Title: Effects of semaglutide on clinical events in heart failure with preserved ejection fraction (HFpEF): a pooled, participant-level analysis of SELECT, FLOW, STEP-HFpEF and STEP-HFpEF DM trials

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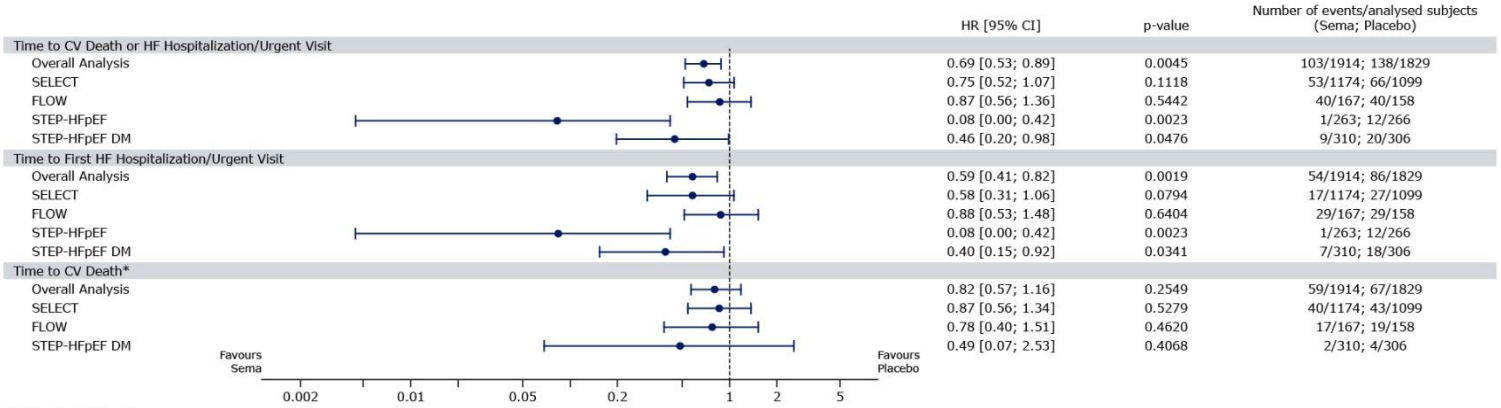
Introduction: HFpEF is associated with a high risk of hospitalization and death, representing the majority of HF cases. In the STEP-HFpEF program, semaglutide improved HF-related symptoms and physical limitations. This meta-analysis was conducted to determine whether semaglutide reduces the risk of worsening HF events.

Methods: In this pooled analysis of four double-blind, randomized, placebo-controlled trials, we examined the effects of once-weekly semaglutide (2.4 mg in SELECT, STEP-HFpEF, STEP-HFpEF DM; 1.0 mg in FLOW) on HF events. Time to first cardiovascular (CV) death or worsening HF (hospitalizations or urgent visits for HF), first worsening HF and CV death were analysed using Cox regression, stratified by trial.

Results: Out of 22,282 participants across trials, 3,743 had HFpEF (semaglutide:1,914; placebo:1,829) with median age 64-years-old, 38% women, 25% with type 2 diabetes and 83% on ACE-I/ARB/ARNI at baseline. Compared with placebo, semaglutide reduced the risk of combined CV death or HF hospitalizations/urgent visits (103 versus 138 events HR 0.69, 95% CI: 0.53-0.89; P=0.0045, Figure 1) and worsening HF (54 versus 86 events, HR 0.59, 95% CI: 0.41-0.82, P=0.0019) with no significant effect on CV death (59 versus 67 events HR 0.82, 95% CI: 0.57-1.16, P=0.25). Semaglutide versus placebo-treated patients experienced fewer SAEs across the trials (29.9% versus 38.7%, respectively).

Conclusion(s): Semaglutide significantly reduced the risk of combined CV death or worsening HF, and worsening HF events, whereas its effects on CV death alone were non-significant. These data further support semaglutide as an efficacious and safe treatment in HFpEF, which currently has few therapeutic options.

Figure 1



Data from the in-trial period.
The overall analysis of the time from randomisation to relevant endpoint was analysed using a Cox proportional hazards model with treatment as a fixed factor, stratified by study.
The by study analyses of the time from randomisation to relevant endpoint were analysed using a Cox proportional hazards model with treatment as a fixed factor, stratified by strata (if applicable).
CI: confidence interval, CV: cardiovascular, HF: heart failure, HR: hazard ratio.
*There was only 1 CV death in STEP-HFpEF, and that was in the placebo group.

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Conflict of Interest: Darshan Khangura is a shareholder for Alera Clinical - chief medical officer; received speaking honoraria from Abbott, Bayer, Boehringer Ingelheim, CPD Network Association, Dexcom, Eli Lilly, Endocrine Society, HLS Therapeutics, Novo Nordisk, Pfizer.