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ORIGINAL ARTICLE

Effect of albiglutide on cardiovascular outcomes in older adults: A post hoc analysis of a randomized controlled trial

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Abstract

Aim: To analyse the effects of albiglutide, a glucagon-like peptide 1 receptor agonist, on cardiovascular outcomes in older adults aged ≥65 years with type 2 diabetes and cardiovascular disease who participated in the Harmony Outcomes trial (NCT02465515).

Materials and methods: We conducted a post hoc analysis of the primary endpoint of the Harmony Outcomes trial—time to first occurrence of a major adverse cardiovascular event—in subgroups of participants aged <65 and ≥65 years and <75 and ≥75 years at baseline. Hazard ratios and 95% confidence intervals (CIs) were generated using Cox proportional hazards regression.

Results: The analysis population included 9462 Harmony Outcomes participants, including 4748 patients ≥65 and 1140 patients ≥75 years at baseline. Hazard ratios for the prevention of major adverse cardiovascular events were 0.66 (95% CI, 0.53-0.82) in persons <65 and 0.86 (95% CI, 0.71-1.04) in those ≥65 years (age interaction $p = .07$), and 0.78 (95% CI, 0.67-0.91) in <75 and 0.70 (95% CI, 0.48-1.01) in ≥75 year age groups (interaction $p = .6$). When analysed as a continuous variable, age did not modify the effect of albiglutide on the primary endpoint.

Conclusions: This post hoc analysis adds to the body of literature showing that glucagon-like peptide 1 receptor agonists added to standard type 2 diabetes therapy safely reduce the incidence of cardiovascular events in older adults with established cardiovascular disease. In this analysis, the risk-benefit profile was similar between younger and older age groups treated with albiglutide.

KEYWORDS
cardiovascular disease, elderly, glucagon-like peptide 1 analogue, randomized trial, type 2 diabetes

1 | INTRODUCTION

Among US adults ≥65 years of age, 29.2% have diabetes, which is almost twice the rate of diabetes (14.7%) in the general adult population.[1] The incidence of cardiovascular (CV) events is also higher in older versus younger adults, and the presence of diabetes exacerbates the risk of such events.[2] Management of type 2 diabetes (T2D) and comorbidities often requires multiple medications, which increases the potential for drug interactions and adverse events (AEs), particularly in older adults, and may reduce treatment adherence.[3–5] Diabetes also increases the risk of kidney disease, which is another condition that disproportionately affects older individuals and often alters drug metabolism.[5–8] Yet clinical trial data are frequently lacking in older adults, who are often excluded, directly or indirectly (based on comorbidities), from clinical trials.[9] Regulatory bodies have recommended the collection of comprehensive data, particularly for patients aged ≥75 years, to inform better the appropriate treatment of this growing population.[10,11]

To reduce the risk of CV events in persons with T2D, the American Diabetes Association and the European Association for the Study of Diabetes recommend the use of antihyperglycaemic agents with proven CV benefits, including the glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in patients with pre-existing CV disease (CVD) or at high CV risk.[12] This class improves beta-cell function and reduces body weight, both of which may slow disease progression, and the glucose-dependent action improves glycaemic control without increasing the risk of hypoglycaemia.[13–16] Several GLP-1 RAs also showed robust reductions in major adverse CV events (MACE), including CV death, myocardial infarction (MI), or stroke, which appear to be independent of glycated haemoglobin (HbA1c) decreases.[17–21] In the Harmony Outcomes trial, the once-weekly GLP-1 RA albiglutide reduced the occurrence of MACE by 22% in patients with T2D and CVD. Of 9463 randomized participants, 1140 (12%) were ≥75 years of age at baseline. The relative risk of the composite MACE endpoint was reduced by 31% in this age group in the primary, intent-to-treat analysis.[17] We sought to expand on the initial publication by providing additional efficacy and safety information in older adults with diabetes. Thus, in this post hoc analysis, we compared MACE reductions and AEs across two sets of age subgroups: <65 and ≥65 years and <75 and ≥75 years.

2 | METHODS

Harmony Outcomes was a multicentre, double-blind, randomized, placebo-controlled, event-driven trial conducted across North and South America, Europe, Africa and Asia. The trial population included men and women aged ≥40 years who had T2D and established CVD (either coronary, cerebrovascular, or peripheral arterial disease). Patients were randomly assigned to albiglutide or placebo in addition to standard-of-care treatment for T2D and CVD and were followed for a median of 1.6 years. The trial was conducted in accordance with the Declaration of Helsinki, and all patients provided written informed consent. Full design details and results have been published.[17,22] This post hoc analysis was approved as exempt research by the University of Vermont Committees on Human Research.

Due to the use of a secondary source, the data were missing for one patient of 9463 patients in the 65–75 age group from the original Harmony Outcomes population.[17]

2.1 | Statistical analysis

The primary outcome of this post hoc analysis was time to the first occurrence of MACE (i.e. any component of the composite primary outcome from the original publication: death from CV causes, MI and stroke, in an intention-to-treat population) over the full duration of the study in two sets of age subgroups (<65 and ≥65 years; <75 and ≥75 years), with the question being whether there is evidence of an age group × treatment interaction. Other outcomes of interest were time to first non-fatal MI, time to first stroke and time to CV death. Cox proportional hazards regression models were used to assess the interaction effect. These models included treatment arm, age group, their interaction and the following categorical baseline characteristics as covariates: sex, country, duration of diabetes, number of diagnosed CVD conditions that were Harmony Outcomes entry criteria (i.e. coronary artery disease, cerebrovascular disease, or peripheral arterial disease), smoking history, estimated glomerular filtration rate, body mass index and antihyperglycaemic agent category as defined in the original trial.[22] Hazard ratios (HRs) adjusted for these covariates and 95% confidence intervals (CIs) are reported. Statistical significance was defined as $p < .05$.

Cox regression models were run with age as a continuous factor for MACE. A fractional polynomial was constructed of age and included in the model as an interaction term with treatment arm.[23] All covariates mentioned above were also included in the models. The results of the interaction were displayed graphically using the mfpi command in Stata (StataCorp).[24]

Descriptive statistics are provided for demographic and baseline clinical characteristics. Rates of AEs, serious AEs (SAEs), discontinuations because of AEs, fatal SAEs and AEs occurring in ≥5% of albiglutide-treated patients are presented. All analyses, except for the modelling of age as a continuous factor, were run using SAS v9.4 (SAS Institute Inc.).

3 | RESULTS

3.1 | Baseline characteristics

Table 1 displays baseline characteristics and medication use for 9462 randomized trial participants divided into subgroups of patients <65 and ≥65 years and <75 and ≥75 years. Mean weight at baseline decreased with age, and fewer older patients had a body mass index ≥30 kg/m^2. Across all subgroups, 38%-43% of patients had a duration of diabetes of 10-20 years; 44% of patients <65 years and 27% of

TABLE 1 Baseline demographic and clinical characteristics, by age at baseline.

	<65 years		≥65 years		<75 years		≥75 years	
	Albiglutide (n = 2385)	Placebo (n = 2329)	Albiglutide (n = 2345)	Placebo (n = 2403)	Albiglutide (n = 4155)	Placebo (n = 4167)	Albiglutide (n = 575)	Placebo (n = 565)
Age, years; mean ± SD	57.1 ± 5.5	57.1 ± 5.5	71.2 ± 4.8	71.0 ± 4.8	62.2 ± 7.4	62.3 ± 7.3	78.0 ± 2.9	78.1 ± 2.9
Male, n (%)	1675 (70)	1627 (70)	1628 (69)	1638 (68)	2908 (70)	2873 (69)	395 (69)	392 (69)
Weight, kg; mean ± SD	95.1 ± 20.5	94.7 ± 20.4	89.4 ± 18.3	89.2 ± 18.0	93.2 ± 19.8	92.9 ± 19.6	85.5 ± 16.9	84.5 ± 16.3
BMI ≥30 kg/m^2, n (%)	1555 (65)	1521 (65)	1359 (58)	1365 (57)	2623 (63)	2629 (63)	291 (51)	257 (45)
Duration of diabetes, n (%)								
<10 years	1045 (44)	1026 (44)	615 (26)	669 (28)	1553 (37)	1549 (37)	107 (19)	146 (26)
≥10 to <20 years	980 (41)	935 (40)	1006 (43)	1003 (42)	1743 (42)	1722 (41)	243 (42)	216 (38)
≥20 years	355 (15)	366 (16)	717 (31)	729 (30)	851 (20)	894 (21)	221 (38)	201 (36)
CAD, n (%)	1618 (68)	1591 (68)	1714 (73)	1754 (73)	2923 (70)	2934 (70)	409 (71)	411 (73)
No. cardiovascular diseases, n (%)[a]								
1	2024 (85)	1977 (85)	1821 (78)	1879 (78)	3398 (82)	3434 (82)	447 (78)	422 (75)
2 or 3	356 (15)	345 (15)	521 (22)	520 (22)	750 (18)	722 (17)	127 (22)	143 (25)
Smoking history, n (%)								
Never	917 (38)	905 (39)	993 (42)	1076 (45)	1654 (40)	1696 (41)	256 (45)	285 (50)
Former	961 (40)	895 (38)	1121 (48)	1104 (46)	1794 (43)	1748 (42)	288 (50)	251 (44)
Current	506 (21)	528 (23)	231 (10)	223 (9)	706 (17)	722 (17)	31 (5)	29 (5)
eGFR, n (%)								
<60 ml/min/1.73 m^2	349 (15)	341 (15)	749 (32)	783 (33)	855 (21)	867 (21)	243 (42)	257 (45)
≥60 to <90	1059 (44)	1032 (44)	1148 (49)	1177 (49)	1942 (47)	1968 (47)	265 (46)	241 (43)
≥90	977 (41)	956 (41)	448 (19)	443 (18)	1358 (33)	1332 (32)	67 (12)	67 (12)
Antihyperglycaemic medications, n (%)								
None	15 (1)	12 (1)	27 (1)	23 (1)	32 (1)	29 (1)	10 (2)	6 (1)
1 non-insulin agent	394 (17)	433 (19)	368 (16)	378 (16)	668 (16)	703 (17)	94 (16)	108 (19)
2 non-insulin agents	435 (18)	454 (19)	365 (16)	414 (17)	713 (17)	777 (19)	87 (15)	92 (16)
>2 non-insulin agents	119 (5)	129 (6)	148 (6)	152 (6)	236 (6)	250 (6)	31 (5)	31 (5)
Insulin only	337 (14)	325 (14)	459 (20)	429 (18)	661 (16)	639 (15)	135 (23)	115 (20)
Insulin +1 non-insulin agent	721 (30)	632 (27)	638 (27)	674 (28)	1217 (29)	1163 (28)	142 (25)	143 (25)
Insulin +2 non-insulin agents	315 (13)	283 (12)	291 (12)	273 (11)	537 (13)	497 (12)	69 (12)	59 (10)
Insulin + >2 non-insulin agents	49 (2)	61 (3)	49 (2)	60 (2)	91 (2)	110 (3)	7 (1)	11 (2)
Specific agents, n (%)								
Alpha-glucosidase inhibitor	12 (1)	19 (1)	22 (1)	18 (1)	29 (1)	33 (1)	5 (1)	4 (1)
Biguanide	1860 (78)	1821 (78)	1603 (68)	1684 (70)	3121 (75)	3143 (75)	342 (59)	363 (64)
DPP4i	331 (14)	333 (14)	367 (16)	406 (17)	601 (14)	648 (16)	97 (17)	91 (16)
GLP-1 RA	2 (0)	1 (0)	0 (0)	1 (0)	2 (0)	2 (0)	0 (0)	0 (0)
Meglitinide	24 (1)	26 (1)	42 (2)	70 (3)	52 (1)	70 (2)	14 (2)	26 (5)
SGLT2i	176 (7)	153 (7)	134 (6)	112 (5)	286 (7)	245 (6)	24 (4)	20 (4)
Sulphonylurea	670 (28)	693 (30)	676 (29)	686 (29)	1181 (28)	1231 (30)	165 (29)	148 (26)
Thiazolidinedione	42 (2)	62 (3)	50 (2)	40 (2)	89 (2)	96 (2)	3 (1)	6 (1)
Insulin	1422 (60)	1301 (56)	1437 (61)	1436 (60)	2506 (60)	2409 (58)	353 (61)	328 (58)
Other antihyperglycaemic agent	29 (1)	30 (1)	48 (2)	74 (3)	61 (1)	78 (2)	16 (3)	26 (5)

(Continues)

TABLE 1 (Continued)

	<65 years		≥65 years		<75 years		≥75 years	
	Albiglutide (n = 2385)	Placebo (n = 2329)	Albiglutide (n = 2345)	Placebo (n = 2403)	Albiglutide (n = 4155)	Placebo (n = 4167)	Albiglutide (n = 575)	Placebo (n = 565)
Cardiovascular medications, n (%)								
ACEi	1190 (50)	1221 (52)	1072 (46)	1132 (47)	2000 (48)	2113 (51)	262 (46)	240 (42)
ARB	740 (31)	653 (28)	859 (37)	858 (36)	1398 (34)	1305 (31)	201 (35)	206 (36)
Beta blocker	1542 (65)	1519 (65)	1586 (68)	1663 (69)	2769 (67)	2787 (67)	359 (62)	395 (70)
CCB	662 (28)	611 (26)	766 (33)	820 (34)	1242 (30)	1250 (30)	186 (32)	181 (32)
Loop diuretic	394 (17)	363 (16)	501 (21)	536 (22)	748 (18)	760 (18)	147 (26)	139 (25)
Thiazide diuretic	526 (22)	477 (20)	563 (24)	560 (23)	960 (23)	901 (22)	129 (22)	136 (24)
Statin	1963 (82)	1937 (83)	2003 (85)	2051 (85)	3480 (84)	3511 (84)	486 (85)	477 (84)
Aspirin	1878 (79)	1832 (79)	1773 (76)	1807 (75)	3241 (78)	3230 (78)	410 (71)	409 (72)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CV, cardiovascular; DPP4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SD, standard deviation; SGLT2i, sodium-glucose cotransporter 2 inhibitor.
[a]Coronary artery disease, cerebrovascular disease, or peripheral arterial disease.

those aged ≥65 years had a duration of diabetes <10 years, while 37% of those aged <75 years and 22% of those aged ≥75 years had had diabetes for <10 years. Proportions of patients with coronary artery disease, ≥2 CV risk factors, and an estimated glomerular filtration rate ≤60 ml/min/1.73 m^2 were somewhat larger in the ≥65 and ≥75 year subgroups than in the <65 and <75 year age groups, respectively (Table 1).

3.2 | Risk of composite major adverse CV event outcomes and components by age group

In the primary publication and the unadjusted analysis reported here (Figure S1), the overall HR for MACE was 0.78 (95% CI, 0.68-0.90).[17] After adjustment for the covariates used in this analysis, the overall HR was 0.77 (95% CI, 0.66-0.89). Figure 1 shows the adjusted risks of MACE, CV death, non-fatal MI and stroke in the overall population and in adults aged <65 and ≥65 years and those <75 and ≥75 years. The effect of treatment was not modified by age.

When age was analysed as a continuous variable, the continuous HR for the treatment effect of albiglutide versus placebo remained consistent across the full age range from 40 to 90 years, with an interaction *p* value of .66 for MACE (Figure 2).

3.3 | Safety of albiglutide across age groups

In total, 9431 patients included in this post hoc analysis received a minimum of one dose and were included in the safety analyses. Overall, the rates of AEs were higher among older than younger patients (<65 vs. ≥65 and <75 vs. ≥75 years) but within each age category were similar between the albiglutide and placebo treatment groups (Table 2). Across age subgroups, more SAEs, including fatal SAEs, occurred in patients receiving placebo than albiglutide. Within each age group, discontinuations were more common among patients treated with albiglutide versus placebo, but the relative risk did not differ by age.

Rates of individual AEs followed similar patterns. More albiglutide than placebo-treated patients experienced gastrointestinal events, the frequency of which was higher in older patient subgroups (Table 2). Hypoglycaemia was also more common in older than younger age subgroups but was less frequent in the albiglutide than in the placebo group.

4 | DISCUSSION

In this post hoc age group analysis of the Harmony Outcomes data, albiglutide treatment reduced the risk of MACE across the full age range of trial participants. The effects of albiglutide on risk of MACE did not differ statistically in subgroups aged <65 and ≥65 and <75 and ≥75 years, with no age interaction when the effects of albiglutide on the risk of CV death, MI and stroke were analysed individually in patients aged <65 and ≥65 and <75 and ≥75 years. The trial was not powered to detect treatment differences within subgroups, but the lack of an age interaction shows that the risk of MACE events does not increase with age.

Our findings are consistent with other analyses of GLP-1 RA treatment in older populations. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial in patients aged <60, 60-74 and ≥75 years, differences in treatment effect among age groups were not significant ($p = .54$ for age group interaction), and AEs were similar across age groups.[25] In the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) trial, the MACE benefits of once-weekly semaglutide were similar in patients

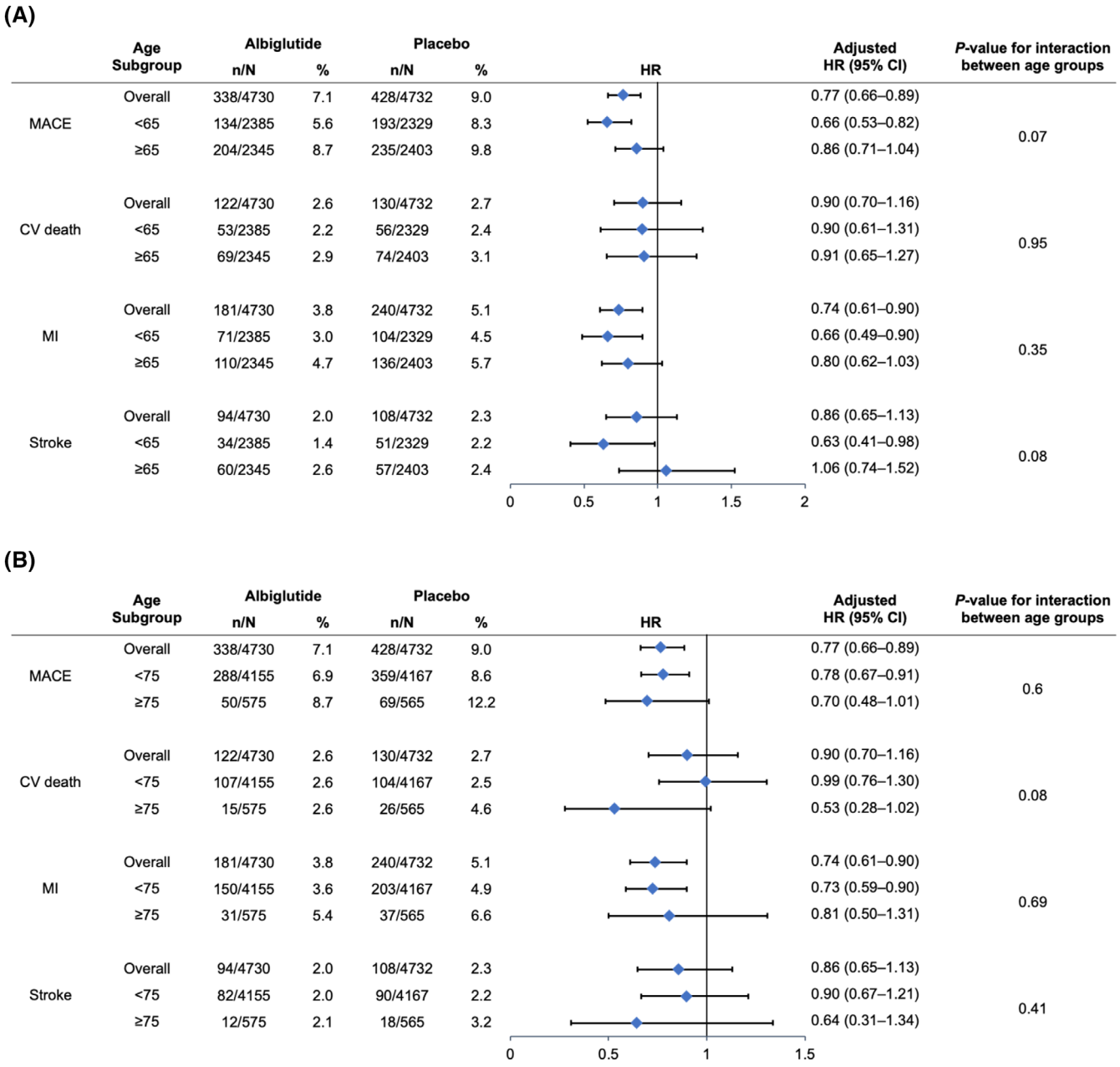

FIGURE 1 Adjusted hazard ratios (HR) with 95% confidence intervals (CI) of the first occurrence of major adverse cardiovascular event (MACE) and components, cardiovascular (CV) death, myocardial infarction (MI) and stroke, in patients aged (A) <65 and ≥65 years and (B) <75 and ≥75 years.

older than 65 years and those aged 65 years or younger ($p = .92$ for age group interaction), with consistent results across the components of the MACE endpoint (CV death, MI and stroke) and other CV endpoints, including hospitalization for unstable angina, heart failure, or revascularization.[26] Likewise, similar reductions in MACE were observed in patients aged <65 and ≥65 years ($p = .797$ for age group interaction) in Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND), with no major differences in AEs.[27] In the AMPLITUDE-O trial (Effect of Efpeglenatide on Cardiovascular Outcomes), the reduction in MACE was likewise similar between patients <65 and ≥65 years of age.[18] A recent meta-analysis showed that across GLP-1 RA CV outcome trials, the risk of MACE is significantly reduced in patients ≥65 years [HR 0.86 (95% CI, 0.80-0.92)], similar to younger patients ($p = .78$ for age group interaction).[28] Our study included patients aged ≥75 as a separate group, further supporting these results. We chose to examine older patients ≥75 years because the risk of CV events is substantially increased in this population.[2,29,30]

Our findings further strengthen support for use of GLP-1 RAs in older patients with T2D at high risk of CVD events because the Harmony Outcomes population was generally older and at higher risk of CV events. In the LEADER, SUSTAIN-6, AMPLITUDE-O and REWIND

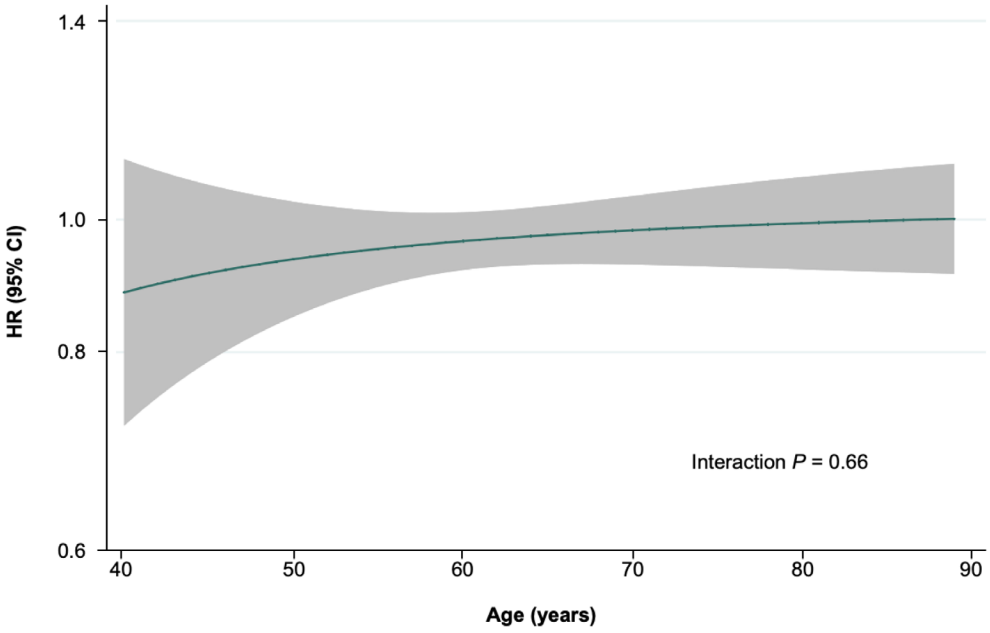

FIGURE 2 Effect of albiglutide on the occurrence of major adverse cardiovascular events with age analysed as a continuous variable. The dark green line represents the continuous hazard ratio (HR) and grey area the 95% confidence interval (CI), which was adjusted for the following baseline characteristics: sex, country, duration of diabetes, number of cardiovascular risk factors, smoking history, estimated glomerular filtration rate, body mass index and antihyperglycaemic therapy.

trials, 81%, 83%, 90% and 31% of participants, respectively, had established CVD, compared with 100% of Harmony Outcomes participants.[17,18,20,21,28] In addition, a larger proportion of Harmony participants were ≥75 years of age at baseline (12%) than in LEADER (9%; the proportion ≥75 years); details on patients ≥75 years were not reported for the other trials.[25]

Previous analyses suggest that the CV benefits of GLP-1 RAs are mediated minimally if at all by changes in HbA1c or body weight. Consequently, in this analysis we did not analyse changes in HbA1c or body weight as mediators of CV outcomes. In other analyses, the clinical efficacy and AEs do not differ by age group. In a pooled analysis of six randomized, placebo-controlled trials of liraglutide, improvements in HbA1c and the tolerability profile were similar between older and younger patients, and body weight reductions were greater in the older age group.[31] Another pooled data analysis of six lixisenatide trials showed that age did not affect HbA1c reductions and that AEs were similar across age groups.[32] In an age-based comparison with the effects of the combination of dulaglutide and insulin in patients aged <65 and ≥65 years, glycaemic reductions and the proportions of patients achieving HbA1c targets were similar between age groups, with similar rates of AEs.[33] Importantly, in these studies the rates of hypoglycaemia were low and similar in older and younger adults treated with GLP-1 RAs, even when used in combination with insulin or other agents.[31–33]

With advancing age and increased frailty, older adults become increasingly vulnerable to hypoglycaemia and its sequelae (including CV events). To avoid hypoglycaemia, clinicians are often encouraged to set higher HbA1c targets for older patients, particularly those with greater frailty, a shorter life expectancy, or for whom complex treatment regimens might be burdensome.[5,9,34] Glucose-dependent approaches (i.e. incretin agents that promote insulin secretion only upon ingestion of carbohydrates and thus reduce blood glucose levels without increasing the risk of hypoglycaemia) may offer advantages to older patients, even in cases of similar clinical and CV outcomes. In the Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Type 2 Diabetes (CAROLINA) trial, linagliptin significantly reduced rates of hypoglycaemia, falls and bone fractures versus glimepiride. In addition, a significant interaction between age and treatment group ($p = .0463$) suggested linagliptin more profoundly reduced the risk of falls in patients aged ≥75 years relative to younger patients.[35] Despite this safer profile, linagliptin and other dipeptidyl peptidase 4 inhibitors have not been associated with CV protection, whereas CV benefits have been proven for several GLP-1 RAs.[36]

In the present study, the rates of hypoglycaemia were lower in the albiglutide than the placebo subgroups. The ability of older persons to tolerate the gastrointestinal side effects of GLP-1 RAs is a concern for clinicians.[9,34] Consistent with other GLP-1 RA studies, we observed higher rates of gastrointestinal events in albiglutide-treated patients, with a higher frequency in older versus younger patients. However, the highest rates of discontinuations because of AEs were observed in the youngest age group, and the difference in discontinuations between the albiglutide and placebo groups was not significant among patients ≥75 years of age.

Harmony Outcomes enrolled >4000 patients aged ≥65 years (approximately 50% of the trial population) and showed a significant secondary protection benefit of GLP-1 RA therapy in a population with high rates of statin and antihypertensive use to control other CV risk factors (Table 1). As shown in the present analysis, these benefits extend across age groups, protecting older patients. Because only patients with established CVD were enrolled, our results cannot be applied to a primary prevention population. In addition, the majority of Harmony Outcomes participants were white, and although 21% were Hispanic, these results may not be generalizable to other racial or ethnic groups. In addition, the Harmony Outcomes trial was

TABLE 2 AEs by age at baseline.

	<65 years		≥65 years		<75 years		≥75 years	
	Albiglutide (n = 2376)	Placebo n = 2326)	Albiglutide (n = 2340)	Placebo (n = 2389)	Albiglutide (n = 4142)	Placebo (n = 4155)	Albiglutide (n = 574)	Placebo (n = 560)
Any AE	664 (27.9)	620 (26.7)	781 (33.4)	772 (32.3)	1236 (29.8)	1194 (28.7)	209 (36.5)	198 (35.4)
Any SAE	419 (17.6)	458 (19.7)	513 (21.9)	564 (23.6)	793 (19.1)	880 (21.2)	139 (24.2)	142 (25.4)
Discontinued treatment because of any AE	178 (7.5)	130 (5.6)	249 (10.6)	204 (8.5)	354 (8.5)	266 (6.4)	73 (12.7)	68 (12.1)
Fatal SAE	30 (1.3)	42 (1.8)	52 (2.2)	57 (2.4)	67 (1.6)	76 (1.8)	15 (2.6)	23 (4.1)
AEs reported for ≥0.5% of subjects in albiglutide group								
Pneumonia	56 (2.4)	47 (2)	67 (2.9)	80 (3.3)	105 (2.5)	99 (2.4)	18 (3.1)	28 (5)
Renal impairment	43 (1.8)	59 (2.5)	81 (3.5)	69 (2.9)	99 (2.4)	98 (2.4)	25 (4.4)	30 (5.4)
Atrial fibrillation	30 (1.3)	34 (1.5)	63 (2.7)	79 (3.3)	78 (1.9)	86 (2.1)	15 (2.6)	27 (4.8)
Nausea	26 (1.1)	4 (0.2)	50 (2.1)	19 (0.8)	58 (1.4)	14 (0.3)	18 (3.1)	9 (1.6)
Acute kidney injury	32 (1.3)	29 (1.2)	38 (1.6)	51 (2.1)	56 (1.4)	70 (1.7)	14 (2.4)	10 (1.8)
Diarrhoea	23 (1)	2 (0.1)	32 (1.4)	15 (0.6)	46 (1.1)	11 (0.3)	9 (1.6)	6 (1.1)
Injection site reaction	34 (1.4)	3 (0.1)	18 (0.8)	3 (0.1)	50 (1.2)	5 (0.1)	2 (0.3)	1 (0.2)
Diabetic retinopathy	30 (1.3)	30 (1.3)	21 (0.9)	21 (0.9)	46 (1.1)	48 (1.2)	5 (0.9)	3 (0.5)
Anginal pectoris	18 (0.8)	17 (0.7)	19 (0.8)	19 (0.8)	32 (0.8)	30 (0.7)	5 (0.9)	6 (1.1)
Hypoglycaemia	10 (0.4)	19 (0.8)	21 (0.9)	36 (1.5)	22 (0.5)	44 (1.1)	9 (1.6)	11 (2)
Peripheral arterial occlusive disease	12 (0.5)	17 (0.7)	21 (0.9)	24 (1)	30 (0.7)	36 (0.9)	3 (0.5)	5 (0.9)
Gamma-glutamyltransferase increased	18 (0.8)	12 (0.5)	11 (0.5)	6 (0.3)	28 (0.7)	17 (0.4)	1 (0.2)	1 (0.2)
Urinary tract infection	7 (0.3)	7 (0.3)	19 (0.8)	16 (0.7)	17 (0.4)	21 (0.5)	9 (1.6)	2 (0.4)
Vomiting	11 (0.5)	3 (0.1)	17 (0.7)	11 (0.5)	21 (0.5)	9 (0.2)	7 (1.2)	5 (0.9)
Coronary artery disease	11 (0.5)	17 (0.7)	13 (0.6)	14 (0.6)	20 (0.5)	27 (0.6)	4 (0.7)	4 (0.7)
Renal failure	8 (0.3)	6 (0.3)	14 (0.6)	23 (1)	17 (0.4)	25 (0.6)	5 (0.9)	4 (0.7)
Sepsis	9 (0.4)	11 (0.5)	14 (0.6)	17 (0.7)	19 (0.5)	22 (0.5)	4 (0.7)	6 (1.1)

Abbreviations: AE, adverse event; SAE, serious adverse event.

conducted before sodium-glucose cotransporter 2 inhibitors were recommended as standard therapy for patients with heart failure or chronic kidney disease. Consequently, utilization of these agents was low in the trial, and the effects of the combination of GLP1-RA and sodium-glucose cotransporter 2 inhibitor cannot be evaluated from our results.

Our findings provide additional supportive evidence that long-acting GLP-1 RAs effectively reduce the risk of CV events in older adults with T2D and CVD, and that the relative risk of AEs with GLP-1 RA versus placebo is not increased in older populations. Along with data from other age group analyses, our findings showed that advancing age does not diminish the positive impact of GLP-1 RA therapy on clinical efficacy, MACE, or other CV outcomes. These results may help inform clinical decisions regarding the use of GLP-1RA for the management of T2D in older adults with established CVD.

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CONFLICT OF INTEREST STATEMENT

MPG is a consultant for Novo Nordisk. JS has no financial interests to declare. AFH reports receiving grants or contracts from AstraZeneca, Merck, Amgen, Novartis, Boehringer Ingelheim and NovoNordisk and consulting fees from Boehringer Ingelheim and NovoNordisk. JBG reports receiving research support from Roche, Merck and Boehringer Ingelheim/Lilly; consultant for AstraZeneca, Bayer, Boehringer

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PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15479.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Vivli, Inc. Restrictions apply to the availability of these data, which were used under license for this study.

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REFERENCES

1. Centers for Disease Control and Prevention. Prevalence of both diagnosed and undiagnosed diabetes. 2022 https://www.cdc.gov/diabetes/data/statistics-report/diagnosed-undiagnosed-diabetes.html Accessed 31 August 2023.
2. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics–2023 update: a report from the American Heart Association. *Circulation*. 2023;147(8):e93-e621.
3. Del Prato S, Heine RJ, Keilson L, Guitard C, Shen SG, Emmons RP. Treatment of patients over 64 years of age with type 2 diabetes: experience from nateglinide pooled database retrospective analysis. *Diabetes Care*. 2003;26(7):2075-2080.
4. Fialova D, Onder G. Medication errors in elderly people: contributing factors and future perspectives. *Br J Clin Pharmacol*. 2009;67(6):641-645.
5. ElSayed NA, Aleppo G, Aroda VR, et al. 11. Chronic kidney disease and risk management: standards of care in diabetes–2023. *Diabetes Care*. 2023;46(Suppl 1):S191-s202.
6. ElSayed NA, Aleppo G, Aroda VR, et al. 13. Older adults: standards of care in diabetes–2023. *Diabetes Care*. 2023;46(Suppl 1):S216-S229.
7. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int*. 2020;98(4s):S1-s115.
8. Nobili A, Pasina L, Tettamanti M, et al. Potentially severe drug interactions in elderly outpatients: results of an observational study of an administrative prescription database. *J Clin Pharm Ther*. 2009;34(4):377-386.
9. Sinclair AJ, Heller SR, Pratley RE, et al. Evaluating glucose-lowering treatment in older people with diabetes: lessons from the IMPERIUM trial. *Diabetes Obes Metab*. 2020;22(8):1231-1242.
10. Food and Drug Administration. *Guidance for Industry—E7 Studies in Support of Special Populations: Geriatrics–Questions and Answers*. Center for Drug Evaluation and Research (CDER); 2012. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM189544.pdf. Accessed 18 October 2023.
11. European Medicines Agency. *Committee for Human Medicinal Products (CHMP)–Adequacy of Guidance on the Elderly Regarding Medicinal Products for Human Use*. EMEA; 2006. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500049541.pdf. Accessed 18 October 2023.
12. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2020;43(2):487-493.
13. Pratley RE, Gilbert M. Targeting incretins in type 2 diabetes: role of GLP-1 receptor agonists and dpp-4 inhibitors. *Rev Diabet Stud*. 2008;5(2):73-94.
14. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38(1):140-149.
15. Levin PA, Nguyen H, Wittbrodt ET, Kim SC. Glucagon-like peptide-1 receptor agonists: a systematic review of comparative effectiveness research. *Diabetes Metab Syndr Obes*. 2017;10:123-139.
16. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368(9548):1696-1705.
17. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and

cardiovascular disease (harmony outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*. 2018;392(10157):1519-1529.
18. Gerstein HC, Sattar N, Rosenstock J, et al. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. *N Engl J Med*. 2021; 385(10):896-907.
19. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394(10193): 121-130.
20. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4): 311-322.
21. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016; 375(19):1834-1844.
22. Green JB, Hernandez AF, D'Agostino RB, et al. Harmony outcomes: a randomized, double-blind, placebo-controlled trial of the effect of albiglutide on major cardiovascular events in patients with type 2 diabetes mellitus–rationale, design, and baseline characteristics. *Am Heart J*. 2018;203:30-38.
23. Royston P, Sauerbrei W. A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials. *Stat Med*. 2004;23(16):2509-2525.
24. Royston P, Sauerbrei W. Two techniques for investigating interactions between treatment and continuous covariates in clinical trials. *Stata J*. 2009;9(2):230-251.
25. Gilbert MP, Bain SC, Franek E, et al. Effect of liraglutide on cardiovascular outcomes in elderly patients: a post hoc analysis of a randomized controlled trial. *Ann Intern Med*. 2019;170(6):423-426.
26. Leiter LA, Bain SC, Hramiak I, et al. Cardiovascular risk reduction with once-weekly semaglutide in subjects with type 2 diabetes: a post hoc analysis of gender, age, and baseline CV risk profile in the SUSTAIN 6 trial. *Cardiovasc Diabetol*. 2019;18(1):73.
27. Riddle MC, Gerstein HC, Xavier D, et al. Efficacy and safety of dulaglutide in older patients: a post hoc analysis of the REWIND trial. *J Clin Endocrinol Metab*. 2021;106(5):1345-1351.
28. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol*. 2021;9(10):653-662.
29. Helber I, Alves CMR, Grespan SM, et al. The impact of advanced age on major cardiovascular events and mortality in patients with ST-elevation myocardial infarction undergoing a pharmaco-invasive strategy. *Clin Interv Aging*. 2020;15:715-722.
30. Rodgers JL, Jones J, Bolleddu SI, et al. Cardiovascular risks associated with gender and aging. *J Cardiovasc Dev Dis*. 2019;6(2):19.
31. Bode BW, Brett J, Falahati A, Pratley RE. Comparison of the efficacy and tolerability profile of liraglutide, a once-daily human GLP-1 analog, in patients with type 2 diabetes ≥65 and <65 years of age: a pooled analysis from phase III studies. *Am J Geriatr Pharmacother*. 2011;9(6):423-433.
32. Raccah D, Miossec P, Esposito V, Niemoeller E, Cho M, Gerich J. Efficacy and safety of lixisenatide in elderly (≥65 years old) and very elderly (≥75 years old) patients with type 2 diabetes: an analysis from the GetGoal phase III programme. *Diabetes Metab Res Rev*. 2015;31(2):204-211.
33. Pantalone KM, Patel H, Yu M, Fernandez LL. Dulaglutide 1.5 mg as an add-on option for patients uncontrolled on insulin: subgroup analysis by age, duration of diabetes and baseline glycated haemoglobin concentration. *Diabetes Obes Metab*. 2018;20(6):1461-1469.
34. Munshi MN, Meneilly GS, Rodríguez-Mañas L, et al. Diabetes in ageing: pathways for developing the evidence base for clinical guidance. *Lancet Diabetes Endocrinol*. 2020;8(10):855-867.
35. Espeland MA, Pratley RE, Rosenstock J, et al. 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. *Diabetes Obes Metab*. 2021;23(2):569-580.
36. Gilbert MP, Pratley RE. GLP-1 analogs and DPP-4 inhibitors in type 2 diabetes therapy: review of head-to-head clinical trials. *Front Endocrinol (Lausanne)*. 2020;11:178.

SUPPORTING INFORMATION

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

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