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

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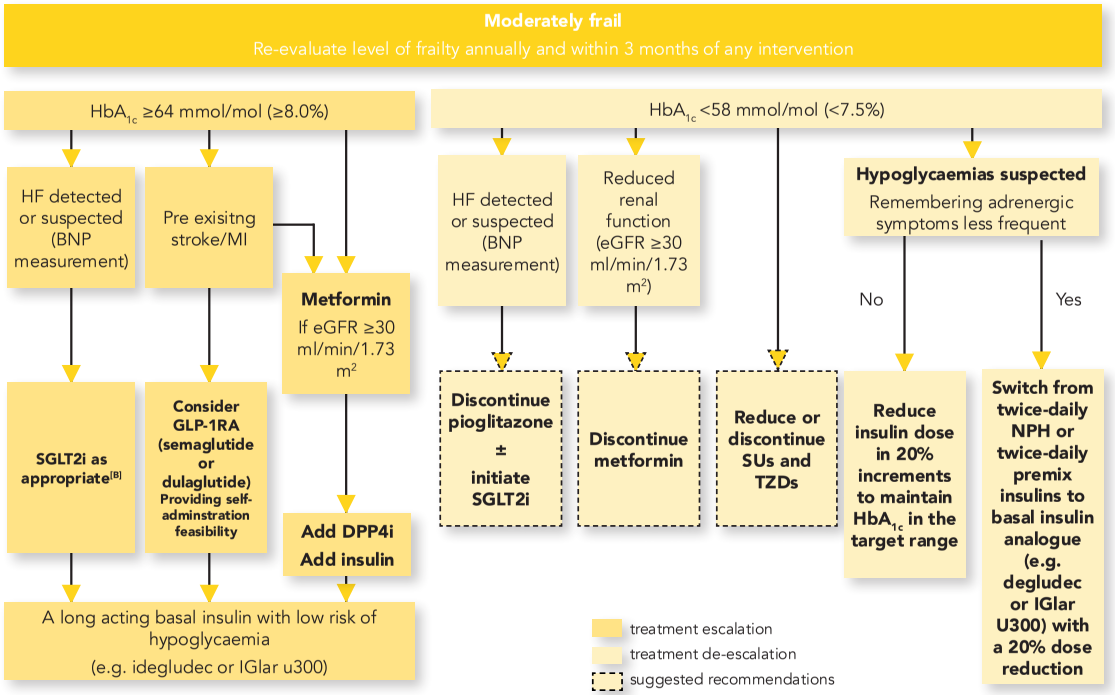
Figure 1a: Treatment escalation and simplification/de-escalation plan for older adults living with type 2 diabetes and a) no or mild frailty, b) moderate frailty, or c) severe frailty[1]

ASCVD=atherosclerotic cardiovascular disease; BNP=B-type natriuretic peptide; DPP-4i=dipeptidyl peptidase-4 inhibitor; eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide 1; GLP-1RA=glucagon-like peptide 1 receptor agonist; HbA_{1c}=glycated haemoglobin; HF=heart failure; iGlar=insulin glargine; MI=myocardial infarction; NPH=neutral protamine Hagedorn; SGLT2i=sodium-glucose cotransporter-2 inhibitor.

[A] Saxagliptin has been associated with an increased risk of symptomatic heart failure. [B] At time of publication, any SGLT-2i can be initiated at eGFR>60 ml/min/1.73 m^2 for the management of hyperglycaemia: canagliflozin can be initiated at >45 ml/min/1.73 m^2 or >30 ml/min/1.73 m^2 in people with proteinuria, dapagliflozin can be initiated at any HbA_{1c} for the management of heart failure. All SGLT-2i are less efficacious at reducing hyperglycaemia at lower eGFRs. [C] Expert recommendation.

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[1]

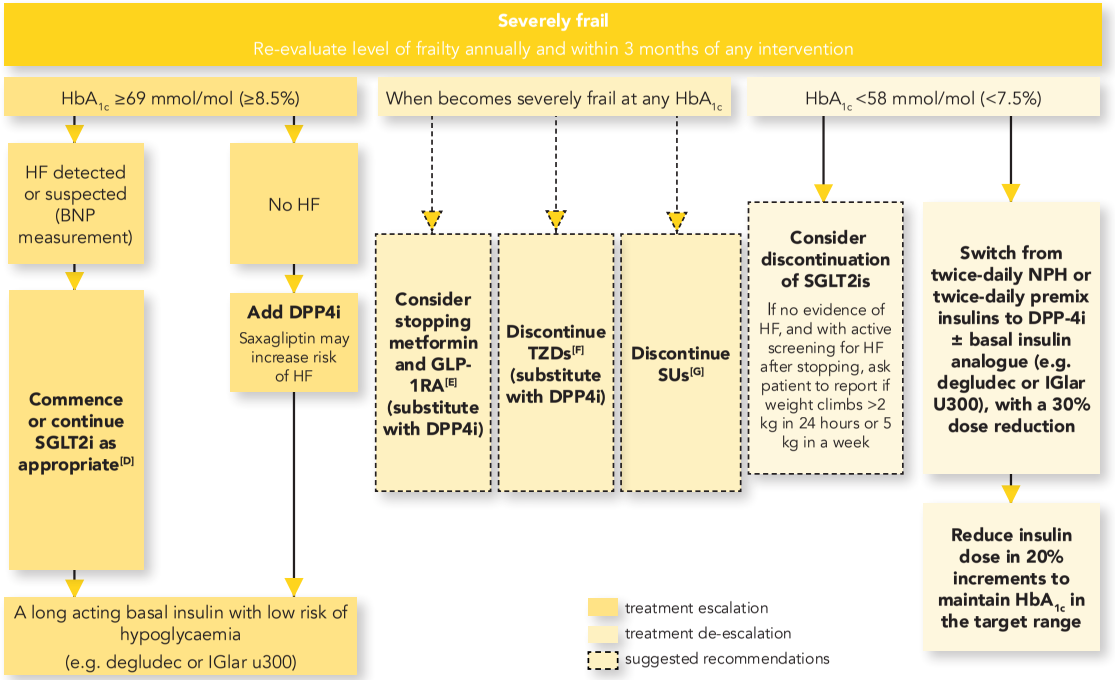
- *Moderate frailty* is defined as individuals with >2 comorbidities, some impairments in activities of daily living with a reduced life expectancy



BNP=B-type natriuretic peptide; DPP-4i=dipeptidyl peptidase-4 inhibitor; eGFR=estimated glomerular filtration rate; GLP-1RA=glucagon-like peptide 1 receptor agonist; HbA_{1c}=glycated haemoglobin; HF=heart failure; iGlar=insulin glargine; MI=myocardial infarction; NPH=neutral protamine Hagedorn SGLT2i=sodium-glucose cotransporter-2 inhibitor; SUs=sulfonylureas; TZDs=thiazolidinediones.

Figure 1c: 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[1]

- *Severe frailty* comprises significant comorbidity, functional deficits, and limited independence, likely to cause a markedly reduced life expectancy. Severe frailty guidelines are largely "evidence-free" and represent stakeholders' recommendations. Patients may already be receiving treatment with metformin, SUs, or their combination plus or minus basal or premix insulin



[D] Mitigate risk of dehydration/infection. [E] Risks of reduced appetite and weight loss. [F] HF and fracture risk. [G] Risk of hypoglycaemia. BNP=B-type natriuretic peptide; DPP-4i=dipeptidyl peptidase-4 inhibitor; eGFR=estimated glomerular filtration rate; GLP-1RA=glucagon-like peptide 1 receptor agonist; HbA_{1c}=glycated haemoglobin; HF=heart failure; NPH=neutral protamine Hagedorn; SGLT2i=sodium-glucose cotransporter-2 inhibitor; SUs=sulfonylureas; TZDs=thiazolidinediones.

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.[2] 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.[3] For example, older and more frail people with diabetes who have

Table 1: Known modifiers of HbA_{1c} older adults

Artificially increases HbA_{1c} **(higher risk of hypoglycaemia if aggressive targets established)**	**Artificially reduces HbA_{1c}** **(higher risk of complications of hyperglycaemia and hyperosmolarity)**
Iron deficiency	Bleeding conditions (e.g. peptic ulcer disease)
B12 deficiency	Haemolytic conditions (e.g. valvular cardiac disease)
Anaemia of chronic disease	Haemoglobinopathies (e.g. thalassaemia, sickle cell)
Chronic opioid use	Chronic liver disease

HbA_{1c}=glycated haemoglobin.

Table 2: Target setting, recommended intervention, and treatment goals according to frailty[H] in older adults

	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 unless contraindicated/not tolerated	■ HbA_{1c} <58 mmol/mol (<7.5%), but ≥42 mmol/mol (≥6%) ■ FPG 5.0–7.2 mmol/l ■ BP <140/90 mm Hg
Moderate frailty	■ >2 comorbidities ■ Reduced life expectancy	■ Prevent decline in QoL ■ Limit the progression of microvascular complications ■ Avoid metabolic emergencies such hypoglycaemia	■ Glycaemic control ■ Assess and reduce cognitive decline ■ Statin unless contraindicated/not tolerated	■ HbA_{1c} <64 mmol/mol (<8.0%) ■ FPG 5.0–8.3 mmol/l ■ BP <140/90 mm Hg
Severe frailty	■ Significant comorbidity and functional deficits, and limited independence ■ Markedly reduced life 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 increase risk of infections and cause urinary incontinence, thirst, and dehydration ■ Consider whether statin therapy is beneficial	■ HbA_{1c} <69 mmol/mol (<8.5%) ■ FPG 5.6–10.0 mmol/l ■ BP <150/90 mm Hg

[H] A significant part of clinical decision making in older people with diabetes involves consideration of their frailty status, but this will vary in importance depending on the presence of other factors including severe comorbidity, vascular complications and cognitive impairment. BP=blood pressure; FPG=fasting plasma glucose; HbA_{1c}=glycated haemoglobin; QoL=quality of life.

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 HbA_{1c} 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.[4] 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.

	Pro	Con
Metformin Alters mitochondrial cell energetics to inhibit gluconeogenesis, oppose the action of glucagon, and increase insulin sensitivity[5]	• Inexpensive • Well established, generally well tolerated standard therapy • Potential CV benefit (demonstrated in UKPDS study)[6] • Low hypoglycaemia risk • Can be combined with all other diabetes therapies	• Reduced appetite and gastrointestinal disturbance • Possible association with vitamin B12 deficiency[7] • Moderate weight loss seen in some patients may be undesirable with frailty • Contraindicated in renal impairment • Should be used with caution in those with impaired hepatic function or cardiac failure, due to increased risk of lactic acidosis
Sulphonylureas and glinides Stimulate pancreatic insulin secretion regardless of blood glucose concentration[8]	• Inexpensive • Can be combined with other therapies • Increased potency in older adults may sometimes be beneficial	• Require functioning beta cells • Hypoglycaemia risk[9] • 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[8]	• Well tolerated • Formally tested in older adults[10] • May delay disease progression if used early with metformin • Low risk of hypoglycaemia[11] • Safe in all stages of renal failure, at an appropriate dose • No effect on weight	• Moderate glucose lowering efficacy • 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 • Possible issues with increased hospitalisation for heart failure, with saxagliptin (± alogliptin)[13] • Relatively expensive
SGLT-2 inhibitors Inhibit reabsorption (from renal tubules) of glucose, leading to increased urinary glucose output and osmotic diuresis[14]	• CVOTs have shown reduction in MACE[15] • Benefits demonstrated for people with diabetes and heart failure[12] • Potential benefit in reducing progression of renal impairment[16] • Low hypoglycaemia risk	• Weight loss could result in sarcopenia • Risk of candidiasis • Potential increased urinary incontinence • Lack of glucose-lowering efficacy if established renal impairment[17] • Risk of euglycaemic diabetic ketoacidosis • Fluid volume depletion
GLP-1RAs Stimulate insulin secretion, inhibit glucagon secretion, and also reduce appetite. GLP-1 RAs work in a glucose-dependent manner[8]	• CVOTs have shown CV benefits with some, particularly in patients with ASCVD, and those at high risk of CV events[15,18] • Renoprotective effects[16] • Low hypoglycaemia risk despite good glucose-lowering efficacy • Once-weekly administration possible with some[19] • A once-daily oral formulation of semaglutide is now available[20]	• Weight loss could result in sarcopenia • Nausea is common, and reduced appetite could be problematic • Most are given by s.c. injection • Relatively expensive

TZDs Increase cellular expression of glucose transporters, thereby increasing insulin sensitivity and peripheral glucose uptake[21]	■ Generally well tolerated ■ Low hypoglycaemia risk ■ Potential CV benefit with pioglitazone[22]	■ Fluid retention may exacerbate heart failure[23] ■ Risk of osteoporosis and fractures[24-26] ■ Ongoing debate regarding risk of bladder cancer[27]
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[28]	■ Established efficacy ■ Inexpensive	■ Requires resuspension ■ Need for twice daily injections ■ Weight gain (limited harm) ■ Hypoglycaemia risk ■ Variable glucose-lowering effect from injection to injection
First generation basal insulin analogues[12] 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[29] 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)

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.

in health status and three months after any intervention (escalation or de-escalation), and targets may need to be re-evaluated based on development and diagnosis of co-existing chronic illnesses, cognitive function, and functional status.

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,[32,33] 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, CV events (thought to involve cardiac conduction disturbances), and all-cause mortality[36]

- 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 (SGLT2i)[29,39]

- 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 HbA_{1c} (<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 HbA_{1c} 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 HbA_{1c} (rebound hyperglycaemia). This highlights the importance of monitoring HbA_{1c} and reviewing the individual if medication is de-escalated. HbA_{1c} 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 HbA_{1c} 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.

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About this management algorithm

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