Diabetes and frailty: guidance on the management of older adults with type 2 diabetes

This summary was developed by Guidelines and Dr Strain, based on the guidance developed by Strain WD et al., with the support of a sponsorship from Novo Nordisk UK. See end of summary for full disclaimer.

**Figure 1a: Treatment escalation and simplification/de-escalation plan for older adults living with type 2 diabetes and a) no or mild frailty, b) moderate frailty, or c) severe frailty.**

**Healthy/pre-frail/mild frailty**

- Re-evaluate level of frailty annually and within 3 months of intervention.

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**Figure 1a: Treatment escalation and simplification/de-escalation plan for older adults living with type 2 diabetes and a) no or mild frailty, b) moderate frailty, or c) severe frailty.**

- Re-evaluate level of frailty annually and within 3 months of intervention.
Figure 1b: Treatment escalation and simplification/de-escalation plan for older adults living with type 2 diabetes and a) no or mild frailty, b) moderate frailty, or c) severe frailty.

- **Moderate frailty** is defined as individuals with >2 comorbidities, some impairments in activities of daily living with a reduced life expectancy.

### Moderately frail
Re-evaluate level of frailty annually and within 3 months of any intervention.

- **HbA₁c ≥64 mmol/mol (≥8.0%)**
  - HF detected or suspected (BNP measurement)
  - Pre-existing stroke/MI
  - Metformin
    - If eGFR ≥30 ml/min/1.73 m²
    - Consider GLP-1RA (semaglutide or dulaglutide)
    - Providing self-administration feasibility
  - SGLT2i as appropriate
  - Add DPP4i
  - Add insulin
  - A long-acting basal insulin with low risk of hypoglycaemia (e.g., idegludec or Iglar U300)

- **HbA₁c <58 mmol/mol (<7.5%)**
  - HF detected or suspected (BNP measurement)
  - Reduced renal function (eGFR ≥30 ml/min/1.73 m²)

### Treatment escalation
- Hypoglycaemias suspected
  - Remembering adrenergic symptoms less frequent

### Treatment de-escalation
- No
- Yes

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BNP = B-type natriuretic peptide; DPP-4i = dipeptidyl peptidase-4 inhibitor; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide 1 receptor agonist; HbA₁c = glycated haemoglobin; HF = heart failure; Iglar = insulin glargine; MI = myocardial infarction; NPH = neutral protamine Hagedom; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SUs = sulfonylureas; TZDs = thiazolidinediones.
Severe frailty comprises significant comorbidity, functional decline, and limited independence. Likely to cause a markedly reduced life expectancy.

Severe frailty guidelines are largely "evidence-free" and present stakeholders' recommendations. Patients may already be receiving treatment with metformin, SUs, or their combination, plus or minus basal or premix insulins as explained in the preceding text.

- Consider stopping metformin and GLP-1 RA (substitute with DPP4i)
- Discontinue SUs
- Discontinue TZDs (substitute with DPP4i)

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

- HF detected or suspected (BNP measurement)
- No HF

HbA1c >55 mmol/l (7.5%)

Switch from twice daily NPH or twice daily premix insulin to DPP4i

A long acting basal insulin with low risk of:

- Hypoglycaemia
- Mitigate risk of dehydration/infection
- Risks of reduced appetite and weight loss
- HF and fracture risk
- Risk of hypoglycaemia

BNP = B-type natriuretic peptide; DPP4i = dipeptidyl peptidase-4 inhibitor; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide 1 receptor agonist; HbA1c = glycated haemoglobin; HF = heart failure; NPH = neutral protamine Hagedorn; SGLT2i = sodium-glucose cotransporter 2 inhibitors.
Overview

- This Guidelines summary provides the key points for primary care. Please refer to the full guideline for the complete set of recommendations and a review of the evidence.

Background and aims

- This guidance aims to provide prescriptive guidance for glycaemic management in older adults with diabetes, according to frailty, including frailty-specific glycaemic targets.

- For the assessment of frailty in older adults with type 2 diabetes, and on appropriate glucose target setting, please refer to the Guidelines summary on Type 2 diabetes mellitus in older people.

- Detailed advice is needed for healthcare professionals caring for older people with diabetes on how to safely prescribe newer glucose-lowering therapy, and when to intensify or de-escalate treatment.

- In order to overcome treatment inertia, it is important to provide guidance on de-prescribing/de-escalation, and to highlight the complications and comorbidities of type 2 diabetes in older adults that should be considered as part of a holistic management and multifactorial management approach.

- Medical, psychological, and functional issues such as sarcopenia, heart failure, hypertension, lipid profile, urinary incontinence, cognitive decline, depression, diet, physical condition, falls and fractures, swallowing difficulties, an increased need for assistance with administration of medication by carers or care home staff, and polypharmacy can all impact upon adherence and the pharmacodynamic response to glucose-lowering therapies.

Degrees of frailty and treatment goals in older adults with type 2 diabetes

- Frailty is not a simple correlate of age, necessarily progressive, nor irreversible. Some older adults with diabetes have numerous diabetes-related comorbidities, limited cognitive or physical functioning, and a severe degree of frailty, whereas others may have few or no comorbidities and be very active with only a mild degree of frailty.

- Prognosis and hence appropriate diabetes treatment goals for older adults with diabetes vary greatly according to frailty and therefore need to be individualised. For example, older and more frail people with diabetes who have

<table>
<thead>
<tr>
<th>Table 1: Known modifiers of HbA₁c older adults</th>
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<tbody>
<tr>
<td>Artificially increases HbA₁c (higher risk of hypoglycaemia if aggressive targets established)</td>
</tr>
<tr>
<td>Iron deficiency</td>
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<td>B12 deficiency</td>
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<tr>
<td>Anaemia of chronic disease</td>
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<tr>
<td>Chronic opioid use</td>
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</table>

HbA₁c = glycated haemoglobin.
significant comorbidity or substantial cognitive or functional impairments are less likely to live long enough to reap the benefits of long-term intensive diabetes management, such as a reduced risk of vascular complications. They are also more likely to suffer serious adverse effects from hypoglycaemia.

A further issue to consider when assessing HbA1c in older adults is the accuracy of the metric itself. There are multiple comorbidities that confound glycated haemoglobin (see Table 1).

Once established, apart from age and gender, frailty is the single biggest predictor of mortality in older adults. As a result, frailty, rather than comorbidity, underpins target setting, recommended interventions and treatment goals in older adults with diabetes (see Table 2).

It is important to remember that frailty is a dynamic process; a patient’s frailty categorisation may change. Re-evaluation of frailty should occur, as a minimum, at the annual diabetes review but earlier if there has been a change.
Table 3: Pros and cons of anti-diabetic therapies for the treatment of type 2 diabetes in older adults

For a review of the available therapies, please refer to the full guideline.

<table>
<thead>
<tr>
<th>Pro</th>
<th>Con</th>
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<tbody>
<tr>
<td><strong>Metformin</strong></td>
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<tr>
<td>Alters mitochondrial cell energetics to inhibit gluconeogenesis, oppose the action of glucagon, and increase insulin sensitivity(^7)</td>
<td>Reduced appetite and gastrointestinal disturbance</td>
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<td></td>
<td>Possible association with vitamin B12 deficiency(^9)</td>
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<td></td>
<td>Moderate weight loss seen in some patients may be undesirable with frailty</td>
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<td></td>
<td>Contraindicated in renal impairment</td>
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<tr>
<td></td>
<td>Should be used with caution in those with impaired hepatic function or cardiac failure, due to increased risk of lactic acidosis</td>
</tr>
<tr>
<td><strong>Sulphonylureas and glinides</strong></td>
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<tr>
<td>Stimulate pancreatic insulin secretion regardless of blood glucose concentration(^8)</td>
<td>Require functioning beta cells</td>
</tr>
<tr>
<td></td>
<td>Hypoglycaemia risk(^9)</td>
</tr>
<tr>
<td></td>
<td>Increased potency following weight loss (with improved insulin sensitivity) may further increase hypoglycaemia risk</td>
</tr>
<tr>
<td><strong>DPP-4 inhibitors</strong></td>
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<tr>
<td>Inhibit breakdown of endogenous GLP-1, which glucose-dependently stimulates insulin secretion and inhibits glucagon secretion(^8)</td>
<td>Moderate glucose lowering efficacy</td>
</tr>
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<td></td>
<td>Neutral effect (apart from saxagliptin) on CV death, MI, stroke, and hospitalisation for heart failure,(^12) in contrast to SGLT-2is and GLP-1 RAs</td>
</tr>
<tr>
<td></td>
<td>Possible issues with increased hospitalisation for heart failure, with saxagliptin (± alogliptin)(^{13})</td>
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<tr>
<td></td>
<td>Relatively expensive</td>
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<tr>
<td><strong>SGLT-2 inhibitors</strong></td>
<td></td>
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<tr>
<td>Inhibit reabsorption (from renal tubules) of glucose, leading to increased urinary glucose output and osmotic diuresis(^{14})</td>
<td>Weight loss could result in sarcopenia</td>
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<td>Risk of candidiasis</td>
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<td></td>
<td>Potential increased urinary incontinence</td>
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<td></td>
<td>Lack of glucose-lowering efficacy if established renal impairment(^{17})</td>
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<td></td>
<td>Risk of euglycaemic diabetic ketoacidosis</td>
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<td></td>
<td>Fluid volume depletion</td>
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<td><strong>GLP-1RAs</strong></td>
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<tr>
<td>Stimulate insulin secretion, inhibit glucagon secretion, and also reduce appetite. GLP-1 RAs work in a glucose-dependent manner(^8)</td>
<td>Weight loss could result in sarcopenia</td>
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<tr>
<td></td>
<td>Nausea is common, and reduced appetite could be problematic</td>
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<tr>
<td></td>
<td>Most are given by s.c. injection</td>
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<td></td>
<td>Relatively expensive</td>
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\(^{1}\) For a review of the available therapies, please refer to the full guideline.
### Hypoglycaemia in older adults with diabetes

- In frail older adults, hypoglycaemic symptoms such as dizziness, confusion, and visual disturbances, which often present more commonly than adrenergic symptoms (palpitations, sweating, tremors), can be mistaken for dementia or neurological problems\(^{30,31}\).
- Older adults with type 2 diabetes are more prone to hypoglycaemia as a result of various factors including polypharmacy,\(^{22,23}\) endocrine deficits, suboptimal water and food intake, and cognitive impairment, as well as cardiovascular disease (CVD) and renal dysfunction\(^{32,34,35}\).
- In addition to being at increased risk of hypoglycaemia, frail older adults are more vulnerable to its consequences. Hypoglycaemia in older people increases the risk of serious outcomes such as falls, fractures, cognitive decline, hospitalisation, CVD (thought to involve cardiac conduction disturbances), and all-cause mortality\(^{36}\).

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### TZDs

| TZDs
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<tr>
<td>Increase cellular expression of glucose transporters, thereby increasing insulin sensitivity and peripheral glucose uptake(^{21})</td>
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### 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

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<th>Exogenous basal insulin</th>
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<tr>
<td>NPH insulin(^{28})</td>
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<tr>
<td>First generation basal insulin analogues(^{12})</td>
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<tr>
<td>Insulin glargine</td>
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<td>Insulin detemir</td>
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<tr>
<td>Ultra-long acting insulin analogues(^{29})</td>
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<tr>
<td>Insulin degludec</td>
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<td>Insulin glargine U300</td>
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ASCVD=atherosclerotic cardiovascular disease; CV=cardiovascular; CVOT=cardiovascular outcome trial; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide 1; GLP-1RA=glucagon-like peptide 1 receptor agonist; NPH=neutral protamine Hagedorn; PROactive=PROspective pioglitAzone Clinical Trial In macroVascular Events; SGLT2is=sodium/glucose cotransporter-2 inhibitors; s.c=subcutaneous; TZD=thiazolidinedione; UKPDS=UK Prospective Diabetes Study.
The avoidance of hypoglycaemia must be a paramount concern in the diabetes management of the frail older adult, and it cannot be assumed that regimens previously well tolerated in this respect will remain so. The treatments for type 2 diabetes with the greatest propensity for causing hypoglycaemia are insulin and the insulin secretagogues—sulphonylureas (SUs) and glinides (see Table 3).

Glycaemic management in older adults with diabetes, according to frailty

- The choice of agents in the management of diabetes in older adults should be based on frailty status and the extent of co-existing chronic illness and cognitive and functional status.\(^{11,37,38}\)
- It is recommended to follow the simple glycaemic management algorithm depicted in (Figure 1) for older adults with type 2 diabetes, according to their level of frailty.
- Individuals may already be receiving treatment with metformin, SUs, or their combination plus or minus basal or premix insulin. In some cases, discontinuation of certain drugs is advocated, but with suitable replacements suggested. When escalating therapy, the risk of hypoglycaemia should be considered for those on insulin or SUs. It is not necessary to automatically discontinue an SU if there is no evidence of hypoglycaemia, although the dose should be reduced in the short term. For people on neutral protamine Hagedorn (NPH) or premix insulin, switching to a basal insulin analogue (glargine, detemir, or degludec) with a DPP-4i can be considered.

Treatment simplification/de-escalation guidance in the glycaemic management of older adults with diabetes

- As a person with diabetes gets older, regimen simplification, switching or de-escalation may be necessary, depending on their level of frailty and HbA\(_1c\) levels. When contemplating modification of a diabetes regimen, it is helpful to conduct a basic audit of the status of the person with diabetes. An individual at advanced age (e.g., ≥75 years), identified as being moderately or severely frail, with an HbA\(_1c\) value <53 mmol/mol (<7.0%) would suggest a high risk of occurrence of complications from hypoglycaemia. Consideration should be given to de-escalation of therapies that may induce this feared complication, such as SUs, or SU and insulin combinations.
- Many frail older adults with type 2 diabetes will have had their regimens intensified over preceding years when they were in better health, and many others will have been intensified or started on SUs or insulin more recently during acute hospital admissions, e.g., for infections, when their blood glucose levels might have been atypically high. In addition, in older frail adults who start to receive assistance in taking their medications, either following admittance to a care home or in another setting, treatment adherence that may previously have been poor can suddenly improve dramatically, leading to a fall in HbA\(_1c\) levels.
- It should not be assumed that treatment regimens that have been intensified historically, or were initiated in hospitals should continue indefinitely. In the latter case, a return to pre-admission medications may be needed to avoid hypoglycaemia, although, in the case of longstanding symptomatic poor control, the escalated regimen may be appropriate if it is tolerated and the older adult is not severely frail.
- Primary care teams therefore need to consider each person with diabetes individually, but they should feel empowered to de-escalate a discharge regimen if appropriate.
- As frailty ensues, older adults lose adipose tissue, which, in turn, reduces underlying insulin resistance. As a result, much smaller doses of insulin are often sufficient to provide adequate and reproducible glycaemic control.
- Older adults with diabetes who have inadequate glycaemic control or recurrent hypoglycaemia on their current treatment regimen, who have had a
significant change in circumstances, e.g., a move into a care home, or who are no longer be able to manage complex insulin therapy (may also apply to those with mild frailty whose cognitive or functional ability declines), may benefit from regimen simplification or de-escalation.

- It is recommended to follow the simple algorithm depicted in (Figure 1) for treatment simplification/de-escalation in the glycaemic management of older adults with type 2 diabetes.

- De-escalation of non-insulin glucose-lowering regimens can be achieved by either lowering the dose or discontinuing some medications.

- Insulin regimens can either be de-escalated by reduction of the dose or simplified by switching to more manageable regimens with lower risk of hypoglycaemia, for example from premix insulins to a basal insulin analogue with or without glucagon-like peptide 1 receptor agonist (GLP-1RA) or sodium-glucose cotransporter-2 inhibitor (SGLT2).

- It is important to be mindful that SUs and GLP-1RAs raise endogenous insulin secretion, hence they decrease the unit dose requirement for exogenous insulin compared with insulin monotherapy. A sensible approach would be either to reduce the dose of SU when administered in combination with insulin or to discontinue SU treatment altogether, in favour of insulin monotherapy.

- Thiazolidinediones also increase sensitivity to insulin, so again, compensatory dose adjustments are required when these are used in combination with insulin. In a small proportion of individuals, stopping insulin suddenly can precipitate diabetic ketoacidosis, so insulin should be withdrawn slowly and response to each dose adjustment should be monitored, ideally within a month.

- Often during reviews of frail older adults, individuals will be identified with a low HbA1c (<48 mmol/mol; <6.5%). It should be considered that insulin resistance may have subsided sufficiently that no therapies are required. In this scenario, it is reasonable to discontinue all antihyperglycaemic agents and review control after 3 months, against an individualised HbA1c goal.

- Anti-hyperglycaemic therapies can work in synergy, hence the removal of one (even low-dose) component of a regimen can result in a dramatic rise in HbA1c (rebound hyperglycaemia). This highlights the importance of monitoring HbA1c and reviewing the individual if medication is de-escalated. HbA1c can rise sharply after stopping a SU, even if this has been taken for many years, so it may be appropriate to restart at a lower dose in such cases.

- Patients should be reviewed after each change in regimen (i.e. a 3-month review program with an HbA1c measurement after every withdrawal) to check that glycaemic control (and other risk factor management) is appropriate for the patient’s frailty category, and also to check whether frailty status has changed.

- In all cases it is important to explain to the individual (and relatives) that the reasons for de-escalation are concerned with improving symptoms, function and QoL, frailty status, and comorbidity. This is to avoid the misconception that de-escalation represents ‘giving up hope’ on the patient.

Conclusion

- The management of older adults with type 2 diabetes is complicated by comorbidities, shortened life expectancy, and exaggerated consequences of adverse effects from treatment, such as hypoglycaemia.

- The assessment of frailty should be a routine component of a diabetes review for all older adults, and then glycaemic targets and therapeutic choices should be modified accordingly. After each intervention, frailty should be re-assessed, cognisant of the fact that frailty is a dynamic process and may be
improved by the elimination of both hyper- and hypoglycaemia.

References


29. Valentine V, Goldman J, Shubrook JH. Rationale for, initiation and titration of the basal insulin/GLP-1RA fixed-ratio combination products, IDegLira and IGLarLixi, for the management of type 2 diabetes. Diabetes Ther 2017; 8: 739–752.


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**About this management algorithm**

**Sponsor:** Guidelines identified a need for clinical guidance in a specific area and approached Novo Nordisk for a sponsorship to support the development of a management algorithm. This algorithm was developed by Guidelines and Dr. Strain. The content is independent of and not influenced by Novo Nordisk. The views and opinions expressed in this summary are not necessarily those of Novo Nordisk, or of Guidelines, its publisher, advisers, or advertisers. No part of this publication may be reproduced in any form without the permission of the publisher.


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