NHS
Central London
Community Healthcare
NHS Trust

NHS
South West London

Type 2 Diabetes & Frailty Prescribing Guideline

Target audience

For General Practitioners, Community Nurses, Diabetes Specialist Nurses, Diabetes Dietitians, Consultants, and any health care professionals involved in Diabetes Care who are considering treatment changes to improve patient care through improving clinical targets such as HbA1c.

Introduction

Prognosis and appropriate treatment goals for older adults with diabetes vary greatly according to frailty. It is now recognised that changes may be needed to diabetes management in some older people. Whilst there is clear guidance on the evaluation of frailty and subsequent target setting for people living with frailty, there remains a lack of formal guidance for healthcare professionals in how to achieve these targets (Strain et al 2021).

The management of type 2 diabetes in older adults can be challenging due to its heterogeneity, the presence of comorbidities and the risk of overtreatment.

Older adults are more prone to hypoglycaemia and are more vulnerable to its consequences, including falls, fractures, hospitalisation, cardiovascular events and all-cause mortality. Thus, assessment of frailty should be a routine component of a diabetes review for all older adults, and glycaemic targets and therapeutic choices should be chosen accordingly.

This guideline will help identify adults with diabetes who are affected by frailty and manage them in a more appropriate way to minimise the risk of adverse health events or outcomes. It advises on the use of available glucose-lowering therapies in older adults and recommends simple glycaemic management algorithms according to their level of frailty.

Identifying frailty is more important than age itself. Several approaches are available to detect the presence of frailty in community-dwelling older adults which are applicable to adults with diabetes (Clegg A 2013). These have been subjected to feasibility and validity reviews by the British Geriatric Society (BGS 2014). The importance of detecting frailty lies with the opportunity to consider targeted interventions that reduce functional decline and the risk of disability.

Definitions of acronyms used in this document

- Atherosclerotic Cardiovascular Disease (ASCVD)
- Dipeptidyl Peptidase-4 inhibitors (DPP-4i)
- Estimated Glomerular Filtration Rate i.e. kidney function (eGFR)
- Fasting Plasma Glucose (FPG)

- Glucagon-Like Peptide-1 receptor agonists (GLP-1RA)
- Gastrointestinal (GI)
- Heart Failure (HF)
- Myocardial Infarction (MI)
- Neutral Protamine Hagedorn insulin (NPH)
- Quality of Life (QOL)
- Sodium-Glucose Co-transporter 2 inhibitors (SGLT2i)
- Sulfonylurea (SU)
- Thiazolidinedione e.g. Pioglitazone (TZD)

Identifying Frailty

Consider frailty in any acute presentations suggestive of a frailty syndrome such as:

- Falls (e.g. 'collapse', 'legs gave way', 'found lying on floor)'
- Immobility (e.g. sudden change in mobility, 'gone off legs' 'stuck on toilet')
- Delirium (e.g. acute confusion, worsening of pre-existing confusion/short term memory loss)
- Incontinence (e.g. new onset or worsening of urinary or faecal incontinence)
- Susceptibility to side effects of medications (e.g. confusion with codeine, hypotension with antidepressants).

N.B. Assess for the presence of frailty in any individual above the age of 65 years with type 2 diabetes at non-acute clinic encounters using a screening tool recommended by the British Geriatric Society entitled 'Prisma 7 questionnaire' (BGS 2014).

Grading Frailty

Although there are many complex grading scales for frailty any of the following can be used:

- NHS England (2023) electronic Frailty Index (eFI)
- Comprehensive Geriatric Assessment (CGA) toolkit (CGA 2023a)
- Rockwood Clinical Frailty Scale using the CGA toolkit (CGA 2023b)
- Prisma 7
- Timed up and go test - time taken to get up from a chair, walk three metres, turn around and sit down.
    - Frail if greater than 8 seconds underage of 70 years old , greater than 9 seconds if 70 to 80years , greater than 10 seconds if 80 to 90 years
- Gait speed- taking more than five seconds to cover four metres.

Any of these will identify the degree of frailty as well as the assessment of self-care skills, annual cognitive assessment Mini-Cog, PHQ9 depression questionnaire and screening for sarcopenia.

Pragmatically however there are only three grades worth identifying, namely "Healthy/pre-frail/mild frailty", "Moderate frailty" and "Severe frailty". Table 1 gives an overview of recommendations at different levels of frailty. It is recommended that the level of frailty should be reviewed annually.

Target setting, recommended interventions and treatment goals according to the level of frailty (Table 1)

Healthy/pre-frail/ mild frailty

- Status
  - Functional and independent, life expectancy of more than 10 years
- Treatment goals
  - Reverse frailty or limit its progression, maintain functional status, independence and quality of life, prevent or delay macrovascular and microvascular complications
- Recommended interventions
  - Tight glycaemic control, resistance exercise and nutritional interventions, statin therapy unless contraindicated or not tolerated
- Recommended targets
  - HbA1c 58 mmol/mol but greater than or equal to 53 mmol/mol
  - FPG 5.0 to 8.0 mmol/L
  - BP less than140/90 mmHg

Moderate frailty

- Status
  - More than 2 comorbidities and reduced life expectancy
- Treatment goals
  - Prevent decline in quality of life, limit the progression of microvascular complications, avoid metabolic emergencies such as hypoglycaemia
- Recommended targets
  - HbA1c less than 64 mmol/mol but greater than or equal to 58 mmol/mol
  - FPG 6.0 to 10.0 mmol/L
  - BP less than140/90 mmHg

Severe frailty

- Status
  - Significant comorbidity, functional deficits, and limited independence, markedly reduced life expectancy
- Treatment goals

- Improve quality of life by reducing symptoms or hospitalisations, maintain functional status, preventing further lower limb dysfunction, preventing significant disability.

- Recommended interventions
  - Less aggressive glycaemic targets but avoid hypoglycaemia and be aware that hyperglycaemia can increase risk of infection and cause urinary incontinence, thirst and dehydration, consider whether statin therapy is beneficial.

- Recommended targets
  - HbA1c less than 69 mmol/mol but greater than or equal to 64 mmol/mol
  - FPG 7.0 to 12.0 mmol/L
  - BP less than 150/90 mmHg

Table 1 Target setting, recommended interventions and treatment goals according to the level of frailty

Level of frailty	Status	Treatment goals	Recommended interventions	Recommended targets
Healthy/pre-frail/mild frailty	• Functional and independent • Life expectancy of >10 years	• Reverse frailty or limit its progression • Maintain functional status, independence and QoL • Prevent or delay macro/ microvascular complications	• Tight glycaemic control • Resistance exercise and nutritional interventions. • Statin therapy unless contraindicated/ not tolerated	• HbA1c 58 mmol/mol but ≥53 mmol/mol • FPG 5.0–8.0 mmol/L • BP <140/90 mmHg
Moderate frailty	• > 2 comorbidities • Reduced life expectancy	• Prevent decline in QoL • Limit the progression of microvascular complications • Avoid metabolic emergencies such as hypoglycaemia	• Glycaemic control. • Assess and reduce cognitive decline • Statin therapy unless contraindicated/ not tolerated	• HbA1c <64 mmol/mol but ≥ 58 mmol/mol • FPG 6.0– 10.0 mmol/L • BP <140/90 mmHg

Severe frailty	• Significant comorbidity, functional deficits, and limited independence • Markedly reduced expectancy	• Improve QoL by reducing symptoms or hospitalisations • Maintain functional status, preventing further lower limb dysfunction, preventing significant disability	• Less aggressive glycaemic targets but avoid hypoglycaemia and be aware that hyperglycaemia can increased risk of infection and cause urinary incontinence, life thirst and dehydration • Consider whether statin therapy is beneficial	• HbA1c <69 mmol/mol but ≥ 64 mmol/mol • FPG 7.0–12.0 mmol/L • BP <150/90 mmHg

Diet & Lifestyle

- Do not restrict diet if the BMI is low or the person is losing weight.
- Frail older people with diabetes may also suffer from malnutrition or sarcopenia. Therefore, the management of diabetes in older people should also focus on diet and exercise. Any resulting weight loss from lifestyle intervention in frail older people with diabetes or overweight should be modest (e.g. 5 to 7%) (Strain et al 2021).
- The ageing process is characterised by a progressive loss of function, a negative impact on nutrition associated with malnutrition, a resistance to anabolism and increased likelihood of frailty and death (Bauer et al 2013). Poor nutrition intake is common in this population group, and a spontaneous reduction in protein intake is observed (Tamura et al 2020). Optimal protein intake recommendations are for 1 to 1.5g/kg/day, but older people with severe kidney disease (eGFR less than 30ml/min) and not on dialysis, may need to limit their protein intake (Bauer et al 2013; Volkert et al 2022).

Choosing medications

- SWL T2DM guidelines can be used to support decision-making with choosing the most appropriate medication classes, and the SWL formulary can be referred to when deciding on the most appropriate agent to prescribe in each class.
- Management of older people with diabetes needs to be individualised to take into consideration multiple long-term conditions, frailty status and age-related changes in physiology, as well as the pharmacokinetics and pharmacodynamics of diabetes drugs.
- There is an increased risk of harm, affecting both quality and quantity of life, if these factors are not addressed.
- The ACCORD, ADVANCE & VADT studies demonstrated that intensive glycaemic control in older patients with a longer duration of type 2 diabetes with

co-morbidities and at high CV risk did not improve microvascular, macrovascular or mortality outcomes and may do harm (Pozzilli et al 2014)

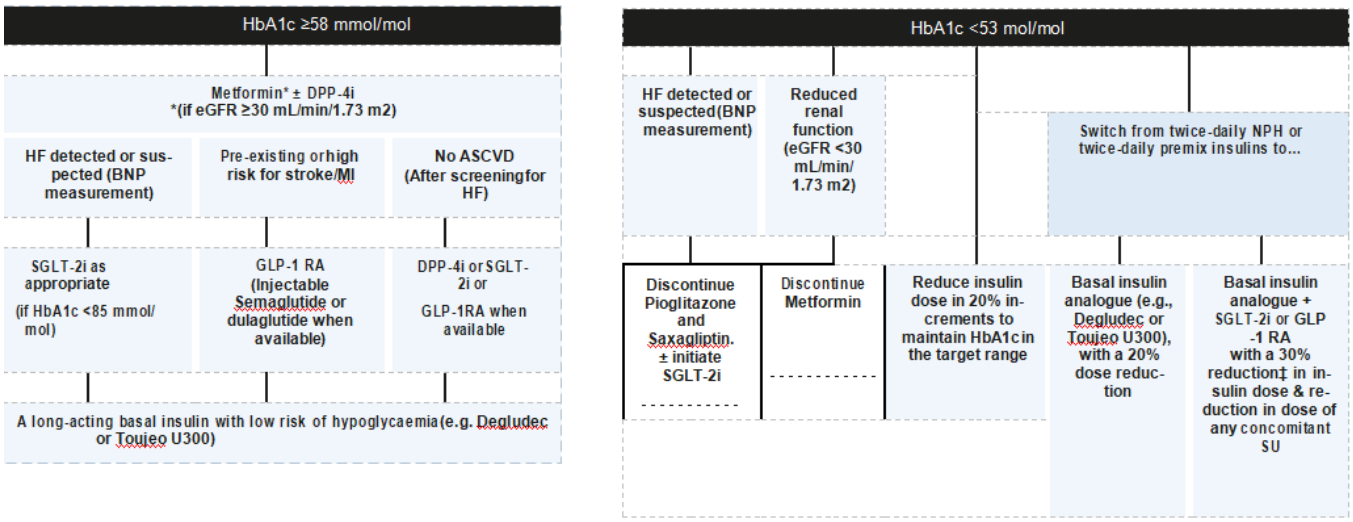
- These patients will benefit from less stringent glycaemic targets aiming for an HbA1c of 58 to 64mmol/mol, or sometimes higher may be appropriate. The NICE decision aid can be used to support the conversation to agree targets with patients.
- Consider basal insulin and test urine for c-peptide in underweight sarcopenia type cohorts.
- Patients who have symptomatic hyperglycaemia with HbA1c greater than or equal to 97 mmol/l or random glucose greater than or equal to 20 mmol/l. Please refer to Pan London Hyperglycaemia pathway.
- Re-evaluate level of frailty and diabetes control within 3 months of any intervention.
- A recently published expert consensus statement authored by Strain and colleagues (2021) summarised the relative merits of various drug classes in older people with diabetes and recommend simple glycaemic management algorithms according to frailty status.
- Tables 2,3 and 4 show both treatment escalation and simplification or de-escalation plan for older Type 2 adults with mild frailty **(2)**, moderate frailty **(3)** or severe frailty **(4)**.
- For sick day rules please follow NICE (2023) https://cks.nice.org.uk/topics/diabetes-type-2/management/management-adults/#sick-day-rules

Healthy/pre-frail/mild frailty (Table 2)

- In those with HbA1c of 58 mmol/mol or higher
    - Metformin (if eGFR $\geq$30mL/min) $\pm$ DPP4i are first line choices
    - If Heart Failure (HF) detected or suspected (BNP measurement) consider adding SGLT-2i as appropriate (if HbA1c <85 mmol/mol)
    - If pre-existing or high risk for stroke or MI, consider adding GLP-1 RA (Injectable semaglutide or dulaglutide when available)
    - If no Atherosclerotic Cardiovascular Disease (ASCVD- after screening for HF) can use DPP-4i or SGLT-2i or GLP-1RA when available.
    - As a third line choice after the above options, consider adding a long-acting basal insulin with low risk of hypoglycaemia (e.g. Degludec® or Toujeo® U300)
- In those with HbA1c less then 53mmol/mol

- If renal function is eGFR less than 30 mLmin/1.73 m2, discontinue metformin
- If HF detected or suspected (BNP measurement), discontinue Pioglitazone and Saxagliptin ± initiate SGLT-2i
- For those on insulin, consider reducing the insulin dose in 20% increments to maintain HbA1c in the target range
- Consider switching from twice-daily NPH or twice-daily premix insulins to either
    - Basal insulin analogue (e.g., Degludec or Toujeo U300), with a 20% dose reduction or
    - Basal insulin analogue with SGLT-2i or GLP-1 RA with a 30% reduction in insulin dose and reduction in dose of any concomitant SU

Table 2- Healthy/pre-frail/mild frailty: (Figure 1a Strain et al 2021).



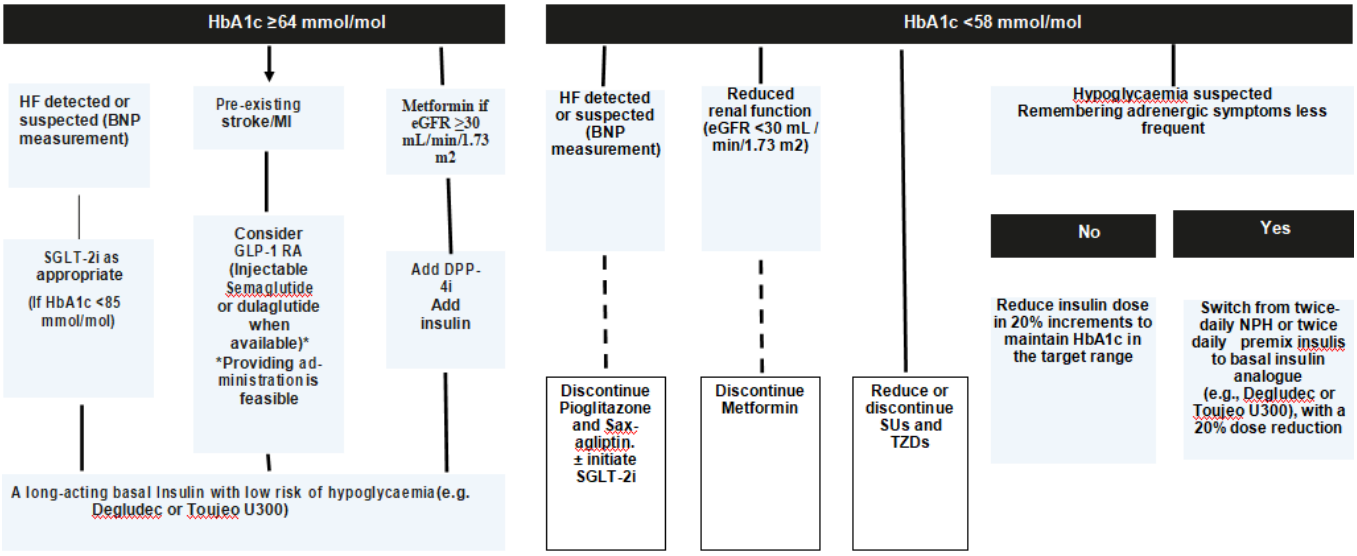
Moderate frailty (Table 3)

Re-evaluate the level of frailty and diabetes control within 3 months of any intervention.

- For those with HbA1c is 64mmol/mol or more
    - If HF detected or suspected (BNP measurement), consider SGLT2i if HbA1c is less then 85mmol/mol.
    - If pre-existing stroke/MI; Consider GLP-1 RA (Injectable semaglutide or dulaglutide when available if administration is feasible)
    - Use metformin if eGFR greater than or equal to 30 mL/ min/1.73 m^2; consider adding DPP-4i or insulin
    - consider a long-acting basal insulin with low risk of hypoglycaemia (e.g. Degludec or Toujeo U300)
- For those with HbA1c less than 58mmol/mol

- If HF detected or suspected (BNP measurement), discontinue pioglitazone and saxagliptin with or without SGLT-2i
- Reduce or discontinue SUs and TZDs
- Reduced renal function (eGFR less than 30 mL/min/1.73 m^2) discontinue Metformin
- If hypoglycaemia is suspected (remembering adrenergic symptoms less frequent), switch from twice-daily NPH or twice daily premix insulins to basal insulin analogue (e.g., Degludec or Toujeo U300), with a 20% dose reduction
- If hypoglycaemia not suspected, reduce insulin dose in 20% increments to maintain HbA1c in the target range

Table 3: **Moderately frail (Figure 1b Strain et al 2021).**



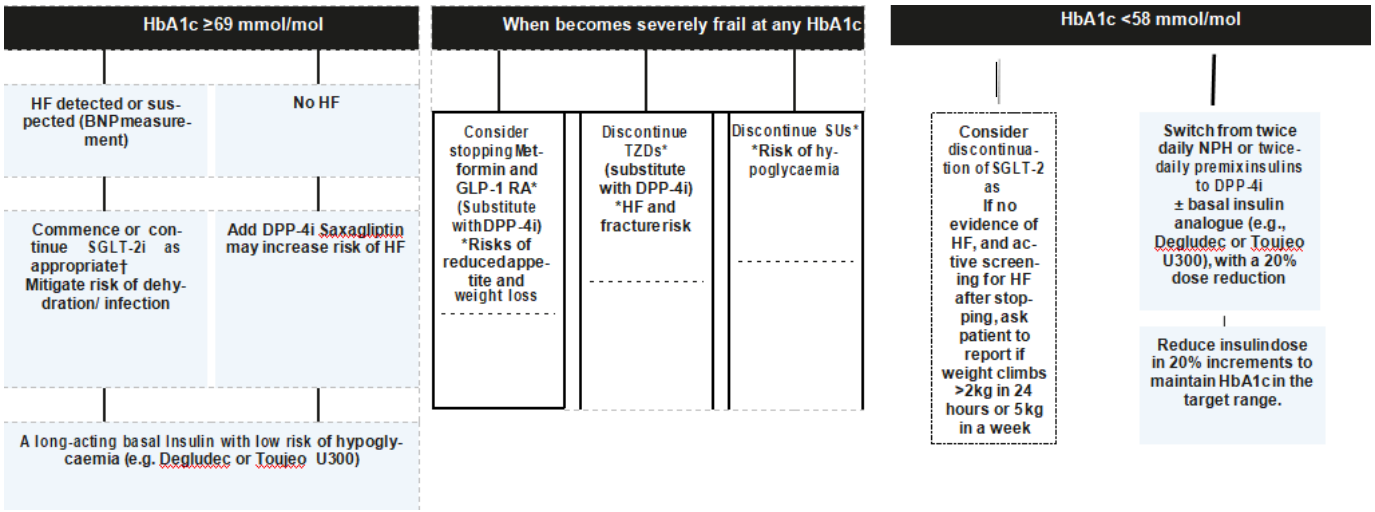
Severe frailty (Table 4)

Re-evaluate level of frailty and diabetes control within 3 months of any intervention.

- Consider stopping Metformin and GLP-1 RA due to risks of reduced appetite and weight loss and substitute with DPP-4i
- Consider stopping TZDs due to HF and fracture risk (substitute with DPP-4i)
- Consider stopping SU's due to risk of hypoglycaemia
- If HbA1c is 69mmol/mol or greater
    - If HF detected or suspected (BNP measurement), consider starting or continue SGLT-2i as appropriate, (mitigate risk of dehydration or infection)
    - If no HF, consider adding a DPP-4i, note that saxagliptin may increase risk of HF
    - If needed, consider a long-acting basal insulin with low risk of hypoglycaemia (e.g. Degludec or Toujeo U300)
- If HbA1c is less than 58mmol/mol

- Consider discontinuation of SGLT-2i's if no evidence of HF, and active screening for HF after stopping, ask patient to report if weight climbs more than 2kg in 24 hours or 5kg in a week
- Switch from twice daily NPH or twice-daily premix insulins to DPP-4i with or without a basal insulin analogue (e.g., Degludec or Toujeo U300), with a 20% dose reduction. Reduce insulin dose in 20% increments to maintain HbA1c in the target range.

Table 4: **Severely frail (Figure 1c Strain et al 2021).**



- Severe frailty guidelines are largely "evidence-free" and represent stakeholders' recommendations.
- Guidance for the last 6 months of life are being formulated at a national level. There is an overview of diabetes management in the last days of life from TREND (2021) that can be found in Appendix 2.

References and resources

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Document History

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Appendix 1: Pros and cons of antidiabetic therapies for the treatment of type 2 diabetes in older adults (Table 3 Strain et al 2021).

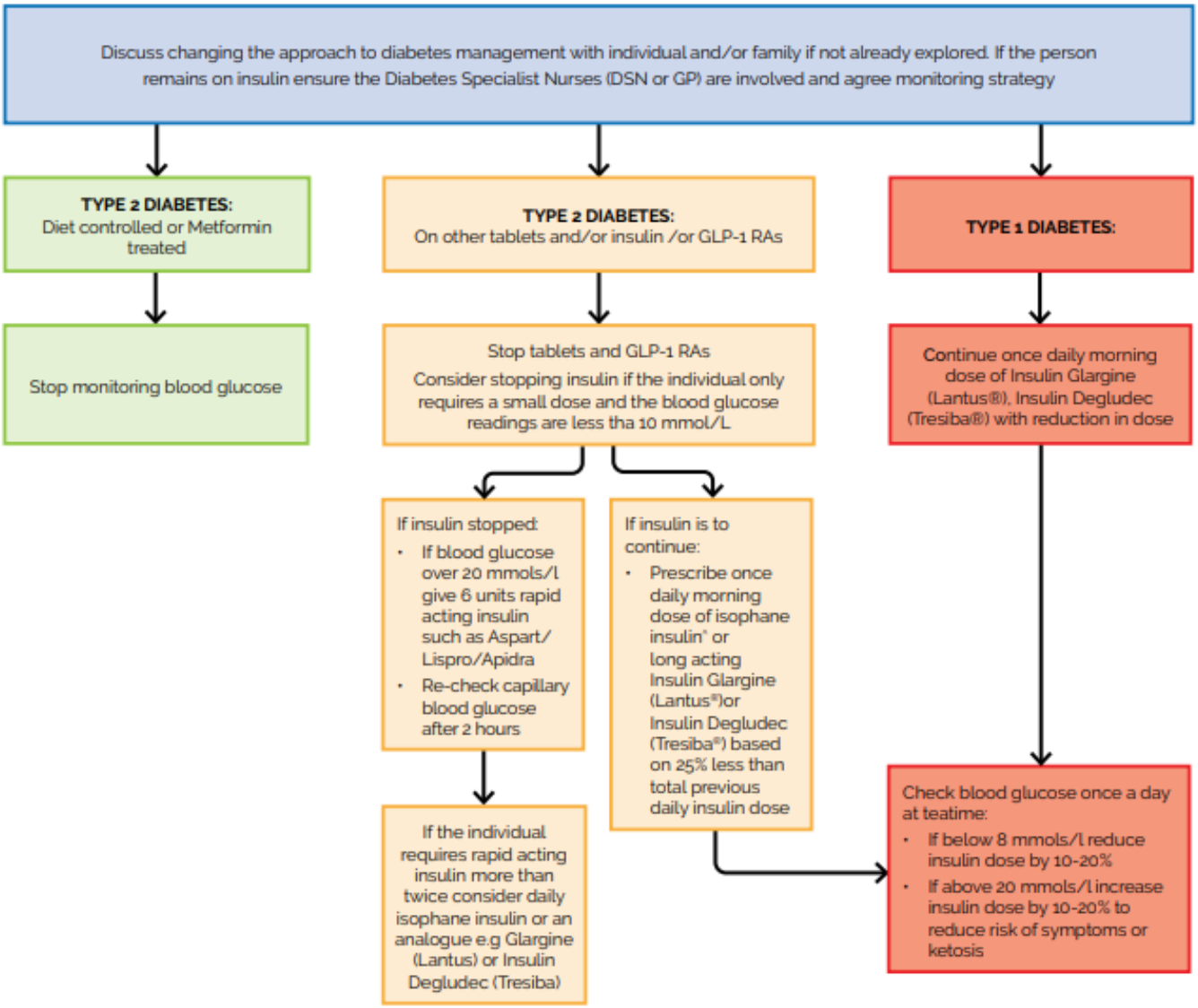
Drug	Pro	Con
Metformin Alters mitochondrial cell energetics to inhibit gluconeogenesis, oppose the action of glucagon, and increase insulin sensitivity	• Inexpensive • Well-established, generally well-tolerated standard therapy • Potential CV benefit demonstrated in UKPDS study • Low hypoglycaemia risk • Can be combined with all other diabetes therapies	• Reduced appetite and gastrointestinal disturbance. • Possible association with vitamin B12 deficiency • Moderate weight loss seen in some patients may be undesirable with frailty. • Contraindicated in severe renal failure (eGFR<30 ml/min). • Should be used with caution in those with impaired hepatic function or cardiac failure, recurrent dehydration/AKI episodes due to increased risk of lactic acidosis
Sulfonylureas and glinides Stimulate pancreatic insulin secretion regardless of blood glucose concentration	• Inexpensive • Can be combined with other therapies. • Increased potency in older adults may sometimes be beneficial	• Require functioning beta-cells. • Hypoglycaemia risk especially with renal impairment • Increased potency following weight loss (with improved insulin sensitivity) may further increase hypoglycaemia risk
DPP-4 inhibitors Inhibit breakdown of endogenous GLP-1, which glucose-dependently stimulates insulin secretion and inhibits glucagon secretion	• Well tolerated. • Formally tested in older adults • May delay disease progression if used early with Metformin. • Low risk of hypoglycaemia • Safe in all stages of renal failure, at an appropriate dose • No effect on weight	• Moderate glucose-lowering efficacy • Neutral effect on CV death, MI, stroke, and hospitalisation for heart failure, in contrast to SGLT-2is and GLP-1 RAs • Possible issues with increased hospitalisation for heart failure with Saxagliptin or Alogliptin) • Hepatic impairment — avoid vildagliptin; avoid Saxagliptin and Alogliptin if severe hepatic impairment.

Drug	Pro	Con
		• Generic Sitagliptin is most cost-effective with dose adjustment for renal impairment • Relatively expensive
SGLT-2 inhibitors Inhibit reabsorption of glucose (from renal tubules), leading to increased urinary glucose output and osmotic diuresis	• CVOTs have shown reduction in MACE. • Benefits demonstrated for patients with heart failure. • Potential benefit in reducing progression of renal impairment. • Low hypoglycaemia risk	• Weight loss could result in sarcopenia. • Risk of candidiasis • Potential increased urinary incontinence • Lack of glucose-lowering efficacy in established renal impairment. • Risk of euglycaemic diabetic ketoacidosis • Fluid volume depletion • Urinary Tract Infection
GLP-1 RAs DPP-4-resistant analogues of GLP-1 stimulate insulin secretion and inhibit glucagon secretion proportionately to blood glucose concentration, and also reduce appetite	• CVOTs have shown CV benefits with some, particularly in patients with ASCVD, and those at high risk of CV events. • Reno-protective effects • Low hypoglycaemia risk despite good glucose-lowering efficacy • Once-weekly administration possible with some • A once-daily oral formulation of Semaglutide is available	• Weight loss could result in sarcopenia. • Nausea is common, and reduced appetite could be problematic. • Most are given by s/c injection. • Relatively expensive • Oral Semaglutide is restricted for use in patients, with genuine needle-phobia or, those requiring healthcare assistance to administer an injectable GLP-1
TZDs Increase cellular expression of glucose transporters, thereby	• Generally well tolerated. • Low hypoglycaemia risk	• Fluid retention may exacerbate heart failure

Drug	Pro	Con
increasing insulin sensitivity and peripheral glucose uptake	• Potential CV benefit with pioglitazone	• Risk of osteoporosis and fractures Ongoing debate regarding risk of bladder cancer
Exogenous basal insulin Binds to insulin receptors in liver to inhibit glycogenolysis and gluconeogenesis, and binds to peripheral insulin receptors (muscle, adipose) to stimulate glucose uptake		
NPH insulin	• Established efficacy. • Inexpensive	• Requires resuspension. • May need twice daily injections • Weight gain (limited harm) • Hypoglycaemia risk • Variable glucose-lowering effect from injection to injection
First-generation basal insulin analogues [41] Insulin glargine Insulin detemir	• Established efficacy. • Lower hypoglycaemia risk than NPH insulin • Cost lower than ultra-long-acting insulins. • Once-daily injection possible • Insulin detemir associated with relatively little weight gain	• Requirement for injection at same time each day may be problematic. • Hypoglycaemia risk
Ultra-long-acting insulin analogues [54] Insulin Degludec Insulin glargine U300	• Established efficacy. • Increased dosing flexibility • Lower hypoglycaemia risk than other basal insulins • Stable glucose-lowering action	• More expensive than other basal insulins (possibly offset by reduced need for nurse visits ± reduced doses and longer lasting pens)

Appendix 2 Algorithm for the last days of life

(full leaflet available from TREND)



IMPORTANT INFORMATION:

- Aim for capillary blood glucose readings of 6-15 mmol/L
- Keep tests to a minimum. It may be necessary to perform some tests to ensure unpleasant symptoms do not occur due to low or high blood glucose
- It is difficult to identify symptoms due to "hypo" or hyperglycaemia in a dying person
- If symptoms are observed it could be due to abnormal blood glucose levels
- Test urine or blood for glucose if the person is symptomatic
- Observe for symptoms in previously insulin treated individual where insulin has been discontinued
- Flash glucose monitoring may be useful in these individuals to avoid finger prick testing