptomatic hyperglycaemia

(A Box on page 3 shows likely benefits of reducing HbA1c by 1% (11mmol/mol) in a hypothetical case of 86 year old man with diabetes and dementia and baseline HbA1c of 8.5% (69 mmol/mol)
- Consider relaxing HbA1c targets in people in whom tight control poses a high risk of the consequences for hypos, e.g. people who are at risk of falling, people with impaired awareness of hypos, & those who drive or operate machinery.^{1,2,3}
- Exercise caution with insulin use in the above-mentioned groups of people as it can increase risk of hypos and offsets any benefits of improved glycaemic control.⁴

‡ Blood Glucose Self-Monitoring^{1,2} : Do not routinely offer blood glucose self monitoring unless;

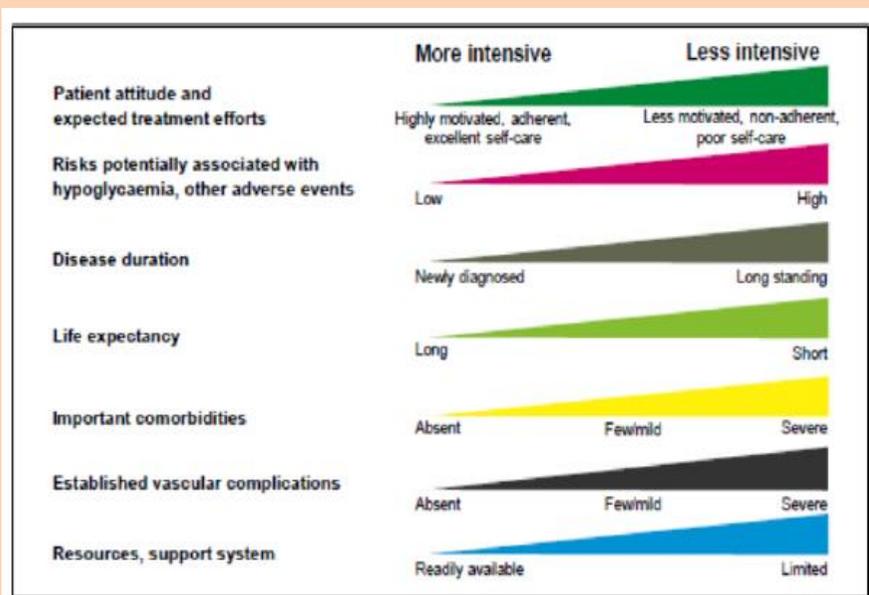
- The person is on insulin **OR**
- There is evidence of hypos **OR**
- The person is on oral medication (e.g. sulphonylureas or glinides) that may increase the risk of hypos while driving or operating machinery **OR**
- The person is pregnant or planning to become pregnant

Notes

- a) **Metformin:** Used in most cases at or within days of diagnosis. 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.* Use lower dose of Metformin initially - 500mg BD-TDS, then increase to 1g BD or 850mg TDS or maximum 1g TDS. Consider Metformin SR if poor tolerability. Use highest tolerated dose. Reduce Metformin dose if GFR < 45 and stop it if GFR < 30.²
- b) **Gliclazide:** Use low dose initially e.g. 40mg OD or BD and titrate it up to 80 mg BD if needed to maximum 160mg BD. Gliclazide MR useful if concordance an issue (max 120mg OD). DVLA guidance must be followed, monitoring in most cases.
- c) **Repaglinide:** can be useful in shift workers, irregular meal patterns e.g. shift workers.
- d) **DPP inhibitors:** HbA1c reduction varies from 0.7% (8 mmol/mol) with alogliptin to around 1.0% (11 mmol/mol) with the other DPP-4 inhibitors. Linagliptin no dose adjustment in CKD 3 or 4 or ESRD. *Alogliptin/saxagliptin: caution in heart failure.*
- e) **SGLT2 inhibitors:** #SGLT2 inhibitors as monotherapies are recommended as options 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.¹⁹ Empagliflozin may be preferably used in people with established CHD.⁵ *Exercise caution with use of canagliflozin in people with foot ulcers as increased risk of toe amputation. SGLT2 inhibitors may be associated with acute kidney injury and it appears this occurs during the first four to six weeks of initiation, particularly in patients on ACE-I/ ARBs or diuretics. Therefore, it is advisable to check UEs at least once in 4 weeks after initiation and thereafter repeat it as required. SGLT2 inhibitors usually are not be used with loop diuretics.*
- f) **Pioglitazone:** contraindicated/concerns in post-menopausal women, haematuria, osteoporosis and heart failure. Useful for initial 5 years or so after diagnosis. At review of treatment check for heart failure. Consider BNP.
- g) **GLP-1 agonists (sc):** Liraglutide has positive CVD outcomes.⁶ Once weekly GLP-1 can be very convenient for many patients especially those in the "care" environment. NICE advise considering discontinuing if weight not reduced by > 3% or HbA1c reduction of 1% (11 mmol/mol) after 6 months treatment

Inzucchi Diagram for individualization of the HbA1c Targets

(Diabetes Care 2012;35:1367-137)⁴



Likely benefits of reducing HbA1c by 1% (11 mmol/mol) by initiation of insulin in a 86 year old man with diabetes and early dementia with baseline HbA1c of 8.5% (69 mmol/mol) are shown below. (BMJ 2016;353:i3147)⁷

- Cardiovascular disease**
 - Fatal event—no effect
 - Non-fatal event—13% reduction in relative risk
 - Absolute risk reduction—3.7% at 10 years
 - Blindness**
 - 25% reduction in relative risk (from surrogate endpoints)
 - Absolute risk reduction 2.3% at 10 years
 - End stage renal failure**
 - 25% reduction in relative risk (from surrogate endpoints)
 - Absolute risk reduction 0.03% at 10 years
 - Life expectancy gain**
 - About 5 weeks
- *Estimates are derived from the UKPDS outcomes model

Table from a BMJ article providing information on choosing HbA1c targets in older people with type 2 diabetes, based on their baseline status. (BMJ 2016;353:i2200)⁸

Table 2 | Comparison of clinical recommendations for HbA_{1c} goals in older patients with type 2 diabetes

American Geriatrics Society ⁶⁸		Department of Veterans Affairs ⁶⁹		American Diabetes Association ⁸		European Diabetes Working Party for Older People ⁹	
Description of patient stratum	HbA _{1c} goal	Description of patient stratum	HbA _{1c} goal	Description of patient stratum	HbA _{1c} goal	Description of patient stratum	HbA _{1c} goal
Healthy	7.0-7.5%	None or very mild microvascular complications; life expectancy of 10-15 years	<7.0%	Healthy (few coexisting chronic illnesses; intact cognitive and functional status)	<7.5%	Without major comorbidities	7.0-7.5%
Moderate comorbidities	7.5-8.0%	Long duration of diabetes (>10 years); requires combination drug regimen including insulin	<8.0%	Complex/intermediate (examples: multiple coexisting chronic illnesses*, ≥2 instrumental ADL impairments, or mild-moderate cognitive impairment)	<8.0%	Frail patients (dependent; multi-system disease; care home residency, including those with dementia)	7.6-8.5%
Multiple comorbidities	8.0-9.0%	Advanced microvascular complications and/or major comorbid illness; life expectancy <5 years	8.0-9.0%	Very complex/poor health (examples: long term care, end stage chronic illnesses†, moderate-severe cognitive impairment, or ≥2 ADL dependencies)	<8.5%‡		

ADL=activities of daily living.

*Conditions serious enough to require drugs or lifestyle management; may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke (multiple means ≥3, but many patients may have ≥5).

†Presence of single end stage chronic illness such as stages III-IV congestive heart failure or oxygen dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer may cause considerable symptoms or impairment of functional status and significantly reduce life expectancy.

‡HbA_{1c} of 8.5% equates to estimated average glucose of ~200 mg/dL; less strict glycemic targets than this may expose patients to acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome

Diabetes therapies; Treatment options – Cost and clinical comparisons

Standard Therapies

Drug class	Cost per patient per year		Daily doses of metformin in combination products	Monotherapy Clinical impact ^{1,10,11,12}					Further information
	Drug alone	Combination with metformin		Hypos	Weight (kg gain/loss)	HbA1c [Efficacy]	Lipids	CVD Safety ^{14,15,16}	
Metformin – Standard Release	£50			Low Risk	Neutral to loss	High	Improved		Combination therapy lowers HbA _{1c} by approx. 1% ¹¹
Metformin – Modified Release	£85								
SUs – Standard Release (Gliclazide)	£50	£100 - 135		High Risk	1.99	High	Small improvements Mainly TGs	Caution in intensive control	Order of impact by outcome ^{17,18} HbA1c: Ins > metformin > GLP-1s > Pio > SUs > Gliptins / Flozins > Glinides
SUs – Modified Release (Gliclazide)	£65	£105 – 130							
Pioglitazone	£150	£468	1.7g	Low Risk	2.30	High	Improved HDL & TG	Oedema, heart failure	Hypos: Ins > SUs / Glinides > GLP-1s > Gliptins > Pio > Flozins / acarbose / metformin
Repaglinide/nateglinide (The Glinides)	£70-135	£120 – 415		High Risk	0.91	Inter-mediate	Unknown	Unknown	
Acarbose	£220			None	-1.80	Low	Unknown	Unknown	Weight gain: Ins / SUs / Pio > Glinides Weight Loss: GLP-1s > Flozins

Newer therapies and insulin – Primary care least costly options at top of each list and in bold

Drug	Standard Dose	Cost per patient per year		Daily doses of metformin in combination products	Monotherapy Clinical impact ^{1,10,11,12}					Comments
		Drug Alone	Combination with metformin		Hypos	Weight (kg gain/loss)	HbA1c [Efficacy]	Lipids	CVD Safety ^{14,15,16}	

NICE NG28²
If 2 drugs in the same class are appropriate, choose option with lowest acquisition cost

DPP-4 Inhibitors – The Gliptins [[Click here for APC drug comparisons chart](#)]

Alogliptin ▼	25mg daily	£347	£347	2g	Low risk	-0.09	Inter mediate	Unknown	Alogliptin & Saxagliptin may increase risk of heart failure	All products are flat priced across all strengths and combinations but vildagliptin combination product is a 30 day pack but rest 28 days
Saxagliptin	5mg daily	£412	£412	1.7 or 2g						
Vildagliptin	50mg daily	£414	£414	1.7 or 2g						
Sitagliptin	100mg daily	£434	£434	2g						
Linagliptin ▼	5mg daily	£434	£434	1.7 or 2g						

SGLT2 Inhibitors – The Flozins [[Click here for APC drug comparisons chart](#)]

Dapagliflozin ▼	10mg daily	£477	£477	1.7 or 2g	Low risk	Modest loss	Inter mediate	Increase LDL-C	Studies ongoing but *EMPA-REG ⁵ may indicate benefit	Whole range same price
Canagliflozin ▼	100mg daily	£477	£477	1.7 or 2g						Whole range same price but 30 day packs
Empagliflozin ▼*	10mg daily	£477	£477	1.7 or 2g						Whole range same price

GLP-1s [[Click here for APC drugs comparisons chart](#)]

Lixisenatide ▼	20mcg daily	£812			Low risk	-1.76	High	Improved	Studies ongoing but ⁵ LEADER trial ⁶ may indicate benefit	
Exenatide ▼	5mcg twice daily	£830								Twice daily dosing
Albiglutide ▼	30mcg weekly	£925								New to market
Dulaglutide ▼	750mcg weekly	£952								New to market
Exenatide PR	2mg weekly	£954								
Liraglutide ⁵	1.2mg daily	£955								NNT for prevention of a CV event = 66

									over 3 years ⁵	
Insulin – intermediate/long acting: Costs expressed per units per day dosing										
NPH insulin	20 units daily	£96								NICE recommended initial choice ²
^^Abasaglar▼	20 units daily	£172								Bioequivalent to Lantus®
Insulin glargine	20 units daily	£202								
Insulin glargine U300	20 units daily	£202		High risk	Gain	Highest	Improved	Caution in intensive control		Not interchangeable with Lantus®
Insulin detemir	20 units daily	£204								Often prescribed BD
Insulin degludec▼	20 units daily	£227								APC checklist must be completed before request for GP prescription

References

- Inzucchi et al. Management of Hyperglycaemia in Type 2 Diabetes: A Patient-Centred Approach-Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015;**38**: 140-149
- NICE Clinical Guideline - Type 2 diabetes in adults: Management (NG28) <https://www.nice.org.uk/guidance/ng28>
- <http://www.idf.org/sites/default/files/IDF-Guideline-for-older-people-T2D.pdf>
- McEwan et al. Understanding the inter-relationship between improved glycaemic control, hypoglycaemia and weight change within a long-term economic model. *Diabetes Obes Metab.* 2010 May;**12**(5):431-436
- Zinman et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015;**373**:2117-2128
- Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2016, June 13, DOI: 10.1056/NEJMoa1603827
- Yudkin et al. Guidelines for treating risk factors should include tools for shared decision making. *BMJ* 2016;**353**:i3147
- Huang et al. Management of diabetes mellitus in older people with comorbidities. *BMJ* 2016;**353**:i2200
- Coventry & Warwickshire APC Drug Positioning Statement DPS038 <https://www.gpfusion.co.uk/mf.ashx?ID=e074367f-19c7-4c28-8461-c90d891a6e29>
- Kurukulasuriya, et al. Therapies for type 2 diabetes: lowering HbA1c and associated cardiovascular risk factors. *Cardiovascular Diabetology* 2010; **9**(45) : 1-13
- Bennett et al. Comparative Effectiveness and Safety of Medications for Type 2 Diabetes: An update Including New Drugs and 2-Drug Combinations. *Ann Intern Med* 2011; **154**(9):602 - 613
- Phung et al. Effect of Noninsulin Antidiabetic Drugs added to Metformin Therapy on Glycaemic Control, Weight Gain , and Hypoglycemia in Type 2 Diabetes. *JAMA* 2010;**303**(14);1410-1418
- Bolen et al. Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus. *Ann Intern Med* 2007; **147**(6):386-399
- Tzoulaki et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *BMJ* 2009;**339**:b4731
- Holman et al. Cardiovascular outcome trials of glucose lowering drugs or strategies in type 2 diabetes. *Lancet* 2014; **383** : 2008-2017
- Snell-Bergeon et al. Hypoglycemia, Diabetes, and Cardiovascular Disease. *Diabetes Technology and Therapeutics* 2012; **15** (S1): S51-S58
- O'Hare, JP et al. The new NICE guidelines for type 2 diabetes - a critical analysis. *The British Journal of Diabetes & Vascular Disease* 2015;**15**(1): 3-7
- Clar C, Gill JA, Court R, et al. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. *BMJ Open* 2012;**2**: 1-12

APPENDIX 1

Insulin

- Typical total insulin dose daily 0.25 to 0.33 units/kg body weight per day initially, *e.g.*
 - 80kg man: 20 to 26 units daily
 - 60 kg woman: 15 to 20 units daily
- **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
- **Initial suspicion Type 2 diabetes but poor response to 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). **If poor response to diet, low dose gliclazide (40-80mg bd) can be used to get rapid control and then in most cases stop gliclazide and use metformin and diet, weight control and physical activity.**
- **Safe Insulin prescribing and monitoring:** ensure that the HCP is adequately trained in safe insulin prescribing, dose calculation and adjustment, glucose monitoring, driving safely and employment issues.
- **Inadequate response to non-insulin therapies:** If poor response to any intensification stage consider insulin
- **Regimes to consider:**
 - **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 Abasaglar®) and detemir. Insulin degludec is recommended only after a trial has been conducted by the specialist in line with APC recommendations and a checklist is provided when prescription is requested in primary care⁹. Toujeo® (glargine 300 units/ml) useful if erratic control, nocturnal hypoglycaemia or those requiring high dose insulin. **Initial dose 0.25 units per kg nocte.**
 - **Basal plus:** consider adding a single bolus 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. The choices of bolus insulin are given below.
 - **Biphasic Pre-mix Insulins:** consider in patients with “stable lifestyles”. Initial total daily dose is 0.25 to 0.33 units per kg. Use two thirds of the total daily dose at breakfast and the remaining third with evening meal; *e.g.* an 80 kg adult should have 16 units pre-breakfast and 12 units before evening meals. The choices include:
 - Humalog Mix 25®
 - Novomix 30®
 - Humulin M3®
 - Insuman Comb25®
 - **Basal-bolus regime:** Initial total daily dose is 0.25 to 0.33 units per kg. 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). For example, in an 80 kg adult starting on 0.25 units/kg/day of total insulin dose, give 10 units as basal insulin and 3 units of bolus insulin before each main meal;
 - **Basal insulin:** The choices are as listed above
 - **Bolus insulin:** The choices are Apidra®, Humalog®, NovoRapid®