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ORIGINAL RESEARCH ARTICLE

Observational Study of Once-Daily Insulin Detemir in People with Type 2 Diabetes Aged 75 Years or Older

A Sub-Analysis of Data from the Study of Once-Daily Levemir (SOLVE)

Eddy Karnieli · Florian M. M. Baeres · Grzegorz Dzida · Qiuhe Ji · Robert Ligthelm · Stuart Ross · Anne Louise Svendsen · Jean-François Yale

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Abstract

Objectives Older patients are particularly vulnerable to hypoglycaemia. The aim of this study was to evaluate the response to initiation of once-daily insulin detemir in patients aged ≥75 years with type 2 diabetes mellitus (T2DM) treated with one or more oral antidiabetic drugs (OADs).

Methods A sub-analysis was conducted using data from SOLVE (Study of Once daily LeVEmir), a 24-week observational study involving 3,219 investigators and 2,817 project sites from ten countries. Routine clinical practice was followed; there were no study-prescribed procedures. The total cohort comprised 17,374 participants, of whom 2,398 (14 %) were aged ≥75 years. The physicians collected information from patient recall, the patients' medical records and their self-monitored blood glucose diaries (if kept).

Results Pre-insulin glycated haemoglobin (HbA_{1c}) was similar between participants aged ≥75 years and those aged <75 years (HbA_{1c} 8.8 ± 1.5 % vs. 8.9 ± 1.6 % [mean ± SD], respectively). After 24 weeks of treatment, similar reductions in HbA_{1c} were observed in the two subgroups: 7.6 ± 1.1 % and 7.5 ± 1.2 % in participants aged ≥75 years and those aged <75 years, respectively. The incidence of severe hypoglycaemia (episodes per patient-year) decreased during the study in both age groups (from 0.057 to 0.007 in patients aged ≥75 years; from 0.042 to 0.005 in patients aged <75 years), while minor hypoglycaemia increased from 1.1 to 2.0 and from 1.7 to 1.8 episodes per patient-year in the older and younger age groups, respectively. Average weight reduction was similar in both groups: −0.5 kg (≥75 years) and −0.6 kg (<75 years).

Conclusion In both the older and younger age groups, the addition of once-daily insulin detemir to existing OAD regimens was effective and safe. In older patients, an improvement in HbA_{1c} of 1.2 % was not associated with an increased risk of severe hypoglycaemia or weight gain.

On behalf of the SOLVE Study Group.

E. Karnieli (✉)
Endocrinology, Diabetes and Metabolism, Rambam Medical Center and Rappaport Faculty of Medicine, Technion, 12 Halia St, Samy Ofer Tower, Fl #8, Haifa 31096, Israel
e-mail: eddy@rambam.health.gov.il

F. M. M. Baeres
Global Medical Affairs, Novo Nordisk A/S, Søborg, Denmark

G. Dzida
Department of Internal Diseases, Medical University of Lublin, Lublin, Poland

Q. Ji
Department of Endocrinology and Metabolism, Xijing Hospital, Fourth Military Medical University, Xi'an, China

R. Ligthelm
Executive Health Management Clinic, Hoofddorp, The Netherlands

S. Ross
Faculty of Medicine, University of Calgary, Calgary, AB, Canada

A. L. Svendsen
Department of Biostatistics and Epidemiology, Novo Nordisk A/S, Søborg, Denmark

J.-F. Yale
McGill Nutrition and Food Science Centre, Royal Victoria Hospital, Montreal, QC, Canada

1 Introduction

The difficulties in managing type 2 diabetes mellitus (T2DM) in the elderly are myriad. Factors to consider in relation to advancing age that influence treatment decisions include co-morbidity, polypharmacy, visual and cognitive impairment, severity of vascular complications, psychosocial limitations, renal insufficiency, an increased risk of falling, and a limited life expectancy [1, 2]. These considerations are in addition to the regular management principles of diabetes—those with the overall aim of achieving good glycaemic control [3].

Diabetes mellitus is a common metabolic problem affecting an estimated 336 million people worldwide [4]. Of people aged ≥25 years, the 2008 prevalence was thought to be approximately 10 % [5]. This rate is increasing. Improvements in cardiovascular risk factors and the management of diabetic complications have contributed to the increasing longevity of people living with diabetes, which in turn has led to the increase in prevalence. In 2011, an estimated 25.8 million people of all ages in the USA had diabetes. In people aged over 65 years, 26.9 % had diabetes, representing 10.9 million people and over 40 % of the total number of people with diabetes in the USA [6]. Globally, the current largest cohort living with diabetes is the 40–59-years age group, but by 2030, the 60–79-years age group is expected to supersede them, with 196 million people affected [7]. Most patients with diabetes over 65 years of age are presently between the ages of 65 and 75 years; however, there will continue to be a shift in demography over the coming decades, so that the majority of the elderly population with diabetes will be ≥75 years of age [8].

The annual global costs of the disease burden of diabetes mellitus are thought to have been in the range of US$465 billion in 2011. By 2030, this cost is predicted to rise to US$595 billion [9]. The average per-person healthcare expenditure of people with diabetes in the USA is 2.3 times that of those without the disease, [10] with three-quarters of global healthcare spending on diabetes involving people aged 50–70 years [9]. Furthermore, elderly patients have a higher rate of diabetes-related hospitalizations compared with younger patients with diabetes. The former are responsible for 65.1 % of all diabetes-related healthcare costs compared with 34.8 % for patients <65 years of age in the USA [11].

In managing people with T2DM, as glycaemic targets are approached, the risk of hypoglycaemia increases. The risk of hypoglycaemia is even higher in the elderly because of age-related complications, including co-morbidity, renal impairment, drug–drug interactions, irregular meal patterns, and poor self-monitoring of blood glucose [1, 12]. The risk of serious morbidity as a result of hypoglycaemia is higher in this elderly cohort [1], and may include cardiac ischaemia [13] and an increased risk of falling [14–16]. In addition, as a result of longer duration of diabetes, older people with diabetes may be at increased risk of developing hypoglycaemic unawareness [17].

In absolute terms, although severe hypoglycaemia remains a rare event, the rate increases rapidly amongst certain groups. These include very elderly persons with co-morbid conditions, those who are unaware of hypoglycaemic symptoms, and those on insulin therapy [18]. It has been shown that hypoglycaemia in the elderly with T2DM is common [19], but actual rates may be higher than reported [20]. Currently, there is also a paucity of data on the pharmacological treatment of T2DM in the elderly [21].

The purpose of this sub-analysis is to evaluate the response to once-daily insulin detemir in patients aged 75 years or above, compared with those aged below 75 years, using data from SOLVE (Study of Once Daily LeVEmir), which included a large number of older people. The primary objective of the overall SOLVE study was to assess the incidence of serious adverse drug reactions (SADRs), including severe hypoglycaemic events, during 24 weeks in patients initiating once-daily treatment with insulin detemir in real-life clinical practice.

2 Methods

SOLVE was a multinational, open-label observational study of patients with T2DM treated with one or more oral antidiabetic drugs (OADs) initiating insulin detemir treatment. The study involved 3,219 investigators and 2,817 project sites from ten countries: Canada, China, Germany, Israel, Italy, Poland, Portugal, Spain, Turkey and the UK.

The study duration was 24 weeks, and data were collected on each patient during three routinely scheduled clinic visits (baseline, interim and final) approximately 12 weeks apart. Data were collected during the period 4 February 2008 (first patient's first visit) to 28 March 2011 (last patient's last visit).

2.1 Measurements

In addition to the primary objective of measuring the incidence of SADRs and severe hypoglycaemia during 24 weeks of once-daily basal insulin treatment, secondary endpoints included glycated haemoglobin (HbA_{1c}), mean and variability of fasting plasma glucose (FPG), 7-point blood glucose profile (self-monitored), full lipid profile, and proportion of patients using anti-hypertensive and lipid-lowering drugs. Information on insulin dose, minor and nocturnal hypoglycaemic episodes, non-SADRs,

weight, body mass index (BMI), waist and hip circumference, and blood pressure were also recorded.

Minor hypoglycaemia was defined as a blood glucose measurement of <3.1 mmol/L (<56 mg/dL) with or without symptoms; a severe hypoglycaemic event was defined as an event requiring third-party assistance; and a nocturnal hypoglycaemic event was defined as any episode occurring between bedtime and awakening the next morning. Minor hypoglycaemic events were recorded as events recalled within the preceding 4 weeks, and severe hypoglycaemic events were recorded as events recalled within the preceding 12 weeks in all countries except the UK, where a recall period of 4 weeks was used. The same definitions of hypoglycaemia were used at all time points (i.e. pre-insulin, interim and final visits).

The full analysis set comprised all enrolled patients prescribed basal insulin at baseline. The effectiveness analysis set comprised all patients from the full analysis set with a final visit between 16 and 32 weeks, and at least one measurement of FPG, HbA_{1c}, or weight or record of hypoglycaemia from pre-insulin and final visit. The effectiveness analysis set was used for the analyses of HbA_{1c}, blood glucose and lipid profiles. The full analysis set was used for the reporting of pre-insulin characteristics, and analysis of all other variables (including SADRs and hypoglycaemia).

As this was an observational study, there were no study-specific procedures or measurements—all were part of routine clinical care and at the discretion of the treating physician. Information was obtained from patients' recall, clinical notes, and (if present) self-monitored blood glucose diaries.

2.2 Eligibility Criteria

Patients all had a diagnosis of T2DM, and were managed with diet, exercise and at least one OAD. Selection was at the treating physicians' discretion after a decision to initiate insulin detemir had been made. There were some variations between countries with respect to patient eligibility, which have been described in detail previously [22]. For example, some countries allowed the entry of patients who had already initiated insulin prior to the baseline visit. For these cases, pre-insulin data were obtained retrospectively from medical records.

2.3 Statistical Methods

Continuous measurements are described using mean and standard deviation (SD) while the number and percentage in each category summarize categorical variables. Paired *t* tests were used for comparison of continuous data before and after initiation with insulin detemir. The Wilcoxon test was employed for ordinal categorical variables, and the McNemar test was used for discrete variables (e.g. hypoglycaemic episodes). Sub-analysis was performed according to pre-specified grouping of patients according to age: ≥75 and <75 years. Two-sided testing was used, with a level of significance set at $p = 0.05$.

3 Results

The full analysis set comprised 17,374 patients, of whom 13,767 (79 %; effectiveness analysis set) had a measurement of FPG, HbA_{1c}, weight or hypoglycaemia at baseline and final visit. Of all the patients included in the full analysis set, 2,398 (13.8 %) were aged ≥75 years. The proportion of patients aged ≥75 years varied between the ten countries, ranging from 5 % in China and Turkey, to more than 18 % in some participating Western European countries (Table 1).

Table 1 shows the pre-insulin characteristics of the population by age ≥75 and <75 years. There were a higher proportion of female patients in the subgroup aged ≥75 years (55.4 % vs. 45.7 %), and a higher proportion of the older age group was White than of 'other' ethnicity (87.5 % vs. 72.0 %). Unsurprisingly, the older cohort also had a longer mean (± SD) duration of diabetes (14 ± 9 vs. 9 ± 6 years) and OAD treatment (12 ± 8 vs. 8 ± 6 years). The older age group also had a lower average (± SD) weight (75.6 ± 14.8 vs. 81.7 ± 17.8 kg) and BMI (28.5 ± 4.8 vs. 29.3 ± 5.4 kg/m^2) than the younger cohort.

Pre-insulin OAD treatments differed between the two age cohorts, with a lower proportion of patients aged ≥75 years prescribed more than two OADs compared with those aged <75 years (10.8 % vs. 16.9 %). Patients aged ≥75 years were more likely to be prescribed sulphonylurea (65.0 %) and glinides (18.3 %) than the younger group (58.6 % and 15.7 %, respectively), but the proportion of older patients prescribed metformin, thiazolidinedione, and α-glucosidase inhibitors was lower (Table 1).

Pre-insulin average HbA_{1c} and FPG measurements were similar in both age groups.

3.1 Changes in Glycated Haemoglobin, Fasting Plasma Glucose and Hypoglycaemia

After 24 weeks of treatment with insulin detemir, a reduction in HbA_{1c} levels was found across both age cohorts. Mean (± SD) HbA_{1c} was 7.6 ± 1.1 % (a change of −1.2 %; $p < 0.001$) in the ≥75-years age group, and 7.5 ± 1.2 % (a change of −1.3 %; $p < 0.001$) in the <75-years age group. There was a similar FPG reduction in both age groups over the course of the study. Mean (± SD) FPG

Table 1 Pre-insulin demography by age <75 or ≥75 years

Parameter	Age (years)		*p* Value
	<75	≥75	
Total number of participants [*n* (%)]	14,873 (86.1)	2,398 (13.9)	<0.0001
Canada	944 (89.1)	115 (10.9)	
China	3,110 (95.2)	157 (4.8)	
Germany	1,627 (80.5)	394 (19.5)	
Israel	669 (90.9)	67 (9.1)	
Italy	3,576 (77.3)	1,048 (22.7)	
Poland	1,080 (92.5)	87 (7.5)	
Portugal	225 (77.9)	64 (22.1)	
Spain	749 (78.5)	205 (21.5)	
Turkey	2,277 (95.1)	117 (4.9)	
UK	616 (81.1)	144 (18.9)	
Age (years; mean ± SD)	59 ± 10	79 ± 4	<0.0001
Female (%)	45.7	55.4	<0.0001
Ethnicity (%)			<0.0001
White	72.0	87.5	
Black	0.7	0.7	
Other	27.3	11.8	
Duration of diabetes (years; mean ± SD)	9 ± 6	14 ± 9	<0.0001
Duration of OAD therapy (years; mean ± SD)	8 ± 6	12 ± 8	<0.0001
Previous medical history (%)			
Microvascular disease	30.8	46.7	<0.0001
Neuropathy	17.0	24.3	<0.0001
Retinopathy	15.4	22.0	<0.0001
Nephropathy	9.3	21.8	<0.0001
Macrovascular disease	24.1	42.4	<0.0001
Myocardial Infarction	8.0	12.5	<0.0001
Angina pectoris	10.0	15.6	<0.0001
Coronary artery bypass graft	3.1	5.2	<0.0001
Angioplasty	4.5	6.6	<0.0001
Cerebrovascular accident	3.6	9.3	<0.0001
Transient ischaemic attack	3.1	7.7	<0.0001
Peripheral vascular disease	7.6	15.2	<0.0001
Weight (kg; mean ± SD)	81.7 ± 17.8	75.6 ± 14.8	<0.0001
BMI (kg/m^2; mean ± SD)	29.3 ± 5.4	28.5 ± 4.8	<0.0001
FPG (mmol/L; mean ± SD)	10.1 ± 3.0	10.1 ± 2.9	0.8964
HbA_{1c} (%; mean ± SD)	8.9 ± 1.6	8.8 ± 1.5	0.2410
Number of OADs (%)			<0.0001
1	29.3	32.6	<0.0001
2	53.8	56.6	
>2	16.9	10.8	
Types of OAD (%)			
Biguanide	82.7	73.0	<0.0001
Glinide	15.7	18.3	<0.0001
α-Glucosidase inhibitor	12.8	8.9	<0.0001
Sulphonylurea	58.6	65.0	<0.0001
Thiazolidinedione	12.9	8.0	<0.0001
DPP-IV inhibitor	6.6	5.5	0.0562

BMI body mass index, *DPP-IV* dipeptidyl peptidase-IV, *FPG* fasting plasma glucose, *HbA_{1c}* glycated haemoglobin, *OAD* oral antidiabetic drug

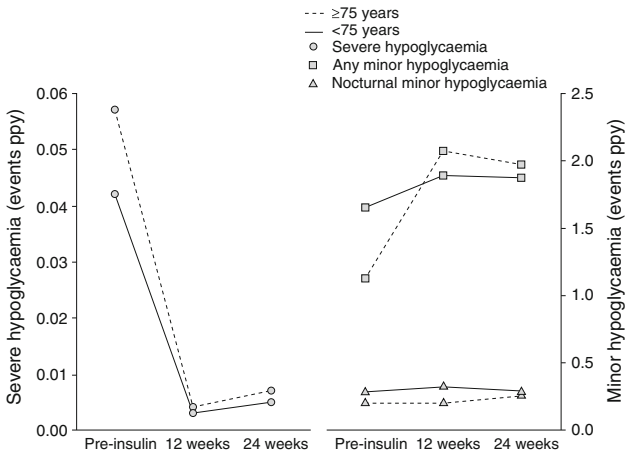

Fig. 1 Incidence of severe, any minor and minor nocturnal hypoglycaemia, according to age group: <75 and ≥75 years. *ppy* per patient-year

was 7.0 ± 1.6 mmol/L (a change of −3.1 mmol/L; $p < 0.001$) in the ≥75-years age group, and 7.1 ± 1.8 mmol/L (a change of −3.1 mmol/L; $p < 0.001$) in the <75-years age group.

The incidence of severe, any minor and minor nocturnal hypoglycaemic events are shown in Fig. 1. The incidence of severe hypoglycaemic episodes in those aged ≥75 years decreased from 0.057 to 0.007 per patient-year (a change −0.05 per patient-year; $p = 0.006$). For the younger cohort, this rate decreased from 0.042 to 0.005 per patient-year (a change of −0.037 per patient-year, $p < 0.001$). Episodes of minor hypoglycaemia increased over the period of the study from 1.12 to 1.97 events per patient-year in those aged ≥75 years ($p = 0.303$), and from 1.65 to 1.82 events per patient-year in the younger cohort ($p < 0.001$), although the change was not statistically significant for patients ≥75 years. The increase in minor hypoglycaemia was largely confined to the daytime, with no statistically significant change in the incidence of nocturnal hypoglycaemia over the period of the study in either age subgroup: +0.003 events per patient-year ($p = 0.150$) and +0.052 events per patient-year ($p = 0.239$) in patients aged <75 and ≥75 years, respectively.

No relationship between pre-insulin HbA_{1c} and the proportion of patients reporting any hypoglycaemic episodes was apparent for either age group.

During the study, 13 patients aged <75 years and five patients aged ≥75 years experienced at least one SADR.

3.2 Other Secondary Endpoints

Changes were also found in the other secondary endpoints measured (Table 2). A reduction of mean (± SD) weight was apparent in both groups: −0.46 ± 6.4 kg (95 % CI −0.74 to −0.18) in those aged ≥75 years, and −0.58 ± 5.5 kg (95 % CI −0.67 to −0.48) in those aged <75 years. Statistically significant reductions in systolic and diastolic blood pressure and BMI were also found across both cohorts.

3.3 Changes in Oral Antidiabetic Drug and Insulin Use

Figure 2 shows the percentage change in the prescribing of OADs from pre-insulin to the end of the 24-week study. The largest changes to OAD prescribing in patients aged ≥75 years were a reduction of sulphonylurea (from 65.0 to

Table 2 Changes in weight, body mass index (BMI) and blood pressure, according to age group: <75 years and ≥75 years

Secondary endpoint	Age (years)		*p* Value for difference in change
	<75	≥75	
Weight (kg)			
Pre-insulin	81.7 ± 17.8	75.6 ± 14.8	
24-Weeks	81.1 ± 17.2	75.1 ± 14.1	
Change	−0.58 (−0.67 to −0.48)	−0.46 (−0.74 to −0.18)	0.4392
BMI (kg/m^2)			
Pre-insulin	29.3 ± 5.4	28.5 ± 4.8	
24-Weeks	29.1 ± 5.2	28.4 ± 4.7	
Change	−0.17 (−0.20 to −0.14)	−0.14 (−0.21 to −0.07)	0.3759
Systolic blood pressure (mmHg)			
Pre-insulin	135 ± 17	139 ± 17	
24-Weeks	131 ± 14	135 ± 15	
Change	−4.0 (−4.3 to −3.7)	−4.5 (−5.4 to −3.6)	0.3032
Diastolic blood pressure (mmHg)			
Pre-insulin	81 ± 10	78 ± 10	
24-Weeks	79 ± 8	77 ± 9	
Change	−2.1 (−2.3 to −1.9)	−1.5 (−2.0 to −1.0)	0.0261

Values are given as mean ± standard deviation, except for change values, which are given as mean (95 % CI)

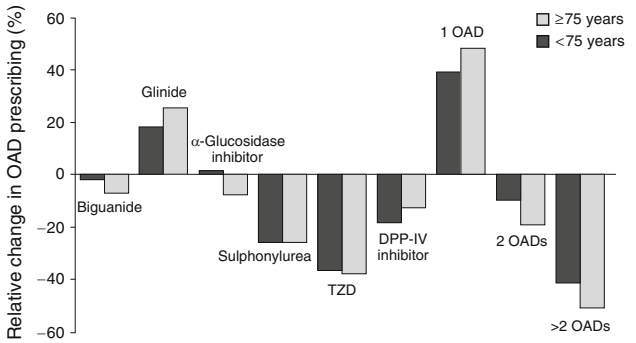

Fig. 2 Relative change in oral antidiabetic drug (OAD) use, from pre-insulin to the end of the study, according to age group. *DPP-IV* dipeptidyl peptidase-IV, *TZD* thiazolidinedione

48.1 %) and thiazolidinedione use (from 8.0 to 5.0 %). Conversely, glinide use amongst this group increased from 18.3 to 23.0 %. Similar trends of decreasing sulphonylurea and thiazolidinedione use, and increasing glinide use, were apparent in the younger cohort. There was a reduction in the proportion of patients prescribed two or more OADs in both groups.

Mean (± SD) daily insulin doses increased throughout the study, and were broadly similar across both age groups: 19 ± 12 IU (0.26 ± 0.16 IU/kg) and 22 ± 16 IU (0.27 ± 0.17 IU/kg) in the ≥75- and <75-years age groups at the end of the study, respectively.

3.4 Physician Resource Utilization

Table 3 shows the insulin devices used and the time taken to train patients how to self-inject and self-adjust, as well as to attend to other parameters related to insulin detemir treatment, according to age subgroup. In general, the FlexPen® was the most commonly used insulin delivery device, irrespective of patient age. The total time taken by physicians and their staff to train older patients to self-inject was approximately 15 min in both groups, and training in dose adjustment and other aspects of diabetes were similar irrespective of patient age. Physicians reported being less confident about how older patients would manage their insulin treatment at the time of insulin initiation, and they also rated ease of use and dose self-adjustment of insulin as less easy in older patients. However, physicians reported similar levels of satisfaction with insulin achieving the targeted HbA_{1c} levels in both age groups.

4 Discussion

This subgroup analysis comparing patients with T2DM aged ≥75 years to those aged <75 years showed similar improvements in glycaemic control without an increased risk of severe hypoglycaemia or minor nocturnal hypoglycaemia in both age groups. The presented analyses highlight differences in OAD prescribing before and during the initiation of insulin. Also apparent is a lack of confidence among healthcare professionals in prescribing insulin to older age patients, although the time taken to train patients and the satisfaction of insulin achieving target HbA_{1c} reported by healthcare professionals in this observational study was similar irrespective of patient age.

Historically, previous studies have found similarly low rates of prevalence of severe hypoglycaemia. In the USA, the Veterans Affairs Cooperative Study (VA CSDM) compared 'standard' (one injection per day) against intensive 'stepped' insulin regimens amongst veterans with a mean age of 60 years and found a rate of severe hypoglycaemia of 2 episodes per 100 patient-years, with no difference between treatment groups [23]. Higher incidence rates were found in the UK Prospective Diabetes Study (UKPDS). In patients undergoing 'intensive' management of T2DM, severe hypoglycaemic episode rates per year were higher in insulin-treated groups (1.8 %) than in those treated with glibenclamide (1.4 %), chlorpropamide (1.0 %) or 'conventional' treatment (0.7 %). These findings should be interpreted in the context of an average HbA_{1c} amongst the intensive group of 7.0 %, and the fact that the UKPDS was not focused on an elderly cohort [24]. A retrospective observational population-based study from Tennessee looked at the incidence of serious hypoglycaemia amongst Medicaid T2DM patients aged ≥65 years. The reported incidences were 1.23 and 2.76 episodes per 100 patient-years amongst the sulphonylurea- and insulin-treated groups, respectively [25].

There appears to be some variation in reported rates of minor hypoglycaemia. While basal insulin analogues have been previously shown to lower the risk of hypoglycaemia with respect to human insulin preparations and more intensive regimens including rapid-acting insulin [26, 27], there remains a paucity of clinical trial data concerning the ≥75-years age group [21], and definitions of hypoglycaemia also vary [28]. In this sub-analysis, there was an increase in the number of minor hypoglycaemic episodes throughout the study period from 1.1 to 2.0 and 1.7 to 1.8 episodes per patient-year in both the ≥75- and <75-years age groups, respectively. The incidence of all hypoglycaemic episodes amongst insulin-treated diabetic veterans in the VA CSDM study was 1.5 per patient-year with once-daily standard injections versus 16.5 per patient-year amongst the intensive group [23]. Recall reliability of minor hypoglycaemia amongst patients with insulin-dependent T2DM is unknown [28], but in people with type 1 diabetes, it has been found to be poor after 1 week [29, 30]. Thus, there may be gross under-reporting of

Table 3 Injection device and resource utilization, according to age group: <75 years and ≥75 years

Device/resource	Age (years)	
	<75	≥75
Injection device [*n* (%)]		
FlexPen	8,402 (60.2)	1,735 (78.0)
NovoPen 3	217 (1.6)	35 (1.6)
NovoPen 4	3,569 (25.6)	285 (12.8)
InnoLet	111 (0.8)	64 (2.9)
NovoLet	29 (0.2)	4 (0.2)
Solostar	8 (0.1)	0 (0)
Other	1,620 (11.6)	100 (4.5)
Total time spent training patients [min; mean (95 % CI)]		
To self-inject himself/herself with insulin detemir	14.7 (14.5–14.9)	15.5 (15.0–16.0)
To self-adjust the insulin dose	11.4 (11.2–11.6)	10.9 (10.5–11.4)
For other reasons	17.0 (16.7–17.3)	16.4 (15.8–17.1)
Physician resource utilization questionnaire [*n* (%)]		
How confident are you that this patient can correctly inject himself/herself and self-adjust the insulin detemir dose?[a]		
Very confident	2,410 (17.1)	204 (9.1)
Confident	7,821 (55.5)	964 (43.1)
Somewhat confident	3,261 (23.2)	808 (36.1)
Not confident	441 (3.1)	150 (6.7)
Not at all confident	57 (0.4)	28 (1.3)
During insulin detemir treatment how would you rate the ease of use and dose self-adjustment of insulin detemir in this patient?[a]		
Very easy	2,541 (20.6)	285 (14.6)
Easy	7,214 (58.4)	1,207 (61.8)
Neutral	1,954 (15.8)	311 (15.9)
Difficult	576 (4.7)	134 (6.9)
Very difficult	62 (0.5)	17 (0.9)
Considering the HbA_{1c} target that you have set for this patient, how satisfied are you with insulin detemir achieving the targeted HbA_{1c}?[a]		
Very satisfied	2,810 (22.9)	392 (20.1)
Satisfied	6,185 (50.3)	1,050 (53.9)
Neutral	1,956 (15.9)	297 (15.3)
Dissatisfied	1,173 (9.5)	189 (9.7)
Very dissatisfied	166 (1.4)	19 (1.0)

HbA_{1c} glycated haemoglobin

[a] Patients for whom this item was not applicable are not included

hypoglycaemia. In one study of elderly patients with HbA_{1c} levels of 8 % or greater, continuous glucose monitoring over 3 days found that 93 % of hypoglycaemic episodes were not recognized by symptoms or four-times-daily blood glucose monitoring [20].

Evidence on the safety of tighter glycaemic control remains mixed. One study comparing intensive versus standard treatment of people with T2DM with high HbA_{1c} levels found a statistically significant increase in the rate of all-cause mortality in the intensive therapy group, with no differences according to age in a subgroup analysis of patients aged <65 versus ≥65 years [31]. A similar study found no difference in cardiovascular mortality amongst veterans with poorly controlled T2DM given intensive or standard treatment [32]. Both studies conveyed some modest benefit in regard to microvascular complications associated with the disease [31, 32].

A move toward more individualized HbA_{1c} targets in the elderly—specifically, more lenient targets in the frail elderly or those with limited life expectancy—has been mooted [33, 34], as treatment is placed in a risk–benefit context between good glycaemic control and the risk of hypoglycaemia [2, 20, 35, 36]. Current American Diabetes Association guidelines seem to reinforce this notion of loosening targets in the face of increasing risk, seen especially in the elderly [37]. Conversely, in those patients

with few co-morbidities and lengthy life expectancy, tighter glycaemic control may be a viable option as long as significant hypoglycaemia does not occur [37]. However, one study implementing such higher HbA_{1c} targets (8 % or less as proposed by the American Geriatrics Society) in a poorly controlled population resulted in fewer overall hyperglycaemic episodes, but more hypoglycaemic episodes requiring emergency room attendance during the early implementation phase [38]. Clearly, such relaxed targets are no panacea for preventing hypoglycaemic episodes, and raising HbA_{1c} targets alone may not be enough to prevent hypoglycaemia in the elderly [20]. Conversely, there is some evidence to suggest that in elderly patients with tight glycaemic control ($HbA_{1c} \leq 6$ %), reducing or withdrawing diabetic medications is safe and may decrease the risk of hypoglycaemia [19].

Nevertheless, there is still a need for appropriate management of T2DM in the elderly that considers the heterogeneous needs of the patient and targets all aspects of their care, including hypertension, hyperglycaemia, hyperlipidaemia, mood problems, and other geriatric syndromes [2, 21, 34]. Many patients with T2DM will eventually require insulin therapy to reach glycaemic goals because of contraindications to OADs or progressive worsening of pancreatic β-cell function [2, 21]. Further, renal dysfunction associated with advancing age can often herald the inability to use oral agents. There is some evidence of a tendency amongst clinicians to continue prescribing OADs in the elderly, especially sulphonylurea, despite contraindications (for example, renal impairment). This practice is thought to substantially adversely impact the risk of severe hypoglycaemia in this population, and alternative therapies minimizing the risk of hypoglycaemia have been called for [39].

4.1 Limitations

As an observational study, the lack of blinding and control groups is a potential source of confounding. In this subgroup analysis, results of the safety and efficacy of once-daily insulin detemir were directly compared between those aged ≥75 and <75 years. All other entry criteria remained constant between groups (within each country). A number of other specific limitations included missing data, and minor variations to the patient inclusion and exclusion criteria between countries, which were made to comply with national legislation [22]. As already discussed, recall bias was also one of the principle limitations of this study, which may have resulted in an under-reporting of hypoglycaemic events. Despite these limitations, SOLVE remains the largest observational study of insulin initiation in a routine clinical practice setting, to date. Furthermore, it is one of the few trials to have included a pre-specified analysis of the patient subgroup aged ≥75 years.

5 Conclusions

The treatment of T2DM in the elderly is complex, and involves consideration of multiple factors that may not be present in a younger population. The situation is further complicated by a general lack of clinical trial data pertaining specifically to the elderly population. This sub-analysis of the SOLVE study data shows that treatment with insulin detemir in patients aged ≥75 years was effective at improving HbA_{1c}, and safe in terms of the risk of hypoglycaemia. Long-acting basal insulin analogues are a useful treatment option in elderly patients with T2DM, where polypharmacy or medication adverse effects associated with OADs may become a barrier to achieving appropriate glycaemic control.

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