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SYSTEMATIC REVIEW

Systematic review of guideline recommendations for older and frail adults with type 2 diabetes mellitus

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Abstract

Background: The application of clinical practice guidelines (CPGs) across the spectrum of individuals living with diabetes can be challenging, particularly in older adults, where factors such as frailty and multimorbidity exacerbate the complexity of management.
Objective: This systematic review aimed to explore the guidance provided within diabetes CPGs for management of individuals who are older and/or frail, including recommendations for haemoglobin A1C (HbA1c) target and pharmacotherapeutic management.
Methods: A systematic search was completed in Medline and Embase to identify national or international type 2 diabetes CPGs published in the last 10 years. Data extracted included recommendations for HbA1c targets and pharmacotherapy in older and frail adults, frailty screening and deprescribing. Quality of included CPGs was appraised with the AGREE II tool.
Results: Twenty-three CPGs were included, within which older adults and frailty were discussed in 21 and 14 CPGs, respectively. Specific HbA1c targets for older and/or frail adults were provided by 15 CPGs, the majority of which suggested a strict target (<7.0%–7.5%) in healthier older adults and a more relaxed target (<8.0%–8.5%) in those who are frail or medically complex. Ten CPGs provided recommendations for insulin therapy and 16 provided recommendations for non-insulin antihyperglycaemic agents that were specific to older and/or frail populations, which primarily focused on minimising risk of hypoglycaemia.
Conclusion: Most diabetes CPGs recommend strict HbA1c targets in healthier older adults, with more relaxed targets in those living with frailty or medical complexity. However, significant variability exists in pharmacotherapy recommendations and there were proportionately less recommendations for individuals who are frail.

Keywords: frail; aged; diabetes mellitus; systematic review; practice guidelines; older people

Key Points

- Diabetes clinical practice guidelines are increasingly integrating recommendations specific for older adults.
- Most diabetes clinical practice guidelines recommend a strict HbA1c target for healthier older adults and a more relaxed target older adults who are frail, medically complex or functionally impaired.
- Most clinical practice guidelines place hypoglycaemic risk as central consideration in medication selection in all older adults.
- Relatively few clinical practice guidelines provide pharmacotherapeutic recommendations for management of diabetes in individuals who are frail.

Introduction

Diabetes is one of the most common chronic health conditions worldwide, affecting 529 million individuals globally. With the current rate of growth, it is estimated that >1.31 billion people will have diabetes by 2050 [1]. These numbers are driven almost entirely by type 2 diabetes mellitus (T2DM), accounting for 90% of the diabetes population [1]. Without proper management, people living with diabetes are at increased risk of micro- and macrovascular complications and shortened life expectancy [2].

The prevalence of diabetes increases with age, reaching 24.4% of the global population aged 75–79 years [1]. Older adults are especially vulnerable to health complications of diabetes, as they are generally more medically complex and more likely to experience frailty than younger populations [2]. Frailty is a complex syndrome marked by increased vulnerability to stressors, predisposing individuals to poor quality of life and negative health outcomes including falls, cognitive and functional impairment, hospitalisations and death [2, 3]. Much like diabetes, the prevalence of frailty increases with age, affecting millions of older adults globally [2].

Frailty can significantly influence the management of diabetes [4, 5]. In frail adults, altered physiology and the presence of multisystem impairment influence the pharmacokinetic parameters of antihyperglycaemic medications. A decrease in muscle mass relative to adipose tissue and reduced renal and hepatic function in frail older adults elevate the risk of adverse drug effects, such as hypoglycaemia and weight loss [3–6]. Additionally, decreased caloric intake, commonly seen in this population, further increases the hypoglycaemia risk and diminishes the ability to recover from a hypoglycaemia event [3, 7]. Beyond this, the management of diabetes in older and frail adults may be influenced by changes in patient-specific goals of care, such as placing a stronger emphasis on preventing consequences of symptomatic hypo- and hyperglycaemia, compared to reducing cardiovascular events [4, 7].

It is imperative that clinical practice guidelines (CPGs) reflect the considerations for older and frail adults, as CPGs are often referred to by health care providers when making clinical decisions for this population. A recent review of three diabetes CPGs revealed a lack of consistency in haemoglobin A1C (HbA1c) targets and comprehensive treatment algorithms for older adults [8]. Beyond this, little is known about the extent to which existing diabetes CPGs support the care of frail and older persons. Therefore, the purpose of this systematic review was to summarise the guideline-based recommendations for the management of T2DM in older adults, including healthy older adults and those who are frail. The primary objective was to identify the percentage of diabetes CPGs that provide specific recommendations for management of older and frail adults. Secondary objectives were to describe CPG recommendations for frailty screening and identification, management strategies for older and frail adults, including HbA1c targets and pharmacotherapy selection, and deprescribing of antihyperglycaemic agents.

Methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 and PRISMA-S statements [9, 10].

Search strategy and selection criteria

A systematic search strategy was designed by investigators and informed by a medical librarian. OVID Medline and Embase databases were searched from 1 January 2013 to 23 November 2023, using database-specific keywords for 'diabetes mellitus', 'type 2 diabetes', 'hypoglycemic agents', 'guideline' and 'practice guideline'. No language restrictions were used. The complete search strategy is available in Appendix 1.

CPGs were eligible for inclusion if they provided recommendations on comprehensive management of T2DM, were explicitly identified within the content of the article as a 'guideline' or 'practice guideline', were published or updated within the last 10 years by nationally or internationally recognised diabetes or related organisations, and were the most updated version, if multiple versions of the CPG exist.

CPGs were excluded if they focused solely on the management of comorbid conditions associated with diabetes (e.g. chronic kidney disease, heart failure, dyslipidaemia); only concerned the management of diabetic complications (e.g. diabetic ketoacidosis, diabetic foot infection) or a certain aspect of diabetes management [e.g. the role of sodium-glucose cotransporter-2 (SGLT-2) inhibitors for the treatment of T2DM]; pertained to paediatric or gestational diabetes or diabetes care for palliative or end-of-life patients; were labelled consensus statement, report or recommendation; or were withdrawn.

Screening and data extraction

Results of the literature search were imported into Covidence (https://www.covidence.org), which was used for screening, data extraction and quality assessment. Articles that were only available in a non-English language were machine translated. Two reviewers (J.B., V.C.) independently screened the titles and abstracts of all retrieved articles and assessed the full-text records against the inclusion and exclusion criteria. Any discrepancies in assessment were resolved by consensus.

The following data were independently extracted by two reviewers (J.B., V.C.): CPG definitions of older adults and frailty; recommended frailty screening tools and threshold scores for frailty; recommended management strategies for older and frail adults, including HbA1c targets and use of insulin and non-insulin antihyperglycaemic agents; and any recommendations for deprescribing of diabetes pharmacotherapy. HbA1c targets reported in units of millimoles

per mole were converted to percentages using the following equation [11]:

$$\text{HbA1c}(\%) = \frac{\text{HbA1c}\left(\frac{\text{mmol}}{\text{mol}}\right)}{10.929} + 2.15.$$

Quality assessment

Two reviewers (J.B., V.C.) independently evaluated the quality of the included CPGs using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument, which is a validated appraisal tool to assess the methodological rigour and transparency of CPGs [12]. AGREE II contains 23 items across 6 domains (Scope and Purpose, Stakeholder Involvement, Rigour of Development, Clarity of Presentation, Applicability and Editorial Independence) and requires users to rate each item on a 7-point Likert scale. Item scores that differed by ≥3 points were discussed and resolved by consensus. The scores given by both reviewers for items in each domain were summed to yield a total domain score. An overall score for the CPG was obtained by taking a weighted average of the six scaled domain scores. CPGs that had an overall score of ≥60% were considered high quality, those that had an overall score of 30 to <60% were moderate quality and those that had an overall score of <30% were deemed low quality [12]. Further details of the quality assessment are outlined in Appendix 2.

Results

The initial search identified 2918 citations that underwent title and abstract screening. Of these, 2785 were excluded and the full text of 131 citations were reviewed, with 23 CPGs ultimately being included (Figure 1). Included CPGs were from North American, European, South American and Asian associations. Over half (n = 13, 57%) were published in the past 5 years and two CPGs (8.7%) were specific for older adults [13, 14]. Six CPGs (26%) were machine translated [14–19], and the HbA1c target was converted from millimoles per mole to percentage for one CPG [14]. Nine CPGs (39.1%) were high quality, nine (39.1%) were moderate quality and five (21.7%) were considered low quality.

Content related to both older adults and frailty was present in 14 CPGs (61%), while 7 (30.4%) included older adults but not frailty [16–18, 20–23], and 2 (8.7%) mentioned neither older adults nor frailty [15, 24] (Table 1). A definition of older adults was provided in 11 (52.4%) of the 21 CPGs that provided recommendations for older adults. Older adults were defined as aged ≥65 years [13, 14, 16, 23, 25–29], ≥70 years [30] and ≥75 years [31]. Out of the 14 CPGs that mentioned frailty, 7 (50.0%) provided a definition. Frailty definitions included unintentional weight loss or malnutrition [26, 30, 32], vulnerability due to physiological or psychological stressors [13, 27], decline in physical performance/mobility or increased falls risk [25–27, 30, 32], exhaustion, weakness or fatigue [14, 25, 26, 30, 32], increased risk of institutionalisation [25, 32], as well as several other factors [14]. Four CPGs provided recommendations for frailty screening and identification. The Clinical Frailty Scale (CFS) was recommended by one CPG, which defined frailty as a CFS score of 6–8 [30]. Two CPGs listed frailty screening tools, including the Fried Score [13], Clinical Frailty Scale [13], FRAIL score [13] and Edmonton Frailty Scale [32], without giving thresholds scores for frailty. One CPG recommended screening for functional impairments of instructional activities of daily living (iADL) or basic ADL (bADL) without a threshold of impairment to indicate frailty [31].

Haemoglobin A1C targets

A specific HbA1c target for older adults was provided in 15 (71.4%) of the 21 CPGs that provided recommendations for older adults, while 1 (4.8%) suggested relaxing HbA1c targets in older adults [33], 1 (4.8%) suggested lower targets [20] and 4 (19%) provided no specific guidance regarding HbA1c targets in this population [17, 21, 23, 34] (Table 1; Figure 2). Twelve CPGs provided an HbA1c target for healthier older adults, including those with a low disease burden or longer life expectancy, with the majority suggesting similar targets to the general population (<7.0% to 7.5%) [13, 14, 18, 25–27, 29, 30, 32]. HbA1c targets varied for individuals with multiple comorbidities, shortened life expectancy, cognitive impairment, impairments in ADL and/or longer duration of diabetes. For these populations, most CPGs suggested an HbA1c target of ≤8.0% [16, 18, 25, 27, 29, 32, 35], or ≤8.5%–8.6% [13, 14, 19, 22, 30, 31], while one CPG recommended an HbA1c of ≤9.0% [28] (Table 1). A specific HbA1c range for patients who are frail was provided by 6 (42.9%) of the 14 CPGs that mentioned frailty. HbA1c targets for frail individuals ranged from 7.0% to 8.5% [14, 25, 26, 30, 32, 34], and one CPG stated that targets should be individualised in this population [28].

Pharmacological therapy

Among the 21 CPGs that provided recommendations specific to older adults, 16 (76.2%) discussed non-insulin antihyperglycaemic agents (Table 2). Hypoglycaemia risk was considered by all 16 CPGs. Metformin was specifically recommended as a first-line agent in older adults by six CPGs [13, 18, 26, 27, 29, 30] and seven suggested dipeptidyl peptidase-4 (DPP-4) inhibitors as an alternative or second-line agent [18, 19, 26, 27, 29–31]. The risk of hypoglycaemia with sulfonylureas was highlighted, with four advising against their use [13, 14, 21, 26] and nine suggesting caution [17, 18, 22, 23, 27, 28, 30–32]. This included six CPGs that recommended avoiding long-acting sulfonylureas [13, 18, 26, 27, 30, 35], three of which suggested short-acting sulfonylureas, if this class of medication is used [26, 27, 30]. Caution with glucagon-like peptide-1 receptor (GLP-1) agonists was advised by two CPGs due to the potential to cause weight loss [19, 26], while one CPG

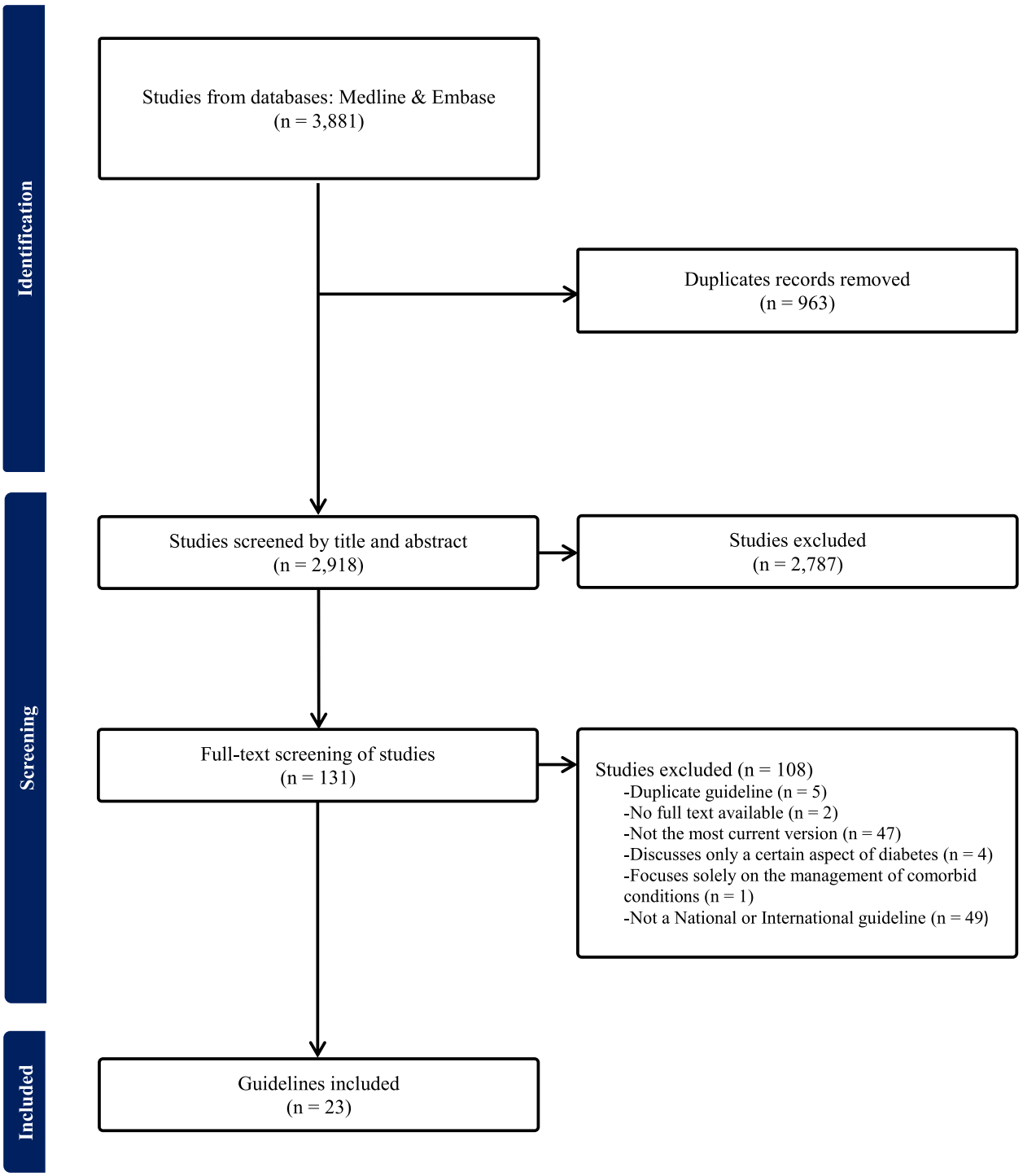

Figure 1. PRISMA flow diagram: selection process for inclusion of guidelines.

recommended their use in older patients with or at risk of atherosclerotic cardiovascular disease [27]. Seven CPGs advised against the use of thiazolidinediones in older adults due to risk of fluid retention and worsening heart failure [13, 14, 18, 22, 26, 27, 29].

Ten (47.6%) out of the 21 CPGs mentioning older adults discussed insulin therapy in this population [13, 14, 18, 26–31, 35] (Table 2). Six CPGs recommended initial use of basal insulins [13, 14, 18, 26, 27, 30], three of which suggested that premixed insulin could be as an alternative to basal insulin [14, 18, 30], and one recommended low-dose short- or rapid-acting insulins before meals without basal insulins in patients >80 years [29].

Among the 14 CPGs mentioning frailty, 3 (21.4%) provided recommendations for non-insulin antihyperglycaemic agents and 2 (14.3%) for insulin therapy. Metformin was

Table 1. Summary of guidelines and HbA1c % targets for hypoglycaemic drug treatments in older adults

Guideline (region)	Year	Definition	Target of hypoglycaemic drug treatment (HbA1c %) in older adults	Quality assessment
ADA (USA) [27]	2023	Older adult: >65 years Frail: decline in physical performance and an increased risk of poor health outcomes due to physiologic vulnerability and functional or psychological stressors	• Healthy, few coexisting chronic illnesses, intact cognitive function and functional status: <7.0%–7.5% • Multiple comorbidities, mild–moderate cognitive impairment, or two or more iADL impairments: <8.0% • End-stage chronic illnesses, moderate–severe cognitive impairment, or two or more ADL impairment: avoid reliance on HbA1c	94% (High)
GMA and NASHIP (Germany) [19][a]	2023	Older adults: not defined Frail: not defined	• Multiple comorbidities and/or severely limited life expectancy: <8.0%–8.5% • >70 years of age < 8.5%	88% (High)
VA/Dod (USA) [28]	2023	Older adult: ≥65 years Frail: not defined	• Major comorbidities present or 5–10 years of life expectancy: 7.0%–8.5% (7.0%–8.0% for mild/absent microvascular complications; 7.5%–8.5% for moderate/advanced microvascular complications) • Marked major comorbidities (end-stage or management is significantly challenging) or <5 years of life expectancy: 8.0%–9.0% • Frail: individualised HbA1c target range	86% (High)
SID and AMD (Italy) [24]	2023	No mention of older adults or frailty	No recommendations	84% (High)
Diabetes Canada [30]	2023	Older adult: ≥70 years Frail: ≥3 are present: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and low physical activity	• Functionally independent with life expectancy >10 years: ≤7.0% • Functionally dependent: 7.1%–8.0% • Frail and/or dementia: 7.1%–8.5%	81% (High)
SBD, SBEM, APDP and SPEDM (Brazil and Portugal) [34]	2023	Older adults: not defined Frail: not defined	• Older adults: not given • Frail: ≤8.0%	50% (Moderate)
KDA (Korea) [20]	2023	Older adult: not defined No mention of frailty	• Long duration of DM, history of severe hypoglycaemia, advanced diabetic complications, limited life expectancy or advanced age: lower glycaemic control targets	35% (Moderate)
ÖDG (Austria) [15][a]	2023	No mention of older adults or frailty	No recommendations	22% (Low)
AACE (USA) [35]	2022	Older adults: not defined Frail: not defined	• History of severe hypoglycaemia, hypoglycaemia unawareness, limited life expectancy, advanced renal disease, extensive comorbidities or long-standing DM: 7.0%–8.0%	75% (High)
NICE (UK) [33]	2022	Older adult: not defined Frail: not defined	• Those who are unlikely to achieve longer term risk reduction benefit, reduced life expectancy, at risk of hypoglycaemia, significant comorbidities: consider relaxing target HbA1c	75% (High)
RSSDI (India) [26]	2022	Older adults: ≥65 years Frail: associated with weight loss, weakness, exhaustion, decreased physical activity, slowness of gait and undernutrition	• Independent, healthy and >10–15 years life expectancy: 7.0%–7.5% • Moderate cognitive impairment, microvascular complications and comorbid conditions, life expectancy <5 years and who are functionally dependent: 7.5%–8.5% • Severe cognitive impairment, advanced microvascular complications and/or major comorbid illness who are frail, functionally dependent and life expectancy <5 years: >8.5%	38% (Moderate)
ESE (Europe) [13][a]	2019	Older adult: ≥ 65 years Frail: state of increased vulnerability to physical or psychological stressors	• Good health, no functional impairment: <7.5% (7.0%–7.5% if on drugs that can cause hypoglycaemia) • Intermediate health, functional impairment and/or mild cognitive impairment/early dementia: <8.0% (7.5%–8.0% if on drugs that can cause hypoglycaemia) • Poor health, end-stage medical conditions, functional impairment and/or moderate to severe dementia: <8.5% (8.0%–8.5% if on drugs that can cause hypoglycaemia)	50% (Moderate)

(*Continued*)

Table 1. Continued

Guideline (region)	Year	Definition	Target of hypoglycaemic drug treatment (HbA1c %) in older adults	Quality assessment
JDS (Japan) [31]	2019	Older adult: ≥75 years Frail: not defined	• Intact/mild cognitive impairment to mild dementia or impairments of iADL: <7.0% (7.0%–8.0% if on drugs that can cause hypoglycaemia) • Moderate/severe dementia, impairment of bADL, functional impairment or presence of multiple comorbidities: <8.0% (7.5–8.5% if on drugs that can cause hypoglycaemia)	24% (Low)
PTD (Poland) [29]	2018	Older adult: >65 years Frail: not defined	• Healthy (life expectancy >10 years): ≤7.0% • Comorbidities, limited life expectancy (<10 years): relaxed therapeutic targets • Patients at advanced age with long-standing DM, and significant macroangiopathic complications (myocardial infarction or stroke) ≤8.0%	40% (Moderate)
SIGN (Scotland) [23]	2017	Older adults: ≥65 years No mention of frailty	No recommendations	79% (High)
IDF (Europe) [32]	2017	Older adults: not defined Frail: combination of significant fatigue, recent weight loss, severe restriction in mobility, increased propensity to falls and increased risk of institutionalisation	• Healthy: <7.0% • Comorbidities, limited life expectancy (<10 years), cognitive impairment, CKD or severe CVD: 7.5%–8.0% • Frail: <8.0%	57% (Moderate)
Ministry of Health of the Russian Federation [18][a]	2017	Older adult: not defined No mention of frailty	• No severe macrovascular complications and/or risk of severe hypoglycaemia: <7.5% • Severe macrovascular complications and/or risk of severe hypoglycaemia: <8.0%	36% (Moderate)
NADEP (Pakistan) [21]	2017	Older adults: not defined No mention of frailty	No recommendations	16% (Low)
CM (Colombia) [25]	2016	Older adult: ≥65 years Frail: significant fatigue and severe restrictions on mobility or strength, who are at greater risk of falls and institutionalisation	• Functionally independent and are free of other major comorbidity factors: ≤7.0% • Fragility, dementia or higher risk of hypoglycaemia: 7.0% to 8.0%	67% (High)
Croatian Society for Diabetes and Metabolic Diseases of the Croatian Medical Association [16][a]	2016	Older adult: ≥65 years No mention of frailty	• Long duration of diabetes, prone to hypoglycaemia, older, microvascular or macrovascular complications, or present comorbidities: 7.5% to 8.0%	24% (Low)
MOH (Singapore) [22]	2014	Older adult: not defined No mention of frailty	• Long duration of diabetes, history of severe hypoglycaemia, advanced atherosclerosis and/or advanced age: 7.0%–8.5%	35% (Moderate)
IMSS (Mexico) [17][a]	2013	Older adults: not defined No mention of frailty	No recommendation	30% (Moderate)
CDS (Czech Republic) [14][a,b]	2013	Older adults: >65 years Frailty: presence of one of the following signs: deconditioning, hypokinesis, psychomotor retardation, increased fatigue, limitation of self-sufficiency, cognitive impairment, depression, serious complications of an inter-current illness or other serious change	• Able-bodied: 7.0% • Serious comorbidities, limited life expectancy: 7.6% • History of severe hypoglycaemia, poor life prognosis, advanced complications and comorbidities, frail, uncooperative: 8.6%	16% (Low)

ADL, activities of daily living; bADL, basic activities of daily living (e.g. self-care abilities such as dressing, mobility, bathing and toileting); iADL, instrumental activities of daily living (e.g. abilities to maintain an independent household such as shopping, meal preparation, taking medication and handling finances); CVD, cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HbA1c, haemoglobin A1C.
[a]Guidelines specific to older adults. [b]Machine translated.

Guideline	Healthier Older Adults[a]	More Complex Older Adults[b]	Frail Older Adults
ADA (United States) [27]	≤7.5	≤8.0	
GMA & NASHIP (Germany) [19]	≤8.5	≤8.5	
VA/Dod (United States) [28]	≤8.0	≤9.0	
SID & AMD (Italian) [24]			
Diabetes Canada [30]	≤7	≤8.5	≤8.5
SBD, SBEM, APDP & SPEDM (Brazil & Portugal) [34]			≤8.0
KDA (Korea) [20]			
ÖDG (Austria) [15]			
AACE (United States) [35]		≤8.0	
NICE (United Kingdom) [33]			
RSSDI (India) [26]	≤7.5	>8.5	>8.5
ESE (Europe) [13]	≤7.5	≤8.5	
JDS (Japan) [31]	≤8.0	≤8.5	
PTD (Poland) [29]	≤7.0	≤8.0	
SIGN (Scotland) [23]			
IDF (Europe) [32]	≤7.0	≤8.0	≤8.0
Ministry of Health of the Russian Federation [18]	≤7.5	≤8.0	
NADEP (Pakistan) [21]			
CM (Colombia) [25]	≤7.0	≤8.0	≤8.0
Croatian Society for Diabetes and Metabolic Diseases of the Croatian Medical Association [16]		≤8.0	
MOH (Singapore) [22]		≤8.5	
IMSS (Mexico) [17]			
CDS (Czech Republic) [14]	≤7.0	≤8.6	≤8.6

Upper limits of A1c target range	≤7.0%	≤7.5	≤8.0%	≤8.5-8.6%	>8.6%	No specific guidance provided for older adults

Figure 2. Upper limit of guideline-recommended HbA1c target for older adults based on health status, complexity and frailty.

specifically recommended as first-line agent by two CPGs [14, 26], with one suggesting DPP-4 inhibitors as an alternative [26], and two suggesting use of low-dose sulfonylureas [26], or sulfonylureas with low risk of hypoglycaemia [14]. Two CPGs advised against GLP-1 agonists and SGLT-2 inhibitors in those who are frail due to weight loss risk [19, 26]. Both CPGs that gave recommendations for insulin therapy in frail adults recommended the use of basal insulins [14, 26].

Deprescribing

Seven (30.4%) out of the 23 included CPGs provided recommendations for deprescribing. One CPG provided explicit criteria for when to deprescribe, including instances of severe or recurrent hypoglycaemia on non-insulin therapies, wide glucose excursions, hospitalisations resulting in adverse effects, or medication use without clear benefit [27]. Two CPGs provided nonspecific recommendations of when to deprescribe, including when there is a need to reduce polypharmacy, when the risks outweigh the benefits, the medication has limited efficacy, targets are not being met or during acute illness [19, 26]. Three CPGs provided recommendations for deprescribing specific medications. These included discontinuing sulfonylureas [24, 30], and medications causing hypoglycaemia when adding GLP-1 agonists and SGLT-2 inhibitors [28]. Three CPGs gave nonspecific recommendations on medications to deprescribe, including agents with a high hypoglycaemia risk [26, 27] or medications with no impact on glycaemic control or weight, unless other clinical benefits are present [33]. No CPGs provided a specific strategy or algorithm by which to deprescribe medications.

Discussion

This systematic review was performed to identify CPG recommendations for the management of T2DM in older adults, including both healthy and frail populations. Out of the 23 included CPGs, 21 (91.3%) contained content related to the population of interest. Recommendations regarding HbA1c targets ranged from <7.0% to 9.0% and differed based on overall health, life expectancy, frailty, and

Table 2. Pharmacologic considerations for type 2 diabetes mellitus treatment in older adults

Guideline (region)	Oral hypoglycaemic agents considerations	Insulin therapy considerations
ADA (USA) [27]	• Prefer medication classes with low hypoglycaemia risk • First line: metformin • DPP4i have few side effects and low risk of hypoglycaemia • GLP1a have CV benefit in those with/at risk of ASCVD • TZDs should be used cautiously, if used lower doses reduce side effects • SUs should be used with caution, if used SUs with shorter duration of action are preferred and glyburide should be avoided • SGLT2i side effects may be more common in older people	• Insulin doses should be titrated to meet individual glycaemic targets and avoid hypoglycaemia • Prefer once-daily basal insulin, associated with minimal side effects • Consider long-acting insulin analogues to minimise hypoglycaemia • Insulin therapy requires individuals or their caregivers to have good visual, motor and cognitive skills
GMA and NASHIP (Germany) [19]	• Prefer DPP4i over SUs **Older adults and/or frail:** use GLP1a and SGLT2i with caution due to weight loss risk	Not specified
VA/Dod (USA) [28]	• Prioritise drug classes other than SUs or meglitinides to minimise hypoglycaemia risk	• Prioritise drug classes other than insulin
SID and AMD (Italy) [24]	Not specified	Not specified
Diabetes Canada [30]	• DPP4i preferred over SUs as second-line therapy to metformin • Caution with SUs and other antihyperglycaemic agents that increase hypoglycaemia risk • Initial SU dose should be half of typical starting dose. Doses should be increased slowly • Gliclazide, glimepiride and meglitinides (particularly in individuals with irregular eating habits) should be used instead of glyburide due to reduced risk of hypoglycaemia **Frail:** discontinue antihyperglycaemic agents increasing hypoglycaemia risk	• Long-acting[a] insulin analogues is considered over NPH or 30–70 insulin to reduce hypoglycaemic events • To reduce dosing errors, use premixed insulins and prefilled insulin pens
SBD, SBEM, APDP and SPEDM (Brazil and Portugal) [34]	Not specified	Not specified
KDA (Korea) [20]	Not specified	Not specified
ÖDG (Austria) [15]	Not specified	Not specified
AACE (USA) [35]	• SU risk of hypoglycaemia increased when long-acting formulations are used in older adults • Monitor for postural hypotension with SGLT2i in older adults on loop diuretics	• Lower starting insulin doses (0.2 to 0.3 IU/kg/day) are recommended
NICE (UK) [33]	Not specified	Not specified
RSSDI (India) [26]	• First line: metformin • DPP4i are considered safe • SUs not preferred. If used, short-acting[c] SUs should be used and long-acting[b] SUs should be avoided • Avoid meglitinides and TZDs • GLP1a use is limited due to weight loss side effect • SGLT2i recommended for patients <70 years who are average weight/obese **Frail:** first line: metformin, alternative: low-dose SUs • Oral GLP1a and SGLT2i not suitable • Meglitinides and insulin require attention in frail patients or elderly patients with multiple comorbidities	• Start low and go slow to avoid adverse effects • Long-acting[a] insulins preferred. Starting dose lower than typical 0.2 IU/kg/day • Short-acting[d] insulins associated with higher risk of hypoglycaemia • If there is frequent hypoglycaemia when using premix insulin, 70% of the total premix dose can be given as a single, morning-time basal insulin dose • Insulin should only be prescribed after the evaluation of administering abilities, regular glucose monitoring and understanding of hypoglycaemia **Frail:** long-acting insulin analogues preferred

(*Continued*)

Table 2. Continued

Guideline (region)	Oral hypoglycaemic agents considerations	Insulin therapy considerations
ESE (Europe) [13]	• First line: metformin • Diabetes regimens should avoid hypoglycaemia • Avoid using SUs and meglitinides due to risk of hypoglycaemia. If used, glyburide should be avoided • TZDs may cause fluid retention and may worsen heart failure • Simplify medication regimens for patients with cognitive impairment	• Use insulin sparingly, use when oral agents do not provide sufficient glycaemic control • Initially, a single long-acting insulin can be added • If fasting glucose in near goal but HbA1c remains above target: rapid-acting insulin can be added first prior to the largest meal, then prior to other meals when necessary. Alternatively, premixed insulin given twice daily may be simpler but lack flexibility and may increase risk of hypoglycaemia, especially in patients who skip/delay meals • Metformin can be continued when insulin is started
JDS (Japan) [31]	• Prefer DPP4i for their lower risk of hypoglycaemia • Start SUs at minimum doses and titrate cautiously based on renal function, HbA1c and hypoglycaemia risk • Use meglitinides cautiously due to risk of hypoglycaemia	• Measures need to be taken to protect patients against hypoglycaemia and to ensure patients and caregivers are well informed about the measures being taken
PTD (Poland) [29]	• First line: metformin; alternatives: DPP4i, GLP1a, alpha-glucosidase inhibitor, TZD, SGLT2i • SUs should be started at low doses due to risk of hypoglycaemia • Do not use TZDs in heart failure	• If indicated, insulin therapy should not be delayed • Select insulin agents with low risk of hypoglycaemia • In those >80 years of age, use low doses of a short-acting insulin or rapid-acting insulin analogues before main meals without basal insulin
SIGN (Scotland) [23]	• Use SUs cautiously due to hypoglycaemia risk	Not specified
IDF (Europe) [32]	• Avoid agents with risk of hypoglycaemia	Not specified
Ministry of Health of the Russian Federation [18]	• In general, the treatment is the same for all adults (first line: metformin; alternatives: DPP4i, GLP1as, SGLT2i) • Prefer DPP4i due to safety profile. • SUs used with caution. If used, doses should be halved and increased slower than in younger patients. Glyburide is not recommended for people >60 years • SGLT2i used with caution • TZDs are not indicated	• Start with basal insulins or combination drugs (ready-made insulin mixtures and ready-made combinations of insulin analogues)
NADEP (Pakistan) [21]	• Avoid SUs due to risk of hypoglycaemia	Not specified
CM (Colombia) [25]	Not specified	Not specified
Croatian Society for Diabetes and Metabolic Diseases of the Croatian Medical Association [16]	Not specified	Not specified
MOH (Singapore) [22]	• Low-dose, short-acting oral agents recommended • Consider cardiac function and volume overload risks with TZDs • Caution with long-acting SUs, insulin secretagogues and insulin due to hypoglycaemia risk	Not specified
IMSS (Mexico) [17]	• Exercise caution with SUs due to the risk of hypoglycaemia	Not specified
CDS (Czech Republic) [14]	• Avoid insulin and SU derivatives due to risk of hypoglycaemia. If used, prefer SUs with low risk of hypoglycaemia[f] • Avoid TZDs due to risk of fluid retention and worsening heart failure **Frail:** first line: metformin; alternative: DPP-4 inhibitor or SU with low risk	• Maintain oral antidiabetics in combination with insulin • Prefer simple insulin regimens • Long-acting analogues and/or premixed mixtures of short- and medium-acting insulins may be used • Intensified insulin regimens (basal insulins with short-acting analogues) should only be used in well-fit older diabetics who are independent and well motivated or temporarily during hospitalisations **Frail:** Long-acting insulin analogues once a day is preferred

ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; DPP4i, dipeptidyl peptidase-4 inhibitors; GLP-1a, glucagon-like peptide-1 agonists; HbA1c, haemoglobin A1C; MR, modified release; NPH, neutral protamine Hagedorn; PPAR-g, peroxisome proliferator-activated receptor gamma; SGLT2i, sodium-glucose transporter-2 inhibitors; SUs, sulfonylureas; TZDs, thiazolidinediones. [a]Detemir, glargine U-100 and U-300, and degludec. [b]Glyburide. [c]Gliclazide and glipizide. [d]Aspart, glulisine and lispro**.** [e]NPH, glargine, detemir and degludec. [f]Gliclazide and glimepiride

functional and cognitive abilities. Pharmacologic recommendations for oral and injectable antihyperglycaemic medications focused on reducing the risk of hypoglycaemia and avoiding medications associated with weight loss or fluid retention.

Eleven CPGs [13, 14, 18, 25–32] provided different HbA1c targets for healthier older adults and those who are frail, living with multiple comorbidities, reduced life expectancy and cognitive and/or functional decline. Targets for healthier older adults were similar to younger adults, ranging from <7.0% to 7.5%, while for frail, functionally impaired or medically complex older adults, CPGs suggested less strict targets (≤8.0%–9.0%) or provided nonspecific recommendations to relax the glycaemic control. A previous systematic review of recommendations for older adults in diabetes CPGs found different HbA1c targets within the three included CPGs [8]. We similarly found different HbA1c targets within CPGs; however, there was an overarching theme of strict control for healthier older adults and relaxed targets for frail or medically complex individuals.

Landmark clinical trials, such as UKPDS, ADVANCE and ACCORD, have informed diabetes CPGs worldwide [36–38]. These studies support strict HbA1c targets to reduce the risk of micro- and macrovascular complications. While data suggest that older adults do benefit from strict control, they are also at an increased risk of hypoglycaemia and complications [39]. In a *post hoc* analysis of older and frail adults in the ADVANCE trial, intensive blood glucose lowering was consistently found to be beneficial throughout all ages [39]. However, age and frailty were associated with increased risk of hypoglycaemia and higher mortality in participants with one or more episodes of severe hypoglycaemia irrespective of the treatment arm [39–41]. In a subgroup analysis of the ACCORD trial, older and younger adults achieved similar HbA1c levels, and experienced similar rates of death and macrovascular complications [42]. However, those in intensive glycaemic control group had approximately three times the rate of severe hypoglycaemia compared to the standard glycaemic control group with a greater absolute annual incidence in older individuals [42]. These data appear to have been integrated into most of the included CPGs in our study with recommendations to maintain strict control in healthier older adults and de-intensify HbA1c targets in those at greatest risk of hypoglycaemia and associated complications.

The risk of hypoglycaemia is an important consideration in pharmacotherapy choice in older individuals across the health and frailty spectrum [5–7]. Hypoglycaemic events are linked to heightened mortality and elevated risks for falls and associated injuries, dementia, and macro- and microvascular events [43]. Of the 16 CPGs that discussed non-insulin pharmacotherapy in older adults, 6 suggested the use of metformin as a first-line agent and 7 recommended DPP-4 inhibitors as a second-line agent. Metformin has an established role in this population because of its low risk of hypoglycaemia and neutral effects on weight [6, 44]. Sulfonylureas were traditionally a second-line agent for T2DM; however, 13 CPGs [13, 14, 17, 18, 21–23, 26–28, 30–32] now recommended avoidance or caution in older adults due to their high hypoglycaemia risk. Sulfonylureas have largely been replaced in this population by DPP-4 inhibitors due to a lower risk of hypoglycaemic events [44].

Two CPGs recommended caution with use of GLP-1 agonists and SGLT-2 inhibitors in frail older adults. Avoidance of weight-reducing agents is important in those who are frail, as these medications may diminish the muscle reserve, worsening sarcopenia [5, 6]. Moreover, GLP-1 agonists and SGLT-2 inhibitors can contribute to dehydration, increasing risks for falls and acute kidney injury, and SGLT-2 inhibitors can also cause orthostatic hypotension and urinary tract infections [5, 6]. These recommendations differ from those for younger adults and overweight/obese individuals, in whom these medications are often recommended as initial therapy due to their multiple benefits of glucose control, prevention of cardiovascular and renal events, and weight reduction [6]. Weight reduction should be monitored and moderated in frail older population since, unlike the younger individuals who may manage worse with higher weight, functionality is better in frail, obese older adults than malnourished ones [6].

Along with sulfonylureas, insulin poses an increased risk of hypoglycaemia and remains a common cause for drug-related hospitalisations in older populations [7, 45]. Despite the heightened risk, insulin remains a widely utilised therapy even in older and frail populations [45]. This is attributed to the many challenges in glucose management in older individuals [6, 7, 45, 46]. However, the therapeutic goal shifts when using insulin in older adults, wherein a primary focus is to minimise risks [4, 7]. Accordingly, 6 of 10 included CPGs that made recommendations on the use of insulin therapy in older and frail adults recommended the use of basal insulins and/or lower starting doses in this population. Basal insulin is preferred due to its once-daily dosing and decreased risk of hypoglycaemic events [7, 45]. However, it is crucial to continually evaluate individual's cognitive and functional ability to ensure adherence to insulin regimens, as conditions such as cognitive impairment, retinopathy and neuropathy may impede adherence as was highlighted in three of the CPGs [7, 14, 26, 27].

Beyond influencing medication selection, frailty also significantly impacts the prognosis of T2DM, exacerbating diabetes-related complications, adverse events and hospitalisations, and should be recognised as an important consideration in treatment decisions [6]. Integrating frailty screening into the ongoing health assessment as a routine part of diabetes care is necessary for identifying the higher risk group that require a treatment adjustment. Multiple tools exist that are effective at identifying frailty and associated shortened life expectancy [47–49]. While there is no consensus on the best tool to quantify frailty, it has been suggested that any tool that conceptualises frailty in a clinical manner is appropriate [3, 50].

Deprescribing is an important practice when the decision is made to change to a less strict HbA1c target. The

underlying theme behind deprescribing recommendations was the avoidance of hypoglycaemia and polypharmacy. While CPGs acknowledged the need for therapy de-escalation, they lacked guidance on the process. This is converse to the detailed algorithms provided for therapy intensification. Instead, CPGs provide only high-level guidance on when to deprescribe, such as recurrent hypoglycaemia and lack of medication efficacy. More research is needed on effective methods for deprescribing, which would allow for stronger recommendation and development of deprescribing algorithms from diabetes organisations.

Beyond deprescribing, more research is warranted in the management of diabetes in older and frail individuals. The two frailty phenotypes are at polar ends of the frail metabolic spectrum. The sarcopenic obese frail phenotype has increased visceral fat and increased insulin resistance, while the malnourished frail phenotype has significant loss of muscle and fat mass and reduced insulin resistance [4–6]. These individuals likely require an individualised approach to diabetes management, and more research focused specifically on diabetes management in older and frail individuals will help to support recommendations made within CPGs.

Strengths and limitations

This is not the first review of diabetes CPGs in older adults. However, we not only screened for HbA1c targets but also for the pharmacotherapy algorithms and were more inclusive of international CPGs. In our attempt to be inclusive of non-English-language publications, we used machine translation of non-English international papers, and as such, there is the risk of misinterpretation of recommendations. While our search strategy resulted in 23 CPGs, it only included two databases and therefore may lack comprehensiveness. We included CPGs that were published in the last 10 years, including two published from 2013 [14, 17]. There have been significant advancements in diabetes research over the past 10 years, and some older CPGs may not be relevant today. However, we did search for updated versions of all included CPG, minimising the risk of including outdated CPGs. Lastly, the focus for this systematic review was only on T2DM in non-palliative and non-end-of-life patients and as such is not applicable to all older adults with diabetes.

Conclusion

This systematic review aimed to consolidate the CPG recommendations for management of T2DM in older and frail populations. A significant portion of CPGs acknowledge the influence of ageing, yet few address frailty, and among those, only a small number offer comprehensive recommendations. Despite efforts to standardise diabetic management, variability was present within CPGs. However, a pattern of stricter HbA1c target for healthier older adults and more relaxed target for those who are frail or medically complex, as well as a focus on avoiding hypoglycaemia and other adverse effects in all older adults, was found. Additional guidance specific to older and frail adults would help to standardise the management of diabetes worldwide.

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References

1. Ong KL, Stafford LK, McLaughlin SA *et al.* Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*. 2023; **402**:203–34.
2. O'Neil H, Todd A, Pearce M *et al.* What are the consequences of over and undertreatment of type 2 diabetes mellitus in a frail population? A systematic review. *Endocrinol Diabetes Metab*. 2024;**7**:e00470.
3. Clegg A, Young J, Iliffe S *et al.* Frailty in elderly people. *Lancet*. 2013;**381**:752–62.
4. Sinclair AJ, Abdelhafiz AH. Metabolic impact of frailty changes diabetes trajectory. *Metabolites*. 2023;**13**:295.
5. Sinclair AJ, Pennells D, Abdelhafiz AH. Hypoglycaemic therapy in frail older people with type 2 diabetes mellitus—a choice determined by metabolic phenotype. *Aging Clin Exp Res*. 2022;**34**:1949–67.
6. Bahat G, Ozkok S, Petrovic M. Management of type 2 diabetes in frail older adults. *Drugs Aging*. 2023;**40**:751–61.
7. Sircar M, Bhatia A, Munshi M. Review of hypoglycemia in the older adult: clinical implications and management. *Can J Diabetes*. 2016;**40**:66–72.
8. Christiaens A, Henrard S, Zerah L *et al.* Individualisation of glycaemic management in older people with type 2 diabetes: a systematic review of clinical practice guidelines recommendations. *Age Ageing*. 2021;**50**:1935–42.
9. Page MJ, McKenzie JE, Bossuyt PM *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;**372**:n71.
10. Rethlefsen ML, Kirtley S, Waffenschmidt S *et al.* PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. *Syst Rev*. 2021;**10**:39.
11. Day C, Bailey CJ. HbA1c - changing units. *Diabetes Vasc Disease*. 2009;**9**:134–6.
12. AGREE Next Steps Consortium: The AGREE II Instrument (Electronic version): Canada. https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf (6 March 2024, date last accessed).
13. LeRoith D, Biessels GJ, Braithwaite SS *et al.* Treatment of diabetes in older adults: an Endocrine Society∗ clinical practice guideline. *J Clin Endocrinol Metabol*. 2019;**104**: 1520–74.
14. Svacina Š, Jind O, Jurašková B *et al.* Recommended practices in the treatment in of elderly patients with diabetes mellitus

in the CR (Czech). *Diabetologie Metabolismus Endokrinologie Výživa*. 2013;**16**:82–89.
15. Clodi M, Abrahamian H, Brath H *et al.* Antihyperglycemic treatment guidelines for diabetes mellitus type 2 (update 2023) (German). *Wien Klin Wochenschr*. 2023;**135**:32–44.
16. Raheiÿ D, Altabas V, Bakula M *et al.* Croatian guidelines for the pharmacological treatment of type 2 diabetes (Croatian). *Lijeÿ Vjesn*. 2016;**138**:1–21.
17. Gil-Velázquez LE, Sil-Acosta MJ, Domínguez-Sánchez ER *et al.* Clinical practice guide: diagnosis and treatment of type 2 diabetes mellitus (Spanish). *Revista Medica del IMSS*. 2013;**51**:104–19.
18. дедов ИИ, Шестакова МВ, Майоров АЮ *et al.* Standards of specialized diabetes care (Russian). Сахарный диабет. 2017;**20**:1–121.
19. Programm für Nationale Versorgungs Leitlinien. Clinical Practice Guideline: Shared Decision Making, Diagnostic Evaluation, and Pharmacotherapy in Type 2 Diabetes. *National Disease Management Guideline*. Germany: German, 2023. https://www.leitlinien.de/themen/diabetes (23 February 2024, date last accessed).
20. Choi JH, Lee KA, Moon JH *et al.* 2023 clinical practice guidelines for diabetes mellitus of the Korean Diabetes Association. *Diabetes Metab J*. 2023;**47**:575–94.
21. National Association of Diabetes Educators of Pakistan. *Pakistan's Recommendations for Optimal Management of Diabetes from Primary to Tertiary Care Level*. Pakistan, 2017. https://regroup-production.s3.amazonaws.com/documents/ReviewReference/879732147/BIDE-Prompt-Book.pdf?response-content-type=application%2Fpdf&X-Amz-Algorithm=AWS4-HMAC-SHA256&X-Amz-Credential=AKIAYSFKCAWYQ4D5IUHG%2F20240412%2Fus-east-1%2Fs3%2Faws4_request&X-Amz-Date=20240412T145658Z&X-Amz-Expires=604800&X-Amz-SignedHeaders=host&X-Amz-Signature=ee296d08fd554b0197cc2bd6c35673b8ea596e56df14f03b8496a16f1f35c6ff (23 February 2024, date last accessed).
22. Ministry of Health Singapore. *MOH Clinical Practice Guidelines: Diabetes Mellitus*. Singapore, 2014. https://www.moh.gov.sg/hpp/doctors/guidelines/GuidelineDetails/cpgmed_diabetes_mellitus. (23 February 2024, date last accessed).
23. Scottish Intercollegiate Guidelines Network. *Management of Diabetes: A National Clinical Guideline*. Scotland, 2010. https://www.sign.ac.uk/media/1054/sign116.pdf (23 February 2024, date last accessed).
24. Mannucci E, Candido R, Monache LD *et al.* 2023 update on Italian guidelines for the treatment of type 2 diabetes. *Acta Diabetol*. 2023;**60**:1119–51.
25. Aschner P, Muñoz OM, Giron D *et al.* Clinical practice guideline for the prevention, early detection, diagnosis, management and follow up of type 2 diabetes mellitus in adults. *Colomb Med (Cali)*. 2016;**47**:109–30.
26. Makkar BM, Kumar CV, Saboo B *et al.* RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2022. *Int J Diabetes Dev Ctries*. 2022;**42**:1–143.
27. ElSayed NA, Aleppo G, Aroda VR *et al. 13. Older Adults: Standards of Care in Diabetes – 2023 Diabetes Care*. 2023;**46**:S216–S229. https://diabetesjournals.org/care/issue/46/Supplement_1 (23 February 2024, date last accessed).
28. U.S. Department of Veterans Affairs, U.S. Department of Defense. *Management of Type 2 Diabetes Mellitus*. United States of America, 2023. https://www.healthquality.va.gov/guidelines/cd/diabetes/ (23 February 2024, date last accessed). **2023**.
29. Diabetology C. 2018 guidelines on the management of diabetic patients. A position of Diabetes Poland. *Clin Diabetol*. 2018;**7**:1–90.
30. Diabetes Canada Clinical Practice Guidelines Expert Committee. Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes*. Diabetes Canada, 2018;**42**:S1–S325. https://guidelines.diabetes.ca/cpg (23 February 2024, date last accessed).
31. Araki E, Goto A, Kondo T *et al.* Japanese clinical practice guideline for diabetes 2019. *Diabetol Int*. 2020;**11**:165–223.
32. International Diabetes Federation. *Managing Older People with Type 2 Diabetes*. Belgium: Global Guideline, 2017:**2012**. https://ifa.ngo/wp-content/uploads/2014/02/IDF-Guideline-for-Older-People.pdf (23 February 2024, date last accessed).
33. National Institute for Health and Care Excellence. *Type 2 Diabetes in Adults: Management*. England: National Institute for Health and Care Excellence, 2022;**2023**. https://www.nice.org.uk/guidance/ng28 (23 February 2024, date last accessed).
34. Bertoluci MC, Silva Júnior WS, Valente F *et al.* 2023 UPDATE: Luso-Brazilian evidence-based guideline for the management of antidiabetic therapy in type 2 diabetes. *Diabetol Metab Syndr*. 2023;**15**:160.
35. Blonde L, Umpierrez GE, Reddy SS *et al.* American Association of Clinical Endocrinology Clinical Practice Guideline: developing a diabetes mellitus comprehensive care plan—2022 update. *Endocr Pract*. 2022;**28**:923–1049.
36. UK Prospective Diabetes Study Group. UK Prospective Diabetes Study (UKPDS). *Diabetologia*. 1991;**34**:877–90.
37. ADVANCE Collaborative Group, Patel A *et al.* Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;**358**:2560–72.
38. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;**358**:2545–59.
39. Ohkuma T, Chalmers J, Cooper M *et al.* The comparative effects of intensive glucose lowering in diabetes patients aged below or above 65 years: results from the ADVANCE trial. *Diabetes Obes Metab*. 2021;**23**:1292–300.
40. Nguyen TN, Harris K, Woodward M *et al.* The impact of frailty on the effectiveness and safety of intensive glucose control and blood pressure–lowering therapy for people with type 2 diabetes: results from the ADVANCE trial. *Diabetes Care*. 2021;**44**:1622–9.
41. Zoungas S, Patel A, Chalmers J *et al.* Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010;**363**:1410–8.
42. Miller ME, Williamson JD, Gerstein HC *et al.* Effects of randomization to intensive glucose control on adverse events, cardiovascular disease, and mortality in older versus younger adults in the ACCORD trial. *Diabetes Care*. 2014;**37**:634–43.
43. Mattishent K, Loke YK. Meta-analysis: association between hypoglycemia and serious adverse events in older patients treated with glucose-lowering agents. *Front Endocrinol*. 2021;**12**:571568.
44. Doni K, Bühn S, Weise A *et al.* Safety of dipeptidyl peptidase-4 inhibitors in older adults with type 2 diabetes: a systematic

review and meta-analysis of randomized controlled trials. *Ther Adv Drug Saf* . 2022;**13**:20420986211072383.
45. Weiner JZ, Gopalan A, Mishra P *et al.* Use and discontinuation of insulin treatment among adults aged 75 to 79 years with type 2 diabetes. *JAMA Intern Med*. 2019;**179**:1633.
46. Lipska KJ, Huang ES, Liu JY *et al.* Glycemic control and diabetes complications across health status categories in older adults treated with insulin or insulin secretagogues: The Diabetes & Aging Study. *J Am Geriatr Soc*. 2023;**71**:3692–700.
47. Aravindhan K, Mat S, Bahyah S *et al.* Comparing four frailty assessment tools against seven-year mortality in the Malaysian elders longitudinal research study. *Arch Gerontol Geriatr*. 2024;**118**:105304.
48. Kim DJ, Massa MS, Potter CM *et al.* Systematic review of the utility of the frailty index and frailty phenotype to predict all-cause mortality in older people. *Syst Rev*. 2022;**11**: 187.
49. Falk Erhag H, Guðnadóttir G, Alfredsson J *et al.* The association between the clinical frailty scale and adverse health outcomes in older adults in acute clinical settings - a systematic review of the literature. *CIA*. 2023;**18**:249–61.
50. Faller JW, Pereira DN, de Souza S *et al.* Instruments for the detection of frailty syndrome in older adults: a systematic review. *PloS One*. 2019;**14**:e0216166.

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