COMMENTARY

The Value of Insulin Degludec in Frail Older Adults with Type 2 Diabetes

W. David Strain · Angharad R. Morgan · Marc Evans

ABSTRACT

Insulin represents a mainstay of glucose-lowering therapy for many adults with type 2 diabetes mellitus (T2DM). Insulin treatments prescribed as standard care for the majority of people with T2DM, such as basal human insulin, may not be optimal in the treatment of frail older adults because of the increased demand on health care staff to administer multiple daily injections and monitor the patient. When choosing an insulin regimen for a frail older person with T2DM, predictability of glucose lowering effect, risk of hypoglycaemia, ease of administration, and simplicity and flexibility of dosing are major determining factors. Multiple daily injections may be too complex for older frail adults, whilst providing an unnecessary degree of tight glycaemic control and low doses of once-daily basal insulin analogues such as insulin degludec may be a reasonable option as cognitive decline or functional disability increases. Although insulin degludec has a substantially higher acquisition cost than routinely used basal human insulin, it has a longer, more predictable pharmacological profile and is more amenable to once-daily administration, translating into a reduced burden of care and potential cost savings for insulin-treated frail older adults. Insulin acquisition cost represents only a small proportion of the total cost of treatment, and it is important to consider the value perspective of insulin therapy in frail older adults from all stakeholders in the health care system.

Keywords: Frail elderly; Health care costs; Human insulin; Insulin analogue; Insulin degludec; Type 2 diabetes mellitus

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Key Summary Points

There are several different insulin treatment options for type 2 diabetes in older adults; however, current available treatment strategies are derived from findings in younger adults that do not commonly present with the issues associated with frailty and age, such as cognitive impairment and the presence of physical disabilities.

The presence of frailty, functional impairments, and cognitive decline in older adults with type 2 diabetes highlights the importance of community nursing support for insulin administration.

The protracted duration of insulin degludec facilitates flexible dosing and convenience with once-daily administration, translating into clinical and economic value, particularly in frail older adults.

Although insulin degludec has a substantially higher acquisition cost than basal human insulin, when considering the value of insulin, it is important to include insulin resource use beyond acquisition costs and, in particular, potential health care service use.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a major health burden for older adults, with prevalence increasing with age (Fig. 1). It affects one in five people > 65 years old (135.6 million people worldwide) [1], and this number is expected to increase dramatically in the future with the global burden of T2DM in individuals ≥ 65 years projected to reach 276.2 million by 2045 [1]. In addition to the usual complications of diabetes, the older population with

diabetes also has a higher risk of other conditions such as falls and fractures, depression, physical disability, pain, polypharmacy due to co-morbidities, and urinary incontinence (Fig. 2). Therefore, the management of diabetes in these older adults demands different treatment strategies dependent on the presence or absence of comorbidities as well as on the patients' living situation and available resources.

Whilst the majority of older adults with T2DM are high functioning, medically stable, and able to perform self-care, diabetes can reduce physical functioning [2]. Sarcopenia (age-related muscle loss associated with reduced power) is a newly emerging and high-impact complication of T2DM in older adults [3, 4], with a prevalence in the range of 7–29% in different populations [5]. Sarcopenia leads to frailty, a condition in which an individual has decreased physical reserves [6], and is usually defined based on the presence of three or more of the following: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity [7]. Furthermore, T2DM has been consistently associated with an increased risk of cognitive decline, including Alzheimer's disease and vascular dementia [8–10], and compared to people without diabetes, individuals with diabetes have a greater rate of cognitive decline [11]. As the decline in cognitive function continues, older people with diabetes and dementia are
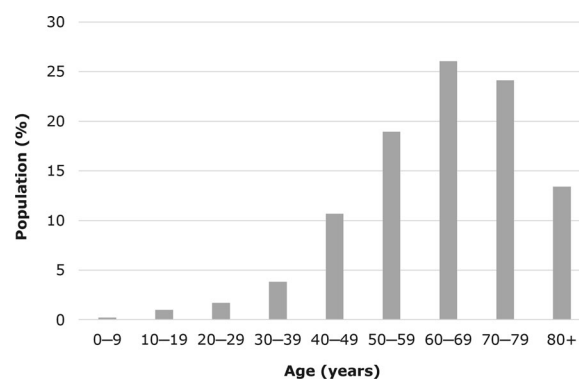

Fig. 1 Prevalence of diabetes by age group in England and Wales [44]
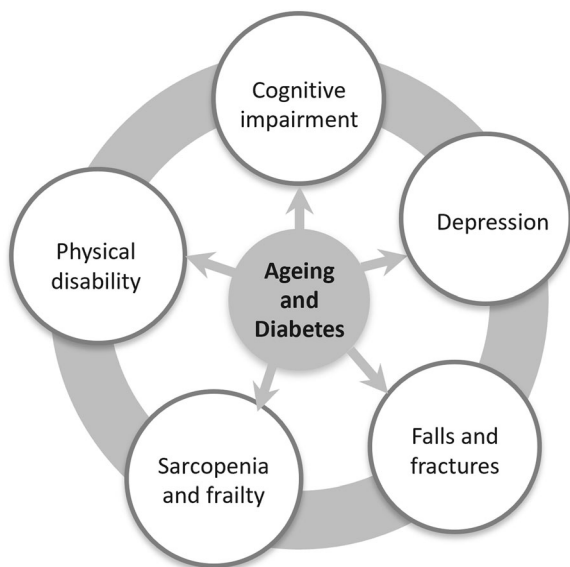
Fig. 2 Comorbidities in older adults with diabetes

liable to struggle to follow complex treatment regimens. The consequences of a mistake in self-medication of diabetes treatments can be devastating; missed doses can result in a hyperosmolar hyperglycaemic state, or diabetic ketoacidosis in those with insulin deficiency, whereas excess dosing can lead to devastating hypoglycaemia. As a result, when cognitive decline ensues, these individuals often require considerable support from both health care and social care practitioners in diabetes management, including treatment administration. Consequently, the treatment of T2DM and its complications in older adults represents a significant cost to the NHS with approximately 61% of all health care costs attributed to T2DM being incurred by people with T2DM who are > 65 years of age [12]. With this in mind, it is imperative to optimise the clinical and economic value with respect to treatment regimens in the population of frail older adults with T2DM.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

INSULIN TREATMENT IN FRAIL OLDER ADULTS WITH T2DM

T2DM treatments in frail older adults need to be carefully prescribed and monitored, taking into consideration the patient cognitive capacities, presence of other comorbidities, cardiovascular risk, and importance of avoiding hypoglycaemia. Although there are several different treatment options for older adults with T2DM, these treatment strategies are based on trial data in younger adults that do not commonly present with the issues associated with frailty and age. Despite the recommendations of international regulatory agencies to include a wide range of patients with T2DM, exclusion of older individuals from ongoing trials regarding T2DM is frequent [13]. This exclusion limits the level of evidence that clinicians require when treating frail older adults with T2DM. In the absence of clear clinical data, guidance is often based on expert consensus [14, 15].

Current treatment recommendations for frail older adults are limited to dipeptidyl peptidase-4 (DPP-4) inhibitors, which have limited efficacy sodium-glucose co-transporter-2 (SGLT2) inhibitors for those with heart failure, and insulin [15]. Although there are many different approaches to insulin initiation, in many health care systems use of a basal insulin is the preferred approach to commencing insulin therapy in people with T2DM. The action profile of human basal insulin peaks within a few hours of administration, translating into a potential increased risk of hypoglycaemia, and in particular nocturnal hypoglycaemia if human insulin is administered in the evening. By contrast, insulin analogues provide slower, more prolonged absorption rates and a relatively constant pharmacokinetic/pharmacodynamic (PK/PD) 24 h profile [16], reducing the potential of hypoglycaemia and furthermore offering the potential for more predictable once-daily dosing [17].

Insulin degludec is a basal insulin analogue with an ultra-long duration of action. This ultra-long duration of action, as well as the low variability in glucose-lowering activity of insulin degludec, has translated into real clinical

benefits, in particular a reduced risk of hypoglycaemic events [18, 19].

Furthermore, the pharmacokinetic profile and protracted half-life of insulin degludec render this insulin a truly once-daily insulin and enables the potential for flexible dosing with a time interval of between 8 and 40 h without comprising its efficacy or safety profile. This dosing flexibility is particularly relevant when considering frail older adults that require assistance with insulin administration from a health care worker, carer, or relative. Consequently, even though there are limited data related to insulin degludec, or indeed any insulin, in frail older adults, the pharmacokinetic profile, greater convenience, and less variable glycaemic control render insulin degludec a very appealing therapy option for insulin administration in frail older adults.

CLINICAL EFFICACY OF INSULIN DEGLUDEC FOR TREATING FRAIL OLDER ADULTS WITH T2DM

The ultra-long-acting insulin degludec with reduced intra- and inter-individual variability in time-action profiles compared with other insulins can provide a more stable glucose-lowering action and improved PK/PD profile, which translates clinically into a reduced risk of hypoglycaemia [20]. Reduced risks of hypoglycaemia have been observed with insulin degludec across age groups including older adults. The results of a meta-analysis of pooled patient-level data in older adults ≥ 65 years from five BEGIN trials involving patients with T2DM [18, 19, 21–23] demonstrated 24% and 36% lower estimated rates of overall hypoglycaemia and nocturnal hypoglycaemia, respectively, with insulin degludec compared to insulin glargine [24]. The hypoglycaemic benefits demonstrated with insulin degludec in older adults were consistent with those seen in the full adult patient population [25]. A post hoc analysis of data from the SWITCH 2 trial demonstrated that treatment with insulin degludec lowered the rates of overall severe and blood glucose-confirmed symptomatic hypoglycaemia by 30% and 31% versus insulin glargine in individuals aged > 65 years and ≤ 65 years, respectively. The reduction in the rate of nocturnal symptomatic hypoglycaemia or blood glucose-confirmed symptomatic hypoglycaemia with insulin degludec versus insulin glargine was 41 and 43%, respectively, in individuals aged > 65 years and ≤ 65 years [26]. The reduced risk of hypoglycaemia with insulin degludec compared to glargine across the age groups was consistent with post hoc analysis of data from the DEVOTE trial, which also demonstrated that patients randomised to insulin degludec had a lower risk of severe hypoglycaemia and nocturnal hypoglycaemia compared to those randomised to insulin glargine across age groups (50–64 and 65–74 years), although a non-significant trend was demonstrated in patients aged ≥ 75 years [27]. In addition, the cardiovascular safety data of insulin degludec versus glargine were also observed across age groups [27], which is an important consideration for clinicians managing older adults with T2DM in clinical practice, since this category of patients typically has high cardiovascular risk.

The reduction in hypoglycaemia is particularly important for frail, older adults with T2DM as this population is more vulnerable to the occurrence and consequences of hypoglycaemia, with episodes of severe hypoglycaemia in this population having been associated with increased risk of cardiac autonomic dysfunction [28], falls [29, 30], and dementia [31] (a 26% increase in the risk for developing dementia after a single event with 3 or more 'events' increases the risk of dementia by 96% [31]). Moreover, hypoglycaemia awareness in frail older adults may be impaired, and as this population often live alone the consequences of hypoglycaemia can result in significant morbidity for this particular group of patients.

HEALTH ECONOMIC IMPACT OF INSULIN DEGLUDEC FOR TREATING FRAIL OLDER ADULTS WITH T2DM

As the acquisition cost for insulin degludec is greater than that of human insulin, many people with T2DM are preferentially prescribed human insulin primarily based on price considerations. However, as people become increasingly frail, the potential limitations of basal human insulin are likely to become more apparent particularly with respect to administration, flexibility of dosing, predictability of the glucose-lowering effect, and risk of hypoglycaemia. The dangers of inappropriate administration and dosing along with the patient's ability to appropriately administer insulin are critical factors that require regular review and assessment.

As cognitive decline or functional disability increases, the burden of insulin delivery will typically pass on to a family member, carer, or nursing staff. Therefore, when considering treatment costs, health visitor costs should be taken into account. A recent report 'Behind closed doors? The hidden impact of diabetes in social care found that there are > 70,000 people in the UK in a social care setting and the direct care costs of T2DM amount to approximately £1.4 billion, five times more than is spent on the drug treatment itself [32].

The introduction of updated clinical guidelines for managing T2DM, with less stringent glycaemic targets for frail older adults [33, 34], aims to limit the risk of hypoglycaemia. However, a reduced risk does not negate the burden of hypoglycaemia completely. Hypoglycaemia carries a large cost burden as a result of hospitalisation for severe episodes [35]. It has been demonstrated that the occurrence of hypoglycaemia in older adults is associated with a 36% increase in diabetes related expenditure [36]. Whilst some of this is in the direct cost of the hypoglycaemia, a significant proportion of this is based on the increased risk of complications such as stroke, fractures, and increased use of social care [37]. Even non-severe hypoglycaemia can have economic consequences in older

patients as they lose confidence and have increased dependency on social support [38]. Insulin analogues, with a low risk of hypoglycaemia, may be preferred in frail older adults with T2DM, as the drug acquisition cost has the potential to be offset by the cost saving from reduced hypoglycaemia-related health care resource utilisation.

Insulin regimens tend to be either a once- or twice-daily basal insulin. The latter requires administration with morning and evening meals within a relatively narrow time window. Staffing for the community nursing team can be a challenge with the team's core hours between 8 a.m. and 6 p.m. and there being a high demand for insulin administration around the start and finish of these core hours. This poses two challenges, the first is the logistics of administering the insulin within a short time window and the second is the cost of the visit itself in the setting of limited staffing. This has been exacerbated throughout the Covid-19 pandemic when community staff have been redeployed and the concerns regarding footfall and risk of coronavirus spread. Given that the NHS is currently facing a shortage of resources, in terms of both costs and the availability of health care workers to deliver this care, it is vital to evaluate the economic value, alongside the clinical efficacy, of different treatment regimens, such as insulin degludec, in frail older adults with T2DM.

In a UK health care setting, whereby district nurses in the community met regularly to review the diabetes patients they attend for insulin injections and where clinically appropriate, based mainly but not wholly on frailty status, a switch from twice- to a once-daily insulin regimen was implemented; the daily visit rate was reduced from 300 to 166 visits (23 patients had their insulin stopped and 121 switched to a once-daily insulin regimen) [39]. Although the cost saving associated with this initiative has not been reported, a reduction of 134 visits per day, 365 days per year, is likely to equate to a huge cost reduction.

Insulin degludec has a substantially higher acquisition cost (£46.60 a month) than routinely used basal human insulin (i.e., Insulatard, Humulin; £19.08 per month) [40, 41]. However,

due to its pharmacological profile, patients using insulin degludec would only require a maximum of one nurse visit per day compared to patients prescribed human insulin, which are likely to require multiple visits to ensure safe and optimal insulin dosing, administration, and monitoring. Furthermore, the biological stability when administered from 8 to 40 h apart increases the flexibility of administration [42], a notable advantage at times of stress on service, such as weekends, holidays, and times of significant staff pressure such as the Covid-19 pandemic. Consequently, the use of a more expensive, longer acting insulin that requires less monitoring and administration may ultimately translate into whole health care system cost savings when the cost of external assistance in included (Fig. 3). As the current NHS tariff for a nurse visit is £30 (based on a 15-min visit for a band 7 nurse) [43], costs would be expected to be approximately £900 per month (30-day month) for degludec visits (once a day) and £1800 per month for human insulin visits (twice a day). Consequently, the estimated cost per month including drug acquisition cost and treatment administration is £946.60 for insulin degludec compared to £1819.08 for human insulin, resulting in a saving of £872.48 per patient per month (£10,469.76 per year) associated with nursing visits alone (in addition to the use of fewer needles and test strips).

SUMMARY

Insulin remains an important cornerstone of diabetes management for many frail older adults with T2DM. Age-related cognitive impairment and the presence of physical disabilities and other age-related problems, such as frailty, malnutrition, pain, and depression, may adversely affect self-care abilities, particularly around insulin administration, in older frail adults with T2DM. Consequently, there has been significant unmet need with respect to insulin therapy in this population. The requirement for the simplification of insulin regimens has been further highlighted over the past 18 months as a consequence of the Covid-19 pandemic and the consequent stress this has
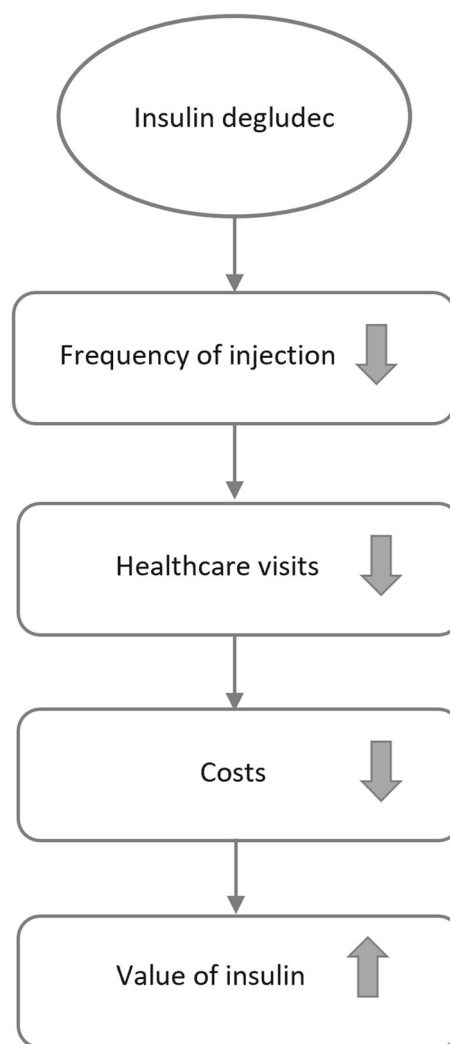

Fig. 3 Value of insulin degludec

placed on all stakeholders in the health care system including patients, carers, and community-based services. There has become a need to re-evaluate the insulin regimens of people who require district nursing visits for insulin administration to reduce contact and therefore reduce risk of contamination as well as to address the ever-increasing demand for community nursing services.

Insulin degludec represents a significant evolution with respect to insulin therapy in frail older adults, with the potential for flexible true once daily dosing that has obvious service resource utilisation impacts as well as quality of

life benefits for patients as well as their family members and carers.

It is important to consider value of any therapy from a multiple stakeholder perspective, and while insulin degludec may have a higher acquisition cost compared to basal human insulin, it has a longer, more predictable pharmacological profile and is more amenable to once-daily administration, consequently reducing the burden of care and thus cost associated with supported insulin administration. Consequently, from both a clinical and health economic perspective, insulin degludec could be considered the basal insulin of choice in frail older adults with T2DM.

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