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## Journal Pre-proof

Increased risk of heart failure hospitalization with GLP-1 receptor agonists in patients with reduced ejection fraction: a meta-analysis of the EXSCEL and FIGHT trials

João Sérgio Neves MD , Milton Packer MD ,  
João Pedro Ferreira MD, PhD

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**JCF Ignite!****Increased risk of heart failure hospitalization with GLP-1 receptor agonists in patients with reduced ejection fraction: a meta-analysis of the EXSCEL and FIGHT trials**

João Sérgio Neves, MD<sup>1,2,\*</sup> jsneves@med.up.pt, Milton Packer, MD<sup>3,4</sup>, João Pedro Ferreira, MD, PhD<sup>1,5,\*</sup> jpferreira@med.up.pt

<sup>1</sup>Cardiovascular R&D Centre - UnIC@RISE, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Porto, Portugal

<sup>2</sup>Department of Endocrinology, Diabetes and Metabolism, Faculty of Medicine of the University of Porto, Centro Hospitalar Universitário de São João, Porto, Portugal

<sup>3</sup>Baylor University Medical Center, Dallas, Texas, USA

<sup>4</sup>Imperial College, London, United Kingdom

<sup>5</sup>Université de Lorraine, Inserm, Centre d'Investigations Cliniques, - Plurithématique 14-33, and Inserm U1116, CHRU Nancy, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France

\*Contact to: Dr. João Sérgio Neves or Prof. João Pedro Ferreira, Cardiovascular R&D Centre - UnIC@RISE, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Alameda Hernâni Monteiro, Porto, 4200-319, Portugal, Tel.: +351 225 513 600, Fax: +351 225 513 601

GLP-1 receptor agonists (GLP-1 RA) are usually described as having beneficial effects on atherosclerotic cardiovascular disease (ASCVD) and neutral effects on heart failure (HF) events. However, recent data suggests that the effect of GLP-1 RA may differ according to baseline HF status, with decreased risk of HF events in those without established HF and increased risk of HF events among those with HF with reduced ejection fraction (HFrEF) [1-4]. Treatment with GLP1-RA liraglutide did not improve clinical stability in the FIGHT (Functional

Impact of GLP-1 for Heart Failure Treatment) trial and did not improve left ventricle ejection fraction (LVEF) in the LIVE (Effect of Liraglutide on Left Ventricular Function in Stable Chronic Heart Failure Patients with and without Diabetes) trial [2, 3]. In both randomized clinical trials (RCTs), all patients had HFrEF and there was a trend to increased risk of adverse outcomes. Whether this risk is limited to those with severe HFrEF or is also observed in stable ambulatory type 2 diabetes patients with reduced LVEF is unknown. To this moment, the only RCT with GLP-1 RA in type 2 diabetes that presented data on LVEF was the EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial. However, in the EXSCEL trial, the influence of baseline LVEF on the effects of GLP-1 RA on HFH has not been previously evaluated.

In this report, we aimed to evaluate the interaction of GLP-1 RA effect on the risk of HFH according to baseline LVEF in the EXSCEL trial and to perform a meta-analysis of the effect of GLP-1 RA on HFH among patients with LVEF <40%.

Data for HFH in the EXSCEL trial according to LVEF was extracted from the tables 2 and S4 of the secondary analysis assessing the effects of exenatide by baseline HF status (of note, in this publication there was an error in table S4 where the headers of groups were switched) [5]. Data for HFH in the FIGHT trial was extracted from the primary analysis of the trial [2]. The odds ratio (OR) of HFH was calculated using logistic regression models. Estimates from the FIGHT trial and the subgroup with LVEF <40% in the EXSCEL trial were combined by the use of inverse variance-weighted averages of logarithmic OR in random-effects analysis. In the EXSCEL trial, the effect modification of baseline LVEF (<40%, 40-55% or ≥55%) on the effect of exenatide on HFH was

evaluated using a treatment-by-LVEF interaction term. A two-sided P value of <0.05 was considered statistically significant. All analyses were performed with Stata 17.

In the EXSCEL trial, there were 249 first HFH during a median follow-up of 3.2 years among the 4892 participants (with or without HF) with baseline LVEF available (33.2% of EXSCEL population). There was a significant interaction of LVEF with the effect of exenatide on HFH: LVEF >55% OR 0.73, 95%CI 0.48-1.13; LVEF 40-55% OR 0.77, 95% CI 0.50-1.20; LVEF <40% OR 1.70, 95%CI 1.02-2.83 (p-interaction=0.027). *Figure 1A*. When restricting to participants diagnosed with HF, a similar pattern was observed: LVEF ≥40% OR 0.71, 95%CI 0.44-1.15, LVEF <40% OR 1.49, 95%CI 0.82-2.72 (p-interaction=0.059).

In the FIGHT trial, there were 113 first HFH events during a follow-up of 180 days. The OR for HFH with liraglutide vs. placebo was 1.33, 95% CI 0.83-2.12.

The meta-analyzed GLP-1 RA effect on the risk of HFH in patients with LVEF <40% gave an OR of 1.49, 95%CI 1.05-2.10 (p-value=0.02, I<sup>2</sup>=0%). *Figure 1B*.

The results of the LIVE, also support an increased risk of adverse events with GLP-1 RA in HFREF [3]. In the LIVE, there was a significant increase in the risk of serious cardiac events with liraglutide, including one death caused by ventricular tachycardia (VT) non-fatal VT, atrial fibrillation, aggravation of ischemic heart disease and one case of worsening of HF over a period of 24 weeks. LIVE was not included in our meta-analysis because only 1 case of worsening of HF was reported.

From a biological perspective, GLP-1 RA are known to increase heart rate and intracellular cyclic AMP (cAMP), and both are known to adversely affect outcomes in HFrEF [4]. While drugs that decrease cAMP improve the prognosis in HFrEF (e.g., beta-blockers), drugs that increase cAMP (e.g., milrinone) increase the risk of HFH, ventricular arrhythmias and death in HFrEF.

In conclusion, GLP-1 RA may increase the risk of HFH in patients with a LVEF <40%. These results must be interpreted as exploratory and hypothesis generating because they are based on a subgroup of the EXSCEL trial with LVEF available (n=4892, 33.2% of the study population; which may not be missing at random) and on a small trial with a short follow-up (the FIGHT trial). More dedicated RCTs evaluating the effects of GLP-1 RA among patients with HF, particularly HFrEF, are needed. Until then, the use of GLP-1 RA should be avoided in patients with reduced LVEF.

#### Declaration of Competing Interest

JSN has received consulting or speaker fees from AstraZeneca, BIAL, Boehringer Ingelheim, Lilly, Merck, and Novo Nordisk. MP has received personal fees from Abbvie, Actavis, Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, Caladrius, Casana, CSL Behring, Cytokinetics, Imara, Lilly, Moderna, Novartis, Reata, Relypsa, and Salamandras. JPF is a consultant for Boehringer Ingelheim and AstraZeneca. He has received research support from Novartis, Boehringer Ingelheim, AstraZeneca and Bayer through his institution.

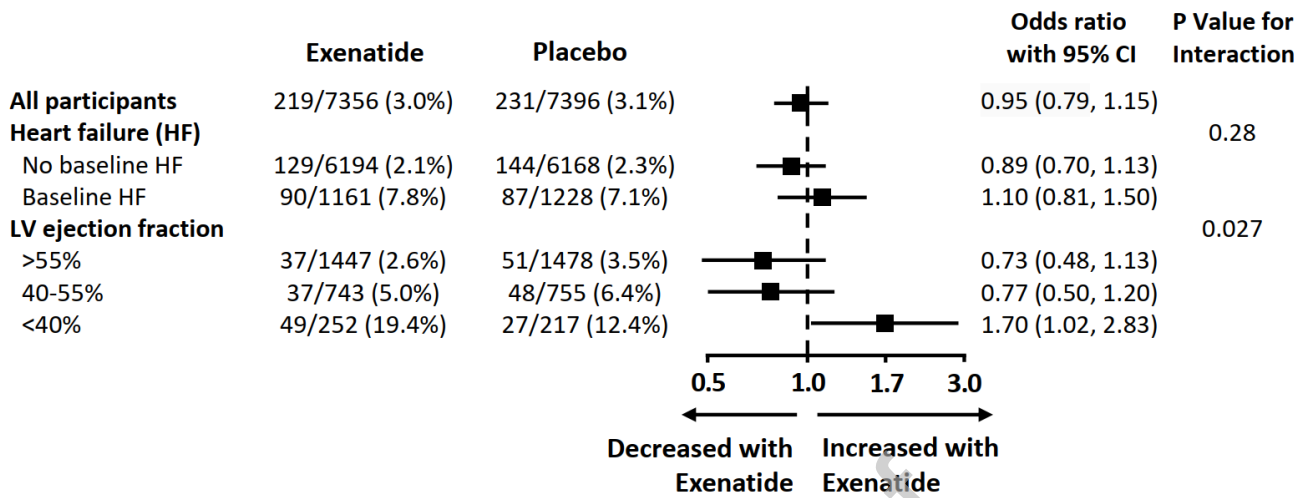
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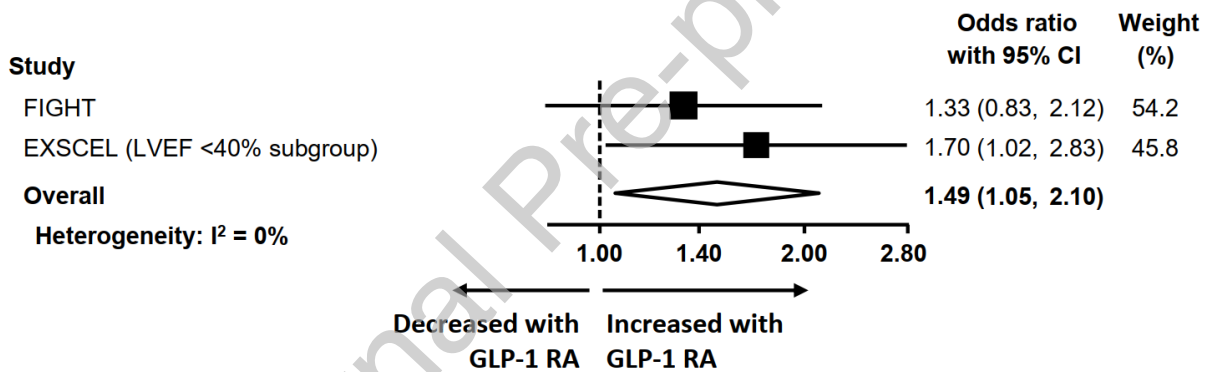
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## A. Heart Failure Hospitalization in the EXSCEL trial



## B. Meta-analysis of Heart Failure Hospitalization with GLP-1 RA (FIGHT trial and subgroup with LVEF <40% in the EXSCEL trial)



**Figure 1.** Panel A: Heart failure hospitalization in the EXSCEL trial according to HF status and LVEF. Panel B: Meta-analysis of Heart failure hospitalization with GLP-1 RA in patients with LVEF <40% (FIGHT trial and subgroup with LVEF <40% in the EXSCEL trial). EXSCEL, Exenatide Study of Cardiovascular Event Lowering; FIGHT, Functional Impact of GLP-1 for Heart Failure Treatment; GLP-1 RA, GLP-1 receptor agonists; HF, heart failure; LV, left ventricle; LVEF, left ventricle ejection fraction.





João Sérgio Neves GLP-1 RA may increase the risk of HF hospitalization in patients with a reduced LV ejection fraction. Dedicated RCTs of GLP-1 RA in HF, particularly HFrEF, are needed. Until then, GLP-1 RA should be avoided in patients with reduced LV ejection fraction.

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