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# **Glucagon-like peptide 1 receptor agonists in patients with type 2 diabetes with and without chronic heart failure: a meta-analysis of randomized placebo-controlled outcome trials**

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## **Abstract**

*Background:* Glucagon-like peptide 1 receptor agonists (GLP1-RA) reduce atherosclerotic events in patients with type 2 diabetes (T2D) and a high cardiovascular risk. The effect of GLP1-RA to reduce heart failure (HF) has been inconsistent across T2D trials, and individual trials were underpowered to assess the effect of GLP1-RA according to HF history. In this meta-analysis we aim to assess the effect of GLP1-RA in patients with and without HF history in stable ambulatory patients with T2D.

*Methods:* Random-effects meta-analysis of placebo-controlled trials. The hazard ratio (HR) and 95% confidence intervals (95%CI) were extracted from the treatment effect estimates of HF subgroup analyses reported in each individual study. The primary outcome was a composite of HF hospitalization or cardiovascular death.

*Results:* A total of 54092 patients with T2D from 7 randomized controlled trials were included, of whom 8460 (16%) had HF history. Compared to placebo, GLP1-RA did not reduce the composite of HF hospitalization or cardiovascular death in patients with HF history: HR 0.96, 95%CI 0.84-1.08, but reduced this outcome in patients without HF history: HR 0.84, 95%CI 0.76-0.92. GLP1-RA did not reduce all-cause death in patients with HF history: HR 0.98, 95%CI 0.86-1.11, but reduced mortality in patients without HF history: HR 0.85, 95%CI 0.79-0.92. GLP1-RA reduced atherosclerotic events regardless of HF history: HR 0.85, 95%CI 0.75-0.97 with HF, and HR 0.88, 95%CI 0.83-0.93 without HF.

*Conclusions:* Treatment with GLP1-RA did not reduce HF hospitalizations and mortality in patients with concomitant T2D and HF, but may prevent new-onset HF

and mortality in patients with T2D without HF. The reduction of atherosclerotic events with GLP1-RA was not influenced by HF history status.

*Key-words:* Glucagon-like peptide 1 receptor agonists; Heart failure; Treatment effects; Meta-analysis.

## **Introduction**

Glucagon-like peptide 1 receptor agonists (GLP1-RA) reduce atherosclerotic events in patients with type 2 diabetes (T2D) and a high cardiovascular risk.<sup>1-3</sup> The effect of GLP1-RA to reduce heart failure (HF) events has been modest and inconsistent across T2D trials.<sup>4</sup>

Small trials in patients with HF with reduced ejection fraction (HFrEF) with and without T2D, suggest that GLP1-RA may be harmful to these patients due to a potential increase in HF hospitalizations and ventricular arrhythmias.<sup>5,6</sup> Still, HFrEF patients have been largely excluded from T2D trials, where only a minority of patients with mildly symptomatic stable HF and a presumably preserved ejection fraction (HFpEF) were included.<sup>7</sup>

Patients with HF represent between 10-20% of the population in T2D trials with GLP1-RA,<sup>8-15</sup> thus, each individual trial was underpowered to assess the effect of GLP1-RA in HF patients. A meta-analysis of large outcome randomized controlled trials (RCTs) provides more power to study the effect of GLP1-RA among patients with T2D with and without HF history.

The aim of this meta-analysis is to study the effect of GLP1-RA vs. placebo on HF outcomes in stable ambulatory patients with T2D according to HF history.

## **Methods**

### **Search strategy and selection criteria**

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.<sup>16</sup> We

defined both MeSH terms (controlled language) and free text terms to express each component of PICO expression: P) Population, stable ambulatory patients with T2D; I) Intervention, GLP1-RA; C) Comparison, placebo and O) Outcomes, cardiovascular events. The PubMed search query included the following and it was last searched on 08 September 2022: ("diabetes mellitus"[Mesh Terms] OR "type 2 diabetes") AND ("Glucagon-Like Peptide 1"[MeSH Terms] OR GLP1RA OR "glucagon-like peptide 1 receptor agonists") AND ("placebos"[MeSH Terms] OR placebo) AND ("randomized controlled trial" [Publication Type] OR "randomized controlled trial" OR random\*[Title/Abstract]) AND ("cardiovascular death" OR "cardiovascular events" OR death) NOT (("meta-analysis"[Publication Type]) OR ("review"[Publication Type])). We did not restrict the search by language, date, or publication status. Sixty-five studies were initially identified, of which 58 were excluded because of inadequate study design, outcomes, or topic of interest, as we were only interested in large outcome placebo controlled RCTs. Then we have assessed whether the identified trials displayed subgroup analyses in patients with and without HF history, resulting in 7 selected RCTs: 1) Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER; NCT01179048);<sup>9,17</sup> 2) Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6; NCT01720446);<sup>10,18</sup> 3) Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL; NCT01144338);<sup>7,11</sup> 4) Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus (Harmony Outcomes; NCT02465515);<sup>12,19</sup> 5) Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND; NCT01394952);<sup>13,20</sup> 6) A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes

(PIONEER-6; NCT02692716);<sup>14,18</sup> and 7) A Study to Evaluate Cardiovascular Outcomes in Patients With Type 2 Diabetes Treated With ITCA 650 (FREEDOM; NCT01455896).<sup>21</sup> Trial eligibility was confirmed by 2 independent reviewers (J.P.F., F.A.S), data extraction was performed by J.P.F, and the study quality assessment was performed by J.P.F., F.A.S., and J.S.N. Additionally, the risk of bias in randomised trials was assessed with the RoB 2 tool.<sup>22</sup> We have also cross-checked the RCTs selected to the present analysis with other recently published meta-analyses and the agreement was perfect.<sup>1-3</sup> We have completed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.

The Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O; NCT03496298) trial<sup>15</sup> did not report treatment effects in HF subgroups and was not included in this analysis. Moreover, only 71 first HF events were reported in AMPLITUDE-O which would not weight much in the present meta-analysis.<sup>15</sup>

The Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide (ELIXA; NCT01147250);<sup>8</sup> was an acute myocardial infarction trial in patients with T2D; thus, it was not included in our main analysis which is focused on stable ambulatory patients with T2D. Still, HF outcomes were reported in ELIXA, and we display these in the *Supplementary Material*.

A detailed description of each individual trial is provided in the respective main reports as above referenced.

The analyses were performed to assess whether the HF history could modify the GLP1-RA effect in outcomes in patients with and without HF history at baseline i.e., before any randomized treatment administration.



## **Outcomes**

The primary outcome in the present meta-analysis was a composite of first HF hospitalization or cardiovascular death stratified by HF status. Secondary outcomes included the individual components of the primary outcome (i.e., HF hospitalization and cardiovascular death), all-cause death, and composite of time-to-first of myocardial infarction, stroke, or cardiovascular death (MACE) stratified by HF status.

All the studied outcomes were independently adjudicated in the respective trials. In the REWIND trial, HF hospitalizations included ER visits for worsening HF. In the FREEDOM trial, MACE also included hospitalization for unstable angina.

The studied trials and the respective studied outcomes are displayed in the *Supplementary Table 1*.

## **Statistical analysis**

A random-effect meta-analysis approach was used with heterogeneity assessed using the Cochran Q test statistic and Higgins and Thompson  $I^2$ .<sup>23</sup> Heterogeneity was considered to be low, moderate, or high if  $I^2$  was <25%, 25% to 75%, or >75%, respectively. The hazard ratio (HR) and respective 95% confidence intervals (95%CI) were extracted from the treatment effect estimates of HF subgroup analyses reported in the publications of each individual study. Estimates from each study were combined by use of inverse variance-weighted averages of logarithmic HR in random-effects analysis. We assessed publication bias by visual inspection of funnel plots, with the ascertainment for potential asymmetry of published results by Egger's regression test and Duval and Tweedie's trim-and-fill method. The statistical analyses were performed using Stata® software version 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

## Results

### Patient's characteristics

A total of 54092 patients with T2D from 7 RCTs were included in this analysis, of whom 8460 (16%) had HF history. SUSTAIN-6 (N =3297), PIONEER-6 (N =3183) and FREEDOM (N =4156) reported MACE by HF history status but did not report HF hospitalizations or mortality by HF status; thus, for HF-related outcomes a total of 43456 patients were included (as available in LEADER, EXSCEL, Harmony Outcomes, and REWIND), of whom 6831 (16%) had HF history.

The distribution of patients with HF history at baseline was 1667 (18%) in LEADER, 2389 (16%) in EXSCEL, 1922 (20%) in HARMONY, and 853 (9%) in REWIND, plus 573 (17%) in SUSTAIN-6, 388 (12%) in PIONEER-6 and 668 (16%) in FREEDOM.

The median follow-up in years was 3.8 in LEADER, 3.2 in EXSCEL, 1.6 in HARMONY, 5.4 in REWIND, 2.1 in SUSTAIN-6, 1.3 in PIONEER-6 and 1.3 in FREEDOM. The median age ranged from 62 years in EXSCEL to 66 years in REWIND. Most patients were White (>70%) and men (>60%). Nearly one-quarter of the patients had chronic kidney disease (CKD). The majority were treated with ACEi/ARBs and  $\beta$ -blockers, and only a small minority was treated with sodium glucose co-transporter 2 (SGLT2) inhibitors. *Table 1.*

### Risk associated with HF history

In the placebo group of the respective trials, compared to patients without HF history, those with HF had a  $\approx$ 3-fold higher risk of experiencing HF hospitalization or cardiovascular death, a  $\approx$ 3 to 5-fold higher risk of experiencing HF hospitalization, a  $\approx$ 2-fold higher risk of cardiovascular death and all-cause death, and a  $\approx$ 1.5 to 2-fold

higher risk of experiencing a MACE event during the follow-up. *Supplementary Figure 1.*

### **Effect of GLP1-RA vs. placebo according to HF history**

The event number and treatment effects in each individual trial are displayed in the *Supplementary Table 2.*

Compared to placebo, GLP1-RA did not reduce the composite of HF hospitalization or cardiovascular death in patients with HF history: HR 0.96, 95%CI 0.84-1.08 ( $I^2 = 7\%$ ) but reduced the composite of HF hospitalization or cardiovascular death in patients without HF history: HR 0.84, 95%CI 0.76-0.92 ( $I^2 = 13\%$ ); treatment-by-HF interaction  $P = 0.09$ . *Figure 1a.*

GLP1-RA did not reduce HF hospitalizations in patients with HF history: HR 0.95, 95%CI 0.81-1.11 ( $I^2 = 0\%$ ) but showed a tendency for reduction of HF hospitalizations in patients without HF history, despite moderate between-trial heterogeneity: HR 0.81, 95%CI 0.63-1.03 ( $I^2 = 69\%$ ); treatment-by-HF interaction  $P = 0.26$ . *Figure 1b.* Including the ELIXA trial in the analysis of HF hospitalizations did not modify the estimates as ELIXA had a neutral effect on HF hospitalizations in patients with and without HF history. *Supplementary Figure 2.*

GLP1-RA did not reduce cardiovascular death in the subgroup with HF history: HR 0.96, 95%CI 0.82-1.12 ( $I^2 = 0\%$ ) but reduced cardiovascular death in patients without HF history: HR 0.85, 95%CI 0.76-0.94 ( $I^2 = 0\%$ ); treatment-by-HF interaction  $P = 0.20$ . *Figure 1c.*

GLP1-RA did not reduce all-cause death in patients with HF history: HR 0.98, 95%CI 0.86-1.11 ( $I^2 = 0\%$ ) but did reduce all-cause death in patients without HF history: HR 0.85, 95%CI 0.79-0.92 ( $I^2 = 0\%$ ); treatment-by-HF interaction  $P = 0.07$ . *Figure 1d.*

GLP1-RA reduced MACE regardless of HF history: HR 0.85, 95%CI 0.75-0.97 in patients with HF history ( $I^2 = 20\%$ ) and HR 0.88, 95%CI 0.83-0.93 in patients without HF history ( $I^2 = 0\%$ ); treatment-by-HF interaction  $P = 0.69$ . *Figure 1e*.

Assessment of publication bias by funnel plots, Egger's regression test and trim-and-fill method support the absence of bias. *Supplementary Figure 3*.

## **Discussion**

The present meta-analysis, including 54092 ambulatory patients with T2D of whom 8460 (16%) had HF history, showed that patients with HF history have a  $\approx 3$ -fold higher risk of being hospitalized for worsening HF or dying from cardiovascular causes compared to patients without HF history. However, compared to placebo, treatment with GLP1-RA did not reduce HF hospitalizations or cardiovascular death in patients with HF history (i.e., those with a high risk of HF-related events) but reduced HF hospitalizations or cardiovascular death (16% relative reduction) in patients without HF history (i.e., those with a low risk of HF-related events). Similarly, GLP1-RA did not reduce cardiovascular and all-cause death in patients with HF history but did reduce mortality among patients without HF history. The differences in GLP1-RA treatment effect by HF history on HF and mortality outcomes were not seen for atherosclerotic events, which were reduced irrespective of HF history status (with a relative reduction of  $\approx 15\%$ ). These findings suggest that GLP1-RA may not reduce HF hospitalizations and mortality in patients with T2D and HF but may prevent new-onset HF and mortality in patients with T2D without HF. Additionally, GLP1-RA may be considered to reduce atherosclerotic events irrespective of HF status.

These results are clinically relevant highlighting that in patients with T2D and no HF, treatment with GLP1-RA may prevent new-onset HF, reduce atherosclerotic events, and mortality. On the other hand, in patients with T2D and HF who are at high risk of subsequent HF hospitalizations and mortality, the use of GLP1-RA may not be useful to reduce such events.

These results contrast with those from SGLT2 inhibitors, which showed a marked reduction of HF-related events in patients with and without HF.<sup>24-27</sup> Despite this meta-analysis not suggesting a harmful effect of GLP1-RA in patients with HF, it should be highlighted that patients with advanced HF, a recent HF decompensation or severely reduced left ventricular ejection fraction were excluded from these trials. Such patients with severely symptomatic HF, a reduced ejection fraction, and who had been recently hospitalized for worsening HF were included in the FIGHT trial (the Heart Failure Network Functional Impact of GLP-1 for Heart Failure Treatment) and randomized to either liraglutide or placebo (N =300). In FIGHT, 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).<sup>5</sup> The LIVE trial (Effect of Liraglutide on Left Ventricular Function in Stable Chronic Heart Failure Patients with and without Diabetes), in which 241 stable HF rEF patients were enrolled, suggested an increased risk of adverse cardiac events with GLP1-RA. Particularly, the risk of serious cardiac events was higher in the group treated with liraglutide as compared to placebo, which was driven by ventricular tachycardias and atrial fibrillation.<sup>6</sup>

The mechanisms underlying the GLP1-RA effect attenuation in patients with HF history are probably multifactorial. GLP1-RA are known to increase heart rate which may be deleterious to HF patients.<sup>28</sup> Furthermore, GLP1 receptors, expressed in

cardiomyocytes and sinoatrial node cells, signal through a cyclic AMP (cAMP)-dependent pathway which may induce calcium overload in the cardiomyocytes which may be increase the risk of ventricular ectopy in high-risk patients.<sup>4,29,30</sup> In fact, the effect of GLP1-RA may differ between HFrEF and HFpEF. Among the studies included in this meta-analysis, only EXSCEL reported left ventricular ejection fraction (LVEF). In EXSCEL LVEF was available in 33% (n =4892) of the patients, and of these only 10% (n =469) had a LVEF lower than 40% i.e., ≥90% of the patients with echocardiographic data available had an ejection fraction of 40% or greater.<sup>7</sup> These findings from EXSCEL support the notion that most patients with HF included in T2D trials had a preserved ejection fraction. Given the central role of cAMP-dependent pathways in the progression of HFrEF, it is plausible that the risk of adverse events with GLP1-RA may be higher in HFrEF than in HFpEF.<sup>31</sup>

Whether similar effects are observed with the dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist tirzepatide is uncertain. In this regard, 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. Despite the clinical importance of this trial, it will have a short follow-up (52 weeks) and will be underpowered to assess the impact of tirzepatide on HF hospitalizations or mortality. Further large outcome RCTs should test the efficacy and safety of GLP1-RA in HF patients across a wide range of ejection fractions.

Some limitations should be acknowledged in this study. Differences in eligibility criteria, patient characteristics, baseline risk, HF prevalence, HF definition, trial duration, and outcome definition may have influenced the treatment effects and

contributed to some of the heterogeneity found in the meta-analysis. Particularly, the REWIND trial analysed patients with HF at baseline (9%, n =853), but ignored patients having HF history (10%, n =915). This explains the small proportion of patients with HF reported in REWIND, which was the lowest among all studied trials, reporting 15-20% of patients with HF. The low proportion of patients considered as having HF in REWIND contributed to the low precision of the estimates observed in this HF subgroup and may have introduced bias in this analysis. The absence of data on left ventricular ejection fraction and other measures of severity of HF for most RCTs is also a limitation of this analysis. We report treatment-by-HF interaction P values in the results section of the manuscript; however, these tests lack statistical power and were not adjusted for multiplicity, and they should be interpreted with caution and not replace clinical judgement. The trials SUSTAIN-6, PIONEER-6 and FREEDOM did not report HF outcomes by HF history status. More than 70% of the patients included in the analysis were White, which limits the generalizability of these results to other populations. The HF subgroups were not stratified at randomization and were imbalanced in the trials; therefore, these subgroup analyses do not portend the same level of evidence as a dedicated and adequately powered outcome RCT, which should be performed.

## **Conclusions**

Treatment with GLP1-RA did not reduce HF hospitalizations and mortality in patients with concomitant T2D and HF, but may prevent new-onset HF and mortality in patients with T2D but without HF. The reduction of atherosclerotic events with GLP1-RA was not influenced by HF history status.

## **Disclosures**

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Drs Ferreira and Neves are the grantors of this work and takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

### **Data sharing**

The data here presented are publicly available in the respective publications.

### **Contributors**

JPF and JSN had the idea, conceptualized the study, supervised data collection, and wrote the first and subsequent drafts of the manuscript. All other authors provided critical input and edits to the manuscript.

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Table 1. Main baseline characteristics of the patients in the studied trials

<b>Characteristic</b>	<b>LEADER</b>	<b>SUSTAIN-6</b>	<b>EXSCEL</b>	<b>HARMONY</b>	<b>PIONEER-6</b>	<b>REWIND</b>	<b>FREEDOM</b>
Total, N	9340	3297	14752	9463	3183	9901	4156
GLP1-RA	Liraglutide	Semaglutide	Exenatide	Albiglutide	Semaglutide	Dulaglutide	Exenatide
HF history	1667 (18)	573 (17)	2389 (16)	1922 (20)	388 (12)	853 (9)	668 (16)
NYHA I/II	1439 (86)	-	2071 (87)	1635 (87)	-	-	-
Median F-U, yr	3.8	2.1	3.2	1.6	1.3	5.4	1.3
Men	6003 (64)	2002 (61)	9149 (62)	6569 (69)	2176 (68)	5312 (54)	2631 (63)
Mean/median Age, yr	64	65	62	64	66	66	63
White Race	7238 (77)	2736 (83)	11175 (76)	6583 (70)	2300 (72)	7498 (76)	3822 (92)
Mean/median HbA1c, %	8.7	8.7	8.0	8.7	8.2	7.4	8.0
Established CVD	7598 (81)	2735 (83)*	10781 (73)	9462 (100)	2695 (85)*	3114 (31)	3159 (76)
CKD	2307 (25)	939 (29)	3191 (22)	2157 (23)	856 (27)	2199 (22)	408 (10)
ACEi/ARB	7741 (83)	2753 (84)	11788 (80)	7726 (82)	-	8068 (81)	3154 (76)
Beta-blocker	5181 (55)	1894 (57)	8211 (56)	6310 (67)	-	4511 (46)	2206 (53)
SGLT2i	0	5 (<1)	77 (<1)	575 (6)	305 (10)	-	-
Metformin	7144 (76)	2414 (73)	11295 (77)	6969 (74)	2463 (77)	8037 (81)	3526 (85)
DPP4i	6 (<1)	5 (<1)	2203 (15)	1437 (15)	2 (<1)	564 (6)	-
Insulin	4169 (45)	1913 (58)	6836 (46)	5597 (59)	1930 (61)	2363 (24)	1474 (35)

Results presented as n. (%), unless otherwise specified.

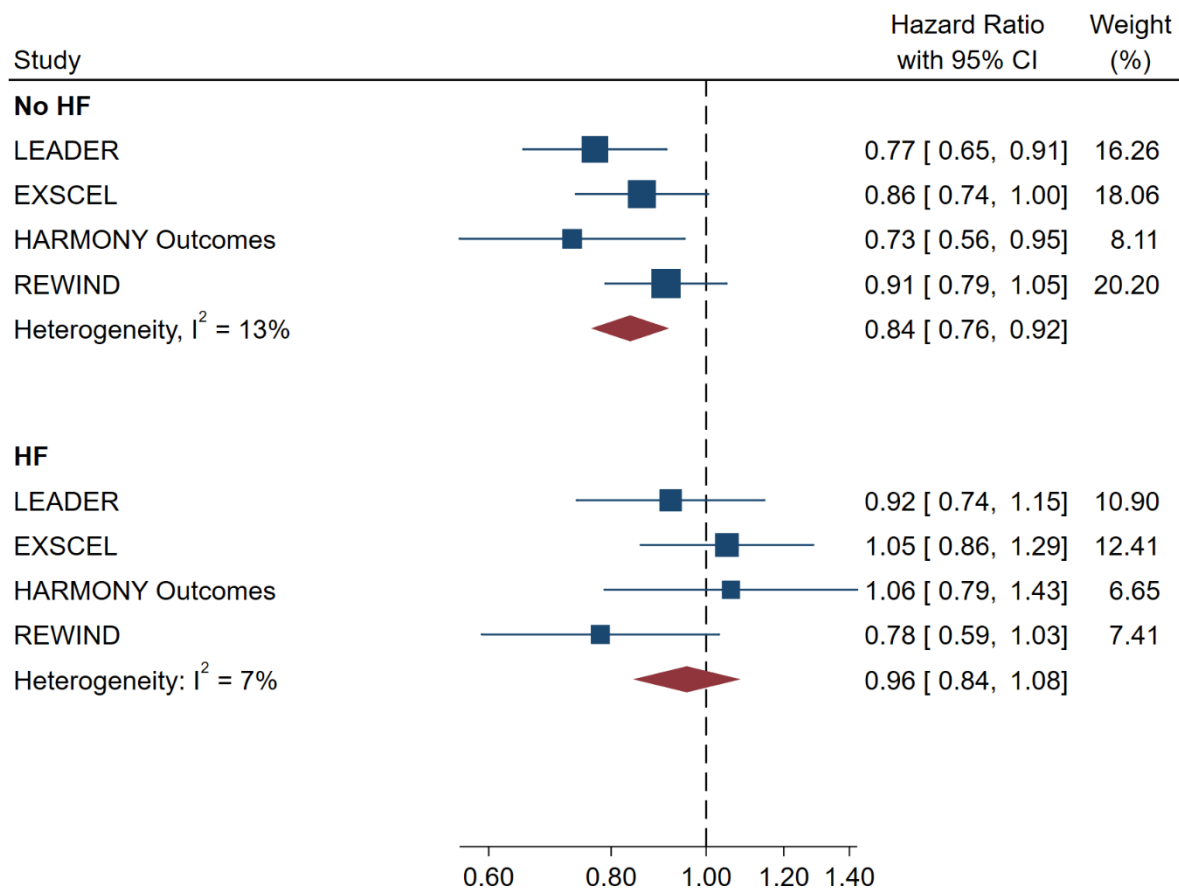
\*Established cardiovascular disease or chronic kidney disease.

Legend: HF, heart failure; NYHA, New York Heart Association Functional Class; F-U, follow-up; ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CKD, chronic kidney disease or kidney impairment as displayed in each trial; CVD, cardiovascular disease; DPP4i, dipeptidyl peptidase 4 inhibitors; SGLT2i, sodium-glucose cotransporter 2 inhibitor; -, not reported. LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; HARMONY, Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and

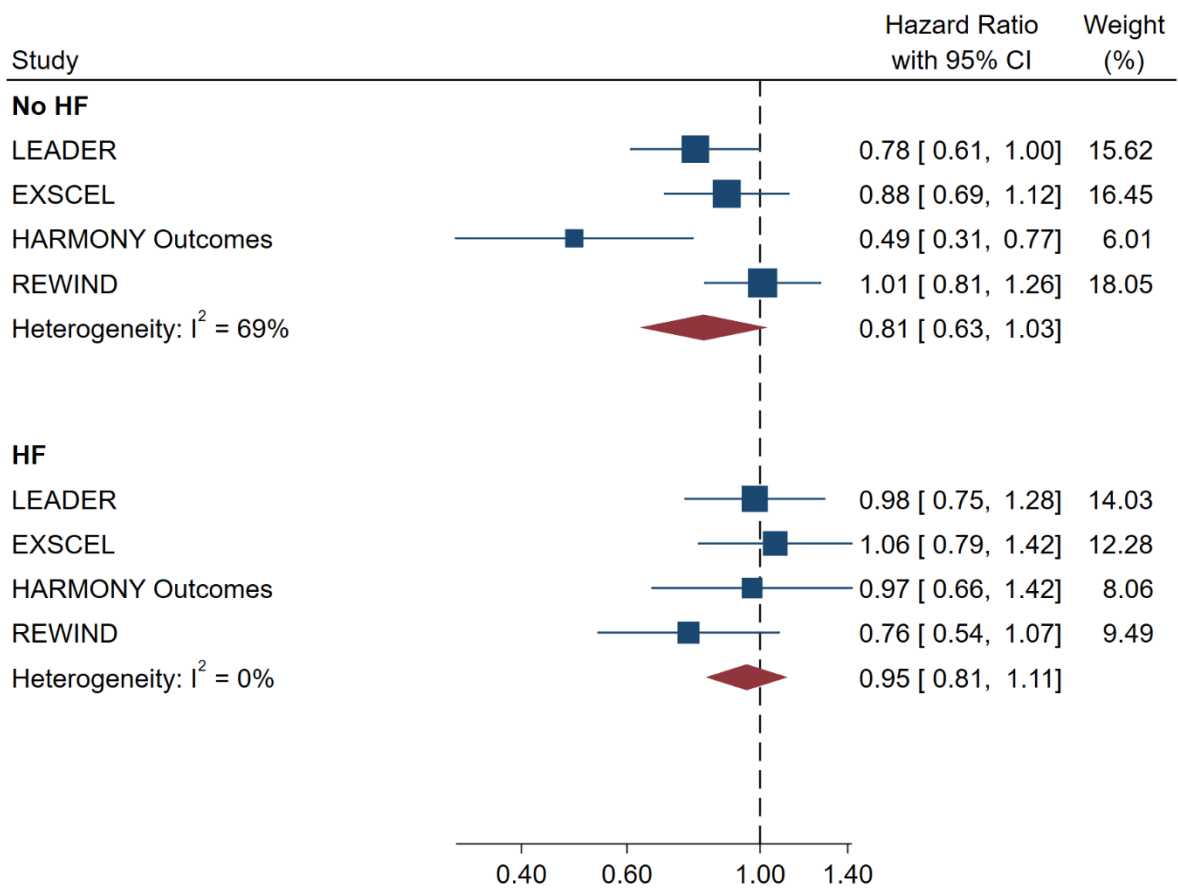
Cardiovascular Disease; PIONEER-6, Peptide Innovation for Early Diabetes Treatment; REWIND, Researching Cardiovascular Events with a Weekly Incretin in Diabetes; FREEDOM, A Study to Evaluate Cardiovascular Outcomes in Patients With Type 2 Diabetes Treated With ITCA 650.

Figure 1. Treatment effects according to HF history status

A) Composite of HF hospitalization or cardiovascular death

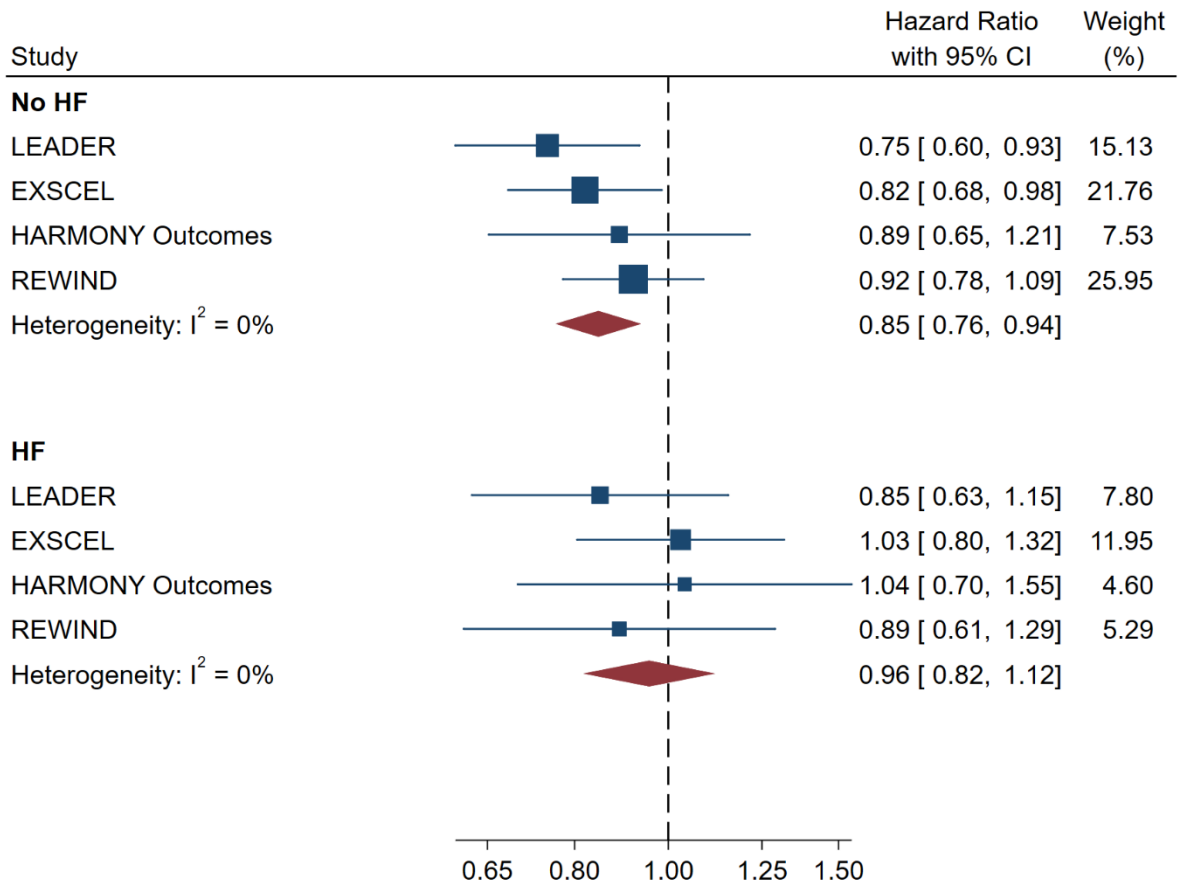


## B) HF hospitalization

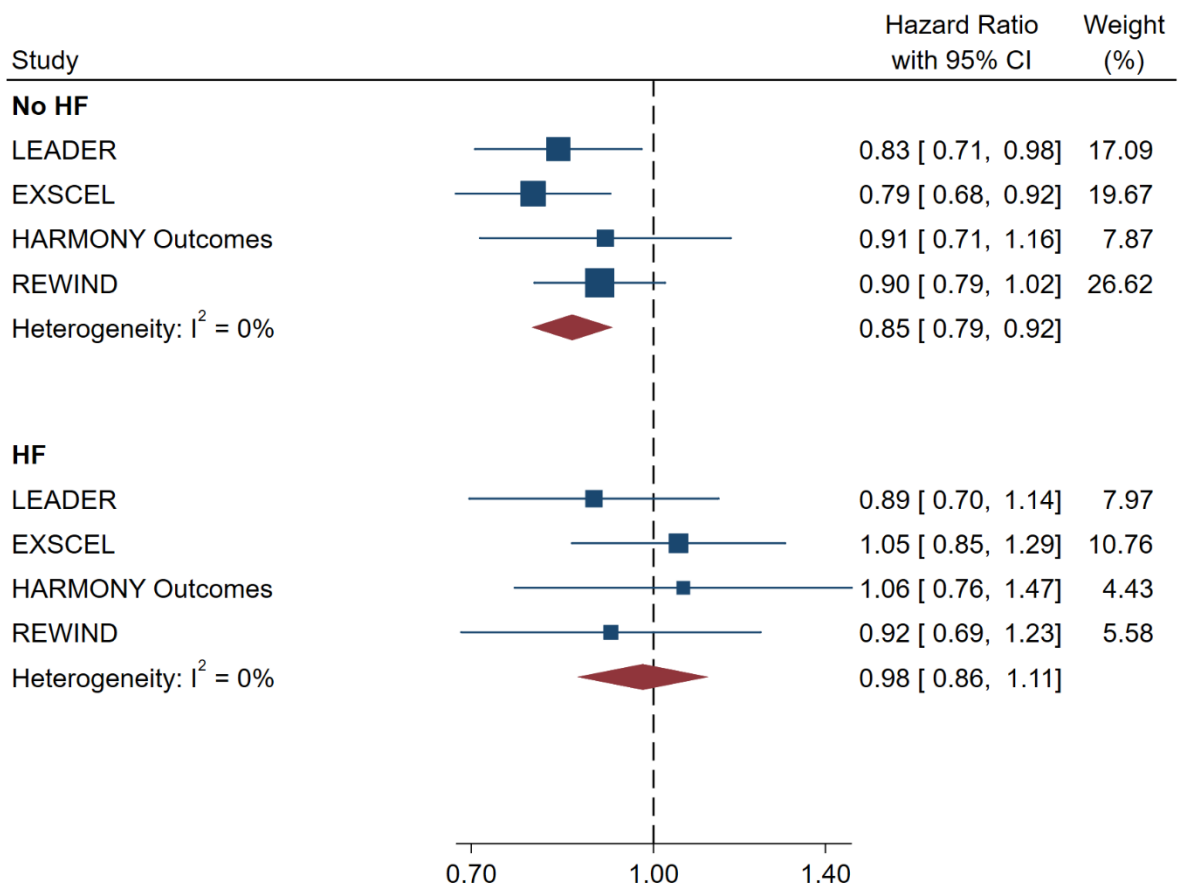




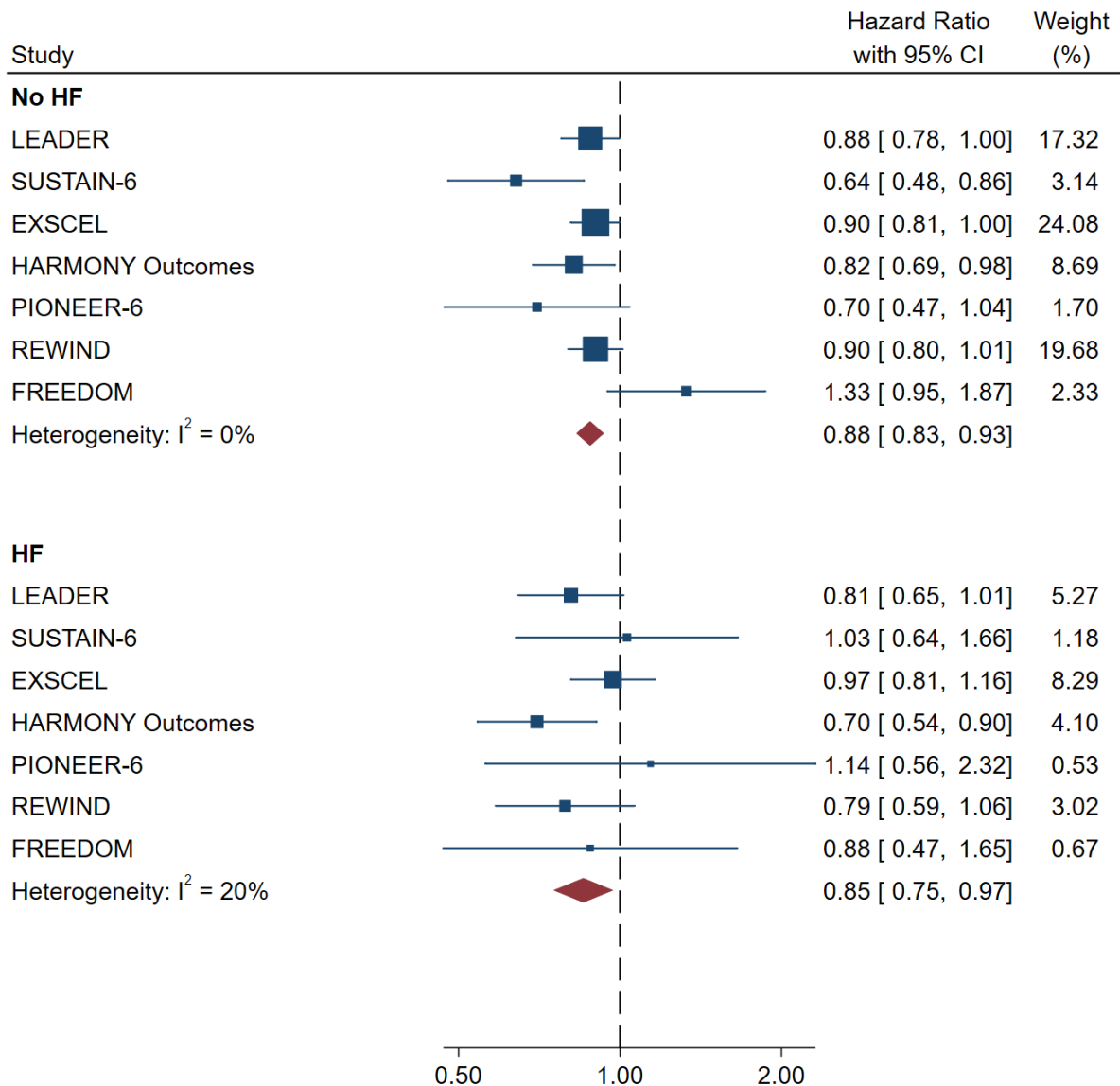
### C) Cardiovascular death



### D) All-cause death



### E) MACE



Legend: HF, heart failure; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; HARMONY, Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease; PIONEER-6, Peptide Innovation for Early Diabetes Treatment; REWIND, Researching Cardiovascular Events with a Weekly Incretin in Diabetes.

Treatment-by-HF interaction P-value: A) =0.09; B) =0.26; C) =0.20; D) =0.07; E) =0.69.