Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: a prespecified analysis of the SELECT trial

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Summary

Background Semaglutide, a GLP-1 receptor agonist, reduces the risk of major adverse cardiovascular events (MACE) in people with overweight or obesity, but the effects of this drug on outcomes in patients with atherosclerotic cardiovascular disease and heart failure are unknown. We report a prespecified analysis of the effect of once-weekly subcutaneous semaglutide 2·4 mg on ischaemic and heart failure cardiovascular outcomes. We aimed to investigate if semaglutide was beneficial in patients with atherosclerotic cardiovascular disease with a history of heart failure compared with placebo; if there was a difference in outcome in patients designated as having heart failure with preserved ejection fraction compared with heart failure with reduced ejection fraction; and if the efficacy and safety of semaglutide in patients with heart failure was related to baseline characteristics or subtype of heart failure.

Methods The SELECT trial was a randomised, double-blind, multicentre, placebo-controlled, event-driven phase 3 trial in 41 countries. Adults aged 45 years and older, with a BMI of 27 kg/m² or greater and established cardiovascular disease were eligible for the study. Patients were randomly assigned (1:1) with a block size of four using an interactive web response system in a double-blind manner to escalating doses of once-weekly subcutaneous semaglutide over 16 weeks to a target dose of 2·4 mg, or placebo. In a prespecified analysis, we examined the effect of semaglutide compared with placebo in patients with and without a history of heart failure at enrolment, subclassified as heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, or unclassified heart failure. Endpoints comprised MACE (a composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death); a composite heart failure outcome (cardiovascular death or hospitalisation or urgent hospital visit for heart failure); cardiovascular death; and all-cause death. The study is registered with ClinicalTrials.gov, NCT03574597.

Findings Between Oct 31, 2018, and March 31, 2021, 17 604 patients with a mean age of 61·6 years (SD 8·9) and a mean BMI of 33·4 kg/m² (5·0) were randomly assigned to receive semaglutide (8803 [50·0%] patients) or placebo (8801 [50·0%] patients). 4286 (24·3%) of 17 604 patients had a history of investigator-defined heart failure at enrolment: 2273 (53·0%) of 4286 patients had heart failure with preserved ejection fraction, 1347 (31·4%) had heart failure with reduced ejection fraction, and 666 (15·5%) had unclassified heart failure. Baseline characteristics were similar between patients with and without heart failure. Patients with heart failure had a higher incidence of clinical events. Semaglutide improved all outcome measures in patients with heart failure at random assignment compared with those without heart failure (hazard ratio [HR] 0·72, 95% CI 0·60–0·87 for MACE; 0·79, 0·64–0·98 for the heart failure composite endpoint; 0·76, 0·59–0·97 for cardiovascular death; and 0·81, 0·66–1·00 for all-cause death; all $p_{interaction}>0·19$). Treatment with semaglutide resulted in improved outcomes in both the heart failure with reduced ejection fraction (HR 0·65, 95% CI 0·49–0·87 for MACE; 0·79, 0·58–1·08 for the composite heart failure endpoint) and heart failure with preserved ejection fraction groups (0·69, 0·51–0·91 for MACE; 0·75, 0·52–1·07 for the composite heart failure endpoint), although patients with heart failure with reduced ejection fraction had higher absolute event rates than those with heart failure with preserved ejection fraction. For MACE and the heart failure composite, there were no significant differences in benefits across baseline age, sex, BMI, New York Heart Association status, and diuretic use. Serious adverse events were less frequent with semaglutide versus placebo, regardless of heart failure subtype.

Interpretation In patients with atherosclerotic cardiovascular diease and overweight or obesity, treatment with semaglutide 2·4 mg reduced MACE and composite heart failure endpoints compared with placebo in those with and without clinical heart failure, regardless of heart failure subtype. Our findings could facilitate prescribing and result in improved clinical outcomes for this patient group.

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Research in context

Evidence before this study

Heart failure is more common in patients with overweight or obesity than in the general population and is typically heart failure with preserved ejection fraction, which has had few treatment options until recently. Semaglutide, a GLP-1 receptor agonist, has been shown to improve quality of life and exercise performance in patients with heart failure with preserved ejection fraction, with and without diabetes, in the STEP-HFpEF and STEP-HFpEF DM trials, in association with weight loss. However, to our knowledge, no data have been published on cardiovascular outcomes for major adverse cardiovascular events (MACE), heart failure complications, cardiovascular death, or all-cause death with semaglutide in patients with heart failure with preserved ejection fraction. The outlook for such patients is poor and is worse with overweight and obesity. In small studies, not limited to patients with heart failure with reduced ejection fraction and obesity, it was suggested that treatment with a GLP-1 receptor agonist, liraglutide, could result in harm. The safety profile of GLP-1 receptor agonists in patients with different clinical heart failure subtypes has not been reported in adequately powered studies.

Added value of this study

In the SELECT trial, the largest study of GLP-1 receptor agonists to date, we evaluated the effect of semaglutide in 4286 patients with a history of heart failure at enrolment and showed, for the first time to our knowledge, that baseline status does not alter the benefits of semaglutide on MACE, heart failure outcomes, cardiovascular mortality, and all-cause mortality in patients with overweight or obesity without diabetes with established cardiovascular disease. We found no difference in the effect of semaglutide in patients with heart failure with preserved ejection fraction or heart failure with reduced ejection fraction, based on baseline characteristics (age, sex, and weight) or glycaemic status. Patients with heart failure with reduced ejection fraction, who had higher absolute event rates than those with heart failure with preserved ejection fraction, had an equivalent reduction in all prespecified endpoints with semaglutide treatment, without increased serious adverse events and with reduced all-cause mortality.

Implications of all the available evidence

Semaglutide reduced MACE, heart failure composite, cardiovascular death, and all-cause death in patients with atherosclerotic cardiovascular disease and overweight or obesity and heart failure, and can be administered safely regardless of heart failure subtype. Our findings could facilitate prescribing and result in improved clinical outcomes for this patient group.

Introduction

The worldwide increase in the prevalence of obesity is contributing to a rapid rise in cardiovascular disease and diabetes, with resulting stress on health-care systems.[1] Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, first introduced to manage dysglycaemia, results in both weight loss[2] and reductions in major adverse cardiovascular events (MACE) in patients with diabetes.[3] The Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT) trial showed that once-weekly, subcutaneous semaglutide 2·4 mg reduced MACE by 20% compared with placebo in patients with pre-existing atherosclerotic cardiovascular disease and overweight or obesity (BMI ≥27 kg/m²), but who did not have diabetes.[4]

The increase in obesity in the general population has also been associated with a rise in heart failure prevalence. A large proportion of patients with heart failure and obesity have heart failure with preserved ejection fraction, which is likely to be causally related to the pathophysiological consequences of obesity.[5] Heart failure with reduced ejection fraction and heart failure with preserved ejection fraction share many clinical features, but their cause and response to treatment are different, with benefits of traditional treatments for heart failure with reduced ejection fraction being less clear in patients with heart failure with preserved ejection fraction.[5,6] Although SGLT2 inhibitors have been shown to improve heart failure outcomes in both heart failure with preserved ejection fraction and heart failure with reduced ejection fraction in patients with or without diabetes,[7–9] there remains a considerable unmet clinical need, especially in patients with overweight or obesity. In the STEP-HFpEF trials, semaglutide 2·4 mg weekly reduced heart failure symptoms and improved exercise function in patients with obesity-related heart failure with preserved ejection fraction with and without diabetes, by targeting metabolic drivers associated with obesity rather than myocardial loading or neurohumoral mediators.[10,11] However, the size of those clinical trials precluded the investigators from drawing conclusions about the effect of semaglutide on clinical heart failure events, MACE, or mortality. The effect of semaglutide on heart failure outcomes and MACE in patients with heart failure with reduced ejection fraction has not been studied in dedicated clinical trials, and this is of clinical importance because there has been concern that some GLP-1 receptor agonists might be ineffective or potentially harmful in this setting.[12–16]

In SELECT, 4286 of the enrolled patients had a history of investigator-defined heart failure, categorised to be heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, or unclassified. We report a prespecified analysis of the effect of once-weekly subcutaneous semaglutide 2·4 mg on ischaemic and heart failure cardiovascular outcomes. In these

patients, we asked the following questions. First, was semaglutide compared with placebo beneficial in patients with atherosclerotic cardiovascular disease with a history of heart failure? Second, was there a difference in outcome in patients designated as having heart failure with preserved ejection fraction or heart failure with reduced ejection fraction? Finally, was the efficacy and safety of semaglutide in patients with heart failure related to baseline characteristics or subtype of heart failure?

Methods

Study design and patients

The SELECT trial was a randomised, double-blind, multicentre, placebo-controlled, event-driven phase 3 trial in 41 countries (804 sites), which evaluated whether once-weekly subcutaneous semaglutide 2·4 mg, when given as an adjunct to standard of care recommendations for the time period of intervention, was superior to placebo in reducing the risk of MACE in patients with established cardiovascular disease and overweight or obesity, without a history of diabetes. The protocol for SELECT was approved by the institutional review board and ethics committee at each participating centre. All patients provided written informed consent before any trial-specific activity. Details of study design, population, and primary outcome have been reported previously.[4,17,18]

Adults aged 45 years and older, with a BMI of 27 kg/m² or greater and established cardiovascular disease were eligible for the study. Established cardiovascular disease was defined as at least one of: previous myocardial infarction, previous ischaemic or haemorrhagic stroke, or symptomatic peripheral artery disease. Exclusion criteria included previous myocardial infarction, stroke, hospitalisation for unstable angina pectoris, or a transient ischaemic attack within 60 days of screening; glycated haemoglobin (HbA_{1c}) of 6·5% (48 mmol/mol) or greater; history of any form of diabetes; New York Heart Association (NYHA) class IV heart failure; presence of end-stage kidney disease; or need for chronic or intermittent dialysis. Sex was investigator reported as being either male or female.

The present, prespecified analysis explored the effects of semaglutide versus placebo in patients who were enrolled with an investigator-defined history of heart failure and stratified by heart failure subtype. Patients were classified as having heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, or unclassified heart failure at the time of enrolment. For inclusion in SELECT, investigators were asked to provide an NYHA class, and although echocardiographic analyses were not required for inclusion, investigators were asked to provide key parameters from the most recent echocardiogram (ECG; within 18 months), including left ventricular ejection fraction (LVEF). After the first 1783 patients were recruited to the study, investigators were asked to define LVEF into three categories: less than 40%, 40–49%, and 50% and greater (appendix p 7). The study is registered with ClinicalTrials.gov, NCT03574597.

See Online for appendix

Randomisation and masking

Patients were randomly assigned (1:1) with a block size of four using an interactive web response system in a double-blind manner to escalating doses of once-weekly subcutaneous semaglutide over 16 weeks to a target dose of 2·4 mg, or placebo.[4,17] The trial product (the pen device) containing the semaglutide and the placebo was visually identical and was packed in a manner that maintained masking. Investigators were allowed to reduce the study product if there were tolerability issues. It was recommended that patients were treated according to the evidence-based standard of care. The protocol and baseline characteristics have been published previously.[4,17,18]

Outcomes

In this prespecified analysis, our primary outcomes were time from random assignment to first occurrence of MACE (defined as a composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke); a heart failure composite (consisting of cardiovascular death or hospitalisation or urgent hospital visit for heart failure); cardiovascular death; and all-cause death. All reported clinical events were adjudicated by an independent committee, who were masked to trial group assignment, in accordance with these prespecified criteria (appendix pp 2–3). Safety was assessed as the number and nature of serious adverse events in the trial or those leading to discontinuation of the trial product.

Statistical analysis

This event-driven trial was designed to provide 90% power to detect a relative risk reduction of 17% for a primary endpoint event in the semaglutide group compared with the placebo group (hazard ratio [HR] 0·83) at an overall one-sided significance level of 0·025. This design required that a minimum of 1225 primary endpoint events be accrued.

Statistical analyses were based on the intention-to-treat principle and included all randomly assigned patients (with and without heart failure), irrespective of adherence to semaglutide or placebo or changes to background medications using in-trial data. All analyses were done using time to first event from random assignment. For composite endpoints, the endpoint was said to occur when the first component of the composite took place. For reporting of individual components of composites (cardiovascular death, myocardial infarction, stroke, and hospitalisation or urgent hospital visit for heart failure) the reported rates were for the first event of the particular component, thus providing full accounting of the total number of cardiovascular deaths, first myocardial infarctions, first strokes, or first hospitalisation or urgent hospital visit for heart failure. In the analysis by heart

failure subtype, only patients with a documented clinical subtype of heart failure with preserved ejection fraction or heart failure with reduced ejection fraction were included.

Demographics and baseline characteristics were summarised according to heart failure type at baseline (no heart failure, heart failure, and subtype within heart failure: heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, and unclassified heart failure). Time from random assignment to an outcome was analysed with a Cox proportional hazards model with treatment group (semaglutide or placebo) as a fixed factor. The HRs with 95% CIs and two-sided p values are presented. Patients who withdrew from the trial, died from causes not included in the endpoint, or were lost to follow-up were censored at the time of withdrawal, death, or last contact with the treating physician. Subgroup analyses for time-to-event endpoints were based on the same Cox proportional hazards model by adding the specific subgroup as a factor and an interaction between treatment group (semaglutide and placebo) and the subgroup. Similarly, time-to-event outcomes were plotted by treatment group and subgroup using the Aalen–Johansen estimator and presented as cumulative incidences, considering non-cardiovascular death or all-cause death as a competing event dependent on the outcome.

Selected types of serious adverse events were summarised by the proportion of patients with an event by system organ class and treatment discontinuation, using in-trial data according to heart failure subtype. CIs were not adjusted for multiplicity and should therefore not be used to infer definitive treatment effects. A two-sided significance level of 5% was considered significant.

Statistical analyses were done with SAS (version 9.4). An independent data monitoring committee reviewed unblinded efficacy and safety data on an ongoing basis and at prespecific timepoints.

Role of the funding source

The funder of the study was responsible, along with an academic steering committee, for the study design, contributed to data collection, data analysis, and data interpretation, and participated in the review of the manuscript in collaboration with the authors.

Results

The baseline characteristics of the SELECT study population have been previously reported.[4] Briefly, between Oct 31, 2018, and March 31, 2021, 17 604 patients with a mean age of 61·6 years (SD 8·9) and a mean BMI of 33·4 kg/m² (5·0) were randomly assigned to receive semaglutide (8803 [50·0%] patients) or placebo (8801 [50·0%] patients). 12 732 (72·3%) of 17 604 participants were male and 4872 (27·7%) were female. 4286 (24·3%) of 17 604 patients had a history of heart failure at enrolment. Based on the treating investigator's assessment, 2273 (53·0%) of 4286 patients had heart failure with preserved ejection fraction, 1347 (31·4%) had heart failure with reduced ejection fraction, and 666 (15·5%) had unclassified heart failure. ECG data were available for 2159 (95·0%) of 2273 patients with heart failure with preserved ejection fraction, 1296 (96·2%) of 1347 patients with heart failure with reduced ejection fraction, and 293 (44·0%) of 666 patients with unclassified heart failure. Data on LVEF for the different heart failure subtypes are provided in the appendix (p 7).

The clinical characteristics of patients with a history of heart failure (overall and by subtypes) and those without a history of heart failure were well balanced across the treatment groups (table). In the heart failure subgroups, a higher proportion of the heart failure with preserved ejection fraction group were female compared with the heart failure with reduced ejection fraction group. As expected, a higher proportion of the patients with heart failure with reduced ejection fraction had previous myocardial infarction compared with those with heart failure with preserved ejection fraction, and the same pattern was observed for those with two or more inclusion criteria for cardiovascular disease. At enrolment, 1371 (32·0%) of 4286 patients with heart failure were in NYHA class I, 2540 (59·3%) were in class II, and 364 (8·5%) were in class III. Bodyweight, waist circumference, and estimated glomerular filtration rate were similar in the heart failure with preserved ejection fraction and heart failure with reduced ejection fraction groups. The incidence of heart failure with preserved ejection fraction (n=2273) was associated with increasing BMI at enrolment, calculated as the proportion in the overall population with reported heart failure status at baseline (n=17 600; BMI <30 kg/m², 546 (10·9%) of 5023 patients; 30 kg/m² to <35 kg/m², 970 (13·0%) of 7474 patients; 35 kg/m² to <40 kg/m², 471 (14·1%) of 3344 patients; 40 kg/m² to <45 kg/m², 190 (16·2%) of 1173 patients; ≥45 kg/m², 96 (16·4%) of 586 patients). This pattern was not seen in patients with heart failure with reduced ejection fraction or unclassified heart failure (data not shown). Mean systolic blood pressure was lower in patients with heart failure with reduced ejection fraction compared with patients with heart failure with preserved ejection fraction.

There were expected differences in medications at baseline, with a higher proportion of patients with heart failure with reduced ejection fraction receiving loop diuretics and aldosterone antagonists compared with those with heart failure with preserved ejection fraction (table). No patients were receiving an SGLT2 inhibitor at enrolment, but 545 (3·1%) of 17 604 patients started using an SGLT2 inhibitor during the study. Plasma lipid levels and blood pressure were well treated in all groups at trial entry.

There were some minor differences between patients with heart failure with preserved ejection fraction and

	Patients with heart failure (n=4286)	Patients without heart failure (n=13 314)	Patients with heart failure with preserved ejection fraction (n=2273)	Patients with heart failure with reduced ejection fraction (n=1347)	Patients with unclassified heart failure (n=666)
Age, years	61·9 (8·7)	61·5 (8·9)	61·7 (8·7)	61·7 (8·7)	63·0 (8·7)
Sex					
Male	3148 (73·4%)	9582 (72·0%)	1567 (68·9%)	1147 (85·2%)	434 (65·2%)
Female	1138 (26·6%)	3732 (28·0%)	706 (31·1%)	200 (14·8%)	232 (34·8%)
Race*					
White	3841 (89·6%)	10 948 (82·2%)	2072 (91·2%)	1169 (86·8%)	600 (90·1%)
Asian	206 (4·8%)	1241 (9·3%)	106 (4·7%)	87 (6·5%)	13 (2·0%)
Black or African American	137 (3·2%)	533 (4·0%)	50 (2·2%)	48 (3·6%)	39 (5·9%)
Other†	91 (2·1%)	435 (3·3%)	44 (1·9%)	33 (2·4%)	14 (2·1%)
Ethnicity*					
Hispanic or Latino	407 (9·5%)	1414 (10·6%)	195 (8·6%)	138 (10·2%)	74 (11·1%)
Region					
North America	661 (15·4%)	3739 (28·1%)	259 (11·4%)	220 (16·3%)	182 (27·3%)
South America	335 (7·8%)	817 (6·1%)	166 (7·3%)	121 (9·0%)	48 (7·2%)
Europe	1256 (29·3%)	5434 (40·8%)	540 (23·8%)	544 (40·4%)	172 (25·8%)
Africa	108 (2·5%)	736 (5·5%)	26 (1·1%)	50 (3·7%)	32 (4·8%)
Asia	317 (7·4%)	1884 (14·2%)	146 (6·4%)	146 (10·8%)	25 (3·8%)
Other	1609 (37·5%)	704 (5·3%)	1136 (50·0%)	266 (19·7%)	207 (31·1%)
Cardiovascular inclusion criteria					
Myocardial infarction only	2959/4170 (71·0%)	8946/13 083 (68·4%)	1552/2209 (70·3%)	1044/1319 (79·2%)	363/642 (56·5%)
Stroke only	563/4170 (13·5%)	2571 (19·7%)	347/2209 (15·7%)	63/1319 (4·8%)	153/642 (23·8%)
Peripheral artery disease only	108/4170 (2·6%)	669 (5·1%)	69/2209 (3·1%)	13/1319 (1·0%)	26/642 (4·0%)
≥2 inclusion criteria	540/4170 (12·9%)	897 (6·9%)	241/2209 (10·9%)	199/1319 (15·1%)	100/642 (15·6%)
New York Heart Association class					
Class I	1371 (32·0%)	..	749 (33·0%)	371 (27·5%)	251 (37·7%)
Class II	2540 (59·3%)	..	1342 (59·0%)	840 (62·4%)	358 (53·8%)
Class III	364 (8·5%)	..	181 (8·0%)	134 (9·9%)	49 (7·4%)
Unknown	11 (0·3%)	..	1 (<0·1%)	2 (0·1%)	8 (1·2%)
Smoking status					
Current smoker	758 (17·7%)	2192 (16·5%)	404 (17·8%)	265 (19·7%)	89 (13·4%)
Never smoked	1542 (36·0%)	4577 (34·4%)	917 (40·3%)	348 (25·8%)	277 (41·6%)
Previous smoker	1986 (46·3%)	6544 (49·2%)	952 (41·9%)	734 (54·5%)	300 (45·0%)
Concomitant medication					
β blockers	3573 (83·4%)	8782 (66·0%)	1868 (82·2%)	1211 (89·9%)	494 (74·2%)
Angiotensin-converting-enzyme inhibitors	2123 (49·5%)	5805 (43·6%)	1126 (49·5%)	681 (50·6%)	316 (47·4%)
Angiotensin receptor blockers	1408 (32·9%)	3778 (28·4%)	765 (33·7%)	432 (32·1%)	211 (31·7%)
Thiazides	381 (8·9%)	1645 (12·4%)	218 (9·6%)	87 (6·5%)	76 (11·4%)
Loop diuretics	1275 (29·7%)	933 (7·0%)	513 (22·6%)	586 (43·5%)	176 (26·4%)
Aldosterone antagonists	1171 (27·3%)	648 (4·9%)	404 (17·8%)	642 (47·7%)	125 (18·8%)
Thiazide-like diuretics	409 (9·5%)	627 (4·7%)	287 (12·6%)	54 (4·0%)	68 (10·2%)
Other potassium-sparing diuretics	6 (0·1%)	37 (0·3%)	2 (0·1%)	3 (0·2%)	1 (0·2%)
Angiotensin receptor-neprilysin inhibitor	217 (5·1%)	48 (0·4%)	28 (1·2%)	168 (12·5%)	21 (3·2%)
Bodyweight, kg	98·5 (18·7)	96·1 (17·3)	97·9 (18·5)	98·7 (18·0)	100·3 (20·4)
BMI, kg/m²					
<30	1059 (24·7%)	3964 (29·8%)	546 (24·0%)	366 (27·2%)	147 (22·1%)
≥30 to <35	1781 (41·6%)	5693 (42·8%)	970 (42·7%)	571 (42·4%)	240 (36·0%)
≥35 to <40	915 (21·3%)	2429 (18·2%)	471 (20·7%)	282 (20·9%)	162 (24·3%)
≥40 to <45	354 (8·3%)	819 (6·2%)	190 (8·4%)	95 (7·1%)	69 (10·4%)
≥45	177 (4·1%)	409 (3·1%)	96 (4·2%)	33 (2·4%)	48 (7·2%)

(Table continues on next page)

	Patients with heart failure (n=4286)	Patients without heart failure (n=13 314)	Patients with heart failure with preserved ejection fraction (N=2273)	Patients with heart failure with reduced ejection fraction (n=1347)	Patients with unclassified heart failure (n=666)
(Continued from previous page)					
BMI, kg/m²	33·9 (5·3)	33·1 (4·9)	34·0 (5·4)	33·4 (4·9)	34·9 (6·0)
BMI, kg/m²	32·7 (30·0–36·6)	32·0 (29·6–35·5)	32·8 (30·1–36·7)	32·3 (29·8–35·8)	33·6 (30·3–37·8)
Waist circumference, cm	112·4 (13·5)	111·0 (13·0)	111·6 (13·5)	112·8 (12·9)	114·3 (14·4)
Systolic blood pressure, mm Hg	129·4 (15·0)	131·5 (15·5)	130·7 (13·6)	126·0 (15·8)	131·6 (16·5)
Diastolic blood pressure, mm Hg	78·7 (9·9)	79·5 (10·0)	79·4 (9·3)	77·3 (10·2)	79·4 (11·0)
Pulse, beats per min	69·0 (10·0)	68·7 (10·9)	69·0 (9·5)	68·6 (10·5)	70·0 (10·6)
Glycated haemoglobin, %	5·80 (0·33)	5·78 (0·34)	5·80 (0·33)	5·82 (0·32)	5·78 (0·34)
Median high-sensitivity C-reactive protein, mg/L	2·0 (0·9–4·5)	1·8 (0·9–4·0)	2·0 (0·9–4·4)	1·9 (0·9–4·3)	2·4 (1·1–5·5)
Median lipid, mmol/L					
Total cholesterol	4·1 (3·5–5·0)	3·9 (3·4–4·7)	4·2 (3·5–5·0)	3·9 (3·4–4·7)	4·3 (3·6–5·2)
HDL cholesterol	1·1 (1·0–1·3)	1·1 (1·0–1·4)	1·1 (1·0–1·3)	1·1 (0·9–1·3)	1·2 (1·0–1·4)
LDL cholesterol	2·1 (1·6–2·9)	2·0 (1·6–2·6)	2·2 (1·7–2·9)	2·0 (1·6–2·6)	2·3 (1·7–3·1)
Triglycerides	1·6 (1·2–2·2)	1·5 (1·1–2·1)	1·6 (1·2–2·2)	1·5 (1·2–2·1)	1·5 (1·1–2·2)
Renal—eGFR and ACR					
eGFR, mL/min per 1·73m²	79·6 (18·3)	83·4 (17·0)	80·6 (17·9)	78·2 (18·8)	79·0 (18·7)
ACR, mg/g	92·1 (2772·6)	80·7 (3262·1)	120·4 (3793·1)	53·0 (264·0)	74·2 (424·9)
ACR, mg/g	7·7 (4·5–17·0)	7·3 (4·5–15·0)	7·2 (4·3–15·0)	8·2 (4·6–18·8)	8·6 (4·9–18·5)

Data are mean (SD), n (%), n/N (%), or median (IQR). Four patients had unknown heart failure status at baseline. For the overall population, race was not reported for 95 (1·1%) patients in the semaglutide group and 74 (0·8%) patients in the placebo group. Information on whether patients identified as Hispanic or Latino was not reported for 95 (1·1%) patients in the semaglutide group and 76 (0·9%) patients in the placebo group. ACR=albumin–creatinine ratio. eGFR=estimated glomerular filtration rate. *Race and ethnicity were self-reported by patients. †The category Other includes patients who reported their race as American Indian or Alaska Native, Native Hawaiian or Pacific Islander, or other.

Table: **Baseline characteristics of the SELECT cohort by heart failure status at enrolment**

patients with heart failure with reduced ejection fraction and those with unclassified heart failure (table). For example, patients with unclassified heart failure were slightly older and more likely to be female, had higher high-sensitivity C-reactive protein levels, and had lower NYHA class. Fewer patients with unclassified heart failure were treated with β blockers at baseline compared with patients with heart failure with preserved ejection fraction and patients with heart failure with reduced ejection fraction.

Patients with heart failure at baseline who were treated with placebo had a higher rate of MACE, heart failure composite, cardiovascular death, and all-cause death, than those without heart failure who were treated with placebo (figure 1). Semaglutide improved all outcome measures in patients with heart failure at random assignment compared with those without heart failure (HR 0·72, 95% CI 0·60–0·87 for MACE; 0·79, 0·64–0·98 for the heart failure composite endpoint; 0·76, 0·59–0·97 for cardiovascular death; and 0·81, 0·66–1·00 for all-cause death). Differences in event rates between those treated with semaglutide versus placebo emerged within 6 months and continued to expand over a mean follow-up of 39·8 months. Semaglutide also improved MACE (0·84, 0·74–0·97) and all-cause mortality (0·81, 0·67–0·97) in patients without a history of heart failure at enrolment to a similar degree (figure 1). Analysis of the effect of semaglutide on the individual components of MACE and the heart failure composite was not prespecified but the results are provided in the appendix (pp 8–9). Patients with heart failure at enrolment had a higher incidence of cardiovascular death and hospitalisation or urgent hospital visit for heart failure, and both components were reduced by semaglutide treatment compared with placebo.

Within the heart failure population at baseline, in those treated with placebo, patients with heart failure with reduced ejection fraction had a higher rate of MACE, heart failure composite, cardiovascular death, and all-cause death than those with heart failure with preserved ejection fraction (figure 2; appendix pp 10–11). Treatment with semaglutide resulted in improved outcomes in both the heart failure with reduced ejection fraction (HR 0·65, 95% CI 0·49–0·87 for MACE) and heart failure with preserved ejection fraction groups (0·69, 0·51–0·91 for MACE), with no indication of treatment heterogeneity in these outcomes (figure 2; appendix p 13). Over half of the observed composite heart failure events in each treatment group for each subgroup were ascribed to cardiovascular death before any hospitalisation or urgent hospital visit for heart failure (36 [67·9%] of 53 events for the semaglutide group and 39 [59·1%] of 66 events for the

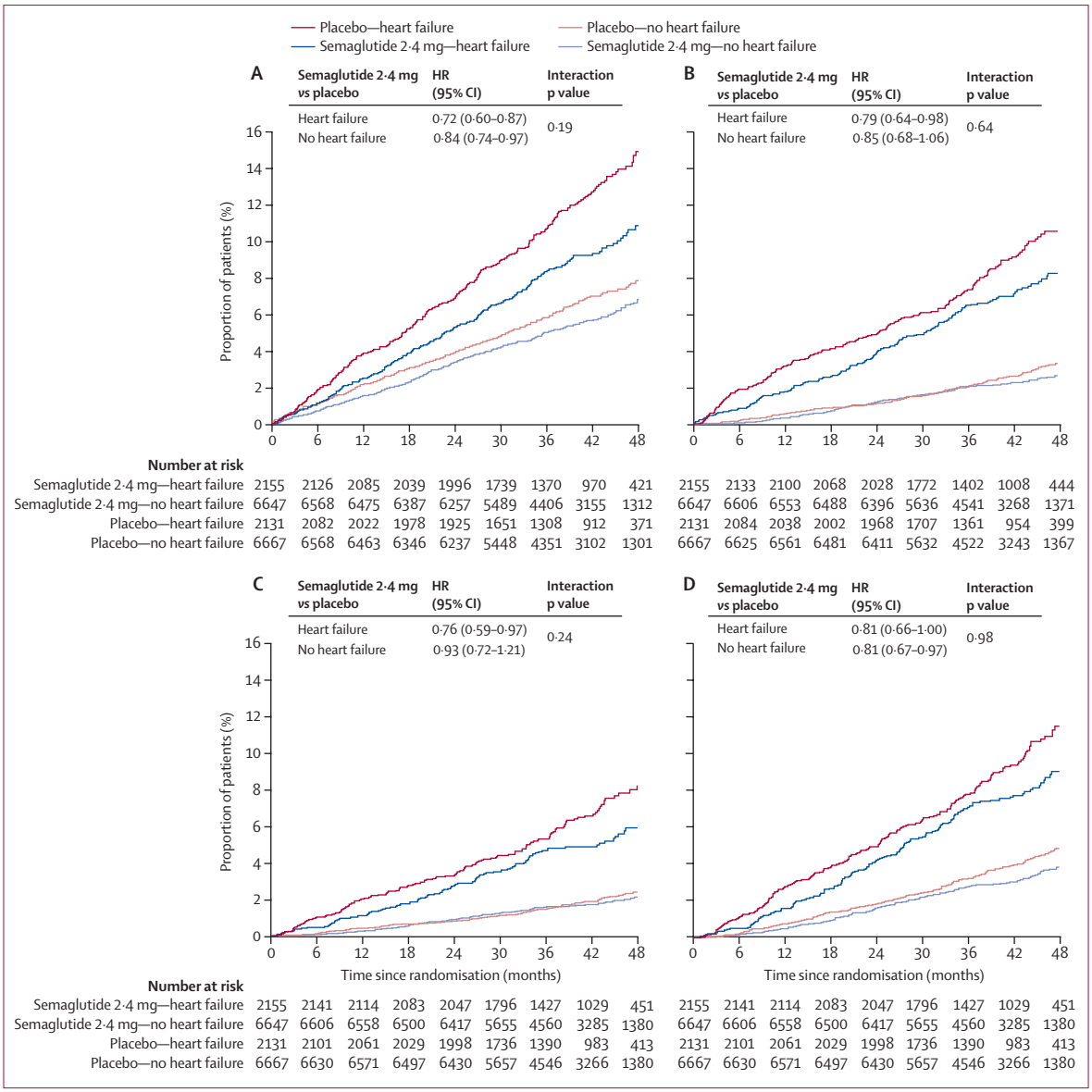

Figure 1: **The effect of semaglutide versus placebo according to presence or absence of heart failure at enrolment**
Cumulative incidence curves comparing the risk of major adverse cardiovascular events (A), heart failure composite (B), cardiovascular death (C), and all-cause death (D) comparing semaglutide with placebo according to presence or absence of heart failure. The cumulative incidence rate is calculated using the Aalen–Johansen method. HR=hazard ratio.

placebo group in patients with heart failure with preserved ejection fraction, and 37 [50·7%] of 73 events for the semaglutide group and 61 [63·5%] of 96 events for the placebo group in patients with heart failure with reduced ejection fraction; appendix pp 8–9). Sensitivity analyses were done using LVEF in patients with ECGs. When patients with heart failure with an LVEF of less than 50% were compared with those with an LVEF of 50% or more, the results were consistent with those based on prespecified investigator-defined heart failure subtype (appendix p 14). Similar results were found when patients with heart failure with an LVEF of less than 40% were compared with those with an LVEF of 40% or more (appendix p 16).

Treatment outcomes for MACE (figure 3) and the heart failure composite (figure 4) are shown by baseline patient characteristics. For MACE and the heart failure composite, there were no significant differences in benefits across baseline age, sex, BMI, NYHA status, and diuretic use. There were similar findings for the other adiposity measures (data not shown). There was no difference in the treatment effect of semaglutide versus placebo among patients with HbA_{1c} less than 5·7% (normoglycaemia) and those with levels of 5·7–6·5%

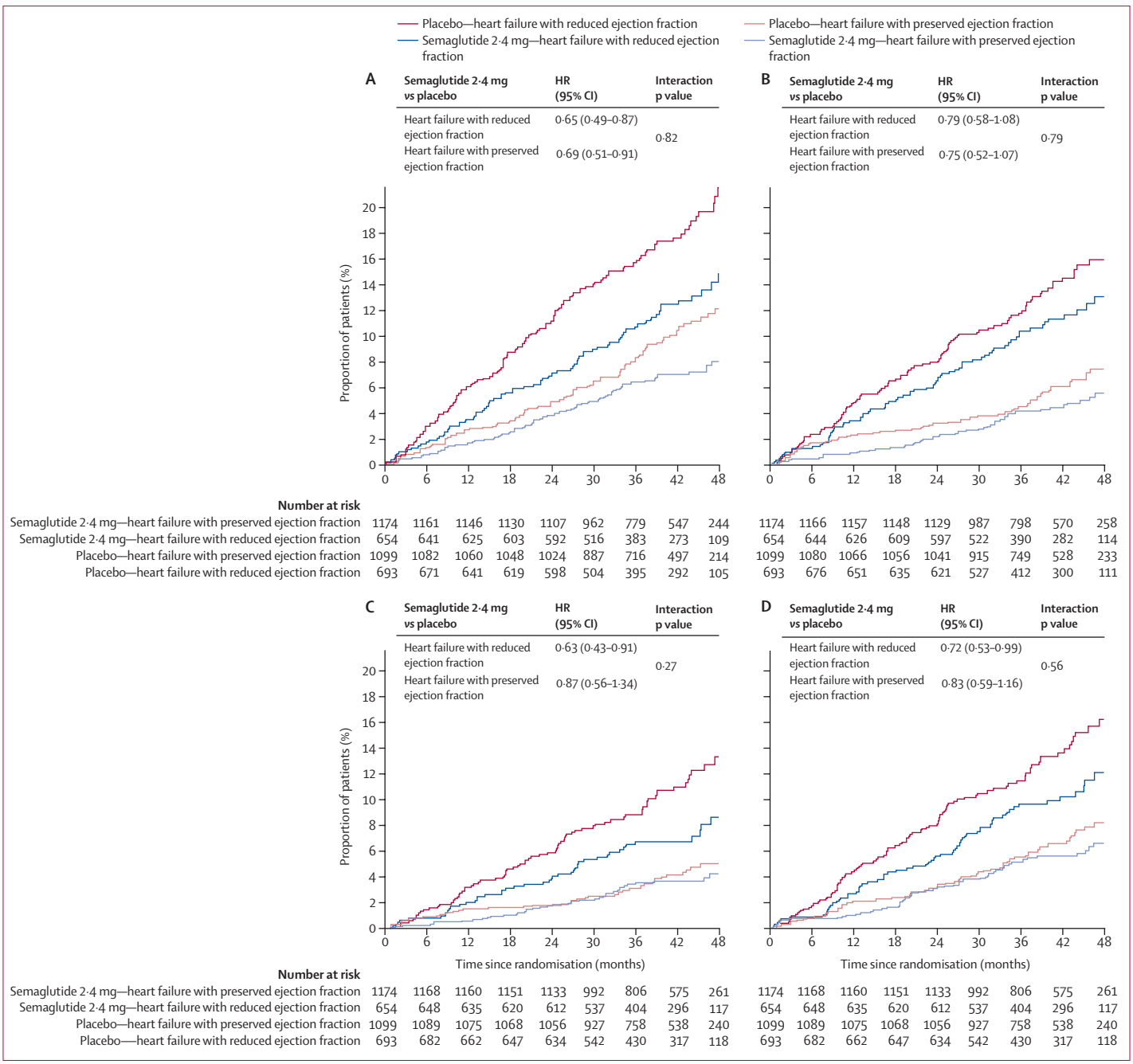

***Figure 2*: The effect of semaglutide versus placebo according to heart failure subtype**
Cumulative incidence curves comparing the risk of major adverse cardiovascular events (A), heart failure composite (B), cardiovascular death (C), and all-cause death (D) comparing semaglutide with placebo according to heart failure subtype. The cumulative incidence rate is calculated using the Aalen–Johansen method. HR=hazard ratio.

(prediabetes).[19] There was concordance of treatment effects across the predefined subgroups of patients.

The use of SGLT2 inhibitors as standard of care was not indicated when SELECT was initiated in 2018; this accounts for the absence of patients taking an SGLT2 inhibitor at the time of enrolment. However, 179 (13·3%) of 1347 patients with heart failure with reduced ejection fraction (78 [11·9%] of 654 patients in the semaglutide group and 101 [14·6%] of 693 in the placebo group) and 79 (3·5%) of 2273 patients with heart failure with preserved ejection fraction (32 [2·7%] of 1174 patients in the semaglutide group and 47 [4·3%] of 1099 patients in the placebo group) initiated SGLT2 inhibition therapy during the study.

Serious adverse events occurred less frequently in the semaglutide groups compared with the placebo groups

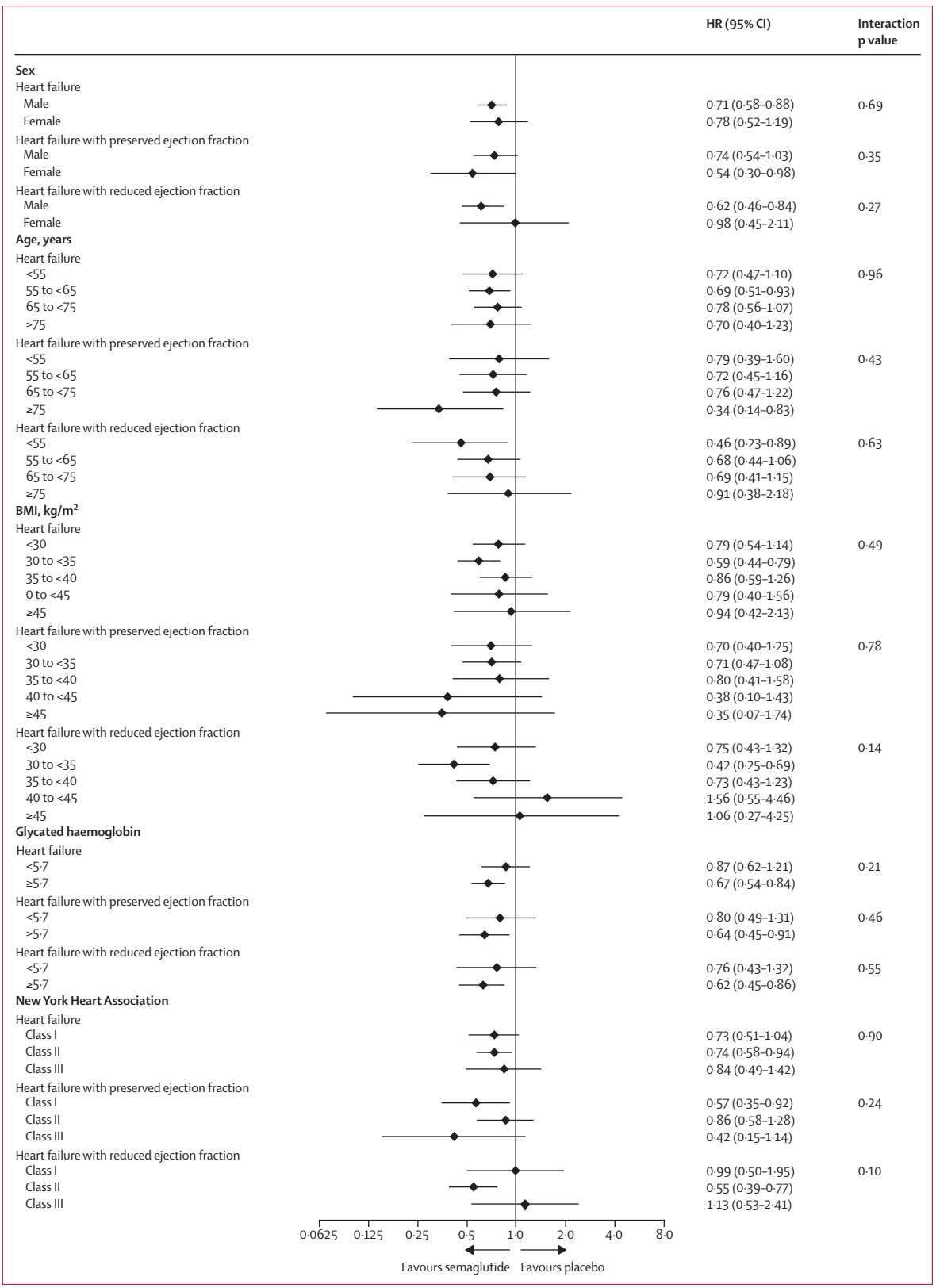

Figure 3: **MACE outcome according to heart failure and heart failure subtypes**
Forest plot showing HRs for MACE by baseline characteristics in patients with heart failure and heart failure subtypes. HR=hazard ratio. MACE=major adverse cardiovascular events.

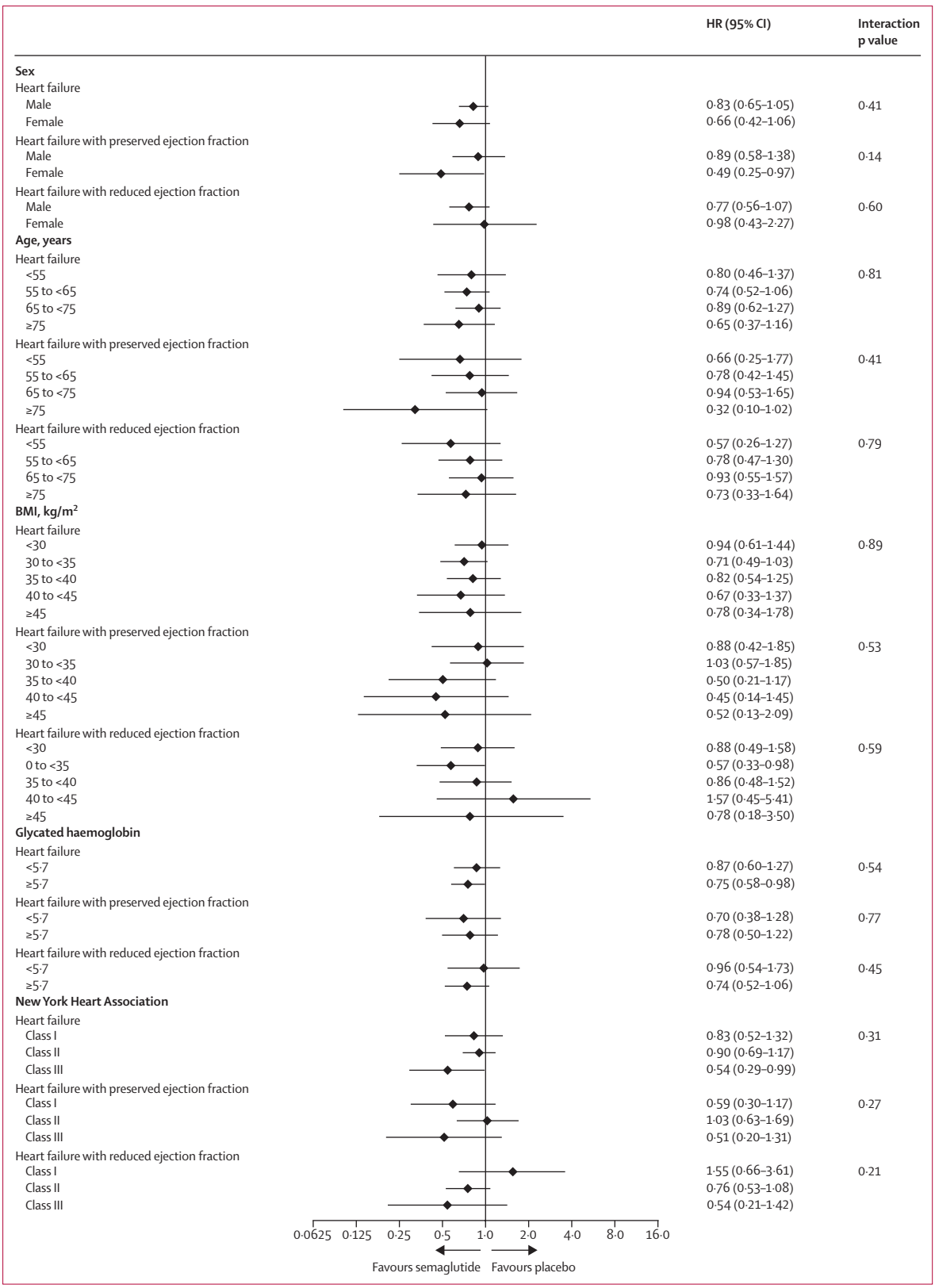

Figure 4: **Heart failure composite outcome according to heart failure and heart failure subtypes**
Forest plot showing HRs for heart failure composite by baseline characteristics in patients with heart failure and heart failure subtypes. HR=hazard ratio.

for patients with and without heart failure (appendix p 12). A similar pattern was observed in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. Cardiac disorders were the most common serious adverse events and the difference in the overall serious adverse event rates between patients with and without heart failure was primarily due to a difference in reported cardiac serious adverse events. There were no other consistent patterns of differences in adverse events of special interest between treatment groups or in the heart failure subgroups. In the semaglutide group, permanent discontinuation of treatment due to adverse events was primarily driven by gastrointestinal disorders and was higher than in placebo-treated patients (316 [14·7%] of 2155 patients *vs* 191 [9·0%] of 2131 patients in those with heart failure; 1145 [17·2%] of 6647 patients *vs* 527 [7·9%] of 6667 patients in those without heart failure). The discontinuation rate in patients receiving semaglutide was lowest in patients with heart failure with preserved ejection fraction (149 [12·7%] of 1174 patients) compared with patients with heart failure with reduced ejection fraction (114 [17·4%] of 654 patients) or unclassified heart failure (53 [16·2%] of 327 patients).

Discussion

In this prespecified analysis of the SELECT trial, we showed that semaglutide treatment reduced MACE and a heart failure composite endpoint, comprising cardiovascular death and hospitalisation or urgent hospital visit for heart failure, in over 4000 patients with atherosclerotic cardiovascular disease and overweight or obesity but no diabetes, who had a history of heart failure at enrolment. The improved outcomes were seen early after initiation of therapy and persisted over the trial period. The benefits of semaglutide for MACE, heart failure composite, cardiovascular death, and all-cause death did not differ in those with heart failure with preserved ejection fraction compared with those with heart failure with reduced ejection fraction. Patients with heart failure with reduced ejection fraction have a higher cardiovascular absolute risk than those with heart failure with preserved ejection fraction and previous reports suggested GLP-1 receptor agonists could be ineffective or even harmful in such patients.[12–14] Furthermore, clinical benefit with semaglutide was independent of age, sex, baseline BMI, and clinical status. These efficacy findings, together with an acceptable safety profile, support the use of semaglutide, in addition to usual care, to reduce the risk of MACE in a broad population of patients with established atherosclerotic cardiovascular disease and overweight or obesity, irrespective of their type of heart failure.

Patients with obesity are at increased risk for cardiovascular morbidity and mortality. The prevalence of heart failure in this population has been underestimated,[5] and our study indicates a poor outlook for patients with atherosclerotic cardiovascular disease and overweight or obesity but no diabetes, in terms of higher event rates versus patients without heart failure. The benefit we observed from semaglutide was seen in addition to usual care recommendations during the period of the trial and could represent a new clinical opportunity. In many countries, patients with clinical atherosclerotic cardiovascular disease often have either overweight or obesity, and the incidence is increasing.[1] Since the SELECT trial targeted a population with a BMI of 27 kg/m² or greater and established cardiovascular disease without diabetes, the equal clinical benefit in those with heart failure and without heart failure, independent of BMI at study entry, is reassuring.

Obesity has also changed the clinical spectrum of heart failure, and has been linked to the rising proportion of patients with heart failure with preserved ejection fraction, which is now the dominant clinical presentation of heart failure.[5] The treatment options for heart failure with preserved ejection fraction have, until recently, been few. Our study adds to the findings of the STEP-HFpEF trials, in which semaglutide improved heart failure-related symptoms, physical limitations, and exercise function in patients with obesity-related heart failure with preserved ejection fraction, with and without diabetes, compared with placebo.[10,11] However, these trials were not powered to assess hard outcome endpoints of morbidity and mortality. In SELECT, we showed the benefits of semaglutide on MACE, a heart failure composite, and cardiovascular death in patients with investigator-defined heart failure with preserved ejection fraction.

The prognosis of patients with heart failure with reduced ejection fraction is also worsened by coexisting obesity.[20] We showed, for the first time to our knowledge, that patients with atherosclerotic cardiovascular disease, overweight or obesity, and heart failure with reduced ejection fraction (who had a greatest absolute risk) had significant reductions in MACE with semaglutide, and the treatment effect on the heart failure composite was observed to be similar to that seen in the population with heart failure with preserved ejection fraction. This finding contrasts with previous smaller studies, LIVE and FIGHT, involving the GLP-1 receptor agonist liraglutide, which were not limited to patients with obesity and were not adequately powered to assess clinical outcomes.[12–14]

Semaglutide treatment improved our prespecified outcomes in patients with heart failure across a spectrum of baseline patient characteristics including age, sex, adiposity measures, glycaemic control, lipids, and blood pressure. The mechanisms underlying MACE reduction and other possible cardiovascular benefits of GLP-1 receptor agnosists are likely to be complex. GLP-1 receptor agonists modulate multiple metabolic and inflammatory pathways and have direct myocardial and vascular effects.[21] Behavioural changes that occur with treatment, including exercise, diet composition, and

eating patterns, might have also contributed.[22] Our findings, particularly the improved outcomes independent of heart failure subtype, should encourage future research, with more detailed phenotyping to characterise the complex pathophysiology of obesity-related heart failure. The observation of a reduction in all-cause mortality in all heart failure groups suggests the potential for other, as yet unknown, benefits.

The patient population in SELECT differs from those normally recruited to dedicated heart failure trials. Patients were enrolled based on atherosclerotic cardiovascular disease and overweight or obesity and were not required to have symptomatic heart failure for participation. Therefore, patients were less symptomatic, were taking fewer heart failure medications, and were at lower risk than those in dedicated heart failure trials. Most patients were in NYHA class I or II (<10% in class III at enrolment) and patients with NYHA class IV were specifically excluded. These differences, plus other differences in trial methodology, hamper cross-trial comparison.

In previous trials, SGLT2 inhibitors have been shown to result in a significant reduction in cardiovascular death and heart failure events[7–9] in patients with established heart failure, with and without diabetes, independent of ejection fraction. In SELECT, the improvement in the heart failure composite measure with semaglutide was mainly driven by reduced cardiovascular mortality. However, the observed reduction in mortality by semaglutide attenuates our ability to discern a treatment effect on the endpoint of hospitalisation or urgent hospital visit for heart failure, in part because mortality acts as a competing risk. We cannot be precise about what is driving the reduction in patients designated as having cardiovascular death, which included sudden cardiovascular death, as well as death from acute myocardial infarction and heart failure. Therefore, caution should be applied when interpreting our findings, and the analyses of the components of the heart failure composite were not prespecified. At the onset of recruitment into SELECT, SGLT2 inhibitors were not yet part of standard of care for heart failure. During the trial, SGLT2 inhibitors were initiated in only a small proportion of patients with heart failure. Future studies will be needed to explore the effect of GLP-1 receptor agonists in combination with SGLT2 inhibitors, which appear to have different and potentially complementary modes of action and therefore benefits, as suggested in the STEP HFpEF DM trial.[11,23] Additionally, combinations with other emerging drug therapies for heart failure might be beneficial.[23,24]

Our study has both strengths and limitations. The large number of patients with heart failure and long observation time allowed for robust assessment of the effect of semaglutide in terms of clinical outcomes, adverse events, and durability of effects. SELECT was done in 41 countries and thus represents a diverse global population. Nevertheless, most participants were White men, and future GLP-1 receptor agonist trials should be designed to examine the response by ethnicity and sex. In SELECT, the diagnosis of heart failure and its clinical subtype was made by investigators and based on medical health records, without an explicit requirement for echocardiography and heart failure biomarker measurement. This approach reflects clinical practice but results in the characterisation of groups of patients with a history of previous heart failure being less precise than in dedicated heart failure trials. Nevertheless, the investigator-defined heart failure group had substantially higher rates of MACE, heart failure composite, and all-cause mortality compared with those without heart failure. Furthermore, those classified as having a history of heart failure with reduced ejection fraction had nearly twice the rate of these events compared with those classified as having heart failure with preserved ejection fraction. ECGs were available for most patients with heart failure, and a time-to-event outcome analysis, based on ejection fraction categories, was consistent with the results for the prespecified investigator-defined heart failure groups. Patients recruited to SELECT had established astherosclerotic cardiovascular disease with one or more of previous myocardial infarction, stroke, and peripheral vascular disease. We showed that this population benefited from semaglutide, irrespective of whether they had investigator-designated heart failure at enrolment. Our study population differs from those recruited into dedicated heart failure trials and the benefits should not be extrapolated to other populations with heart failure. Further trials are warranted to evaluate in more detail the effect on heart failure-related outcomes and physiological and biomarker endpoints. Additionally, future research must define whether earlier preventive treatment can favourably affect the trajectory to clinical disease and heart failure. The number of incident hospitalisation or urgent hospital visit for heart failure events in the patients without heart failure at enrolment in our study was small. Therefore, although the current data provide evidence for cardiovascular efficacy of semaglutide in patients with atherosclerotic cardiovascular disease and prevalent heart failure, we were not able to determine whether semaglutide can reduce incident heart failure; this remains an important and unanswered question.

In conclusion, our findings suggest that a large population of patients with atherosclerotic cardiovascular disease who have overweight or obesity and heart failure could benefit from semaglutide, without the need for previous detailed cardiovascular risk stratification. The safety profile and discontinuation rates for semaglutide were similar in those with and without a history of heart failure and between heart failure subtypes, providing additional reassurance regarding the favourable risk–benefit balance of semaglutide in these patient groups. In patients with atherosclerotic cardiovascular disease with overweight or obesity but without diabetes, treatment with once-weekly subcutaneous semaglutide

2·4 mg compared with placebo reduced MACE, heart failure composite, cardiovascular mortality, and all-cause mortality in patients with and without clinical heart failure, regardless of clinical heart failure subtype.

Contributors

JD designed the study, researched data, contributed to the discussion, and wrote the manuscript. SR undertook the statistical analyses, contributed to the discussion, and reviewed and edited the manuscript. JD and SR directly accessed and verified the study data. BMS, SV, SEK, SSE, DR, IL, HMC, JP, MNK, GKH, OF, PEW, SH-L, and AML designed the study, researched data, and reviewed and edited the manuscript. SV, AG, CCL, MU-T, and MP recruited patients, contributed to the discussion, and reviewed and edited the manuscript. All authors approved submission of the final version of the manuscript and had access to the data. JD is the guarantor and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

JD declares having received consulting honoraria from Amgen, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk, and Bayer, and research grants from British Heart Foundation, Medical Research Council (UK), National Institute for Health and Care Research, Public Health England, MSD, Pfizer, Aegerion, Colgate, and Roche. BMS declares having received institutional research grants to Brigham and Women's Hospital from Better Therapeutics, Merck, Novo Nordisk, and Pfizer, and consulting fees from Allergan, Boehringer Ingelheim, Better Therapeutics, Elsevier PracticeUpdate Cardiology, Esperion, Hanmi, Lexicon, Novo Nordisk, and equity in health at Scale and Doximity. SV reports speaking honoraria or consulting fees from Abbott, Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Canadian Medical and Surgical Knowledge Translation Research Group, Eli Lilly, HLS Therapeutics, Janssen, Merck, Novartis, Novo Nordisk, Pfizer, PhaseBio, and TIMI. 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MNK declares having served as a consultant or on an advisory board for 35Pharma, Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Dexcom, Eli Lilly, Esperion Therapeutics, Imbria Pharmaceuticals, Janssen, Lexicon Pharmaceuticals, Merck (Diabetes and Cardiovascular), Novo Nordisk, Pharmacosmos, Pfizer, Sanofi, scPharmaceuticals, Structure Therapeutics, Vifor Pharma, and Youngene Therapeutics; has received research grants from AstraZeneca, Boehringer Ingelheim, and Pfizer; holds stocks in Artera Health and Saghmos Therapeutics; and has received honoraria from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. MNK has also received other research support from AstraZeneca. 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Data sharing

Data will be shared with bona fide researchers who submit a research proposal approved by an independent review board. Individual patient data will be shared in datasets in a de-identified and anonymised format. Information about data access request proposals can be found at novonordisk-trials.com.

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