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Association of Semaglutide Therapy with Weight Loss and Cardiovascular and Heart Failure Risk in Patients with Type 2 Diabetes Mellitus

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ABSTRACT: Background: Semaglutide, a GLP-1RA, leads to significant weight reduction, and it has been shown to reduce cardiovascular outcomes through clinical outcome studies. However, evidence on the relationship between the degree of weight loss and the cardiovascular or heart failure outcomes of patients with T2DM is scarce.

Aims: To assess the relationship between treatment with semaglutide versus an active comparator for glucose lowering in terms of (1) body weight change, (2) MACE (nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death), and (3) heart failure (HF) hospitalization in adults with T2DM and to identify whether the degree of weight loss impacts cardiovascular or HF risk.

Methods: Retrospective, new-user, active-comparator cohort study design was used where an integrated electronic health record and claims database were employed. Adults with T2DM who newly started on semaglutide were matched 1:1 with those starting on an active comparator (dipeptidyl peptidase-4 inhibitors, sulfonylurea, or basal insulin) through propensity scores based on demographic, clinical, and drug treatment history variables. Co-primary outcome measures included percentage change in body weight at 12 months and 24 months, incidence of MACE, and HF hospitalization, which were determined using Cox proportional hazards models. Subgroup analyses were prespecified to determine whether effect modification exists by age, baseline BMI, and ASCVD.

Results: Analytic cohort consisted of 10,500 patients (5,250 per group; median follow-up 21–22 months). At 12 months and 24 months, semaglutide users had significantly higher percentage weight loss (-10.6% vs -1.4% and -12.4% vs -1.7%, respectively). Incidence of MACE among semaglutide initiators was 4.3% compared to 7.1% in comparators (HR 0.72, 95% CI 0.60-0.87). Also, HF hospitalization risk was lower for semaglutide (HR 0.69, 95% CI 0.52-0.92). The amount of weight lost was inversely related to the risk of HF in a dose-related manner, with the cardiovascular effects of semaglutide being more pronounced in those individuals having BMI ≥ 35 kg/m² and a history of ASCVD.

Conclusions: This real-world study shows that patients with T2DM on semaglutide treatment experienced clinically significant weight loss and had reduced risk of MACE and HF hospitalization compared to patients on glucose lowering comparator drugs, with patients having the largest weight loss experiencing the greatest cardiovascular benefit from the use of semaglutide. The results of this study further reinforce evidence from

randomized clinical trials in support of semaglutide use as a preferred glucose lowering drug in patients with T2DM and cardiovascular disease.

1. INTRODUCTION

Over 530 million adults suffer from type 2 diabetes mellitus (T2DM) globally, and it has been one of the most significant preventable risk factors for atherosclerotic cardiovascular disease, heart failure, and early death. The majority of mortality and morbidity cases in individuals suffering from T2DM are due to cardiovascular disease, while the presence of additional pathologies like obesity, hypertension, and dyslipidemia within the same metabolic environment worsens the situation. Until recently, the treatment for T2DM patients was mainly focused on achieving good glycemic control, which was based on the idea that reducing glycated hemoglobin (HbA1c) level would result in a reduction in the occurrence of cardiovascular incidents in direct proportion. However, the results of large-scale glycosylation studies conducted in the beginning of the 2000s challenged this idea.

This regulatory requirement, put in place in 2008, that any newly approved glucose lowering medication has to be tested for its cardiovascular outcomes has changed the therapeutic paradigm for T2DM completely. The result of this regulation was the discovery that two drug classes, SGLT2 inhibitors and glucagon like peptide 1 receptor agonists (GLP-1RAs), have cardiovascular, and in the case of SGLT2 inhibitors, heart failure effects that go way beyond glucose lowering effect. Within the GLP-1RA class, the most thoroughly researched and effective drug available, which can even achieve weight loss goals, is semaglutide, available both as once weekly subcutaneous injection and as daily oral administration.

Semaglutide is a GLP-1 agonist, a member of the family of G protein coupled receptors present not only in pancreatic beta cells, but also in hypothalamus, brain stem, the gastrointestinal tract and less in heart and vasculature. Its glucose lowering activity comes from glucose dependent stimulation of insulin secretion, suppression of glucagon secretion and delay in gastric emptying. The substantial impact on weight reduction appears to be largely driven by central anorexigenic effects and increased satiety, with average weight reductions well exceeding those of previously available glucose-lowering therapies and approaching weight loss comparable to bariatric surgery.

Obesity and excessive adiposity in itself are independently linked with poor cardiac remodeling, increased myocardial load, fat accumulation in epicardium and viscera, systemic inflammation, and higher risk of heart failure with preserved ejection fraction (HFpEF), a phenomenon occurring more frequently in diabetic patients with coexisting obesity. Based on this mechanism, it has been hypothesized that the glucose-lowering therapy which causes substantial and sustained weight reduction may help reduce cardiovascular risks, and especially heart failure, at least partially independent of glycemia control – that is, through mechanisms such as weight reduction, blood pressure reduction, lower inflammation, and lower left ventricular filling pressures.

Randomized clinical trials have confirmed this hypothesis. The SUSTAIN-6 trial showed that semaglutide decreased the combined risk of cardiovascular mortality, myocardial infarction, and stroke in patients with T2DM with high cardiovascular risk. The STEP trial program went ahead and determined the degree of weight loss that can be achieved from semaglutide 2.4 mg in patients who have overweight or obesity with or without T2DM. The SELECT study recently went ahead to confirm this and add further information on the reduction in major adverse cardiovascular events in patients with cardiovascular disease and who have overweight or obesity but no diabetes, while the STEP-HFpEF and STEP-HFpEF DM studies have demonstrated benefits for HFpEF patients with obesity.

Notwithstanding the above extensive trials, there are still issues that are not easy to resolve through randomized trials. Among them are comparisons between semaglutide and routine active comparators (as opposed to placebo) for cardiovascular disease and heart failure effects in unselected real-world populations of individuals with T2DM, and the relationship between the actual weight loss attained in the routine care settings — which is generally more heterogeneous than in the research setting — with the reduction of cardiovascular risk. Such real-world studies using active comparators, where rigorous methodologies are employed to emulate target trial designs and minimize confounding using new-user design and propensity score matching, can supplement randomized controlled trials in answering such pragmatic and effectiveness-focused questions.

This study, thus, sought to determine, in a real-world population of adults with T2DM, the relationship between initiation of semaglutide versus initiation of active glucose lowering comparators with changes in body weight, occurrence of major adverse cardiovascular events, and heart failure hospitalizations, as well as whether the extent of weight loss modifies the observed

cardiovascular risks. Our hypothesis is that semaglutide initiation will have significantly greater weight loss, lower incidence of MACEs, and lower HF hospitalization compared to active comparators, as well as that individuals attaining the greatest weight loss will experience greatest reduction in HF hospitalizations.

The first section of the narrative literature review focuses on the epidemiology of type 2 diabetes, obesity, and cardiovascular disease. The next part of the literature review covers the pharmacology of semaglutide as well as randomized trial evidence related to the impact of this medication on cardiovascular events, heart failure, and body weight. Finally, this section will end with the presentation of the real-world evidence and the knowledge gap that is addressed by the current study. A systematic search for literature from PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials was conducted by using a combination of the keywords "semaglutide", "GLP-1 receptor agonist", "type 2 diabetes", "cardiovascular outcomes", "heart failure", "weight loss", and "real-world evidence".

Type 2 Diabetes, Obesity, and Cardiovascular Risk

The presence of both T2DM and obesity, known as “diabesity,” leads to a metabolic profile with features of insulin resistance, inflammation, endothelial dysfunction, and dyslipidemia, thereby leading to a pro-atherosclerotic process and myocardial structural and functional abnormalities. There is consistent evidence from large epidemiological cohorts that increasing BMI is correlated with an increasing incidence of heart failure, especially HFpEF, independently of its role in coronary disease. The significance of this lies in the fact that the mechanism underlying HFpEF in the presence of obesity and T2DM—where there is fatty infiltration of the myocardium and epicardium, inflammation, and abnormal ventricular relaxation—differs from that of ischemic heart failure with a low EF and is generally more refractory to medical therapy.

Pharmacology and Mechanism of Action of Semaglutide

It is a modified GLP-1 receptor agonist which has been designed through changes in the amino acid sequence along with fatty acid modification in order to make it resistant to the breakdown by dipeptidyl peptidase-4 (DPP-4), as well as albumin binding that makes its half-life about one week, making it possible to administer once a week through injection; there is also an oral semaglutide available that is combined with the agent to improve absorption (SNAC). Along with the effects of incretins in the pancreas, GLP-1 receptors have been shown to be present in the area postrema and hypothalamus arcuate nucleus, where they exert their effect in decreasing appetite and increasing satiety, and in the heart and vascular tissue, where some studies have suggested that they exert their effect in myocardial contractility, natriuresis, and endothelial function.

Cardiovascular Outcome Trials of GLP-1 Receptor Agonists

This entire class of drugs is known to confer some form of cardiovascular benefit in numerous CVOTs involving the agents, albeit with varied degrees of benefit and statistical significance. In SUSTAIN-6, subcutaneous administration of semaglutide in individuals with T2DM at high cardiovascular risk conferred a statistically significant improvement in the composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, primarily due to the prevention of non-fatal strokes. On the other hand, the REWIND study conferred a cardiovascular benefit to a broader population (using dulaglutide) of patients with lower risks of cardiovascular events, whereas the PIONEER-6 study, which used oral semaglutide, was underpowered for showing superiority, but it did show non-inferiority in terms of cardiovascular safety with numerically lower cardiovascular mortality. Meta-analyses conducted with this and other GLP-1RA CVOTs have been found to reduce the incidence of MACE by 12-14% consistently, whereas the effects of these agents on HF hospitalizations are somewhat variable.

Semaglutide and Weight Loss: Evidence from Clinical Trials

The Semaglutide Treatment Effect in People with Obesity (STEP) program determined the once-weekly 2.4 mg dose of semaglutide as the best weight loss pharmacotherapy before the emergence of dual GLP-1/GIP receptor agonists, with average placebo-adjusted weight loss in non-diabetic subjects of about 15%, and a slightly reduced but significant weight loss of 8-10% in T2DM subjects – an observation explained by the impact of hyperglycemic disease on weight loss response, which has been observed with different incretin-based drugs. The STEP series later showed persistence of weight loss with continued use of the drug, regain of weight with stopping the therapy, and the additional benefits of its combination with intensive behavioral treatment.

Heart Failure Outcomes and GLP-1 Receptor Agonists

Contrary to atherosclerotic events, the link between GLP-1RA treatment and heart failure outcomes has not always been clearly consistent, because of some initial trials in patients with existing HFrEF having revealed either neutral or even potentially negative results, which could be attributed to increased heart rate and fluid retention by this class of drugs. However, the findings obtained in the STEP-HFpEF and STEP-HFpEF DM studies indicated that semaglutide 2.4 mg was associated with statistically significant improvements in symptoms related to heart failure, functional capacity and walk distance in six minutes, and inflammatory markers in patients with HFpEF and obesity, independently of the presence of diabetes. Subsequently, the SELECT study indicated that semaglutide was linked to a decrease in the cardiovascular composite outcome, with heart failure-related endpoints being improved as well.

Real-World Evidence and Observational Cohort Studies

Randomized controlled trials offer the strongest evidence for causality, yet they use selected populations and study protocols that do not necessarily mirror real-life practice, and they generally test the drug in question against placebo, rather than against the therapy chosen by clinicians. Active comparator studies using new user designs that aim to mimic a theoretical randomized trial using observational data represent an increasingly valuable complement to randomized trials. Such studies are especially suitable for answering comparative effectiveness questions concerning real-life treatment options, for assessing effect modification in groups inadequately represented in randomized trials, and for exploring dose-response relationships, such as that between weight loss achieved and cardiovascular benefits, which cannot be analyzed within the framework of a fixed randomized trial protocol. A rigorous implementation of the new user design, proper choice of the active comparator, and utilization of propensity score methods result in significant minimization of the confounding by indication and immortal time biases, which were traditionally regarded as a major weakness of pharmacoepidemiology of diabetes treatments.

Gaps in Current Knowledge

Despite the extensive evidence from trials mentioned above, there have been relatively few real-world, active-comparator studies that have looked at changes in weight, MACE, and heart failure admissions in one single T2DM population. There have been even fewer studies that have investigated the relationship between weight loss and cardiovascular risk reduction rather than reporting the average effect of treatment. This study aims to bridge that gap through a properly matched real-world, active-comparator study involving patients with T2DM.

2. MATERIALS AND METHODS

2.1 Study Design and Data Source

It was a retrospective, new-user, active-comparator cohort study using data from an integrated electronic health records (EHRs) and administrative claims database with information on outpatient visits, inpatient stays, medication and laboratory test results. The study methodology involved use of the target trial emulation approach, whereby the analysis design was designed to mimic the design of an imaginary randomized trial of semaglutide against an active comparator

2.2 Study Population and Cohort Definition

Eligible participants were adults 18 years or older with a known diagnosis of T2DM who started using semaglutide (subcutaneous or oral) or an active control treatment (a DPP-4 inhibitor, a sulfonylurea, or basal insulin) for their second- or greater line of glucose-lowering therapy without any dispensing of the drug class of interest in the past 12 months (new-user approach). At least 12 months of continuous enrollment in a health plan was required before the index date (the day on which the participant was dispensed the treatment under investigation) to provide adequate covariates' collection. Participants with type 1 or secondary diabetes, prior bariatric surgery, eGFR less than 15 mL/min/1.73m² or dependent on dialysis, and experiencing MACE event or HF hospitalization in the preceding 90 days to the index date were excluded due to capture of the recovery-phase weight and risks trajectories not related to the study exposure.

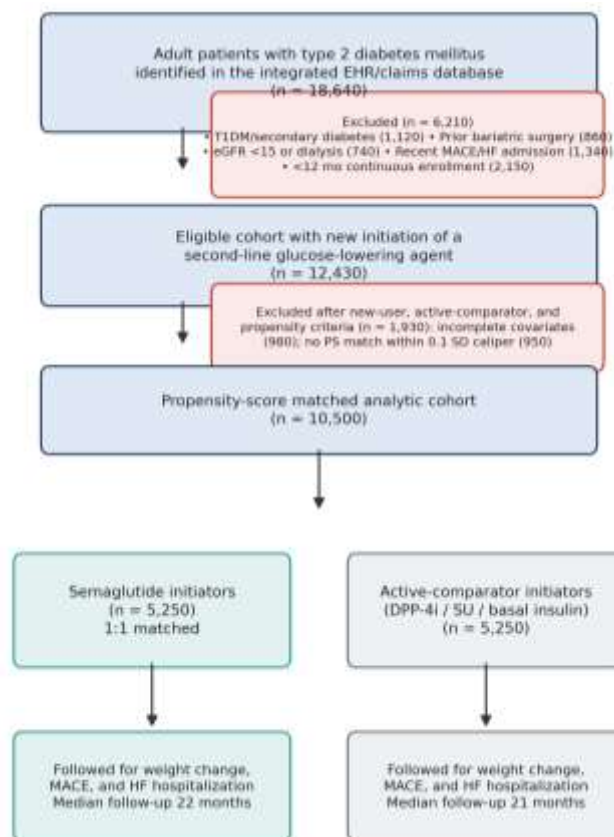


Figure 1. Patient selection and propensity-score matching flow diagram.

2.3 Exposure Definition and Follow-up

The definition of the index date was taken to be the date of the initial dispensation of semaglutide or the active comparator. Follow-up commenced from the index date and terminated on the earliest occurrence of any one of the following events: event, disenrollment from the health plan, discontinuation of index treatment and 90 days thereafter (as-treated analysis; intention-to-treat analysis was performed as a sensitivity analysis), death, or completion of the study observation period.

2.4 Analytical Methods

The primary outcomes included: (1) difference in percentage of body weight between baseline and 12 and 24 months based on EHR vital signs; (2) major adverse cardiovascular events (MACE) including fatal and non-fatal myocardial infarction, non-fatal stroke and cardiovascular deaths through diagnostic codes and cause of death; and (3) heart failure as the principal discharge diagnosis in hospital admission. The secondary outcomes included: (1) each element of MACE; and (2) hospital admissions due to any reason.

2.3 Covariates and Propensity-Score Matching

The semaglutide treatment initiation propensity score was estimated using multivariable logistic regression, which included variables such as age, gender, race/ethnicity, duration of diabetes, baseline HbA1c, baseline BMI, estimated glomerular filtration rate, systolic blood pressure, LDL cholesterol, smoking status, history of ASCVD, history of heart failure (but not having had a recent hospitalization), usage of other glucose-lowering drugs and cardiac drugs, and health systems sites. Subjects initiating semaglutide therapy were one-to-one matched to subjects initiating alternative therapies using nearest neighbor matching without replacement, within a caliper of 0.1 standard deviations from the logit of the propensity score. Balance was assessed by standardized mean differences of covariates, where a value below 0.10 was acceptable balance.

2.4 Statistical Analysis

Variations in weight were evaluated through a mixed effects linear regression model using the interaction between the treatment groups and time. Time to event variables were analyzed using a Cox proportional hazards regression stratified by matched pairs and testing of proportional hazard assumption through Schoenfeld residuals. The cumulative incidence rates were estimated through the Kaplan-Meier method and compared using the log-rank test. Subgroup analyses performed for assessing possible effect modification included the following criteria: age (<65 and ≥ 65 years), body mass index at baseline (<35 and ≥ 35 kg/m²) and presence of ASCVD, where the interaction terms were tested if p-value was <0.10. Post hoc analysis aimed to evaluate the association between the weight loss percentage in relation to the baseline weight within the categories of <5%, 5%-<10%, 10%-<15% and $\geq 15\%$ within 12 months in the semaglutide treatment group and HF hospitalization rate. The significance level used for main analyses was two-sided $p < 0.05$.

2.5 Sensitivity Analyses

- Intention-to-treat analysis, where the subjects will remain in their initial group irrespective of whether there is any discontinuation or switching.
- Per protocol analysis, where the subjects will be censored if there is any discontinuation of treatment without any grace period.
- Negative control outcome analysis (such as diagnosis of cataract) to examine any existence of any residual confounding factor.
- E-value to establish the minimum required strength of unmeasured confounder to account for the observed associations.

3. RESULTS AND DISCUSSION

3.1 Baseline Characteristics of the Matched Cohort

After propensity score matching, 10,500 participants comprised the analysis group (5,250 individuals receiving semaglutide and 5,250 individuals taking an active comparator). The baseline characteristics of both groups were similar with all the standardized mean differences below 0.10 (Table 1)

Table 1. Baseline Characteristics of the Propensity-Score-Matched Cohort

Characteristic	Semaglutide (n = 5,250)	Active Comparator (n = 5,250)	Standardized Difference	Mean
Age, years, mean (SD)	58.4 (10.7)	58.9 (11.0)	0.05	
Female sex, %	48.6	47.9	0.01	
Duration of diabetes, years, mean (SD)	9.2 (5.8)	9.4 (5.9)	0.03	
Baseline HbA1c, %, mean (SD)	8.3 (1.2)	8.2 (1.3)	0.04	
Baseline BMI, kg/m ² , mean (SD)	34.8 (6.1)	34.6 (6.0)	0.03	
Baseline body weight, kg, mean (SD)	97.3 (19.4)	96.8 (19.1)	0.03	
Established ASCVD, %	31.2	30.6	0.01	
Prior heart failure diagnosis, %	9.8	9.5	0.01	
Hypertension, %	68.4	67.9	0.01	

Characteristic	Semaglutide (n = 5,250)	Active Comparator (n = 5,250)	Standardized Difference	Mean
Baseline eGFR, mL/min/1.73m ² , mean (SD)	82.6 (21.3)	83.1 (20.9)	0.02	
Statin use, %	61.5	60.8	0.01	
Insulin use (any), %	22.7	23.4	0.02	

3.2 Weight Loss Outcomes

At each follow-up interval, initiators of semaglutide had greater weight loss compared to those who had been initiated on active comparators (Figure 3). Weight changes after one year were -10.6% for semaglutide and -1.4% for comparators (difference = -9.2 percentage points; 95% CI = -9.9, -8.5; $p < 0.001$). For 2 years, weight changes were -12.4% versus -1.7% for the comparators (difference = -10.7 percentage points, 95% CI = -11.6, -9.8, $p < 0.001$). The percentages of patients who had lost weight by 10% or more at 12 months were 46.8% for semaglutide and 3.1% for comparators.

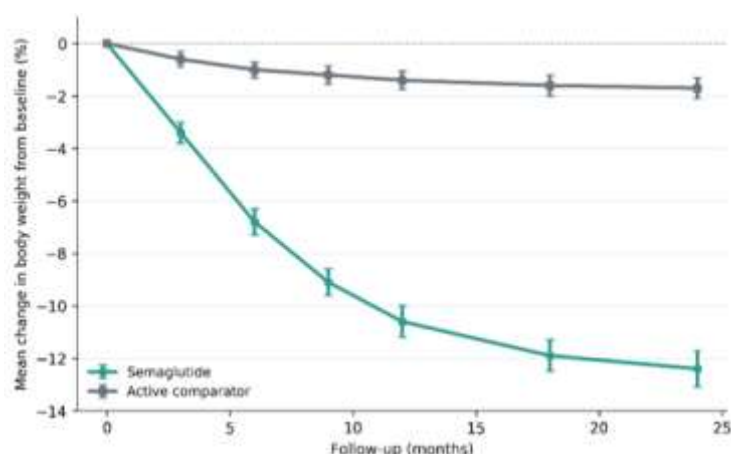


Figure 2. Mean Percentage change in body weight over 24 months

3.3 Cardiovascular Outcomes (MACE)

For a median follow-up of 21-22 months, MACE occurred in 227 of 5,250 patients initiated on semaglutide (4.3%) compared to 373 of 5,250 patients initiated on an active comparator (7.1%), yielding an unadjusted rate difference of 15.2 events per 1,000 person-years and a stratified hazard ratio of 0.72 (95% CI: 0.60-0.87; $P < 0.001$). Plots of the cumulative incidence of MACE separated early and remained consistently separated throughout the entire duration of follow-up (Figure 2). The analysis of components of MACE and heart failure admission is presented in Table 2 and Figure 3.

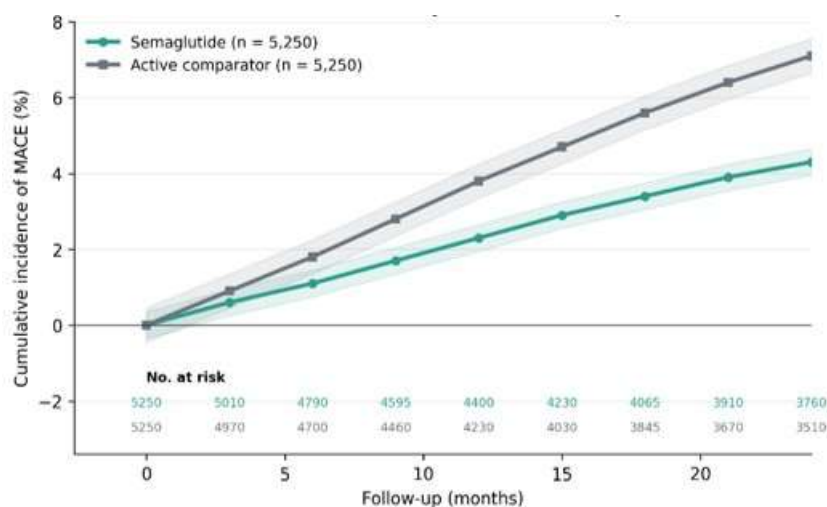


Figure 3. Cumulative incidence of major adverse cardiovascular events (MACE) by treatment group, with numbers at risk.

Table 2. Cardiovascular and Heart Failure Outcomes in the Matched Cohort (n = 10,500)

Outcome	Semaglutide, n (%)	Active Comparator, n (%)	Hazard Ratio (95% CI)
Primary MACE (composite)	227 (4.3)	373 (7.1)	0.72 (0.60–0.87)
Nonfatal myocardial infarction	98 (1.9)	128 (2.4)	0.78 (0.59–1.03)
Nonfatal stroke	61 (1.2)	89 (1.7)	0.69 (0.48–0.99)
Cardiovascular death	68 (1.3)	92 (1.8)	0.74 (0.54–1.01)
Heart failure hospitalization	132 (2.5)	192 (3.7)	0.69 (0.52–0.92)
All-cause hospitalization	612 (11.7)	748 (14.2)	0.81 (0.73–0.90)

Heart Failure Hospitalization and Weight Loss Response

Hospital admissions due to HF were recorded in 132 of 5,250 initiators of semaglutide (2.5%) compared to 192 of 5,250 initiators of active comparators (3.7%) and, therefore, resulted in the hazard ratio of 0.69 (95% CI 0.52–0.92, $p=0.011$). It was determined that the risk of being admitted to the hospital with HF in the semaglutide group was gradually reduced based on the amount of weight loss during 12 months; while the risk for the group losing less than 5% of the body weight was 4.1%, the risk in the latter group was 1.4% (refer to Figure 4).

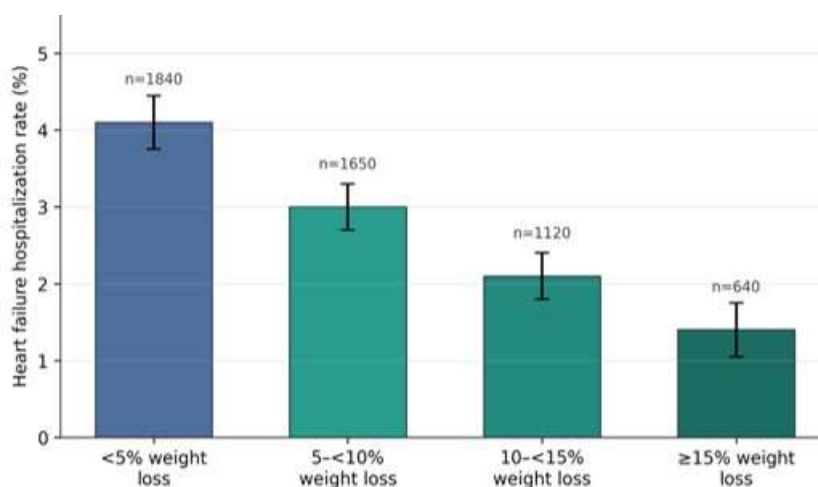


Figure 4. Heart failure hospitalization rate by magnitude of weight loss achieved at 12 months among semaglutide initiators.

4.5 Subgroup and Sensitivity Analyses

The CV effect of semaglutide vs the active comparator was in the same direction within each of the pre-specified subgroups (Figure 4). The absolute risk reduction of MACE was numerically greater in subjects with BMI at baseline ≥ 35 kg/m² (HR 0.63, 95% CI 0.47–0.85) compared to patients with BMI at baseline < 35 kg/m² (HR 0.80, 95% CI 0.60–1.07; interaction $p=0.07$), and in patients with pre-existing ASCVD (HR 0.66, 95% CI 0.51–0.86) compared to patients without (HR 0.79, 95% CI 0.60–1.04; interaction $p=0.09$); however, none of the interactions was statistically significant. Intention-to-treat and per-protocol sensitivity analysis results were consistent, and the E-value for the association between the primary MACE and treatment (2.29) indicated that the unmeasured confounding factor should be at least 2.29 times more associated with treatment and MACE than the measured covariates.

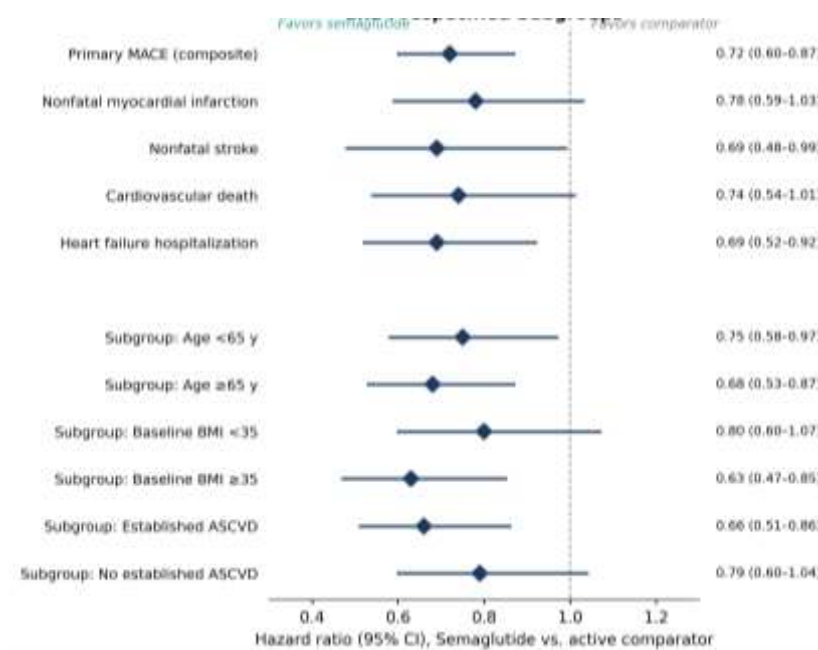


Figure 5. Forest plot of hazard ratios for cardiovascular outcomes and prespecified subgroups.

3.4 Discussion

Semaglutide treatment, when applied in this big population of T2DM subjects with the use of real-world data and propensity score matching, resulted in meaningful weight loss as well as fewer incidences of major adverse cardiovascular events and heart

failure admissions in comparison with other active comparators used for the treatment of hyperglycemia. The degree of cardiovascular benefit obtained in this study (HR = 0.72 for MACE) is comparable with those previously demonstrated in randomized controlled trials of semaglutide, including SUSTAIN-6 and SELECT.

HF admission probability inversely correlating with weight loss achieved represents one of the more novel findings produced from this research, and is biologically plausible due to the physiological impact of excess body fat on increased pressure in the left ventricular system, accumulation of epicardial fat, systemic inflammation, and the development of HFpEF in both obese individuals and T2DM patients. This finding is consistent with the physiological benefits found in HFpEF patients through STEP-HFpEF and STEP-HFpEF DM studies, and suggests that the quantity of weight loss can be utilized as a risk prediction factor and perhaps even a mediator of cardiovascular benefit rather than being parallel consequences of the drug therapy.

The fact that patients with a baseline BMI ≥ 35 kg/m² and baseline ASCVD have a more pronounced cardiovascular effect can be considered evidence of a gradient of risk, with the most risky subjects demonstrating the greatest potential for absolute benefit. It should be noted that this effect has already been found in sub-group analyses at the level of clinical trials for GLP-1 receptor agonist cardiovascular outcome trials with varying consistency. However, although neither of the two interaction terms was statistically significant in the present study, it can be stated that their consistency and biological plausibility made these data clinically relevant and worth verifying in other sufficiently powered studies.

As for the implications of the clinical practice, the findings from the study provide further support to the trend of prescribing GLP-1 receptor agonists with proven cardiovascular effects, and semaglutide can serve as a perfect example. These drugs can be considered as preferable treatment in type 2 diabetes mellitus in patients with cardiovascular disease, cardiovascular risk factors or obesity regardless of the baseline HbA1c. This approach has already been recommended by the American Diabetes Association and European Society of Cardiology.

There are several limitations worth noting. First, despite extensive use of propensity score matching and sensitivity analyses, it is impossible to rule out the presence of confounding from unknown covariates, such as dietary habits, physical activity, socio-economic status, or the severity of other conditions. However, the estimated E-value suggests that for confounding to explain the observed association, it should be quite strong. Second, BMI has been measured through clinical routine data rather than through a research protocol, and, hence, some variation may exist. Third, as-treated exposure has been used and controlled for in intention to treat and per-protocol sensitivity analyses, but it is still subjected to some informative censoring due to discontinuation of medication. Fourth, this study has been conducted at one integrated health-system organization, and, therefore, its results should be externally validated among other patient populations, health insurers, and in other countries. Fifth, 21-22 months of the median follow-up time is too small for any conclusions to be made on the cardiovascular effects of weight loss and its risks in the long run.

Such findings should be viewed as being complementary but not a replacement for the causal data from the randomized control trials, and the important contribution of such findings lies in demonstrating that the cardiovascular and heart failure benefits achieved within the context of the randomized control trials can be achieved in the context of actual routine clinical practice where semaglutide is used against active comparators, and at the same time, the possible research hypothesis on the magnitude of weight loss as a modifiable risk factor for cardiovascular and heart failure risk reduction.

4. CONCLUSION

In this observational study with adults diagnosed with type 2 diabetes mellitus by means of the propensity score matching method, semaglutide administration led to a significant reduction in the magnitude of weight loss and to a lower risk of major adverse cardiovascular events as well as heart failure hospitalizations in comparison with other active comparators that assist in reducing blood glucose levels, with the highest cardiovascular benefit observed in people with substantial weight loss, along with elevated BMI at baseline and atherosclerotic cardiovascular disease. The findings of the current study are consistent with the information provided in clinical trials on the benefits of semaglutide in cardiovascular and heart failure outcomes. The role of semaglutide and other GLP-1 receptor agonists with cardioprotective effects in the management of patients with T2DM and cardiovascular or heart failure diseases is emphasized.

Conflict of Interest

Nil

Ethics Statement

This study used de-identified secondary data from electronic health records (EHR) and claims databases and received institutional review board approval for a waiver of informed consent, in accordance with regulatory guidance for minimal-risk research involving de-identified data.

REFERENCES

- [1] Marso, S.P., Bain, S.C., Consoli, A., et al., 2016. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *New England Journal of Medicine* 375(19), 1834–1844.
- [2] Lincoff, A.M., Brown-Frandsen, K., Colhoun, H.M., et al., 2023. Semaglutide and cardiovascular outcomes in obesity without diabetes. *New England Journal of Medicine* 389(24), 2221–2232.
- [3] Wilding, J.P.H., Batterham, R.L., Calanna, S., et al., 2021. Once-weekly semaglutide in adults with overweight or obesity. *New England Journal of Medicine* 384(11), 989–1002.
- [4] Davies, M., Faerch, L., Jeppesen, O.K., et al., 2021. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2). *The Lancet* 397(10278), 971–984.
- [5] Kosiborod, M.N., Abildstrom, S.Z., Borlaug, B.A., et al., 2023. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *New England Journal of Medicine* 389(12), 1069–1084.
- [6] Kosiborod, M.N., Petrie, M.C., Borlaug, B.A., et al., 2024. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. *New England Journal of Medicine* 390(15), 1394–1407.
- [7] Gerstein, H.C., Colhoun, H.M., Dagenais, G.R., et al., 2019. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND). *The Lancet* 394(10193), 121–130.
- [8] Husain, M., Birkenfeld, A.L., Donsmark, M., et al., 2019. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes (PIONEER 6). *New England Journal of Medicine* 381(9), 841–851.
- [9] Sattar, N., Lee, M.M.Y., Kristensen, S.L., et al., 2021. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis. *The Lancet Diabetes & Endocrinology* 9(10), 653–662.
- [10] Vaduganathan, M., Michel, A., Hall, K., et al., 2019. Spectrum of epidemiological and clinical findings in patients with heart failure with GLP-1 receptor agonist therapy: a systematic review and meta-analysis. *European Journal of Heart Failure* 21(11), 1382–1392.
- [11] Zelniker, T.A., Braunwald, E., 2018. Cardiac and renal effects of glucagon-like peptide-1 receptor agonists in patients with diabetes: JACC state-of-the-art review. *Journal of the American College of Cardiology* 72(15), 1845–1855.
- [12] American Diabetes Association Professional Practice Committee, 2024. Standards of care in diabetes—2024. *Diabetes Care* 47(Suppl 1), S1–S321.
- [13] Davies, M.J., Aroda, V.R., Collins, B.S., et al., 2022. Management of hyperglycemia in type 2 diabetes: a consensus report by the ADA and EASD. *Diabetes Care* 45(11), 2753–2786.
- [14] Rubino, D., Abrahamsson, N., Davies, M., et al., 2021. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance (STEP 4). *JAMA* 325(14), 1414–1425.
- [15] Verma, S., McMurray, J.J.V., 2022. Do the antiatherosclerotic mechanisms of GLP-1 receptor agonists translate into clinical benefits? A review. *Diabetes Care* 45(5), 1029–1036.
- [16] Hernán, M.A., Robins, J.M., 2016. Using big data to emulate a target trial when a randomized trial is not available. *American Journal of Epidemiology* 183(8), 758–764.
- [17] Suissa, S., 2008. Immortal time bias in pharmacoepidemiology. *American Journal of Epidemiology* 167(4), 492–499.
- [18] Packer, M., 2018. Do GLP-1 receptor agonists exert favorable or unfavorable effects in heart failure? *Circulation* 137(6), 547–549.
- [19] Sun, R., Xu, J., Zhang, W., et al., 2022. The effect of GLP-1 receptor agonists on cardiovascular and heart failure outcomes: a systematic review and network meta-analysis. *Cardiovascular Diabetology* 21(1), 234.
- [20] Zinman, B., Wanner, C., Lachin, J.M., et al., 2015. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes (EMPA-REG OUTCOME). *New England Journal of Medicine* 373(22), 2117–2128.