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Cardiovascular outcomes and safety with linagliptin, a dipeptidyl peptidase-4 inhibitor, compared with the sulphonylurea glimepiride in older people with type 2 diabetes: A subgroup analysis of the randomized CAROLINA trial

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Abstract

Aim: To compare the cardiovascular (CV) safety of linagliptin with glimepiride in older and younger participants in the CAROLINA trial in both prespecified and post hoc analyses.

Materials and Methods: People aged 40 to 85 years with relatively early type 2 diabetes, inadequate glycaemic control and elevated CV risk were randomly assigned to linagliptin 5 mg or glimepiride 1 to 4 mg. The primary endpoint was time to first occurrence of three-point major adverse CV events (MACE: CV death, non-fatal myocardial infarction, or non-fatal stroke). We evaluated clinical and safety outcomes across age groups.

Results: Of 6033 participants, 50.7% were aged <65 years, 35.3% were aged 65 to 74 years, and 14.0% were aged ≥75 years. During the 6.3-year median follow-up, CV/mortality outcomes did not differ between linagliptin and glimepiride overall (hazard ratio [HR] for three-point MACE 0.98, 95.47% confidence interval [CI] 0.84, 1.14) or across age groups (interaction P >0.05). Between treatment groups, reductions in glycated haemoglobin were comparable across age groups but moderate-to-severe hypoglycaemia was markedly reduced with linagliptin (HR 0.18, 95% CI 0.15, 0.21) with no differences among age groups (P = 0.23). Mean weight was −1.54 kg (95% CI −1.80, −1.28) lower for linagliptin versus glimepiride. Adverse events increased with age, but were generally balanced between treatment groups. Significantly fewer falls or fractures occurred with linagliptin.

Conclusions: Linagliptin and glimepiride were comparable for CV/mortality outcomes across age groups. Linagliptin had significantly lower risk of hypoglycaemia and falls or fractures than glimepiride, including in "older-old" individuals for whom these are particularly important treatment considerations.

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KEYWORDS
cardiovascular disease, clinical trial, DPP-4 inhibitor, hypoglycaemia, linagliptin, sulphonylureas

1 | INTRODUCTION

The prevalence of diabetes increases with age and approximately 27% of people aged over 65 years in the United States are estimated to have this disease, most of whom have type 2 diabetes.[1] Despite this, clinical trials of glucose-lowering drugs in people with type 2 diabetes have generally underrepresented older individuals, particularly those aged over 75 years.[2,3] This is problematic as it can be challenging to treat older patients because of their high prevalence of comorbidities (particularly chronic kidney disease), frailty and polypharmacy.[2,4] Safety is a prime consideration, particularly the avoidance of iatrogenic hypoglycaemia, which occurs more frequently in elderly patients, often with severe consequences such as cognitive impairment, falls, fractures and traffic accidents.[4,5]

As cardiovascular (CV) risk increases with age, the CV safety of glucose-lowering drugs in the elderly is also a key concern. Yet few of the CV outcomes trials (CVOTs) over the past decade have reported detailed analyses of CV safety in the elderly, and none had an active comparator design in relatively early type 2 diabetes. The short-term glycaemic efficacy and tolerability of linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, was established in dedicated randomized clinical trials in older individuals,[6–8] while its long-term CV safety in the elderly was demonstrated in a subgroup analysis[9] of a placebo-controlled CVOT (CARMELINA).[10] The active-controlled CAROLINA CVOT was designed to compare linagliptin with glimepiride, a widely used, second-generation sulphonylurea (SU), with respect to CV safety, and thus to also help resolve the 50-year lingering controversy surrounding the CV safety of SUs.[11,12] The overall findings removed the CV concerns with glimepiride, as indicated by linagliptin demonstrating noninferiority to glimepiride for risk of three-point major adverse CV events (MACE: CV death, nonfatal myocardial infarction, or nonfatal stroke), but also showed benefit of linagliptin for substantially reduced risk of hypoglycaemia and lower mean body weight compared to glimepiride.[13]

Type 2 diabetes patients aged up to 85 years were eligible to participate in CAROLINA. Here, we report an investigation of CV safety and other outcomes by age group in a number of prespecified or post hoc analyses.

2 | MATERIALS AND METHODS

2.1 | CAROLINA study design

The design and overall findings of the CAROLINA trial have been reported previously.[11,13] CAROLINA was a multinational, randomized CVOT of linagliptin versus glimepiride in people aged 40 to 85 years with relatively early type 2 diabetes, insufficient glycaemic control, and elevated CV risk. CAROLINA ran from November 2010 to August 2018 in 43 countries, including the United States (ClinicalTrials.gov identifier: NCT01243424).

Elevated CV risk was defined as ≥1 of the following characteristics: age ≥70 years; previous vascular disease; ≥2 CV risk factors (diabetes duration >10 years, systolic blood pressure >140 mmHg or ≥1 antihypertensive drug, current smoker, low-density lipoprotein (LDL cholesterol 3.5 mmol/L); and/or microvascular complications (estimated glomerular filtration rate [eGFR] 30–59 mL/min/1.73 m^2, urinary albumin-to-creatinine ratio [UACR] ≥30 μg/mg, or proliferative retinopathy). Full inclusion and exclusion criteria were previously reported.[13] Insufficient glycaemic control was defined as glycated haemoglobin (HbA1c) 48 to 69 mmol/mol (6.5%–8.5%) if treatment-naïve or treated with metformin and/or an alpha-glucosidase inhibitor. However, patients receiving an SU or meglitinide (glinide) alone or combined with metformin or an alpha-glucosidase inhibitor had to have an HbA1c level of 48 to 58 mmol/mol (6.5–7.5%; those receiving dual therapy had to have been diagnosed with type 2 diabetes ≤5 years previously). Current or past use of DPP-4 inhibitors, glucagon-like peptide-1 receptor agonists, thiazolidinediones, or insulin were exclusion criteria.

Participants were randomly assigned, with equal probabilities, to receive oral once-daily treatment with linagliptin 5 mg or glimepiride 1 to 4 mg, with treatment allocation masked. SUs and meglitinides were discontinued at the randomization visit. Individuals naive to glimepiride were initiated at 1 mg and uptitrated every 4 weeks to a maximal dose of 4 mg, while those previously taking glimepiride started on their pretrial dose. During follow-up, investigators were encouraged to use additional glucose-lowering drugs (glycaemic rescue therapy) when glycaemic control was considered insufficient, and to manage other CV risk factors according to applicable local guidelines and standards of care. Doses could be reduced for hypoglycaemia or other medical reasons.

The primary endpoint was time to first occurrence of three-point MACE. A key secondary endpoint was time to first occurrence of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina (four-point MACE). Additional key secondary endpoints were two composite outcomes of "treatment sustainability": (1) the proportion of participants who were receiving treatment and maintaining HbA1c ≤7.0% = 53 mmol/mol at the final visit and had not had glycaemic rescue medication, any episodes of moderate or severe hypoglycaemia, or >2% weight gain between end of titration (week 16) and final visit; and (2) the proportion of participants who were receiving treatment and maintaining HbA1c ≤7.0% at the final

visit and had not had rescue medication or >2% weight gain between end of titration and final visit. Additional secondary or tertiary endpoints were the individual components of three-point MACE and four-point MACE, other CV events, non-CV mortality and all-cause mortality. CV outcomes, deaths and cases of pancreatitis or pancreatic cancer were centrally adjudicated by committees masked to treatment assignment. Hypoglycaemia endpoints included: any episodes of hypoglycaemia reported as adverse events by investigators; moderate hypoglycaemia, defined as investigator-reported episodes of symptomatic hypoglycaemia with plasma glucose ≤70 mg/dL = 3.9 mmol/L; and severe hypoglycaemia, defined as episodes requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Other adverse events, including falls and fractures, were classified using the Medical Dictionary for Regulatory Activities Version 21.0.

CAROLINA was designed to continue until an adjudication-confirmed three-point MACE event had occurred in ≥631 participants. Without adjustment for interim analyses, assuming a hazard ratio (HR) of 1.0, this provided 90.9% power to demonstrate noninferiority of linagliptin versus glimepiride with the prespecified noninferiority margin of 1.3 at a one-sided alpha level of 2.5%. If noninferiority was demonstrated, superiority was to be tested based on 80% power, assuming an HR of 0.80.

2.2 | Subgroup analyses by age

Analyses by age group were prespecified and further defined post hoc (Table S1). Prespecified analyses included three-point MACE, four-point MACE and the two key secondary endpoints of treatment sustainability by age groups <65/≥65 years and <70/≥70 years at baseline, and adverse events for age groups <65 years, 65 to <75 years and ≥75 years, and <70 years, 70 to <80 years and ≥80 years. To enhance clinical relevance, further post hoc analyses of the primary, secondary and tertiary endpoints were also performed for subgroups aged <65 years, 65 to <75 years and ≥75 years (the latter including those aged 75 to <80 years and ≥80 years).

Clinical outcomes and hypoglycaemia in the treatment groups were compared using Cox proportional hazards models with terms for treatment, age subgroup, and treatment-by-age subgroup interaction for all randomized participants treated with ≥1 dose of study drug (the treated set). In addition, Kaplan–Meier estimates were calculated. Participants were censored at the day last known to be free of the specific outcome. Because of declining numbers of participants at risk, Kaplan–Meier curves were truncated at 6.5 years after randomization.

Changes from baseline in HbA1c and body weight were evaluated using mixed models for repeated measures that included terms for baseline value-by-week interaction and treatment-by-week interaction for overall analyses and baseline value-by-week interaction and baseline age group-by-treatment-by-week interaction for subgroup analyses, for participants who received ≥1 dose of a study drug and had a baseline and ≥1 postbaseline measurement. The key secondary endpoints of treatment sustainability were analysed using logistic regression models including factors for treatment, age subgroup, and treatment-by-age subgroup interaction.

Adverse events were summarized descriptively for the treated set; all events (including hypoglycaemia) that occurred between first intake of study drug and 7 days after last intake were included, except for pancreatitis and cancer, for which all events until study end were included. Assessment of hospitalizations included any adverse events leading to or prolonging hospitalization from first study drug intake until study end. Time to first falls and bone fractures and their composite with linagliptin versus glimepiride were compared post hoc using Cox proportional hazards models with a term for treatment for the overall cohort and additional terms for subgroup and subgroup-by-treatment interaction for analyses of age subgroups. The potential association of moderate or severe hypoglycaemia with subsequent falls or bone fractures was explored post hoc using a Cox model with terms for treatment, baseline age, gender, baseline eGFR, smoking status, osteoporosis/osteopenia at baseline, bone fractures at baseline, postmenopausal hormone therapy at baseline, and time-dependent hypoglycaemia event for the overall trial cohort, with an additional term for treatment-by-time-dependent-hypoglycaemia-event interaction for the investigation within treatments.

A 95.47% confidence interval (CI) is reported for the primary endpoint, accounting for two interim analyses and change of the primary endpoint (originally four-point MACE).[13] All subgroup analyses were considered exploratory, with no statistical adjustment for multiple comparisons; statistical significance was concluded based on an alpha level of 5%.

3 | RESULTS

3.1 | Baseline characteristics

The trial cohort comprised 6033 individuals aged 36 to 85 years at baseline (mean 64.0 years), including participants aged 65 to <75 years (n = 2129 [35.3%]), ≥75 years (n = 846 [14.0%]) and ≥80 years (n = 197 [3.3%]). Overall, 42% had established atherosclerotic CV disease, with a slightly greater prevalence in the older age groups (∼44%) compared to those aged <65 years (∼40%). Mean HbA1c was 54.0–55.3 mmol/mol (7.1–7.2%) in all age groups. In contrast, diabetes duration, proportion of non-smokers and prevalence of microvascular complications were greater among older individuals, while body mass index and metformin use were lower. Other baseline characteristics were similar across age categories and between treatment groups (Table S2).

3.2 | Clinical outcomes

The overall median observation time and treatment duration were 6.3 and 5.9 years, respectively, in both the linagliptin and the glimepiride group.[13] Median observation times across age groups were very

similar, while median treatment time declined slightly with age (6.1, 5.8 and 5.5 years in participants aged <65 years, 65 to <75 years and ≥75 years, respectively) (Table S3).

In general, the incidence of all CV and mortality outcomes was greater among older participants in both treatment groups (Figures 1 and 2, Figures S1–S4). For the primary endpoint (three-point MACE), the overall HR for time to first event for linagliptin compared with glimepiride was 0.98 (95.47% CI 0.84, 1.14),[13] with no significant interaction between age groups <65 years, 65 to <75 years and ≥75 years and treatment effect (P = 0.39). Across these age groups, the HRs for three-point MACE for linagliptin compared with glimepiride were 1.11 (95% CI 0.88, 1.41) for participants aged <65 years, 0.88 (95% CI 0.69, 1.12) for those aged 65 to <75 years, and 0.99 (95% CI 0.74, 1.31) for those aged ≥75 years (Figures 1 and 2). Similarly, linagliptin was comparable to glimepiride consistently across age groups for four-point MACE, all-cause mortality, CV death, non-CV death, hospitalization for heart failure or CV death, and other secondary and tertiary CV endpoints (Figure 2). Kaplan–Meier curves of time to all-cause mortality, CV death and non-CV death are shown in Figures S1–S3.

Results were similar in a more granular analysis of participants aged ≥75 years subcategorized into ages 75 to <80 years and ≥80 years (Figure S4).

3.3 | Metabolic outcomes and hypoglycaemia

The mean ± SD daily dose of glimepiride in the overall study cohort was 2.9 ± 1.1 mg.[13] The mean daily dose was slightly higher in participants aged <65 years (3.0 ± 1.1) than those aged 65 to <75 or ≥75 years (2.7 ± 1.2 in both groups). By the end of the initial 16-week titration period, the highest dose (4 mg) was being taken by 53.5%, 46.1% and 41.8% of participants aged <65, 65 to <75 years, and ≥75 years, respectively. At week 256, 67.8%, 53.5% and 55.6% of participants, respectively, were using the highest dose.

Mean HbA1c initially decreased more with glimepiride than linagliptin in all age groups (Figure S5). Over the whole trial, however, there was no significant difference between treatment groups, with weighted average mean differences over 256 weeks of −0.01% (95% CI −0.09, 0.06), 0.01% (95% CI −0.06, 0.08) and 0.04% (95% CI −0.08, 0.15) in participants aged <65 years, 65 to <75 years and ≥75 years, respectively. These results were consistent with those in the overall trial cohort.[13]

New glucose-lowering agents were initiated by more participants aged <65 years than those aged 65 to <75 years or ≥75 years, but within each age group similar proportions of the linagliptin and glimepiride groups initiated such medications (Table S4).

In all age groups, a treatment difference in mean body weight was observed over the trial, with weighted average mean differences over 256 weeks with linagliptin versus glimepiride of −1.5 kg (95% CI −1.9, −1.1), −1.6 kg (95% CI −2.0, −1.2) and −1.6 kg (95% CI −2.2, −0.9) in participants aged <65 years, 65 to <75 years and ≥75 years respectively (Figure S6). These results were consistent with those in the overall trial cohort (−1.5 kg [95% CI −1.8, −1.3]).[13]

Across all age groups, substantially fewer participants in the linagliptin group experienced any investigator-reported hypoglycaemia adverse events, moderate or severe hypoglycaemia, or severe hypoglycaemia, compared with the glimepiride group (Table 1). The risk for moderate or severe hypoglycaemia in the overall study cohort was substantially lower with linagliptin than glimepiride (HR 0.18 [95% CI 0.15, 0.21]) with no evidence of heterogeneity across age groups (P = 0.23 for treatment-by-age-group interaction; Figure 3).

3.4 | Achievement of HbA1c ≤7.0% = 53 mmol/mol without glycaemic rescue, hypoglycaemia or weight gain

At the final visit, 16.0% of the linagliptin group and 10.2% of the glimepiride group were on study drug with HbA1c ≤7.0%, without having had glycaemic rescue medication or any episodes of moderate or severe hypoglycaemia or >2% weight gain between end of titration and final visit (odds ratio 1.68 [95% CI 1.44, 1.96]).[13] Furthermore, 17.4% of the linagliptin group and 14.1% of the glimepiride group were on study drug with HbA1c ≤7.0% at the final visit without rescue medication or >2% weight gain between end of titration and final visit (odds ratio 1.29 [95% CI 1.12, 1.48]). The significantly greater occurrence of these composite endpoints with linagliptin compared to glimepiride was consistent across age groups, with no evidence of heterogeneity (all P values for interaction >0.05; Figure S7).

3.5 | Adverse events

The percentage of participants with any adverse event was greater with older age (Table 1), regardless of treatment assignment. Compared with the glimepiride group, a similar proportion of the linagliptin group within each age category reported adverse events overall, as well as serious adverse events or those leading to discontinuation of study drug. Fewer participants in the linagliptin group were hospitalized compared with the glimepiride group among individuals aged 65 to <75 years or ≥75 years. Pancreatitis was rare and balanced between the linagliptin and glimepiride groups within each age category (Table 1), as was pancreatic cancer. Overall, five cases of bullous pemphigoid occurred, all in participants receiving linagliptin. Incidence rates for adverse events showed these same general trends (Table S5).

Among those aged ≥75 years, falls occurred in notably fewer participants receiving linagliptin than glimepiride (Table 1). The incidence rates for falls per 100 patient-years in this age group were 2.30 with linagliptin and 4.12 with glimepiride, compared to 0.74 (linagliptin) and 0.75 (glimepiride) in those aged <65 years, and 1.56 with both linagliptin and glimepiride in those aged 65 to <75 years (Table S5). The imbalance was even greater in the oldest-old, that is those aged

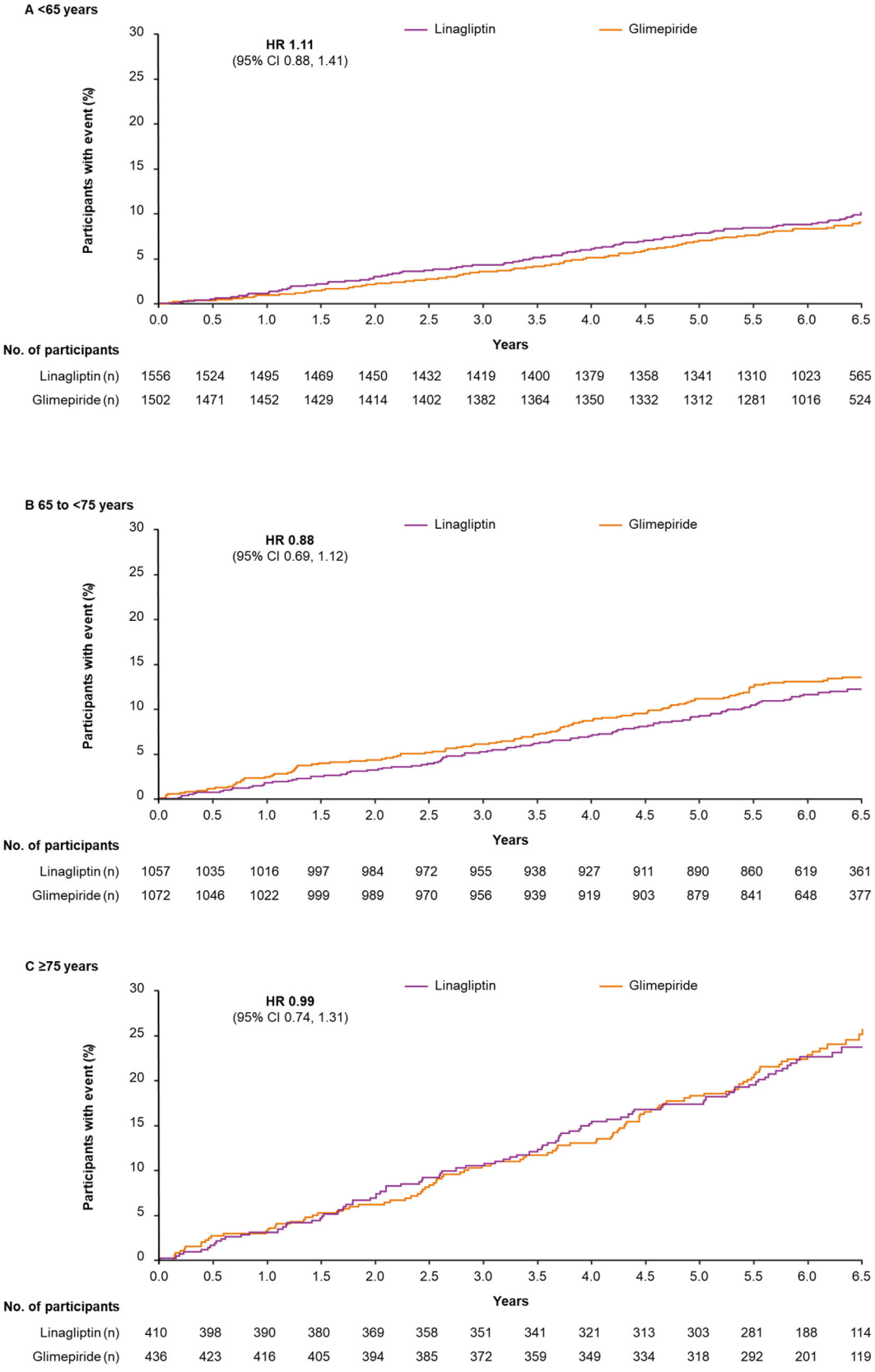


FIGURE 1 Time to first occurrence of three-point major adverse cardiovascular (CV) events (CV death, non-fatal myocardial infarction, or non-fatal stroke). CI, confidence interval; HR, hazard ratio

	Linagliptin		Glimepiride		Hazard ratio (95% CI)	Hazard ratio (95% CI)	*P*-value for treatment-by-age-group interaction
	n with event / N analyzed (%)	Rate per 100 patient-years	n with event / N analyzed (%)	Rate per 100 patient-years			
Three-point MACE	**356/3023 (11.8)**	**2.07**	362/3010 (12.0)	**2.12**	**0.98 (0.84, 1.14)***		0.3949
<65 years	144/1556 (9.3)	1.60	126/1502 (8.4)	1.44	1.11 (0.88, 1.41)		
65 to <75 years	121/1057 (11.4)	2.01	138/1072 (12.9)	2.28	0.88 (0.69, 1.12)		
≥75 years	91/410 (22.2)	4.20	98/436 (22.5)	4.26	0.99 (0.74, 1.31)		
Four-point MACE	**398/3023 (13.2)**	**2.34**	**401/3010 (13.3)**	**2.37**	**0.99 (0.86, 1.14)***		0.4580
<65 years	167/1556 (10.7)	1.87	148/1502 (9.9)	1.71	1.10 (0.88, 1.37)		
65 to <75 years	137/1057 (13.0)	2.30	153/1072 (14.3)	2.56	0.90 (0.71, 1.13)		
≥75 years	94/410 (22.9)	4.39	100/436 (22.9)	4.36	1.01 (0.76, 1.34)		
All-cause mortality	**308/3023 (10.2)**	**1.68**	**336/3010 (11.2)**	**1.84**	**0.91 (0.78, 1.06)**		0.5400
<65 years	92/1556 (5.9)	0.96	84/1502 (5.6)	0.90	1.06 (0.79, 1.42)		
65 to <75 years	118/1057 (11.2)	1.85	130/1072 (12.1)	2.01	0.92 (0.71, 1.18)		
≥75 years	98/410 (23.9)	4.20	122/436 (28.0)	4.94	0.85 (0.65, 1.10)		
CV death	**169/3023 (5.6)**	**0.92**	**168/3010 (5.6)**	**0.92**	**1.00 (0.81, 1.24)**		0.7045
<65 years	57/1556 (3.7)	0.59	50/1502 (3.3)	0.54	1.10 (0.75, 1.61)		
65 to <75 years	64/1057 (6.1)	1.00	61/1072 (5.7)	0.95	1.06 (0.75, 1.50)		
≥75 years	48/410 (11.7)	2.06	57/436 (13.1)	2.31	0.89 (0.60, 1.30)		
Non-CV death	**139/3023 (4.6)**	**0.76**	**168/3010 (5.6)**	**0.92**	**0.82 (0.66, 1.03)**		0.7260
<65 years	35/1556 (2.2)	0.36	34/1502 (2.3)	0.37	0.99 (0.62, 1.59)		
65 to <75 years	54/1057 (5.1)	0.85	69/1072 (6.4)	1.07	0.79 (0.55, 1.13)		
≥75 years	50/410 (12.2)	2.14	65/436 (14.9)	2.63	0.81 (0.56, 1.17)		
Fatal or non-fatal myocardial infarction	**153/3023 (5.1)**	**0.88**	**148/3010 (4.9)**	**0.86**	**1.03 (0.82, 1.29)**		0.4203
<65 years	68/1556 (4.4)	0.75	63/1502 (4.2)	0.71	1.05 (0.74, 1.48)		
65 to <75 years	51/1057 (4.8)	0.84	58/1072 (5.4)	0.95	0.88 (0.60, 1.28)		
≥75 years	34/410 (8.4)	1.54	27/436 (6.2)	1.15	1.34 (0.81, 2.22)		
Fatal or non-fatal stroke	**104/3023 (3.4)**	**0.59**	**120/3010 (4.0)**	**0.69**	**0.86 (0.66, 1.12)**		0.2231
<65 years	43/1556 (2.8)	0.47	37/1502 (2.5)	0.42	1.13 (0.73, 1.75)		
65 to <75 years	31/1057 (2.9)	0.51	48/1072 (4.5)	0.78	0.65 (0.41, 1.02)		
≥75 years	30/410 (7.3)	1.35	35/436 (8.0)	1.49	0.91 (0.56, 1.48)		
Transient ischaemic attack	**25/3023 (0.8)**	**0.14**	**33/3010 (1.1)**	**0.19**	**0.75 (0.45, 1.26)**		0.7613
<65 years	10/1556 (0.6)	0.11	10/1502 (0.7)	0.11	0.97 (0.40, 2.33)		
65 to <75 years	10/1057 (0.9)	0.16	14/1072 (1.3)	0.23	0.72 (0.32, 1.61)		
≥75 years	5/410 (1.2)	0.22	9/436 (2.1)	0.38	0.58 (0.20, 1.74)		
Hospitalization for unstable angina	**60/3023 (2.0)**	**0.34**	**56/3010 (1.9)**	**0.32**	**1.07 (0.74, 1.54)**		0.9614
<65 years	32/1556 (2.1)	0.35	30/1502 (2.0)	0.34	1.04 (0.63, 1.70)		
65 to <75 years	22/1057 (2.1)	0.36	21/1072 (2.0)	0.34	1.06 (0.58, 1.92)		
≥75 years	6/410 (1.5)	0.26	5/436 (1.1)	0.21	Not calculated†		
Coronary revascularization procedure	**202/3023 (6.7)**	**1.18**	**189/3010 (6.3)**	**1.11**	**1.06 (0.87, 1.29)**		0.1249
<65 years	96/1556 (6.2)	1.07	85/1502 (5.7)	0.97	1.10 (0.82, 1.47)		
65 to <75 years	71/1557 (6.7)	1.18	81/1072 (7.6)	1.36	0.87 (0.63, 1.20)		
≥75 years	35/410 (8.5)	1.60	23/436 (5.3)	0.98	1.64 (0.97, 2.78)		
Hospitalization for heart failure or CV death	**236/3023 (7.8)**	**1.34**	**234/3010 (7.8)**	**1.34**	**1.00 (0.84, 1.20)**		0.1912
<65 years	77/1556 (4.9)	0.84	60/1502 (4.0)	0.67	1.25 (0.89, 1.75)		
65 to <75 years	82/1057 (7.8)	1.33	98/1072 (9.1)	1.59	0.84 (0.62, 1.12)		
≥75 years	77/410 (18.8)	3.49	76/436 (17.4)	3.21	1.09 (0.79, 1.50)		
Any adjudication-confirmed CV event‡	**518/3023 (17.1)**	**3.11**	**535/3010 (17.8)**	**3.24**	**0.96 (0.85, 1.09)**		0.0548
<65 years	219/1556 (14.1)	2.50	188/1502 (12.5)	2.20	1.14 (0.94, 1.38)		
65 to <75 years	180/1057 (17.0)	3.09	219/1072 (20.4)	3.80	0.81 (0.67, 0.99)		
≥75 years	119/410 (29.0)	5.80	128/436 (29.4)	5.83	1.00 (0.78, 1.28)		

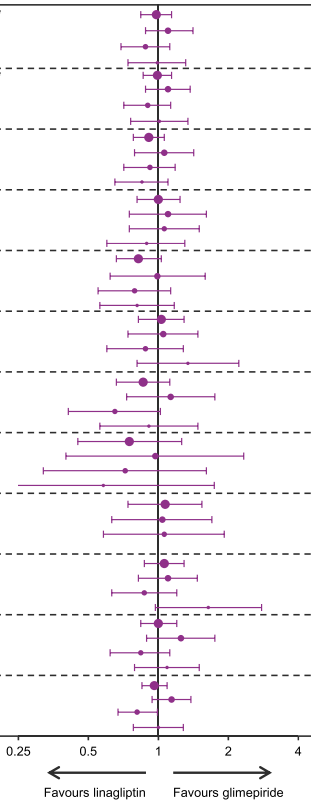


FIGURE 2 Clinical outcomes. CI, confidence interval; CV, cardiovascular; MACE, major adverse CV events. Three-point MACE = CV death, nonfatal myocardial infarction or nonfatal stroke; four-point MACE = CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. *95.47% CI. †Hazard ratio not calculated as <14 events. ‡Any of the following: CV death (including fatal stroke and fatal myocardial infarction), nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, transient ischaemic attack, hospitalization for heart failure, hospitalization for coronary revascularization

≥80 years, where there were 3.61 falls per 100 patient-years with linagliptin and 7.66 with glimepiride, while corresponding rates in those aged 75 to <80 years were 1.94 and 3.18, respectively (Tables S6 and S7). A similar pattern of lower incidence with linagliptin than glimepiride was observed for bone fractures (Table 1, Tables S5-S7). Overall, the risk for falls or fractures, in this post hoc analysis, was significantly lower with linagliptin than glimepiride (HR 0.80 [95% CI 0.69, 0.94]), with no statistical difference in risk across age groups (P = 0.13 for interaction between treatment group and age group), as was the risk of fractures alone (HR 0.76 [95% CI 0.63, 0.93]; P = 0.78 for interaction between treatment and age group) (Figure 4). However, there was a significant treatment interaction with age group for falls (P = 0.0463 for interaction between treatment and age group), suggesting reduced risk with linagliptin versus glimepiride only in participants aged ≥75 years. Episodes of moderate or severe hypoglycaemia were associated with significantly increased risk of subsequent falls or fractures (HR 1.32 [95% CI 1.07, 1.63]) independent of treatment group (P = 0.22 for interaction between treatment and time-dependent hypoglycaemia event), and in the glimepiride group (HR 1.41 [95% CI 1.12, 1.77]; Figure S8).

4 | DISCUSSION

This subgroup analysis of the CAROLINA trial found that, in general, the incidence of CV and mortality events increased with increasing age, but the relative effects of linagliptin versus glimepiride treatment on these outcomes were similar across age groups. However, over a median treatment duration of approximately 6 years, linagliptin had substantially lower risk for hypoglycaemia than glimepiride and a modest relative reduction in body weight. Notably, in a hypothesis-generating post hoc finding, linagliptin was associated with significantly lower risk for falls or fractures than glimepiride, which appeared to be associated with the lower hypoglycaemia risk with linagliptin.

The number of older people with type 2 diabetes has increased over the last few decades. It is estimated that 19.3% of people worldwide aged over 65 years have diabetes[14] while 26.8% of this age group in the United States have the disease.[1] Conversely, 135.6 million of the estimated 463 million people with diabetes globally (29.3%) are aged 65 years or over.[14] In the coming decades, people aged over 65 years will constitute the majority of patients with type 2 diabetes in the United States and most other developed countries.

TABLE 1 Number and percentage of participants with adverse events

	Age <65 years		Age 65 to <75 years		Age ≥75 years	
	Linagliptin (n = 1556)	Glimepiride (n = 1502)	Linagliptin (n = 1057)	Glimepiride (n = 1072)	Linagliptin (n = 410)	Glimepiride (n = 436)
Any AE[a]	1432 (92.5)	1416 (94.8)	993 (94.0)	1017 (95.0)	396 (96.6)	422 (96.8)
Serious AE	606 (38.9)	597 (39.7)	553 (52.3)	578 (53.9)	244 (59.5)	273 (62.6)
AE leading to discontinuation[a]	150 (9.7)	161 (10.8)	169 (16.0)	172 (16.1)	95 (23.2)	115 (26.4)
Any hospitalization	546 (35.1)	522 (34.8)	482 (45.6)	525 (49.0)	217 (52.9)	256 (58.7)
Hypersensitivity reactions[a,b]	206 (13.3)	175 (11.7)	149 (14.1)	115 (10.7)	49 (12.0)	56 (12.8)
Pemphigoid[a,c]	1 (0.1)	0	3 (0.3)	0	1 (0.2)	0
Skin lesions[a,d]	3 (0.2)	3 (0.2)	4 (0.4)	1 (0.1)	2 (0.5)	0
Acute pancreatitis (adjudication-confirmed)	8 (0.5)	6 (0.4)	6 (0.6)	7 (0.7)	1 (0.2)	3 (0.7)
Chronic pancreatitis (adjudication-confirmed)	1 (0.1)	0	2 (0.2)	0	0	0
Cancer[e]	80 (5.1)	93 (6.2)	134 (12.7)	147 (13.7)	66 (16.1)	63 (14.4)
Colorectal cancer[f]	7 (0.4)	7 (0.5)	16 (1.5)	15 (1.4)	9 (2.2)	8 (1.8)
Pancreatic cancer (adjudication-confirmed)	3 (0.2)	6 (0.4)	9 (0.9)	11 (1.0)	4 (1.0)	7 (1.6)
Gastric cancer[g]	3 (0.2)	2 (0.1)	6 (0.6)	2 (0.2)	0	1 (0.2)
Thyroid cancer[h]	0	2 (0.1)	1 (0.1)	1 (0.1)	0	0
Fall[a,c]	57 (3.7)	56 (3.7)	78 (7.4)	77 (7.2)	39 (9.5)	72 (16.5)
Bone fractures[a,i]	72 (4.7)	95 (6.4)	65 (6.2)	75 (7.0)	37 (9.0)	53 (12.2)
Hypoglycaemia[a]						
Any investigator-reported hypoglycaemia AE	175 (11.3)	559 (37.4)	105 (9.9)	416 (38.9)	40 (9.8)	157 (36.0)
Moderate[j] or severe[k] hypoglycaemia	113 (7.3)	465 (31.1)	61 (5.8)	344 (32.1)	21 (5.1)	118 (27.1)
Severe hypoglycaemia[k]	3 (0.2)	19 (1.3)	5 (0.5)	20 (1.9)	2 (0.5)	26 (6.0)

Note: Data are n (%) of participants.

Abbreviation: AE, adverse event.

[a]Percentages based on 1548 linagliptin and 1494 glimepiride participants aged <65 years, 1056 linagliptin and 1070 glimepiride participants aged 65 to <75 years.

[b]Medical Dictionary for Regulatory Activities (MedDRA) narrow standardized MedDRA query (SMQ) "hypersensitivity".

[c]MedDRA preferred term.

[d]MedDRA narrow SMQ "severe cutaneous adverse reactions".

[e]MedDRA narrow SMQs "malignant tumours" and "tumours of unspecified malignancy".

[f]MedDRA high level term "colorectal neoplasms malignant".

[g]MedDRA high level term "gastric neoplasms malignant".

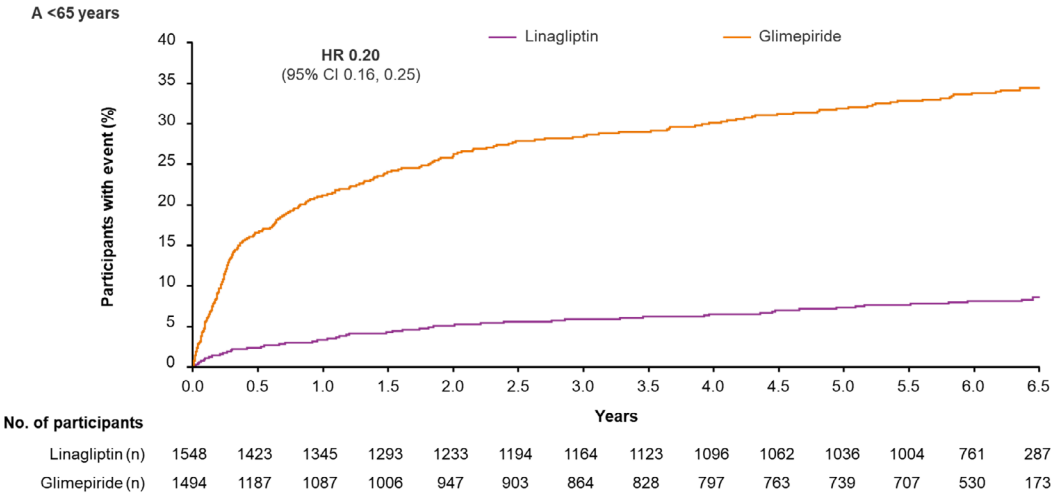
[h]MedDRA high level term "thyroid neoplasms malignant".

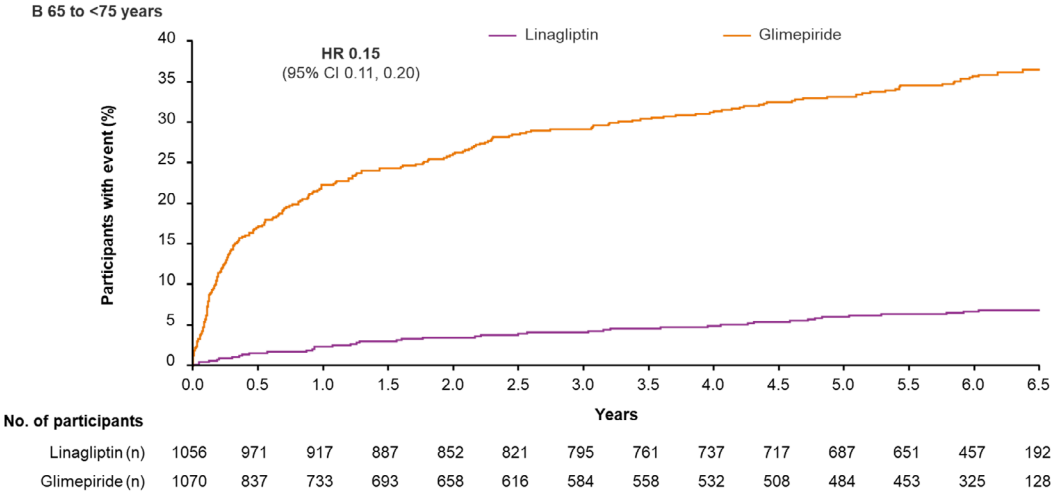
[i]Based on 84 MedDRA preferred terms for bone fractures.

[j]Investigator-reported episode of symptomatic hypoglycaemia with plasma glucose ≤70 mg/dL = 3.9 mmol/L.

[k]Requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.

Compared with younger people with type 2 diabetes, older individuals have higher rates of comorbidities such as atherosclerotic heart disease, chronic kidney disease and heart failure. These older individuals also have clinical challenges related to polypharmacy, frailty, cognitive impairment, and propensity towards falls and fractures.[4] Consequently, type 2 diabetes management for older individuals is usually more complicated than for younger people, and cautious selection of glucose-lowering agents to avoid hypoglycaemia takes priority; however, there are few data from clinical trials to guide such choices. An analysis of diabetes clinical trials registered on ClinicalTrials.gov between 2007 and 2010 found that fewer than 1% had specifically targeted patients aged over 65 years, 31% had actively excluded this age group, and most trials had excluded individuals older than 75 years.[3] This underrepresentation of older patients is somewhat surprising given that the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E7 guideline on geriatrics in 1993 called for their representation in clinical trials.[15] The United States Food and Drug Administration has similarly





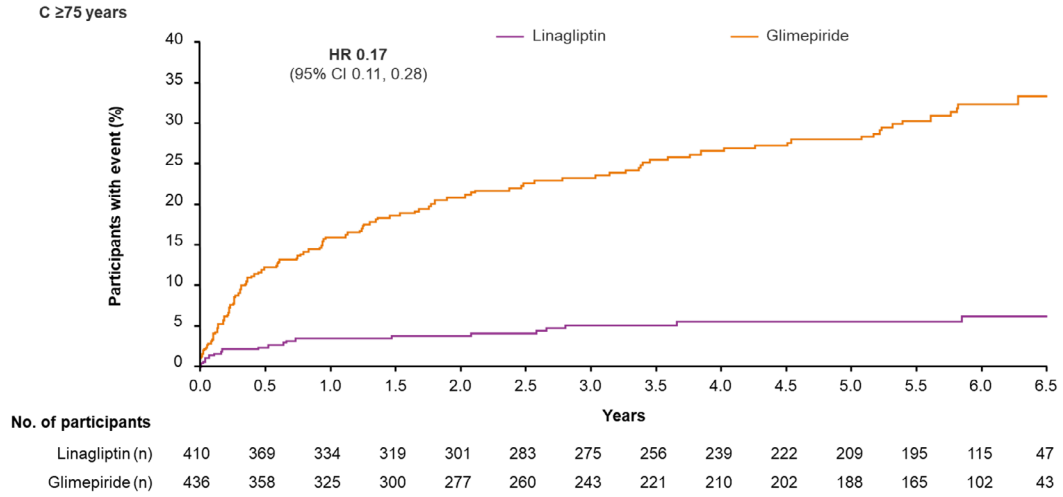


FIGURE 3 Time to first occurrence of moderate or severe hypoglycaemia (investigator-reported episode of symptomatic hypoglycaemia with plasma glucose ≤70 mg/dL or event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions). CI, confidence interval; HR, hazard ratio

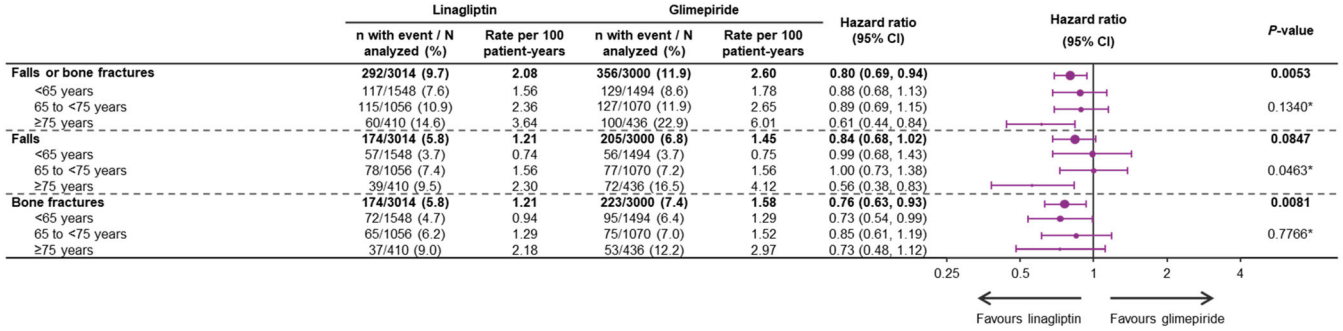


FIGURE 4 Falls and bone fractures. CI, confidence interval. **P* value for treatment-by-age-group interaction

emphasized recently the need to enrich clinical trials with older participants with multiple comorbidities.[16] However, participation has been low, probably reflecting safety concerns, restrictive eligibility criteria, and logistical challenges in recruiting elderly individuals.[17] Nevertheless, the paucity of clinical trial data for glucose-lowering drugs in older patients limits the generalizability of much trial data to routine diabetes care.

This subgroup analysis of CAROLINA provides important comparative data on clinical events and other outcomes in older patients for two of the most common classes of drugs added to first-line metformin therapy: DPP-4 inhibitors and SUs. Previously, a subgroup analysis of the CARMELINA placebo-controlled CVOT found that linagliptin did not increase the risk of CV or renal events in older people with type 2 diabetes, established CV disease with albuminuria, and/or chronic kidney disease – one of the highest-risk cohorts studied in recent CVOTs.[9] Importantly, linagliptin improved glycaemic control in older patients without increasing the risk of hypoglycaemia[9] or affecting cognitive function.[18] In the context of the CV safety of linagliptin having been already established in CARMELINA,[10] the overall results of CAROLINA have largely dissipated the controversy about the CV safety of SUs, which had lingered since the University Group Diabetes Program trial of tolbutamide, a first-generation SU, in the 1960s.[12] The present sub-analysis does the same for elderly individuals, specifically for glimepiride, which was used at a slightly lower dose than in the overall cohort. Additionally, and notably, despite similar improvements in glycaemic control, linagliptin had a substantially reduced risk of hypoglycaemia compared with glimepiride, both overall and in older participants, being about 80% lower for moderate (plasma glucose ≤70 mg/dL) or severe episodes. Our previous analysis of the overall CAROLINA findings showed that there was no dose dependency between glimepiride dose and hypoglycaemia, with increased risk of this adverse event occurring at all doses.[13]

Although many studies have found an association between hypoglycaemia and increased risk of CV events, it is unclear whether this is a causal relationship or whether vulnerable patients are simply more susceptible to both outcomes.[19,20] Regardless, avoiding hypoglycaemia is an important goal in type 2 diabetes and a meaningful outcome to patients, as episodes of low blood glucose are associated with increased risks of falls and hospitalizations, and increased costs of medical care.[21–26] Hypoglycaemia is also associated with adverse psychological outcomes and reduced quality of life, and fear of this side effect contributes to therapeutic inertia by physicians.[22,23,25] Interestingly, in addition to the lower risk of hypoglycaemia with linagliptin in older patients in CAROLINA, there were also significantly fewer falls or bone fractures compared with glimepiride; while bone fractures were consistently reduced, the difference in falls was observed only in patients aged ≥75 years. As younger patients also had reduced risk of hypoglycaemia with linagliptin but not falls, this may imply that older patients are more vulnerable to adverse consequences of hypoglycaemia. Previous research has suggested that SUs may increase the risk of falls in elderly patients.[27] Further post hoc analysis suggested that episodes of moderate or severe hypoglycaemia in CAROLINA were associated with significantly increased risk for subsequent falls or fractures. These are hypothesis-generating findings, which may have implications for treatment choices in the elderly.

The consensus report from the American Diabetes Association and the European Association for the Study of Diabetes on management of hyperglycaemia in type 2 diabetes recommends that patients with indicators of high CV risk or established CV disease receive second-line treatment, or even first-line therapy, with a glucose-lowering drug that has proven CV benefit,[28] which neither linagliptin nor glimepiride has. However, long-term CV benefits may be outweighed by safety considerations for older patients with limited life expectancy. This issue has been subject to in-depth consideration, and several organizations and societies have published guidelines or position statements over the past decade either dedicated to the treatment of older patients or including a consideration of patient age.[2,4,29–37] These geriatric guidelines emphasize that safety of glucose-lowering treatment should be the main consideration for older patients, particularly frail individuals with high risk of adverse events and limited life expectancy. The guidelines also generally suggest that glycaemic goals for older patients may be relaxed compared with younger patients, mainly to avoid hypoglycaemia, but that more stringent targets may be appropriate for non-frail elderly individuals using modern glucose-lowering drugs with low risk of hypoglycaemia, because complications of chronic hyperglycaemia are particularly detrimental in the elderly (eg, dehydration, dizziness, falls, urinary infections, acute hyperglycaemic crises).[32,33,35,36] Our analysis of CAROLINA supports the evidence base underpinning these

recommendations, particularly their focus on safety and avoidance of hypoglycaemia. These findings are therefore relevant for those involved in care of older people with type 2 diabetes, and also underscore the need to consider these relatively frequent events, that is falls and fractures, as important outcomes for future studies in the elderly.

The strengths of this study include its use of adjudicated clinical outcomes for a large number of participants (>6000) over a lengthy treatment period (~6 years) from a modern CVOT. CAROLINA is the longest randomized, double-blind, multinational CVOT of a glucose-lowering drug and the only study to have had an active comparator from a different, frequently used class, as well as a relatively large number of participants aged over 65 and 75 years. The few other analyses of elderly patient outcomes from recent CVOTs have mostly been limited to comparisons with placebo.[9,38–42] The present study therefore expands the evidence base for glucose-lowering treatment of older people. It is, however, subject to the usual limitations of subgroup analyses, including lack of statistical adjustment for multiple comparisons and several analyses being defined post hoc. In addition, as CAROLINA was not a dedicated study in the elderly, the functional status and frailty of the older participants were not assessed. This may limit the generalizability of our findings, as the older participants might have been healthier on average than older diabetes patients seen in clinical practice. Another limitation was that we did not prospectively adjudicate falls or fractures; those findings therefore need to be interpreted with caution, and require confirmation in further prospective investigations.

In conclusion, this analysis of the CAROLINA trial found that treatment with linagliptin or glimepiride had similar CV outcomes across age groups but linagliptin was associated with substantially lower risk of hypoglycaemia and fewer falls or fractures, outcomes that are particularly meaningful for older individuals.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

M.A.E., J.R., B.Z., N.M., D.K.M. and O.E.J. participated in the design of the study, conduct of the study, collection and interpretation of data, and preparation of the manuscript. R.E.P., T.K. and Y.S. participated in interpretation of data and preparation of the manuscript. K.R.A. participated in conduct of the study, interpretation of data and preparation of the manuscript. M.M., A.K. and M.W. participated in statistical analysis and interpretation of data, and preparation of the manuscript. M.A.E, R.E.P. and O.E.J. wrote the first draft of the paper. All authors have approved the final version of the manuscript. M.A.E. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14254.

DATA AVAILABILITY STATEMENT

The sponsor of the clinical trial (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents, and patient-level clinical study data. Researchers are invited to submit inquiries via the following website (https://trials.boehringer-ingelheim.com/).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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