



# Challenges and Strategies for Diabetes Management in Community-Living Older Adults

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The prevalence of diabetes is increasing, especially in older people, mainly because of an increase in life expectancy. The number of comorbidities also increases with increasing age, leading to a unique diabetes phenotype in old age that includes vascular disease, physical and neuropathic complications, and mental dysfunction. These three categories of complications appear to have a synergistic effect that can lead to a vicious cycle of deterioration into disability. Early assessment and appropriate, timely interventions may delay adverse outcomes. However, this complex phenotype constitutes a great challenge for health care professionals. This article reviews the complex diabetes phenotype in old age and explores management strategies that are predominantly based on the overall functional status of patients within this heterogeneous age-group.

With increasing aging of the population and urbanization of lifestyle, the global prevalence of diabetes is expected to rise from 8.4% in 2017 to nearly 10% by 2045 (1). Almost half of patients with diabetes (44%) are >65 years of age, with a prevalence that peaks (22%) at the age-group of 75–79 years (1). In older people, diabetes is a disabling disease as a result of vascular complications, coexisting multiple comorbidities, and an increased prevalence of geriatric syndromes such as cognitive and physical dysfunction, leading to increased risk of frailty and disability (2). Because of the complexity of diabetes in old age and the heterogeneous nature of this age-group (i.e., ranging from fit individuals living independently in the community to fully dependent people residing in a care home), comprehensive geriatric assessment is essential. Adoption of individualized management goals that aim to prevent loss of autonomy, preserve independence, and put quality of life at the heart of care plans is also essential. This article reviews the challenges and suggests management strategies for diabetes in this complex age-group. Its primary focus is on type 2 diabetes, which is the predominant form of the disease in aging populations.

## Diabetes Phenotype in Old Age

In addition to the traditional diabetes-related vascular and neuropathic complications, physical and mental disabilities are only now emerging as important categories of complications in people with diabetes that affect older

people disproportionately (3). Diabetes is directly associated with accelerated loss of muscle strength and muscle quality, increasing the risk of sarcopenia (4,5). Additionally, diabetes-related complications such as renal impairment and diabetes-associated comorbidities such as hypertension increase the likelihood of frailty (6,7). The combination of sarcopenia and frailty, often complicated by various types of neuropathy, mediate the pathway to physical disability and lower-limb dysfunction (3).

On the other hand, persistent hyperglycemia and recurrent episodes of hypoglycemia increase the risk of cognitive dysfunction and all types of dementia by twofold (8). Diabetes also increases the risk of incident depression by 27% (9). The combination of dementia and depression in older people with diabetes mediate the pathway to mental disability.

With the development of physical or mental disabilities, diabetes self-care will be compromised. For example, dementia may limit a patient's ability to recognize or treat hypoglycemia, and depression may compromise self-care compliance leading to persistent hyperglycemia and increased risk of diabetes complications. As a consequence of dementia, poor communication with family members or caregivers may also delay the recognition of these problems. Meanwhile, physical disability manifested by disturbances in activities of daily living may compromise the safety of

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performing a task such as self-administering insulin, create an inability to self-monitor glucose, and, in the case of frailty and particularly if associated with weight loss, increase the risk of hypoglycemia.

### Synergistic and Reciprocal Relations

The vascular, physical, and mental categories of complications in older people with diabetes have synergistic and reciprocal relations among one another, leading to a vicious cycle and downhill deterioration to disability as shown in Figure 1. Some diabetes-related neuropathic complications (e.g., proximal motor neuropathy), although microvascular in origin, have been grouped with the “physical” category, reflecting the clinical consequences and symptom profiles associated with this complication.

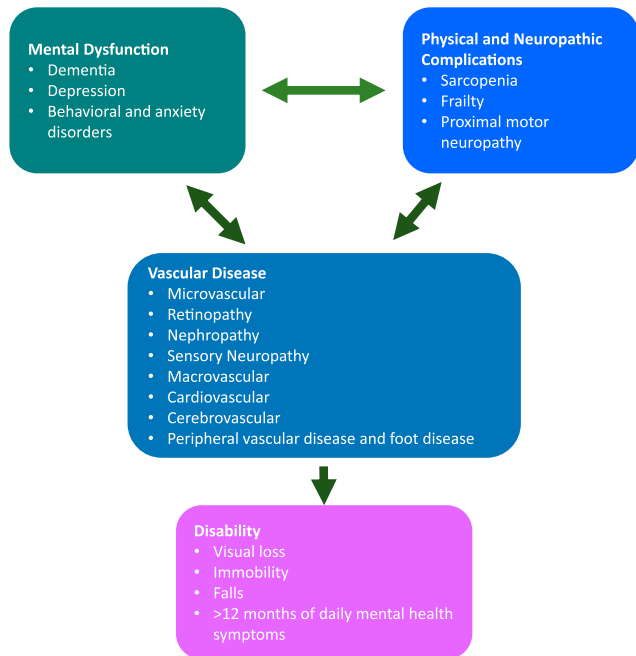
The three categories of complications are likely to share part of a common pathophysiologic mechanism, suggesting that they are a manifestation of a single but complex phenotype (10). For example, the correlation between physical frailty and depression is substantial and suggests that psychological vulnerability is an important component of frailty (11). A recent meta-analysis has shown that the relationship between depression and frailty is reciprocal (12). Similarly, longitudinal data from the Survey of

Health Ageing and Retirement in Europe (SHARE) showed a reciprocal relationship between physical frailty and cognitive impairment (13). Depressive symptoms are associated with increased risk of all types of dementia (14). The SHARE study demonstrated the other direction of this relationship, with lower memory performance at a given age predicting subsequent 2-year increases in depressive symptoms (15). Physical frailty may be an intermediate stage or mediate the associations between diabetes and both dementia and depression (16,17). Similarly, frailty and vascular disease appear to have a bidirectional relationship (18). Frailty predicts vascular disease, and vascular disease is associated with an increased risk of incident frailty (19). Frailty and sarcopenia are associated with reduced muscle mass and increased visceral fat, which lead to atherosclerosis via a complex interplay of factors, including increased insulin resistance, proinflammatory cytokines, reduced physical activity, increased oxidative stress, and mitochondrial dysfunction, increasing the risk of vascular disease (20). Also, vascular disease is linked to both cognitive dysfunction and depression (21,22) (Figure 1).

### Clinical Presentation and Diagnosis

Clinical diagnosis of diabetes in old age may not be straight forward. Symptoms may be absent in up to 50% of cases, and, when present, they are usually nonspecific such as general fatigue, which may be attributed to old age (23). Geriatric syndromes or diabetes-related complications such as falls or urinary incontinence and hyperglycemic hyperosmolar state, respectively, may be the first manifestation of diabetes. Osmotic symptoms are less prominent because of the increased renal threshold for glucose filtration (reducing the intensity of polyuria) and impairment of thirst sensation (reducing the intensity of polydipsia).

Diagnostic criteria for diabetes are the same regardless of age and are based on high fasting plasma glucose (FPG)  $\geq 7$  mmol/L (126 mg/dL) or 2-hour plasma glucose during oral glucose tolerance test (OGTT)  $\geq 11.1$  mmol/L (200 mg/dL) (24). Clinicians should be aware that, in older adults, FPG is less sensitive in diagnosing diabetes, but the 2-hour plasma glucose with OGTT appears to capture most cases (25). An A1c  $\geq 6.5\%$  (48 mmol/mol) is another diagnostic test for diabetes. It has the advantages of less day-to-day variability, high specificity for diabetes diagnosis (98.7%), and international standardization. However, it has a low sensitivity (46.8%), which means that it can miss  $>50\%$  of diabetes cases (Table 1) (26). Because of the asymptomatic nature of diabetes in old age, testing for A1c should be included in the routine annual checkups of older people. In patients with normal A1c but for whom there is clinical suspicion of diabetes, a random blood glucose or 2-hour plasma glucose during OGTT is required.



**FIGURE 1** Reciprocal relations among the three categories of complications in older people with diabetes that eventually lead to disability. These complications likely share a common pathogenic pathway that includes a complex interplay of factors such as increased insulin resistance, proinflammatory cytokines, increased oxidative stress, and mitochondrial dysfunction.

**TABLE 1** Clinical Presentation, Diagnosis, and Assessment of Diabetes in Older People

Notes	
Clinical presentation	<ul style="list-style-type: none"> <li>• Osmotic symptoms are less prominent because of an increased renal threshold for glucose (reducing the intensity of polyuria) and impairment of thirst sensation (reducing the intensity of polydipsia).</li> <li>• Diabetes can be asymptomatic in up to 50% of older patients.</li> <li>• When symptoms are present, they may be nonspecific such as being generally unwell, fatigued, or lethargic and can mistakenly be attributed to aging.</li> <li>• A diabetes complication such as visual loss or neuropathy or an unexplained fall may be the first presentation.</li> </ul>
Diagnosis	<ul style="list-style-type: none"> <li>• Fasting glucose in the early stages of diabetes may be normal.</li> <li>• Two-hour plasma glucose during OGTT appears to capture undiagnosed cases.</li> <li>• A1C is specific but less sensitive (i.e., a normal A1C may miss cases of diabetes).</li> </ul>
Assessment	<p>In addition to screening for macrovascular and microvascular complications, comprehensive geriatric assessment should be performed on diagnosis, including screenings for:</p> <ul style="list-style-type: none"> <li>• Vascular disease</li> <li>• Physical and neuropathic function</li> <li>• Mental/cognitive function</li> </ul>

## Diabetes Management

In general, interventions should be functionally dependent, starting with tighter metabolic control in independent people, with gradual relaxation of targets as patients' functional level declines (Figure 2). Considering the often-complex phenotype of diabetes in old age, management should be focused on early assessment and reducing the risks of the three major complication categories (Table 2) (27–30).

### Vascular Disease

Managing vascular disease risk includes treatment of risk factors such as hyperglycemia, hypertension, and dyslipidemia (31).

### Hyperglycemia

Tight glycemic control will have a cardiovascular benefit after at least 10 years of treatment; however, the risk of hypoglycemia increases by 1.5- to 3-fold with tight control (32). For fit, independent patients, an A1C goal of 7.0–7.5% (53.0–58.5 mmol/mol) is acceptable because hypoglycemia risk increases with A1C levels below this target range. For frail, dependent patients with multiple comorbidities, a target A1C of 8.0–9.0% (63.9–74.9 mmol/mol) is reasonable

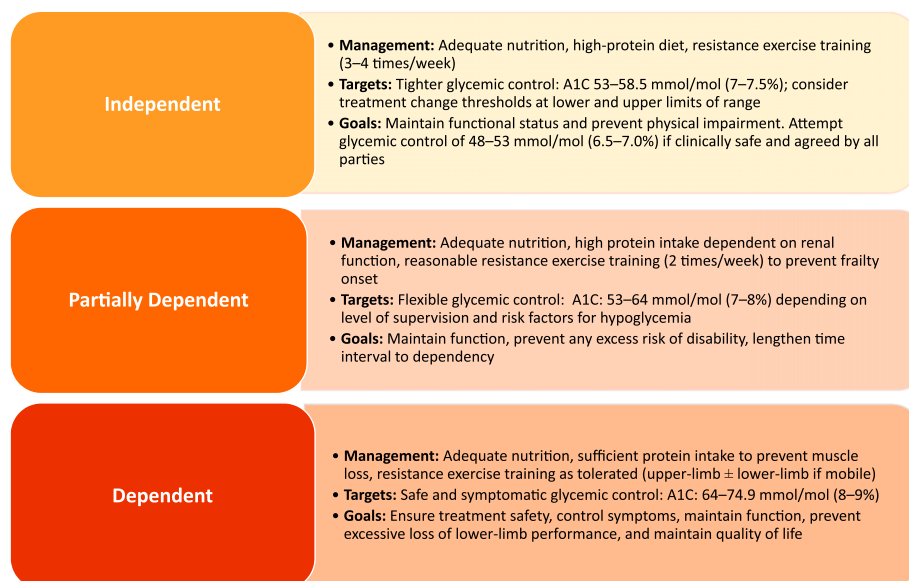
to avoid side effects of medications and the risk of hypoglycemia (32).

Metformin therapy appears to be associated with lower long-term ( $\geq 2$  years) cardiovascular mortality compared with sulfonylureas in patients with or without multiple morbidities (33,34). Pioglitazone has been shown to reduce the risk of major adverse cardiovascular events (MACE) and recurrent stroke in patients with a history of ischemic stroke (35). However, pioglitazone should be carefully used in patients with heart failure (HF) because it increases the risk of peripheral edema, weight gain, and HF (36).  $\alpha$ -Glucosidase inhibitors as add-on therapy significantly reduced the risk of myocardial infarction (MI), whereas sulfonylureas may be associated with increased cardiovascular risk, but there have been no large randomized trials to confirm this (37,38). Dipeptidyl peptidase-4 (DPP-4) inhibitors have shown mixed safety results, with mostly marginal but nonsignificant increases in HF risk, especially with saxagliptin (39). Meta-analysis of the glucagon-like peptide 1 (GLP-1) receptor agonists trials showed a significant risk reduction for all-cause mortality, cardiovascular mortality, and incidence of MI but no effect on stroke or HF (40). Another meta-analysis of the trials of sodium–glucose cotransporter 2 (SGLT2) inhibitors showed a significant reduction of MACE and hospitalization for HF and a slowing of the progression of renal disease (41). The advantages and disadvantages of antidiabetic medications in older people are summarized in Table 3, and their cardiovascular safety and benefits are shown in Table 4.

### Hypertension

A target systolic blood pressure (SBP) of 140 mmHg is reasonable in older people with diabetes because it is associated with a reduction of cardiovascular risk compared with SBP  $>140$  mmHg. Several meta-analyses have concluded that lower SBP of  $<130$  mmHg is not associated with better cardiovascular outcomes because cardiovascular benefits appear to reach a plateau after attaining an SBP of 140 mmHg. More intensive SBP reduction to  $<130$  mmHg may be beneficial in patients with high risk of stroke, but this is likely to be associated with a significant increase in serious adverse events (42–44).

The recently published SPRINT (Systolic Blood Pressure Intervention Trial) showed that treating to an SBP target  $<120$  mmHg compared with an SBP target  $<140$  mmHg resulted in significantly lower rates of fatal and nonfatal MACE (hazard ratio [HR] 0.66, 95% CI 0.51–0.85) and death from any cause (HR 0.67, 95% CI 0.49–0.91) in older people  $\geq 75$  years of age. However, this study did not enroll older people with diabetes, stroke, heart failure, dementia,



**FIGURE 2** Management, targets, and goals of therapy based on functional level in older adults with diabetes. Independent signifies independently living in the community, partially dependent signifies living in community with some assistance, and dependent signifies receiving full assistance in community or while living in a nursing home.

limited life expectancy of <3 years, unintentional weight loss (>10% of body weight during the preceding 6 months), or who resided in a nursing home (45).

Individuals with these conditions may not benefit from such intensive treatment and may be at increased risk of adverse events. It has been shown that higher SBP is positively correlated with mortality in healthier and functionally capable older people, but negatively correlated with mortality in frail and functionally less able populations, and particularly in those with slow gait speeds (46). Therefore, it appears logical to base blood pressure targets on overall function, with tighter control targets for fit individuals and more relaxed targets for frail individuals.

However, caution should be undertaken in intensive blood pressure reduction, especially in those with systolic hypertension, which may cause postural drop in blood pressure and an increased risk of falls. It has been shown that a higher daily dose of antihypertensive medications is independently associated with a greater risk of falls (relative risk 1.07, 95% CI 1.02–1.11, *P* = 0.004) (47). Therefore, risk reduction and prevention strategies for falls should be discussed with patients when commencing or increasing antihypertensive therapy.

### Dyslipidemia

The evidence for statin therapy for older people with diabetes is generally extrapolated from studies conducted in younger populations with or without a diagnosis of diabetes. The PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) trial was designed for older people aged 70–82 years (10.5% with diabetes), who had either preexisting vascular disease (secondary prevention) or elevated

risk of vascular disease because of smoking, hypertension, or diabetes (primary prevention). It showed 15% lower incidence of cardiovascular end points in the statin group (48). Similar results were shown in the Heart Protection Study (primary prevention), which included 20,536 patients between the ages of 40 and 80 years (28% were >70 years old, and 28% of all study patients had diabetes) (49).

The magnitude of risk reduction in older people appears to be similar to younger patients (50). However, the absolute benefit of statin therapy depends on an individual's baseline risk and is likely to be higher in older age, as demonstrated in the post hoc analysis of the CARDS (Collaborative Atorvastatin Diabetes Study) primary prevention trial, which compared the efficacy and safety of atorvastatin in 1,129 patients aged 65–75 years with that in 1,709 younger patients. Relative risk reduction of cardiovascular events was similar in both groups (38% in the older group vs. 37% in the younger group), but the absolute risk reductions were 3.9 vs. 2.7%, and the numbers needed to treat were 21 and 33, respectively, reflecting the higher absolute risk in older people, with a similar safety profile in both groups (51).

Therefore, the evidence for statin therapy is established for older people with diabetes up to the age of 80 years whether they do not have underlying heart disease (primary prevention) or already have established heart disease (secondary prevention). Observational studies have shown some extra evidence of benefit, although not significant, for those >80 years of age (52). There was also a trend toward mortality benefit in those aged 80–85 years compared with those >85 years of age (52). However, there are no clear data for benefit for those >85 years of age.



**TABLE 2** Screening for the Three Main Categories of Complications in Older People With Diabetes (27–30)

Category	Screening
Vascular disease	Regular checks of risk factors such as A1C, blood pressure, serum lipids, and urine albumin excretion and regular foot examination for early detection of peripheral vascular disease
Physical and neuropathic complications	<p><b>FRAIL</b> Scale: presence of <math>\geq 3</math> of the following is diagnostic of frailty:</p> <ol style="list-style-type: none"> <li>1. Fatigued (self-reported)</li> <li>2. Resistance (unable to climb a flight of stairs)</li> <li>3. Ambulation (unable to walk a block)</li> <li>4. Illness (<math>&gt;5</math> comorbidities)</li> <li>5. Lost weight (<math>&gt;5</math> kg in the previous 6 months)</li> </ol> <p><b>SARC-F</b> Scale*: total score <math>\geq 4</math> for the following is predictive of sarcopenia and adverse outcomes:</p> <ol style="list-style-type: none"> <li>1. Strength (difficulty lifting a 10-lb weight)</li> <li>2. Assistance in walking (difficulty walking across a room)</li> <li>3. Rise from a chair (difficulty in transferring from chair to bed)</li> <li>4. Climbing stairs (difficulty in climbing a flight of stairs)</li> <li>5. Falls (number of falls in the past year)</li> </ol> <p>*Answer options: For items 1–4, 0 = none, 1 = some difficulty, 2 = unable; for item 5, 0 = no falls, 1 = 1–3 falls, 2 = <math>\geq 4</math> falls</p>
Mental dysfunction	<p><b>Mini-Cog</b>*: a score <math>\leq 3</math> of the 5 items below defines cognitive impairment:</p> <ul style="list-style-type: none"> <li>• Ask the patient to draw the numbers of the clock face (task).</li> <li>• Ask the patient to draw the hands of the clock to show the time as 10 minutes to 3:00 (task).</li> <li>• Ask the patient to recall the three items (recall memory items).</li> </ul> <p>*Provide a clock face for the first two items. Ask the patient to recall three things such as lemon, key, and balloon for the final item. Score 1 for each task performed and for each item recalled.</p> <p><b>Two-Item Patient Health Questionnaire (PHQ-2)</b>*</p> <ul style="list-style-type: none"> <li>• Ask whether patient has little interest in doing things.</li> <li>• Ask whether patient is feeling down, depressed, or hopeless.</li> </ul> <p>*Any positive answer triggers assessment using the nine-item PHQ-9.</p>

### Physical and Neuropathic Complications

Diabetes is associated with an increased risk of sarcopenia and frailty, which mediate the pathway to physical dysfunction and physical disability (53). Exercise training and adequate nutrition are important interventions to slow down the progression of physical decline and maintain functional capacity (54).

Resistance exercise training has been shown to be effective in reducing muscle mass loss and improving the performance status of older people with diabetes (55). A large, European, randomized controlled trial (the MID-Frail [Multi-Modal Intervention in Diabetes in Frailty]) in prefrail and frail older adults ( $>70$  years of age) with type 2 diabetes has shown that twice-weekly resistance training with nutritional education leads to significant improvement in physical performance as measured by the Short Physical Performance Battery and a reduction of health care costs (56).

Diabetes-related peripheral neuropathy can increase the risk of frailty and is likely to play a role in other complications such as balance disorders and falls risk (57).

Diabetes nutritional therapy has been shown to reduce the risk of frailty (58). Dietary protein supplementation (1.0 g/body weight/day) combined with resistance exercise training increase muscle hypertrophy, muscle strength, muscle mass, and performance (59). Vitamin D supplementation of at least 400 IU/day has also been shown to increase muscle strength, especially in people who are deficient in vitamin D or those who are  $\geq 65$  years of age (60). A diet rich in vitamin D and the amino acid leucine were associated with an increase in muscle mass and improvement in muscle function (61). A Mediterranean diet, which includes an especially high intake of vegetables and fruits, was associated with a reduced risk of frailty syndrome in older women with type 2 diabetes (62).

### Mental/Cognitive Dysfunction

Diabetes is associated with increased risks of dementia and depression, which mediate the pathway to mental dysfunction and mental disability. Management should focus on the prevention of factors involved in increasing the risk of mental dysfunction such as reduction of insulin resistance through achieving ideal body weight and regular

**TABLE 3** Advantages and Disadvantages of Antidiabetic Medications in Older People With Diabetes

Medication or Medication Class	Advantages	Disadvantages
Sulfonylureas	Suitable for those with renal impairment or at lower risk of hypoglycemia	Associated with increased risk of hypoglycemia and weight gain; long-acting sulfonylureas should be avoided
Metformin	Lower risk of hypoglycemia; weight neutral	Increased risk of lactic acidosis in those with renal impairment, HF, sepsis, or dehydration
Meglitinides	Short-acting; suitable for those with erratic eating patterns	Risk of hypoglycemia and weight gain, but less than with sulfonylureas
α-Glucosidase inhibitors	Lower risk of weight gain and hypoglycemia	Weak hypoglycemic action; gastrointestinal side effects
Pioglitazone	Suitable for those with renal impairment; less risk of hypoglycemia	Fluid retention; worsens HF; increases fracture risk; possibly increases risk of bladder cancer
DPP-4 inhibitors	Low risk of hypoglycemia; weight loss	Gastrointestinal side effects; dosages for most drugs in this class need to be adjusted with renal impairment
GLP-1 receptor agonists	Low risk of hypoglycemia; weight loss	Injectable; weight loss in frail individuals; not suitable in renal failure; nausea is common; and possible risk of pancreatitis
SGLT2 inhibitors	Low risk of hypoglycemia; weight loss	Not suitable for frail elderly with weight loss; heavy glucosuria increases risk of urinary tract infections, candidiasis, dehydration, and hypotension
Insulin	Effective; tailored rapidly to changes in need; improves quality of life	High risk of hypoglycemia and weight gain

exercise training, prevention of persistent hyperglycemia, and avoidance of recurrent episodes of hypoglycemia and other diabetes-related complications.

Exercise and nutrition appear to maintain cognitive function in older people with diabetes (63). Structured aerobic or resistance training for a period of 12 weeks has been shown to promote several aspects of cognitive function, including improved attention and concentration in people with diabetes (64).

Glycemic control with avoidance of A1C variability or hyperglycemic fluctuations also may have a long-term positive effect on cognitive function (65,66). In the Look AHEAD (Action for Health in Diabetes) study, an intensive lifestyle intervention significantly reduced the incidence of depressive symptoms (HR 0.85, 95% CI 0.75–0.97,  $P = 0.02$ ) and preserved better function in the intervention group ( $P < 0.01$ ) (67). Although this study included relatively younger participants with a mean age of 58.7 years (SD 6.8) at baseline, the range was wide (45–76 years), and the follow-up period was relatively long (9.6 years) (67). At baseline, 31.5% of participants were between the ages of 45 and 54 years, 51.5% were 55–64 years of age, and 17.0% were ≥65 years of age, which may suggest that, after the specified follow-up period, the study likely included a significant proportion of older people ≥65 years of age.

Moderate-intensity physical activity may help to relieve stress and depressive symptoms in older people with diabetes (68). Greater adherence to the Mediterranean diet and daily tea drinking has also been shown to have a beneficial effect on depressive symptoms (69).

### Special Considerations in Old Age

Delivering care for older people with diabetes is complex and constitutes a challenge to health care professionals (70). Special considerations unique to this age-group should be considered when formulating their individualized care plans.

### Hypoglycemia

Symptomatic mild and severe hypoglycemia are not only associated with increased risk of cardiovascular events, all-cause hospitalization, and all-cause mortality (71), but are also linked to concerns about driving competence, socialization issues, self-care capacity, serious falls, physical and cognitive status, and impairments in emotional well-being and quality of life (72).

Hypoglycemia is more common in older than in younger people with diabetes because it is associated with comorbidities, geriatric syndromes, polypharmacy, long duration of diabetes, and the hepatic and renal dysfunction

**TABLE 4** Cardiovascular Safety of Antidiabetic Medications

Types of Medications	Notes
Older agents	<ul style="list-style-type: none"> <li>• Metformin appears to have cardiovascular benefits and can be safely used in patients with HF with low risk of lactic acidosis.</li> <li>• Pioglitazone has shown cardiovascular benefits and can be used in patients with compensated HF, but regular monitoring for HF exacerbation is required.</li> <li>• <math>\alpha</math>-Glucosidase inhibitors may have cardiovascular benefits when added to metformin.</li> <li>• Sulfonylureas may increase cardiovascular events, but there have been no large randomized trials to confirm this.</li> <li>• Insulin appears to have a neutral cardiovascular effect.</li> </ul>
Newer agents	<ul style="list-style-type: none"> <li>• DPP-4 inhibitors have neutral effects on cardiovascular events; however, hospitalization for HF significantly increases with saxagliptin, nonsignificantly increases with alogliptin, and is neutral with sitagliptin.</li> <li>• SGLT2 inhibitors may reduce cardiovascular events and hospitalization for HF and slow the progression of renal failure.</li> <li>• GLP-1 receptor agonists reduce cardiovascular events, including mortality, but have no clear effects with regard to stroke prevention.</li> </ul>

that increase with prevalence in older age. In a prospective, observational study of 3,810 people in primary care, 11% of participants reported having at least one episode of hypoglycemia of any severity in a 12-month period. People  $\geq 70$  years of age reported more episodes than those  $< 60$  years of age (12.8 vs. 9.0%,  $P < 0.01$ ). Significant differences were also seen for symptomatic episodes without the need for help (9.2 vs. 5.6%) and symptomatic episodes that required medical assistance (0.7 vs. 0.1%) (73). Continuous glucose monitoring has shown that asymptomatic hypoglycemia is common in this population regardless of A1C level (74).

Severe hypoglycemic episodes may lead to serious acute consequences such as stroke, MI, acute cardiac failure, and ventricular arrhythmias, and recurrent episodes of hypoglycemia lead to chronic complications such as physical and cognitive dysfunction, frailty, disability, and increased mortality (75,76).

Recognition of hypoglycemia may be a challenge for health care professionals because of the nonspecific nature of symptoms in old age (77). Therefore, educational programs for health care professionals, patients, and caregivers should be in place to facilitate early recognition of the

atypical presentation of hypoglycemia. Patients should be regularly reviewed to identify factors that increase the risk of hypoglycemia such as polypharmacy, and medications with less hypoglycemic potential should be chosen where appropriate.

### Care Homes

Residents with diabetes in care homes are more likely than older people living in the community to be frail and to have multiple comorbidities, advanced dementia, possible behavioral problems, and erratic eating patterns, which increase their risk of hypoglycemia. These patients are potentially at risk for harm from insulin and oral glucose-lowering agents, and hypoglycemic events are likely to be underreported (78).

Careful attention to the hypoglycemic regimen of individuals residing in care homes is required. For example, sulfonylureas should be avoided in these patients. Long-acting basal insulin analogs may be a good option because they have less risk of hypoglycemia and can be conveniently injected once daily (79). In a 150-facility, cross-sectional study of 2,258 Italian nursing home patients with a mean age of 82 years (SD 8) and type 2 diabetes, of whom 1,138 had dementia, rapid- and long-acting insulin analogs were associated with reduced odds of severe hypoglycemia compared with sulfonylurea monotherapy or combined metformin and sulfonylurea therapy in patients with, but not those without, dementia (80). The reasons for this finding may be related to the ability to flexibly adjust insulin doses according to patients' irregular eating habits (80). Short-acting insulin analogs can also be administered after meals rather than before and can therefore be omitted when a meal is not consumed.

Care homes should have a policy for diabetes care, including diabetes screening on admission and individualized care plans for residents (81). These care plans should be tailored to patients' needs, which requires giving consideration to their values, preferences, life expectancy, and comorbidities, as well as the impact of diabetes management (e.g., polypharmacy and glucose monitoring) on their quality of life (82).

### Polypharmacy

Polypharmacy is associated with increased risks of frailty and dementia (83,84). Many frail older patients with diabetes are treated inappropriately with multiple medications to achieve inappropriately tight glycemic control (85). Polypharmacy in these patients may lead to drug errors and unnecessary hospital admissions (86).

Therapy deintensification opportunities are missed in about 20% of older patients with tight glycemic control, putting them at increased risk of adverse outcomes (87). Deintensification opportunities are also missed in older patients who are hospitalized with diabetes-related complications (88). Deintensification or withdrawal of antidiabetic medications has been shown to be safe in frail older patients with type 2 diabetes who had significant weight loss, tight glycemic control, comorbid dementia, and recurrent hypoglycemia, without causing deterioration in their glycemic control (89,90). These approaches provide increasing evidence for revising future clinical guidelines to take into account the need for therapy deintensification with advancing age (91).

Simplification of insulin regimens is another option to reduce polypharmacy and side effects and improve quality of life. In an intervention study, multiple daily insulin injections were switched to a once-daily injection regimen with or without the addition of noninsulin agents. This change resulted in fewer hypoglycemic episodes, stable A1C levels, and improvement in diabetes-related distress scores (92).

## Conclusion

Diabetes is increasingly becoming a disease of older age because of overall population aging and increased life expectancy. The phenotype of diabetes in old age is complex and associated with three main categories of complications, including vascular disease, physical and neuropathic complications, and mental dysfunction. Therefore, the assessment of older people with diabetes on diagnosis and annually thereafter should be comprehensive and should include screenings for these complications. Early and timely intervention is required to delay progression into disability.

Older people are a highly heterogeneous population, and diabetes management should therefore be individualized with variable metabolic targets based on overall function. More attention should be considered for those at increased risk of hypoglycemia, those with unnecessary polypharmacy, and frail individuals living in care homes. Improving nutrition and maintaining physical activity are important to help delay disability. Quality of life should be at the heart of diabetes management plans.

## DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

## AUTHOR CONTRIBUTIONS

Both authors researched data, wrote the manuscript, and reviewed/edited the manuscript. A.J.S. is the guarantor of this work and, as such,

had full access to all the data reported and takes responsibility for the integrity of the review.

## REFERENCES

1. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract* 2018;138:271–281
2. Wong E, Backholer K, Gearon E, et al. Diabetes and risk of physical disability in adults: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2013;1:106–114
3. Sinclair AJ, Abdelhafiz AH, Rodríguez-Mañás L. Frailty and sarcopenia: newly emerging and high impact complications of diabetes. *J Diabetes Complications* 2017;31:1465–1473
4. Kalyani RR, Metter EJ, Egan J, Golden SH, Ferrucci L. Hyperglycemia predicts persistently lower muscle strength with aging. *Diabetes Care* 2015;38:82–90
5. Yoon JW, Ha YC, Kim KM, et al. Hyperglycemia is associated with impaired muscle quality in older men with diabetes: the Korean Longitudinal Study on Health and Aging. *Diabetes Metab J* 2016;40:140–146
6. Lee S, Lee S, Harada K, et al. Relationship between chronic kidney disease with diabetes or hypertension and frailty in community-dwelling Japanese older adults. *Geriatr Gerontol Int* 2017;17:1527–1533
7. Castrejón-Pérez RC, Gutiérrez-Robledo LM, Cesari M, Pérez-Zepeda MU. Diabetes mellitus, hypertension and frailty: a population-based, cross-sectional study of Mexican older adults. *Geriatr Gerontol Int* 2017;17:925–930
8. Pal K, Mukadam N, Petersen I, Cooper C. Mild cognitive impairment and progression to dementia in people with diabetes, prediabetes and metabolic syndrome: a systematic review and meta-analysis. *Soc Psychiatry Psychiatr Epidemiol* 2018;53:1149–1160
9. Hasan SS, Mamun AA, Clavarino AM, Kairuz T. Incidence and risk of depression associated with diabetes in adults: evidence from longitudinal studies. *Community Ment Health J* 2015;51:204–210
10. Panza F, Seripa D, Solfrizzi V, et al. Targeting cognitive frailty: clinical and neurobiological roadmap for a single complex phenotype. *J Alzheimers Dis* 2015;47:793–813
11. Lohman M, Dumenci L, Mezuk B. Depression and frailty in late life: evidence for a common vulnerability. *J Gerontol B Psychol Sci Soc Sci* 2016;71:630–640
12. Soysal P, Veronese N, Thompson T, et al. Relationship between depression and frailty in older adults: a systematic review and meta-analysis. *Ageing Res Rev* 2017;36:78–87
13. Godin J, Armstrong JJ, Rockwood K, Andrew MK. Dynamics of frailty and cognition after age 50: why it matters that cognitive decline is mostly seen in old age. *J Alzheimers Dis* 2017;58:231–242
14. Liu YC, Meguro K, Nakamura K, et al. Depression and dementia in old-old population: history of depression may be associated with dementia onset: the Tome Project. *Front Aging Neurosci* 2017;9:335
15. Aichele S, Ghisletta P. Memory deficits precede increases in depressive symptoms in later adulthood. *J Gerontol B Psychol Sci Soc Sci* 2019;74:943–953
16. Thein FS, Li Y, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Physical frailty and cognitive impairment is associated with diabetes and adversely impact functional status and mortality. *Postgrad Med* 2018;130:561–567
17. Almeida OP, McCaul K, Hankey GJ, et al. Duration of diabetes and its association with depression in later life: the Health In Men Study (HIMS). *Maturitas* 2016;86:3–9
18. Afilalo J, Karunanathan S, Eisenberg MJ, Alexander KP, Bergman H. Role of frailty in patients with cardiovascular disease. *Am J Cardiol* 2009;103:1616–1621



19. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 2014;63:747–762
20. Sakuma K, Yamaguchi A. Sarcopenic obesity and endocrinal adaptation with age. *Int J Endocrinol* 2013;2013:204164
21. Dichgans M, Leys D. Vascular cognitive impairment. *Circ Res* 2017;120:573–591
22. Dhar AK, Barton DA. Depression and the link with cardiovascular disease. *Front Psychiatry* 2016;7:33
23. Meneilly GS, Tessier D. Diabetes in the elderly. In *Endocrinology of Aging*. Morley JE, van den Berg L, Eds. Totowa, NJ, Humana Press, 2000, p. 181–203
24. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003;26(Suppl. 1):S5–S20
25. Sinclair AJ, Gadsby R, Penfold S, Croxson SC, Bayer AJ. Prevalence of diabetes in care home residents. *Diabetes Care* 2001;24:1066–1068
26. Peter A, Fritsche A, Stefan N, Heni M, Häring HU, Schleicher E. Diagnostic value of hemoglobin A1c for type 2 diabetes mellitus in a population at risk. *Exp Clin Endocrinol Diabetes* 2011;119:234–237
27. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging* 2012;16:601–608
28. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. *J Cachexia Sarcopenia Muscle* 2016;7:28–36
29. Sinclair AJ, Gadsby R, Hillson R, Forbes A, Bayer AJ. Brief report: use of the Mini-Cog as a screening tool for cognitive impairment in diabetes in primary care. *Diabetes Res Clin Pract* 2013;100:e23–e25
30. Maurer DM. Screening for depression. *Am Fam Physician* 2012;85:139–144
31. Sinclair AJ, Abdelhafiz AH, Forbes A, Munshi M. Evidence-based diabetes care for older people with type 2 diabetes: a critical review. *Diabet Med* 2019;36:399–413
32. Lipska KJ, Krumholz H, Soones T, Lee SJ. Polypharmacy in the aging patient: a review of glycemic control in older adults with type 2 diabetes. *JAMA* 2016;315:1034–1045
33. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2016;164:740–751
34. Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. *Ann Intern Med* 2017;166:191–200
35. Lee M, Saver JL, Liao HW, Lin CH, Ovbiagele B. Pioglitazone for secondary stroke prevention: a systematic review and meta-analysis. *Stroke* 2017;48:388–393
36. Liao H-W, Saver JL, Wu Y-L, Chen TH, Lee M, Ovbiagele B. Pioglitazone and cardiovascular outcomes in patients with insulin resistance, pre-diabetes and type 2 diabetes: a systematic review and meta-analysis. *BMJ Open* 2017;7:e013927
37. Chang YC, Chuang LM, Lin JW, Chen ST, Lai MS, Chang CH. Cardiovascular risks associated with second-line oral antidiabetic agents added to metformin in patients with type 2 diabetes: a nationwide cohort study. *Diabet Med* 2015;32:1460–1469
38. Azoulay L, Suissa S. Sulfonylureas and the risks of cardiovascular events and death: a methodological meta-regression analysis of the observational studies. *Diabetes Care* 2017;40:706–714
39. Elgendy IY, Mahmoud AN, Barakat AF, et al. Cardiovascular safety of dipeptidyl-peptidase IV inhibitors: a meta-analysis of placebo-controlled randomized trials. *Am J Cardiovasc Drugs* 2017;17:143–155
40. Monami M, Zannoni S, Pala L, et al. Effects of glucagon-like peptide-1 receptor agonists on mortality and cardiovascular events: a comprehensive meta-analysis of randomized controlled trials. *Int J Cardiol* 2017;240:414–421
41. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019;393:31–39
42. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ* 2016;352:i717
43. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2015;313:603–615
44. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and bayesian random-effects meta-analyses of randomized trials. *Circulation* 2011;123:2799–2810
45. Williamson JD, Supiano MA, Applegate WB, et al.; SPRINT Research Group. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged  $\geq 75$  years: a randomized clinical trial. *JAMA* 2016;315:2673–2682
46. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. *Arch Intern Med* 2012;172:1162–1168
47. Callisaya ML, Sharman JE, Close J, Lord SR, Srikanth VK. Greater daily defined dose of antihypertensive medication increases the risk of falls in older people: a population-based study. *J Am Geriatr Soc* 2014;62:1527–1533
48. Shepherd J, Blauw GJ, Murphy MB, et al.; PROSPER Study Group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623–1630
49. Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;361:2005–2016
50. Baigent C, Keech A, Kearney PM, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267–1278
51. Neil HAW, DeMicco DA, Luo D, et al.; CARDS Study Investigators. Analysis of efficacy and safety in patients aged 65–75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). *Diabetes Care* 2006;29:2378–2384
52. Foody JM, Rathore SS, Galusha D, et al. Hydroxymethylglutaryl-CoA reductase inhibitors in older persons with acute myocardial infarction: evidence for an age-statin interaction. *J Am Geriatr Soc* 2006;54:421–430
53. Castro-Rodríguez M, Carnicero JA, Garcia-Garcia FJ, et al. Frailty as a major factor in the increased risk of death and disability in older people with diabetes. *J Am Med Dir Assoc* 2016;17:949–955
54. Rejeski WJ, Bray GA, Chen SH, et al.; Look AHEAD Research Group. Aging and physical function in type 2 diabetes: 8 years of an

- intensive lifestyle intervention. *J Gerontol A Biol Sci Med Sci* 2015; 70:345–353
55. Cadore EL, Izquierdo M. Exercise interventions in polypathological aging patients that coexist with diabetes mellitus: improving functional status and quality of life. *Age (Dordr)* 2015;37:64
  56. Rodríguez-Mañas L, Laosa O, Vellas B, et al.; European MID-Frail Consortium. Effectiveness of a multimodal intervention in functionally impaired older people with type 2 diabetes mellitus. *J Cachexia Sarcopenia Muscle* 2019;10:721–733
  57. Tuttle LJ, Bittel DC, Bittel AJ, Sinacore DR. Early-onset physical frailty in adults with diabetes and peripheral neuropathy. *Can J Diabetes* 2018;42:478–483
  58. García-Esquinas E, Graciani A, Guallar-Castillón P, López-García E, Rodríguez-Mañas L, Rodríguez-Artalejo F. Diabetes and risk of frailty and its potential mechanisms: a prospective cohort study of older adults. *J Am Med Dir Assoc* 2015;16:748–754
  59. Rahi B, Morais JA, Dionne IJ, Gaudreau P, Payette H, Shatenstein B. The combined effects of diet quality and physical activity on maintenance of muscle strength among diabetic older adults from the NuAge cohort. *Exp Gerontol* 2014;49:40–46
  60. Beaudart C, Buckinx F, Rabenda V, et al. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 2014;99:4336–4345
  61. Bauer JM, Verlaan S, Bautmans I, et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults: the PROVIDE study: a randomized, double-blind, placebo-controlled trial. *J Am Med Dir Assoc* 2015;16:740–747
  62. Lopez-Garcia E, Hagan KA, Fung TT, Hu FB, Rodríguez-Artalejo F. Mediterranean diet and risk of frailty syndrome among women with type 2 diabetes. *Am J Clin Nutr* 2018;107:763–771
  63. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet* 2015;385:2255–2263
  64. Teixeira RB, Marins JCB, Amorim PRS, et al. Evaluating the effects of exercise on cognitive function in hypertensive and diabetic patients using the mental test and training system. *World J Biol Psychiatry* 2019;20:209–218
  65. Forbes A, Murrells T, Mulnier H, Sinclair AJ. Mean HbA<sub>1c</sub>, HbA<sub>1c</sub> variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study. *Lancet Diabetes Endocrinol* 2018;6:476–486
  66. Rawlings AM, Sharrett AR, Mosley TH, Ballew SH, Deal JA, Selvin E. Glucose peaks and the risk of dementia and 20-year cognitive decline. *Diabetes Care* 2017;40:879–886
  67. Rubin RR, Wadden TA, Bahnson JL, et al.; Look AHEAD Research Group. Impact of intensive lifestyle intervention on depression and health-related quality of life in type 2 diabetes: the Look AHEAD Trial. *Diabetes Care* 2014;37:1544–1553
  68. Kim D-J. Effects of physical activity on depression in adults with diabetes. *Osong Public Health Res Perspect* 2018;9:143–149
  69. Masana MF, Haro JM, Mariolis A, et al. Mediterranean diet and depression among older individuals: the multinational MEDIS study. *Exp Gerontol* 2018;110:67–72
  70. Sinclair A, Dunning T, Rodríguez-Mañas L. Diabetes in older people: new insights and remaining challenges. *Lancet Diabetes Endocrinol* 2015;3:275–285
  71. Hsu PF, Sung SH, Cheng HM, et al. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes mellitus: a nationwide population-based study. *Diabetes Care* 2013;36:894–900
  72. Sinclair AJ, Bellary S. Preventing hypoglycaemia: an elusive quest. *Lancet Diabetes Endocrinol* 2016;4:635–636
  73. Bramlage P, Gitt AK, Binz C, Krekler M, Deeg E, Tschöpe D. Oral antidiabetic treatment in type-2 diabetes in the elderly: balancing the need for glucose control and the risk of hypoglycemia. *Cardiovasc Diabetol* 2012;11:122
  74. Munshi MN, Slyne C, Segal AR, Saul N, Lyons C, Weinger K. Liberating A1C goals in older adults may not protect against the risk of hypoglycemia. *J Diabetes Complications* 2017;31: 1197–1199
  75. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. *BMJ* 2013;347:f4533
  76. Abdelhafiz AH, Rodríguez-Mañas L, Morley JE, Sinclair AJ. Hypoglycemia in older people: a less well recognized risk factor for frailty. *Aging Dis* 2015;6:156–167
  77. Abdelhafiz AH, Bailey C, Eng Loo B, Sinclair A. Hypoglycaemic symptoms and hypoglycaemia threshold in older people with diabetes: a patient perspective. *J Nutr Health Aging* 2013;17: 899–902
  78. Milligan FJ, Krentz AJ, Sinclair AJ. Diabetes medication patient safety incident reports to the National Reporting and Learning Service: the care home setting. *Diabet Med* 2011;28: 1537–1540
  79. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care* 2005;28:950–955
  80. Abbatecola AM, Bo M, Barbagallo M, et al.; Italian Society of Gerontology and Geriatrics (SIGG), Florence, Italy. Severe hypoglycemia is associated with antidiabetic oral treatment compared with insulin analogs in nursing home patients with type 2 diabetes and dementia: results from the DIMORA study. *J Am Med Dir Assoc* 2015;16:349.e7–349.e12
  81. Sinclair AJ, Gadsby R, Abdelhafiz AH, Kennedy M. Failing to meet the needs of generations of care home residents with diabetes: a review of the literature and a call for action. *Diabet Med* 2018;35: 1144–1156
  82. Sinclair AJ; Task and Finish Group of Diabetes UK. Good clinical practice guidelines for care home residents with diabetes: an executive summary. *Diabet Med* 2011;28:772–777
  83. Veronese N, Stubbs B, Noale M, et al. Polypharmacy is associated with higher frailty risk in older people: an 8-year longitudinal cohort study. *J Am Med Dir Assoc* 2017;18:624–628
  84. Park HY, Park JW, Song HJ, Sohn HS, Kwon JW. The association between polypharmacy and dementia: a nested case-control study based on a 12-year longitudinal cohort database in South Korea. *PLoS One* 2017;12:e0169463
  85. Müller N, Khunti K, Kuss O, et al. Is there evidence of potential overtreatment of glycaemia in elderly people with type 2 diabetes? Data from the GUIDANCE study. *Acta Diabetol* 2017;54: 209–214
  86. Geller AI, Shehab N, Lovegrove MC, et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. *JAMA Intern Med* 2014;174: 678–686
  87. McCoy RG, Lipska KJ, Yao X, Ross JS, Montori VM, Shah ND. Intensive treatment and severe hypoglycemia among adults with type 2 diabetes. *JAMA Intern Med* 2016;176:969–978
  88. Caughey GE, Barratt JD, Shakib S, Kemp-Casey A, Roughead EE. Medication use and potentially high-risk prescribing in older patients hospitalized for diabetes: a missed opportunity to improve care? *Diabet Med* 2017;34:432–439

89. Sjöblom P, Tengblad A, Löfgren UB, et al. Can diabetes medication be reduced in elderly patients? An observational study of diabetes drug withdrawal in nursing home patients with tight glycaemic control. *Diabetes Res Clin Pract* 2008;82: 197–202
90. Abdelhafiz AH, Chakravorty P, Gupta S, Haque A, Sinclair AJ. Can hypoglycaemic medications be withdrawn in older people with type 2 diabetes? *Int J Clin Pract* 2014;68:790–792
91. Abdelhafiz AH, Sinclair AJ. Deintensification of hypoglycaemic medications: use of a systematic review approach to highlight safety concerns in older people with type 2 diabetes. *J Diabetes Complications* 2018;32:444–450
92. Munshi MN, Slyne C, Segal AR, Saul N, Lyons C, Weinger K. Simplification of insulin regimen in older adults and risk of hypoglycemia. *JAMA Intern Med* 2016;176: 1023–1025