Factors influencing safe glucose-lowering in older adults with type 2 diabetes : a PeRsOn-centred ApproaCh To IndiVidualisEd (PROACTIVE) Glycemic Goals for older people: a position statement of Primary Care Diabetes Europe

Factors influencing safe glucose-lowering in older people with type 2 diabetes: **An Holistic Approach to Glycaemic Goals for Older People**

A Position Statement of Primary Care Diabetes Europe

Met opmerkingen [MK1]: To Clare: Please provide a title for all of the tables

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Met opmerkingen [MK2]: To Clare: Is appendix C required as you don't refer to it within the text?

Met opmerkingen [MOU3R2]: We could call it a supplement? Supplement 1

Conflict of interests

Met opmerkingen [MOU4]: Please can you let me know of any COI or confirm NONE, if that is the case

Funding

Acknowledgements

Met opmerkingen [MOU5]: CEH/SS will add details here on completion of the PS

Met opmerkingen [MK6]: To Clare: Abbreviations need to be placed after the abstract and before the acknowledgements. Please define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

Statement of intent:

This consensus position statement is intended to support holistic, person-centred clinical decision-making in the primary care management of older adults with type 2 diabetes. Clinical judgement is essential for quality healthcare, which requires well-informed healthcare professionals who are knowledgeable of current best practice recommendations developed following appraisal of the available evidence and expert opinion. It must also consider the wishes and views of the person living with diabetes and involve thorough discussion of available options with the individual, their carer(s) or other healthcare professionals involved in providing care.

This position statement is not intended as a standard of care. Standards of care are determined in the light of all available knowledge and clinical detail regarding an individual and are subject to change as scientific knowledge advances, the clinical picture changes and care plans need to evolve. Adherence to the recommendations contained herein will not ensure a successful outcome in every case, nor can recommendations include all proper methods of care or exclude other acceptable methods of care aimed at the same result.

This position statement focuses on people aged 70 years or older, with type 2 diabetes, although ageing should be assessed on an individual basis and clinicians may adopt similar principles in caring for older people with type 1 diabetes or some younger people with clinical complexity, premature ageing or approaching the end-of-life.

1. Abstract

Diabetes in later life is associated with a myriad of factors that increase the complexity of glycaemic management. This Position Statement, developed from an extensive literature review of the subject area, represents a consensus opinion of primary care physicians and diabetes specialists. It highlights many challenges facing older people living with type 2 diabetes and aims to support primary care clinicians in advocating a holistic, comprehensive geriatric assessment approach. It emphasises the importance of the wishes of the individual and their carers when determining glycaemic goals, as well as the need to balance intended benefits of treatment against the risk of adverse treatment effects. Its ultimate aim is to promote consistent high-quality care for older people with diabetes.

Keywords

Type 2 diabetes; older people; frailty; functional disability; geriatric syndromes; hypoglycaemia

2. Introduction and rationale

Ageing is a major risk factor for type 2 diabetes (1,2), now estimated to affect 19.4% of Europeans aged 65–99 years old (2). With current trends in ageing, population growth and declining mortality (3), the International Diabetes Federation (IDF) predicts that the number of older Europeans living with diabetes will rise to 43.9 million by 2045 (2).

Older people represent a diverse population, with varying cultural, health and social care needs. Although many older people live well and independently, others suffer progressive physical or mental ill health, frailty, cognitive decline or disability, with increasing dependency. Diabetes in later life imposes a significant burden on individuals and healthcare resources (4). It is associated with premature ageing, frailty and the ageing syndromes, increasing vulnerability (4); advancing age and diabetes duration are risk factors for all diabetes-related complications (5), including hypoglycaemia, increasing emergency ambulance call-outs (6), unplanned admissions (7), adverse outcomes and mortality (8,9).

Primary care clinicians provide holistic care, encompassing all elements of wellbeing. Planning diabetes care for older people with complex health and social care needs necessitates clinical support focusing on these specific challenges. Older people are likely to benefit from individualised glycaemic goals following a comprehensive geriatric approach, balancing benefits against harms of treatment, aimed at minimising complications and optimising wellbeing.

Most guidelines now advocate individualised glycaemic targets, acknowledging the needs of people with clinical complexity or limited life-expectancy (10–13). However, guidance varies by clinical descriptors defining risk and recommended glycaemic parameters.

Purpose of position statement

This position statement aims to support primary care clinicians in advocating holistic, individualised glycaemic goals, avoiding overtreatment of older people with type 2 diabetes. It highlights challenges facing older people with diabetes and draws on recommendations from major guideline groups, informed by a review of the available evidence, to develop a consensus opinion of primary care and specialist clinicians with an interest in diabetes, who strive for safe, holistically balanced glycaemic goals in

older people with type 2 diabetes. It is hoped that consistent, high-quality care will emerge for this vulnerable population.

Although developed from the available guidance and evidence concerning older adults with type 2 diabetes, similar principles might apply when caring for older people with type 1 diabetes or some younger people with complex healthcare needs or limited life-expectancy.

3. Method

A literature review (EMBASE, Medline, PubMed, Web of Science and Cochrane Database of Systematic Reviews) was undertaken to identify English language articles published since 2010. Search terms included: 'diabetes', 'type 2', 'older people', 'sarcopenia', 'functional disability', 'cognitive impairment', 'dementia', 'frailty', 'geriatric syndrome', 'multimorbidity', 'polypharmacy' and 'hypoglycaemia'. Given the breadth of this consensus statement and reference limits for publication, review articles were included. Guidelines regarding the management of adults with type 2 diabetes from major groups of Europe, North America and international bodies were reviewed. Embedded cited articles, landmark studies and publications of which authors had prior knowledge were included (contributors CEH, KK, AS, SS). Identified articles were screened for relevance, prioritising those pertaining to people aged ≥ 65 years old. Of 1331 articles identified, y were finally included.

Met opmerkingen [JD7]: To Clare: Is this correct? Usually if there are reference limits for publication, you might exclude reviews. Please check this.

Met opmerkingen [MOU8R7]: We included reviews – reviews cover more, not fewer, publications and therefore helps limit the number you need to included

Met opmerkingen [MOU9]: To be finalised on completion

Synthesis of the position statement:

Supported by a writing group, a document was drafted, following which cycles of review and revision were undertaken. Section headings, determining the focus of the position statement were agreed, with further rounds of correspondence until consensus was reached between all members, with disputes resolved by discussion.

4. Diabetes in later life

Diabetes is associated with premature ageing (4) affecting health and wellbeing across the geriatric domains, physical and mental health, functional and social wellbeing. Earlier onset of frailty, the geriatric syndromes, functional disability (14), cognitive decline or dementia (15) and depression or social isolation contribute to poor health-related outcomes. Multimorbidity, with consequential polypharmacy, is almost

inevitable (16,17), contributing to morbidity and mortality. The ageing syndromes and diabetes-related complications are interrelated, negatively impacting each other. Prevalence varies with ethnicity, socioeconomic factors and health inequalities (18). Understanding this myriad is fundamental to determining clinical priorities and personalising care. Recognising the challenges facing older people offers an opportunity for earlier intervention and support, aimed at improving wellbeing and quality of life.

4.1. Frailty and sarcopenia

Frailty predisposes to adverse health-related outcomes, disability (19), care-home admission (20) and mortality (21). Diabetes and frailty are interrelated, with sarcopenia and both hyperglycaemia and hypoglycaemia implicated. Sarcopenia – age-related loss of muscle mass and strength – contributes to the pathophysiology of insulin resistance, creating a vicious cycle, exacerbating both glucose homeostasis and frailty (Figure 1) (22). Amongst community-dwelling older adults, frailty increases incident diabetes (23), and in middle-aged and older Asian adults, low muscle mass is associated with incident diabetes (24). In the Women's Health and Aging Study, hyperglycaemia was associated with frailty (25), and in the Korean Longitudinal Study on Health and Aging, men with hyperglycaemia suffered reduced muscle mass and function (26). A Japanese study of older people with diabetes reported a negative correlation between HbA_{1c} and frailty scores (27) and diabetes overtreatment amongst older care home residents (28) increases weakness, predisposing to frailty (29).

Weight and frailty are also interrelated, with both underweight and obesity (30,31), as well as weight loss and weight gain in obese people, associated with frailty (32).

Screening for frailty (Appendix A) facilitates proactive intervention. Targeting exercise, nutrition and cognitive support may be beneficial, reducing disability and improving quality of life (33).

4.2. Functional disability and social isolation

Diabetes is associated with functional and social disability in older people (34). Increasing with ageing and multimorbidity (34), disability affects activities of daily living, mobility and social functioning (14). Social isolation is associated with prevalent and incident diabetes (35), cardiovascular (CV), and mental health morbidity and mortality

(36). Multidimensional interventions aimed at managing functional disability and social isolation demonstrate improved health outcomes (4,37,38).

4.3. Cognitive impairment and dementia

Cognitive impairment complicates diabetes self-management (39) and increases hypoglycaemia risk (40). Both vascular dementia and Alzheimer's disease are more common in people with diabetes, with an earlier age of onset (41). Risk increases with diabetes duration but a causal association with hyperglycaemia remains uncertain (41). Currently, there is no evidence that intensive glycaemic management slows cognitive decline (42). Conversely, evidence suggests a bidirectional relationship between hypoglycaemia and dementia: hypoglycaemia increasing the risk for dementia and dementia predisposing to hypoglycaemia (8,41). Consequently, intensive glycaemic management in older people with cognitive impairment or dementia is not recommended (42).

4.4. Depression in older people

Depression is prevalent in older people with diabetes, negatively impacting on self-management, physical and social functioning, and quality of life, as well as increasing morbidity and mortality (4,43). The Translating Research into Action for Diabetes (TRIAD) study suggests a stronger association between depression and mortality in older compared with younger people (43). Proactive intervention in the Prevention of Suicide in Primary Care Elderly Collaborative Trial (PROSPECT) demonstrated a 53% reduction in mortality (44), highlighting the benefits of proactive depression management.

4.5. Geriatric syndromes

Geriatric syndromes, including pain, falls, incontinence, weight loss and low body mass index (BMI), dizziness, sensory impairment, and malnutrition commonly affect middle-aged and older people with diabetes, contributing to morbidity and functional disability (45).

Falls increase morbidity, unplanned admissions and mortality. Injury or fear of falling impact on mobility, risking muscle loss, frailty and functional disability (46). Sarcopenia is a plausible contributory mechanism (47). Risk factors include insulin use (48), hypoglycaemia (49) and cognitive or functional impairment (49,50). Autonomic neuropathy, with orthostatic hypotension, may also contribute (51).

Malnutrition is a risk factor for frailty, although frailty and malnourishment are not necessarily interdependent (52). Poor dentition may be a modifiable contributory factor (53).

4.6. Multimorbidity and polypharmacy

Multimorbidity is inevitable with ageing (16,17), increasing clinical complexity, morbidity, mortality and healthcare use and expenditure (16). Evidence guiding care in people with multimorbidity is limited, although comorbidity unrelated to diabetes may adversely affect healthcare quality (54). Improving overall wellbeing necessitates a holistic approach, identifying clinically dominant conditions, prioritising management of these above asymptomatic conditions (55).

Polypharmacy further increases clinical complexity, risking drug–disease or drug–drug interactions, contributing to poor health outcomes, including frailty (56), functional disability and cognitive decline (57); glucose-lowering therapies remain a common cause of emergency hospital admissions (58). Even approaching end-of-life, older people are prescribed preventive medicines for asymptomatic conditions (59). Medication review is recommended to reduce unnecessary prescribing, avoid drug–drug or drug–disease interactions, and minimise risk of frailty, functional disability or cognitive decline (54,56–58).

4.7. Macrovascular and microvascular disease in older people with diabetes

Cardiovascular disease (CVD) remains an important cause of morbidity and mortality in older people with diabetes. The English CALIBER programme identifies heart failure (HF), cerebrovascular disease (stroke or transient ischaemic attack) and peripheral arterial disease (PAD) as the commonest incident manifestations of CVD in adults with type 2 diabetes (60), and the French GERODIAB study highlights CVD burden in older people and poor outcomes associated with HF and PAD (61). PAD remains an important risk factor in diabetic foot disease and lower extremity amputation (LEA), carrying high mortality (62).

Multifaceted risk factor management reduces CVD events, improving life expectancy (63,64). Even at an advanced age, managing modifiable CVD risk factors and smoking cessation are recommended by major guideline groups, accepting less stringent blood pressure targets to avoid orthostatic hypotension (11,13). For those experiencing treatment side effects and people with clinical complexity, frailty or limited life expectancy, clinical judgement is recommended – balancing benefit against risks of adverse treatment effects. Aspirin increases bleeding risk, with most guidelines

advising against aspirin for primary CVD prevention in older people with type 2 diabetes (10,12,65–67).

Diabetic peripheral neuropathy (DPN) affects 22–55% of older people with type 2 diabetes (68,69), predisposing to injury, ulceration and diabetic foot disease. With PAD, DPN is a major risk factor for LEA (70). Diabetic retinopathy (DR) accounts for 8.4% of visual impairment amongst older Europeans, the third commonest cause after macular degeneration and cataract (71).

Diabetic nephropathy remains a leading cause of chronic kidney disease (CKD), although, in older people, comorbid hypertension, vascular disease, urosepsis, obstructive uropathy or nephrotoxic medications contribute (72). In the US, CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2) affects 43.1% of people 65 years or older (73). Moreover, CKD increases the complexity of glycaemic management, limiting prescribing options and increasing hypoglycaemia risk (74).

Met opmerkingen [MOU10]: Do we need this or could this bit go?

Screening for microvascular complications is recommended, although may confer limited benefit for those with extreme frailty, clinical complexity or limited life-expectancy, and clinical judgement should determine appropriateness (Table 2).

Met opmerkingen [MOU11]: I'm confused as to the numbering of tables. As it is, Table 2 is a list of all recommendations and might be better with a short additional sentence concluding this section and signposting to that? Otherwise, this looks like it is specific to this paragraph. Also, Table 1 is not previously mentioned, which might need to be

5. Intensive glycaemic management and hypoglycaemia in type 2 diabetes

Glycaemic management aims to treat symptomatic hyperglycaemia and prevent long-term complications, while minimising hypoglycaemia risk. Age and diabetes duration are risk factors for all diabetes-related complications, including hypoglycaemia (5).

5.1. Multifaceted risk factor management versus intensive glycaemic management

Multifaceted risk factor management in type 2 diabetes confers a benefit, reducing CVD events, the progression of microvascular disease and mortality (63) and improving life expectancy (64). The importance of early intervention is emphasised by all major guideline groups (12,13,65,77). The extent to which glycaemic control alone contributes is less clear, particularly for older people in whom evidence is sparse since older people are often excluded from clinical trials by age (78) or clinical complexity (79). Meta-analyses suggest that intensive glycaemic management reduces non-fatal myocardial infarction (80) and progression of albuminuria and retinopathy (76), without a reduction in mortality (80). Excessive mortality associated with intensive glycaemic management in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial

(81) raised safety concerns and, although the cause remains unclear, severe hypoglycaemia (SH) is postulated (82). Amongst older people, iatrogenic hypoglycaemia is now more common than other diabetes-related complications (5), and several guidelines now qualify glycaemic targets, including lower limit thresholds, aimed at avoiding overtreatment (10,11,77,83,84).

Appendix B summarises the guideline recommendations from the IDF and major guideline groups of Europe and North America.

5.2. Hypoglycaemia in older people

In England, hospital admissions for SH remain higher than a decade ago (7,85) and, in the US, exceed those for hyperglycaemia (86). Older people are most affected (7,85,86), with multiple contributing risk factors (Table 3). Blunted physiological counter-regulation with ageing causes weakness, faintness or sleepiness, rather than typical autonomic symptoms, delaying recognition of hypoglycaemia, and confusion or disability may impair self-management (87). Serious adverse outcomes include CVD events, the progression of microvascular disease, falls, fractures, cognitive decline, dementia and increased mortality (8,9). Despite this harm, intensive glycaemic management in people with clinical complexity remains common, doubling the risk of SH (88). Unless achieved without hypoglycaemia, the risk associated with intensive glycaemic management in older people may outweigh the intended benefit and is not recommended (Table 4).

6. Glycaemic goals for older people requiring glucose-lowering therapies

Ageing risks a sudden change in clinical or social circumstances that clinicians must remain alert to. Person-centred care aims to involve individuals and/or carer(s) in shared decision-making to determine priorities and optimise health and wellbeing. Glycaemic goals in fit older people should aim to minimise the risk of long-term diabetes-related complications, although prioritising management of clinically dominant conditions other than diabetes may confer greater benefit for overall wellbeing and quality of life (55).

6.1. Glycaemic target ranges

Meta-analysis suggests that the relationship between mortality and HbA_{1c} in people with type 2 diabetes is U-shaped, increasing with HbA_{1c} <48 mmol/mol (6%) and >64 mmol/mol (8%) (89). Overall, evidence might support an optimal glycaemic range,

dependent on individual characteristics, shifting from lower to higher HbA_{1c}, with increasing clinical or treatment complexity, which many guidelines now advocate (Appendix B).

Holistic assessment is recommended following a comprehensive geriatric approach considering physical, mental, functional and social domains (74), life expectancy and the wishes of the individual and/or their carer(s) to determine clinically focused glycaemic targets. Where hypoglycaemia remains a risk, lower limit thresholds are recommended to avoid harm from inadvertent overtreatment (Table 5).

6.2. Prescribing and de-prescribing of glucose-lowering therapies

'Therapeutic inertia' is a failure to intensify or deintensify therapy where clinically appropriate (90). In diabetes care, managing symptomatic hyperglycaemia must take priority but, in the absence of symptomatic hyperglycaemia, glucose-lowering therapies are prescribed to prevent long-term diabetes-related complications that develop over the years. For older people, prescribing decisions should be undertaken in a holistic context, weighing benefits against adverse effects and, in particular, the risk of hypoglycaemia. Healthcare professionals with prescribing responsibility should familiarise themselves with the benefits, cautions, contraindications and side-effect profiles of the main glucose-lowering therapies (Table 6). Consideration should be given to medications with low risk of hypoglycaemia or those "adding value", with the potential to confer benefit for comorbid conditions (Table 6), as well as "lag time" – the time required to accrue benefit – which may be long when considering hyperglycaemia alone.

Shared decision-making should involve the individual with diabetes and/or their carer(s). Where benefit from new or additional medication is anticipated and considered to outweigh the risk of harm, intensification of therapies is recommended.

Where possible, new medications should commence at a low dose, with gradual titration – "start low, go slow" – aiming to minimise adverse effects, including hypoglycaemia. Although the risk is greatest with sulphonylurea (SU) or insulin therapies, all glucose-lowering therapies have the potential to cause hypoglycaemia, particularly in combination. Of the SUs, glibenclamide carries the greatest hypoglycaemia risk and is not recommended (91). Where insulin therapy is required, hypoglycaemia risk assessment is recommended routinely at annual review and following any episode of SH.

High and low HbA_{1c}, or glycaemic variability, are associated with hypoglycaemia (92) but low HbA_{1c} may suggest avoidable overtreatment, which remains commonplace, even where SU or insulin therapies are prescribed (93), increasing SH risk (80,88) and potential for harm (9). Although limited evidence guides de-prescribing of glucose-lowering therapies (94), safety is paramount. A recent systematic review highlights overtreatment amongst older people with type 2 diabetes, frailty and multimorbidity, suggesting that, in these circumstances, de-intensifying treatment is safe (95). In vulnerable older people intensively managed on glucose-lowering therapies, the balance of risk is likely to outweigh the benefit, and therapeutic de-intensification is recommended.

Figure 2 proposes algorithms supporting glycaemic review in older people with type 2 diabetes. The NEW MEDS Plan aims to support clinical decision-making when considering new medications for older people with long-term conditions, with the DEINTENSIFY pneumonic prompting de-intensification of glucose-lowering therapies in older people at risk of SH (95).

Met opmerkingen [MK12]: To Clare: It might be a good idea to relabel the four figures as a-d and to cite them individually in the article. e.g. Figure 2 proposes algorithms supporting glycaemic review in older people with type 2 diabetes. The NEW MEDS Plan (Figure 2b) aims to support clinical decision ...

Met opmerkingen [MOU13R12]: Yes, that is a good idea

6.3. Education and support for older people with diabetes and their carers

Older people with diabetes and their carers should receive support to empower self-management and promote healthy ageing in a holistic context, sensitive to cultural, physical, mental, functional and social needs. Few programmes are described, yet evidence suggests older people benefit from structured education (Table 7) (96).

Care home residents with diabetes are a vulnerable group who are characterised by their often highly comorbid heath state complicated by emerging frailty and cognitive dysfunction, high rates of hospital admission for hypoglycaemia and infection, and a high risk of mortality within 1–2 years of admission to the care home. These older adults pose one of the greatest challenges to effective diabetes management. This subject area has been extensively reviewed recently (97).

Met opmerkingen [MOU14]: Do we need a subheading here?

7.0. End-of-life

End-of-life care requires the highest degree of clinical expertise and compassion at all times but caring for a dying person with diabetes must consider the complexity of balancing hyperglycaemia and hypoglycaemia, the impact of other medications and

the changing clinical picture, as well as addressing fears, concerns and expectations of the individual and their loved ones or carer(s) (98). Diabetes UK has recently updated expert consensus guidance regarding the end-of-life care (98). Primary care practitioners are integral to the clinical team providing end-of-life care and knowledge of the guiding principles and expert recommendations may provide invaluable support at this difficult time. Clinicians are directed to: https://www.diabetes.org.uk/Professionals/Position-statements-reports/Diagnosis-ongoing-management-monitoring/End-of-Life-Care

- Ensure effective symptom control during the dying stage
- Tailor glucose-lowering therapy and minimise diabetes-related adverse treatment effects
- Avoid metabolic de-compensation and diabetes-related emergencies:
  - Frequent and unnecessary hypoglycaemia
  - Diabetic ketoacidosis
  - Hyperosmolar hyperglycaemic state
  - Persistent symptomatic hyperglycaemia
- Avoid foot complications and pressure sores in frail, bed-bound individuals
- Avoid symptomatic clinical dehydration
- Provide an appropriate level of intervention according to stage of illness, symptom profile, and respect for dignity
- Support and maintain the empowerment of the individuals (in their diabetes self-management) and carer(s) for as long as possible

Met opmerkingen [JD15]: To Clare: Is this symbol correct? and below?

Guiding principles in diabetes management at the end of life (reproduced from Diabetes UK, END OF LIFE DIABETES CARE Clinical Care Recommendations, 3rd Edition, March 2018, with kind permission from Diabetes UK).

8. Conclusion

In providing care for older people, primary care physicians aim to be holistic. In the management of type 2 diabetes, numerous interrelated factors affecting physical, mental, functional and social status add complexity. Both hyperglycaemia and hypoglycaemia risk adverse outcomes and functional decline, highlighting the need to balance treatment of hyperglycaemia against the risk of harm associated with intensive glycaemic management and hypoglycaemia. Adopting a holistic geriatric approach, routinely reviewing and individualising glycaemic targets and selecting glucose-lowering therapies within that context is likely to be important in providing safe and effective glycaemic management with ageing. Listening to older people, eliciting

factors that cause concern, their priorities and goals, addressing multiple risk factors and supporting healthy ageing are key elements in providing holistic care.

The evidence base that informs optimal diabetes management for older people is limited. Given the current and predicted prevalence of diabetes, research must focus on older people, including those with clinical complexity.

Conflict of interest

C.E.H. has received educational sponsorship and honoraria for speaking at meetings and/or serving on Advisory Boards for Astra Zeneca, Boehringer Ingelheim, Lilly, NAPP, NovoNordisk, Sanofi Aventis and Takeda.

(Add here if appropriate)

Funding

(To be added)

Acknowledgements

(To be added)

Table 1:

Met opmerkingen [MOU16]: Note to OmniaMed:
I'm not certain these need to be here – wondering if could go in an appendix for supplement or the paper – Sam should be able to advise. If we produce printed versions, then this should come right at the top as it was before

Evidence grading is given in line with those of the European Society of Cardiology:

Classes of recommendation

Classes of recommendation	*Definition*	*Suggested wording*
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Is recommended/is indicated
Class II	Conflicting evidence and/or divergence of opinion about the usefulness of the given treatment or procedure	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the treatment/procedure is not useful/effective and in some cases, may be harmful	Is not recommended

Levels of evidence

Level of evidence	*Definition*
A	Data derived from multiple randomised clinical trials or meta-analyses
B	Data derived from a single randomised clinical trial or large non-randomised studies
C	Consensus opinion of the experts and/or small studies, retrospective studies, registries

Table 2:

Recommendation	*Rationale*	*Class*	*Level*
Screening for frailty in older people with type 2 diabetes is recommended as part of the annual review	Frailty highlights vulnerability, and assessment offers an opportunity to identify areas for proactive intervention aimed at reducing adverse outcomes (56)	I	C
In an older person with type 2 diabetes and a recent change in weight, either weight loss or weight gain, a review of frailty status should be considered	The risk of frailty increases with both underweight and obesity (BMI <20 kg/m^2 and ≥30 kg/m^2) (30,31) Changing weight, either weight loss or weight gain, even in obese individuals, is associated with frailty (32)	IIa	B
Where frailty is established, assessment of nutritional status is recommended	Frailty and malnutrition are related but not interchangeable geriatric conditions. Amongst older people with frailty, almost 10% also have evidence of malnourishment (52)	I	A
In older people with frailty, weight loss or malnutrition, dental assessment should be considered	Poor dentition is a potentially modifiable risk factor for malnutrition (53)	IIa	C

Enquiry regarding symptomatic conditions contributing to functional disability, social isolation or the geriatric syndromes, is recommended	Multidimensional interventions aimed at identifying and managing symptomatic conditions contributing to disability, functional impairment or social isolation, offer potential to improve health outcomes (4,37,38) and may be more important for general wellbeing than managing hyperglycaemia (55)	I	A
In older people with type 2 diabetes and cognitive impairment or dementia, intensive glycaemic management is not recommended	The relationship between dementia and hypoglycaemia is bidirectional: severe hypoglycaemia (SH) increases the risk of dementia and dementia predisposes to SH (8) SH in older people is associated with risk of injury and increases mortality (9) There is currently no evidence that intensive glycaemic management slows the progression of cognitive decline or dementia (42)	III	A
In older people with diabetes and depression, active management is recommended	Depression is highly prevalent in older people with diabetes, negatively impacting on self-management, physical and social functioning, quality of life and increasing diabetes-related morbidity and mortality (4,43). Active primary care management of depression in the Prevention of Suicide in Primary Care Elderly Collaborative Trial (PROSPECT) demonstrated significant benefit in older people with diabetes, reducing mortality by 53% (44)	I	B

In older people with multimorbidity, holistic, patient-centred care that identifies and prioritises management of individual concerns is recommended	Prioritising the management of clinically important or symptomatic conditions is likely to confer greater benefit for overall wellbeing than management of asymptomatic conditions (55)	I	C
Medication review is recommended to reduce unnecessary prescribing, drug–drug or drug–disease interactions and to identify medications contributing to frailty, falls, functional disability or cognitive decline	Polypharmacy risks drug–disease and drug–drug interactions, contributing to poor health outcomes, frailty, falls, functional disability and cognitive decline in older people with diabetes (56,57,75). Glucose-lowering therapies remain a common cause of unplanned hospital admissions (58)	I	C
Identification and management of modifiable CV risk factors, including smoking cessation, blood pressure and lipid-lowering, is recommended for most older people with type 2 diabetes	Vascular disease remains a leading cause of morbidity and mortality in people with type 2 diabetes, including older people (5,61) Multifaceted risk factor management in type 2 diabetes reduces the risk of vascular disease and improves life expectancy (63,64)	I	A
For older people experiencing treatment side effects, e.g. orthostatic hypotension or myalgia, those with clinical complexity, frailty or limited life expectancy, a clinical judgement that balances potential benefit of treatment against risks of adverse effects is recommended	Orthostatic hypotension is common in people with diabetes, increasing the risk of falls, CV events and mortality (51) Older people are more vulnerable to treatment side effects, e.g. statin-induced myalgia, which is likely to negatively impact on function and wellbeing (11)	I	C

Aspirin is not recommended in primary prevention of vascular disease in older people with type 2 diabetes	Aspirin increases bleeding risk and is not recommended in primary prevention of vascular disease in people with type 2 diabetes (10,12,65,66)	III	A
Screening for and management of microvascular complications of type 2 diabetes in older people is recommended in line with international and national guidance: • *Foot check (annually and with any clinical concern)* • *Renal function and urinary albumin:creatinine ratio (ACR) (annually and with any anticipated change)* • *Retinal screening (in line with local or national guidance)*	Older people with diabetes are at risk of all diabetes-related complications (5,68,69,71,73) PAD and DPN are common diabetes-related complications in older people with diabetes (60,61,68,69) and major risk factors for diabetic foot disease and LEA (70), which carries high mortality (62) DR remains common, accounting for 8.4% of visual impairment in older Europeans (71) CKD is common in older people. Diabetic nephropathy remains a leading cause of CKD, with CKD3A–5 (eGFR <60 mL/min/1.73m^2) reported to affect 43.1% people aged ≥65 years (73). CKD of any aetiology increases the complexity of glycaemic management and risk of hypoglycaemia and limits prescribing options (74). Multifaceted risk factor management reduces the risk of microvascular disease (63,64,76)	!	A

BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; LEA, lower extremity amputation; PAD, peripheral arterial disease; SH, severe hypoglycaemia

Table 3:

Characteristics predisposing to hypoglycaemia in older people with type 2 diabetes.

Personal characteristics	Biochemical markers	Medication	Physical health	Mental health	Functional domain	Social domain
Advancing age	Low HbA_{1c}	Insulin therapy*	Frailty	Cognitive impairment	Frailty or prefrailty	Living alone
Diabetes duration	High HbA_{1c}	Sulfonylurea therapy*	Geriatric Syndromes	Dementia	Functional disability	Diet/nutrition
Frailty/pre-frailty	Glycaemic variability	Polypharmacy	Falls, malnutrition, poor dentition	Depression, anxiety	Impaired ADL	Poor dentition
Low BMI	Low albumin	Intensification of diabetes medications	CKD		Cognitive impairment	Low income
Changing weight		Drug–drug interactions	Multimorbidity		Dementia	Being a carer
Previous severe hypoglycaemia		Poor medication adherence	Vascular disease		Geriatric syndromes	Alcohol
			Microvascular complications		Falls	Lower or higher educational attainment
			Adrenal insufficiency		Malnutrition	Number of healthcare professionals involved in care
					Urinary incontinence	

Poor dentition

ADL, activities of daily living; BMI, body mass index; CKD, chronic kidney disease (usually taken to mean estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2).

**Insulin and sulfonylurea therapies carry particular risk of hypoglycaemia but it should be noted that all glucose-lowering therapies, particularly when used in combination, have potential to cause hypoglycaemia.*

Salive, 2013, Bordier et al, 2015, Holbrook et al, 2017 (others)

Met opmerkingen [SD17]: Note to Clare: please advise where these references should be included.

Met opmerkingen [MOU18R17]: Thx Sean – this was a reminder to self – will check with Alan as to whether we need to specifically reference all the entries on table 3 – if so, these authors are pertinent

Table 4:

Recommendation	*Rationale*	*Class*	*Level*
Intensive glycaemic management in older people with clinical complexity is not recommended	Few clinical trials have specifically examined the effects or benefits of intensive glycaemic management in an older population Intensive glycaemic management confers limited clinical benefit, reducing non-fatal CV events and progression of retinopathy and nephropathy but doubles the risk for SH (80) and, in people with clinical complexity, may increase mortality (81) Intensive glycaemic management in people with clinical complexity doubles the risk of SH (88) SH risks serious injury or harm and increases mortality (8,9)	III	A

CV, cardiovascular; SH, severe hypoglycaemia

Met opmerkingen [MOU19]: To OmniaMed:
Does this sit here alone or should it be included in the earlier table of recommendations

Table 5:

Recommended glycaemic target ranges for older people requiring glucose-lowering therapies.

Functional status	Description	Recommended target ranges	Caveats/qualifiers
Healthy or relatively healthy *Fit and functionally independent, with relatively longer anticipated life expectancy* *and* *managed on diet alone or oral glucose-lowering therapies associated with low risk of hypoglycaemia* *(For fit older people prescribed SU or insulin therapies, see below)*	Older people should be considered by their clinician to have good functional status and to be at low risk of hypoglycaemia or at low risk of harm arising from hypoglycaemia: • Living independently, no major impairment of activities of daily living (ADL) • No or minimal care giver support • Cognitively intact • Comorbid conditions should be well controlled with no significant impact on functional wellbeing • No established vascular disease • Prescribed glucose- lowering therapies, with low risk of hypoglycaemia • No previous history of severe hypoglycaemia • Renal function: CDK3A or better (eGFR >45 ml/min/1.73 m^2)	HbA_{1c} 53*–59 mmol/mol (6.5–7.5%) (Home glucose monitoring is unlikely to be clinically indicated)	Regular (at least annual) review should include reappraisal of functional status and appropriateness of glycaemic target, with enquiry regarding symptoms of hypoglycaemia. At every opportunity, encouragement to adopt lifestyle advice for healthy ageing should be considered. Fit, healthy older people should be offered escalation of glucose-lowering therapies where the agreed glycaemic goal is not achieved or down titration or de-prescribing of glucose-lowering therapy in the presence of overtreatment** and/or declining functional status. *HbA_{1c} <48 mmol/mol (6.5%) on monotherapy or <53 mmol/mol (7%) on ≥2 therapies carrying low risk of hypoglycaemia may be considered clinically appropriate

	• Not frail (see Appendix A) e.g. FRAIL score: 0 Electronic Frailty Index: 0–0.12 When determining glycaemic goals, diabetes is likely to be the main medical focus but other factors should be considered, within a geriatric framework, including physical and mental health comorbidity and functional social status		for some older people but relative overtreatment for others. Clinical judgment and shared decision-making are required to determine management **requires clinical judgment and discussion with the person with diabetes:
Complex/intermediate health or social care needs with intermediate life-expectancy or mild–moderate frailty and requiring oral glucose-lowering therapies *Or fit older people requiring SU or insulin therapy*	Older people fulfilling these criteria are considered to have some vulnerability to hypoglycaemia or to be at risk of harm from adverse consequences of hypoglycaemia and may have: • Multiple co-existing chronic illnesses[a] or • Requirement for SU or insulin therapy (even where functional status is good) or any of • chronic illnesses with impairment of ADL • Functional dependency (living in the community with social support for	HbA_{1c} 53–64 mmol/mol* (7.0–8.0%)* For those using glucose monitoring, aim for Fasting or pre-prandial glucose 5.2–8.3 mmol/L* Bedtime glucose 6.0–10.0 mmol/L*	Regular (at least 6-monthly) review should include reappraisal of functional status and appropriateness of glycaemic goals, with enquiry regarding symptoms of hypoglycaemia. At every opportunity and where possible for the individual, encouragement to adopt lifestyle advice for healthy ageing should be considered. Where achieved HbA_{1c} >64 mmol/mol (8.0%) or <53 mmol/mol (<7.0%), escalation, down-titration or de-prescribing of therapies, respectively, should be considered [a]Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include

	ADL, e.g. may need assistance with bathing, dressing or personal care) • Mild to moderate cognitive impairment • Established vascular disease • Established CKD* (eGFR <45) • Intermediate life expectancy • High treatment burden • At risk of falls or a Frailty score (Appendix 1) identifying pre-frailty or mild frailty, e.g. FRAIL score: 1–2 Electronic Frailty Index: >0.12–0.24		arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, MI, and stroke. Multiple means at least three, but many patients may have five or more (American Diabetes Association, 2018)
Very complex/poor health/frail *Or older people with complex/ intermediate health or social care needs and/or mild frailty requiring insulin therapy*	Older people fulfilling these criteria are considered vulnerable to hypoglycaemia and at risk of harm arising from hypoglycaemia and may have: • chronic illness with dependency for ADL • Moderate or severe frailty (see below)	HbA_{1c} 59–69 mmol/mol[c] (7.5–8.5%) For those using glucose monitoring, aim for Fasting or pre-prandial glucose	Regular review should include reappraisal of functional status and appropriateness of glycaemic goal, with enquiry regarding symptoms of hypoglycaemia. At every opportunity and where possible for the individual, encouragement to adopt lifestyle advice for healthy ageing should be considered

	• Moderate or severe cognitive impairment or dementia • Advanced CKD Stage 4 or 5 (eGFR <30 mL/min/1.73 m^2) • At high risk of falls • End-stage chronic illness[b] • Need for long-term care • Hypoglycaemia unawareness with continuing requirement for insulin therapy **or** • complex/ intermediate health or social care needs and/or mild frailty requiring insulin therapy Frailty scores identifying moderate/severe frailty: FRAIL score: ≥3 Rockwood CFS: ≥6 Electronic Frailty Index: >0.36	7.0–8.5 mmol/L bedtime glucose >8.0 mmol/mol	[b]The presence of any end-stage chronic illness such as stage III–IV congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer. These may cause significant symptoms or impairment of functional status and significantly reduce life expectancy (13) [c]HbA_{1c} of 69 mmol/mol (8.5%) equates to an estimated average glucose of ~11 mol/L. Higher levels of glycaemia than this may expose patients to acute risks from glycosuria, dehydration, hyperglycaemic hyperosmolar syndrome, and poor wound healing (13)
End-of-life palliative care	Any older person approaching the end-of-life and receiving palliative care	No target ranges Avoid symptomatic hyperglycaemia and hypoglycaemia	

Table 6:

Summary of medications used in management of hyperglycaemia in older people with type 2 diabetes (adapted from Inzucchi et al, 2015).

Tabel met opmaak

Drug Class	Biguanide	Sulfonylurea (SUs)[A][a]	Meglitinides	Thiazolidinediones (TZDs)[B][b]	a-glucosidase inhibitor	DPP-4 inhibitor	SGLT-2 inhibitors	GLP-1 receptor agonists	Insulins
Medication(s)	Metformin	Gliclazide Glimepiride Glipizide	Nateglinide Repaglinide	Pioglitazone	Acarbose	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Canagliflozin Dapagliflozin Empagliflozin	Albiglutide Dulaglutide Exenatide Liraglutide Lixisenatide	- Short-acting: including soluble insulin and rapid-acting insulin analogues - Intermediate: isophane (NPH insulin) - Long-acting basal insulins - Premixed biphasic insulins
Action(s)	Actions include inhibition of hepatic gluconeogenesis, increased GI utilisation of	Augment insulin secretion from beta cells	Augment insulin secretion from beta cells	Reduces peripheral insulin resistance	Inhibits intestinal alpha-glucosidase, slowing carbohydrate absorption	Inhibits DPP-4, enhancing endogenous incretin hormones, resulting in glucose-dependent	Reversibly inhibit SGLT2 in the renal proximal tubule to reduce glucose reabsorption	Augment glucose-dependent insulin secretion and slow gastric emptying	Direct action on insulin receptors to increase glucose uptake in tissues, with suppression of

	glucose and suppression of inflammatory cytokines (98)					increase in insulin and decrease in glucagon secretion	and increase urinary glucose excretion		hepatic glucose production
Hypoglycaemia risk[c]	Low	High[d]	High	Low	Low[e]	Low	Low	Low	High*
Weight	Neutral or beneficial	Increase	Increase	Increase		Neutral	Beneficial	Beneficial	Increase
Cost	Cheap	Cheap	Moderate	Cheap	Moderate	High	High	High	High
Advantages	Well established; may be associated with CV benefits (99); safe in HF (100); now considered safe in moderate renal impairment (reduce dose)	Useful where glycaemic symptoms predominate	Reduce PPG excursions; dose can be individualised to different meals or withheld if meal not taken	Can be used in moderate-to-severe renal impairment; associated with reduced risk of MACE (101)	Reduce PPG excursions; may be associated with CV benefits (99)	Mostly well tolerated	Glycosuria contributes to calorie and weight loss; may be associated with CV benefits including reduction in hospitalisations for HF (99)	May be associated with CV benefits (may be different with named products, class effect not yet established) (99)	Regimen can be individualised; Maybe most effective therapy when clinically necessary
Disadvantages[f]	GI side effects may limit use;	Risk of hypoglycaemia increases	Risk of hypoglycaemia (see SUs);	Side effects may limit use: Increased risk	Requires more frequent dose administration;	Inconsistent findings regarding risk	Polyuria; risk of volume depletion or	Administered by subcutaneous	Risk of hypoglycaemia and severe

Met opmerkingen [JD20]: Suggest using either cheap/expensive or low/high regarding cost

Met opmerkingen [MOU21R20]: Yes, ok

	caution advised in older people with weight loss, malnutrition or frailty, where GI side effects may have greater impact (102); long-term use increases risk of vitamin B12 deficiency (102)	with advancing age, impaired renal or hepatic function, recent hospital admission, polypharmacy, alcohol use and reduced calorie intake (102); conflicting evidence regarding CV safety and HF risk (100)	frequency of dose administration; repaglinide not recommended in people ≥75 years; avoid in hepatic impairment	of HF, oedema, bone fractures and weight gain (101); Avoid in established HF; may precipitate HF (particularly when used in conjunction with insulin) (100); other common side effects include anaemia, arthralgia, visual disturbance	GI side effects may limit use; contraindicated in IBD or in people at risk of intestinal obstruction; requires clear instructions regarding management of hypoglycaemia	of HF, with increased risk of hospitalisation for HF reported with alogliptin and saxagliptin (100)(FDA warning for saxagliptin and alogliptin[g]); FDA warning regarding DPP-4 inhibitors and joint pain (resolves on withdrawal of medication)[h]	dehydration; postural hypotension; raised serum creatinine; raised haematocrit; genito-urinary infections; DKA; increased risk of LEA (mostly toes)	injection; Different dosing regimens (refer to named product license); GI side effects may limit use; injection site reactions; AF (albiglutide); AV block (dulaglutide)	hypoglycaemia (increases with advancing age, frailty, comorbidity and polypharmacy); requires blood glucose monitoring; training and education required for safe use, recognition and management of hypoglycaemia (for people with diabetes, carers and healthcare professionals)
Special precautions[f]	Lactic acidosis[j]; iodine-containing contrast agents[k]	Drivers need to avoid hypoglycaemia and should be warned of the risk	Avoid in hepatic impairment	Contraindicated in: HF, previous or current history of bladder cancer or uninvestigated haematuria[l]	Hypoglycaemia must be treated with glucose specifically	Vildagliptin requires liver function monitoring prior to initiation and every 3 months for the	Consider interrupting treatment if volume depletion occurs; EMA warning regarding	Discontinue if symptoms of pancreatitis; some in class carry advice regarding timing of administration	Driving, driving regulations, hobbies and occupation; cultural awareness required with insulins

						first year; Alogliptin, saxagliptin and vildagliptin caution in hepatic impairment; discontinue if symptoms of pancreatitis	atypical DKA[m]; EMA warning regarding LEA[n]; dapagliflozin not recommended in adults ≥75 years; Initiation of empagliflozin not recommended in adults ≥85 years	of other medications (refer to named product licenses)	derived from animal sources; initiation should only be undertaken by healthcare professional with appropriate training
CKD	Reduce dose in moderate renal impairment (eGFR 30–60 mL/min/1.73 m^2); contraindicated with eGFR <30 mL/min/1.73 m^2	Increases risk of hypoglycaemia (advice to avoid in severe renal impairment)	Caution advised for use of repaglinide in CKD	No dose adjustment advised	Avoid if eGFR <25 mL/min/1.73 m^2	With exception of linagliptin, dose adjustment in CKD is advised for all in class (see named product license)	For all in class, avoid initiation at eGFR <60 mL/min/1.73 m^2; for all in class, dose adjustment and/or withdrawal advised in CKD (see named product license)	For all in class, dose adjustment is advised in CKD (see named product license)	Increases risk of hypoglycaemia (may require dose reduction, which should be assessed on an individual basis)

*Emerging evidence suggests hypoglycaemia prevalence *in older people may vary depending on the insulin preparation prescribed*

[a]*Glibenclamide is NOT recommended in people >60 years (Chahal, 2013)*

[b]*Rosiglitazone no longer available in Europe. Information here refers specifically to pioglitazone*

[c]*Clinicians should be aware that all glucose-lowering therapies have the potential to cause hypoglycaemia and that the risk increases when agents are used in combination*

[d]*SU-induced hypoglycaemia may persist for many hours and may require treatment in hospital*

[e]*Requires treatment with glucose specifically as sucrose and complex carbohydrates will be ineffective*

[f]*Main side effects as detailed in British National Formulary (BNF), November 2017 (https://www.medicinescomplete.com)* and as referenced; clinicians should refer to the Summary of Product Characteristics for full details.

[g]*Rare but serious; avoid in situations with risk of dehydration or tissue hypoxia, including vomiting and diarrhea, acute or worsening renal impairment, acute cardiorespiratory illness, sepsis (see: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Metformin_and_metformin-containing_medicines/human_referral_000397.jsp&mid=WC0b01ac05805c516f)*

[h]*Contrast-induced nephropathy increases risk of lactic acidosis; Metformin may need withheld 48 hours before and after administration of contrast agents but advice varies, dependent on local policy, age & prior renal function and clinicians are advised to refer to local guidance (see European Society of Urogenital Radiology: http://www.esur.org/guidelines/)*

[i]*http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109176.pdf*

[j]*https://www.fda.gov/Drugs/DrugSafety/ucm486096.htm* (accessed 27.11.17)

[k]*https://www.fda.gov/Drugs/DrugSafety/ucm459579.htm* (accessed 27.11.17)

[m]*http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors__20/European_Commission_final_decision/WC500202393.pdf* (published 26.02.16, accessed 28.11.17)

[n]~~*http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors_Canagliflozin_20/European_Commission_final_decision/WC500227101.pdf*~~[n]*http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors_Canagliflozin_20/European_Commission_final_decision/WC500227101.pdf* (published 08.05.17, accessed 28.11.17)

Met opmerkingen [MK22]: J was changed to I. Please confirm that this change is correct and add it to the table as well.

Met opmerkingen [MK23]: L is missing from the list. Could you please provide a reference for it?

AF, atrial fibrillation; CKD, chronic kidney disease; CV, cardiovascular; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; EMA, European Medicines Agency; GI, gastrointestinal; HF, heart failure; IBD, irritable bowel disease; LEA, lower extremity amputation; MACE, major adverse cardiovascular events; PPG, postprandial glucose; SGLT2, sodium-glucose co-transporter 2.

Table 7:

Recommendation	*Rationale*	*Class*	*Level*
Person-centred care, involving individuals and/or their carer(s) in the assessment and shared decision-making, is recommended	Person-centred care is a fundamental principle in healthcare	I	C
A comprehensive review that considers physical, mental, functional and social wellbeing, eliciting what is important to the individual and facilitating prioritisation of concerns and care needs is recommended	Addressing dominant and symptomatic concerns may offer a potential for greater improvement in general health and wellbeing than addressing diabetes management alone (55)	I	C

Individualised glycaemic goals, taking into account physical and mental health, functional and social status, life-expectancy and the wishes of the person with diabetes and/or his/her carers, are recommended for older people with diabetes *Where hypoglycaemia is considered a risk, lower limit thresholds are recommended to avoid harm from inadvertent overtreatment*	Intensive glycaemic management confers a limited clinical benefit, reducing non-fatal CV events and progression of retinopathy and nephropathy but doubles the risk for SH (80) and, in people with clinical complexity may increase mortality (81) Intensive glycaemic management in people with clinical complexity doubles the risk of SH (88) SH risks serious injury or harm and increases mortality (8,9)	I	A
Where overtreatment or poorly selected glucose-lowering agents are identified, clinical judgement, taking appropriate steps to down-titrate or de-prescribe glucose-lowering therapies, ensuring patient safety is recommended	Overtreatment in older people with type 2 diabetes is commonplace (88,93) In people with type 2 diabetes and clinical complexity, intensive glycaemic management doubles the risk of SH (88)	I	C

Prescribing of diabetes medicines for older people with type 2 diabetes should be considered where the benefit is anticipated and likely to outweigh the risk of harm	All medications have the potential to cause unintended side effects All diabetes medications, even those with low risk, have potential to cause hypoglycaemia, particularly when used in combination (74)	IIa	A
Clinicians should consider initiating any new glucose-lowering therapy at a low dose, with gradual titration, dependent on clinical response	All medications have potential to cause unintended side effects All diabetes medications, even those with low risk, have potential to cause hypoglycaemia, particularly when used in combination (74) Gradual dose titration may reduce the risk of unintended adverse medication effects, including the risk of hypoglycaemia	IIa	C

When commencing new or additional therapies, the clinical need, anticipated benefit, risk of harm from unwanted adverse effects, benefit for or impact on comorbid conditions, social environment and potential for drug–drug interactions should be considered. *In the management of asymptomatic long-term conditions, lag-time, the time required for clinical benefit from the medication should be considered in the context of benefit and anticipated life expectancy*	All medications have the potential to cause unwanted adverse effects. The potential for benefit should be weighed against any risk of harm, within a holistic context that considers individual needs and circumstances (74)	IIa	C
Glibenclamide (glyburide) is not recommended in the management of type 2 diabetes in older people	Glibenclamide is associated with greater risk of SH than other SU therapies and the WHO advises against its use in older people with type 2 diabetes (91)	III	A
Prescribing decisions for older people should be undertaken in a holistic context, including discussion and shared decision-making with the older person with diabetes and/or their carer(s)	Polypharmacy contributes to poor health outcomes, functional disability and cognitive decline in older people with diabetes (57)	I	C

Provision of, or referral to, structured education that empowers self-management and promotes healthy ageing should be considered for older people with diabetes and their carers	Limited evidence suggests that older people benefit from structured education (96)	IIa	C
The development and dissemination of educational programmes and resources for carers and care home staff looking after older people living with diabetes should be considered	Few programmes for older people are described, yet evidence suggests older people benefit from structured education (96)	IIa	C

CV, cardiovascular; SH, severe hypoglycaemia; SU, sulfonylurea; WHO, World Health Organization

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Met opmerkingen [MK24]: To Clare: Could you please provide the date last accessed for refs. 2, 11, 12, 65, 91, 97 and 110?

Met opmerkingen [JD25]: I can't see an example in the author guidelines but in an open access article on their website, the punctuation after each ref is a full stop not a semicolon. Please check and change in your ref manager. Also, the journal names have full stops after each abbreviated word in the example I found.

Met opmerkingen [MOU26R25]: This has been a challenge – my citation manager has not been working properly for about 8 weeks now, which has held be back and minor changes may need to be done manually – sorry!

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