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

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Summary

Background **A substantial proportion of patients with type 2 diabetes are elderly (≥65 years) but this group has been largely excluded from clinical studies of glucose-lowering drugs. We aimed to assess the effectiveness of linagliptin, a dipeptidyl peptidase-4 inhibitor, in elderly patients with type 2 diabetes.**

Methods **In this randomised, double-blind, parallel-group, multinational phase 3 study, patients aged 70 years or older with type 2 diabetes, glycated haemoglobin A_{1c} (HbA_{1c}) of 7·0% or more, receiving metformin, sulfonylureas, or basal insulin, or combinations of these drugs, were randomised (by computer-generated randomisation sequence, concealed with a voice–response system, stratified by HbA_{1c} level [<8·5% *vs* ≥8·5%] and insulin use [yes *vs* no], block size four) in a 2:1 ratio to once-daily oral treatment with linagliptin 5 mg or matching placebo for 24 weeks. Investigators and participants were masked to assignment throughout the study. The primary endpoint was change in HbA_{1c} from baseline to week 24. This trial is registered with ClinicalTrials.gov, number NCT01084005.**

Findings **241 community-living outpatients were randomised (162 linagliptin, 79 placebo). Mean age was 74·9 years (SD 4·3). Mean HbA_{1c} was 7·8% (SD 0·8). At week 24, placebo-adjusted mean change in HbA_{1c} with linagliptin was −0·64% (95% CI −0·81 to −0·48, p<0·0001). Overall safety and tolerability were much the same between the linagliptin and placebo groups; 75·9% of patients in both groups had an adverse event (linagliptin n=123, placebo n=60). No deaths occurred. Serious adverse events occurred in 8·6% (14) of patients in the linagliptin group and 6·3% (five) patients in the placebo group; none were deemed related to study drug. Hypoglycaemia was the most common adverse event in both groups, but did not differ between groups (24·1% [39] in the linagliptin group, 16·5% [13] in the placebo group; odds ratio 1·58, 95% CI 0·78–3·78, p=0·2083).**

Interpretation **In elderly patients with type 2 diabetes linagliptin was efficacious in lowering glucose with a safety profile similar to placebo. These findings could inform treatment decisions for achieving individualised glycaemic goals with minimal risk in this important population of patients.**

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Introduction

Elderly people (≥65 years) are the main users of medications but have been substantially under-represented in clinical trials.[1,2] About a quarter of people aged 65 years or older have diabetes mellitus,[3] nearly all of whom have type 2 disease.[4] However, an analysis[5] showed that only 0·6% of interventional trials in diabetes specifically targeted this age group, 31% excluded patients older than 65 years, and almost all excluded those older than 75 years. Glucose-lowering treatment of elderly patients with type 2 diabetes is generally deemed necessary to alleviate symptoms associated with hyperglycaemia, improve general wellbeing, and, in some cases, to reduce the risk of long-term complications;[4] untreated hyperglycaemia is also frequently associated with cognitive impairment.[6] Randomised clinical trials of glucose-lowering treatments in elderly patients with type 2 diabetes are particularly rare in those whose hyperglycaemia is uncontrolled by common antidiabetes treatments.[4] This evidence gap hinders clinical decision making for elderly patients, because the risks and benefits of treatment are unclear.[4,7,8]

Treatment of elderly patients with type 2 diabetes is challenging because of the high prevalence of comorbidities, use of polypharmacy, frailty, and age-related reduction in pancreatic islet function.[9] Safety is therefore an important consideration for treatment, especially avoidance of iatrogenic hypoglycaemia, which occurs frequently in elderly patients and can have severe consequences.[4,7] Renal impairment is also very common in elderly patients with type 2 diabetes, increasing their risk for hypoglycaemia and complicating treatment strategies.[10] Consequently, although the general goal for patients with type 2 diabetes of a glycated haemoglobin A_{1c} (HbA_{1c}) level of less than 7% might still be reasonable for some elderly patients, it is judged important to individualise this target to balance potential benefits and risks of treatment.[4,9,10] For some

patients, a more appropriate treatment goal might be, for example, HbA_{1c} of 7·5% or higher, depending on individual circumstances.

Many glucose-lowering drugs have potential disadvantages for elderly patients, particularly a risk for hypoglycaemia (sulfonylureas, insulin) or fractures (thiazolidinediones, of which pioglitazone is the only agent remaining widely available), or contraindication or dose adjustments for renal impairment (most oral and injectable agents).[4] Additionally, efficacy of glucose-lowering drugs can be affected by disease duration, because of deterioration over time in pancreatic β-cell function. Dipeptidyl peptidase-4 (DPP4) inhibitors are oral agents with little risk for hypoglycaemia and are generally well tolerated.[11] Unlike other DPP4 inhibitors, linagliptin, given in a once-daily, single-dose 5 mg regimen, is excreted mainly by non-renal pathways and dose adjustment is not needed for renal impairment or any other factor.[12] Linagliptin also has minimal drug interactions.[12] In phase 3 studies in patients with type 2 diabetes aged up to 80 years, linagliptin elicited meaningful glucose-lowering effects and was well tolerated with little intrinsic risk for hypoglycaemia.[13–17] This pharmacological profile suggests that linagliptin might be particularly useful for treatment of elderly patients with type 2 diabetes.

The aim of this study was to investigate the glucose-lowering efficacy, safety, and tolerability of linagliptin in patients aged 70 years and older with type 2 diabetes with inadequate glycaemic control on other common glucose-lowering drugs.

Methods

Study design and patients

This randomised, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial was done at 33 clinics in five countries (Australia, Canada, Denmark, the Netherlands, and Sweden). The first patient was enrolled on March 10, 2010, and the last patient visit occurred on June 22, 2011.

Men and women with type 2 diabetes were eligible to participate if they were aged 70 years or older, had insufficient glycaemic control (HbA_{1c} ≥7·0%), and had been receiving stable doses of metformin, sulfonylureas, or basal insulin, or combinations of these drugs, for at least 8 weeks. The main exclusion criteria were: fasting plasma glucose (FPG) greater than 13·3 mmol/L; impaired hepatic function (serum concentrations of alanine transaminase [ALT], aspartate transaminase [AST], or alkaline phosphatase [ALP] more than three times the upper limit of normal); myocardial infarction, stroke, or transient ischaemic attack within 3 months before the study; previous bariatric surgery; present treatment with rapid-acting or premixed insulin or systemic steroids; treatment within the previous 3 months with a thiazolidinedione, α-glucosidase inhibitor, meglitinide, GLP1 analogue, DPP4 inhibitor, or anti-obesity drug.

The study protocol was approved by the independent ethics committee or institutional review board of participating centres, and the study was done in accordance with the principles of the Declaration of Helsinki and the International Conference of Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice. All patients provided written informed consent before study initiation.

Randomisation and masking

Randomisation was done in a 2:1 ratio (linagliptin:placebo) for ethical reasons (so that only a third of patients received inert treatment); this allocation also provided additional safety information for the active treatment. Randomisation was stratified by HbA_{1c} level (<8·5% *vs* ≥8·5%) and insulin use (yes *vs* no) with a block size of four. Computer-generated randomisation lists were produced by the sponsor, with allocation concealed using a central interactive voice–web response system. Linagliptin and placebo tablets were identical in appearance, and investigators and patients were masked to treatment assignment throughout the study.

Procedures

After screening, eligible patients underwent a 2 week, open-label, placebo run-in period. Patients were then randomised to receive once-daily oral treatment with linagliptin 5 mg or placebo for 24 weeks, in addition to their existing glucose-lowering treatment. Doses of background treatments were maintained for the first 12 weeks of randomised treatment, after which dose adjustments were permitted. Rescue medication for hyperglycaemia (confirmed glucose level: fasting >13·3 mmol/L in weeks 1–12, >11·1 mmol/L in weeks 13–24; or random test >22·2 mmol/L; two or more measurements on different days, one done after an overnight fast) was permitted during randomised treatment.

The primary endpoint was change in HbA_{1c} from baseline to week 24. Secondary endpoints were the

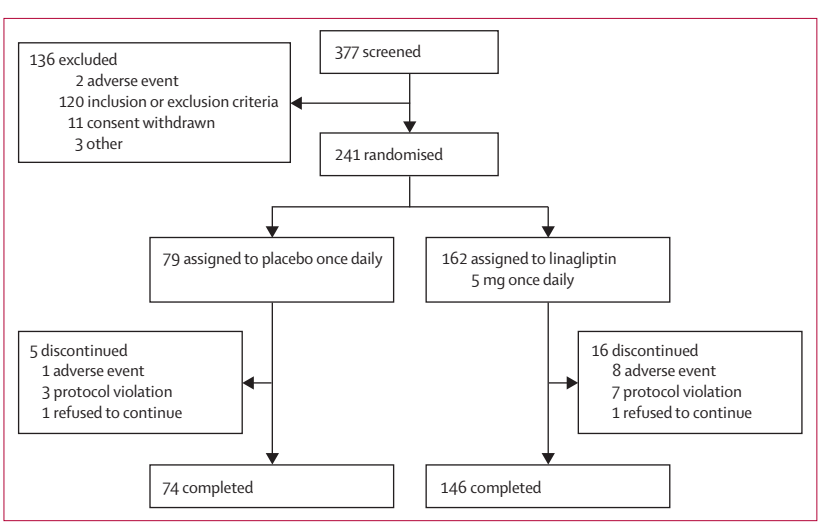

Figure 1: **Trial profile**

proportion of patients achieving HbA_{1c} less than 7·0% after 24 weeks, the proportion of patients with a 0·5% or greater reduction in HbA_{1c} after 24 weeks, change in HbA_{1c} from baseline over time, change in FPG from baseline at week 24, change in FPG from baseline over time, and use of rescue therapy. The proportion of patients achieving other levels of HbA_{1c} (<7·5%, <8·0%, <8·5%) was analysed post hoc.

Safety endpoints were incidence and intensity of adverse events (including adverse changes noted during physical examinations or 12-lead electrocardiographs [ECGs]); withdrawals because of adverse events; hypoglycaemia; cardiovascular events; and changes in vital signs, laboratory variables, and background treatment. Adverse events were categorised using the Medical Dictionary for Regulatory Activities (version 14.1). Events suspected to be stroke or cardiac ischaemia (including myocardial infarction) were reviewed by an independent clinical endpoint committee (CEC), consisting of three academic cardiologists and three academic neurologists who were masked to assignment. Hypoglycaemia was defined as plasma glucose of 3·9 mmol/L or less, with or without symptoms; severe hypoglycaemia was defined as needing assistance from another person to administer resuscitative action, irrespective of plasma glucose concentration. On the basis of clinical experience with other DPP4 inhibitors, significant adverse events prespecified for investigation were hypersensitivity reactions (angio-oedema, angio-oedema-like event, anaphylaxis), renal events (kidney failure, two times or greater increase in creatinine), increases in hepatic enzymes (ALT, AST, or ALP above more than three times the upper limit of normal), severe cutaneous adverse reactions, and pancreatitis.

	Linagliptin (n=162)	Placebo (n=79)
Age (years)		
All patients	74·9 (4·4)	74·9 (4·2)
<75 years	91 (56·2%)	43 (54·4%)
≥75 years	71 (43·8%)	36 (45·6%)
Sex		
Men	116 (71·6%)	49 (62·0%)
Women	46 (28·4%)	30 (38·0%)
Race		
White	157 (96·9%)	76 (96·2%)
Asian	3 (1·9%)	2 (2·5%)
Black	2 (1·2%)	1 (1·3%)
Weight and BMI		
Bodyweight (kg)	86·3 (16·4)	84·4 (15·3)
BMI (kg/m^2)	29·6 (4·7)	29·8 (4·5)
Renal function (eGFR, mL/min per 1·73 m^2, according to MDRD)		
Normal (≥90)	36 (22·2%)	15 (19·0%)
Mild impairment (60 to <90)	83 (51·2%)	42 (53·2%)
Moderate impairment (30 to <60)	41 (25·3%)	21 (26·6%)
Severe impairment (<30)	2 (1·2%)	1 (1·3%)
HbA_{1c}* (%) and FPG* (mmol/L)		
All patients	7·8 (0·8)	7·7 (0·7)
HbA_{1c} <7%†	11 (6·9%)	6 (7·7%)
HbA_{1c} ≥7% and <8%	91 (56·9%)	52 (66·7%)
HbA_{1c} ≥8% and <9%	45 (28·1%)	15 (19·2%)
HbA_{1c} ≥9%	13 (8·1%)	5 (6·4%)
FPG (mmol/L)	8·5 (1·6)	8·0 (1·6)
Time since diagnosis of type 2 diabetes*		
≤1 year	3 (1·9%)	0
>1 to ≤5 years	20 (12·5%)	7 (9·0%)
>5 to ≤10 years	48 (30·0%)	29 (37·2%)
>10 years	89 (55·6%)	42 (53·8%)
Antidiabetes drugs at screening*		
Drug class		
Metformin	133 (83·1%)	69 (88·5%)
Sulfonylurea	94 (58·8%)	43 (55·1%)
Insulin	35 (21·9%)	15 (19·2%)
Meglitinide‡	1 (0·6%)	0
α-glucosidase inhibitor‡	1 (0·6%)	0
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Specific regimen		
Metformin	43 (26·9%)	21 (26·9%)
Metformin plus sulfonylurea	64 (40·0%)	36 (46·2%)
Metformin plus sulfonylurea plus α-glucosidase inhibitor‡	1 (0·6%)	0
Metformin plus sulfonylurea plus insulin	9 (5·6%)	0
Metformin plus meglitinide‡	1 (0·6%)	0
Metformin plus insulin	15 (9·4%)	12 (15·4%)
Sulfonylurea	16 (10·0%)	6 (7·7%)
Sulfonylurea plus insulin	4 (2·5%)	1 (1·3%)
Insulin	7 (4·4%)	2 (2·6%)
Concomitant drugs (non-diabetes)		
≥1	159 (98·1%)	77 (97·5%)
≥3	141 (87·0%)	67 (84·8%)
≥5	96 (59·3%)	54 (68·4%)
Total drugs (diabetes and non-diabetes)		
1	1 (0·6%)	0
2–3	13 (8·0%)	7 (8·9%)
4–5	38 (23·5%)	11 (13·9%)
>5	110 (67·9%)	61 (77·2%)

Data are n (%) or mean (SD). Treated set consisted of all patients who received at least one dose of study drug. BMI=body-mass index. FPG=fasting plasma glucose. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin A_{1c}. MDRD=Modification of Diet in Renal Disease equation. *Full analysis set (all randomised patients who received at least one dose of study drug, and who had a baseline and at least one on-treatment HbA_{1c} measurement; linagliptin n=160, placebo n=78). †These patients had an HbA_{1c} level of 7·0% or more at screening and therefore were eligible for inclusion. ‡These patients were enrolled by investigators despite being on drugs that were not listed as permitted in this study (meglitinides, α-glucosidase inhibitors).

Table 1: **Baseline demographics and clinical characteristics in the treated set of patients**

During assessments at randomisation and every 6 weeks thereafter, patients reported to their local study centre for blood sampling for HbA_{1c} and fasting glucose, examination of vital signs, and documentation of any adverse events and use of concomitant therapies. Bodyweight and 12-lead ECGs were recorded at randomisation and week 24; urine and blood samples for laboratory safety assessments were taken at randomisation and weeks 12 and 24. Physical examinations were done at the start of the placebo run-in period and at week 24. Health-related quality-of-life data were collected using the short-form health survey 36 (SF-36) at randomisation, and the European quality of life-5 dimensions (EQ-5D) at randomisation and weeks 6, 12, and 24. Charlson combined age-comorbidity scores at baseline were calculated post hoc, using previously described methods.[18]

Laboratory measurements were done by a central laboratory (Quintiles Laboratories: Livingston, UK; Singapore; Atlanta, GA, USA).

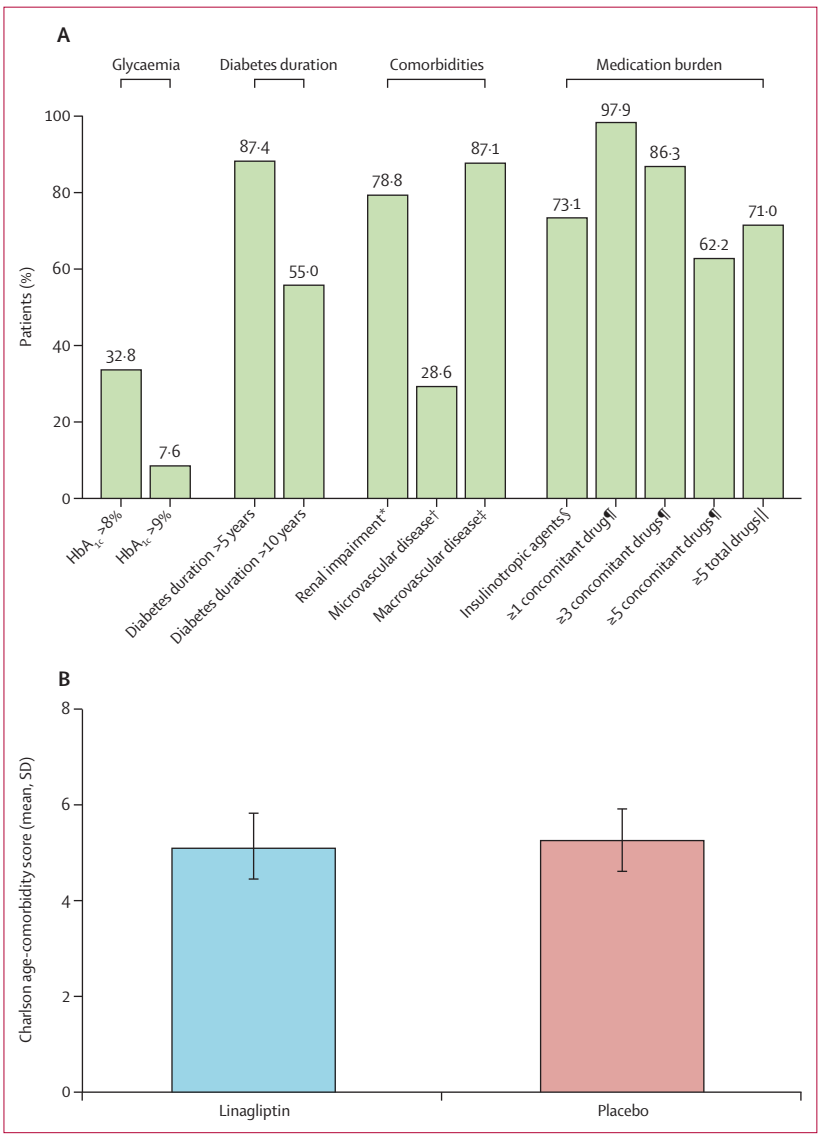

Figure 2: **Baseline disease-related characteristics and comorbidities (A) and Charlson age-comorbidity score (B) in the treated set of patients**

Treated set consisted of all patients who received at least one dose of study drug. FPG=fasting plasma glucose. GFR=glomerular filtration rate. HbA_{1c}=glycated haemoglobin A_{1c}. *Renal function according to GFR estimated by the Modification of Diet in Renal Disease equation. †Microvascular disease consisted of diabetic retinopathy, nephropathy, and neuropathy. ‡Macrovascular disease consisted of coronary artery disease, peripheral artery disease, cerebrovascular disease, and hypertension. §Sulfonylureas, or meglitinides, or insulin, or combination thereof. ¶Drug in addition to glucose-lowering drugs. ||Glucose-lowering drugs and other drugs.

Statistical analysis

231 patients (linagliptin n=154, placebo n=77) were needed to achieve 90% power to detect a 0·5% difference in HbA_{1c} change from baseline to week 24, with a two-sided test with a significance level (α) of 0·05, assuming a common SD of 1·1% for change in HbA_{1c} and a baseline HbA_{1c} of 8%. Hence, randomisation of about 243 patients was needed, assuming 5% dropout.

The primary efficacy analysis, change in HbA_{1c} from baseline to week 24, was done with the full analysis set (all randomised patients who received at least one dose of study medication, and who had a baseline and at least one on-treatment HbA_{1c} measurement), using a last-observation-carried-forward approach to impute missing data. ANCOVA was used, with treatment and previous insulin use as fixed classification effects, and baseline HbA_{1c} as a linear covariate. Superiority of linagliptin versus placebo for change in HbA_{1c} from baseline to week 24 was tested using the two-sided p value and the 95% CI of the treatment difference (linagliptin minus placebo). The effect of the study centre on the primary endpoint was explored with an ANCOVA model that included a treatment by centre interaction.

Change in FPG from baseline to week 24 was assessed for the full analysis set with the same ANCOVA model with baseline FPG as an additional linear covariate. Change in HbA_{1c} over time was analysed with a mixed model for repeated measurements with treatment, previous use of insulin, visit, and visit by treatment interaction as fixed classification effects, and baseline HbA_{1c} as a linear covariate. Available measurements were used (observed cases) with no imputation of missing data. Change in FPG over time was analysed using a similar mixed model for repeated measurements with baseline FPG as an additional linear covariate. For analysis of patients achieving HbA_{1c} of less than 7·0% or a reduction in HbA_{1c} of 0·5% or more, missing values were imputed using the non-completers-considered-failure approach. Logistic regression models were used to calculate odds ratios (OR) for achievement of HbA_{1c} of less than 7·0% and use of rescue therapy.

Safety data were generally analysed descriptively for the treated set, which consisted of all randomised patients who received at least one dose of study drug. The effect of treatment on occurrence of hypoglycaemia was explored with logistic regression.

This study is registered with ClinicalTrials.gov, number NCT01084005, and the European Clinical Trials database (EudractCT), number 2009–015255–25.

Role of the funding source

The sponsor was involved in study design, and data collection, review, and analysis. Individual authors, some of whom are employees of the sponsor, interpreted the data. All authors had full access to the data and had final responsibility for the content of the manuscript. AHB had the final decision to submit for publication.

Results

241 community-living outpatients (the treated set) were randomised to linagliptin 5 mg (n=162) or placebo (n=79), of whom 220 (91·3%) completed 24 weeks of treatment (figure 1). The full analysis set consisted of 238 patients (160 linagliptin, 78 placebo). The mean age of patients at baseline was 74·9 years (range 70–91), with 44·4% aged 75 years or older, and nearly all were white (table 1). Overall, patients had mean baseline HbA_{1c} of 7·8% (SD 0·8), FPG of 8·3 mmol/L (1·6), bodyweight of 85·7 kg (16·0), and body-mass index of 29·7 kg/m² (4·7). Baseline demographic and clinical characteristics were generally much the same between treatment groups. Overall, there was a very high prevalence of long-standing diabetes, cardiovascular disease, renal impairment, use of insulin or sulfonylureas, and use of concomitant drugs and polypharmacy (figure 2A); mean Charlson age-comorbidity score was 5·1 (SD 0·7; figure 2B). One patient (in the linagliptin group) had Alzheimer's disease. About one in five patients were taking basal insulin (table 1), the mean daily dose for different types of insulin ranged from 30 to 60 IU.

After 24 weeks, the placebo-adjusted mean change from baseline in HbA_{1c} with linagliptin was –0·64% (95% CI –0·81 to –0·48, p<0·0001; table 2). Change in HbA_{1c} over time is shown in figure 3. HbA_{1c} of less than 7·0%, when baseline level was 7·0% or greater, was achieved by more patients in the linagliptin group (38·9%, 58 of 149) than in the placebo group (8·3%, six of 72; OR 8·32, 95% CI 3·32 to 20·84, p<0·0001), as was an HbA_{1c} reduction of 0·5% or more (54·4% [87 of 160] *vs* 12·8% [ten of 78]). In patients with baseline HbA_{1c} above these levels, in the linagliptin group, HbA_{1c} of less than 7·5% was achieved by 49·5% (51 of 103) of patients, of less than 8·0% by 63·8% (37 of 58), and of less than 8·5% by 71·4% (20 of 28); in the placebo group the corresponding values were 27·3% (12 of 44), 30·0% (six of 20), and 45·5% (five of 11). The placebo-adjusted mean reduction in FPG from baseline with linagliptin was –1·15 mmol/L (95% CI –1·68 to –0·62, p<0·0001; table 2). Mean FPG decreased from baseline at every timepoint with linagliptin but increased with placebo (data not shown). Rescue treatment was needed by fewer patients in the linagliptin group than in the placebo group (4·4% [seven of 160] *vs* 14·1% [11 of 78]; OR 0·21, 95% CI 0·07–0·63, p=0·0048). From weeks 12 to 24, insulin dosage changes (defined as a change of ≥20%) occurred in one of 35 patients in the linagliptin group and one of 15 patients in the placebo

	Linagliptin	Placebo	Difference (linagliptin–placebo)	p value
HbA_{1c} in overall population				
n	160	78	..	..
Adjusted* mean percentage change from baseline (SE)	–0·61% (0·06)	0·04% (0·07)	–0·64% (0·08)	<0·0001
95% CI	..	..	–0·81 to –0·48	..
FPG in overall population				
n	160	78	..	..
Adjusted† mean change from baseline, mmol/L‡ (SE)	–0·59 (0·18)	0·56 (0·24)	–1·15 (0·27)	<0·0001
95% CI	..	..	–1·68 to –0·62	..
HbA_{1c} in patients aged <75 years				
n	90	42	..	..
Adjusted mean percentage change from baseline (SE)	–0·59% (0·07)	–0·01% (0·10)	–0·58% (0·11)	<0·0001
HbA_{1c} in patients aged ≥75 years				
n	70	36	..	..
Adjusted mean percentage change from baseline (SE)	–0·62% (0·08)	0·10% (0·11)	–0·73% (0·12)	<0·0001
HbA_{1c} in patients with type 2 diabetes for >1 year and ≤5 years				
n	20	7	..	..
Adjusted mean percentage change from baseline (SE)	–0·60% (0·14)	0·17% (0·23)	–0·77% (0·27)	0·0042
HbA_{1c} in patients with type 2 diabetes for >5 years and ≤10 years				
n	48	29	..	..
Adjusted mean percentage change from baseline (SE)	–0·61% (0·10)	–0·11% (0·12)	–0·50% (0·14)	0·0005
HbA_{1c} in patients with type 2 diabetes for >10 years				
n	89	42	..	..
Adjusted mean percentage change from baseline (SE)	–0·62% (0·07)	0·11% (0·10)	–0·73% (0·11)	<0·0001
HbA_{1c} in patients with normal renal function				
n	34	15	..	..
Adjusted mean percentage change from baseline (SE)	–0·44% (0·11)	–0·06% (0·16)	–0·39% (0·19)	0·0397
HbA_{1c} in patients with mild renal impairment				
n	83	42	..	..
Adjusted mean percentage change from baseline (SE)	–0·62% (0·07)	0·12% (0·10)	–0·74% (0·11)	<0·0001
HbA_{1c} in patients with moderate renal impairment				
n	41	20	..	..
Adjusted mean percentage change from baseline (SE)	–0·70% (0·10)	–0·05% (0·14)	–0·64% (0·17)	0·0001
HbA_{1c} in patients with severe renal impairment				
n	2	1	..	..
Adjusted mean percentage change from baseline (SE)	–0·51% (0·43)	0·23% (0·61)	–0·73% (0·74)	0·3262
HbA_{1c} in patients on metformin				
n	44	21	..	..
Adjusted mean percentage change from baseline (SE)	–0·61% (0·09)	–0·12% (0·13)	–0·49% (0·16)	0·0024

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	Linagliptin	Placebo	Difference (linagliptin–placebo)	p value
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HbA_{1c} in patients on sulfonylurea, with or without metformin				
n	81	42	..	..
Adjusted mean percentage change from baseline (SE)	–0·73% (0·07)	–0·01% (0·09)	–0·72% (0·12)	<0·0001
HbA_{1c} in patients on insulin (alone or in combination)				
n	35	15	..	..
Adjusted mean percentage change from baseline (SE)	–0·53% (0·10)	0·14% (0·16)	–0·66% (0·19)	0·0005

Full analysis set consisted of all randomised patients who received at least one dose of study drug, and who had a baseline and at least one on-treatment HbA_{1c} measurement. FPG=fasting plasma glucose. HbA_{1c}=glycated haemoglobin A_{1c}. *Model includes treatment, continuous baseline HbA_{1c}, and previous insulin use. †Model includes treatment, continuous baseline FPG, continuous baseline HbA_{1c}, and previous insulin use. ‡FPG was analysed in units of mg/dL and converted to mmol/L values.

Table 2: **Change from baseline in HbA_{1c} and FPG after 24 weeks in the full analysis set of patients, last observation carried forward**

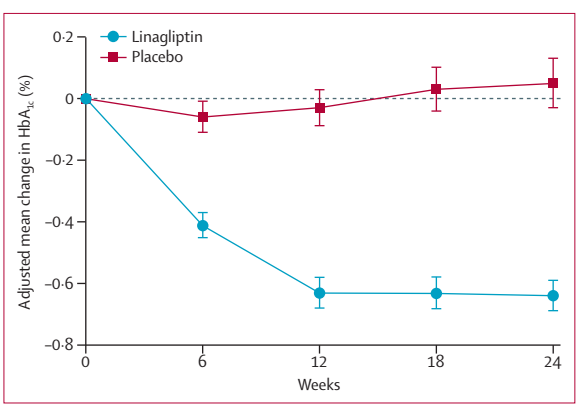

Figure 3: **Change from baseline in HbA_{1c} over 24 weeks in the full analysis set**
Adjusted mean changes in HbA_{1c}. Error bars are SE. Full analysis set consisted of all randomised patients who received at least one dose of study drug, and who had a baseline and at least one on-treatment HbA_{1c} measurement. Data are from a mixed model for repeated measurements, using observed cases with treatment, visit, previous use of insulin, and visit by treatment interaction as fixed classification effects, and baseline HbA_{1c} as a linear covariate. HbA_{1c}=glycated haemoglobin A_{1c}.

group; in those taking sulfonylureas, dosage changes occurred in four of 94 linagliptin patients (one increase, three decrease) and in seven of 43 placebo patients (six increase, one decrease).

Placebo-adjusted mean changes in HbA_{1c} with linagliptin were generally similar between subgroups of age, duration of diabetes, renal function, and concomitant therapy (table 2). Notably, efficacy was much the same across subgroups for disease duration, with a placebo-adjusted HbA_{1c} reduction of –0·73% in patients with diabetes for more than 10 years (table 2).

The proportion of patients reporting adverse events was the same in both treatment groups (75·9%) (table 3). Most events were mild or moderate in intensity with severe events reported for nine (5·6%) patients in the linagliptin group and three (3·8%) in the placebo group. 21·0% of patients in the linagliptin group and 13·9% of those in the placebo group had adverse events deemed to be related to study drug (table 3). No deaths occurred. Serious adverse events occurred in 14 (8·6%) patients in the linagliptin group and five (6·3%) patients in the placebo group; none were deemed related to study drug. Drug-related adverse events leading to discontinuation of study drug occurred in one patient in the linagliptin group (insomnia) and one patient in the placebo group (depressed mood). CEC-confirmed cardiovascular events occurred in no placebo patients and in two linagliptin patients (non-fatal ischaemic stroke, admission to hospital because of unstable angina), but were judged to be unrelated to study drug. Neoplasms occurred in one (0·6%) patient in the linagliptin group (melanocytic naevus) and three (3·8%) patients in the placebo group (lung adenocarcinoma, malignant melanoma, and prostate cancer), and were all judged to be unrelated to study drug. No cases of pancreatitis were recorded. There were no clinically relevant changes in bodyweight in patients with available data (mean change at week 24 of –0·2 kg [SD 2·3] with linagliptin [n=146] and –0·6 kg [2·2] with placebo [n=63]; data were not adjusted for background sulfonylureas or insulin, which were used by slightly more patients in the linagliptin group than in the placebo group). Nor were there clinically relevant changes in renal function (figure 4), laboratory variables, physical examination, ECGs, or vital signs, including heart rate and blood pressure (data not shown). Fewer of the patients not receiving a concomitant sulfonylurea had an adverse event with linagliptin (73%) than with placebo (83%), although slightly more patients in the linagliptin group reported drug-related, serious, severe, or treatment-ending events (table 4).

Investigator-defined hypoglycaemia occurred in 39 (24·1%) patients in the linagliptin group and 13 (16·5%) in the placebo group (figure 5; OR for linagliptin *vs* placebo 1·58, 95% CI 0·78–3·78, p=0·2083). Severe hypoglycaemia occurred in one patient, who was receiving linagliptin with metformin and sulfonylurea. The slightly higher overall incidence of hypoglycaemia with linagliptin, although not statistically significant, was mainly because of increased incidence in patients receiving sulfonylureas (30·5% linagliptin, 16·3% placebo); hypoglycaemia was much the same between groups in patients not receiving sulfonylureas (14·9% linagliptin, 16·7% placebo), and in those receiving metformin alone or insulin (figure 5).

Discussion

In this randomised clinical trial, linagliptin improved glycaemia and was well tolerated in elderly patients with type 2 diabetes with inadequate glycaemic control from other glucose-lowering drugs, a group generally excluded from clinical trials despite being a large and growing proportion of the population of patients with type 2 diabetes.

	Linagliptin (n=162)	Placebo (n=79)
Overall		
Any adverse event	123 (75·9%)	60 (75·9%)
Drug-related adverse event*	34 (21·0%)	11 (13·9%)
Serious adverse event†	14 (8·6%)	5 (6·3%)
Death	0	0
Needing admission to hospital	14 (8·6%)	4 (5·1%)
Other	0	2 (2·5%)
Individual serious adverse event		
Atrial fibrillation	1 (0·6%)	0
Atrioventricular block complete	1 (0·6%)	0
Bradycardia	1 (0·6%)	0
Cerebrovascular accident	1 (0·6%)	0
Coronary artery disease	1 (0·6%)	0
Dehydration	1 (0·6%)	0
Fall	2 (1·2%)	0
Limb traumatic amputation	1 (0·6%)	0
Lower limb fracture	1 (0·6%)	0
Lower respiratory tract infection	0	1 (1·3%)
Lung adenocarcinoma	0	1 (1·3%)
Malignant melanoma	0	1 (1·3%)
Pneumonia	3 (1·9%)	0
Presyncope	1 (0·6%)	0
Prostate cancer	0	1 (1·3%)
Rectal haemorrhage	1 (0·6%)	0
Thoracic vertebral fracture	1 (0·6%)	0
Urinary bladder polyp	0	1 (1·3%)
Vestibular neuronitis	1 (0·6%)	0
Adverse event leading to discontinuation	8 (4·9%)	1 (1·3%)
Severe adverse event‡	9 (5·6%)	3 (3·8%)
Significant adverse event§	4 (2·5%)	0
CEC-confirmed cardiovascular event	2 (1·2%)	0
Adverse events with an incidence ≥3·0% in either group¶		
Hypoglycaemia	37 (22·8%)	13 (16·5%)
Nasopharyngitis	17 (10·5%)	7 (8·9%)
Diarrhoea	9 (5·6%)	2 (2·5%)
Hyperglycaemia	9 (5·6%)	8 (10·1%)
Back pain	7 (4·3%)	0
Fall	7 (4·3%)	2 (2·5%)
Urinary tract infection	7 (4·3%)	5 (6·3%)
(Continues in next column)		

	Linagliptin (n=162)	Placebo (n=79)
(Continued from previous column)		
Dizziness	6 (3·7%)	4 (5·1%)
Headache	6 (3·7%)	3 (3·8%)
Upper respiratory tract infection	6 (3·7%)	5 (6·3%)
Arthralgia	5 (3·1%)	0
Pain in extremity	5 (3·1%)	2 (2·5%)
Vertigo	5 (3·1%)	0
Influenza	3 (1·9%)	3 (3·8%)
Fatigue	2 (1·2%)	3 (3·8%)
Lower respiratory tract infection	1 (0·6%)	3 (3·8%)
Musculoskeletal pain	1 (0·6%)	3 (3·8%)

Data are n (%). Treated set consisted of all patients who received at least one dose of study drug. CEC=clinical endpoint committee. *Judged to be related to study drug by the investigator. †14 patients in the linagliptin group had 17 serious adverse events (none judged related to study drug). Five patients in the placebo group had five serious adverse events (none judged related to study drug). ‡In the linagliptin group, one patient had two severe adverse events (fall, lower limb fracture), and eight patients had one severe adverse event (atrial fibrillation, atrioventricular block complete, chest pain, pneumonia, back pain, cerebrovascular accident, dizziness, urinary retention). Three patients in the placebo group had one severe adverse event each (lower respiratory tract infection, lung adenocarcinoma, urinary bladder polyp). §Hypersensitivity reaction, renal adverse event, hepatic adverse event. ¶Preferred terms from the Medical Dictionary for Regulatory Activities (version 14.1).

Table 3: **Summary of adverse events during 24 weeks in the treated set of patients**

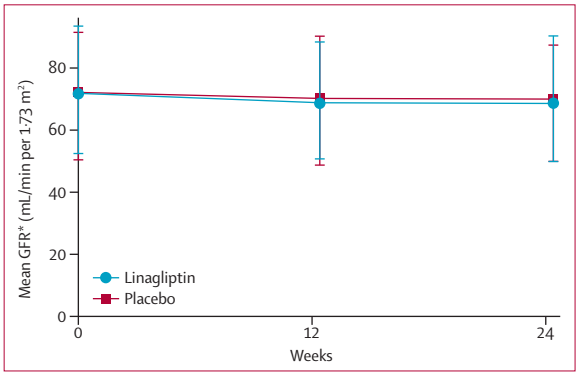

Figure 4: **Renal function over 24 weeks in the treated set of patients**
Treated set consisted of all patients who received at least one dose of study drug. Data are from observed cases, including those from patients who received glycaemic rescue drugs. Error bars are SD. GFR=glomerular filtration rate. *GFR was estimated by the Modification of Diet in Renal Disease equation.

There was a high prevalence of long-standing diabetes (>10 years in more than half the patients) and comorbidities—particularly cardiovascular disease (87%) and renal impairment (79%)—and a generally high use of concomitant drugs. The mean Charlson age-comorbidity score of more than 5 suggests a high-risk population.[18] These characteristics are typical of elderly patients with type 2 diabetes who are encountered in clinical practice and show why safety is a key consideration for glucose-lowering treatment.[10] Linagliptin was well tolerated with no new safety signals compared with previous phase 3 trials in younger patients.[13–17] More than 75% of patients in the linagliptin group did not have an episode of hypoglycaemia. Although hypoglycaemia was reported by more linagliptin (24·1%) than placebo patients (16·5%), this difference seems to be because more linagliptin than placebo patients received sulfonylureas; in patients not receiving sulfonylureas, hypoglycaemia was not increased with linagliptin (14·9%, placebo 16·7%), consistent with previous studies.[13–16] Hypoglycaemia in elderly patients is of particular concern because it is more common

	Linagliptin (n=67)	Placebo (n=36)
Overall		
Any adverse event	49 (73·1%)	30 (83·3%)
Drug-related adverse event*	11 (16·4%)	5 (13·9%)
Serious adverse event	5 (7·5%)	2 (5·6%)
Death	0	0
Needing admission to hospital	5 (7·5%)	1 (2·8%)
Other	0	1 (2·8%)
Adverse event leading to discontinuation	4 (6·0%)	1 (2·8%)
Severe adverse event	3 (4·5%)	1 (2·8%)
Significant adverse event†	2 (3·0%)	0
CEC-confirmed cardiovascular event	1 (1·5%)	0
Adverse events with an incidence ≥3·0% in either group‡		
Hypoglycaemia	8 (11·9%)	6 (16·7%)
Nasopharyngitis	7 (10·4%)	4 (11·1%)
Upper respiratory tract infection	4 (6·0%)	2 (5·6%)
Vertigo	4 (6·0%)	0
Cystitis	3 (4·5%)	0
Fall	3 (4·5%)	1 (2·8%)
Gastroenteritis	3 (4·5%)	0
Peripheral oedema	3 (4·5%)	0
Rhinorrhoea	3 (4·5%)	0
Urinary tract infection	3 (4·5%)	2 (5·6%)
Headache	2 (3·0%)	1 (2·8%)
Dry mouth	1 (1·5%)	2 (5·6%)
Hyperglycaemia	1 (1·5%)	2 (5·6%)
Lower respiratory tract infection	0	2 (5·6%)
Fatigue	0	2 (5·6%)

Data are n (%). Treated set consisted of all patients who received at least one dose of study drug. CEC=clinical endpoint committee. *Deemed to be related to study drug by the investigator. †Hypersensitivity reaction, renal adverse event, hepatic adverse event. ‡Preferred terms from the Medical Dictionary for Regulatory Activities (version 14.1).

Table 4: **Summary of adverse events during 24 weeks in the treated set of patients not receiving concomitant sulfonylurea treatment**

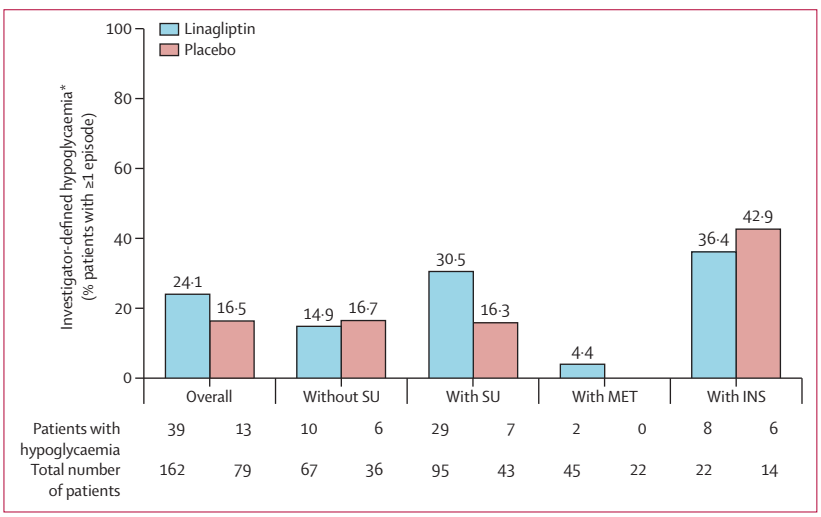

Figure 5: **Hypoglycaemia in the treated set of patients**
Treated set consisted of all patients who received at least one dose of study drug. INS=insulin (with or without metformin). MET=metformin only. SU=sulfonylurea (with or without other antidiabetes drugs). *Confirmed plasma glucose concentration of 3·9 mmol/L or less, or symptoms attributed to hypoglycaemia, or both.

than in younger patients because of age-related impairment of the counter-regulatory response to low plasma glucose and of symptom awareness. Furthermore, hypoglycaemia in elderly individuals frequently has severe consequences (falls, fractures, admissions to hospital, and possibly an increased risk for cardiovascular events and mortality).[10,19] Elderly populations have a high prevalence of renal impairment, which itself increases the risk of hypoglycaemia,[10] particularly when patients are receiving sulfonylureas.[20] About 80% of cases of sulfonylurea-induced severe hypoglycaemia occur in elderly patients.[21,22] Position statements by expert groups of diabetologists and gerontologists underscore the growing awareness that hypoglycaemia in the elderly is highly prevalent, under-recognised, and has severe consequences.[4,7]

Despite the possible risks of glucose-lowering treatment, the potential for hyperglycaemic crises and vascular complications in elderly patients means that undertreatment also has risks.[4] Although there is a scarcity of data for glucose-lowering treatment in elderly patients, it is thought to be beneficial because of improved clinical outcomes identified in younger patients with type 2 diabetes,[23,24] possible improvements in cognitive function,[6] and the benefit of modification of other cardiometabolic risk factors in elderly individuals (dyslipidaemia, hypertension).[4,10] In the present study, linagliptin treatment was associated with a clinically meaningful improvement in glycaemic control on average (placebo-corrected change in HbA_{1c} of –0·64% from a baseline of 7·8%) and in most individuals (HbA_{1c} reduction of ≥0·5%). The efficacy of linagliptin was unaffected by age, renal impairment, or diabetes duration—an important finding in view of the advanced disease and many comorbidities prevalent in both the study population and clinical practice. More patients in the linagliptin than in the placebo group achieved HbA_{1c} in the ranges recommended by European clinical guidelines[8] for elderly patients with type 2 diabetes (7–7·5% for those without major comorbidities; 7·6–8·5% for frail individuals). The notable efficacy identified in patients with diabetes for more than 10 years might be indicative of suppression of inappropriate glucagon secretion, which could be an important aspect of DPP4 inhibition in this age group. Consistent efficacy irrespective of diabetes duration has been previously identified with linagliptin and other DPP4 inhibitors,[25–28] although not in elderly patients with such long-standing disease.

This study was done in a clinically relevant population of patients with type 2 diabetes (aged ≥70 years) with long-standing disease inadequately controlled by common glucose-lowering drugs, including basal insulin (panel). Few drugs from other classes have been rigorously investigated in elderly patients,[4,9] but many have noteworthy limitations for elderly patients: for example, metformin, the usual first-line drug, is contraindicated for some degrees of renal impairment and

can cause intolerable gastrointestinal side-effects; sulfonylureas are associated with hypoglycaemia and weight gain; pioglitazone can cause fluid retention, fractures, and weight gain, and has risk for congestive heart failure and possibly bladder cancer; and injectables (insulin and GLP1 receptor agonists) might not be convenient for elderly individuals. The higher direct cost of DPP4 inhibitors compared with generic oral drugs is an issue, but this difference could be balanced or even outweighed by reduced indirect costs—eg, lower rates of admissions to hospital for hypoglycaemia.[33,34] Health-related quality of life is an important consideration for treatment of elderly patients, and data collected with the SF-36 and EQ-5D standardised instruments in the present study are under analysis.

This study has certain strengths and limitations. Like most randomised trials, the robust design confers high internal validity for comparison of the study drugs. Equally importantly, the patients' age and characteristics render the results highly relevant to clinical practice, although most participants were white. Clinical trials are frequently done in younger and healthier patients than are encountered in clinical practice;[2] although this is usually done for safety or logistical reasons (difficulty enrolling patients who are elderly or have comorbidities), it limits their external validity. The paucity of data on glucose-lowering in elderly patients—either from studies of glycaemic efficacy and tolerability or clinical-outcome studies—poses a challenge for clinical practitioners because many of the patients with type 2 diabetes who they encounter will be elderly.[4,10] A consensus report[4] on diabetes in elderly people recommended that clinical studies broaden inclusion criteria to address this evidence gap. This trial, like most of glucose-lowering drugs, was short (24 weeks) and consequently did not assess long-term clinical outcomes. However, the CAROLINA cardiovascular outcomes study of linagliptin[32] is enrolling patients up to 80 years old; a predefined requirement for enrolment is high risk for cardiovascular events, for which age 70 years or older is sufficient to qualify. Other limitations include possible under-representation of patients with cognitive impairment (although they were not specifically excluded), absence of frailty assessment, and use of an inert control (placebo) rather than an active comparator. Of relevance to the last point, further analysis of a 2 year comparative study in patients inadequately controlled by metformin—about a third of whom were older than 65 years[17]—showed that significantly more linagliptin (54%) than glimepiride patients (23%) achieved a composite endpoint of HbA_{1c} of less than 7·0% without hypoglycaemia or weight gain.[35]

In conclusion, the present study showed that linagliptin added to existing glucose-lowering drugs was well tolerated, weight neutral, and improved glycaemic control in patients with type 2 diabetes aged 70 years or older with characteristics typical of those encountered in clinical practice (eg, long-standing diabetes, renal impairment, use of combination therapies, including basal insulin). Hypoglycaemia was increased only with concomitant sulfonylureas, providing further evidence that sulfonylureas should be used with caution in elderly patients. Linagliptin might be a useful glucose-lowering drug for elderly patients with type 2 diabetes, a prevalent population for which other treatment options are understudied and have important limitations.

Panel: Research in context

Systematic review

We searched PubMed and ISI Web of Science for papers published before June 3, 2013, reporting randomised, double-blind clinical trials of dipeptidyl peptidase-4 (DPP4) inhibitors done exclusively in elderly patients with type 2 diabetes, using the terms "type 2 diabetes", "dipeptidyl peptidase-4", "elderly", and various synonyms. We identified three manuscripts reporting studies in patients aged 65 years or older in which monotherapy with sitagliptin,[26] vildagliptin,[29] or alogliptin[30] elicited reductions in glycated haemoglobin A_{1c} (HbA_{1c}) in patients not receiving other glucose-lowering drugs. Whereas sitagliptin was tested versus placebo, metformin was the comparator in the vildagliptin study and had much the same glycaemic efficacy and tolerability. In the alogliptin study, the sulfonylurea comparator, glipizide, was associated with substantially more hypoglycaemia (5% *vs* 26% of patients).[30] Additionally, in another vildagliptin study that enrolled elderly patients who were treatment-naive or receiving oral glucose-lowering drugs, more vildagliptin than placebo patients achieved individualised glycaemic targets set by the study investigators, most of whom had a target HbA_{1c} of less than 7·0%,[31] the lowest level recommended for elderly patients.[7] By contrast with the vildagliptin study, the present linagliptin study had a more vulnerable patient population (including those receiving insulin and those with severe renal impairment) with high use of polypharmacy, used a conventional definition of hypoglycaemia (blood glucose <3·9 mmol/L compared with <3·1 mmol/L), and provided data showing efficacy irrespective of diabetes duration.[31] We additionally searched ClinicalTrials.gov and identified completed studies in elderly patients of sitagliptin (NCT01189890) and saxagliptin (NCT01006603), for which results are not yet published.

Interpretation

Clinical decision making for glucose-lowering treatment in elderly patients with type 2 diabetes is challenging because of their comorbidities, potential frailty, and use of polypharmacy, as well as the scarcity of data from clinical trials to guide treatment selection. The importance of balancing efficacy with safety might unfavourably shift the risk–benefit profile of many glucose-lowering drugs in elderly individuals, particularly those that carry a substantial risk for hypoglycaemia, such as sulfonylureas, or have restrictions for renal impairment. Oral DPP4 inhibitors improve glycaemia in elderly patients with minimal risk for hypoglycaemia or other side-effects. The previous studies assessed DPP4 inhibitors as monotherapy, an uncommon treatment regimen in elderly patients, or in those not receiving insulin; by contrast, linagliptin showed these effects in patients whose glycaemia was not controlled by up to three other glucose-lowering drugs, including basal insulin. The present linagliptin study, therefore, closely represents a real-world situation, particularly in view of the patients' age (mean 75 years), polypharmacy burden, and clinical characteristics, since most had long-standing diabetes and comorbidities such as cardiovascular disease or renal impairment. Further efforts are needed to address the evidence gap in glucose-lowering treatment for elderly patients, including clinical-outcome studies to establish whether glycaemic efficacy and tolerability translate into reduced morbidity; the CAROLINA cardiovascular outcomes study of linagliptin will provide useful information in this regard.[32]

Contributors

AHB participated in design of the study, collection and interpretation of data, and drafting and revision of the manuscript. HH participated in design of the study, interpretation of data, and drafting and revision of the manuscript. RJ participated in design of the study, performed the statistical analysis, and participated in interpretation of data and drafting and revision of the manuscript. MvE participated in design of the study, interpretation of data, and drafting and revision of the manuscript. SP participated in design of the study, interpretation of data, and drafting and revision of the manuscript. H-JW participated in design of the study, interpretation of data, and drafting and revision of the manuscript. All authors have approved the final version of the manuscript.

Conflicts of interest

AHB has received honoraria for lectures and advisory work from Boehringer Ingelheim (the manufacturer of linagliptin), MSD, Novartis, Bristol-Myers Squibb/AstraZeneca, Takeda, Eli Lilly, Novo Nordisk and Sanofi-Aventis. HH, RJ, MvE, SP, and H-JW are employees of Boehringer Ingelheim.

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