Effects of Liraglutide Compared With Placebo on Events of Acute Gallbladder or Biliary Disease in Patients With Type 2 Diabetes at High Risk for Cardiovascular Events in the LEADER Randomized Trial. Diabetes Care 2019;42:1912–1920

Michael A. Nauck,[1] Eskil Kreiner,[2] Søren Rasmussen,[2] Hans A. Saevereid,[2] and John B. Buse,[3] on behalf of the LEADER Trial Investigators

Diabetes Care 2020;43:e30–e31 | https://doi.org/10.2337/dci19-0067

Skelin et al. (1) have raised an important issue about competing risk in time-to-event analyses of acute gallbladder or biliary disease in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial (2). We thank them for the opportunity to discuss the data in the light of competing risk from a lower frequency of all-cause death with liraglutide compared with placebo in LEADER (3).

As reported previously, when analyzed using a Cox proportional hazards model, the hazard ratio (HR) for gallbladder- or biliary tract–related events with liraglutide compared with placebo was 1.60 (95% CI 1.23, 2.09) (2). In this analysis, patients were censored at time of death. Therefore, while this was not presented as a competing risk analysis, its results are equal to the cause-specific HR for these events. The HRs reported previously for the four categories of gallbladder- or biliary tract–related events (uncomplicated gallbladder stones, complicated gallbladder stones, cholecystitis, and biliary obstruction) (2) are also equal to the cause-specific HRs for these events. Results of a Fine-Gray analysis, as suggested by Skelin et al. (1), were consistent with the main analysis of overall gallbladder- or biliary tract–related events: the subdistribution HR was 1.61 (95% CI 1.24, 2.10). We will elaborate on what is meant by "consistent."

In time-to-event analyses, competing risk is generally considered using two approaches: a graph providing the cumulative incidence function and a statistical regression model that essentially alters the well-known Cox proportional hazards model. Additionally, an analysis of the competing risk is needed.

Within the regression approach, either the cause-specific hazard model or the subdistribution hazard model (Fine-Gray model) is used. Results obtained from these two models are interpreted differently. The cause-specific hazard model provides information about the hazard (instantaneous rate) of an event of interest in patients who have not experienced a competing event, for example, all-cause death (4). When using the Fine-Gray model, patients who previously experienced a competing event are still included in the risk set as opposed to being censored (4). A caveat of this model is that the subdistribution HR cannot be interpreted as an HR quantifying the magnitude of associations—at best, it can describe the direction of associations (5).

In general, reporting of the cause-specific HR is recommended when the research question is of an etiologic nature (4). The Fine-Gray model may be more suitable for prediction of events (e.g., a risk score of events according to different risk factors) (4), as the subdistribution hazard is difficult to interpret, as already discussed.

In conclusion, Fine-Gray analysis accounting for death as a competing risk for development of acute gallbladder or biliary disease with liraglutide compared with placebo was consistent with the main analysis (2), which accounted for death using censoring. In studies in which all-cause death is accounted for, it may be enough to interpret the results from the Cox proportional hazards model carefully and to use the cumulative incidence function instead of the Kaplan-Meier function (the latter of which results in incidence estimates that are biased upwards) (4).

Acknowledgments. The authors thank David D. Ørsted (Novo Nordisk A/S) for review of and input into this response letter. The authors are grateful to the participants, investigators, and all of those involved in the conduct of the trial. Medical writing and editing assistance were provided by Watermeadow Medical, an Ashfield Company,

[1]*Diabetes Division, St. Josef-Hospital (Ruhr University), Bochum, Germany*
[2]*Novo Nordisk A/S, Søborg, Denmark*
[3]*University of North Carolina School of Medicine, Chapel Hill, NC*

Corresponding author: Michael A. Nauck, michael.nauck@rub.de

Clinical trial reg. no. NCT01179048, clinicaltrials.gov

part of UDG Healthcare plc, funded by Novo Nordisk A/S.

Funding. J.B.B. is supported by grants from the National Institutes of Health (UL1TR002489, U01DK098246, UC4DK108612, U54DK118612), Patient-Centered Outcomes Research Institute (PCORI), and the American Diabetes Association.

Duality of Interest. This analysis was sponsored by Novo Nordisk. M.A.N. reports fees for serving on advisory boards from AstraZeneca, Berlin-Chemie, Eli Lilly & Co., Fractyl, Hanmi, Merck Sharp & Dohme, Novo Nordisk, and Intarcia Therapeutics/Servier; lecture fees from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Eli Lilly, Medscape, Merck Sharp & Dohme, and Novo Nordisk; travel support from Berlin-Chemie, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, and Intarcia Therapeutics/Servier; and grant support (to his institution) from AstraZeneca, Eli Lilly, GlaxoSmithKline, Intarcia Therapeutics/Servier, Merck Sharp & Dohme, Novartis, and Novo Nordisk. E.K., S.R., and H.A.S. are employees of Novo Nordisk. E.K. and S.R. are shareholders of Novo Nordisk. J.B.B.'s contracted consulting fees are paid to the University of North Carolina by Adocia, AstraZeneca, Dance Biopharm, Eli Lilly, MannKind, NovaTarg, Novo Nordisk, Senseonics, vTv Therapeutics, and Zafgen, and he has received grant support from Novo Nordisk, Sanofi, Tolerion, and vTv Therapeutics. J.B.B. is a consultant to and receives personal compensation from Cirius Therapeutics, Inc., CSL Behring, Mellitus Health, Neurimmune AG, Pendulum Therapeutics, and Stability Health. He holds stock/options in Mellitus Health, Pendulum Therapeutics, PhaseBio, and Stability Health. No other potential conflicts of interest relevant to this article were reported.

References

1. Skelin M, Rahelić D, Skelin P, Lucijanic M. Comment on Nauck et al. Effects of liraglutide compared with placebo on events of acute gallbladder or biliary disease in patients with type 2 diabetes at high risk for cardiovascular events in the LEADER randomized trial. Diabetes Care 2019;42:1912–1920 (Letter). Diabetes Care 2020;43:e28–e29. DOI: 10.2337/dc19-2039

2. Nauck MA, Muus Ghorbani ML, Kreiner E, Saevereid HA, Buse JB; LEADER Publication Committee on behalf of the LEADER Trial Investigators. Effects of liraglutide compared with placebo on events of acute gallbladder or biliary disease in patients with type 2 diabetes at high risk for cardiovascular events in the LEADER randomized trial. Diabetes Care 2019;42:1912–1920

3. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322

4. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016;133:601–609

5. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med 2017;36:4391–4400