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Glucagon-Like Peptide 1 Receptor Agonists in Heart Failure: the need for a rewind

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Glucagon-like peptide 1 receptor agonists (GLP1-RA) reduce atherosclerotic events in patients with type 2 diabetes (T2D) and a high cardiovascular risk.¹ However, the effect of GLP1-RA to reduce heart failure (HF) events has been inconsistent.²

Regarding HF-related events, it is important to differentiate treatment of patients with established HF from prevention of new-onset HF in patients without HF history. In fact, the effect of GLP1-RA may be influenced by HF status. In patients with severe heart failure with reduced ejection fraction (HFrEF) included in the FIGHT trial (the Heart Failure Network Functional Impact of GLP-1 for Heart Failure Treatment), the GLP1-RA liraglutide might have increased the risk of emergency department visit, HF hospitalization, or all-cause death compared to placebo (HR 1.36, 95%CI 0.99 to 1.85, P =0.05).³ In a post-hoc analysis of the FIGHT trial, the risk of total events of HF hospitalizations or all-cause deaths with liraglutide was particularly increased among patients in NYHA class III-IV (IRR 1.86, 95%CI 1.21-2.85 vs IRR 0.62, 95%CI 0.31-1.23 in NYHA class I-II, interaction P-value =0.008).⁴ The LIVE trial (Effect of Liraglutide on Left Ventricular Function in Stable Chronic Heart Failure Patients with and without Diabetes) also suggested an increased risk of adverse cardiac events with GLP1-RA in patients with stable HFrEF.⁵

Patients with HF represent between 10-20% of the population in T2D trials with GLP1-RA.⁶⁻¹¹ Still, it is worth noting that HF patients enrolled in T2D trials have not been well-characterized, with most patients not having natriuretic peptides measured or an echocardiogram performed. Notwithstanding, it is likely that most HF patients enrolled in T2D trials were stable outpatients with heart failure with preserved ejection fraction (HFpEF). This statement is supported with data from the EXSCEL (Exenatide Study of Cardiovascular Event Lowering Trial) trial where ejection fraction data was available for 58% of the population, and only 37% of the patients with HF

and ejection fraction available had HFrEF. The effects of GLP1-RA may be influenced by HF severity and ejection fraction. GLP1-RA increase heart rate and intracellular cAMP levels which has been associated with worsening HF and increased mortality in HFrEF.¹²

Despite the limitations in HF characterization in T2D trials, several trials have assessed the effect of GLP1-RA according to HF history status at baseline. Overall, the findings suggest that GLP1-RA do not reduce HF hospitalizations or cardiovascular death in T2D patients with HF history, but may prevent new-onset HF among patients without HF. In patients with T2D and HF history enrolled in LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) the hazard ratio (HR) and respective 95% confidence interval (CI) for the effect of GLP1-RA vs. placebo on the composite outcome of HF hospitalization or cardiovascular death was HR 0.92, 95%CI 0.74-1.15, in EXSCEL the corresponding estimates were HR 1.05, 95%CI 0.86-1.29, and in HARMONY-Outcomes (Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus) were HR 1.06, 95%CI 0.79-1.43. In contrast, among patients with T2D without HF history, GLP1-RA prevented HF hospitalizations and cardiovascular mortality. The effect of GLP1-RA vs. placebo in patients without HF history in LEADER was HR 0.77, 95%CI 0.65-0.91, in EXSCEL was 0.86, 95%CI 0.74-1.00, and in HARMONY-Outcomes was 0.73, 95%CI 0.56-0.95.

In this edition of the *Journal*, Branch KR and colleagues provide an important addition to the literature by analyzing the effect dulaglutide vs. placebo according to HF status at baseline in the REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) enrolling 9901 patients with T2D of whom 853 (8.6%)

had HF at baseline.¹³ In REWIND the effect of dulaglutide on HF hospitalizations or cardiovascular death was neutral irrespective of HF status at baseline with HR 0.78, 95%CI 0.59-1.03 in patients with HF at baseline and HR 0.91, 95%CI 0.79-1.05 in patients without HF at baseline, interaction P-value =0.31. Concordantly neutral effects were observed for HF hospitalizations and cardiovascular death, individually. These findings should be placed in the context of the other trials with GLP1-RA in T2D. REWIND included a small proportion of patients with HF (8.6%, n =853), which was the lowest proportion among all the above referenced trials, which on average included 15-20% of patients with HF. The low proportion of HF patients in REWIND certainly contributed to the low precision of the treatment effect estimates observed in the HF subgroup with 95%CI ranging from 0.59 to 1.03. Despite the point estimate of 0.78 in patients with HF at baseline and the low proportion of patients with HF, the 95%CI crossing the unit suggest that these findings are similar to those found in other trials i.e., a lack of benefit of GLP1-RA to reduce HF hospitalization or cardiovascular death in patients with HF. The absence of reduction of HF hospitalizations and cardiovascular mortality in the subgroup without HF at baseline differs from what was observed in the LEADER, the EXSCEL and the HARMONY- Outcomes trials. However, 915 (10.2%) patients with history of prior HF were included in the group without baseline HF, which may have contributed to some confounding in the estimates according to HF status in REWIND. If these 915 patients with history of prior HF had been included in the HF group, then 1768 (17.9%) patients would have been classified as having HF, a proportion of HF patients similar to other T2D trials. Interestingly, in the *Supplemental Material* of the paper, 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.¹³

These findings are hypothesis-generating, and they mostly highlight the need for further outcome trials with GLP1-RA in diverse HF populations. In contrast to sodium-glucose co-transporter 2 (SGLT2) inhibitors, that have been extensively tested in patients with and without HF, consistently showing a beneficial effect to reduce HF events; GLP1-RA have much less extensive testing in HF, and, from the existing data, these agents do not seem to reduce HF events in patients with HF.

The Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity (STEP-HFpEF; clinicaltrials.gov identifier: NCT04788511) and the Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes (STEP HFpEF DM; clinicaltrials.gov identifier: NCT04916470) are evaluating the effect of the GLP1-RA semaglutide on the function and symptoms of patients with HFpEF. Despite the clinical importance of these trials, they will have a short follow-up (52 weeks) and will be underpowered to assess the impact of semaglutide on HF hospitalizations or mortality.

In a near future, GLP1-RA may be largely replaced in the clinical practice by the newer dual glucose-dependent insulinotropic polypeptide (GIP) and GLP1-RA tirzepatide¹⁴ or by the several dual and triple agonists in development.¹⁵ It is essential that future trials with new molecules that activate GLP-1 receptor also evaluate the effects on HF-events across the spectrum of HF phenotypes. The

ongoing SUMMIT (A Study of Tirzepatide in Participants With Heart Failure With Preserved Ejection Fraction and Obesity; NCT04847557) trial will assess the effect of tirzepatide in 700 patients with HFpEF and obesity over 52 weeks. Similar to the trials with semaglutide in HFpEF, SUMMIT will also be underpowered to assess the effects on HF events and mortality. Furthermore, dedicated trials with tirzepatide in HFrEF are needed to assess its safety in this population.

In the meantime, we need to rewind and rethink what we know about the effects of GLP1-RA on HF events (**Figure 1**). The current data suggests that: 1) in patients without previous HF GLP1-RA may prevent new-onset HF; 2) in patients with stable HF (mostly HFpEF) GLP1-RA are neutral for HF events; and 3) in patients with advanced HFrEF GLP1-RA may promote HF worsening and arrhythmias.

Further large outcome RCTs should test the efficacy and safety of GLP1-RA (and newer dual and triple agonists) in HF patients across a wide range of ejection fractions.

Disclosures

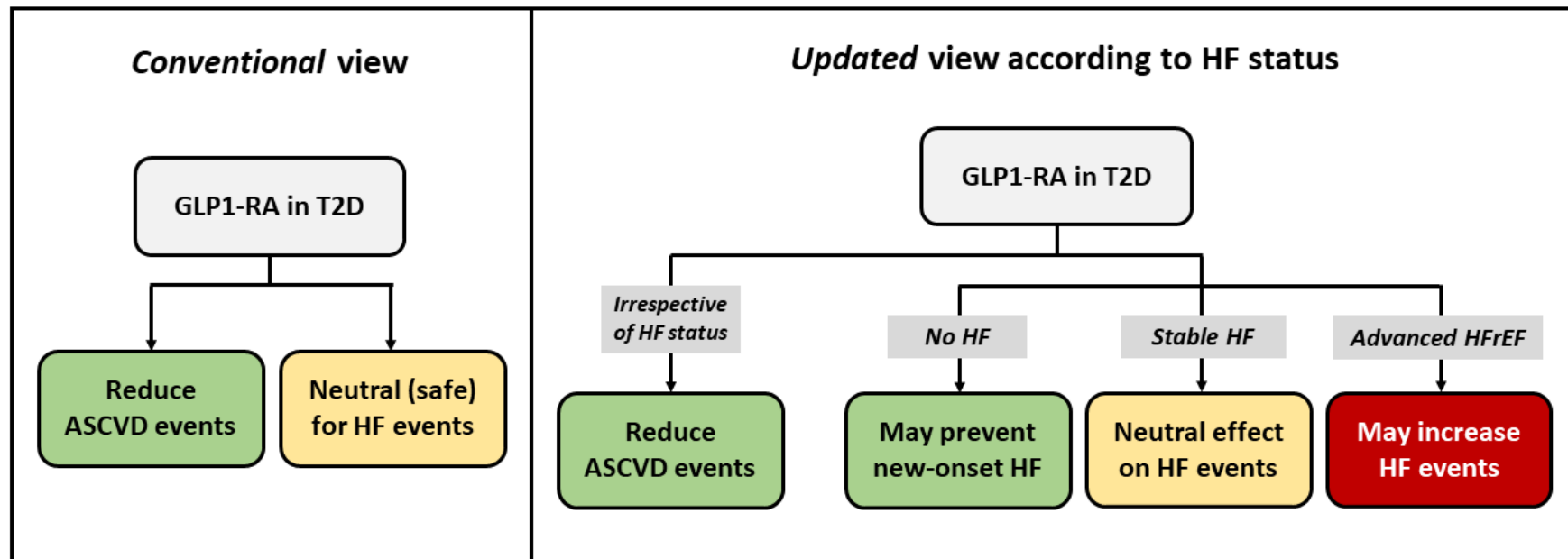
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Figure 1. Effects of GLP1-RA on cardiovascular outcomes in patients with T2D.



The conventional view is that treatment with GLP1-RA in T2D reduces ASCVD events but is neutral for HF events. Data from RCTs in T2D stratified by baseline HF (LEADER, EXSCEL, AMPLITUDE-O, REWIND trials) suggest that GLP1-RA may reduce HF events in participants without previous HF (may prevent new-onset HF) but not in patients with stable ambulatory HF (neutral for

HF events). RCTs in patients with HFrEF (FIGHT and LIVE trials) suggest that GLP1-RA may increase the risk of worsening HF in this population. Further large outcome RCTs should test the efficacy and safety of GLP1-RA in HF patients across a wide range of ejection fractions. GLP1-RA, Glucagon-Like Peptide 1 Receptor Agonists; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; T2D, type 2 diabetes; ASCVD, atherosclerotic cardiovascular disease.