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Letter regarding the article ‘Dulaglutide and cardiovascular and heart failure outcomes in patients with and without heart failure: a post-hoc analysis from the REWIND randomized trial

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To the editor:

Letter regarding the article Dulaglutide and Cardiovascular and Heart Failure Outcomes in Patients With and Without Heart Failure: A Post-Hoc Analysis from the REWIND Randomized Trial by Branch KR and colleagues published in the European Journal of Heart Failure (DOI: 10.1002/ejhf.2670).¹

We read with interested the above referenced manuscript, which adds important information to the literature. However, the low proportion (8.6%, n =853) of patients classified as having heart failure (HF) caught our attention. We are aware that these 853 were classified as having HF at baseline, but by looking at the *Table 1* in the manuscript one may see that additional 915 patients classified has not having HF reported history of “prior HF”. As HF is a chronic condition, we think that these 915 patients should be added to the 853 with HF at baseline. Then the total HF population would comprise 1768 (17.9%) patients, a proportion of HF aligned with other trials of glucagon-like peptide 1 receptor agonists (GLP1-RA) in patients with type 2 diabetes (T2D) i.e., 15-20% of HF.²⁻⁷ This difference in HF classification, might also explain why the precision of the results is poor (i.e., wide confidence intervals) and the point estimate for the treatment effect of dulaglutide vs. placebo in patients with HF at baseline (HR 0.78, 95%CI 0.59-1.03) differs from the point estimates observed in patients with HF history in other GLP1-RA trials, all of which were close to the null (i.e., HR around 1). Moreover, in the *Supplemental Material* of the paper,¹ the authors present the estimates according to history of prior cardiovascular disease, with an HR of 0.95, 95%CI 0.73-1.24 in patients with of prior cardiovascular disease and an HR of 0.88, 95%CI 0.67-1.17 in patients without prior

cardiovascular disease, interaction P-value =0.71. These estimates are more aligned with those by HF status in other T2D trials and suggest that some HF misclassification might have occurred in REWIND.

Therefore, we would kindly request the authors to provide the analysis by HF history status i.e., 1768 with HF history vs. 8094 without HF history, regarding the composite outcome of HF hospitalization or cardiovascular mortality, HF hospitalization, cardiovascular mortality, major adverse cardiovascular events, and all-cause mortality; all with respective numbers, subgroup treatment effect estimates, and treatment-by-HF subgroup interaction P-values. This would certainly align this work with other previously published manuscripts and complement the clinically important information regarding the efficacy and safety of GLP1-RA in HF.

Yours sincerely,

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Disclosures

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