Effects of Liraglutide on Cardiovascular Outcomes in Type 2 Diabetes Patients With and Without Baseline Metformin Use: Post Hoc Analyses of the LEADER Trial

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Glucagon-like peptide 1 receptor agonists (GLP-1RAs) reduce cardiovascular (CV) events among patients with type 2 diabetes and high CV risk. Because consensus professional society recommendations endorse metformin as the first-line medication for type 2 diabetes, the CV efficacy of GLP-1RAs has primarily been studied with background metformin therapy (1). However, the European Society of Cardiology now recommends GLP-1RAs as a first-line type 2 diabetes treatment for patients at high CV risk (2). These discordant recommendations raise the question of how background metformin might influence the CV benefits of GLP-1RAs. Using data from the LEADER trial, we sought to answer this question by exploring possible heterogeneity in the CV efficacy of liraglutide related to baseline metformin treatment (3).

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial (NCT01179048, ClinicalTrials.gov) has been described elsewhere (3). Patients with type 2 diabetes and high CV risk underwent double-blind randomization to daily liraglutide versus placebo in addition to existing care.

Each patient contributed data from randomization until censoring. The primary outcome was time from randomization to first occurrence of a composite of CV death, myocardial infarction, or stroke. Prespecified secondary outcomes included an expanded composite (primary plus coronary revascularization or hospitalization for unstable angina or heart failure), the composite components, and all-cause death. All outcomes were centrally adjudicated.

Metformin treatment was identified at the baseline trial visit and each visit thereafter. Within each baseline metformin treatment subgroup, effect estimates for liraglutide versus placebo (hazard ratio [HR], 95% CI) were derived using Cox proportional hazards regression models; multivariable adjustment for baseline demographic and clinical factors was performed. Inverse probability for treatment weighting (IPTW) was used to account for imbalances in covariates between baseline metformin treatment subgroups (4). For multivariable analyses with IPTW, heterogeneity in the association between baseline metformin treatment and the effect of liraglutide was estimated using stabilized, weighted Cox proportional hazards models with randomization group, baseline metformin treatment, and the interaction of both as fixed factors (5). A $P_{interaction} < 0.05$ was held to indicate a statistically significant difference in the treatment effect of liraglutide across baseline metformin subgroups. In order to explore the impact of post-randomization changes in metformin use, a sensitivity analysis repeated the main IPTW analysis for the primary outcome with censoring for initiation and discontinuation of metformin during the study. All data, methods, and study materials are available on request.

Primary results of the LEADER trial are presented elsewhere (3). Of 9,340 randomized participants, 7,144 (76%) used metformin at baseline. There were multiple differences between baseline metformin subgroups; notably, metformin-treated patients had shorter diabetes duration, higher estimated glomerular filtration rate (eGFR), lower heart failure prevalence, and less insulin use. All differences were attenuated by IPTW adjustment. Irrespective of randomization group, baseline metformin users had lower risk of the primary outcome than nonusers in multivariable analyses with

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IPTW ($HR_{adjusted}$ [95% CI] 0.72 [0.64; 0.81]).

In multivariable analyses with IPTW (Fig. 1), liraglutide did not significantly reduce incidence of the primary outcome versus placebo among baseline metformin users ($HR_{adjusted}$ [95% CI] 0.97 [0.85; 1.10]). Liraglutide did reduce incidence of the primary outcome among baseline metformin nonusers ($HR_{adjusted}$ [95% CI] 0.79 [0.64; 0.97]). Similar results were seen for the expanded composite. The *P* value for the interaction between randomization group and baseline metformin treatment did not achieve statistical significance for the primary outcome ($P_{interaction} = 0.10$), the expanded composite ($P_{interaction} = 0.09$), or other outcomes (Fig. 1).

Among baseline metformin users, 658 (18.6%) receiving liraglutide and 585 (16.2%) receiving placebo discontinued metformin during the trial. Among baseline nonusers, 249 (22.1%) receiving liraglutide and 299 (28.0%) receiving placebo initiated metformin. Sensitivity analysis results were similar to the main analysis for the primary outcome within baseline metformin user ($HR_{adjusted}$ [95% CI] 0.94 [0.82; 1.08]) and nonuser ($HR_{adjusted}$ [95% CI] 0.71 [0.55; 0.90]) subgroups. The interaction between randomization group and baseline metformin treatment did achieve statistical significance in the sensitivity analysis ($P_{interaction} = 0.046$).

Whether background metformin treatment modifies the CV effects of GLP-1RAs is a foundational question underlying debates as to the optimal first-line type 2 diabetes treatment for patients with high CV risk. Although the effects of liraglutide appeared greater in the subgroup without baseline metformin treatment, our main analyses did not show statistically significant interactions between liraglutide treatment and metformin use. These findings may indicate that the CV benefits of liraglutide do not rely upon prior metformin treatment. As such, discussions regarding first-line treatment for type 2 diabetes in individuals with high CV risk should continue to focus on the absolute effectiveness of the agents in question, with appropriate consideration of costs to patients and society.

We conducted a sensitivity analysis exploring how postrandomization changes in metformin treatment impacted the interaction between randomization group and baseline metformin use. While CV effect estimates for liraglutide within the baseline metformin subgroups were similar to the main analysis, the interaction did achieve statistical significance in the sensitivity analysis. Analyzing nonrandomized exposures is challenging, and postrandomization changes in metformin use likely occurred for cause; interpreting this sensitivity analysis thus requires caution.

The present analyses add to existing evidence regarding the potential influence of metformin on the CV efficacy of newer diabetes agents. Previously, one

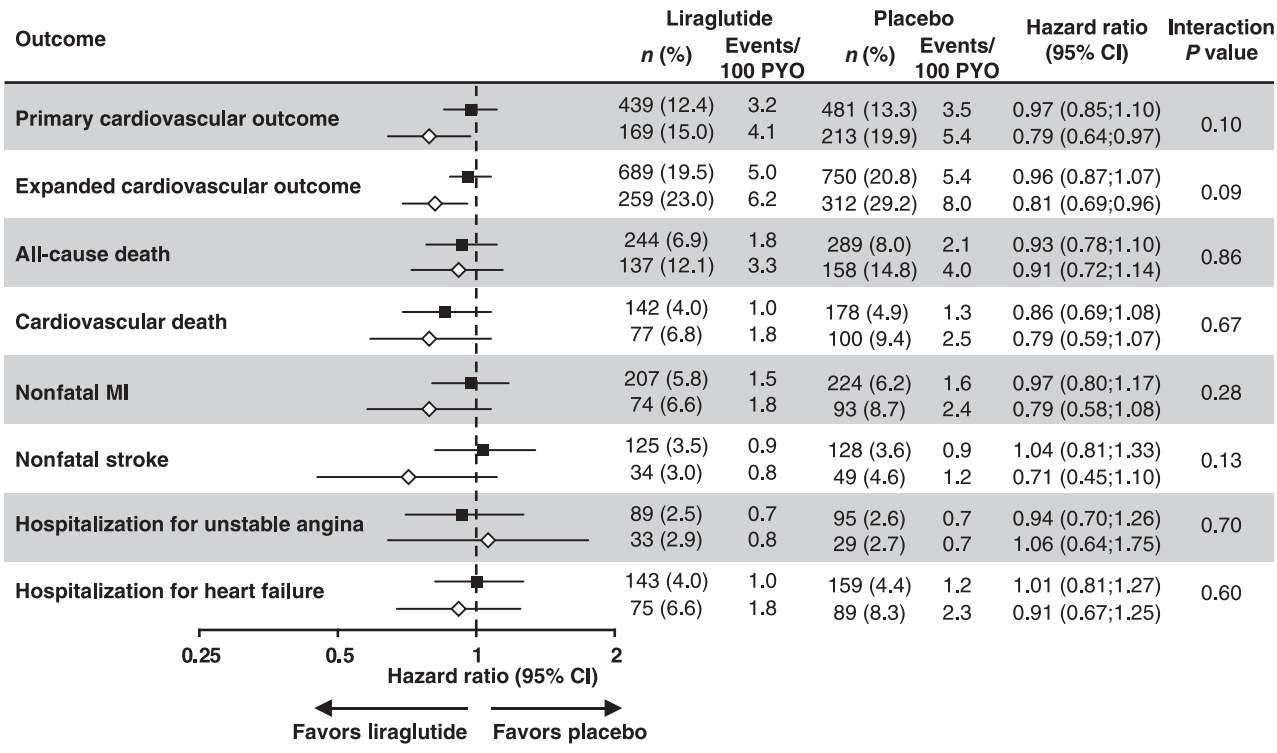

Figure 1—Effects of liraglutide (vs. placebo) on CV outcomes among patients with and without baseline metformin use, adjusted for baseline covariates with inverse probability weighting. Shaded squares = metformin use at baseline; empty diamonds = no metformin use at baseline. HRs derived using a Cox proportional hazards regression model with randomization group, baseline metformin exposure, and the interaction of both as factors, and diabetes duration, eGFR, and age at baseline as additional covariates, adjusted for baseline covariates: age, sex, region, diabetes duration, HbA_{1c}, antihyperglycemic medication, eGFR, smoking, prior myocardial infarction, heart rhythm disorders, heart failure, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, prior ischemic stroke, prior transient ischemic attack, prior hemorrhagic stroke, prior percutaneous coronary intervention, prior coronary bypass surgery, intracranial artery stenosis, carotid artery stenosis, peripheral arterial disease, and ≥50% stenosis of coronary, carotid, or other arteries. MI, myocardial infarction; *n*, number of patients with event; PYO, patient-years of observation; %, proportion of patients in subgroup with event.

GLP-1RA trial reported an unadjusted secondary analysis showing that the CV effects of albiglutide did not differ significantly across baseline metformin subgroups (6). A secondary analysis incorporating adjustment for baseline differences found that empagliflozin was associated with CV benefits irrespective of baseline metformin use (7). A trial-level meta-analysis without adjustment for baseline differences suggested possible variability in CV outcomes with dipeptidyl peptidase 4 inhibitors favoring baseline metformin users (8). Because potentially confounding factors like eGFR and heart failure prevalence may be independently associated with both baseline metformin use and CV outcomes, adjustment for propensity to receive metformin (as well as baseline differences) is critical and was a particular strength of our approach.

Importantly, the LEADER trial was not explicitly designed to evaluate the present research question. An appropriately powered randomized trial would be required to definitively ascertain heterogeneity in the CV efficacy of liraglutide.

In conclusion, we identified no clear evidence for heterogeneity in the CV efficacy of liraglutide based on background metformin use.

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