TYPE 2 DIABETES – MANAGEMENT ALGORITHM

The North West London health and care partnership

Diet & Lifestyle first line therapy [1, 2, 3]
Sick Day Guidance – see page 16

Does the patient have a CARDIO-RENAL COMORBIDITY?

Intensive diet & lifestyle management for all patients [1]

Diabetes remission is a practical target for primary care [2]

Consider enrolment into REWIND **Programme for either low calorie total diet replacement or low carb pathway** [3]

NO

Diet & Lifestyle first line therapy [1, 2, 3]

METFORMIN
If intolerant move to next level

eGFR dependent:

+ SGLT-2i [4]

Dapa strongest primary prevention data (HF) [5]

Alternatives:

+ DPP-4i [6], **+ SU,** **+ TZD** [7]

+ DPP-4i [6*], **+ SU,**

+ SGLT-2i [4*], **+ TZD** [7]

*As per NICE NG28, avoid combining SGLT-2i + DPP-4i on cost grounds, unless clinically justified (hypos, weight gain)

If BMI > 35 kg/m² (>30 if BAME ethnicity)
+ GLP-1 [1]
(and stop DPP-4i)
Dulaglutide +ive CVD data in lower risk cohort [8]

Alternative:
+ BASAL INSULIN [1]

YES

Established CVD [9]

METFORMIN
If intolerant move to next level

eGFR dependent:

+ SGLT-2i [4, 10]

Empa & Cana have shown benefit in eCVD [11,12, 13]

+ GLP-1 [1]

CVD benefit: Semaglutide (SC only)[14], Dulaglutide[8] and Liraglutide[15]

+ SU / BASAL INSULIN [1]

HF or CKD

METFORMIN
If intolerant move to next level

eGFR dependent:

+ SGLT-2i [4, 10]

Dapa strongest HF data [5, 16]
Cana strongest CKD data [17]

HF:
+ GLP-1 [1]
or
+ DPP-4i [6]

CKD:
+ GLP-1 [1]
or
+ DPP-4i [6]
+ TZD [7]

+ SU / BASAL INSULIN [1]

Initial therapy

Intensification if HbA1c>58 or as clinically indicated

Target HbA_{1c}

Rescue therapy: Insulin or SU — Rescue based therapy if symptomatic or high HbA_{1c} Review once symptoms resolved +/- target HbA_{1c} achieved [1]

When initiating a SGLT2i — Consider a 25% dose reduction in any concomitant SU or Basal insulin & monitor for evidence of hypoglycemia

TYPE 2 DIABETES – DOSE ADJUSTMENT IN RENAL /HEPATIC IMPAIRMENT

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Drug	**CKD stage 1** eGFR >90 mL/min	**CKD stage 2** eGFR 60-90 mL/min	**CKD stage 3a** eGFR 45-59 mL/min	**CKD stage 3b** eGFR 30-44 mL/min	**CKD stage 4** eGFR 15-29 mL/min	**CKD stage 5** eGFR <15 mL/min	**Mild to moderate hepatic impairment**	**Severe hepatic impairment**
Metformin	✔	✔	✔	✔ Max 500mg BD	✖	✖	Specialist initiation only	✖
Gliclazide	✔	✔	✔	✔	Use lowest effective dose	✖	✔	✖
Linagliptin	✔	✔	✔	✔	✔	✔	✔	✔
Sitagliptin	100 mg	100 mg	100mg	50mg	25mg	25mg	✔	✖
Alogliptin	25mg	25mg	25mg	12.5mg	6.25mg	6.25mg	✔	✖
Pioglitazone (TZD)	✔	✔	✔	✔	✔	✔	✖	✖
Dapagliflozin	✔ Start 10mg	✔ Start 10mg	✔ Continue 10mg	✖	✖	✖	✔	✔ 5mg
Canagliflozin	✔ Start 100-300mg	✔ Start 100-300mg	✔ Start 100mg	✔ Start 100mg, only if uACR >30mg/mmol	✔ Continue 100mg if uACR >30mg/mmol	✔ Continue 100mg if uACR >30mg/mmol	✔	✖
Empagliflozin	✔ Start 10-25mg	✔ Start 10-25mg	✔ Continue 10mg	✖	✖	✖	✔	✖
Ertugliflozin	✔ Start 5-15mg	✔ Start 5-15mg	✔ Continue 5-15mg	✖	✖	✖	✔	✖
Liraglutide	✔	✔	✔	✔	✔	✖	✔	✖
Semaglutide	✔	✔	✔	✔	✔	✖	✔	Caution: limited information
Dulaglutide	✔	✔	✔	✔	✔	✖	✔	✔
Insulin	✔	✔	✔	✔	✔	✔	✔	✔

Diminished glycaemic effect of SGLT-2i with eGFR < 45 mL/min, however sustained cardio-renal protection

Key

✔ Initiate
✔ No new initiation; continue at stated dose
✖ Discontinue

TYPE 2 DIABETES – ADDITIONAL GUIDANCE

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Sick Day Guidance – to be reiterated to patients at every opportunity

When unwell (acute illness):

Fever, sweats, shaking

Vomiting / diarrhoea

Unable to eat or drink

Miss out / Omit / Pause:

S – SGLT-2i
A – ACEi
D – Diuretics
M – Metformin
A – ARBs
N - NSAIDs

After 2-3 days:

Feeling better = Restart paused medicines

Not better = seek medical attention

Increase blood glucose monitoring during acute illness and check for ketones. If you are using daily insulin or an SUs, you may need to increase (or decrease) the amount taken to maintain appropriate glucose control. Ensure fluid intake to minimise dehydration.

Adapted from Imperial College Healthcare NHS Trust Renal Sick Day Rules

Medication review

Reassess the person's needs and circumstances at each review (3-6 months) and think about whether to stop any medicines that are not effective.
Adjustments for Renal & Hepatic Impairment – see page 15.

GLP-1
Only continue in those with a beneficial metabolic response after **6 months** (reduction of ≥11 mmol/mol [1.0%] in HbA1c and weight loss of ≥ 3% of initial body weight).

SGLT-2i
Stop & reassess if complicated by active foot ulcer or DKA (could be euglycemic).

DPP-4i
Not to be used in conjunction with GLP-1.

TZD
Stop in the event of HF, DKA or bladder cancer.

SU
In the event of significant hypos, stop & reassess.

Lifestyle Counselling – to be reiterated to patients at every opportunity

Dietary Guidance

Seek dietitian input. Individualised approach: low fat diet, low Glycaemic Index diet or Mediterranean diet etc. Alternatives include low calorie total diet replacement programmes (NWL REWIND).

Physical Activity

Realistic targets should be set. The benefits of regular exercise should be explained and people should be advised to perform regular aerobic activity. Clinical studies show that walking for 30 minutes every day has cardiovascular benefits.

Weight Management

Weight loss can help the patient achieve Type 2 diabetes remission. Realistic initial weight loss target of 5% to 10% of starting weight. Consider drug therapy, e.g SLGT-2i or GLP-1. Consider surgical intervention.

Smoking Cessation & Alcohol consumption

Assess patients for smoking status and refer to Smoking Cessation Teams for support. Alcohol may influence blood glycose control (Hyper/Hypo glycaemia respectively).

Diabetes Remission Programme

know diabetes REWIND

Diabetes remission is a practical target for primary care[2]. Consider enrolment into NWL REWIND Programme for either low calorie total diet replacement or low carb pathway[3].

For more details, click here
For full pathways, click here

Given the recent wealth of publications regarding cardiovascular & renal outcome trials in type 2 diabetes, this Type 2 Diabetes Management Algorithm is meant as a quick reference guide as we move away from glucose-centric prescribing, based on current evidence as of August 2020. For more in-depth guidance please refer to full North West London Diabetes Guidelines, the EASD-ADA Consensus Document, or other [inter]national guidelines. Also see CaReMe multi-association position statement.

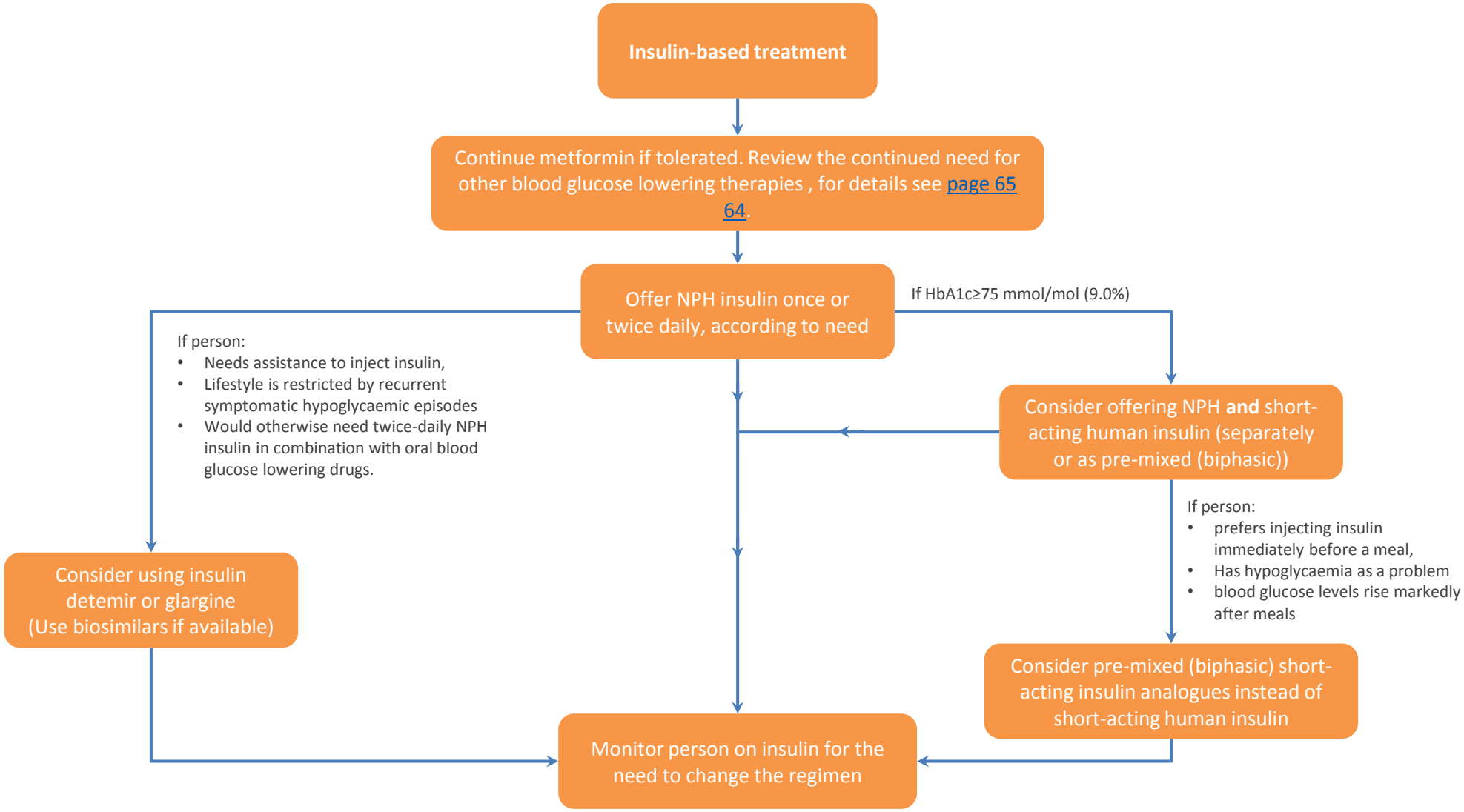
Lifestyle management should be part of the ongoing discussion with individuals with T2DM at each visit. Increasing physical activity and reducing body weight improves glycaemic control and should be encouraged in all people with T2DM[1]. Glycaemic treatment targets should be individualised based on patient preferences and patient characteristics, including frailty and comorbid conditions[1]. All drugs can cause side effects, consult BNF or summary of product characteristics for full side effect profile of individual drugs. Always offer advice on sick day guidance for patients on Metformin and/or SGLT-2i[1]. Stop SGLT-2is peri-operatively or if restricted food intake or dehydration[1]. Patients on insulin treatment should always be advised never to stop or significantly reduce their insulin as part of the sick day response[1]. SU & TZD both have low acquisition cost, this should be taken into consideration alongside increased risk of weight gain and hypoglycaemia risk (SU).

Abbreviations:

T2DM; type 2 diabetes mellitus; NWL REWIND; North West London Reducing Weight with Intensive Dietary support, eGFR, estimated glomerular filtration rate; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; DPP-4i, dipeptidyl peptidase 4 inhibitor (gliptin); SU, sulfonylurea; TZD, thiazolidinedione; BMI, body mass index; GLP-1, glucagon-like peptide-1 receptor agonist; +ive, positive; CVD, cardiovascular disease; eCVD, established cardiovascular disease; MI, myocardial infarction; Cana, canagliflozin; Dapa, dapagliflozin; Empa, empagliflozin; HF, heart failure; CKD, chronic kidney disease; HbA_{1c}, hemoglobin A1C; BD, twice daily; ACEi, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin II receptor blocker; NSAID, Non-steroidal anti-inflammatory drug; DKA, diabetic ketoacidosis.

References:

1. For further guidance please refer to full North West London Diabetes Guidelines - http://tiny.cc/p4egfz
2. DiRECT; Lancet 2018; 391: 541–51 https://doi.org/10.1016/S0140-6736(17)33102-1
3. NWL REWIND Programme (**Re**ducing **W**eight with **In**tensive **D**ietary support) For more details, click here For full pathways, click here.
4. When prescribing an SGLT-2i, consider risk of volume depletion, euglycemia DKA in insulin deficient cohorts and lower limb amputation (class warning, but only observed in Cana and Eurtu). Caution in frail patients and always follow sick day rules. For more information, refer to full North West London Diabetes Guidelines
5. DECLARE TIMI 58; N Engl J Med 2019; 380:347-357; DOI: https://doi.org/10.1056/NEJMoa1812389
6. FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin https://bit.ly/2ZZCNni
7. TZD (Pioglitazone) to be avoided in patients with heart failure. PROactive; Lancet. 2005 Oct 8;366(9493):1279-89 https://doi.org/10.1016/S0140-6736(05)67528-9
8. REWIND (Dulaglutide CVOT); Lancet 2019; 394: 121–30; DOI: https://doi.org/10.1016/S0140-6736(19)31149-3
9. Patients with established atherosclerotic cardiovascular disease having had an ischemic event (e.g myocardial infarction or stroke)
10. Consider initiating Met + SGLT-2i rather than stepwise. This is in line with Position Statement by Primary Care Diabetes Europe; S. Seidu, et al., A disease state approach to the pharmacological management of Type 2 diabetes in primary care: A position statement by Primary Care Diabetes Europe, Prim. Care Diab. (2020), https://doi.org/10.1016/j.pcd.2020.05.004. Alternatively, the European Society of Cardiology (ESC) diabetes guideline states that SGLT-2i could be considered as first line ahead of metformin in patients with eCVD, HF or CKD - European Heart Journal (2019) 00, 169; doi: https://doi.org/10.1093/eurheartj/ehz486
11. EMPA-REG; N Engl J Med 2015; 373:2117-2128; DOI: https://doi.org/10.1056/NEJMoa1504720
12. CANVAS; N Engl J Med 2017; 377:644-657; DOI: https://doi.org/10.1056/NEJMoa1611925
13. Dapa has shown MACE benefit in a post MI analysis; DECLARE prior MI; Circulation. 2019 May 28;139(22):2516-2527; DOI: https://doi.org/10.1161/CIRCULATIONAHA.119.039996
14. SUSTAIN 6; N Engl J Med. 2016 Nov 10;375(19):1834-1844 DOI: https://doi.org/10.1056/NEJMoa1607141
15. LEADER; N Engl J Med 2016; 375:311-322; DOI: https://doi.org/10.1056/NEJMoa1603827
16. DAPA HF; September 19, 2019; DOI: https://doi.org/10.1056/NEJMoa1911303
17. CREDENCE; N Engl J Med 2019; 380:2295-2306; DOI: https://doi.org/10.1056/NEJMoa1811744



NB: Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and on-going support from a consultant-led multidisciplinary team

TYPE 2 DIABETES – SUMMARY OF ANTI-DIABETIC AGENTS

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Please see individual drug monographs on pages 34-37 and 59-60 for more details.

	Hypoglycaemia	Weight	GI side effects	Cardiovascular risks/benefit	Renal dosing	Liver impairment
Metformin	No	Loss	Common	Benefits Caution in chronic stable heart failure	eGFR 30-44: Max 1g daily dose Contraindicated if eGFR<30	Withdraw if risk of tissue hypoxia, predisposes to lactic acidosis
Sulfonylureas	Associated risk	Gain	Common	Neutral	**See page 15 for individual drug breakdown**	
					Higher risk of hypoglycemia; increase patient monitoring	If severe, reduce dose (risk of hypoglycemia)
DPP-4i (-gliptins)	Only when combined with SU/Insulin	Neutral	No known risks Alogliptin - Common Saxagliptin - Possible	Neutral Caution with Alogliptin and Saxagliptin in moderate-severe heart failure	**See page 15 for individual drug breakdown** Dose reduction may be required	Vildagliptin has a risk of liver toxicity
Thiazolidinediones (Pioglitazone)	Only when combined with SU/Insulin	Gain	No known risks	Risk Contraindicated in people with heart failure or a history of heart failure	None	Avoid, risk of liver toxicity
SGLT-2i (-flozins)	Only when combined with SU/Insulin	Loss	No known risks	Established benefits Caution in significant PVD due to increased risk of digital amputation	**See page 15 for individual drug breakdown** Dose reduction may be required	Excluding dapagliflozin, avoid If severe
GLP-1 Agonist (-tides)	No	Loss	Common	Semaglutide, Liraglutide, Dulaglutide have CV benefit	**See page 15 for individual drug breakdown**	
					Except Lixisenatide and Exenatide	Avoid if Liraglutide
Repaglinide	Associated risk	Gain	Common	CVD as a rare side effect	Use with caution	Avoid if severe
Acarbose (AGI)	If prescribed in addition to other blood glucose lowering drugs	Neutral	Common	Neutral	Avoid if eGFR<25	Avoid if severe
Insulin	Associated risk	Gain	No known risks	Neutral Cardiac failure risk when used concurrently with Pioglitazone	Dose reduction required, higher risk of hypoglycemia	Reduced dose required