Guidelines comparison table on the pharmacological management of type 2 diabetes mellitus in adults

ADA/EASD (2019)			NICE Guideline 28 (2020)		SIGN Guideline 154 (2017)	
			Patients who can take metformin	Metformin contraindicated or not tolerated	For patients who can tolerate metformin	If osmotic symptoms or intolerant of metformin
INITIAL THERAPY			**INITIAL THERAPY**		**INITIAL THERAPY, in addition to lifestyle measures**	
Use metformin and comprehensive lifestyle measures (weight management and physical activity)			**If HbA_{1c} rises to 48 mmol/mol (6.5%) on lifestyle interventions:** • offer standard-release metformin (if standard release metformin is not tolerated, consider a trial of modified-release metformin) • support the person to aim for an HbA_{1c} level of 48 mmol/mol (6.5%)	**If HbA_{1c} rises to 48 mmol/mol (6.5%) on lifestyle interventions:** • consider one of the following:[L] – a DPP-4i, pioglitazone[M] or a sulfonylurea – a SGLT-2i[N] instead of a DPP-4i if a sulfonylurea or pioglitazone[M] is not appropriate • support the person to aim for an HbA_{1c} level of 48 mmol/mol (6.5%) for people on a DPP-4i, SGLT-2i or pioglitazone **or** 53 mmol/mol (7%) for people on a sulfoylurea	Set glycaemic target: HbA_{1c} target of <7.0% (53 mmol/mol) **or** individualised as agreed in addition to lifestyle measures Usual approach is metformin[R],[S]	Set glycaemic target: HbA_{1c} target of <7.0% (53 mmol/mol) **or** individualised as agreed Approach in this case is sulfonylurea[R],[S] The following are also accepted by the SMC for first-line use where metformin and sulphonylureas are not tolerated: canagliflozin, dapagliflozin or empagliflozin (SGLT-2 inhibitors); linagliptin, sitagliptin or vildagliptin (DPP-4 inhibitors); pioglitazone (thiazolidinedione IF SEVERE OSMOTIC SYMPTOMS WITH WEIGHT LOSS **OR** POSSIBILITY OF TYPE 1 DIABETES (**URGENT—PHONE SECONDARY CARE IMMEDIATELY**). See *Second intensification* below
FIRST INTENSIFICATION			**FIRST INTENSIFICATION**		**FIRST INTENSIFICATION, in addition to lifestyle measures**	
If high-risk indicators or established ASCVD, CKD, or HF[A] (consider independently of baseline HbA_{1c} or individualised HbA_{1c} target)		No high-risk indicators, ASCVD, CKD, or HF but HbA_{1c} above individualised target and compelling need to minimise hypoglycaemia	**If HbA_{1c} rises to 58 mmol/mol (7.5%):** • consider dual therapy with: – metformin + a DPP-4i – metformin + pioglitazone[M] – metformin + a sulfonylurea – *metformin + an SGLT-2i*[N] • support the person to aim for an HbA_{1c} level of 53 mmol/mol (7.0%)	**If HbA_{1c} rises to 58 mmol/mol (7.5%):** • consider dual therapy[O] with: – DPP-4i + pioglitazone[M] – DPP-4i + a sulfonylurea – pioglitazone[M] + a sulfonylurea • support the person to aim for an HbA_{1c} level of 53 mmol/mol (7.0%)	In addition to lifestyle measures and if not reaching target after 3–6 months,[T] review adherence: then guided by patient profile add one of the following: • sulfonylurea[R],[S] • SGLT-2i[R],[S] • DPP-4i[R],[S] • pioglitazone[R],[S]	
If ASCVD predominates[B]: • established ASCVD • indicators of high ASCVD risk (age ≥55 years + LVH or coronary, carotid, lower extremity artery stenosis >50%)	**If HF[C] or CKD[D] predominates:** • particularly HFrEF (LVEF <45%) • CKD: specifically eGFR 30–60 ml min-1 [1.73m]-2 or UACR >300 mg/g					
Preferably: GLP-1 RA with proven CVD benefit[E] **or** SGLT-2i with proven CVD benefit[E] if eGFR adequate[F]	**Preferably**: SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[G] **or** if SGLT-2i not tolerated or contraindicated or if eGFR less than adequate[F] add GLP-1 RA with proven CVD benefit[E]	**Either**: DPP-4i **or** GLP-1 RA **or** SGLT-2i[F] **or** thiazolidinedione[H]				
SECOND INTENSIFICATION (If HbA_{1c} above target)			**SECOND INTENSIFICATION - (1)**	**SECOND INTENSIFICATION**	**SECOND INTENSIFICATION, in addition to lifestyle measures**	
If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT-2i, choose agents demonstrating CV safety: • for patients on a GLP-1 RA, consider adding SGLT-2i with proven CVD benefit[E] • DPP-4i if not on GLP-1 RA • basal insulin[I] • thiazolidinedione[H] • sulfonylurea[J]	• Avoid thiazolidinedione in the setting of HF Choose agents demonstrating CV safety: • for patients on a SGLT-2i, consider adding GLP-1 RA with proven CVD benefit[E] • DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA) • basal insulin[I] • sulfonylurea[J]	• If on DPP-4i consider adding **either** SGLT-2i[F] **or** thiazolidinedione[H] • If on GLP-1 RA consider adding **either** SGLT-2i[F] **or** thiazolidinedione[H] • If on SGLT-2i[F] consider adding **either** GLP-1 RA **or** DPP-4i **or** thiazolidinedione[H] • If on thiazolidinedione consider adding **either** SGLT-2i[F] **or** DPP-4i **or** GLP-1 RA	**If HbA_{1c} rises to 58 mmol/mol (7.5%):** • consider triple therapy with: – metformin + a DPP-4i + a sulfonylurea – metformin + pioglitazone[M] + a sulfonylurea – *metformin, pioglitazone[M] or a sulfonylurea, + an SGLT-2i*[N] • insulin-based treatment • support the person to aim for an HbA_{1c} level of 53 mmol/mol (7%)	**If HbA_{1c} rises to 58 mmol/mol (7.5%):** • consider insulin-based treatment (refer to full guideline for further information on combinations of insulin with either a SGLT-2i or with GLP-1 mimetic[N],[P],[Q] and types of insulin) • support the person to aim for an HbA_{1c} level of 53 mmol/mol (7%)	If not reaching target after 3–6 months,[U] review adherence, then guided by patient profile: • add *either* an additional oral agent from a different class in addition to lifestyle measures: – sulfonylurea[R],[S] – SGLT-2i[R],[S] – DPP-4i[R],[S] – pioglitazone[R],[S] • **or** an injectable agent[R],[S] – if **BMI >30 kg/m²:** GLP-1 RA[R],[S]—stop DPP-4i, consider reducing sulfonylurea, continue metformin, can continue pioglitazone, can contunue SGLT-2i – if **BMI <30 kg/m²:** basal Insulin[R],[S]—inject before bed, use NPH (isophane) insulin—or longer-acting analogues according to risk of hypoglycaemia,[V] can continue metformin, pioglitazone, DPP-4i or SGLT-2i, can reduce or stop sulfonylurea	
THIRD INTENSIFICATION			**SECOND INTENSIFICATION - (2)**	**THIRD INTENSIFICATION**	**THIRD INTENSIFICATION, in addition to lifestyle measures**	
N/A	N/A	Continue with addition of other agents as outlined above	If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, sulfonylurea and a GLP-1 mimetic[P] for adults with type 2 diabetes who: • have a BMI of 35 kg/m² 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/m², **and** for whom insulin therapy would have significant occupational implications, **or** weight loss would benefit other significant obesity-related co-morbidities	N/A	If not reaching target after 3–6 months, review adherence: then guided by patient profile add additional agent(s) from third-line options (see *Second intensification*) *(need specialist input).* If insulin intensification required (need specialist input): **add prandial insulin or switch to twice daily mixed biphasic insulin**	
		FOURTH INTENSIFICATION Consider the addition of sulfonylurea[J] **or** basal insulin[K] • choose later generation sulfonylurea with lower risk of hypoglycaemia • consider basal insulin with lower risk of hypoglycaemia[K]				

ADA/EASD (2019) FOOTNOTES AND REFERENCE

[A] Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications
[B] Established ASCVD (indicators of high ASCVD risk: age ≥55 years + LVH or coronary, carotid, lower extremity artery stenosis >50%)
[C] Particularly HFrEF (LVEF <45%)
[D] Specifically CKD with eGFR 30–60 ml/min/1.73 m^2 or UACR >30 mg/g, particularly UACR >300 mg/g
[E] Proven CVD benefit means it has label indication of reducing CVD events
[F] Be aware that SGLT-2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
[G] Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary heart failure outcome data from DAPA-HF
[H] Low dose may be better tolerated though less well studied for CVD effects
[I] Degludec or U100 glargine have demonstrated CVD safety
[J] Choose later generation sulfonylurea to lower risk of hypoglycaemia. Glimepiride has shown similar CV safety to DPP-4i
[K] Consider basal insulin with lower risk of hypoglycaemia: degludec/glargine U300 <glargine U100/detemir <NPH insulin

Buse J, Wexler D, Tsapas A, Rossing P, Mingrone G, Mathieu C, D'Alessio D, Davies M. 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). *Diabetologia*. 2020; 63(2): 221–228. Available at: link.springer.com/article/10.1007/s00125-019-05039-w

NICE Guideline 28 (2020) FOOTNOTES AND REFERENCE

[L] Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination
[M] 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. 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'
[N] See NICE technology appraisal guidance 288 and 418, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin, respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions, as options in triple therapy regimens and in combination with insulin. All three are also options as monotherapies in adults in whom metformin is contraindicated or not tolerated. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal
[O] Be aware that the drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug
[P] Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA_{1c} by at least 11 mmol/mol [1.0%] and a weight loss of at least 3% of initial body weight in 6 months)
[Q] A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care

NICE. *Type 2 diabetes in adults: management*. NICE Guideline 28. NICE; 2015 (last updated December 2020). Available at: nice.org.uk/ng28

SIGN Guideline 154 (2017) FOOTNOTES AND REFERENCE

[R] Continue medication at each stage if EITHER individualised target achieved OR HbA_{1C} falls more than 0.5% (5.5 mmol/mol) in 3–6 months. Discontinue if evidence that ineffective
[S] Please refer to the individual drug profiles below.
[T] Do not delay if first-line options not tolerated/inappropriate
[U] Do not combine dapagliflozin with pioglitazone
[V] Driving, occupational hazards, risk of falls, previous history

Scottish Intercollegiate Guidelines Network. *Pharmacological management of glycaemic control in people with type 2 diabetes*. SIGN Guideline 154. Edinburgh: SIGN; 2017. Available at: sign.ac.uk/sign-116-and-154-diabetes.html

ABBREVIATIONS

ASCVD=atherosclerotic cardiovascular disease; BMI=body mass index; BNF=British National Formulary; CKD=chronic kidney disease; CV=cardiovascular; CVD=cardiovascular disease; CVOT=cardiovascular outcome trial; DPP-4i=dipeptidyl peptidase 4 inhibitor; eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease; GLP-1 RA=glucagon-like peptide-1 receptor agonist; GLP-1=glucagon-like peptide 1; HbA_{1c}=glycated haemoglobin; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction; LVH=left ventricular hypertrophy; NPH=neutral protamine Hagedorn; SGLT-2i=sodium-glucose cotransporter 2 inhibitor; SMC=Scottish Medicines Consortium

DRUG PROFILES

	Efficacy	CV benefit	Hypoglycaemia risk	Weight	Main adverse effects	In CKD stage 3a:
Metformin	Moderate	Yes	Low	Reduction	Gastrointestinal	Maximum 2g daily
Sulfonylurea	High	No	High	Gain	Hypoglycaemia	Careful monitoring[A]
SGLT-2i	Moderate	Yes (specific agents)[B]	Low	Loss	Genital mycotic	Do not initiate[C]
DPP-4i	Low/moderate	No	Low	Neutral	Few	Reduce dose[D]
Pioglitazone	Moderate	Probable (but fluid retention)	Low	Gain	Oedema/fractures[E]	Dose unchanged
GLP-1 RA	High	Yes (specific agents)[B]	Low	Loss	Gastrointestinal	Dose unchanged[F]
Basal insulin	High	No	Highest	Gain	Hypoglycaemia	Dose unchanged[G]

[A] Consider dose reduction
[B] See the full SIGN Guideline 154 (pages 23, 26–27) at: sign.ac.uk/sign-116-and-154-diabetes.html
[C] See BNF: specific agents can be continued at reduced dose
[D] See BNF: no dose reduction required for linagliptin
[E] Pioglitazone is contraindicated in people with (or with a history of) heart failure or blood cancer
[F] Caution with exenatide when eGFR <50 ml/min/1.73 m^2
[G] Adjust according to response

This table has been produced by the *Guidelines* team for easy comparison of recommendations from the ADA/EASD, NICE, and SIGN on the pharmacological managment of type 2 diabetes mellitus in adults.