## Effect of Liraglutide on Cardiovascular Outcomes in Elderly Patients: A Post Hoc Analysis of a Randomized Controlled Trial

*Background:* Comorbidities and complications associated with type 2 diabetes mellitus (T2DM) increase with age, making treatment of elderly persons with this condition challenging. Clinical data on the effect of antihyperglycemic treatment on cardiovascular (CV) events in elderly persons are limited (1). The U.S. Food and Drug Administration and European Medicines Agency recommend collecting comprehensive data on elderly patients with diabetes, particularly those aged 75 years or older, to inform appropriate treatment of this growing population (2, 3).

Glucagon-like peptide-1 agonists are among the newer classes of antihyperglycemic agents recommended to treat T2DM because they have high glycemic efficacy and low intrinsic risk for hypoglycemia and promote weight loss (4). The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial showed a 13% reduction in major adverse cardiovascular events (MACEs) with liraglutide versus placebo in patients with T2DM at high risk for CV events (5). According to eligibility criteria, patients younger than 60 years had CV disease and older patients had at least 1 risk factor for CV disease.

*Objective:* To examine the CV effects of liraglutide versus placebo in patients aged 75 years or older and 60 to 74 years with risk factors for CV disease and in patients younger than 60 years with CV disease, focusing on the first 2 age subgroups.

*Methods and Findings:* The study design, methods, and statistical analysis have been described previously (5). The primary outcome was time from randomization to the first MACE, defined as CV death, a nonfatal myocardial infarction, or a nonfatal stroke. Safety end points included the frequency of serious adverse events and medical events of special interest (5). Time-to-event analysis was adjusted for baseline covariates (including baseline CV status and a wider range of CV factors, such as smoking) (5).

Of the 9340 patients randomly assigned in the LEADER trial, 836 were aged 75 years or older, 6183 were aged 60 to 74 years, and 2321 were younger than 60 years. Overall, the baseline characteristics were matched between the treatment groups across the age subgroups (**Table**). Major adverse cardiovascular events occurred more frequently in patients aged 75 years or older than those aged 60 to 74 years, regardless of treatment.

Patients aged 75 years or older had a 34% and 29% risk reduction in the frequency of MACEs and expanded MACE outcomes, respectively, with liraglutide versus placebo. These reductions seemed less prominent between the 2 treatment groups in patients aged 60 to 74 years ($P$ for interaction across all age groups for MACEs and expanded MACE outcomes = 0.054 and 0.084, respectively) (**Figure**). Patients in the liraglutide group had fewer other CV outcomes than those in the placebo group, regardless of age subgroup (**Figure**). The risk reduction in all-cause death with liraglutide versus placebo was 35% in patients aged 75 years or older versus 6% in patients aged 60 to 74 years ($P$ for interaction = 0.088) (**Figure**).

Overall, 63.5% and 61.7% of patients aged 75 years or older reported serious adverse events and nonserious medical events of special interest, respectively, versus 49.5% and 49.8% of patients aged 60 to 74 years. Across these 2 age subgroups, the treatment groups did not notably differ. The most common adverse events were neoplasms (10.3% vs. 14.2% in patients aged 60 to 74 years and 75 years or older, respectively) and gastrointestinal disorders (diarrhea, nausea, and vomiting in 1.2%, 2.4%, and 1.1% of patients aged 60 to 74 years and 2.8%, 2.9%, and 1.2% in those aged 75 years or older, respectively). In the liraglutide group versus the placebo group, more patients had gastrointestinal disorders (46.6% vs. 33.0%, respectively) and the incidence of acute gallstone disease was higher (10.0% vs. 6.3%, respectively), regardless of age subgroup.

*Discussion:* This post hoc analysis of the LEADER trial (2) focused on elderly patients at high risk for CV events and showed that liraglutide significantly reduced the risk for MACEs, expanded MACE outcomes, and all-cause death in this population compared with placebo. Benefits seemed more pronounced in patients aged 75 years or older than in those aged 60 to 74 years. Our analysis provides important information about a population in which clinical trial data are limited.

Limitations of this analysis include the relatively small subgroup of patients aged 75 years or older versus the overall population, short follow-up, and the exploratory nature of post hoc analyses. These results can help physicians make clinical decisions on optimal management of T2DM in elderly patients, a vulnerable population in which treatment options that evidently benefit important clinical end points are limited.

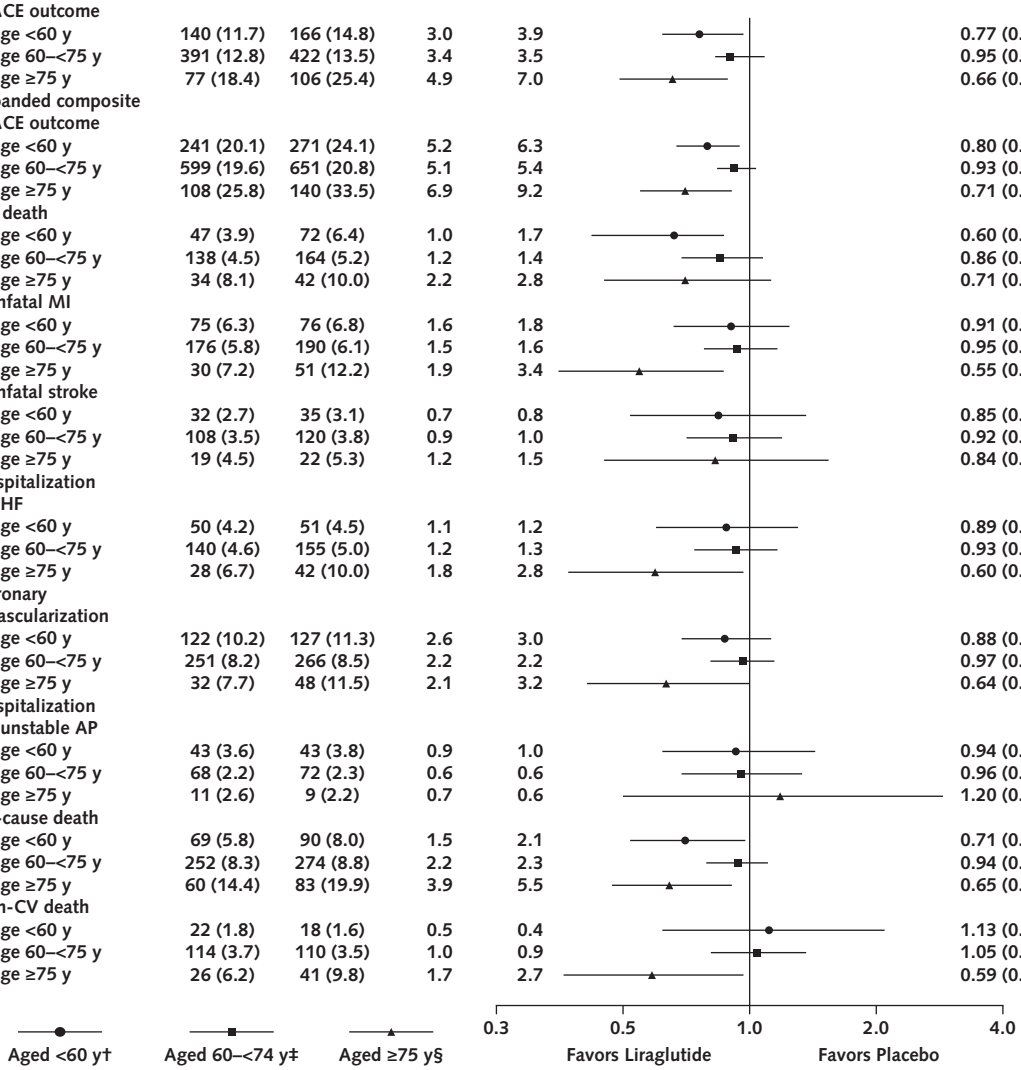
***Table.*** Baseline Demographic and Clinical Characteristics, by Age at Baseline*

| Characteristic | Age at Baseline | | | | | |
|---|---|---|---|---|---|---|
| | <60 Years† | | 60–74 Years | | ≥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) |
| Mean age (SD), *y* | 55.3 (2.8) | 55.3 (2.8) | 65.8 (4.1) | 65.8 (4.1) | 77.9 (2.9) | 78.0 (3.1) |
| Mean BMI (SD), *kg/m²* | 33.4 (6.8) | 33.4 (6.9) | 32.4 (6.2) | 32.4 (6.1) | 30.7 (5.4) | 30.5 (4.8) |
| Mean diabetes duration (SD), *y* | 10.9 (7.0) | 10.4 (6.8) | 13.0 (7.7) | 13.3 (8.1) | 17.0 (10.3) | 15.8 (9.1) |
| Mean $HbA_{1c}$ level (SD), *%* | 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, *n (%)* | 626 (52.3) | 585 (52.0) | 1089 (35.7) | 1083 (34.6) | 150 (35.9) | 159 (38.0) |
| MI | 500 (41.8) | 473 (42.1) | 847 (27.7) | 812 (25.9) | 117 (28.0) | 115 (27.5) |
| Stroke | 173 (14.5) | 142 (12.6) | 332 (10.9) | 361 (11.5) | 41 (9.8) | 54 (12.9) |
| Smoking status, *n (%)* | | | | | | |
| Current | 210 (17.5) | 209 (18.6) | 343 (11.2) | 339 (10.8) | 14 (3.3) | 15 (3.6) |
| Never | 488 (40.8) | 411 (36.6) | 1267 (41.5) | 1310 (41.9) | 195 (46.7) | 199 (47.6) |
| Former | 499 (41.7) | 504 (44.8) | 1443 (47.3) | 1481 (47.3) | 209 (50.0) | 204 (48.8) |
| Mean blood pressure (SD), *mm Hg* | | | | | | |
| Systolic | 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 | 79.6 (9.8) | 78.9 (9.7) | 77.0 (10.2) | 76.7 (10.2) | 72.2 (10.4) | 73.7 (10.3) |
| Mean heart rate (SD), *beats/min* | 74.0 (10.9) | 74.2 (10.6) | 72.5 (11.4) | 72.2 (11.5) | 70.1 (11.4) | 70.7 (12.2) |
| Mean eGFR (SD), *mL/min/1.73 m²*‡ | 89.8 (28.3) | 90.3 (27.8) | 78.8 (26.3) | 79.2 (26.3) | 62.9 (23.2) | 65.0 (22.1) |
| CKD stage, *n (%)* | | | | | | |
| Severe (eGFR <30 mL/min/1.73 $m^2$) | 25 (2.1) | 23 (2.0) | 63 (2.1) | 63 (2.0) | 29 (6.9) | 21 (5.0) |
| Moderate (eGFR, 30–59 mL/min/1.73 $m^2$) | 148 (12.4) | 130 (11.6) | 672 (22.0) | 641 (20.5) | 179 (42.8) | 164 (39.2) |
| Mild (eGFR, 60–89 mL/min/1.73 $m^2$) | 422 (35.3) | 380 (33.8) | 1349 (44.2) | 1420 (45.4) | 161 (38.5) | 175 (41.9) |
| Normal kidney function (eGFR, ≥90 mL/min/1.73 $m^2$) | 602 (50.3) | 591 (52.6) | 969 (31.7) | 1006 (32.1) | 49 (11.7) | 58 (13.9) |
| Mean total cholesterol level (SD) | | | | | | |
| *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) |
| *mg/dL*§ | 173.7 (46.3) | 173.7 (54.0) | 169.8 (46.3) | 169.8 (42.5) | 162.1 (42.5) | 166.0 (38.6) |
| Mean LDL cholesterol level (SD) | | | | | | |
| *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) |
| *mg/dL*§ | 92.6 (38.6) | 92.6 (38.6) | 88.8 (34.7) | 88.8 (34.7) | 84.9 (34.7) | 88.8 (34.7) |
| Mean HDL cholesterol level (SD) | | | | | | |
| *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) |
| *mg/dL*§ | 42.5 (11.6) | 42.5 (11.6) | 46.3 (11.6) | 46.3 (11.6) | 46.3 (11.6) | 50.2 (15.4) |
| Mean triglyceride level (SD) | | | | | | |
| *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) |
| *mg/dL*§ | 203.6 (141.6) | 212.4 (221.3) | 177.0 (123.9) | 177.0 (123.9) | 159.3 (88.5) | 150.5 (88.5) |

BMI = body mass index; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; $HbA_{1c}$ = hemoglobin $A_{1c}$; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction.
* Percentages may not sum to 100 due to rounding.
† All patients in this age group had a history of CV disease in accordance with the eligibility criteria.
‡ Calculated using the Modification of Diet in Renal Disease equation.
§ Values were calculated and not measured.

***Figure.*** First occurrence of a MACE and secondary outcomes, by age at baseline.

| Variable | Patients, *n* (%) | | Events per 100 Person–Years of Observation, *n* | | Hazard Ratio (95% CI) | *P* Value | *P* for Interaction |
|---|---|---|---|---|---|---|---|
| | Liraglutide | Placebo | Liraglutide | Placebo | | | |
| **Primary composite MACE outcome** | | | | | | | |
| Age <60 y | 140 (11.7) | 166 (14.8) | 3.0 | 3.9 | 0.77 (0.62–0.97) | 0.026 | |
| Age 60–<75 y | 391 (12.8) | 422 (13.5) | 3.4 | 3.5 | 0.95 (0.83–1.09) | 0.47 | 0.054 |
| Age ≥75 y | 77 (18.4) | 106 (25.4) | 4.9 | 7.0 | 0.66 (0.49–0.89) | 0.006 | |
| **Expanded composite MACE outcome** | | | | | | | |
| Age <60 y | 241 (20.1) | 271 (24.1) | 5.2 | 6.3 | 0.80 (0.67–0.95) | 0.013 | |
| Age 60–<75 y | 599 (19.6) | 651 (20.8) | 5.1 | 5.4 | 0.93 (0.84–1.04) | 0.23 | 0.084 |
| Age ≥75 y | 108 (25.8) | 140 (33.5) | 6.9 | 9.2 | 0.71 (0.55–0.91) | 0.007 | |
| **CV death** | | | | | | | |
| Age <60 y | 47 (3.9) | 72 (6.4) | 1.0 | 1.7 | 0.60 (0.42–0.87) | 0.007 | |
| Age 60–<75 y | 138 (4.5) | 164 (5.2) | 1.2 | 1.4 | 0.86 (0.69–1.08) | 0.198 | 0.26 |
| Age ≥75 y | 34 (8.1) | 42 (10.0) | 2.2 | 2.8 | 0.71 (0.45–1.13) | 0.147 | |
| **Nonfatal MI** | | | | | | | |
| Age <60 y | 75 (6.3) | 76 (6.8) | 1.6 | 1.8 | 0.91 (0.66–1.25) | 0.55 | |
| Age 60–<75 y | 176 (5.8) | 190 (6.1) | 1.5 | 1.6 | 0.95 (0.78–1.17) | 0.65 | 0.097 |
| Age ≥75 y | 30 (7.2) | 51 (12.2) | 1.9 | 3.4 | 0.55 (0.35–0.87) | 0.010 | |
| **Nonfatal stroke** | | | | | | | |
| Age <60 y | 32 (2.7) | 35 (3.1) | 0.7 | 0.8 | 0.85 (0.52–1.37) | 0.50 | |
| Age 60–<75 y | 108 (3.5) | 120 (3.8) | 0.9 | 1.0 | 0.92 (0.71–1.20) | 0.54 | 0.93 |
| Age ≥75 y | 19 (4.5) | 22 (5.3) | 1.2 | 1.5 | 0.84 (0.45–1.55) | 0.57 | |
| **Hospitalization for HF** | | | | | | | |
| Age <60 y | 50 (4.2) | 51 (4.5) | 1.1 | 1.2 | 0.89 (0.60–1.31) | 0.55 | |
| Age 60–<75 y | 140 (4.6) | 155 (5.0) | 1.2 | 1.3 | 0.93 (0.74–1.17) | 0.52 | 0.27 |
| Age ≥75 y | 28 (6.7) | 42 (10.0) | 1.8 | 2.8 | 0.60 (0.37–0.97) | 0.035 | |
| **Coronary revascularization** | | | | | | | |
| Age <60 y | 122 (10.2) | 127 (11.3) | 2.6 | 3.0 | 0.88 (0.69–1.13) | 0.31 | |
| Age 60–<75 y | 251 (8.2) | 266 (8.5) | 2.2 | 2.2 | 0.97 (0.81–1.15) | 0.69 | 0.23 |
| Age ≥75 y | 32 (7.7) | 48 (11.5) | 2.1 | 3.2 | 0.64 (0.41–1.00) | 0.049 | |
| **Hospitalization for unstable AP** | | | | | | | |
| Age <60 y | 43 (3.6) | 43 (3.8) | 0.9 | 1.0 | 0.94 (0.62–1.44) | 0.79 | |
| Age 60–<75 y | 68 (2.2) | 72 (2.3) | 0.6 | 0.6 | 0.96 (0.69–1.34) | 0.80 | 0.88 |
| Age ≥75 y | 11 (2.6) | 9 (2.2) | 0.7 | 0.6 | 1.20 (0.50–2.91) | 0.68 | |
| **All-cause death** | | | | | | | |
| Age <60 y | 69 (5.8) | 90 (8.0) | 1.5 | 2.1 | 0.71 (0.52–0.98) | 0.035 | |
| Age 60–<75 y | 252 (8.3) | 274 (8.8) | 2.2 | 2.3 | 0.94 (0.79–1.11) | 0.47 | 0.088 |
| Age ≥75 y | 60 (14.4) | 83 (19.9) | 3.9 | 5.5 | 0.65 (0.47–0.91) | 0.012 | |
| **Non-CV death** | | | | | | | |
| Age <60 y | 22 (1.8) | 18 (1.6) | 0.5 | 0.4 | 1.13 (0.61–2.11) | 0.70 | |
| Age 60–<75 y | 114 (3.7) | 110 (3.5) | 1.0 | 0.9 | 1.05 (0.81–1.37) | 0.69 | 0.111 |
| Age ≥75 y | 26 (6.2) | 41 (9.8) | 1.7 | 2.7 | 0.59 (0.36–0.97) | 0.038 | |




AP = angina pectoris; CV = cardiovascular; HF = heart failure; MACE = major adverse cardiovascular event; MI = myocardial infarction.
* For the interaction between treatment and the 3 subgroups by age. A significant value ($P < 0.05$) indicates that the treatment effect was 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 was done for multiple testing. Secondary CV end points included an expanded composite MACE outcome that comprised a MACE (as defined by the primary end point) or coronary revascularization, hospitalization for unstable AP or HF, each component of the composite CV outcomes, and all-cause and non-CV death.
† 1197 patients were in the liraglutide group, and 1124 were in the placebo group.
‡ 3053 patients were in the liraglutide group, and 3130 were in the placebo group.
§ 418 patients were in the liraglutide group, and 418 were in the placebo group.

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