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The cardiovascular benefits associated with liraglutide in the LEADER trial are sustained when analysing both first and recurrent MACE

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Background and aims: In patients with type 2 diabetes and high risk for cardiovascular (CV) events, the LEADER CV outcomes trial (N=9340) showed risk of a first major adverse CV event (MACE) was reduced with liraglutide vs placebo when added to standard of care. Here we further examined liraglutide treatment effects on both first and recurrent ("total observed") CV events, including: 1) a composite MACE endpoint: CV death, non-fatal stroke or non-fatal myocardial infarction; 2) expanded MACE (also included coronary revascularisation and hospitalisation for heart failure or unstable angina); and 3) individual CV endpoints.
Materials and methods: A post hoc analysis utilising an extension of Cox regression modelling of time to event data, with additional sensitivity analyses.
Results: In total, 1302 first and 303 recurrent MACEs occurred: liraglutide, 735 events; placebo, 870 events. Risk for total observed MACEs was reduced by 14% with liraglutide vs placebo (HR=0.86, 95% CI 0.78-0.95). Corresponding analyses for all other CV endpoints suggested risk reductions with liraglutide, with the exception of hospitalisation for unstable angina (Table). Sensitivity analyses using other regression models confirmed the results (Table).
Conclusion: The reduction in risk of first event with liraglutide in LEADER was sustained in this post hoc analysis; this is of clinical relevance to individuals who are at risk of or who have experienced a MACE, and confirms the robustness of the data.

	First and recurrent ("total observed") CV endpoints				First CV endpoints only
Outcome	**No. of events** (lira vs placebo)	**HR*** (lira/placebo) **[95% CI]**	**Sensitivity analysis 1 (Prentice-Williams-Peterson model)†** **HR** (lira/placebo) **[95% CI]**	**Sensitivity analysis 2 (Wei-Lin-Weissfeld model)** **HR** (lira/placebo) **[95% CI]**	**Cox regression model HR** (lira/placebo) **[95% CI]**
MACE	735 vs 870	0.86 [0.78; 0.95]	0.87 [0.78; 0.95]	0.85 [0.77; 0.94]	0.87 [0.78; 0.97]
Expanded MACE	1721 vs 1958	0.92 [0.86; 0.99]	0.91 [0.86; 0.98]	0.90 [0.84; 0.96]	0.88 [0.81; 0.96]
CV death	219 vs 278	NA	NA	NA	0.78 [0.66; 0.93
Non-fatal stroke	174 vs 199	0.87 [0.71; 1.07]	0.88 [0.72; 1.08]	0.89 [0.72; 1.09]	0.89 [0.72; 1.11]
Non-fatal MI	342 vs 393	0.88 [0.76; 1.02]	0.90 [0.77; 1.04]	0.87 [0.75; 1.01]	0.88 [0.75; 1.03]
Coronary revascularisation	503 vs 559	0.93 [0.82; 1.05]	0.92 [0.81; 1.03]	0.92 [0.81; 1.04]	0.91 [0.80; 1.04]
Hospitalisation for heart failure	342 vs 389	0.94 [0.81; 1.10]	0.96 [0.83; 1.11]	0.93 [0.80; 1.08]	0.87 [0.73; 1.05]
Hospitalisation for unstable angina	141 vs 140	1.01 [0.80; 1.28]	1.01 [0.80; 1.27]	1.00 [0.79; 1.26]	0.98 [0.76; 1.26]

*Andersen-Gill intensity model, adjusted for previous events as a continuous time-dependent covariate.
†Based on total time to event. CI, confidence interval; CV, cardiovascular; lira, liraglutide; MACE, major adverse cardiovascular event; MI, myocardial infarction; NA, not applicable.

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