



RESPONSE TO 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

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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).

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