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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

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ABSTRACT

Diabetes in later life is associated with a range of factors increasing 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 clinicians 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 comprehensive,

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holistic 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.

Statement of intent

This position statement is intended to support holistic, person-centred clinical decision-making in the primary care management of older adults with type 2 diabetes, where clinical, social or other factors increase the complexity of ensuring safe glycaemic management. 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 consider the wishes and views of the person living with diabetes and involve discussion of the 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.

For many fit older adults with type 2 diabetes, the recommendations and guidance regarding glycaemic management in adults may be appropriately applied. This position statement focuses on people aged 70 years or older, with type 2 diabetes and factors increasing the complexity of glycaemic management, although it is acknowledged that ageing and clinical complexity should be assessed on an individual basis and clinicians may adopt similar principles in caring for older adults with type 1 diabetes or some younger people with clinical complexity, premature ageing or approaching the end-of-life.

1. Introduction and rationale

Age is a major risk factor for type 2 diabetes [1,2], which is now estimated to affect 19.4% of Europeans aged 65–99 years [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]. These older people represent a diverse population, with varying cultural, health and social care needs. Although many older people with diabetes will continue to live well and independently, with good quality of life and life expectancy, self-managing their diabetes without undue difficulty, others may suffer progressive physical or mental ill health, frailty, cognitive decline or disability, increasing dependency and vulnerability, which may be compounded by social isolation and loneliness.

Multimorbidity and polypharmacy in later life impose a significant burden on affected individuals and impact on healthcare resources [4]. Diabetes is associated with premature ageing, frailty and the ageing syndromes [4] and older people with diabetes are more likely than others to suffer disability [5]; advancing age and diabetes duration are risk factors for all diabetes-related complications [6], including adverse treatment effects and hypoglycaemia, increasing emergency ambulance call-outs [7], unplanned admissions [8], adverse outcomes and mortality [9,10].

Despite these complex factors, glycaemic attainment amongst older adults is often similar regardless of clinical complexity [11,12] and for vulnerable older people, this may inadvertently increase the risk of hypoglycaemia.

Primary care clinicians provide holistic care, encompassing all elements of wellbeing. Planning diabetes care for older adults with complex health and social care needs necessitates professional support focusing on these specific challenges. Older people are likely to benefit from individualised glycaemic goals following a comprehensive, holistic assessment that balances 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 [13–16]. However, guidance varies by clinical descriptors defining risk and recommended glycaemic parameters.

1.1. *Purpose of position statement*

This position statement aims to support primary care clinicians in advocating holistic, individualised glycaemic goals, avoiding overtreatment of older adults 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 potentially vulnerable population.

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

1.2. Terminology

The definition of intensive glycaemic management varies between different observational studies and clinical trials. Where referred to in the context of a referenced study or trial, the definition is as given for that study or clinical trial. Otherwise, for the purpose of this position statement, intensive glycaemic management refers to the attainment of tight glycaemic parameters due to the prescribing of glucose-lowering therapies. This needs to be considered in an individualised context, taking account of personal characteristics and risk factors, including the prescribed glucose-lowering therapy: glycaemic attainment considered appropriate for one individual might be considered relative overtreatment for another. The individualisation of glycaemic goals and glycaemic attainment is explored within this position statement.

Here, intensification of glycaemic management refers to the escalation or up-titration of glucose-lowering therapy by increasing the dose, initiating additional therapy or substituting one agent for another with relatively greater glucose-lowering potential, where as deintensification refers to the de-escalation or down-titration of glucose-lowering therapy by reducing the dose, de-prescribing or substituting one agent for a less potent glucose-lowering therapy.

2. Methods

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. Of 1334 articles identified, 129 were finally included. Classification of recommendations and evidence grading is detailed in Supplementary Appendix A [17].

2.1. 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. A draft was presented at a focus group supporting patient & public involvement in research at the Leicester Diabetes Centre, Leicester, UK, and at the Primary Care Diabetes Europe Professional Conference, Barcelona, in April 2018, with feedback shaping and focusing the direction of this position statement.

3. Diabetes in later life

Diabetes is associated with premature ageing [4] affecting health and wellbeing across the domains of physical and mental health, functional and social wellbeing. For some older people living with diabetes, earlier onset of frailty, the ageing syndromes, functional disability [5], cognitive decline or dementia [18] and depression or social isolation may contribute to poor health-related outcomes. Multimorbidity, with consequential polypharmacy, is almost inevitable [19,20], 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 [21]. Understanding these complexities is fundamental to determining clinical priorities and personalising care. Recognising the challenges facing affected older people offers an opportunity for earlier intervention and support, aimed at improving wellbeing and quality of life.

3.1. Frailty and sarcopenia

Frailty predisposes to adverse health-related outcomes, disability [22], care-home admission [23] and mortality [24]. Diabetes and frailty are interrelated, with sarcopenia and both hyperglycaemia and hypoglycaemia implicated:Sarcopenia – age-related loss of muscle mass and strength – has been implicated in the pathophysiology of insulin resistance in older people with type 2 diabetes. Hyperglycaemia, muscle weakness and inactivity contribute to myocyte loss, muscle fat infiltration and inflammation, leading to impaired protein synthesis, reduced glucose uptake and increased insulin resistance. Resultant inflammatory myocyte responses further exacerbate muscle weakness and insulin resistance, creating a vicious cycle, with worsening glucose homeostasis and frailty (Fig. 1) [25]; Amongst community-dwelling older adults, frailty increases incident diabetes [26], and in middle-aged and older Asian adults, low muscle mass is associated with incident diabetes [27]; In the Women's Health and Aging Study, hyperglycaemia was associated with frailty [28], and in the Korean Longitudinal Study on Health and Aging, men with hyperglycaemia suffered reduced muscle mass and function [29]; A Japanese study of older people with diabetes reported a negative correlation between HbA_{1c} and frailty scores [30] and diabetes overtreatment amongst older care home residents [31] increases weakness, predisposing to frailty [32].

Weight and frailty are also interrelated, with both underweight and obesity [33,34], as well as weight loss and weight gain in obese people, associated with frailty [35].

Screening for frailty (Supplementary Appendix B) facilitates proactive intervention [4,23,36–40]. Targeting exercise, nutrition and cognitive support may be beneficial, reducing disability and improving quality of life [39]. Ensuring adequate glycaemic control, avoiding both hyperglycaemia and hypoglycaemia may be important in preventing sarcopenia and frailty.

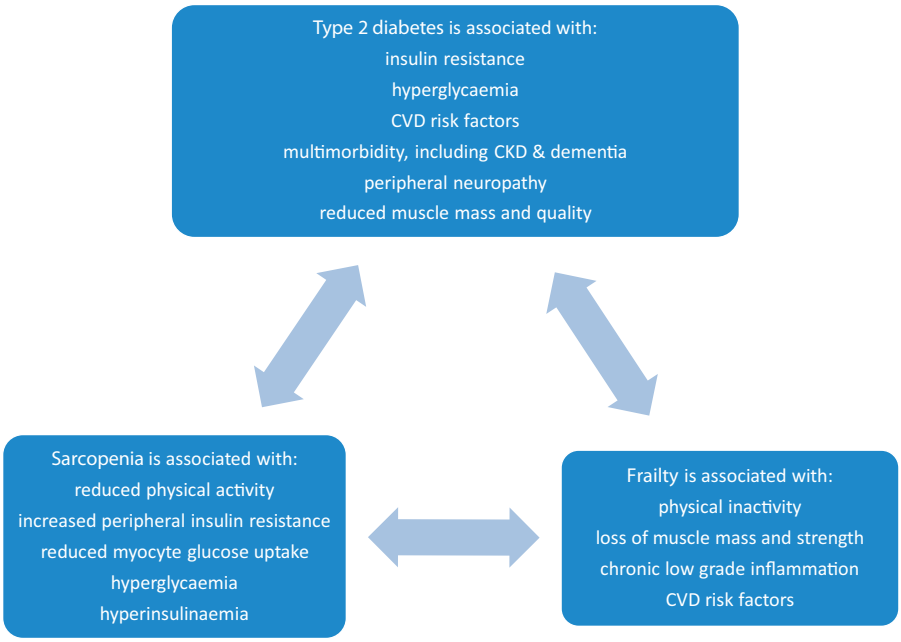

Fig. 1 – The interrelationship between type 2 diabetes, sarcopenia and frailty. Adapted with kind permission from Sinclair et al. [25].

3.2. *Functional disability and social isolation*

Diabetes is associated with functional and social disability in older people [41]. Increasing with ageing and multimorbidity [41], disability affects activities of daily living, mobility and social functioning [5]. Social isolation is associated with prevalent and incident diabetes [42], cardiovascular (CV) and mental health morbidity and mortality [43]. Multidimensional interventions aimed at managing functional disability and social isolation demonstrate improved health outcomes [4,44,45].

3.3. *Cognitive impairment and dementia*

Cognitive impairment complicates diabetes self-management [46] and increases hypoglycaemia risk [47]. Both vascular dementia and Alzheimer's disease are more common in people with diabetes, with earlier age of onset [48]. Risk increases with diabetes duration but a causal association with hyperglycaemia remains uncertain [48]. Currently, there is no evidence that intensive glycaemic management slows cognitive decline [49]. Conversely, evidence suggests a bidirectional relationship between hypoglycaemia and dementia: hypoglycaemia increasing the risk for dementia and dementia predisposing to hypoglycaemia [9,48]. Consequently, intensive glycaemic management in older people with cognitive impairment or dementia is not recommended [49].

3.4. *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 [4,50]. The Translating Research into Action for Diabetes (TRIAD) study suggests a stronger association between depression and mortality in older compared with younger people [50]. Proactive intervention in the Prevention of Suicide in Primary Care Elderly Collaborative Trial (PROSPECT) demonstrated a 53% reduction in mortality [51], highlighting the benefits of proactive depression management.

3.5. *Ageing syndromes*

Ageing 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 [52].

Falls increase morbidity, unplanned admissions and mortality. Injury or fear of falling impact on mobility, risking muscle loss, frailty and functional disability [53]. Sarcopenia is a plausible contributory mechanism [54]. Risk factors for falls include insulin use [55], hypoglycaemia [56] and cognitive or functional impairment [56,57]. Autonomic neuropathy, with orthostatic hypotension, may also contribute [58].

Malnutrition is a risk factor for frailty, although frailty and malnourishment are not necessarily interdependent [59]. Poor dentition may be a modifiable contributory factor [60].

Avoiding hypoglycaemia may reduce the risk of dizziness and falls but guarding against hyperglycaemia in vulnerable older adults is also likely to be important. Hyperglycaemia risks exacerbating tiredness, fatigue, dry mouth, poor dental hygiene or urinary symptoms and increases the risk of infections, such as oral, skin, chest or urogenital infections, which in turn may contribute to confusion or declining physical activity, resulting in progressive frailty, ageing syndromes or deterioration in overall health and wellbeing.

3.6. Multimorbidity and polypharmacy

Multimorbidity is inevitable with ageing [19,20], increasing clinical complexity, morbidity, healthcare use and expenditure, and increasing mortality [19]. Evidence guiding care in people with multimorbidity is limited, although comorbidity unrelated to diabetes adversely affects healthcare quality [61]. Improving overall wellbeing necessitates a holistic approach, identifying clinically dominant conditions, prioritising management of these above asymptomatic conditions [62].

Polypharmacy further increases clinical complexity, risking drug–disease or drug–drug interactions, contributing to poor health outcomes, including frailty [38], falls [63], functional disability and cognitive decline [64]; glucose-lowering therapies remain a common cause of emergency hospital admissions [65]. Even approaching end-of-life, older people are prescribed preventive medicines for asymptomatic conditions [66]. 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 [38,61,64,65].

3.7. Macrovascular 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 [67], and the French GERODIAB study highlights CVD burden in older people and poor outcomes associated with HF and PAD [68]. PAD remains an important risk factor in diabetic foot disease and lower extremity amputation (LEA), carrying high mortality [69].

Multifaceted risk factor management reduces CVD events, improving life expectancy [70,71]. Even at 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 [14,16]. 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 [13,15,72–74].

3.8. Microvascular disease in older people with diabetes

Distal sensorimotor polyneuropathy (DSPN) is common in older people, both with and without diabetes and has been reported to affect 22–55% of older people with type 2 diabetes [75,76], predisposing to injury, ulceration and diabetic foot disease. With PAD, DSPN is a major risk factor for LEA [77].

Diabetic retinopathy (DR) accounts for 8.4% of visual impairment amongst older Europeans, the third commonest cause after macular degeneration and cataract [78].

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 [79]. In the US, CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) affects 43.1% of people 65 years or older [80]. CKD increases the complexity of glycaemic management, limiting prescribing options and increasing hypoglycaemia risk [81].

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

Table 1 summarises recommendations for holistic assessment and principles in the care of older adults with type 2 diabetes.

4. Intensive glycaemic management and hypoglycaemia in type 2 diabetes

Glycaemic management aims to treat symptomatic hyperglycaemia, prevent acute hyperglycaemic emergencies and reduce the risk of long-term diabetes-related complications, while minimising the risk of hypoglycaemia. As described above, poor glycaemic control in older people risks not only the established adverse diabetes-related outcomes [6] but may also contribute to disability associated with diabetes and ageing. Conversely, unnecessary overtreatment risks adverse treatment effects, including hypoglycaemia [82].

4.1. Multifaceted risk factor management versus intensive glycaemic management

Multifaceted risk factor management in type 2 diabetes confers benefit, reducing CVD events, progression of microvascular disease, reducing mortality [70] and improving life expectancy [71]. The importance of early intervention is emphasised by all major guideline groups [15–17,72]. 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 [83] or clinical complexity [84]. Meta-analyses suggest that intensive glycaemic management reduces non-fatal myocardial infarction [85] and progression of albuminuria and retinopathy [86], without reducing mortality [85]. Excessive mortality associated with intensive glycaemic management in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [87] raised safety concerns and, although the cause remains unclear, severe hypoglycaemia (SH) is postulated [88]. Amongst older people, iatrogenic hypoglycaemia is now more common than other diabetes-related complications [6], and several guidelines now qualify glycaemic targets, including lower limit thresholds, aimed at avoiding overtreatment [13,14,17,89,90].

Supplementary Appendix C summarises glycaemic target recommendations for older people in guidelines from the IDF and major guideline groups of Europe and North America [13,14,17,72–74,89–97].

Table 1 – Recommendations for holistic assessment and principles in the care of older adults with type 2 diabetes.

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 [1].	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) [2,3]; changing weight, either weight loss or weight gain, even in obese individuals, is associated with frailty [4].	IIa	B
Where frailty is established, assessment of nutritional status is recommended	Frailty and malnutrition are related but not interchangeable age-related conditions; amongst older people with frailty, almost 10% also have evidence of malnourishment [5].	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 [6].	IIa	C
Enquiry regarding symptomatic conditions or challenging life-factors contributing to functional disability, social isolation or the ageing syndromes, is recommended	Multidimensional interventions aimed at identifying and managing symptomatic conditions or challenging life-factors contributing to disability, functional impairment or social isolation, offer potential to improve health outcomes [7–9] and may be more important for general wellbeing than managing hyperglycaemia alone [10,11].	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 [12]; SH in older people is associated with risk of injury and increases mortality [13]; There is currently no evidence that intensive glycaemic management slows the progression of cognitive decline or dementia [14].	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 [7,15]; 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% [16].	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 [10].	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 [1,17,18]; Glucose-lowering therapies remain a common cause of unplanned hospital admissions [19].	I	C
Identification and management of modifiable CVD risk factors, including smoking cessation, blood pressure and lipid-lowering, is recommended for most older people with type 2 diabetes	CVD remains a leading cause of morbidity and mortality in people with type 2 diabetes, including older people [20,21]; Multifaceted risk factor management in type 2 diabetes reduces the risk of CVD and improves life expectancy [22,23].	I	A

– Table 1 (*Continued*)

Recommendation	Rationale	Class	Level
For older people experiencing treatment side effects, e.g. orthostatic hypotension or myalgia, those with clinical complexity, frailty or limited life expectancy, 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, CVD events and mortality [24]; Older people are more vulnerable to treatment side effects, e.g. statin-induced myalgia, which is likely to negatively impact on function and wellbeing [25].	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 [26–29].	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 as clinically indicated) • Retinal screening (in line with local or national guidance)	Older people with diabetes are at risk of all diabetes-related complications [20,30–33]; PAD and DPN are common diabetes-related complications in older people with diabetes [21,30,31,34] and major risk factors for diabetic foot disease and LEA (35), which carries high mortality [36]; DR remains common, accounting for 8.4% of visual impairment in older Europeans [32]; CKD is common in older people. Diabetic nephropathy remains a leading cause of CKD and CKD3A–5 (eGFR <60 mL/min/1.73m^2) is reported to affect 43.1% people aged ≥65 years [33]. CKD of any aetiology increases the complexity of glycaemic management, risk of hypoglycaemia and limits prescribing options [37]; Multifaceted risk factor management reduces the risk of microvascular disease [22,23,38].	!	A
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 [39] and, in people with clinical complexity, may increase mortality [40]. Intensive glycaemic management in people with clinical complexity doubles the risk of SH [41], risking serious injury or harm and increasing mortality [12,13]	III	A

4.2. *Hypoglycaemia in older people*

In England, hospital admissions for SH remain higher than a decade ago [8,98] and, in the US, exceed those for hyperglycaemia [99]. Older people are most affected [8,98,99], with multiple contributing risk factors (Table 2) [32,100–104]. 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 [105]. In some older people, hypoglycaemia is a marker of vulnerability, with several identifiable predisposing factors, and cultural factors, such as fasting, may also contribute [106] (Table 2).

Severe hypoglycaemia is important because it risks injury or harm and has been associated with serious adverse outcomes, including CVD events, progression of microvascular disease, falls, fractures, cognitive decline, dementia and increased mortality [9,10]. Despite this harm, intensive glycaemic management in people with clinical complexity remains common, doubling the risk of SH [82]. Unless achieved without hypoglycaemia, the risk associated with intensive glycaemic management in older people with clinical complexity may outweigh intended benefits and is not recommended (Table 1).

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

5.1. *Person-centred care*

Ageing risks sudden change in clinical, functional or social circumstances that clinicians must remain alert to. Person-centred care aims to involve individuals and/or carer(s) in shared decision-making, determining priorities to optimise health and wellbeing. Recognising all elements impacting on an individual's ability to self-manage their diabetes and respecting the individual's wishes (or those of carers) is fundamental in agreeing individualised glycaemic goals [107]. Facilitating person-centred diabetes care is feasible in primary care, improving shared decision making and is appreciated by people with diabetes [108]. At any age, prioritising management of clinically dominant conditions or professional support with challenging life-factors, whether or not related to

Table 2 – Characteristics and risk factors predisposing to hypoglycaemia in older people with type 2 diabetes.

Personal characteristics	Biomedical markers	Medication-related	Physical health	Mental health	Functional domain	Social domain	Cultural Factors
Age [32]	Low HbA_{1c} [100–102]	Insulin therapy[a] [32,100]	Multimorbidity [32,100]	Cognitive decline and dementia [32]	Frailty [103]	Social isolation [32]	Fasting [106]
Diabetes duration [100,101]	High HbA_{1c} [100]	SU therapies[a] [32,100]	CKD [32,101,102]	Depression [32,101]	Weight loss [103]	Care home residency [32]	
	Day-to-day glycaemic variability [104]	Intensification of glucose-lowering therapies [102]	Vascular disease [32,101]		Malnutrition [32,103]	Alcohol [106]	
	CKD [32,101,102]	Polypharmacy [32,100]	Weight loss [103]				
	Biomedical markers of malnutrition [32]	Previous hypoglycaemia [32]	Malnutrition [103]				
	Previous hypoglycaemia [32]						

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); SU, sulphonylurea.

[a] Insulin and sulphonylurea 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.

diabetes, may confer greater benefit for overall wellbeing and quality of life than glycaemic management alone [62,107].

5.2. *Glycaemic goals*

Type 2 diabetes is associated with progressive decline in pancreatic beta cell function and, consequently, maintaining glycaemic control over time often requires step-wise increase in glucose-lowering medications, as guidelines advocate [15,16]. However, declining appetite, weight loss, progressive frailty or increasing multimorbidity with ageing, may inadvertently result in relative overtreatment unless frequent proactive review is undertaken and glucose-lowering therapies deintensified where clinically appropriate. Meta-analysis suggests that the relationship between mortality and HbA_{1c} in people with type 2 diabetes is U-shaped, increasing with HbA_{1c} > 64 mmol/mol (8%) and at <48 mmol/mol (6%) [109] and this, at least in part, may reflect relative overtreatment of vulnerable people. 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 (Supplementary Appendix C).

Recommended glycaemic goals by functional status for older people requiring glucose-lowering therapies are given in Table 3. Review, following a comprehensive, holistic assessment that considers physical, mental, functional and social domains [81], life expectancy and the wishes of the individual and/or their carer(s) is recommended, to agree priorities for care and holistically focused glycaemic goals. Generally, fit older people should be supported to achieve glycaemic goals minimising the risk of long-term diabetes-related complications, with progressive relaxation of glycaemic targets as clinical, functional, social and/or prescribing complexity increases. Upper limit glycaemic thresholds are recommended, even with declining health or functional status, to prevent acute hyperglycaemic emergencies, glycosuria, dehydration and poor wound healing [13] and reduce the risk of long-term complications, including functional disability or frailty. For older people prescribed glucose-lowering therapies, lower limit HbA1c thresholds are recommended to avoid inadvertent overtreatment, which may increase the risk of harm arising from severe hypoglycaemia.

5.3. *Prescribing and de-prescribing of glucose-lowering therapies*

'Therapeutic inertia' is a failure to intensify or deintensify therapy where clinically appropriate [110]. 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 years. For older people, prescribing decisions should be undertaken in a holistic context, weighing benefits against adverse treatment effects, 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 4) [111–116]. Where possible, consideration should be given to medications with lower risk of hypoglycaemia or those with "added value", with potential to confer benefit for comorbid conditions, 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 is anticipated and considered likely to outweigh risks of harm from adverse treatment effects, inten-

Table 3 – Recommended glycaemic goals by functional status 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 oral glucose-lowering therapies associated with low risk of hypoglycaemia (For fit older people prescribed SU and/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 • 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) • Not frail (see Supplementary Appendix B) 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 comprehensive holistic framework, considering physical and mental health comorbidity, functional and social status, personal wishes and life-expectancy.	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 up-titration or prescribing 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.
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 ADL, e.g. may need assistance with bathing, dressing or personal care) • Mild to moderate cognitive impairment • Established vascular disease • Established CKD (e.g. eGFR <45 ml/min/1.73 m^2) • Intermediate life expectancy • High treatment burden • At risk of falls or a Frailty score (Supplementary Appendix B) identifying pre-frailty or mild frailty, e.g. FRAIL score: 1–2 Electronic Frailty Index: >0.12–0.24	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 (94–150 mg/dl) Bedtime glucose 6.0–10.0 mmol/L (108–180 mg/dl)	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 the achieved HbA_{1c} is >64 mmol/mol (8.0%) or <53 mmol/mol (<7.0%), up-titration, prescribing or down-titration/de-prescribing of therapies, respectively, should be considered.

– Table 3 (*Continued*)

Functional status	Description	Recommended target ranges	Caveats/qualifiers
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) • Moderate or severe cognitive impairment or dementia • Advanced CKD Stage 4 or 5 (eGFR • <30 mL/min/1.73 m^2) • 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	HbA_{1c} 59–69 mmol/mol[c] (7.5–8.5%) For those using glucose monitoring, aim for Fasting or pre-prandial glucose 7.0–8.5 mmol/L (126–153 mg/dl) bedtime glucose >8.0 mmol/mol (>144 mg/dl)	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
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

ADL, activities of daily living; eGFR, estimated glomerular filtration rate; SU, sulphonylurea; CKD, chronic kidney disease; CFS, clinical frailty scale.

[*] HbA_{1c} <53 mmol/mol (7%) on therapies carrying low risk of hypoglycaemia may be considered appropriate 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 individual and/or carer(s).

[a] Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, CKD, MI, and stroke. Multiple means at least three, but many patients may have five or more [16].

[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 [16]

[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 [16].

sifying glucose-lowering therapy 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 risk is greatest with sulphonylurea (SU) or insulin therapies, all glucose-lowering therapies have potential to cause hypoglycaemia, particularly in combination. Of the SUs, glibenclamide (glyburide) carries the greatest hypoglycaemia risk and is not recommended [116]. Where insulin therapy is required, hypoglycaemia risk assessment is recommended routinely at annual review and as clinically indicated.

High and low HbA_{1c}, or day-to-day glycaemic variability in insulin users, are associated with hypoglycaemia [104] but low HbA_{1c} on glucose-lowering therapy suggests potential overtreatment, which remains commonplace, even where SU or insulin therapies are prescribed [12], increasing hypoglycaemia risk [82,85] and potential for harm [10]. Although limited evidence guides de-prescribing of glucose-lowering therapies [117], safety is paramount. A recent systematic review highlights overtreatment amongst older people with type 2 diabetes, frailty and multimorbidity, suggesting that, in these circumstances, deintensifying treatment is safe [118]. In vulnerable older people intensively managed on glucose-lowering therapies, the balance of risk is likely to outweigh benefit, and therapeutic deintensification is recommended.

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. Continuing need for insulin therapy should be reviewed and, where pos-

Table 4 – Summary of medications used in management of hyperglycaemia in older people with type 2 diabetes (adapted from Inzucchi et al. [92]). The information contained herein was considered accurate by the references and sources given at the time of submission but it is acknowledged that prescribing information may change rapidly in the light of new information and readers are advised to refer to Summary of Product Characteristics or other appropriate sources for full and current details.

Drug Class	Biguanide	Sulphonylurea (SU)[a]	Meglitinides	Thiazolidinediones (TZD)[b]	a-glucosidase inhibitor	DPP-4 inhibitor	SGLT-2 inhibitors	GLP-1 receptor agonists	Insulins
Medication(s)	Metformin	Gliclazide	Nateglinide	Pioglitazone	Acarbose	Alogliptin	Canagliflozin	Albiglutide	- Short-acting: including soluble insulin and rapid-acting insulin analogues
		Glimepiride	Repaglinide			Linagliptin	Dapagliflozin	Dulaglutide	- Intermediate: isophane (NPH insulin)
		Glipizide				Saxagliptin	Empagliflozin	Exenatide	- Long-acting basal insulins
						Sitagliptin		Liraglutide	- Premixed biphasic insulins
						Vildagliptin		Lixisenatide	
Action(s)	Actions include inhibition of hepatic gluconeogenesis, increased GI utilisation of glucose and suppression of inflammatory cytokines [111]	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 increase in insulin and decrease in glucagon secretion	Reversibly inhibit SGLT2 in the renal proximal tubule to reduce glucose reabsorption and increase urinary glucose excretion	Augment glucose-dependent insulin secretion and slow gastric emptying	Direct action on insulin receptors to increase glucose uptake in tissues, with suppression of hepatic glucose production
Hypoglycaemia risk[c]	Low	High[d]	High	Low	Low[e]	Low	Low	Low	High[n]
Weight	Neutral or beneficial	Increase	Increase	Increase		Neutral	Beneficial	Beneficial	Increase
Cost	Low	Low	Moderate	Low	Moderate	High	High	High	High
Advantages	Well established; may be associated with CV benefits [112]; safe in HF [113]; 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 [114]	Reduce PPG excursions; may be associated with CV benefits [112]	Mostly well tolerated	Glycosuria contributes to calorie and weight loss; may be associated with CV benefits including reduction in hospitalisations for HF [112]	May be associated with CV benefits (may be different with named products, class effect not yet established) [112]	Regimen can be individualised; Maybe most effective therapy when clinically necessary

Disadvantages[f]	GI side effects may limit use; caution advised in older people with weight loss, malnutrition or frailty, where GI side effects may have greater impact [115]; long-term use increases risk of vitamin B12 deficiency [115]	Risk of hypoglycaemia increases with advancing age, impaired renal or hepatic function, recent hospital admission, polypharmacy, alcohol use and reduced calorie intake [115]; conflicting evidence regarding CV safety and HF risk [113]	Risk of hypoglycaemia (see SU); frequency of dose administration; repaglinide not recommended in people ≥75 years; avoid in hepatic impairment	Side effects may limit use: Increased risk of HF, oedema, bone fractures and weight gain [114]; Avoid in established HF; may precipitate HF (particularly when used in conjunction with insulin) [113]; other common side effects include anaemia, arthralgia, visual disturbance	Requires more frequent dose administration; GI side effects may limit use; contraindicated in IBD or in people at risk of intestinal obstruction; requires clear instructions regarding management of hypoglycaemia	Inconsistent findings regarding risk of HF, with increased risk of hospitalisation for HF reported with alogliptin and saxagliptin [113] (FDA warning for saxagliptin and alogliptin[g]); FDA warning regarding DPP-4 inhibitors and joint pain (resolves on withdrawal of medication)[h]	Polyuria; risk of volume depletion or dehydration; postural hypotension; raised serum creatinine; raised haematocrit; genito-urinary infections; DKA; increased risk of LEA (mostly toes)	Administered by subcutaneous injection; Different dosing regimens (refer to named product license); GI side effects may limit use; injection site reactions; AF (albiglutide); AV block (dulaglutide)	Risk of hypoglycaemia and severe hypoglycaemia[n] (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[i]; iodine-containing contrast agents[j]	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[k]	Hypoglycaemia must be treated with glucose specifically	Vildagliptin requires liver function monitoring prior to initiation and every 3 months for the first year; Alogliptin, saxagliptin and vildagliptin caution in hepatic impairment; discontinue if symptoms of pancreatitis	Consider interrupting treatment if volume depletion occurs; EMA warning regarding atypical DKA[l]; EMA warning regarding LEA[m]; dapagliflozin not recommended in adults ≥75 years; initiation of empagliflozin not recommended in adults ≥85 years	Discontinue if symptoms of pancreatitis; some in class carry advice regarding timing of administration of other medications (refer to named product licenses)	Driving, driving regulations, hobbies and occupation; cultural awareness required with insulins derived from animal sources; initiation should only be undertaken by healthcare professionals with appropriate training and knowledge of the time-action profiles and risk of hypoglycaemia with available insulin preparations.

– Table 4 (*Continued*)

CKD	Reduce dose in moderate renal impairment (eGFR 30–60 mL/min/1.73 m^2); contraindicated at 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[n] (may require dose reduction, which should be assessed on an individual basis)

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.

[a] Glibenclamide is NOT recommended in people >60 years [116].

[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), accessed August 2018 (https://www.medicinescomplete.com) and as referenced; clinicians should refer to the Summary of Product Characteristics for full details.

[g] https://www.fda.gov/Drugs/DrugSafety/ucm486096.htm (accessed 6.08.18).

[h] https://www.fda.gov/Drugs/DrugSafety/ucm459579.htm (accessed 6.08.18).

[i] 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).

[j] 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/).

[k] http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109176.pdf (accessed 6.08.18).

[l] http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2016/02/WC500202388.pdf (accessed 6.08.18).

[m] http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2017/02/WC500222191.pdf (accessed 6.08.18).

[n] The incidence of hypoglycaemic is dependent on multiple factors, including the insulin preparation and regimen prescribed. Where possible, simplification of the insulin regimen, choosing insulins associated with lower incidence of hypoglycaemia, such as second generation basal insulin analogues [119,120], may be preferred.

Table 5 – Recommendations and principles for agreeing holistically focused glycaemic goals in older people with type 2 diabetes.

Recommendation	Rationale	Class	Level
Person-centred care, involving individuals and/or their carer(s) in the assessment, with shared decision-making, is recommended	Person-centred care aims to involve individuals and/or carer(s) in shared decision-making, determining priorities to optimise health and wellbeing [107]. Recognising all elements impacting on an individual's ability to self-manage their diabetes and respecting the individual's wishes (or those of carers) is fundamental in agreeing individualised glycaemic goals [107]; Facilitating person-centred diabetes care is feasible in primary care, improving shared decision making and is appreciated by people with diabetes [108]; At any age, prioritising management of clinically dominant conditions or professional support with challenging life-factors, whether or not related to diabetes, may confer greater benefit for overall wellbeing and quality of life than glycaemic management alone [62,107].	I	C
Holistic review following a comprehensive holistic approach considering physical, mental, functional and social domains, life expectancy and the wishes of the individual and/or their carer(s) is recommended, to agree priorities for care and holistically focused glycaemic goals (see Table 3)	Managing dominant symptomatic conditions or challenging life-factors may offer greater potential for improvement in general health and wellbeing than diabetes management alone [62,107]; Holistically focused glycaemic goals aim to take account of individual needs, clinical complexity and life-expectancy, balancing potential benefits of treatment against risk of harm from treatment side effects or inadvertent overtreatment.	I	C
Fit older people should be supported to achieve glycaemic goals minimising the risk of long-term diabetes-related complications, with progressive relaxation of glycaemic control as clinical, functional, social and/or prescribing complexity increases (see Table 3)	Age and diabetes duration are risk factors for all diabetes-related complications [6]; Multifaceted risk factor management in type 2 diabetes confers benefit, reducing CVD events, progression of microvascular disease, reducing mortality [70] and improving life expectancy [71].	IIa	B
Upper limit glycaemic thresholds are recommended, even with declining health or functional status, to prevent acute hyperglycaemic emergencies and reduce the risk of long-term complications, including functional disability or frailty (Table 3)	Higher levels of glycaemia (>69 mmol/mol) may expose patients to acute risks from glycosuria, dehydration, hyperglycaemic hyperosmolar syndrome, and poor wound healing [16]; Hyperglycaemia is associated with prevalent and incident frailty [26,27]	IIa	B
Lower limit glycaemic thresholds (HbA_{1c}) are recommended to avoid intensive glycaemic management or inadvertent overtreatment, which increase the risk of harm arising from severe hypoglycaemia (Table 3)	Intensive glycaemic management confers limited clinical benefit, reducing non-fatal CV events and progression of retinopathy and nephropathy but doubles the risk for SH [85] and, in people with clinical complexity may increase mortality [87]; Intensive glycaemic management in people with clinical complexity doubles the risk of SH [82]; SH risks serious injury or harm and increases mortality [9,10].	I	A
Holistic prescribing decisions, weighing benefits against adverse effects and, in particular, the risk of hypoglycaemia, are recommended	Multifaceted risk factor management in type 2 diabetes confers benefit, reducing CVD events, progression of microvascular disease, reducing mortality [70] and improving life expectancy [71]; Intensive glycaemic management confers limited clinical benefit, reducing non-fatal CV events and progression of retinopathy and nephropathy but doubles the risk for SH [85] and, in people with clinical complexity may increase mortality [87]; Intensive glycaemic management in people with clinical complexity doubles the risk of SH [82]; SH risks serious injury or harm and increases mortality [9,10]; Polypharmacy contributes to poor health outcomes, functional disability and cognitive decline in older people with diabetes [64].	I	A B

– Table 5 (*Continued*)

Recommendation	Rationale	Class	Level
Healthcare professionals with prescribing responsibility should familiarise themselves with the benefits, cautions, contraindications and side effect profiles of the main glucose-lowering therapies (see Table 4).	See Table 4	IIa	C
Prescribing of diabetes medicines for older people with type 2 diabetes should be considered where benefit is anticipated and likely to outweigh the risk of harm	Age and diabetes duration are risk factors for all diabetes-related complications [6]; Multifaceted risk factor management in type 2 diabetes confers benefit, reducing CVD events, progression of microvascular disease, reducing mortality [70] and improving life expectancy [71].	IIa	A
Medications with lower risk of hypoglycaemia or those "adding value", with potential to confer benefit for comorbid conditions, should be considered	SH risks serious injury or harm and increases mortality [9,10]; See Table 4	IIa	A/C
New or additional medications should commence at low dose, with gradual titration – "start low, go slow" – aiming to minimise adverse effects, including hypoglycaemia	All medications have potential to cause unintended side effects; All glucose-lowering therapies, even those with low risk, have potential to cause hypoglycaemia, particularly when used in combination [81]; Gradual dose titration may reduce the risk of unintended adverse medication effects, including the risk of hypoglycaemia.	IIa	C
Where insulin therapy is required, hypoglycaemia risk assessment is recommended routinely and as clinically indicated.	SH risks serious injury or harm and increases mortality [9,10]; Age and diabetes duration are risk factors for all diabetes-related complications, including hypoglycaemia [6];	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	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 [118].	I	A
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 [116].	III	A

CV, cardiovascular; SH, severe hypoglycaemia; SU, sulphonylurea; WHO, World Health Organisation.

sible, dose reduction or regimen simplification using insulins associated with lower hypoglycaemia risk, such as second generation basal insulin analogues, should be considered [119,120].

Table 5 summarises recommendations and principles for holistically focused glycaemic goals and safe glucose-lowering in older people with type 2 diabetes.

Fig. 2 proposes algorithms aimed at supporting holistic glycaemic review in older people with type 2 diabetes. The NEW MEDS Plan (Fig. 2b) aims to support clinical decision-making when considering new or changing medications for older people with long-term conditions, with the DEINTENSIFY pneumonic (Fig. 2c), developed as a prompt for clinicians, highlighting some of the factors that might be considered when undertaking a holistic, comprehensive review of glycaemic management in the care of an older person with diabetes. Any decision to deintensify glucose-lowering therapies should be made following holistic assessment, rather than on the basis of any single parameter alone [118].

Supplementary Appendix D details recommendations for educational support, exercise and dietary advice [15,16,59,121–126].

6. Care home residents

Care home residents with diabetes are particularly vulnerable, 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 high risk of mortality within 1–2 years of care home admission. This poses a great challenge for effective diabetes management, warranting a comprehensive, holistic approach as described above. This subject area has been extensively reviewed recently [127].

7. 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)

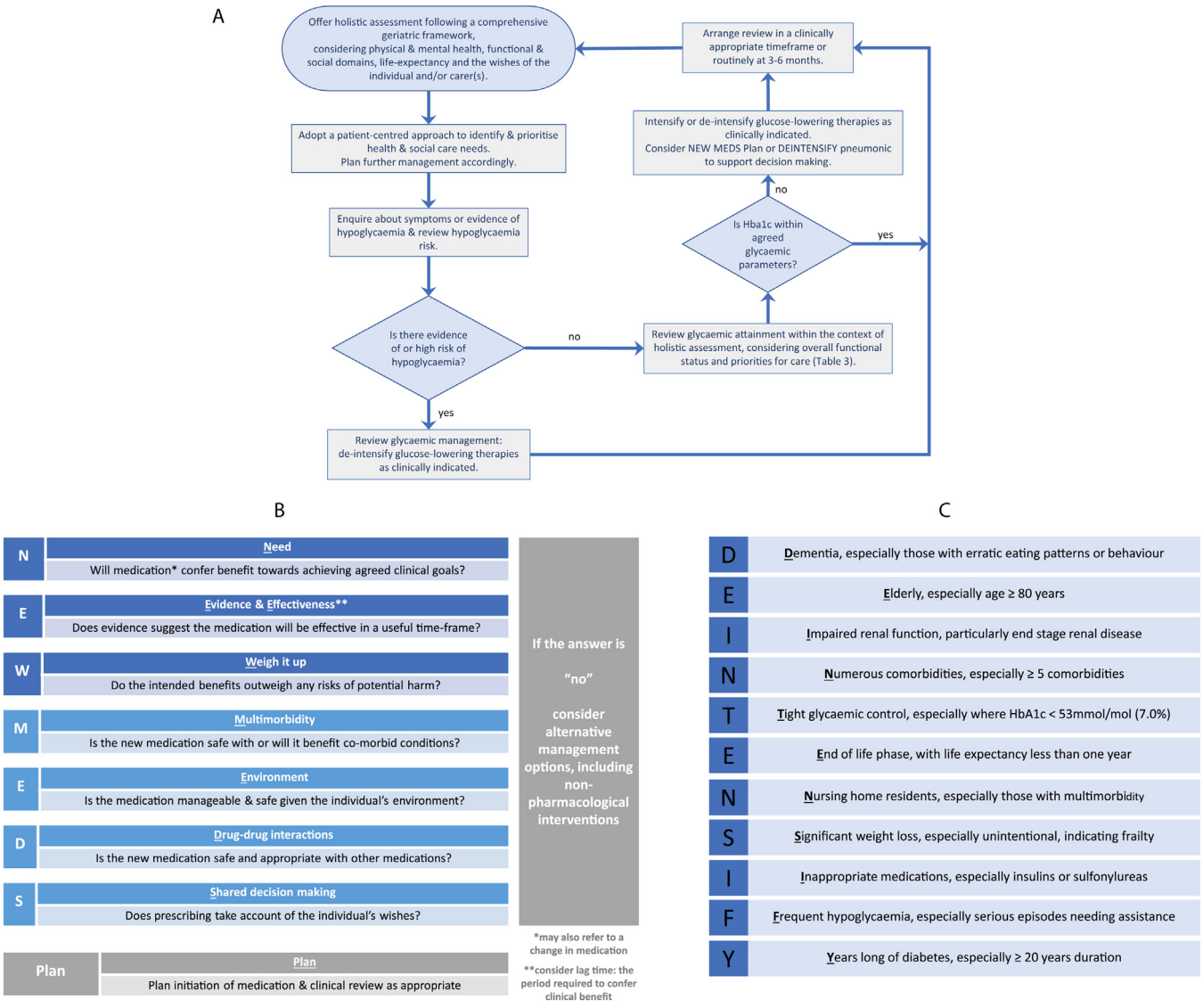

Fig. 2 – (a) A suggested pathway for holistic review of glycaemic parameters in the care of older people living with type 2 diabetes. (b) NEWMEDS Plan, an algorithm aimed at supporting clinicians considering the initiation of any new medication in the care of older people with complex health and social care needs. (c) DEINTENSIFY, a pneumonic developed as a prompt for clinicians, highlighting some of the factors that might be considered when undertaking a holistic, comprehensive review of glycaemic management in the care of an older person with diabetes. Any decision to deintensify glucose-lowering therapies should be made following holistic assessment, rather than on the basis of any single parameter alone. Adapted with kind permission, from Abdelhafiz & Sinclair [118].

[128]. Diabetes UK has recently updated expert consensus guidance regarding end-of-life care [128]. 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	

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 clinicians 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 approach, routinely reviewing and individualising glycaemic goals 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. In accordance with recommendations of the Research Agenda on Mutlimorbidity in Family Practice [129], emphasis needs to focus on research identifying links between complexity and multimorbidity (identifying the index disease to better define the level of comorbidity in clinically complex individuals) to inform the comprehensive, holistic primary care management of people with multimorbidity, including cardiovascular disease and diabetes, targeting preventive, as well as, curative care.

Conflict of interest

No conflicts of interest have arisen for any authors in relation to this work.

Conflicts of interest declared out with this work:

CEH 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.

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AS has received consultancy fees from Merck, Takeda, Novartis and Eli Lilly and Company. He is Director, Foundation for Diabetes Research in Older People, Diabetes Frail Ltd, and lead for older adults for the Association of British Clinical Diabetologists (ABCD).

GS has served on global, European Union and national Advisory Board meetings or has received honoraria for lectures for Amgen AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, NovoNordisk, Sanofi-Aventis, Servier and Takeda.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.pcd.2018.12.005.

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