Effect of liraglutide on cardiovascular outcomes in elderly patients: *post hoc* analysis of a randomized controlled trial

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Background

Comorbidities and complications associated with type 2 diabetes (T2D) increase with age, making treatment of elderly people with T2D particularly challenging. Clinical data, particularly on the effect of antihyperglycemic treatment on cardiovascular (CV) events, are limited in elderly patients (1). Regulatory bodies, such as the Food and Drug administration (FDA) and the European Medicines Agency (EMA), have recommended the collection of comprehensive data in elderly patients with diabetes, with particular focus on patients aged ≥75 years to inform appropriate treatment of this growing population (2,3).

Glucagon-like peptide-1 (GLP-1) agonists are one of the newer classes of antihyperglycemic agents recommended for the treatment of T2D because of their high glycemic efficacy with low intrinsic risk of hypoglycemia and promotion of weight loss (4). The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) CV outcomes trial reported a 13% reduction in major adverse cardiovascular events (MACE) with liraglutide treatment versus placebo in patients with T2D at high risk for CV events (5).

Objective

This *post hoc* analysis examines the CV effects of liraglutide versus placebo in patients aged ≥75, 60–<75 and <60 years.

Methods and findings

Study design, methods and statistical analysis have been described previously (5). The primary endpoint was the time from randomization to first occurrence of a MACE, defined as CV death, non-fatal myocardial infarction (MI), or non-fatal stroke. Safety endpoints included the frequency of serious adverse events (SAEs) and medical events of special interest (MESIs) (5).

Time-to-event analysis was adjusted for baseline covariates (including CV status at baseline and a wider range of CV factors such as smoking) (5).

Of the 9340 patients randomized in the LEADER trial, 836 were aged ≥75, 6183 were aged 60–<75 and 2321 were aged <60 years. All patients in the <60 years age group had existing CV disease (CVD), according to the eligibility criteria. This analysis focuses on patients aged 60–<75 and >75 years, encompassing patients with both existing CVD and CVD risk factors.

Overall, the baseline characteristics were matched between the treatment groups in the age subgroups (Table 1). The primary outcome occurred more frequently in patients aged ≥75 versus those aged 60–<75 years, irrespective of treatment.

A 34% and 29% risk reduction in the frequency of MACE and MACE expanded outcomes, respectively, was observed with liraglutide versus placebo in patients aged ≥75 years. These reductions appeared less prominent between the two treatment groups in patients aged 60−<75 years (Figure 1) (*p*-interaction=0.054 and 0.083, respectively).

Patients randomized to liraglutide also experienced a reduced frequency of other CV outcomes versus placebo, irrespective of age group (Figure 1).

A 35% risk reduction in all-cause death was observed with liraglutide versus placebo in patients aged ≥75 years. This reduction appeared less accentuated between the two treatment groups in patients aged 60–<75 years (Figure 1) (*p*-interaction=0.09).

Overall, a higher proportion of patients aged ≥75 years reported SAEs or non-serious MESIs compared with patients aged 60–<75 years. Across the two subgroups, no notable difference between the treatment groups was observed. The most common adverse events were neoplasms and gastrointestinal disorders (diarrhea, nausea and vomiting) in both subgroups. The proportion of patients with gastrointestinal disorders and the incidence of acute gallstone

disease were higher in patients treated with liraglutide versus placebo, irrespective of the age subgroup.

Discussion

This *post hoc* analysis extends the results from the primary LEADER report (2), specifically to the substantial number of elderly patients at high risk of CV events included in the trial, demonstrating a significant reduction in frequency of the primary MACE and expanded MACE outcomes and all-cause death with liraglutide versus placebo. The benefits appeared more pronounced in patients aged ≥75 years versus those aged 60–<75 years. Our analysis provides important information regarding a special population for which limited clinical trial data have been available.

Limitations of this analysis include the relative small size of the subgroup ≥75 years versus the overall population, short-follow-up time, and the exploratory nature of *post hoc* analysis.

These results can help physicians in clinical decision making on optimal management of T2D in elderly patients, a vulnerable population for whom treatment options with evident benefits regarding important clinical endpoints are limited.

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Author contributions

MG, SB, EF, EJ-G, MN, RP, RR, JS, SR, KT, BJvS and JB conceived the study. SR performed the analysis. MG, SB, EF, EJ-G, MN, RP, RR, JS, SR, KT, BJvS and JB advised on analysis and interpretation of the data. MG, SB, EF, EJ-G, MN, RP, RR, JS, SR, KT, BJvS and JB drafted and revised the manuscript. All authors have approved the final version for submission. MG had full access to the data and takes responsibility for the integrity and completeness of the data, and the accuracy of the analysis. MG is the guarantor for this article, and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted, and any discrepancies from the study as originally planned have been explained. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests

MG has worked as a consultant for Novo Nordisk, and Sanofi.

SB received honoraria, teaching and research sponsorship/grants from Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Cellnovo, Diartis, Eli Lilly & Co, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi-aventis, Schering-Plough, Servier, and Takeda; funding for development of educational programs from Cardiff University, Doctors.net, Elsevier, Onmedica, Omnia-Med, Medscape, and National Institute for Health and Care Excellence (NICE) UK. He owns a share of Glycosmedia and has provided expert advice to the All-Wales Medicines Strategy Group.

EF has attended advisory panels and speakers' bureau for AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, and Novo Nordisk; speakers' bureau for Bristol-Myers Squibb, Eli Lilly & Co, Merck, and Servier.

EJ-G has received consulting and lecture fees, and fees for serving as a clinical investigator from Eli Lilly & Co, Novo Nordisk, GlaxoSmithKline, Janssen, AstraZeneca, Merck, and Sanofi.

MN has received fees for serving on advisory boards from Berlin-Chemie, Boehringer Ingelheim, Eli Lilly & Co, Fractyl, GlaxoSmithKline, Hanmi, Merck Sharp & Dohme, Novo Nordisk, Sanofi-Aventis, and Intarcia Therapeutics/Servier; lecture fees from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Eli Lilly & Co, Merck Sharp & Dohme, Novo Nordisk, Sanofi-Aventis, and Medscape; and travel support in connection with above-mentioned activities.

RP has received research grants for this study (to his institution) from Novo Nordisk, and has previously received speaker and consultancy fees (to his institution) from AstraZeneca and Takeda; consultancy fees (to his institution) from Boehringer Ingelheim, GlaxoSmithKline, Hanmi Pharmaceutical Co., Ltd., Janssen Scientific Affairs, LLC, Ligand Pharmaceuticals, Inc., Lilly, Merck, Novo Nordisk, Pfizer, and Eisai, Inc.; research grants from Gilead Sciences, Lexicon Pharmaceuticals, Ligand Pharmaceuticals, Inc., Lilly, Merck, Novo Nordisk, Sanofi-Aventis US, LLC, and Takeda.

RR is a member of the speaker's bureau for AstraZeneca, Boehringer-Ingelheim, Eli Lilly & Co, Janssen, Merck Sharp & Dohme, Novo Nordisk, Sanofi, and Takeda; grant/research support from AstraZeneca, Bayer, Boehringer-Ingelheim, Eli Lilly & Co, Novo Nordisk, and Sanofi; consulting fees from AstraZeneca, Boehringer-Ingelheim, and Sanofi.

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SR, KT, and BJvS are employees of Novo Nordisk. SR is also an inventor of the potential US patent # PCT/EP2017/054977. SR and KT are shareholders in Novo Nordisk.

JB has received contracted consulting fees, paid to his institution, and travel support from Adocia, AstraZeneca, Dance Biopharm, Dexcom, Elcelyx Therapeutics, Eli Lilly & Co, Fractyl, GI Dynamics, Intarcia Therapeutics, Lexicon, Metavention, NovaTarg, Novo Nordisk, Orexigen, PhaseBio, Sanofi, Senseonics, Shenzhen HighTide, Takeda, and vTv Therapeutics; grant support from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly & Co, GI Dynamics, GlaxoSmithKline, Intarcia Therapeutics, Johnson & Johnson, Lexicon, Medtronic, Merck, Novo Nordisk, Orexigen, Sanofi, Scion NeuroStim, Takeda, Theracos, and vTv Therapeutics. He holds stock options in Mellitus Health and PhaseBio, and served on the board of the AstraZeneca HealthCare Foundation. He is supported by a grant from the National Institutes of Health (UL1TR002489).

The submitted protocol has been published together with the original article and is available at: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1603827/suppl_file/nejmoa1603827_protocol.pdf. The subject level analysis data sets for the research presented in the publication are available from the corresponding author on reasonable request.

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1 **Table 1. Baseline demographics and characteristics by age at baseline**

	Age <60 years*		**Age 60–<75 years**		**Age ≥75 years**	
	Liraglutide (*N=1197*)	**Placebo (*N=1124*)**	**Liraglutide (*N=3053*)**	**Placebo (*N=3130*)**	**Liraglutide (*N*= 418)**	**Placebo (*N*= 418)**
Male, n (%)	775 (64.7)	761 (67.7)	1968 (64.5)	1967 (62.8)	268 (64.1)	264 (63.2)
Age, years	55.3 (2.8)	55.3 (2.8)	65.8 (4.1)	65.8 (4.1)	77.9 (2.9)	78.0 (3.1)
BMI, kg/m^2	33.4 (6.8)	33.4 (6.9)	32.4 (6.2)	32.4 (6.1)	30.7 (5.4)	30.5 (4.8)
Diabetes duration, years	10.9 (7.0)	10.4 (6.8)	13.0 (7.7)	13.3 (8.1)	17.0 (10.3)	15.8 (9.1)
HbA_{1c}, % (mmol/mol)	9.0 (1.7)	8.9 (1.6)	8.7 (1.5)	8.6 (1.4)	8.4 (1.4)	8.3 (1.3)
CV history (MI or stroke)	626 (52.3)	585 (52.0)	1089 (35.7)	1083 (34.6)	150 (35.9)	159 (38.0)
History of MI, n (%)	500 (41.8)	473 (42.1)	847 (27.7)	812 (25.9)	117 (28.0)	115 (27.5)
History of stroke, n (%)	173 (14.5)	142 (12.6)	332 (10.9)	361 (11.5)	41 (9.8)	54 (12.9)
Smoking status						
Current smoker, n (%)	210 (17.5)	209 (18.6)	343 (11.2)	339 (10.8)	14 (3.3)	15 (3.6)
Never smoked, n (%)	488 (40.8)	411 (36.6)	1267 (41.5)	1310 (41.9)	195 (46.7)	199 (47.6)
Previous smoker, n (%)	499 (41.7)	504 (44.8)	1443 (47.3)	1481 (47.3)	209 (50.0)	204 (48.8)
Systolic blood pressure, mmHg	133.4 (17.3)	132.7 (17.0)	136.8 (17.7)	136.7 (17.7)	136.5 (19.4)	138.3 (18.6)
Diastolic blood pressure, mmHg	79.6 (9.8)	78.9 (9.7)	77.0 (10.2)	76.7 (10.2)	72.2 (10.4)	73.7 (10.3)
Heart rate, beats per minute	74.0 (10.9)	74.2 (10.6)	72.5 (11.4)	72.2 (11.5)	70.1 (11.4)	70.7 (12.2)

	Age <60 years*		**Age 60–<75 years**		**Age ≥75 years**	
	Liraglutide (*N=1197*)	**Placebo (*N=1124*)**	**Liraglutide (*N=3053*)**	**Placebo (*N=3130*)**	**Liraglutide (*N*= 418)**	**Placebo (*N*= 418)**
eGFR MDRD, mL/min/1.73 m^2	89.8 (28.3)	90.3 (27.8)	78.8 (26.3)	79.2 (26.3)	62.9 (23.2)	65.0 (22.1)
Severe (<30), n (%)	25 (2.1)	23 (2.0)	63 (2.1)	63 (2.0)	29 (6.9)	21 (5.0)
Moderate (30–59), n (%)	148 (12.4)	130 (11.6)	672 (22.0)	641 (20.5)	179 (42.8)	164 (39.2)
Mild (60–89), n (%)	422 (35.3)	380 (33.8)	1349 (44.2)	1420 (45.4)	161 (38.5)	175 (41.9)
Normal (≥90), n (%)	602 (50.3)	591 (52.6)	969 (31.7)	1006 (32.1)	49 (11.7)	58 (13.9)
Total cholesterol, mmol/L	4.5 (1.2)	4.5 (1.4)	4.4 (1.2)	4.4 (1.1)	4.2 (1.1)	4.3 (1.0)
LDL cholesterol, mmol/L	2.4 (1.0)	2.4 (1.0)	2.3 (0.9)	2.3 (0.9)	2.2 (0.9)	2.3 (0.9)
HDL cholesterol, mmol/L	1.1 (0.3)	1.1 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.3 (0.4)
Triglycerides, mmol/L	2.3 (1.6)	2.4 (2.5)	2.0 (1.4)	2.0 (1.4)	1.8 (1.0)	1.7 (1.0)

2 Data are mean (SD) or n (%) unless otherwise stated.

3 *All patients in the <60 years age group had a history of CV disease in accordance with the eligibility criteria.

4 BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HDL, high-

5 density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; MDRD, calculated using the Modified Diet in Renal

6 Disease equation; n, number of patients, N, total number of patients, SD, standard deviation.

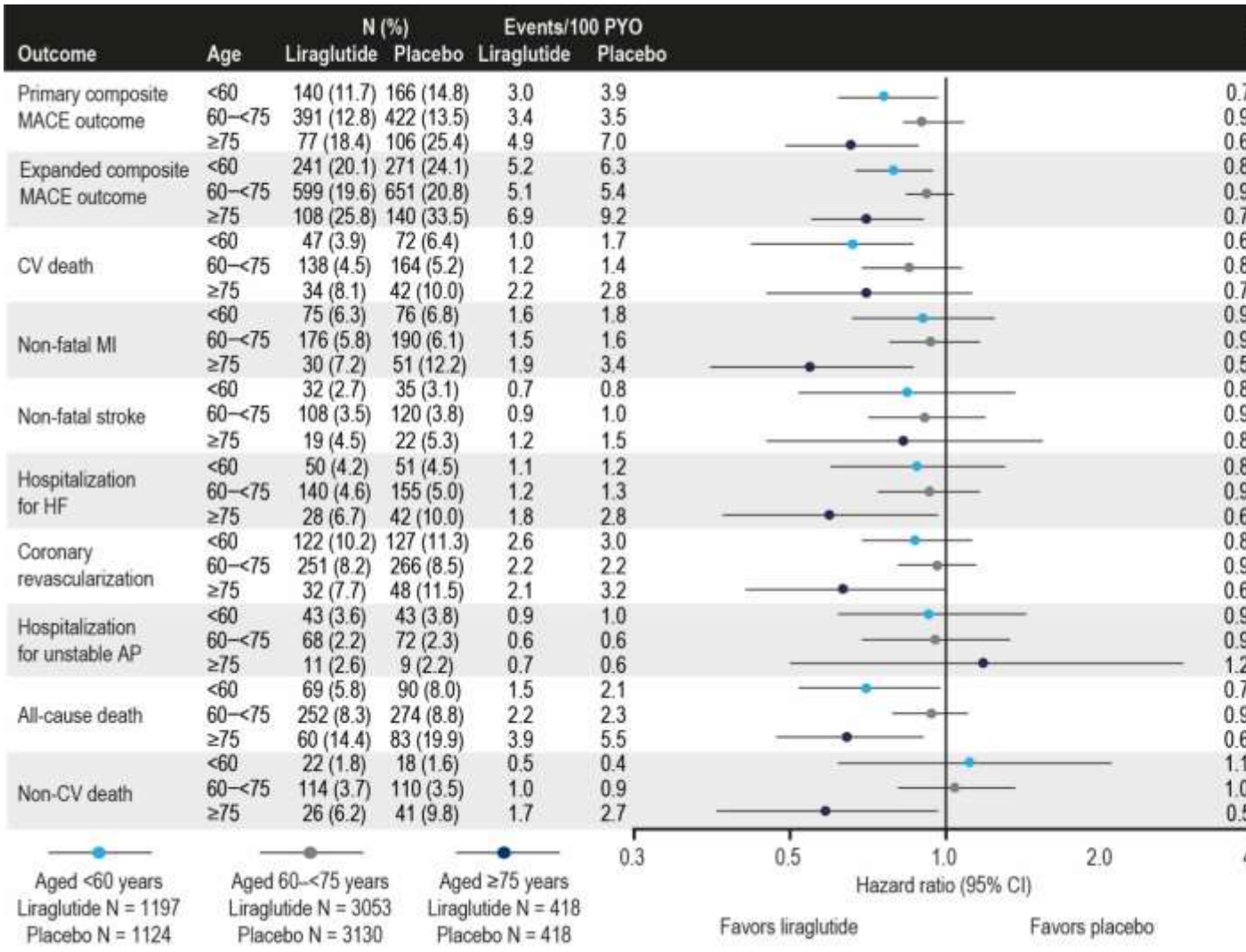
Figure legend

Figure 1. First occurrence of the primary composite MACE outcome and secondary outcomes, stratified by age at baseline

*p-value is for the interaction between treatment and subgroup. A significant p-interaction value (<0.05) indicates that the treatment effect is not consistent across subgroups. Analyses were adjusted for baseline covariates (including CV status at baseline as defined in the primary analysis (5) and a wider range of CV factors such as smoking). No adjustment for multiple testing was performed.

AP, angina pectoris; CI, confidence interval; CV, cardiovascular; HF, heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; n, number of patients; PYO, patient-years of observation.

17


Outcome
Age
N (%)
Liraglutide
Placebo
Events/100 PYO
Liraglutide
Placebo
Primary composite MACE outcome
<60 140 (11.7) 166 (14.8) 3.0 3.9
60–<75 391 (12.8) 422 (13.5) 3.4 3.5
≥75 77 (18.4) 106 (25.4) 4.9 7.0
Expanded composite MACE outcome
<60 241 (20.1) 271 (24.1) 5.2 6.3
60–<75 599 (19.6) 651 (20.8) 5.1 5.4
≥75 108 (25.8) 140 (33.5) 6.9 9.2
CV death
<60 47 (3.9) 72 (6.4) 1.0 1.7
60–<75 138 (4.5) 164 (5.2) 1.2 1.4
≥75 34 (8.1) 42 (10.0) 2.2 2.8
Non-fatal MI
<60 75 (6.3) 76 (6.8) 1.6 1.8
60–<75 176 (5.8) 190 (6.1) 1.5 1.6
≥75 30 (7.2) 51 (12.2) 1.9 3.4
Non-fatal stroke
<60 32 (2.7) 35 (3.1) 0.7 0.8
60–<75 108 (3.5) 120 (3.8) 0.9 1.0
≥75 19 (4.5) 22 (5.3) 1.2 1.5
Hospitalization for HF
<60 50 (4.2) 51 (4.5) 1.1 1.2
60–<75 140 (4.6) 155 (5.0) 1.2 1.3
≥75 28 (6.7) 42 (10.0) 1.8 2.8
Coronary revascularization
<60 122 (10.2) 127 (11.3) 2.6 3.0
60–<75 251 (8.2) 266 (8.5) 2.2 2.2
≥75 32 (7.7) 48 (11.5) 2.1 3.2
Hospitalization for unstable AP
<60 43 (3.6) 43 (3.8) 0.9 1.0
60–<75 68 (2.2) 72 (2.3) 0.6 0.6
≥75 11 (2.6) 9 (2.2) 0.7 0.6
All-cause death
<60 69 (5.8) 90 (8.0) 1.5 2.1
60–<75 252 (8.3) 274 (8.8) 2.2 2.3
≥75 60 (14.4) 83 (19.9) 3.9 5.5
Non-CV death
<60 22 (1.8) 18 (1.6) 0.5 0.4
60–<75 114 (3.7) 110 (3.5) 1.0 0.9
≥75 26 (6.2) 41 (9.8) 1.7 2.7
0.3
0.5
1.0
2.0
Hazard ratio (95% CI)
Favors liraglutide
Favors placebo
Aged <60 years
Liraglutide N = 1197
Placebo N = 1124
Aged 60–<75 years
Liraglutide N = 3053
Placebo N = 3130
Aged ≥75 years
Liraglutide N = 418
Placebo N = 418

18