Semaglutide in heart failure with mildly reduced and preserved ejection fraction: A pooled analysis of the SELECT, FLOW, STEP-HFpEF and STEP-HFpEF DM randomised trials

Mikhail N. Kosiborod, MD

On behalf of SELECT, FLOW, STEP-HFpEF and STEP-HFpEF DM Investigators and Study Committees

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- Dr. Kosiborod reports:
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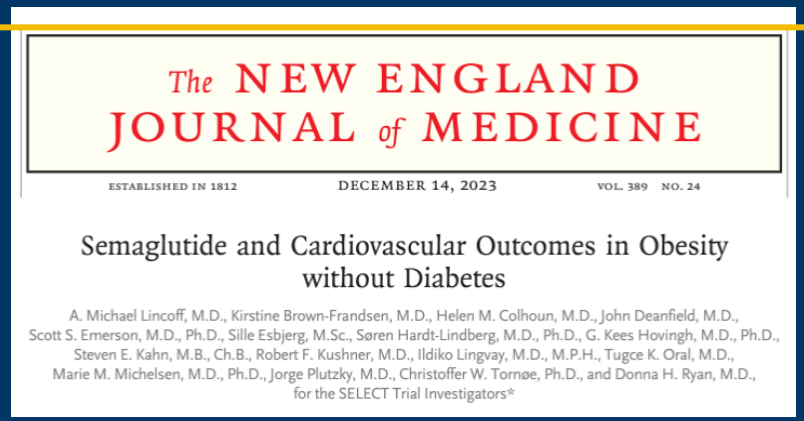
Background

- HF with mildly reduced or preserved ejection fraction (HFpEF) is associated with high burden of symptoms[1] and high risk for CV death and worsening HF events,[2] especially in patients with overweight and obesity who have few efficacious treatment options
- In the STEP-HFpEF programme once-weekly semaglutide 2.4 mg SC improved HF-related symptoms and physical limitations, and reduced body weight in participants with obesity-related HFpEF (with and without T2D)[3,4]
- Whether semaglutide also reduces clinical HF events in this group remains unresolved

We analysed pooled, participant-level data from the SELECT, FLOW, STEP-HFpEF and STEP-HFpEF DM trials to test whether semaglutide reduces the risk of clinical HF events in participants with HFpEF

SELECT[5]
N=17,604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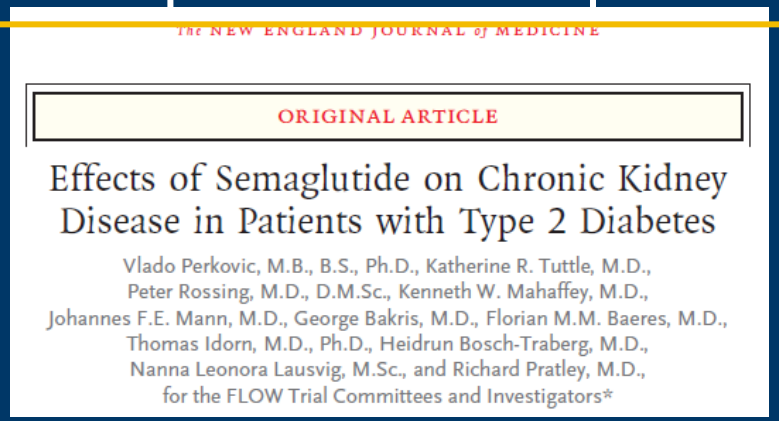
Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

FLOW[6]
N=3533


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators*

ASCVD, atherosclerotic cardiovascular disease; DM, diabetes mellitus; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MACE, major adverse cardiovascular events; SC, subcutaneous; T2D, type 2 diabetes.

1. Reddy YNV et al. *Eur J Heart Fail* 2020;22;1009–1018; 2. Adamson C et al. *Eur Heart J* 2022;43;4406–4417; 3. Kosiborod MN et al. *N Engl J Med* 2023;389:1069–1084; 4. Kosiborod MN et al. *N Engl J Med* 2024;390:1394–1407; 5. Lincoff AM et al. *N Engl J Med* 2023;389:2221–2232; 6. Perkovic V et al. *N Engl J Med* 2024;391:109–121.

Definitions of HFpEF

STEP-HFpEF and STEP-HFpEF DM[1]

Enrolled participants with well-phenotyped, obesity-related HFpEF

SELECT and FLOW*

In participants with a history of HF at enrolment, HF subtype was classified† as:

- HFpEF
- HFrEF
- Unknown type HF

Participants in this analysis included:

- **All participants from STEP-HFpEF** and **STEP-HFpEF DM**: (N=1145)
- **Participants with HFpEF from SELECT (**N=2273**)** and **FLOW (**N=325**)**

*For SELECT and FLOW, Investigators were asked to provide NYHA functional class and measurements from the most recent echocardiogram including LVEF when available. †Classified using a standardised form.
6MWD; 6-minute walk distance; BMI, body mass index; DM, diabetes mellitus; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LV, left ventricle, LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

1. Kosiborod MN et al. *JACC Heart Fail*. 2023;11:1000-1010.

Outcomes and statistical analyses

Main endpoint

Composite of CV death or worsening HF event (hospitalisation or urgent visit due to HF)

- CV deaths adjudicated in all four trials
- HF events adjudicated in SELECT, STEP-HFpEF and STEP-HFpEF DM, investigator reported in FLOW
- IV therapy* a requirement for urgent HF visits in SELECT, STEP-HFpEF and STEP-HFpEF DM, but not in FLOW

Additional endpoints

Worsening HF events alone; CV deaths alone

Safety endpoints

SAEs and AEs leading to permanent treatment discontinuation

Statistical analyses

- Aalen-Johansen method and Cox regression used for all key endpoints
- Sensitivity analyses to account for trial differences

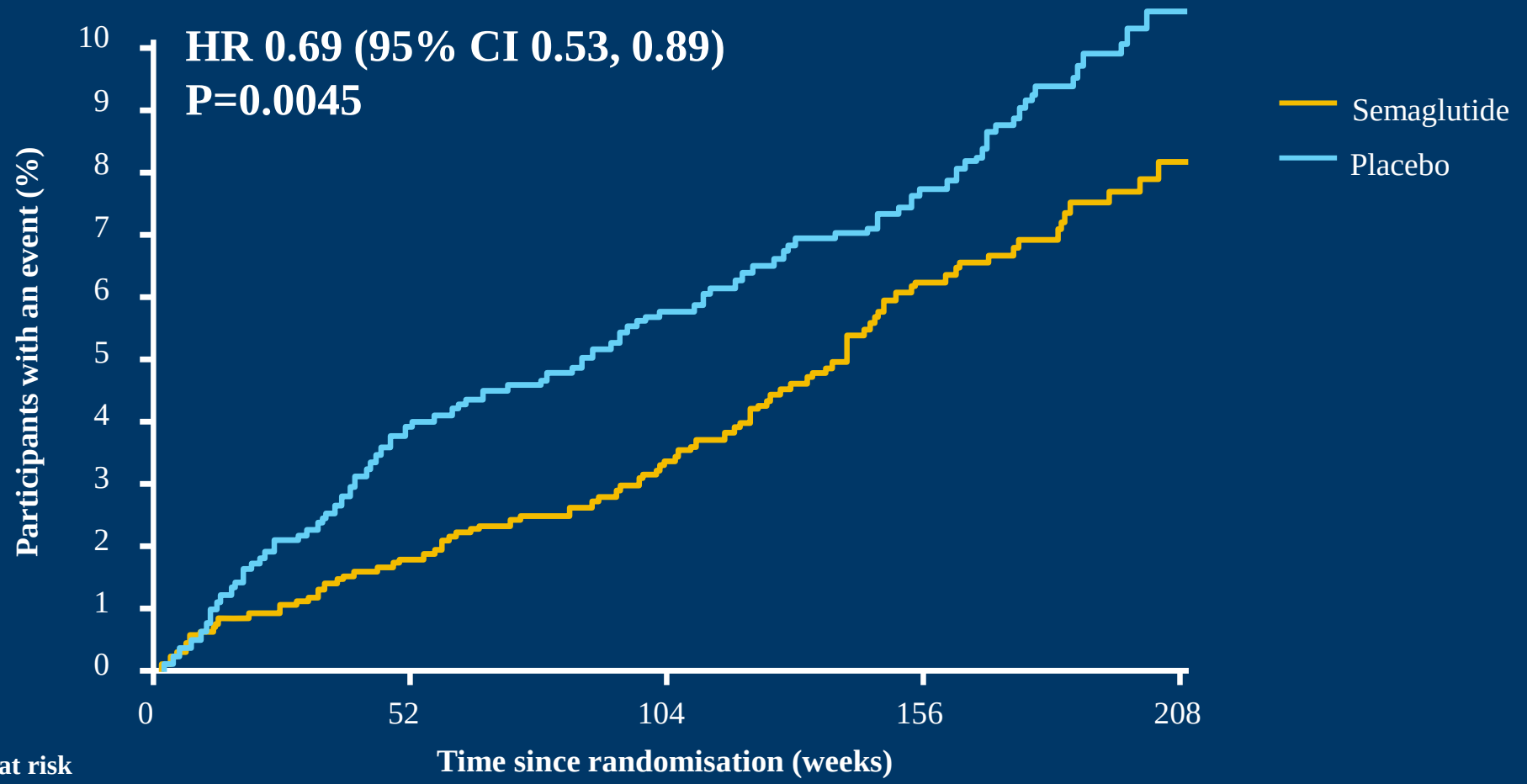
*IV diuretic or vasoactive therapy.
Efficacy and safety endpoints analysed using the full analysis set and in-trial observation period (following intent-to-treat principle).
AE, adverse event; DM, diabetes mellitus; CV, cardiovascular; EAC, Events Adjudication Committee; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; SAE, serious adverse event.

Baseline characteristics of participants with HFpEF

Baseline characteristic	Semaglutide (n=1914)	Placebo (n=1829)
Age, years, median	64.0	64.0
Female sex, %	37.2	39.0
White race, %	90.1	90.7
NYHA class, %*		
I	23.6	22.2
II	62.5	61.0
III/IV	13.9	16.8
LVEF group, %		
<40%	0.1	0.1
40%–<50%	11.0	11.9
≥50%	84.5	84.5
Missing	4.4	3.6
Atrial fibrillation, %	24.1	26.1
Diabetes, %	24.9	25.4
ASCVD,† %	77.0	75.6
BMI group (kg/m^2), %		
<27	0.8	1.2
≥27 to <30	16.3	15.0
≥30 to <35	39.4	39.3
≥35	43.5	44.5
Diuretics, %	59.4	62.2
Beta-blockers, %	80.6	81.7
ACE inhibitor/ARB (ARNI), %	82.9	83.2
MRA, %	22.0	22.7
SGLT2i	6.9	6.8

*One patient in the semaglutide arm had missing NYHA class at baseline. †Participants with history of myocardial infarction, coronary or carotid artery revascularisation, stroke, transient ischaemic attack or peripheral artery disease. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; hsCRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor agonist; NYHA, New York Heart Association; SGLT2i, sodium–glucose co-transporter-2 inhibitor.

Effects of semaglutide on CV death or HF event



Number at risk (number censored)

Semaglutide	1914	1886	1854	1296	1272	1127	892	640	299
	(0)	(9)	(27)	(575)	(587)	(716)	(933)	(1179)	(1513)
Placebo	1829	1785	1734	1190	1162	1029	823	584	271
	(0)	(7)	(23)	(559)	(572)	(691)	(889)	(1114)	(1421)

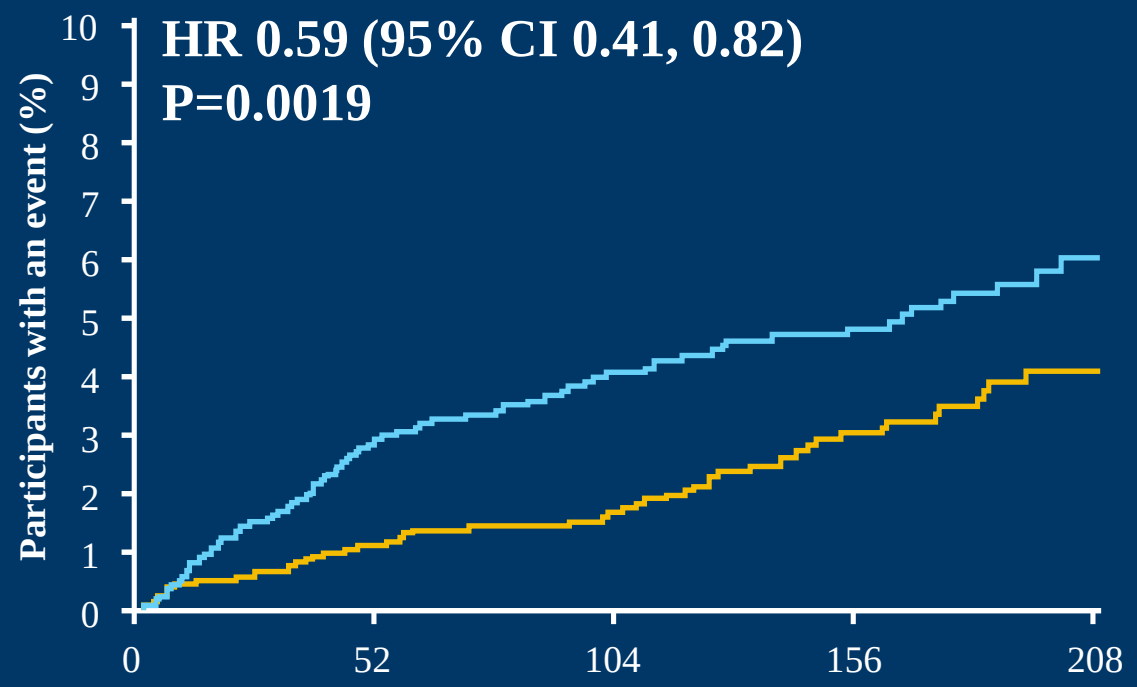
The adjusted cumulative incidence rate was calculated using Aalen–Johansen method for first event with non-CV death as a competing risk. HR and 95% CI were calculated using a Cox regression model, with pooled treatment as a fixed factor, stratified by trial.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio.

Effects of semaglutide on first HF event, and CV death

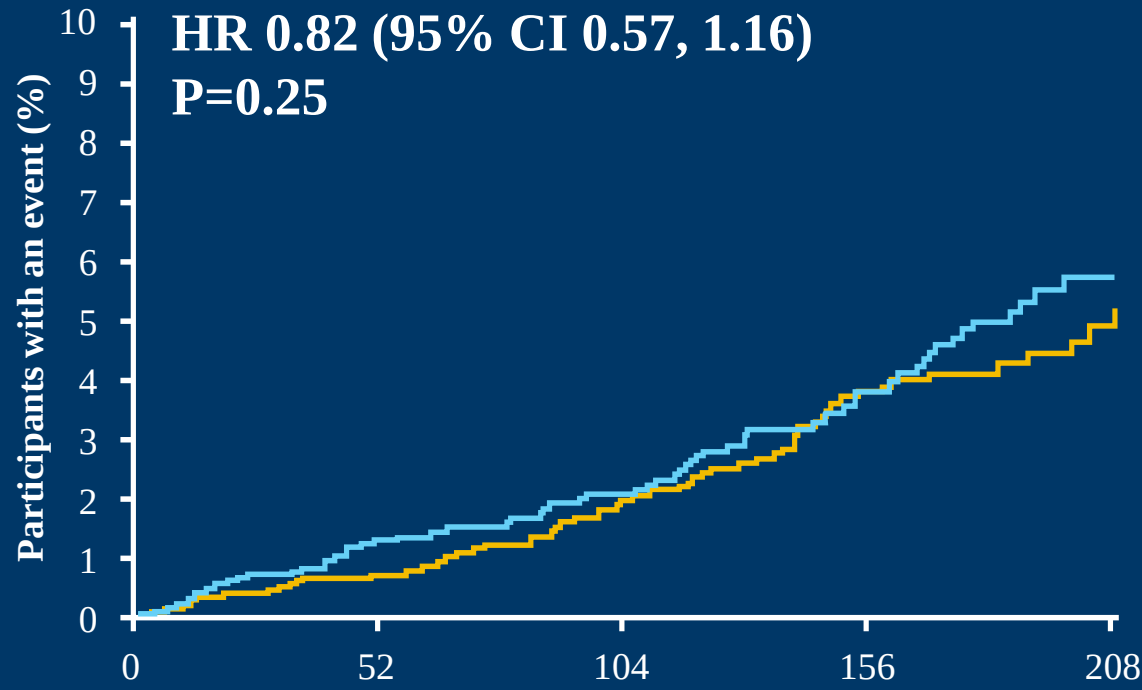
Semaglutide
Placebo

First HF event



Number at risk (number censored)									
Semaglutide	1914	1886	1854	1296	1272	1127	892	640	299
	(0)	(16)	(39)	(592)	(613)	(749)	(977)	(1225)	(1562)
Placebo	1829	1785	1734	1190	1162	1029	823	584	271
	(0)	(17)	(42)	(580)	(599)	(725)	(929)	(1163)	(1473)

CV death

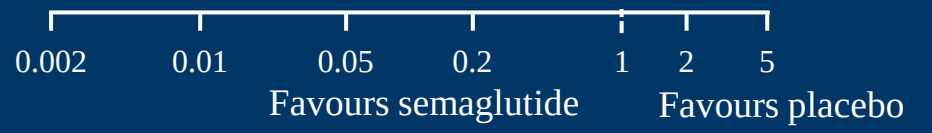


Number at risk (number censored)									
Semaglutide	1914	1896	1868	1308	1284	1145	912	655	307
	(0)	(11)	(33)	(586)	(600)	(731)	(951)	(1205)	(1549)
Placebo	1829	1809	1781	1216	1195	1059	842	599	282
	(0)	(8)	(25)	(587)	(601)	(725)	(935)	(1186)	(1481)

The adjusted cumulative incidence rate was calculated using Aalen–Johansen method for first event with all-cause death as a competing risk. HR and 95% CI were calculated using a Cox regression model, with pooled treatment as a fixed factor, stratified by trial.
CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio.

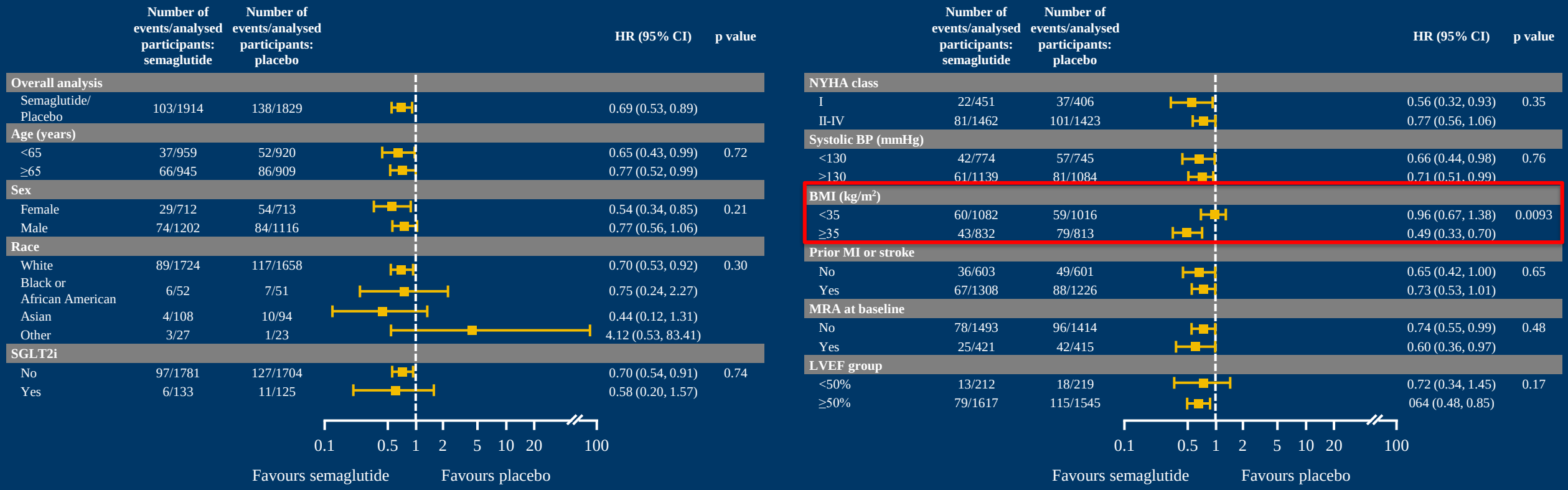
Effect of semaglutide on key endpoints overall and by trial

	Number of events/analysed participants: semaglutide	Number of events/analysed participants: placebo	Incidence rate (semaglutide: placebo)	HR (95% CI)	p value



*There was only one CV death in STEP-HFpEF. The individual study analysis was not included for this endpoint.
Data from the in-trial period. The overall analysis of the time from randomisation to relevant endpoint was performed 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 performed using a Cox proportional hazards model with treatment as a fixed factor, stratified by randomisation strata (if applicable). CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio.

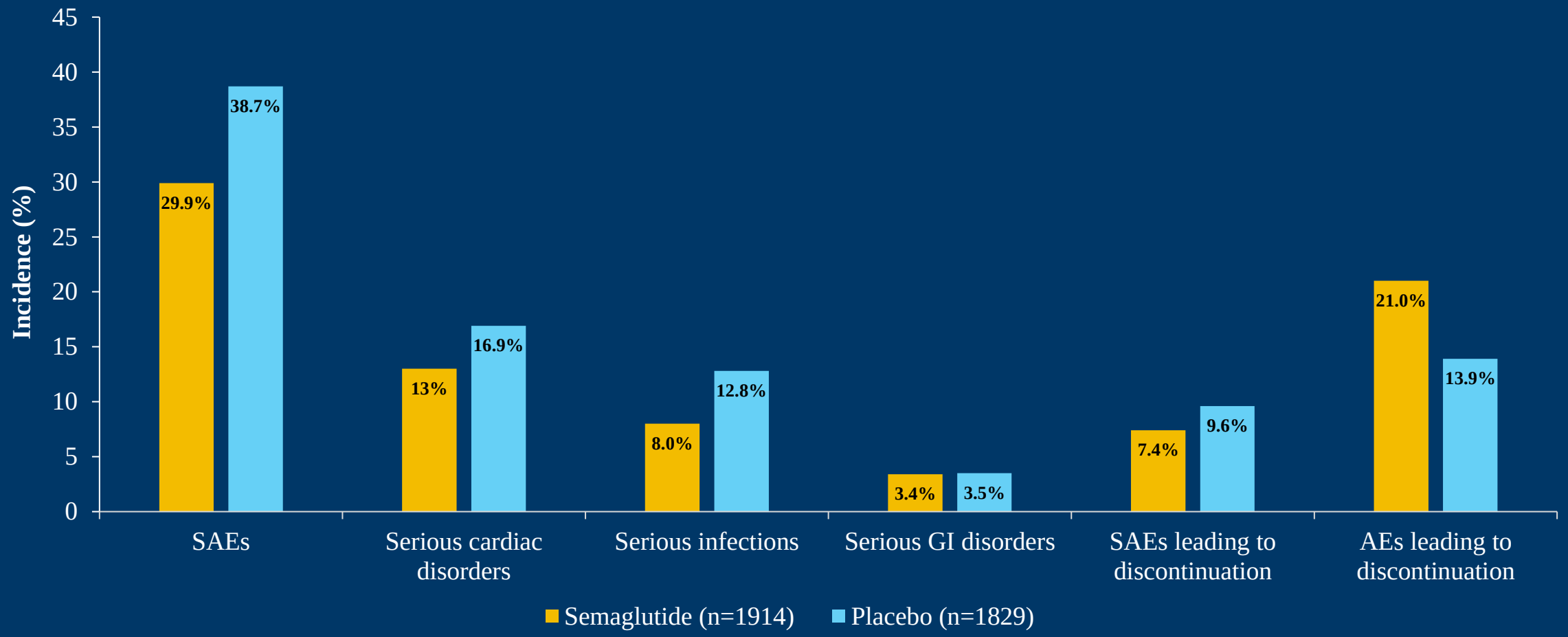
Effects of semaglutide on CV death or HF events across subgroups



Data from the in-trial period. The analysis of the time from randomisation to endpoint was performed using a Cox proportional hazards model with treatment, subgroup and treatment-by-subgroup interaction as fixed factors, stratified by study. p value was for test of no interaction.

BMI, body mass index; BP, blood pressure; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor agonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor.

Safety



AE, adverse event; GI, gastrointestinal; SAE, serious adverse event.

Limitations

- Degree of HF ‘phenotyping’ differed across the trials
- Event rates lower than in recent HFpEF trials
- Target semaglutide dose 1.0 mg weekly in FLOW vs 2.4 mg in other trials
- Different duration of follow-up across trials
- Most participants had overweight or obesity; results may not be applicable to other HFpEF phenotypes
- Few non-White participants, limiting generalisability
- Number of CV deaths not large enough to draw definitive conclusions regarding semaglutide effects on CV mortality

AF, atrial fibrillation; CV, cardiovascular; DM, diabetes mellitus; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor agonist; NTproBNP, N-terminal pro-b-type natriuretic peptide; SGLT2i, sodium–glucose cotransporter-2 inhibitor.

- In this p… …nd STEP-HFpEF Program… …and worsening HF ever…
- Effects … …those with mildly r… …or MRAs
  - Redu… …cipants with grea…
- Semaglu… …d with placebo*
- Collectively, these data provide the most comprehensive evidence to date supporting the potential of semaglutide as … …ng the risk of clinical HF events in patients with HFpEF, wh… …reatment options

Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials

Mikhail N Kosiborod, John Deanfield*, Richard Pratley, Barry A Borlaug, Javed Butler, Melanie J Davies, Scott S Emerson, Steven E Kahn, Dalane W Kitzman, Ildiko Lingvay, Kenneth W Mahaffey, Mark C Petrie, Jorge Plutzky, Søren Rasmussen, Cecilia Rönnbäck, Sanjiv J Shah, Subodh Verma, Peter E Weeke, A Michael Lincoff, for the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM Trial Committees and Investigators*

Summary

Background Heart failure with mildly reduced or preserved ejection fraction (hereafter referred to as HFpEF) is the most common type of heart failure and is associated with a high risk of hospitalisation and death, especially in patients with overweight, obesity, or type 2 diabetes. In the STEP-HFpEF and STEP-HFpEF DM trials, semaglutide improved heart failure-related symptoms and physical limitations in participants with HFpEF. Whether semaglutide also reduces clinical heart failure events in this group remains to be established.

Methods We conducted a post-hoc pooled, participant-level analysis of four randomised, placebo-controlled trials (SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM) to examine the effects of once-weekly subcutaneous semaglutide (2·4 mg in SELECT, STEP-HFpEF, and STEP-HFpEF DM; 1·0 mg in FLOW) on heart failure events. The STEP-HFpEF and STEP-HFpF DM trials enrolled participants with obesity-related HFpEF, the SELECT trial enrolled participants with atherosclerotic cardiovascular disease and overweight or obesity, and the FLOW trial enrolled participants with type 2 diabetes and chronic kidney disease. Hence, for this analysis, we include all participants from the STEP-HFpEF trials and those with an investigator-reported history of HFpEF from SELECT and FLOW. The main outcomes for this analysis were the composite endpoint of time to cardiovascular death or first worsening heart failure event (defined as hospitalisation or urgent visit due to heart failure), time to first worsening heart failure event, and time to cardiovascular death. Efficacy and safety endpoints were analysed with the full analysis set (ie, all

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*Although more patients experienced AEs leading to discontinuation of trial medication with semaglutide than placebo.
BMI, body mass index; CV, cardiovascular; DM, diabetes mellitus; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist; SAE, serious adverse event; SGLT2i, sodium–glucose cotransporter-2 inhibitor.