Drug Saf (2015) 38:17–32
DOI 10.1007/s40264-014-0247-7

LEADING ARTICLE

Optimal Glycaemic Control in Elderly People with Type 2 Diabetes: What Does the Evidence Say?

Supriya Mathur · Nicola N. Zammitt · Brian M. Frier

Published online: 7 December 2014

Abstract The global prevalence of type 2 diabetes mellitus (T2DM) is rising in an ageing population through a combination of lifestyle changes and greater longevity. However, by excluding participants aged over 70 years, most major interventional trials on which current diabetes therapeutic guidelines are based have failed to provide specific evidence to support the prescribed management of diabetes in elderly people. While diabetes per se has a significant impact on the elderly person, the side effects of medications, particularly hypoglycaemia, prevent optimisation of diabetes treatment. Hypoglycaemia is associated with significant morbidity, to which elderly people are often more vulnerable because of factors such as the effects of ageing, progressive renal impairment, frailty, polypharmacy and cognitive decline. T2DM is associated with accelerated cognitive decline in some individuals, and recurrent severe hypoglycaemia has been implicated as a potential contributory factor. Although the evidence for selection of appropriate glycaemic targets in elderly patients is sparse, it is now acknowledged that prevention of hypoglycaemia must influence individualisation of treatment goals in this vulnerable group. This should also be reflected by the choice of anti-diabetes agents that are initiated when diet and lifestyle advice is ineffective. Recently developed international guidelines, which have specifically addressed the management of diabetes in elderly people, highlight the importance of a pragmatic management approach rather than attempting to achieve a generic glycated haemoglobin goal and are summarised in this article.

Key Points

The evidence from clinical trials for appropriate glycaemic targets in older people is limited

Hypoglycaemia resulting from over-zealous treatment has a significant negative impact on the quality of life of an elderly person with diabetes and may be dangerous

Glycaemic targets for the elderly patient with diabetes must be individualised to avoid hypoglycaemia and its related morbidity

1 Introduction

The on-going global diabetes pandemic presents a serious public health crisis, with an estimated 347 million people now suffering from the condition worldwide [1]. It is predicted that the global prevalence of diabetes in adults will increase from 6.4 % in 2010 to 7.7 % by 2030 [2], with type 2 diabetes mellitus (T2DM) representing the major burden of disease in the elderly population.

T2DM is characterised by insulin resistance; although this is a feature of normal ageing, it is compounded by lifestyle factors that promote obesity. These lifestyle factors, along with increasing longevity and improved survival

S. Mathur · N. N. Zammitt · B. M. Frier
Department of Diabetes, Royal Infirmary of Edinburgh, Edinburgh, Scotland, UK

B. M. Frier (✉)
BHF Centre for Cardiovascular Science, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh EH16 4TJ, Scotland, UK
e-mail: brian.frier@ed.ac.uk

of people with diabetes, have promoted the accelerated prevalence of diabetes in an ageing population [1, 3]. It is estimated that 10–20 % of people aged over 60 have T2DM [4, 5]. The burden of diabetes and its complications may be even higher in elderly people as a result of underdiagnosis. The American National Health and Nutrition Examination Survey (NHANES) reported a prevalence of undiagnosed diabetes of 6.9 % in people ≥65 years of age in the USA [6].

A study in 13 European countries used the oral glucose tolerance test to estimate the age- and gender-specific prevalence of diabetes, which increased from 16 % in men and women aged 60–69 years to 19 % in men and 43 % in women aged 80–89 years. The rates of previously undiagnosed diabetes were as high as 8.6 % in the 60–89 years age group [7]. In a cohort of Indian men aged 60–69 years in the Asian arm of this study, the rates of undiagnosed diabetes reached 41 % [8]. The Canadian Study of Health and Ageing concluded that diabetes was associated with a higher mortality [relative risk (RR) 1.87; 95 % confidence interval (CI) 1.59–2.19] and a greater likelihood of requiring institutional care (RR 1.58; 95 % CI 1.28–1.94) [9].

These findings have significant implications for healthcare resources, and yet, specific evidence for the management of diabetes in older people is lacking. An analysis performed by Lakey et al. [10] confirmed that only 0.6 % of interventional trials in diabetes specifically examined elderly people, while 30.8 % of trials excluded those older than 65 years and 55 % excluded those aged over 75 years. Current evidence for optimal glycaemic targets in older people has been extrapolated from data obtained from younger adults, resulting in a blanket approach to the management of T2DM across all age groups. However, it is increasingly being recognised that elderly people are a heterogeneous group with varying levels of comorbidity and functionality, and glycaemic targets, which, when met, represent 'optimal control' in any person with diabetes, need to be individually determined for older adults in order to achieve optimal glycaemic control in a safe manner. Several factors have to be considered when attempting to achieve optimal glycaemic control in elderly people with T2DM, and are summarised in Fig. 1.

Hypoglycaemia is the single greatest barrier to the maintenance of good glycaemic control in people with diabetes treated with insulin and insulin secretagogues [11, 12] and is associated with significant morbidity [12, 13] and mortality [14] in diabetes. In the management of some older people with diabetes, it may be more important to avoid hypoglycaemia than to strive for strict glycaemic control. The present review considers the appropriateness of applying standard glycaemic targets to the older person. It highlights the relevant sections of current guidelines, balances the risks and benefits of medications with a low risk of hypoglycaemia in this population and outlines the direct impact of diabetes on elderly people while addressing the factors which render them vulnerable to hypoglycaemia.

2 Impact of Diabetes on the Elderly Person

2.1 Risk of Hospitalisation

Examination of complication rates in the diabetic population reveals that people aged over 75 have the highest frequency of lower-extremity amputation, myocardial infarction, visual impairment and end-stage renal disease [15].

Two recent population-based prospective studies have highlighted the high rate of hospital admission for severe hypoglycaemia in elderly people. An Italian survey over a period of 8 years found that 11 % of 5,377 patients admitted to hospital for diabetes-related causes were aged 80 years or more and 16.7 % ($n = 99$) of their admissions were caused by severe hypoglycaemia. These patients had diminished cognitive ability and multiple comorbidities. Glycaemic control was strict [mean glycated haemoglobin (HbA_{1c}) = 41 mmol/mol (95.9 %)] and while 76 of the 99 patients were taking glibenclamide, only 25 were performing regular blood glucose monitoring [16]. Another study found that rates of hospital attendance and admission because of insulin-related hypoglycaemia and management errors were highest in people aged over 80. They were more than twice as likely to attend the hospital emergency department (rate ratio 2.5; 95 % CI 1.5–4.3) and nearly five times as likely to be admitted to hospital (rate ratio 4.9; 95 % CI 2.6–9.1) when compared with patients aged 46–64 years (Fig. 2) [17].

2.2 Risk of Cognitive Decline and Dementia

Ageing is associated with cognitive decline and a risk of developing dementia. T2DM is associated with accelerated cognitive decline [18], which in turn increases the risk of hypoglycaemia; recurrent severe hypoglycaemia has been implicated in the development of dementia in adults. The creation of such a vicious cycle complicates the management of diabetes.

Diabetes is associated with a 1.5- to 2.5-fold increase in the risk of developing dementia [19]. Its pathogenesis is probably multifactorial with chronic hyperglycaemia promoting the development of cerebral microvascular disease [19] and recurrent, severe hypoglycaemia being implicated as a potential cause of brain damage [20, 21]. Other processes may include protein glycation, cerebral insulin

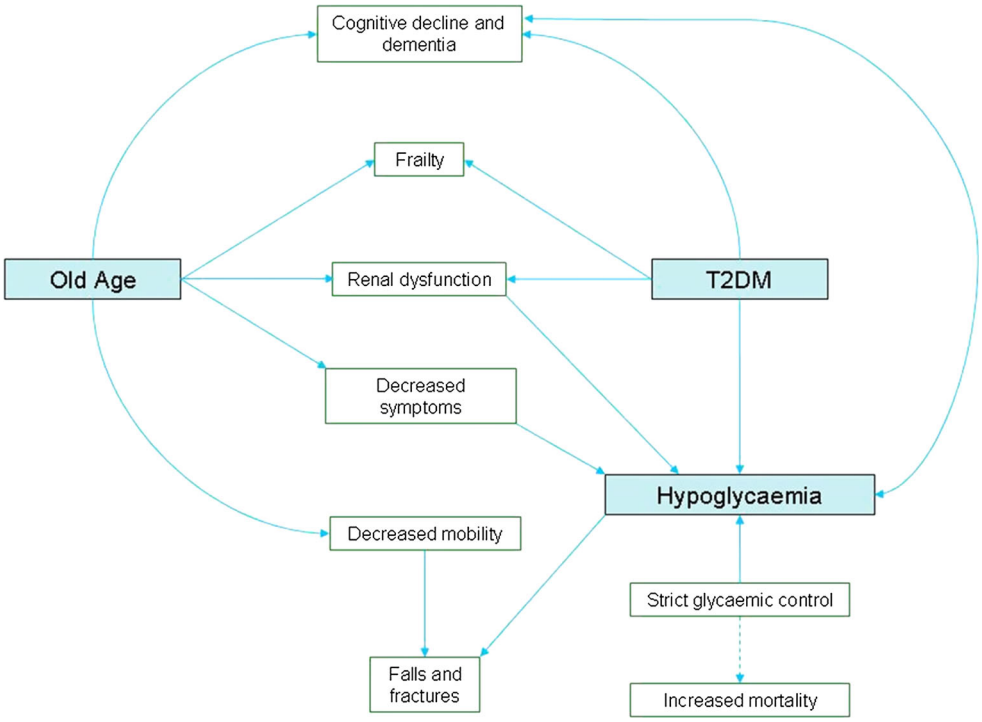

Fig. 1 Factors that should be considered when attempting to achieve optimal glycaemic control in elderly patients with type 2 diabetes mellitus (T2DM) (*broken arrow* indicates a link where the evidence is not strong)

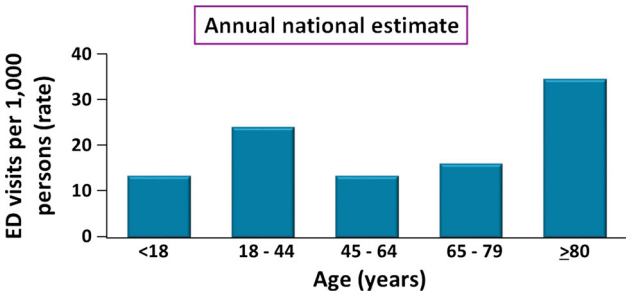

Fig. 2 Emergency department (ED) visits and hospital admissions for hypoglycaemia (2007–2011)—based on 8,100 cases in 63 hospitals in the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project (Source: data derived from Geller et al. [17])

resistance, impairment of central insulin signalling, inflammatory mediators, dysregulation of the hypothalamic-pituitary-adrenal axis and rheological factors [19, 22, 23]. Additionally, diabetes and its treatment may predispose individuals to amyloid deposition in the brain, resulting in pathological changes akin to Alzheimer's disease [18].

The Edinburgh Type 2 Diabetes Study, a cross-sectional population-based study of 1,066 adults with T2DM between the ages of 65 and 70 years, found that general cognitive ability scores were lower in participants who had reported at least one previous episode of severe hypoglycaemia ($n = 113$) [21]. This association persisted after adjustment for previous cognitive ability, suggesting that hypoglycaemia may have contributed to general cognitive decline rather than those with lower baseline cognitive function being at increased risk of severe hypoglycaemia [24]. However, a retrospective population-based study of 783 older people with diabetes suggested the presence of a bidirectional association between hypoglycaemia and dementia [25]. In that study, 14.2 % of patients with diabetes who developed dementia over a 12-year follow-up period subsequently experienced at least one episode of hypoglycaemia. This compared with 6.3 % of those who did not develop dementia [25]. Age-related cognitive dysfunction or lower cognitive ability per se is also a risk factor for hypoglycaemia [26] and must be taken into consideration when determining glycaemic targets for affected individuals. A large community-based study has assessed the knowledge and management of diabetes in older people. This showed that although older people (aged 75 and above) had reasonable comprehension of their diabetes treatment and how to manage hypoglycaemia, those who had co-existing cognitive impairment were significantly less likely to know how to treat hypoglycaemia (error rate of 7 vs. 30 %), rendering them vulnerable to its consequences [27].

In the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study, participants with a Mini Mental State Examination (MMSE) score of <24 (indicating 'severe' dysfunction, $n = 212$) had a hazard ratio (HR) of developing severe hypoglycaemia of 2.1 (95 % CI 1.14–3.87, $p = 0.018$) compared with adults with an MMSE score of >28 ($n = 8,689$) [28]. High rates of undiagnosed cognitive

impairment in older people with diabetes have been identified [27], and periodic screening for cognitive dysfunction is recommended because such dysfunction can hinder self-management of diabetes and increase the risk of hypoglycaemia.

Recently, the insulin sensitisers thiazolidinediones (TZDs) have been associated with the development of dementia in newly diagnosed elderly Taiwanese people [29]. This observational study followed 67,731 people aged ≥65 years without diabetes or dementia at baseline and found that people who progressed to develop diabetes were also more likely to develop dementia. In addition, the relative rate of dementia was 5.31 (95 % CI 1.89–14.96) for participants taking TZDs (n = 28) and 1.22 (95 % CI 0.78–1.91) for those taking sulfonylureas (n = 796) compared with those taking metformin (n = 1,033). The risk of dementia was higher in those who had ever taken a TZD (n = 841) as opposed to those who had never used a TZD (n = 4,579) (HR 1.44; 95 % CI 1.12–1.86). The HR for developing dementia in the metformin cohort (n = 1,033) was 1.0 while that for sulfonylurea (n = 796) was 1.22, although this was not statistically significant (p = 0.375) [29]. The exact mechanism for this observation is unclear, but it is worth noting that even though the HRs for TZDs reached statistical significance (p = 0.005) in this study, the overall number of participants in the TZD group was small (n = 28) and further studies are required to confirm these findings before a definite link between TZD usage and dementia can be established.

2.3 Impact on Physical Function

In a population-based case-control study in the UK that assessed functional status, 403 participants with diabetes with a median age of 75 years were compared with 403 age- and sex-matched controls. The assessments included validated questionnaires such as the Barthel Index of Activities of Daily Living and the Nottingham Extended Activities of Daily Living scale. Not only were significant differences in comorbidities found, such as cardiovascular disease and peripheral neuropathy, but also differences in physical function, with the diabetic cohort being more likely to be using mobility aids [30].

Recently, the Northern Manhattan Study, a population-based study which followed 3,298 stroke-free individuals over the age of 40 (mean age = 69.2 ± 10 years) for a median of 11 years, found that diabetes predicted functional decline over time, even in the absence of vascular events such as stroke and myocardial infarction [31]. A study from Hong Kong has also reported an impact of diabetes on physical function, with older adults with diabetes being more likely to report disability [32].

2.4 Risk of Fractures

In addition to general physical decline, diabetes is associated with an increased risk of osteoporotic fractures. A population-based Canadian study compared hip fracture rates in 197,412 individuals with diabetes over the age of 66 years to over 400,000 age-matched controls and found that diabetes was associated with a 20 % higher risk of hip fractures. The authors of this study speculated that patients with diabetes may be more prone to falling because of higher rates of visual impairment, neuropathy or cerebrovascular disease and were also more likely to have prescriptions for fall-promoting medications. They also observed an association between insulin use and falls, implicating hypoglycaemia as a potential mechanism, although this could not be confirmed [33]. Other studies, however, have made an association between falls, fall-related fractures and hypoglycaemia [34–36] in people with diabetes over the age of 65 years, stressing the importance of avoiding hypoglycaemia in this group. The link between TZDs and osteoporotic fractures is discussed later.

2.5 Effect of Age on Hypoglycaemia

The risk of hypoglycaemia is substantially higher in elderly people. In healthy non-diabetic men (aged 65 ± 3 years), the generation of hypoglycaemic symptoms and development of cognitive dysfunction occurred at almost the same blood glucose threshold (3.0 ± 0.2 mmol/l). This contrasted with younger men (23 ± 2 years) who had an interval of around 1 mmol/l between symptom generation (blood glucose 3.6 mmol/l) and a demonstrable effect on cognitive function shown by slowed reaction time (blood glucose 2.6 mmol/l) [37] (Fig. 3) [38]. The simultaneous occurrence of cognitive impairment and the onset of symptoms in older people may interfere with their ability to treat hypoglycaemia.

Counter-regulation to hypoglycaemia also differs in older people with diabetes [39]. During insulin-induced hypoglycaemia, older adults with T2DM had lower glucagon and growth hormone responses but higher epinephrine (adrenaline) and cortisol responses when compared with age-matched healthy volunteers, but hypoglycaemia symptom scores were similar in both groups [40]. This altered counter-regulation that occurs with diabetes in older people may result in prolongation of the hypoglycaemia.

Symptoms of hypoglycaemia can be subdivided into neuroglycopenic (confusion, drowsiness, speech difficulty) and autonomic (sweating, tremulousness, pounding heart, hunger) categories [41, 42]. Studies of hypoglycaemia symptoms have shown that in older people, while autonomic and neuroglycopenic symptoms occur [43],

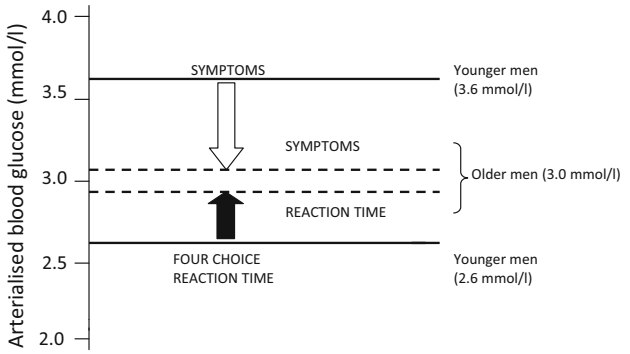

Fig. 3 Glycaemic thresholds for subjective symptomatic awareness of hypoglycaemia and for the onset of cognitive dysfunction in young and elderly non-diabetic males (Source: data originally derived from Matyka et al. [37]. Figure reproduced from *Hypoglycaemia in Clinical Diabetes* [38]. With permission from John Wiley & Sons, Ltd)

symptoms of light-headedness and unsteadiness are more commonly reported, and a group of neurological symptoms, such as incoordination, slurring of speech and visual disturbance, is manifest and may predominate. These symptoms may be mistaken for features of cerebrovascular ischaemia and as a consequence the hypoglycaemia is neither identified nor treated [44]. Furthermore, knowledge of symptoms of hypoglycaemia is very limited in elderly people and among their relatives and carers [45, 46], thus compromising their ability to treat hypoglycaemia.

2.6 Frailty

Ageing leads to frailty, which is a recognised syndrome characterised by sarcopenia, functional decline, neuroendocrine dysregulation, immune impairment, cognitive impairment, mood disorder and sensory impairment [47]. The presence of three or more of the following criteria indicates frailty: unintentional weight loss, self-reported exhaustion, slow-walking speed, poor grip strength or low physical activity levels. Frailty also predict disability [48]. People with diabetes are at greater risk of developing frailty earlier than their non-diabetic peers, as diabetes has been shown to contribute to acceleration of the ageing process [49].

3 Vulnerability to Hypoglycaemia and Its Consequences

In addition to the effect of age-related physiological changes, elderly people are rendered vulnerable to hypoglycaemia because of factors such as longer duration of diabetes, renal dysfunction, declining cognitive function, increasing frailty and inability to self-manage diabetes along with a greater requirement for institutional care [50]. Each of these hypoglycaemic risk factors must be considered when determining treatment options and targets.

3.1 Duration of Diabetes and Its Treatment

Data from NHANES showed that T2DM diagnosed in older age differs from that diagnosed in middle age. Onset of diabetes in old age has a lower likelihood of requiring insulin than the onset of diabetes in middle age. No difference in the prevalences of cardiovascular disease and neuropathy was observed in the two groups, but middle-age onset diabetes carried an increased risk of developing microvascular complications such as retinopathy [6].

Nevertheless, people who develop diabetes when middle-aged are more likely to have indolent cardiovascular disease. Hypoglycaemia can provoke cardiac arrhythmias [51] and precipitate cardiac ischaemia [52]. In the ADVANCE study cohort, a group of 11,140 patients with T2DM were randomised to intensive or standard glucose-lowering treatment, and severe hypoglycaemia was associated with a significantly higher adjusted risk of major macrovascular events (HR 2.88; 95 % CI 2.01–4.12). The authors concluded that while severe hypoglycaemia clearly contributes to adverse outcomes, it may be a marker of increased vulnerability to such events [53]. Thus treatment targets will probably have to be less stringent in older people who have underlying coronary heart disease.

Age-related impairment of hypoglycaemia awareness has also been demonstrated. A hyperinsulinaemic, hypoglycaemic clamp study that compared hypoglycaemia awareness in older (≥65 years) with middle-aged (39–64 years) participants with type 2 diabetes found that the older patients failed to perceive neuroglycopenic symptoms despite the development of cognitive dysfunction and a similar magnitude of counter-regulatory hormonal secretion when compared with the middle-aged cohort. The older group had longer duration of diabetes, and the authors concluded that while this may have biased the results, it is still an important factor to be considered as many older people have advanced T2DM [54]. In advanced T2DM, the glucagon response to hypoglycaemia is virtually absent ($p = 0.0252$), increasing the risk of developing hypoglycaemia-associated autonomic failure, impaired awareness of hypoglycaemia and recurrent severe hypoglycaemia [55].

The risk of hypoglycaemia increases with duration of insulin therapy. The UK Hypoglycaemia Study Group found that the prevalence of severe hypoglycaemia in people with T2DM treated with insulin for >5 years is comparable to that of those with type 1 diabetes of <5 years duration and supports the observation that, in longstanding T2DM, the risk of severe hypoglycaemia

increases with the duration of insulin therapy [56]. Glycaemic targets for this group of patients must therefore receive careful consideration.

3.2 Renal Dysfunction

Diabetes is the leading cause of chronic kidney disease, and moderate to severe renal impairment occurs in up to 25 % of older patients with T2DM [57]. Progressive renal dysfunction increases the risk of hypoglycaemia by reducing the rate of elimination of most anti-diabetes drugs. Therefore, as in all older adults, a regular review of medications should be undertaken in elderly people with T2DM who have renal impairment, to avoid unnecessary prescriptions and adjust the doses when necessary. An Italian cross-sectional review revealed that elderly people with diabetes who had moderate to severe renal impairment were being prescribed oral anti-diabetes drugs, particularly sulfonylureas, inappropriately [58]. Another cross-sectional study found that 50 % of 205,857 people with T2DM aged over 75 with renal and cognitive impairment, who were treated with sulfonylurea and/or insulin, had a HbA_{1c} of <53 mmol/mol (7.0 %), reflecting over-treatment of diabetes and thereby increasing the risk of severe hypoglycaemia [59]. In addition, dose adjustment must be considered during episodes of acute or acute-on-chronic kidney injury, during which the risk of acute hypoglycaemia is greater.

3.3 Increasing Frailty and Inability to Self-Manage Diabetes

Increasing frailty, which has been associated with diabetes, cognitive decline and a reduced lifespan, can affect self-efficacy, which can be defined by an individual's capability to monitor, plan and carry out daily activities related to the management of diabetes [60]. This reduces the ability to self-manage diabetes adequately, therefore increasing the risk of hypoglycaemia [49].

3.4 Institutionalisation

The prevalence of diabetes in residential or care homes is over 25 % [61]. Generally, care home residents are elderly, frail, disabled, cognitively impaired or have limited communication ability [62]. This sub-group of the elderly diabetic population is at particular risk of hypoglycaemia and associated morbidity as a consequence of all the factors mentioned, along with a limited ability to manipulate their dietary intake [63]. The evidence base on which to devise recommendations for diabetes care in such institutions is sparse, but the provision of diabetes-specific education to such patients may have some value [64, 65]. However, patients in long-term care facilities are more likely to be dependent on healthcare professionals for the management of their diabetes, and there is benefit in providing diabetes-specific training to staff that look after such patients on a daily basis [66].

4 Evidence for Glycaemic Targets in Older Adults

Current management of T2DM in general prioritises the prevention of micro- and macro-vascular complications [67, 68]. Findings from the UK Prospective Diabetes Study (UKPDS), one of the largest randomised controlled trials comparing standard versus intensive glycaemic control in T2DM, showed that the rates of myocardial infarction and mortality were lower in the intensive treatment group 10 years after the intervention had ended. This phenomenon has been described as a 'legacy effect' from previous good glycaemic control [69]. Macrovascular disease is a major cause of mortality in T2DM, so the UKPDS findings provide a rationale for the current guidelines provided by the UK National Institute for Clinical Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) that recommend HbA_{1c} targets of ≤53 mmol/mol (7.0 %) for people with newly diagnosed T2DM [67, 68]. However, the UKPDS excluded people over the age of 65 years [69].

In 2008, publication of the results of three major randomised controlled trials that had examined the effects of glycaemic control on cardiovascular morbidity and mortality further influenced this debate. The Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Veterans Affairs Diabetes Trial (VADT) and ADVANCE studies recruited people with a mean age of 60 years at enrolment [15]. In ACCORD, intensive glucose lowering disproportionately increased the risk of cardiovascular disease and death in younger subjects (<65 years) but had a neutral effect on older participants [70]. However, severe hypoglycaemia was more common in the older subjects [71]. The intensive arm of the ACCORD trial had to be terminated early because of a 22 % excess in total mortality.

While ADVANCE did not replicate the association between increased mortality and intensive glycaemic control during a 5-year follow-up, neither did it show any significant cardiovascular benefit. It did however show a 21 % RR reduction in the development of nephropathy, and overall no difference was observed associated with age (aged below or above 65) with respect to the primary outcome of adverse cardiovascular events [72]. Similarly, VADT found no statistically significant difference in cardiovascular morbidity in the two arms of the study but reported a reduction in the onset and progression of microalbuminuria [73].

It was suggested that people who had a shorter duration of diabetes, lower HbA_{1c} and no established cardiovascular disease at baseline demonstrated greater benefits from intensive glucose lowering, whereas the reverse may be true for those with a very long duration of diabetes, known history of severe hypoglycaemia, advanced cardiovascular disease and frailty. In addition, post hoc analysis of the ACCORD study and the VADT showed a strong association between severe hypoglycaemia and cardiovascular mortality, especially in the older group of people [74].

These landmark outcome trials did not provide specific evidence for glycaemic management in elderly people, despite the fact that they represent a large proportion of the diabetic population. Recently published guidelines related to this population have acknowledged this lack of evidence but also recognise the association of increased cardiovascular mortality with strict glycaemic control in older people with established cardiovascular disease [15, 50, 75, 76]. It is now acknowledged that a higher HbA_{1c} is acceptable in a person who is at higher risk of cardiovascular events and exposure to severe hypoglycaemia.

Conversely, a further question that should be addressed is, 'How high is acceptable for HbA_{1c}?' Two retrospective cohort studies looked at the association between HbA_{1c} and mortality. The first, a study with data from the UK General Practice Research database, showed that when treatment was intensified with oral monotherapy, there was a U-shaped association between HbA_{1c} and mortality, with the lowest HR for death being at a HbA_{1c} value of 59 mmol/mol (7.5 %). With a reference HbA_{1c} of 58 mmol/mol (7.5 %), the HR for all-cause mortality for a (median) HbA_{1c} of 46 mmol/mol (6.4 %) was 1.52 (95 % CI 1.32–1.76) versus 1.79 (95 % CI 1.56–2.06) for a (median) HbA_{1c} of 92 mmol/mol (10.6 %). The mean age of participants in that study was 64 years [77].

The Diabetes and Aging Study, a large study of 71,092 adults with T2DM over the age of 60, also examined the relationship between HbA_{1c}, mortality and nonfatal outcomes (cardiovascular, microvascular, acute metabolic events) and found a similar U-shaped relationship between HbA_{1c} and mortality. Mortality risk was lower for HbA_{1c} between 42 mmol/mol (6.0 %) and 75 mmol/mol (9.0 %). For example, the adjusted HR for HbA_{1c} between 53 and 63 mmol/mol (7.0–7.9 %) was 0.83 (95 % CI 0.76–0.90) as compared with 1.31 (95 % CI 1.09–1.57) for HbA_{1c} over 97 mmol/mol (11.0 %) [78].

These studies indicate that while a lower HbA_{1c} that represents strict glycaemic control increases the risk of mortality, a very high HbA_{1c} is not necessarily protective. Indeed, persistent severe hyperglycaemia can lead to complications such as recurrent infections and abscesses, dehydration, falls, poor wound healing and hospital admissions precipitated by hyperglycaemic crises [15].

5 What Do the Guidelines Recommend?

Despite the lack of evidence for glycaemic target setting in elderly people, national and international guidelines have recently been developed in recognition of the fact that older people with type 2 diabetes are a heterogeneous group who need individualised treatment depending upon their differing needs. These guidelines are summarised in Table 1.

The American Diabetes Association (ADA) in collaboration with the American Gerontology Society (AGS) has suggested HbA_{1c} goals should be tailored to patient characteristics or health status rather than age, with an underlying rationale of life expectancy to determine the HbA_{1c} goal (although for the purpose of the guideline, they do define 'older adults' as those aged $\geq$65 years). So, healthy older adults with few coexisting chronic illnesses, intact cognitive and functional status and longer remaining life expectancy should be set a HbA_{1c} goal of <59 mmol/mol (7.5 %). By contrast, in a person with very poor health, in long-term care, with end-stage chronic disease or moderate to severe cognitive impairment, it is reasonable to achieve a HbA_{1c} of under 70 mmol/mol (8.5 %) [15]. This mirrors similar statements made by the International Diabetes Federation [75].

The European Diabetes Working Party for Older People (EDWPOP) also published clinical practice guidelines in 2011 (Fig. 4). They specifically stated that the aims of care should include involving the patient and/or carer while determining the correct treatment option [50]. Patient and carer education is probably more important than rigorous glycaemic targets, as hypoglycaemia may still be a problem in patients who have a higher HbA_{1c} [79]. Although the SIGN guidelines for T2DM do not specify age criteria in their guidance, they do recommend that glycaemic targets should be individualised [68].

The more recent ADA-European Association for the Study of Diabetes (EASD) position statement suggests that the goals of treatment for older T2DM patients who are cognitively intact and have long life expectancy should be the same as those for younger subjects, while less stringent goals are suggested for those with limited life expectancy, advanced diabetes complications, or extensive comorbid conditions [80]. The joint position statement issued in 2012 on behalf of the International Association of Gerontology and Geriatrics, EDWPOP, and the International Task Force of Experts in Diabetes adds that the major aims for management of care home residents with diabetes should be prevention of hypoglycaemia, avoidance of acute metabolic complications, decreased risk of infection and prevention of hospitalisation [76]. Reducing polypharmacy and potential drug interactions that may precipitate hypoglycaemia is also more pertinent in this particular group of

Table 1 Summary of guidelines that include recommendations on glycaemic targets for older patients

Guideline	Patient characteristic	HbA_{1c} target (mmol/mol)	HbA_{1c} target (%)
International Diabetes Federation	Functionally independent	53–59	7.0–7.5
	Functionally dependent	53–64	7.0–8.0
	Frail and/or dementia	Up to 70	Up to 8.6
	End of life	Avoid symptomatic hypoglycaemia	
ADA and EASD position statement	Healthy with long life expectancy	<48–53	<6.5–7.0
	History of severe hypoglycaemia, limited life expectancy, advanced complications, extensive comorbidity	59–64	7.5–8.0
EDWPOP	Single system involvement	53–59	7.0–7.5
	Precise target should depend on existing cardiovascular risk, presence of microvascular complications and ability to self-manage diabetes		
	Frail	60–70	7.6–8.5
	Dependent, multi-system disease, care home residency, dementia		
IAGG, EDWPOP and International Task Force of Experts for Diabetes position statement	Individual comorbidities and cognitive and functional status must be considered	53–59	7.0–7.5
ADA and American Geriatrics Society Consensus report	Healthy	<59	<7.5
	Few coexisting illnesses, intact cognitive and functional status		
	Complex/intermediate	<64	<8.0
	Multiple, coexisting chronic illnesses or 2 or more instrumental activities of daily living impairments or mild to moderate cognitive impairment		
	Very complex/poor health	<70	<8.5
	In long-term care or with end-stage chronic illnesses, moderate to severe cognitive impairment or dependence for more than 2 activities of daily living		

ADA American Diabetes Association, *EASD* European Association for the Study of Diabetes, *EDWPOP* European Diabetes Working Party for Older People, *HbA_{1c}* Glycated Haemoglobin, *IAGG* International Association of Gerontology and Geriatrics

elderly people who are likely to have a limited life expectancy.

Importantly, all these guidelines still stress the importance of diet, exercise and education in managing T2DM in the elderly population.

6 Safety Considerations for Commonly Used Anti-diabetes Therapies in Elderly People

Age per se is not a contraindication to the use of any specific agent. The ADA-EASD position statement on management of hyperglycaemia in T2DM proposes that the choice of anti-diabetes agent for the older person should take drug safety into account with an aim to protect against hypoglycaemia, heart failure, renal impairment, bone fractures and drug interactions [80].

Several classes of drugs are now available for the treatment of T2DM and can be categorised by their mode of action. Drugs that have a mechanism of action independent of insulin secretion will be less likely to contribute to the risk of hypoglycaemia when compared with insulin secretagogues and insulin itself.

Once again, patient education is extremely important, and a cognitive assessment when changing diabetes therapies may be prudent to ensure that the elderly person understands the risks associated with inappropriate administration of the medication. For example, patients taking insulin secretagogues and prandial or biphasic insulin must be warned not to skip meals when taking these medications, in order to prevent hypoglycaemia. An assessment for adequate hypoglycaemia awareness (which diminishes with age) must also be made before escalating anti-diabetes therapy in response to disease progression.

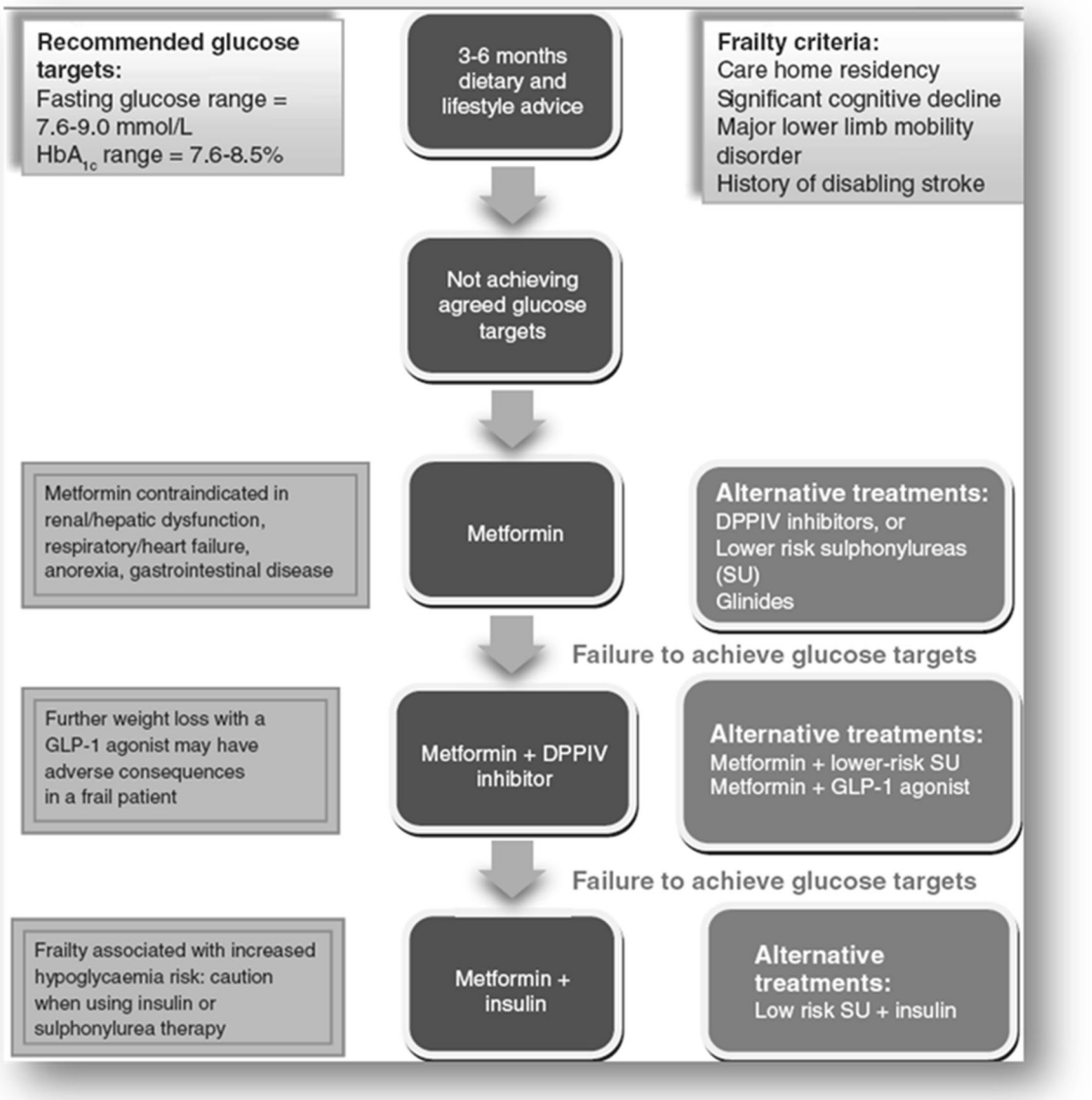

Fig. 4 Clinical guidelines for type 2 diabetes mellitus in the elderly: European Diabetes Working Party for Older People 2011 (Source: reproduced from Sinclair et al. [50]. With permission from Elsevier Masson SAS). *HbA_{1c}* Glycated haemoglobin, *DPPIV inhibitors* Dipeptydyl dipeptidase-IV inhibitors, *GLP-1* Glucagon-like peptide-1

6.1 Insulin Sensitisers: Biguanides and Thiazolidinediones

Metformin, the only biguanide now available in most countries [81], acts primarily by insulin sensitisation of the liver, thereby reducing hepatic glucose production [82]. It is the first-line choice for treating T2DM in the older person in view of its efficacy, weight neutrality and low risk of hypoglycaemia [80, 83]. In fact, it may even have cardiovascular protective benefits [84], although this requires further evidence. It is, however, associated with gastrointestinal side effects and vitamin B_{12} deficiency, which can also affect cognitive function [82].

Presence of chronic kidney disease may prohibit the use of metformin. Metformin is primarily excreted by the kidneys, and cases of lactic acidosis have been described in patients with severe renal failure. Therefore, current UK guidelines recommend avoiding metformin in people with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min, with dose reduction advised at 45 ml/min [67, 68]. This is relevant considering that chronic kidney disease caused by diabetes is highly prevalent in the elderly population [85].

TZDs are peroxisome proliferator–activated receptor-γ modulators and increase the sensitivity of muscle, fat, and liver to insulin [86]. TZDs have a much lower risk of hypoglycaemia when compared with sulfonylureas (9.8 vs.

38.7 %) [87]; however, they have a number of side effects that may preclude their use in elderly patients [15].

The most common adverse effects with TZDs are weight gain and fluid retention. Indeed, TZDs have been strongly associated with an increased risk of congestive cardiac failure, with a meta-analysis of three randomised controlled trials of TZDs versus placebo presenting an odds ratio (OR) of 2.1 for the risk of heart failure [88]. Other meta-analyses have shown similar associations [89, 90], and TZDs are now contraindicated in patients with known heart failure, which is a relatively common comorbidity in the elderly population with diabetes [91]. Long-term TZD use also seems to double the risk of fractures in women with T2DM [92], particularly distal upper and lower limb fractures [93, 94]. Therefore TZDs (of which only pioglitazone is now available) are suitable only in selected patients who are not at high risk of heart failure or bone loss or who do not have a previous history of osteoporosis [76].

6.2 Insulin Secretagogues: Sulfonylureas and Meglitinide Analogues

There is a need to intensify therapy in line with the natural progression of diabetes. However, once other agents are added to metformin, the risk of hypoglycaemia rises [95].

Insulin and sulfonylureas are the most common drug classes associated with hypoglycaemia, with the incidence of severe hypoglycaemia being 2.76 per 100 patients per year with insulin and 1.23 per 100 patients per year with sulfonylureas in older people [96].

The risk of hypoglycaemia with sulfonylureas varies with different agents. Glibenclamide is associated with the highest risk of hypoglycaemia (RR 1.83; 95 % CI 1.35–2.49) when compared with other sulfonylureas [97] and should not be used in people over the age of 60 years. Gliclazide has the lowest hypoglycaemia risk association and is endorsed (along with glipizide and glimepiride as acceptable alternatives) for use in older people with T2DM in the World Health Organisation (WHO) Essential Medicine List for adults [75].

Moreover, since sulfonylureas are metabolised by the cytochrome P450 liver enzymes (CYP2CP), other medications also metabolised through this system might reduce their metabolism and amplify their hypoglycaemic effects [98].

Meglitinide analogues promote insulin secretion from the beta cell in response to glucose. Their advantages include rapid absorption, stimulation of insulin release within a few minutes, rapid metabolism in the liver and excretion via the biliary system rather than via the kidney. They impart a lower risk of hypoglycaemia because of their rapid action and are administered before meals so are beneficial in the reduction of postprandial hyperglycaemia. While they may be beneficial in elderly people who eat irregularly, their dosing frequency and high cost have been found to be a hindrance [15].

6.3 Incretin-Based Therapies: Glucagon-Like Peptide-1 Agonists and Dipeptidyl Dipeptidase-4 Inhibitors

Glucagon-like peptide-1 (GLP-1) agonists augment glucose-mediated insulin release. They can be used as second- or third-line therapy in obese (body mass index >35) older adults with poor tolerance to or lack of response to other agents [76]. Although they are not associated with hypoglycaemia unless combined with sulfonylureas [99], they do cause a high frequency of gastrointestinal side effects and promote weight loss [100], which may not be a suitable outcome in a frail elderly person.

The risk of hypoglycaemia with dipeptidyl dipeptidase-4 (DPP-4) inhibition is also only significant if the drug is co-prescribed with sulfonylureas. Most guidelines now accept DPP-4 inhibitors as a second-line therapeutic option if metformin is poorly tolerated or the risk of hypoglycaemia precludes sulfonylurea use [50, 76].

The Individualised Treatment Targets for Elderly Patients with Type 2 Diabetes Using Vildagliptin Add-on or Lone Therapy (INTERVAL) study examined the feasibility of setting and achieving personalised glycaemic targets in a group of patients aged over 70. In this multinational, double-blind, 24-week study, individualised treatment targets were set for the participants on the basis of age, baseline HbA_{1c}, comorbidities and frailty status before patients were assigned to receive either vildagliptin or placebo. More patients in the vildagliptin group reached their individualised target when compared with placebo (52.6 vs. 27 %; adjusted OR 3.16, 96.2 % CI 1.81–5.52; $p < 0.0001$), and the overall safety and tolerability was comparable in both groups, with a low incidence of hypoglycaemia [101]. However, in this study, hypoglycaemia was defined biochemically as a blood glucose of <3.1 mmol/l, which is lower than the ADA definition of ≤3.9 mmol/l [102] and may explain the relatively low rates of hypoglycaemia seen in this study. Few studies have directly examined the safety and efficacy of DPP-4 inhibitors in the elderly population. Evidence for use of this class of drugs in older people mainly comes from results of analyses. In general, all DPP-4 inhibitors have been found to have similar HbA_{1c}-lowering properties (HbA_{1c} reduction of 0.7–1.2 %) and low hypoglycaemia risk when used as monotherapy or in combination [103]. With the exception of linagliptin, which is not primarily excreted via the kidneys [104], all of these drugs require dose adjustment with progressive renal impairment. However, it is worth noting that no long-term studies to examine the safety of this drug class in elderly people with T2DM have been performed and

some concern has been expressed about possible adverse cardiac effects of DPP-4 inhibitors.

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI) trial, an unexplainable excess of hospitalisation for heart failure was observed despite no effect on overall cardiovascular morbidity and mortality [105]. This finding requires further scientific examination, although it would be prudent to avoid this class in people who are known to have heart failure.

6.4 Insulin

In T2DM, counter-regulatory responses to hypoglycaemia commence at higher blood glucose levels than in non-diabetic people or those with type 1 diabetes [106, 107]. This may provide protection from hypoglycaemia-related morbidity. However, as HbA_{1c} is lowered with intensification of therapy, these thresholds shift to lower blood glucose levels [106].

The Fremantle Diabetes Study, a longitudinal observational cohort study of 616 patients (mean age of participants = 67 years), found that the duration of insulin treatment was an independent risk factor for severe hypoglycaemia. Other predictors of severe hypoglycaemia included renal impairment and a history of previous severe hypoglycaemia. A lower fasting glucose but higher HbA_{1c}, which may represent unstable glycaemic control, was significantly associated with the frequency of severe hypoglycaemia [108]. These findings highlight the potential to identify people with unstable glycaemic control who may be prone to recurrent severe hypoglycaemia and allow insulin therapy to be tailored to meet individual targets.

A retrospective survey of insulin-treated T2DM patients in Edinburgh, where the median age of participants was 68 years, has mirrored these findings [109]. This is unsurprising as insulin clearance decreases with age, which may enhance the risk of hypoglycaemia in elderly people [110–112]. Nevertheless, insulin is often required and can have a beneficial effect on the well-being of elderly people with poorly controlled T2DM [113]. Long-acting basal insulin analogues are often used in this group [114] as their advantages include a reduced risk of nocturnal hypoglycaemia and a more physiological pharmacological profile [15, 115]. An open-label randomised control trial of elderly patients to compare the addition of once-daily insulin glargine to oral hypoglycaemic therapy with the up-titration of existing oral anti-diabetes therapy found that the addition of glargine resulted in fewer hypoglycaemic events (23 vs. 79, $p = 0.030$), which were experienced by fewer of the participants (9 vs. 17, $p = 0.045$) [116]. A pooled post hoc analysis of three open-label randomised studies comparing insulin detemir and isophane insulin revealed comparable efficacy with a lower risk of hypoglycaemia in younger (18–64 years) and in older (≥65 years) patients. The RR of hypoglycaemia from detemir versus isophane insulin was 0.59 (95 % CI 0.42–0.83) in the older group [117].

Similarly, a pooled analysis of data from five randomised controlled trials showed that addition of insulin glargine to oral anti-diabetes drugs in adults aged 65–80 years was associated with greater reductions in HbA_{1c} (−1.5 vs. −1.1 %) and fasting blood glucose (−4.7 vs. −4.1 mmol/l) when compared with isophane insulin. Although this study showed a reduction in the rate of nocturnal hypoglycaemia between insulin glargine and isophane insulin in the 65–80 year age group (1.46 vs. 3.16 events/person per year of symptomatic nocturnal events), this did not reach statistical significance [118]. A recent analysis of private health insurance claims in America highlights the significant financial cost associated with these modest reductions in hypoglycaemia. The use of insulin analogues amongst 123,486 participants rose from 18.9 % in 2000 to 91.5 % in 2010 ($p < 0.001$), while the use of human insulin declined from 96.4 to 14.8 % over the same period ($p < 0.001$). Median costs per insulin prescription rose from US$19 in the year 2000 to US$36 in 2010 ($p < 0.001$). The observed fall in the rate of severe hypoglycaemia from 21.1 events per 1,000 person-years in 2000 to 17.7 per 1,000 in 2010 did not reach statistical significance ($p = 0.054$) [119]. Even so, when hospital admission rates for Medicare beneficiaries in the USA were examined, elderly people over the age of 75 had double the admission rate for hypoglycaemia compared with a younger age group (65–74 years) [120]. Therefore, in this specific group of patients, the cost–benefit ratio may favour basal insulin analogues despite some dubiety about their ability to reduce hypoglycaemia when compared with isophane insulin.

Indeed, the EDWPOP guidelines suggest considering long-acting insulin analogues rather than isophane insulin for older patients who require the assistance of a carer, those residing in care homes or for whom there is a defined higher risk of hypoglycaemia (evidence level 1+; grade of recommendation A) [50]. Similarly, the NICE and SIGN guidelines in the UK recommend using insulin analogues only if significant concern exists about the risk of hypoglycaemia and if assistance from a healthcare professional is required for administration of insulin. The recommendation otherwise is for the use of isophane insulin as standard when initiating insulin therapy [67, 68].

Insulin degludec, the new ultra-long-acting insulin with a half-life of >25 h [121], may have a role in limiting the risk of hypoglycaemia in elderly people. A meta-analysis of seven treat-to-target phase III trials examined hypoglycaemia rates associated with the use of insulin degludec

and insulin glargine in elderly patients with T2DM and found that the estimated rate ratios for overall confirmed hypoglycaemia and nocturnal hypoglycaemia were considerably lower with insulin degludec [0.76 (95 % CI 0.61–0.95) and 0.64 (95 % CI 0.43–0.95), respectively] [122]. Nonetheless, more studies that specifically focus on the safety and efficacy of insulin degludec in older people are required before its use can be widely recommended.

As the decline in beta-cell function progresses, the addition of basal insulin alone may not prove fruitful in achieving the individualised glycaemic targets set for the patient, and prandial or biphasic insulin may be required even in the older age groups [123]. Once again insulin analogues are preferred over soluble (regular) or human insulin in this situation as they offer a better pharmacokinetic profile and greater ease of use [124]. The importance of patient and carer education for safe implementation of insulin therapy cannot be stressed enough [50]. Furthermore, other anti-diabetes medications, in particular sulfonylureas may no longer be required once prandial insulin is commenced, and a review of medications should be undertaken at this point to prevent the later risk of severe hypoglycaemia.

7 Polypharmacy and the Risk of Drug Interactions

Polypharmacy is common in older people, and those with T2DM are often receiving medications to ameliorate cardiovascular risk or symptoms of diabetes-related complications such as peripheral neuropathy. Polypharmacy per se is associated with increased morbidity. For example, one study showed that concomitant use of six or more drugs in elderly people was associated with a greater risk of falls [125]. This must also be considered when intensifying diabetes therapies in the elderly person as this population is already vulnerable to falls and related fractures.

8 Conclusion

Type 2 diabetes is increasingly common in the elderly population and can have detrimental effects on this age group. Evidence for glycaemic targets in frail, elderly people with T2DM is lacking. Nonetheless, the burden of diabetes is greater in this group of patients in view of the co-existence of other geriatric syndromes, along with the usual micro- and macrovascular complications of diabetes. Therefore, current recommendations emphasise that the optimisation of glycaemic control in an older person with diabetes must be individualised. Although the overall goals of management are similar to those of younger people, they must be tailored to the elderly individual depending on their functional status, life expectancy, disease duration and risk of hypoglycaemia, including impaired hypoglycaemia awareness. The choice of anti-diabetes therapies should aim to limit polypharmacy and should follow the same principle of individualised care by taking into account patient preference, ability to self-manage diabetes and available support and resources [80]. This will enable older adults to minimise the consequences of hyperglycaemia safely while avoiding the risk and consequences of acute hypoglycaemia.

Conflicts of interest No sources of funding were used to assist in the preparation of this article.

Supriya Mathur has no conflicts of interest relating to this manuscript but has had travel, accommodation and registration for a conference funded by Sanofi. Nicola N. Zammitt has no conflicts of interest relating to this manuscript but has accepted speaker fees from Astra Zeneca and Bristol Myers Squibb and has had travel, accommodation and registration for conferences funded by Sanofi, Aventis, Novo Nordisk, Lilly and Merck Sharpe and Dohme. Brian M. Frier has no conflicts of interest relating to this manuscript but has received honoraria for lecturing and membership of advisory boards for Novo Nordisk, Lilly, MSD, Sanofi, Boehringer Ingelheim and Janssen.

References

1. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet. 2011;378(9785):31–40.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87(1):4–14.
3. Selvin E, Parrinello CM, Sacks DB, Coresh J. Trends in prevalence and control of diabetes in the United States, 1988–1994 and 1999–2010. Ann Intern Med. 2014;160(8):517–25.
4. Pw W, Km A, Wb K. Epidemiology of diabetes mellitus in the elderly. The Framingham Study. Am J Med. 1986;80(5A):3–9.
5. Fagot-Campagna A, Bourdel-Marchasson I, Simon D. Burden of diabetes in an aging population: prevalence, incidence, mortality, characteristics and quality of care. Diabetes Metab. 2005;31(Spec No. 2):5S35–52.
6. Selvin E, Coresh J, Brancati FL. The burden and treatment of diabetes in elderly individuals in the US Diabetes Care. 2006;29(11):2415–9.
7. Group DS. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. Diabetes Care. 2003;26(1):61–9.
8. Qiao Q, Hu G, Tuomilehto J, Nakagami T, Balkau B, Borch-Johnsen K, et al. Age- and sex-specific prevalence of diabetes and impaired glucose regulation in 11 Asian cohorts. Diabetes Care. 2003;26(6):1770–80.
9. Rockwood K, Awalt E, MacKnight C, McDowell I. Incidence and outcomes of diabetes mellitus in elderly people: report from the Canadian Study of Health and Aging. CMAJ. 2000;162(6):769–72.
10. Lakey WC, Barnard K, Batch BC, Chiswell K, Tasneem A, Green JB. Are current clinical trials in diabetes addressing

important issues in diabetes care? Diabetologia. 2013;56(6):1226–35.
11. Mitchell BD, Vietri J, Zagar A, Curtis B, Reaney M. Hypoglycaemic events in patients with type 2 diabetes in the United Kingdom: associations with patient-reported outcomes and self-reported HbA1c. BMC Endocr Disord. 2013;13(1):59.
12. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. Diabetologia. 2002;45(7):937–48.
13. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes. 2008;57(12):3169–76.
14. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes Care. 2012;35(9):1897–901.
15. Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, et al. Diabetes in older adults. Diabetes Care. 2012;35(12):2650–64.
16. Greco D, Pisciotta M, Gambina F, Maggio F. Severe hypoglycaemia leading to hospital admission in type 2 diabetic patients aged 80 years or older. Exp Clin Endocrinol Diabetes. 2010;118(4):215–9.
17. Geller AI, Shehab N, Lovegrove MC, Kegler SR, Weidenbach KN, Ryan GJ, et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. JAMA Intern Med. 2014;174(5):678–86.
18. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol. 2006;5(1):64–74.
19. Strachan MW, Reynolds RM, Marioni RE, Price JF. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. Nat Rev Endocrinol. 2011;7(2):108–14.
20. Deary IJ, Frier BM. Severe hypoglycaemia and cognitive impairment in diabetes. BMJ. 1996;313(7060):767–8.
21. Feinkohl I, Aung PP, Keller M, Robertson CM, Morling JR, McLachlan S, et al. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes Care. 2014;37(2):507–15.
22. Marioni RE, Strachan MW, Reynolds RM, Lowe GD, Mitchell RJ, Fowkes FG, et al. Association between raised inflammatory markers and cognitive decline in elderly people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes. 2010;59(3):710–3.
23. Marioni RE, Deary IJ, Strachan MW, Lowe GD, Rumley A, Murray GD, et al. Blood rheology and cognition in the Edinburgh Type 2 Diabetes Study. Age Ageing. 2010;39(3):354–9.
24. Aung PP, Strachan MW, Frier BM, Butcher I, Deary IJ, Price JF, et al. Severe hypoglycaemia and late-life cognitive ability in older people with Type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabet Med. 2012;29(3):328–36.
25. Yaffe K, Falvey C, Hamilton N, Schwartz AV, Simonsick EM, Satterfield S, et al. Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. Arch Neurol. 2012;69(9):1170–5.
26. Punthakee Z, Miller ME, Launer LJ, Williamson JD, Lazar RM, Cukierman-Yaffee T, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care. 2012;35(4):787–93.
27. Hewitt J, Smeeth L, Chaturvedi N, Bulpitt CJ, Fletcher AE. Self management and patient understanding of diabetes in the older person. Diabet Med. 2011;28(1):117–22.
28. de Galan BE, Zoungas S, Chalmers J, Anderson C, Dufouil C, Pillai A, et al. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Diabetologia. 2009;52(11):2328–36.
29. Cheng C, Lin CH, Tsai CJ, Chou PH, Lan TH. Type 2 diabetes and antidiabetic medications in relation to dementia diagnosis. J Gerontol A Biol Sci Med Sci. 2014;69(10):1299–305.
30. Sinclair AJ, Conroy SP, Bayer AJ. Impact of diabetes on physical function in older people. Diabetes Care. 2008;31(2):233–5.
31. Dhamoon MS, Moon YP, Paik MC, Sacco RL, Elkind MS. Diabetes predicts long-term disability in an elderly urban cohort: the Northern Manhattan Study. Ann Epidemiol. 2014 May;24(5):362-8.e1.
32. Chou KL, Chi I. Functional disability related to diabetes mellitus in older Hong Kong Chinese adults. Gerontology. 2005;51(5):334–9.
33. Lipscombe LL, Jamal SA, Booth GL, Hawker GA. The risk of hip fractures in older individuals with diabetes: a population-based study. Diabetes Care. 2007;30(4):835–41.
34. Signorovitch JE, Macaulay D, Diener M, Yan Y, Wu EQ, Gruenberger JB, et al. Hypoglycaemia and accident risk in people with type 2 diabetes mellitus treated with non-insulin antidiabetes drugs. Diabetes Obes Metab. 2013;15(4):335–41.
35. Johnston SS, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. Diabetes Obes Metab. 2012;14(7):634–43.
36. Schwartz AV, Vittinghoff E, Sellmeyer DE, Feingold KR, de Rekeneire N, Strotmeyer ES, et al. Diabetes-related complications, glycemic control, and falls in older adults. Diabetes Care. 2008;31(3):391–6.
37. Matyka K, Evans M, Lomas J, Cranston I, Macdonald I, Amiel SA. Altered hierarchy of protective responses against severe hypoglycemia in normal aging in healthy men. Diabetes Care. 1997;20(2):135–41.
38. Zammitt NN, Frier BM. Hypoglycaemia in type 2 diabetes and in elderly people. In: Frier BM, Heller SR, McCrimmon RR, editors. Hypoglycaemia in clinical diabetes. 3rd ed. London: Wiley; 2014. p. 230–62.
39. Marker JC, Cryer PE, Clutter WE. Attenuated glucose recovery from hypoglycemia in the elderly. Diabetes. 1992;41(6):671–8.
40. Meneilly GS, Elahi D. Physiological importance of first-phase insulin release in elderly patients with diabetes. Diabetes Care. 1998;21(8):1326–9.
41. Deary IJ, Hepburn DA, MacLeod KM, Frier BM. Partitioning the symptoms of hypoglycaemia using multi-sample confirmatory factor analysis. Diabetologia. 1993;36(8):771–7.
42. McCrimmon RJ, Deary IJ, Gold AE, Hepburn DA, MacLeod KM, Ewing FM, et al. Symptoms reported during experimental hypoglycaemia: effect of method of induction of hypoglycaemia and of diabetes per se. Diabet Med. 2003;20(6):507–9.
43. Meneilly GS, Cheung E, Tuokko H. Altered responses to hypoglycemia of healthy elderly people. J Clin Endocrinol Metab. 1994;78(6):1341–8.
44. Jaap AJ, Jones GC, McCrimmon RJ, Deary IJ, Frier BM. Perceived symptoms of hypoglycaemia in elderly type 2 diabetic patients treated with insulin. Diabet Med. 1998;15(5):398–401.
45. Pegg A, Fitzgerald F, Wise D, Singh BM, Wise PH. A community-based study of diabetes-related skills and knowledge in elderly people with insulin-requiring diabetes. Diabet Med. 1991;8(8):778–81.
46. Thomson FJ, Masson EA, Leeming JT, Boulton AJ. Lack of knowledge of symptoms of hypoglycaemia by elderly diabetic patients. Age Ageing. 1991;20(6):404–6.
47. Abellan van Kan G, Rolland Y, Houles M, Gillette-Guyonnet S, Soto M, Vellas B. The assessment of frailty in older adults. Clin Geriatr Med. 2010;26(2):275–86.

48. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–56.
49. Chen LK, Chen YM, Lin MH, Peng LN, Hwang SJ. Care of elderly patients with diabetes mellitus: a focus on frailty. Ageing Res Rev. 2010;9(Suppl 1):S18–22.
50. Sinclair AJ, Paolisso G, Castro M, Bourdel-Marchasson I, Gadsby R, Rodriguez Mañas L, et al. European Diabetes Working Party for Older People 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. Diabetes Metab. 2011;37 (Suppl 3):S27–38.
51. Nordin C. The case for hypoglycaemia as a proarrhythmic event: basic and clinical evidence. Diabetologia. 2010;53(8):1552–61.
52. Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V. Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. Diabetes Care. 2003;26(5):1485–9.
53. Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, et al. Severe hypoglycemia and risks of vascular events and death. N Engl J Med. 2010;363(15):1410–8.
54. Bremer JP, Jauch-Chara K, Hallschmid M, Schmid S, Schultes B. Hypoglycemia unawareness in older compared with middle-aged patients with type 2 diabetes. Diabetes Care. 2009;32(8):1513–7.
55. Segel SA, Paramore DS, Cryer PE. Hypoglycemia-associated autonomic failure in advanced type 2 diabetes. Diabetes. 2002;51(3):724–33.
56. Group UHS. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia. 2007;50(6):1140–7.
57. Middleton RJ, Foley RN, Hegarty J, Cheung CM, McElduff P, Gibson JM, et al. The unrecognized prevalence of chronic kidney disease in diabetes. Nephrol Dial Transplant. 2006;21(1):88–92.
58. Solini A, Penno G, Bonora E, Fondelli C, Orsi E, Trevisan R, et al. Age, renal dysfunction, cardiovascular disease, and antihyperglycemic treatment in type 2 diabetes mellitus: findings from the Renal Insufficiency and Cardiovascular Events Italian Multicenter Study. J Am Geriatr Soc. 2013;61(8):1253–61.
59. Tseng CL, Soroka O, Maney M, Aron DC, Pogach LM. Assessing potential glycemic overtreatment in persons at hypoglycemic risk. JAMA Intern Med. 2014;174(2):259–68.
60. Aljasem LI, Peyrot M, Wissow L, Rubin RR. The impact of barriers and self-efficacy on self-care behaviors in type 2 diabetes. Diabetes Educ. 2001 2001 May-Jun;27(3):393-404.
61. Sinclair AJ, Gadsby R, Penfold S, Croxson SC, Bayer AJ. Prevalence of diabetes in care home residents. Diabetes Care. 2001;24(6):1066–8.
62. Chen LK, Lin MH, Lai HY, Hwang SJ. Care of patients with diabetes mellitus in long-term care facilities in Taiwan: diagnosis, glycemic control, hypoglycemia, and functional status. J Am Geriatr Soc. 2008;56(10):1975–6.
63. Hope SV, Strain WD. Hypoglycaemia in the elderly. Diabetic Hypoglycaemia. 2013;6(1):3–10.
64. Sinclair AJ. Diabetes, disability and frailty—a need for greater recognition and focused research. Br J Diabetes Vasc Dis. 2012;12:109.
65. Bourdel-Marchasson I, Dugaret E, Regueme S. Disability in older people with diabetes: issues for the clinician. Br J Diabetes Vasc Dis. 2012;12(3):135–40.
66. Hager KK, Loprinzi P, Stone D. Implementing diabetes care guidelines in long term care. J Am Med Dir Assoc. 2013;14(11):851.e7–15.
67. NICE. CG66 Type 2 diabetes: full guideline. 2008 [cited 12 June 2014]. http://guidance.nice.org.uk/CG66/Guidance/pdf/English.
68. SIGN. 116: management of diabetes. 2010 [cited 12 June 2014]. http://www.sign.ac.uk/guidelines/fulltext/116/index.html.
69. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577–89.
70. Gerstein HC, Miller ME, Byington RP, Goff DC, Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545–59.
71. Miller ME, Williamson JD, Gerstein HC, Byington RP, Cushman WC, Ginsberg HN, 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(3):634–43.
72. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560–72.
73. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129–39.
74. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care. 2009;32(1):187–92.
75. International Diabetes Federation. IDF global guidelines for managing older people with type 2 diabetes. 2012 [cited 12 June 2014]. http://www.idf.org/guidelines/managing-older-people-type-2-diabetes.
76. Sinclair A, Morley JE, Rodriguez-Mañas L, Paolisso G, Bayer T, Zeyfang A, et al. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes. J Am Med Dir Assoc. 2012;13(6):497–502.
77. Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet. 2010;375(9713):481–9.
78. Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. Diabetes Care. 2011;34(6):1329–36.
79. Munshi MN, Segal AR, Suhl E, Staum E, Desrochers L, Sternthal A, et al. Frequent hypoglycemia among elderly patients with poor glycemic control. Arch Intern Med. 2011;171(4):362–4.
80. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35(6):1364–79.
81. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009;32(1):193–203.
82. Bailey CJ, Turner RC. Metformin. N Engl J Med. 1996;334(9):574–9.

83. Holstein A, Plaschke A, Egberts EH. Clinical characterisation of severe hypoglycaemia—a prospective population-based study. Exp Clin Endocrinol Diabetes. 2003;111(6):364–9.
84. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352(9131):854–65.
85. Stevens LA, Viswanathan G, Weiner DE. Chronic kidney disease and end-stage renal disease in the elderly population: current prevalence, future projections, and clinical significance. Adv Chronic Kidney Dis. 2010;17(4):293–301.
86. Yki-Järvinen H. Thiazolidinediones. N Engl J Med. 2004;351(11):1106–18.
87. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355(23):2427–43.
88. Singh S, Loke YK, Furberg CD. Thiazolidinediones and heart failure: a teleo-analysis. Diabetes Care. 2007;30(8):2148–53.
89. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet. 2007;370(9593):1129–36.
90. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA. 2007;298(10):1180–8.
91. Chaggar PS, Shaw SM, Williams SG. Review article: thiazolidinediones and heart failure. Diab Vasc Dis Res. 2009;6(3):146–52.
92. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. CMAJ. 2009;180(1):32–9.
93. Jones SG, Momin SR, Good MW, Shea TK, Patric K. Distal upper and lower limb fractures associated with thiazolidinedione use. Am J Manag Care. 2009;15(8):491–6.
94. Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. Arch Intern Med. 2008;168(8):820–5.
95. Barnett AH. Avoiding hypoglycaemia while achieving good glycaemic control in type 2 diabetes through optimal use of oral agent therapy. Curr Med Res Opin. 2010;26(6):1333–42.
96. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. Arch Intern Med. 1997;157(15):1681–6.
97. Gangji AS, Cukierman T, Gerstein HC, Goldsmith CH, Clase CM. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. Diabetes Care. 2007;30(2):389–94.
98. Becker ML, Visser LE, Trienekens PH, Hofman A, van Schaik RH, Stricker BH. Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther. 2008;83(2):288–92.
99. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care. 2004;27(11):2628–35.
100. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA. 2007;298(2):194–206.
101. Strain WD, Lukashevich V, Kothny W, Hoellinger MJ, Paldánius PM. Individualised treatment targets for elderly patients with type 2 diabetes using vildagliptin add-on or lone therapy (INTERVAL): a 24 week, randomised, double-blind, placebo-controlled study. Lancet. 2013;382(9890):409–16.
102. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384–95.
103. Schwartz SL. Treatment of elderly patients with type 2 diabetes mellitus: a systematic review of the benefits and risks of dipeptidyl peptidase-4 inhibitors. Am J Geriatr Pharmacother. 2010;8(5):405–18.
104. Barnett AH, Huisman H, Jones R, von Eynatten M, Patel S, Woerle HJ. Linagliptin for patients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments: a randomised, double-blind, placebo-controlled trial. Lancet. 2013;382(9902):1413–23.
105. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317–26.
106. Levy CJ, Kinsley BT, Bajaj M, Simonson DC. Effect of glycemic control on glucose counterregulation during hypoglycemia in NIDDM. Diabetes Care. 1998;21(8):1330–8.
107. Spyer G, Hattersley AT, MacDonald IA, Amiel S, MacLeod KM. Hypoglycaemic counter-regulation at normal blood glucose concentrations in patients with well controlled type-2 diabetes. Lancet. 2000;356(9246):1970–4.
108. Davis TM, Brown SG, Jacobs IG, Bulsara M, Bruce DG, Davis WA. Determinants of severe hypoglycemia complicating type 2 diabetes: the Fremantle Diabetes Study. J Clin Endocrinol Metab. 2010;95(5):2240–7.
109. Henderson JN, Allen KV, Deary IJ, Frier BM. Hypoglycaemia in insulin-treated type 2 diabetes: frequency, symptoms and impaired awareness. Diabet Med. 2003;20(12):1016–21.
110. Reaven GM, Greenfield MS, Mondon CE, Rosenthal M, Wright D, Reaven EP. Does insulin removal rate from plasma decline with age? Diabetes. 1982;31(8 Pt 1):670–3.
111. Minaker KL, Rowe JW, Tonino R, Pallotta JA. Influence of age on clearance of insulin in man. Diabetes. 1982;31(10):851–5.
112. Fink RI, Revers RR, Kolterman OG, Olefsky JM. The metabolic clearance of insulin and the feedback inhibition of insulin secretion are altered with aging. Diabetes. 1985;34(3):275–80.
113. Reza M, Taylor CD, Towse K, Ward JD, Hendra TJ. Insulin improves well-being for selected elderly type 2 diabetic subjects. Diabetes Res Clin Pract. 2002;55(3):201–7.
114. Zafon C, Creus C. A comparison on insulin regimen treatment of elderly (>70 years) and younger (<70 years) type 2 diabetic patients in actual clinical practice. Acta Diabetol. 2013;50(1):33–7.
115. Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract. 2009;15(6):540–59.
116. Papa G, Fedele V, Chiavetta A, Lorenti I, Leotta C, Luca S, et al. Therapeutic options for elderly diabetic subjects: open label, randomized clinical trial of insulin glargine added to oral antidiabetic drugs versus increased dosage of oral antidiabetic drugs. Acta Diabetol. 2008;45(1):53–9.
117. Garber AJ, Clauson P, Pedersen CB, Kølendorf K. Lower risk of hypoglycemia with insulin detemir than with neutral protamine hagedorn insulin in older persons with type 2 diabetes: a pooled analysis of phase III trials. J Am Geriatr Soc. 2007;55(11):1735–40.
118. Lee P, Chang A, Blaum C, Vlajnic A, Gao L, Halter J. Comparison of safety and efficacy of insulin glargine and neutral protamine hagedorn insulin in older adults with type 2 diabetes mellitus: results from a pooled analysis. J Am Geriatr Soc. 2012;60(1):51–9.

119. Lipska KJ, Ross JS, Van Houten HK, Beran D, Yudkin JS, Shah ND. Use and out-of-pocket costs of insulin for type 2 diabetes mellitus from 2000 through 2010. JAMA. 2014;311(22):2331–3.
120. Lipska KJ, Ross JS, Wang Y, Inzucchi SE, Minges K, Karter AJ, et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999–2011. JAMA Intern Med. 2014;174(7):1116–24.
121. Haahr H, Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. Clin Pharmacokinet. 2014;53(9):787–800.
122. Sorli C, Warren M, Oyer D, Mersebach H, Johansen T, Gough SC. Elderly patients with diabetes experience a lower rate of nocturnal hypoglycaemia with insulin degludec than with insulin glargine: a meta-analysis of phase IIIa trials. Drugs Aging. 2013;30(12):1009–18.
123. Krentz AJ, Sinclair AJ. Choice of long-acting insulin therapy for type 2 diabetes: how can treatment for older people be optimized? Drugs Aging. 2011;28(12):935–41.
124. Ligthelm RJ, Kaiser M, Vora J, Yale JF. Insulin use in elderly adults: risk of hypoglycemia and strategies for care. J Am Geriatr Soc. 2012;60(8):1564–70.
125. Huang ES, Karter AJ, Danielson KK, Warton EM, Ahmed AT. The association between the number of prescription medications and incident falls in a multi-ethnic population of adult type-2 diabetes patients: the diabetes and aging study. J Gen Intern Med. 2010;25(2):141–6.