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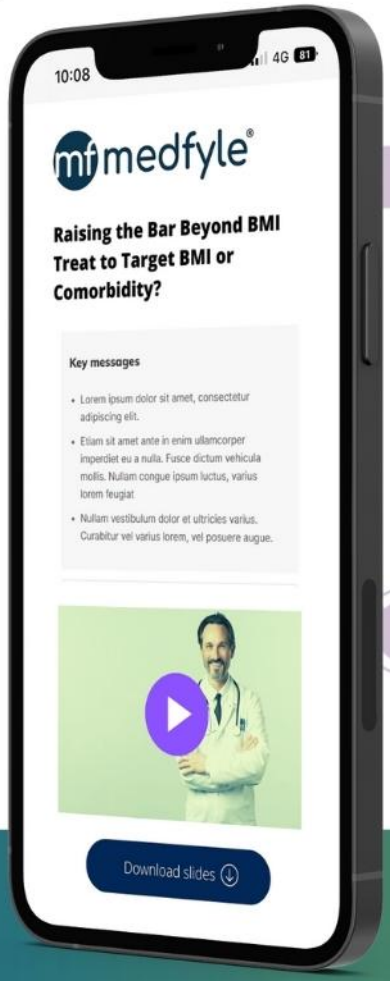


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# Semaglutide for cardiovascular event reduction in people with overweight or obesity: SELECT study baseline characteristics

Ildiko Lingvay[1] | Kirstine Brown-Frandsen[2] | Helen M. Colhoun[3] | John Deanfield[4] | Scott S. Emerson[5] | Sille Esbjerg[2] | Søren Hardt-Lindberg[2] | G. Kees Hovingh[2] | Steven E. Kahn[6] | Robert F. Kushner[7] | A. Michael Lincoff[8] | Steven P. Marso[9] | Tea Monk Fries[2] | Jorge Plutzky[10] | Donna H. Ryan[11] | on behalf of the SELECT Study Group

[1]Department of Internal Medicine/Endocrinology and Department of Population and Data Sciences, UT Southwestern Medical Center, Dallas, Texas, USA

[2]Novo Nordisk A/S, Søborg, Denmark

[3]Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

[4]Farr Institute of Health Informatics Research at London, London, UK and National Institute for Cardiovascular Outcomes Research, University College London, London, UK

[5]Department of Biostatistics, University of Washington, Seattle, Washington, USA

[6]Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle, Washington, USA

[7]Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[8]Cleveland Clinic Coordinating Center for Clinical Research (C5Research) and Department of Cardiovascular Medicine, Cleveland, Ohio, USA

[9]HCA Midwest Health Heart and Vascular Institute, Kansas City, Missouri, USA

[10]Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[11]Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana, USA

**Correspondence**
Ildiko Lingvay, Department of Internal Medicine/Endocrinology and Department of Population and Data Sciences,
UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9302, USA.
Email: ildiko.lingvay@utsouthwestern.edu

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## Abstract

**Objective:** This paper describes the baseline characteristics of the Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT) study, one of the largest cardiovascular (CV) outcome studies in the field of obesity, which evaluates the effect of semaglutide versus placebo on major CV events.

**Methods:** SELECT enrolled individuals with overweight or obesity without diabetes, with prior myocardial infarction, stroke, and/or peripheral artery disease. This study reports participants' baseline characteristics in the full study population and subgroups defined by baseline glycated hemoglobin ($HbA_{1c}$; <5.7%, ≥5.7 to <6.0%, ≥6.0 to <6.5%), baseline waist to height ratio tertile, and qualifying prior CV event or condition.

**Results:** The study enrolled 17,605 participants (72.5% male) with an average (SD) age of 61.6 (8.9) years and BMI of 33.34 (5.04) kg/m$^2$. The most common prior CV event was myocardial infarction (76.3% of participants), followed by stroke (23.3%) and

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peripheral artery disease (8.6%). Furthermore, 24.3% had a heart failure diagnosis. Two-thirds of participants (66%) had $HbA_{1c}$ in the prediabetes range (5.7%-6.4%). Across groups of increasing $HbA_{1c}$, prevalence of all CV risk factors increased.

**Conclusions:** The enrolled population in SELECT includes participants across a broad range of relevant risk categories. This will allow the study to garner information about the CV benefits of semaglutide across these relevant clinical subgroups.

## INTRODUCTION

Obesity is associated with traditional cardiovascular (CV) risk factors, including dyslipidemia, insulin resistance, type 2 diabetes, hypertension, and/or obstructive sleep apnea. Independent of its association with these CV risk factors, obesity also directly promotes atherosclerosis, including CV disease (CVD) morbidity and mortality [1]. Prospective studies have shown that the extent of ectopic and visceral adipose tissue depots, visualized by computed tomography or magnetic resonance imaging, is associated with CV outcomes independent of other traditional risk factors [2]. It has been proposed that the prothrombotic and proinflammatory milieu of these fat deposits plays a key role in CVD pathogenesis [1, 2].

Sustained weight loss induced by bariatric surgery (−20% to −30% on average) is associated with reduced CV events and mortality [3]; whether sustained nonsurgical weight loss also reduces CV events in those with a history of prior CV events remains unknown. Prospective studies that evaluated the effect of nonsurgical weight loss interventions on CV event reduction have been disappointing [4–8]. Those studies have included persons with type 2 diabetes, unlike Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT); it is unknown whether the magnitude of weight loss achieved in these studies or other factors (like enrollment of a lower-risk population without prior CV events or lack of weight loss durability) impacted the outcome. A post hoc analysis of the Action for Health in Diabetes (Look AHEAD) study showed that body weight loss of >10% is associated with a significant decrease in CV events [9]. As such, it is plausible that nonsurgical interventions that achieve on average >10% body weight loss will be associated with CV event reduction.

Subcutaneous semaglutide 2.4 mg, a once-weekly administered long-acting glucagon-like peptide-1 receptor agonist (GLP-1RA), was first approved for chronic weight management in June 2021 in the United States and since then in several other countries. Semaglutide has been shown to lower body weight by up to 16% when used in conjunction with lifestyle recommendations [10–13]. GLP-1RAs such as semaglutide exert direct effects at multiple sites, including glucose-dependent stimulation of insulin secretion, suppression of glucagon secretion, decrease of appetite through central effects on satiety signals, and delayed gastric emptying, while also being postulated to have direct CV effects [14]. GLP-1RAs, including semaglutide, improve many known CV risk factors such as hyperglycemia, insulin resistance, blood pressure, dyslipidemia, body weight, waist circumference, fatty liver, and inflammatory markers [14]. In line with this, subcutaneous semaglutide 0.5 and 1.0 mg once weekly, like other GLP-1RAs [15], has been shown to reduce major adverse CV events (MACE) in patients with type 2 diabetes and high CV risk

### Study Importance

#### What is already known?

- Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been shown to have beneficial effects on multiple cardiovascular risk factors and, in people with type 2 diabetes, reduce cardiovascular events. The Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT) study is evaluating the effect of semaglutide, a weekly GLP-1RA medication, versus placebo on cardiovascular events in people with overweight or obesity and preexistent cardiovascular disease.

#### What does this study add?

- We present the baseline characteristics of the population enrolled in the SELECT trial, made up of 17,605 people from around the world. We contrast the demographic and cardiometabolic characteristics of the full study population, as well as subgroups divided by baseline glycated hemoglobin (<5.7%, ≥5.7% to <6.0%, and ≥6.0 to <6.5%), preexistent cardiovascular event (myocardial infarction, stroke, or peripheral artery disease), and tertiles of adiposity as measured by waist to height ratio.

#### How might these results change the direction of research or the focus of clinical practice?

- The SELECT study will provide evidence as to whether treatment with semaglutide in this population with overweight or obesity but without diabetes can lower cardiovascular events. Given the broad range of relevant risk factors in this population, we will be able to explore the cardiovascular effects of semaglutide in these various relevant subgroups of people.

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[16]. Although the definitive mechanism(s) responsible for the CV event reduction with GLP-1RAs in the type 2 diabetes population remains unknown, based on the available data, it is reasonable to hypothesize that CV benefits might also be observed in those without type 2 diabetes [14].

The SELECT trial was designed to evaluate the effect of a once-weekly subcutaneously administered dose of 2.4 mg semaglutide on CV outcomes compared with placebo in people without diabetes but who were living with overweight or obesity and who suffered from a prior stroke and/or myocardial infarction (MI) and/or peripheral artery disease (PAD). SELECT is one of the largest interventional studies in individuals with overweight or obesity and is the only CV outcome trial (CVOT) to date designed to evaluate the superiority of a weight-lowering agent on 3-point MACE.

Here, we present the baseline demographic and biomedical characteristics of participants enrolled in SELECT. We evaluate the SELECT population according to three prespecified categories: baseline glycated hemoglobin ($HbA_{1c}$), tertiles of waist to height ratio, and type of prior CV event (MI, stroke, or PAD).

# METHODS

## Study design

SELECT [17] is a global, randomized, double-blind, placebo-controlled study designed to evaluate the superiority of subcutaneous semaglutide 2.4 mg once weekly compared with placebo, when added to standard of care, in reducing the incidence of CV events in individuals without diabetes but with overweight or obesity with established CVD (prior MI, stroke, and/or PAD). The design and rationale have been described previously [18].

The protocol for SELECT, which is sponsored by Novo Nordisk, was approved by the institutional review board and ethics committee at each participating center. All patients provided written informed consent before any trial-related activity. The trial is governed by an academic steering committee in conjunction with the sponsor. A global expert panel provides expertise in CVOTs, CV risk management, and GLP-1RA use for all investigators. A data-monitoring committee reviews adverse events on an ongoing basis and at prespecified time points.

The primary objective of SELECT is to examine whether subcutaneous semaglutide 2.4 mg is superior to placebo when given as an adjunct to standard of care in reducing the incidence of 3-point MACE, defined as time from randomization to first occurrence of a composite end point comprising CV death, nonfatal MI, and nonfatal stroke. Hierarchical, confirmatory secondary end points are time from randomization to the following: (1) CV death; (2) first occurrence of a composite heart failure end point consisting of heart failure hospitalization, urgent heart failure visit, or CV death; and (3) all-cause death [18]. Additional secondary objectives have been described previously [18]. Of note, the heart failure end point was elevated from a supportive secondary end point to a confirmatory secondary end point by protocol amendment after the study started, but before unblinding, as it was considered to be very relevant to the patient population and in light of other recent scientific advances in the field [19, 20].

SELECT is an event-driven trial, and with the planned 17,500 patients enrolled, the trial will have 90% power (using a one-sided type I error rate of 0.025) to detect a rate reduction of 17% (hazard ratio of 0.83) in the primary end point based on 1225 events observed. Further information on statistical considerations has been described [18].

## Participants

Overall, 804 sites in 41 countries across six continents recruited 17,605 participants between October 2018 and March 2021. Recruitment continued throughout the COVID-19 pandemic; the study enrolled fully after a 3-month extension of the anticipated recruitment period.

The complete inclusion and exclusion criteria have been published [18]. Briefly, eligible patients were required to be aged ≥45 years with body mass index (BMI) of ≥27 kg/$m^2$ and established CVD with one or more of the following: prior MI, prior ischemic or hemorrhagic stroke, symptomatic PAD in the form of intermittent claudication and ankle–brachial index <0.85 at rest, prior peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease. Patients with $HbA_{1c}$ ≥48 mmol/mol (6.5%) or a history of type 1 or type 2 diabetes, who had MI, stroke, hospitalization for unstable angina pectoris, or a transient ischemic attack within 60 days of screening, or who had New York Heart Association (NYHA) class IV heart failure were excluded. Patients who develop diabetes during the study are to remain in the study and receive concomitant medication (excluding other GLP-1RAs) for diabetes management as directed by the site investigator or other health care providers. A study-level treatment guidance developed by the global expert panel was shared with all sites to ensure best available standard of care is applied across the entire study population, both for CV risk factors and diabetes (if applicable) [18].

## Measurements

The procedures and methodology for assessing waist circumference, height, weight, $HbA_{1c}$, and other measures reported herein are found in the online Supporting Information. For the purpose of this analysis, we identified three categories of glycemia ($HbA_{1c}$ <5.7%, ≥5.7% to <6.0%, and ≥6.0% to <6.5%) and evaluated the demographic and biomedical characteristics of the enrolled population within these categories. The rationale for the selection of these categories was to acknowledge the International Expert Committee's statement that $HbA_{1c}$ 6.0% to 6.5% defines a group at higher risk of progression to diabetes [21]. The current analysis of the SELECT population also evaluated the groups defined by the tertiles of waist to height ratio as a better estimate of distribution of body fat than BMI in a population of varying ethnic and racial backgrounds [22]. We also evaluated the

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**TABLE 1** Baseline characteristics in the overall population and by baseline $HbA_{1c}$ value

| | Overall ($n = 17,605$) | $HbA_{1c}$ <5.7% ($n = 5904$) | $HbA_{1c}$ ≥5.7% to <6.0% ($n = 6087$) | $HbA_{1c}$ ≥6.0% to <6.5% ($n = 5609$) |
|---|---|---|---|---|
| CV inclusion criteria, *n* (%)[a] | | | | |
| MI only | 11,908 (67.6) | 3861 (65.4) | 4198 (69.0) | 3846 (68.6) |
| Stroke only | 3135 (17.8) | 1199 (20.3) | 1049 (17.2) | 886 (15.8) |
| PAD only | 777 (4.4) | 254 (4.3) | 254 (4.2) | 269 (4.8) |
| ≥2 CV inclusion criteria | 1433 (8.1) | 470 (8.0) | 469 (7.7) | 493 (8.8) |
| *Demographics* | | | | |
| Age (y), mean (SD) | 61.6 (8.9) | 61.0 (9.1) | 61.7 (8.8) | 62.1 (8.6) |
| Age group (y), *n* (%) | | | | |
| 45 to <55 | 4150 (23.6) | 1599 (27.1) | 1400 (23.0) | 1150 (20.5) |
| 55 to <65 | 6727 (38.2) | 2149 (36.4) | 2365 (38.9) | 2211 (39.4) |
| 65 to <75 | 5362 (30.5) | 1707 (28.9) | 1848 (30.4) | 1806 (32.2) |
| 75 to <85 | 1318 (7.5) | 435 (7.4) | 458 (7.5) | 424 (7.6) |
| ≥85 | 48 (0.3) | 14 (0.2) | 16 (0.3) | 18 (0.3) |
| Male, *n* (%) | 12,733 (72.3) | 4274 (72.4) | 4409 (72.4) | 4046 (72.1) |
| Region, *n* (%) | | | | |
| North America | 4401 (25.0) | 1717 (29.1) | 1423 (23.4) | 1259 (22.4) |
| South America | 1152 (6.5) | 494 (8.4) | 385 (6.3) | 273 (4.9) |
| Europe | 6507 (37.0) | 1834 (31.1) | 2380 (39.1) | 2291 (40.8) |
| Africa | 845 (4.8) | 273 (4.6) | 280 (4.6) | 292 (5.2) |
| Asia | 2201 (12.5) | 722 (12.2) | 757 (12.4) | 722 (12.9) |
| Other | 2499 (14.2) | 864 (14.6) | 862 (14.2) | 772 (13.8) |
| Race, *n* (%)[b] | | | | |
| Asian | 1447 (8.2) | 446 (7.6) | 501 (8.2) | 500 (8.9) |
| Black | 671 (3.8) | 228 (3.9) | 214 (3.5) | 228 (4.1) |
| White | 14,791 (84.0) | 5033 (85.2) | 5120 (84.1) | 4634 (82.6) |
| Other[c] | 527 (3.0) | 160 (2.7) | 191 (3.1) | 176 (3.1) |
| Ethnicity, *n* (%)[d] | | | | |
| Hispanic or Latino | 1822 (10.3) | 755 (12.8) | 594 (9.8) | 473 (8.4) |
| Not Hispanic or Latino | 15,612 (88.7) | 5111 (86.6) | 5431 (89.2) | 5065 (90.3) |
| Tobacco use, *n* (%) | | | | |
| Current smoker | 2950 (16.8) | 834 (14.1) | 1069 (17.6) | 1046 (18.6) |
| Never smoked | 6123 (34.8) | 2275 (38.5) | 2048 (33.6) | 1800 (32.1) |
| Previous smoker | 8530 (48.5) | 2794 (47.3) | 2970 (48.8) | 2762 (49.2) |
| *Body measurements* | | | | |
| BMI ($kg/m^2$), mean (SD) | 33.34 (5.04) | 32.84 (4.83) | 33.23 (4.94) | 33.97 (5.29) |
| BMI ($kg/m^2$), *n* (%) | | | | |
| <30 | 5024 (28.5) | 1895 (32.1) | 1747 (28.7) | 1382 (24.6) |
| 30 to <35 | 7475 (42.5) | 2521 (42.7) | 2638 (43.3) | 2314 (41.3) |
| 35 to <40 | 3346 (19.0) | 1002 (17.0) | 1117 (18.4) | 1225 (21.8) |
| 40 to <45 | 1174 (6.7) | 330 (5.6) | 403 (6.6) | 440 (7.8) |
| ≥45 | 586 (3.3) | 156 (2.6) | 182 (3.0) | 248 (4.4) |
| Waist to height ratio (cm/cm), mean (SD) | 0.6558 (0.0764) | 0.6463 (0.0741) | 0.6550 (0.0769) | 0.6664 (0.0770) |
| Waist to height ratio tertiles, *n* (%) | | | | |
| Lower tertile, ≤0.6176 | 5833 (33.1) | 2270 (38.4) | 2030 (33.3) | 1532 (27.3) |
| Middle tertile, >0.6176 to ≤0.6757 | 5858 (33.3) | 1945 (32.9) | 2048 (33.6) | 1864 (33.2) |
| Upper tertile, >0.6757 | 5827 (33.1) | 1657 (28.1) | 1981 (32.5) | 2186 (39.0) |

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|---|---|---|---|---|
| Waist circumference (cm), mean (SD) | 111.4 (13.2) | 110.0 (12.9) | 111.2 (13.2) | 113.1 (13.4) |
| Body weight (kg), mean (SD) | 96.68 (17.67) | 95.57 (17.12) | 96.30 (17.32) | 98.25 (18.47) |
| Body weight (kg), *n* (%) | | | | |
| <85 | 4617 (26.2) | 1647 (27.9) | 1603 (26.3) | 1367 (24.4) |
| 85 to <95 | 4469 (25.4) | 1549 (26.2) | 1604 (26.4) | 1316 (23.5) |
| 95 to <105 | 3693 (21.0) | 1257 (21.3) | 1242 (20.4) | 1193 (21.3) |
| ≥105 | 4826 (27.4) | 1451 (24.6) | 1638 (26.9) | 1733 (30.9) |
| *Glycemic variables* | | | | |
| $HbA_{1c}$ (%), mean (SD) | 5.78 (0.34) | 5.42 (0.20) | 5.80 (0.08) | 6.15 (0.18) |
| $HbA_{1c}$ (mmol/mol), mean (SD) | 39.71 (3.68) | 35.72 (2.13) | 39.88 (0.88) | 43.74 (1.95) |
| *Renal variables* | | | | |
| eGFR (mL/min/1.73 $m^2$), mean (SD) | 82.5 (17.4) | 83.2 (17.6) | 82.1 (17.5) | 82.2 (17.1) |
| Renal function, eGFR (mL/min/1.73 $m^2$), *n* (%) | | | | |
| Normal, ≥90 | 6990 (39.7) | 2459 (41.6) | 2363 (38.8) | 2167 (38.6) |
| Mild RI, 60 to <90 | 8577 (48.7) | 2791 (47.3) | 2994 (49.2) | 2790 (49.7) |
| Moderate RI, 30 to <60 | 1826 (10.4) | 575 (9.7) | 655 (10.8) | 595 (10.6) |
| Severe RI, 15 to <30 | 69 (0.4) | 29 (0.5) | 23 (0.4) | 17 (0.3) |
| End-stage renal disease, <15 | 2 (<0.1) | 2 (<0.1) | 0 | 0 |
| Albumin/creatinine ratio (mg/g), median (IQR)[e] | 7.37 (4.46-15.39) | 7.15 (4.32-14.80) | 7.26 (4.44-14.67) | 7.79 (4.65-16.56) |
| Albuminuria (mg/g), *n* (%) | | | | |
| Normoalbuminuria, <30 | 14,846 (84.3) | 4991 (84.5) | 5165 (84.9) | 4687 (83.6) |
| Microalbuminuria, 30 to <300 | 1968 (11.2) | 634 (10.7) | 668 (11.0) | 666 (11.9) |
| Macroalbuminuria, ≥300 | 325 (1.8) | 117 (2.0) | 91 (1.5) | 117 (2.1) |
| eGFR <60 mL/min/1.73 $m^2$ or UACR ≥30 mg/g, *n* (%) | 3697 (21.0) | 1197 (20.3) | 1270 (20.9) | 1229 (21.9) |
| *Lipid and C-reactive protein levels* | | | | |
| High-sensitivity C-reactive protein (mg/L), median (IQR) | 1.83 (0.87-4.12) | 1.66 (0.81-3.72) | 1.80 (0.85-4.01) | 2.08 (0.96-4.54) |
| Total cholesterol (mmol/L), median (IQR) | 3.97 (3.39-4.73) | 4.02 (3.39-4.79) | 3.96 (3.39-4.70) | 3.93 (3.39-4.67) |
| LDL-C (mmol/L), median (IQR) | 2.02 (1.57-2.64) | 2.05 (1.59-2.69) | 2.02 (1.58-2.63) | 2.00 (1.56-2.60) |
| HDL-C (mmol/L), median (IQR) | 1.13 (0.96-1.34) | 1.17 (0.99-1.40) | 1.13 (0.97-1.34) | 1.09 (0.94-1.29) |
| Triglycerides (mmol/L), median (IQR) | 1.52 (1.11-2.12) | 1.43 (1.05-2.02) | 1.52 (1.11-2.10) | 1.60 (1.19-2.24) |
| Free fatty acids (mmol/L), median (IQR) | 0.30 (0.17-0.48) | 0.30 (0.16-0.48) | 0.29 (0.16-0.47) | 0.31 (0.18-0.48) |
| VLDL-C (mmol/L), median (IQR) | 0.68 (0.50-0.95) | 0.64 (0.47-0.91) | 0.68 (0.50-0.95) | 0.72 (0.54-1.01) |
| *Blood pressure and heart rate* | | | | |
| Systolic blood pressure (mmHg), mean (SD) | 131.0 (15.4) | 130.4 (15.4) | 131.0 (15.5) | 131.6 (15.4) |
| Diastolic blood pressure (mmHg), mean (SD) | 79.3 (10.0) | 79.3 (10.0) | 79.4 (10.0) | 79.2 (9.9) |
| Pulse (beats/min), mean (SD) | 68.8 (10.7) | 68.5 (10.7) | 68.5 (10.6) | 69.4 (10.7) |
| *Patient-reported outcomes* | | | | |
| EQ-VAS score, mean (SD) | 77.15 (15.68) | 77.83 (15.68) | 77.08 (15.60) | 76.49 (15.73) |

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|---|---|---|---|---|
| EQ-5D index score, mean (SD) | 0.88 (0.15) | 0.88 (0.15) | 0.88 (0.15) | 0.88 (0.14) |
| WRSS total score, mean (SD) | 1.13 (0.77) | 1.08 (0.77) | 1.13 (0.77) | 1.16 (0.77) |

*Note*: Baseline is defined as the assessment from the randomization visit (or the screening visit if the assessment from the randomization visit was not available). Data for all variables were not obtained for the entire population. Smoking is defined as at least one cigarette or equivalent daily. Tertiles are based on the overall population. The eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; the renal function categories are based on the eGFR as per CKD-EPI.

Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; EQ-5D, EuroQoL 5 Dimensions; EQ-VAS, EuroQoL Visual Analog Scale; $HbA_{1c}$, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; RI, renal impairment; UACR, urinary albumin/creatinine ratio; VLDL-C, very low-density lipoprotein cholesterol; WRSS, weight-related sign and symptom.

[a]Participants were randomized in error and did not fulfill the CV inclusion criteria and/or participants for whom it is unknown whether only one or several of the inclusion criteria were fulfilled are not part of the following (overall population: $n = 352$; 2.0%). Of these 352 participants, 315 participants (1.8%) fulfilled at least one of the inclusion criteria and 37 (0.2%) were randomized in error.

[b]Race was not reported for some participants (overall population: $n = 169$; 1.0%).

[c]The category "Other" for race includes participants whose race was recorded as "American Indian or Alaska Native," "Native Hawaiian or Pacific Islander," or "Other."

[d]Ethnicity was not reported for some participants (overall population: $n = 171$; 1.0%).

[e]To convert albumin/creatinine ratio from mg/g to mg/mmol, divide the mg/g value by 8.849557522.

demographic and biomedical characteristics according to CV history at baseline (presence of MI alone, stroke alone, PAD alone, or a combination of multiple of these). For these analyses of baseline characteristics, we report mean and standard deviation (SD) for continuous measurements with a normal distribution and median and interquartile range (IQR) for measurements with non-normal distributions. For categorical assessments, we report the number and percentage of all participants in that category. The baseline characteristics of the enrolled patients were compiled after completion of enrollment and without knowledge of the randomization assignment. As the trial is ongoing, data may be subject to minor changes until database lock.

## RESULTS

Overall, 21,089 participants were screened and 17,605 randomized. The most common reason for screen failure was a baseline $HbA_{1c}$ ≥6.5% (approximately half of the screen failures), followed by participants declining further participation (35% of screen failures).

### Characteristics of the overall population

The mean (SD) age of the overall enrolled population was 61.6 (8.9) years (Table 1), with a range of 45 to 93 years. The majority (61.8%) of the population was in the 55 to 75 years age group; 7.8% of the population was older than 75 years. Males represented 72.3% of the population; self-identified ethnicity or race included 10.3% Hispanic, 84.0% White (75.5% non-Hispanic White), 8.2% Asian, and 3.8% Black. Race or ethnicity was not reported in <1% of participants. The average BMI was 33.3 (5.04), with 28.5% of the population having overweight (BMI = 27 to <30) at baseline. Most participants (42.5%) had class 1 obesity (BMI = 30 to <35), whereas 19% had class 2 (BMI = 35 to <40), and 10% had class 3 (BMI ≥40; Table 1). Very few (<0.1%) participants were being treated with weight-lowering pharmacotherapy at baseline.

All participants had to have a preexistent CV event or symptomatic PAD [18]. The most common prior CV event was MI (76.3% of participants), followed by stroke (23.3%), whereas 8.6% had PAD; 8% had more than one of these conditions. Although not an inclusion criterion, 24.3% of the SELECT enrollees were previously diagnosed with chronic heart failure (CHF) (Table 2). As expected in this population with overweight or obesity, more than half of the cases of CHF were categorized by the investigators as having preserved ejection fraction (53.1% of those reported to have CHF); 31.4% had reduced ejection fraction (15.5% had an unknown CHF classification). Most of the participants with a history of CHF (67.8%) were symptomatic at the time of study entry, having an NYHA classification of II or III. Overall, 16.8% of participants reported smoking (Table 1). At baseline, 91.8% were receiving CV risk-lowering pharmacotherapy, 89.8% were receiving lipid-lowering agents (87.3% statins, 2.7% fibrates), 85.9% were receiving platelet aggregation inhibitors, and 12.6% were receiving antithrombotic medications (Table 3).

Metabolic comorbidities and CV risk factors were highly prevalent in this population. Prediabetes (per investigators' assessment; based on available medical records, concomitant medication, and laboratory data) was present in 64.5% of participants and the average (SD) $HbA_{1c}$ of all participants was 5.78% (0.34%). Nephropathy (defined as either an estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 $m^2$ or elevated albumin to creatinine ratio [ACR]) was present in 21% of the population (Table 1); 10.8% had eGFR <60 mL/min/1.73 $m^2$ and 13% had an elevated ACR. A hypertension diagnosis was reported in 81.7% of participants (Table 2); the baseline systolic blood pressure

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**TABLE 2** CV history and obesity-related comorbidities at randomization in the overall population and by baseline $HbA_{1c}$ value

| | Overall ($n = 17,605$) | $HbA_{1c}$ <5.7% ($n = 5904$) | $HbA_{1c}$ ≥5.7% to <6.0% ($n = 6087$) | $HbA_{1c}$ ≥6.0% to <6.5% ($n = 5609$) |
|---|---|---|---|---|
| CV history | | | | |
| Coronary heart disease, *n* (%) | 14,453 (82.1) | 4730 (80.1) | 5025 (82.6) | 4694 (83.7) |
| Myocardial infarction, *n* (%) | 13,439 (76.3) | 4376 (74.1) | 4687 (77.0) | 4372 (77.9) |
| Non-ST-segment elevation | 4443 (25.2) | 1412 (23.9) | 1616 (26.5) | 1414 (25.2) |
| ST-segment elevation | 5414 (30.8) | 1724 (29.2) | 1875 (30.8) | 1813 (32.3) |
| Unknown | 2991 (17.0) | 1046 (17.7) | 1002 (16.5) | 942 (16.8) |
| Coronary artery stenosis ≥50%, *n* (%)[a] | 9692 (55.1) | 3037 (51.6) | 3436 (56.4) | 3206 (57.2) |
| Coronary revascularization, *n* (%) | 11,849 (67.3) | 3763 (63.7) | 4162 (68.4) | 3920 (69.9) |
| Percutaneous coronary intervention | 10,337 (58.7) | 3272 (55.4) | 3637 (59.8) | 3424 (61.0) |
| Coronary artery bypass graft | 2057 (11.7) | 652 (11.0) | 719 (11.8) | 685 (12.2) |
| Stroke, *n* (%) | 4108 (23.3) | 1537 (26.0) | 1376 (22.6) | 1193 (21.3) |
| Ischemic stroke | 2983 (16.9) | 1086 (18.4) | 1032 (17.0) | 865 (15.4) |
| Hemorrhagic stroke | 329 (1.9) | 153 (2.6) | 102 (1.7) | 73 (1.3) |
| Undetermined stroke | 517 (2.9) | 203 (3.4) | 154 (2.5) | 159 (2.8) |
| Transient ischemic attack, *n* (%) | 761 (4.3) | 289 (4.9) | 261 (4.3) | 210 (3.7) |
| Carotid artery stenosis ≥50%, *n* (%)[a] | 807 (4.6) | 253 (4.3) | 285 (4.7) | 269 (4.8) |
| Carotid revascularization, *n* (%) | 421 (2.4) | 129 (2.2) | 151 (2.5) | 141 (2.5) |
| Symptomatic peripheral artery disease, *n* (%) | 1522 (8.6) | 471 (8.0) | 502 (8.2) | 549 (9.8) |
| Intermittent claudication with ankle–brachial index <0.85 (at rest) | 751 (4.3) | 226 (3.8) | 253 (4.2) | 272 (4.8) |
| Peripheral artery revascularization procedure | 669 (3.8) | 200 (3.4) | 222 (3.6) | 247 (4.4) |
| Amputation due to atherosclerotic disease | 26 (0.1) | 13 (0.2) | 8 (0.1) | 5 (<0.1) |
| Other | 191 (1.1) | 60 (1.0) | 66 (1.1) | 65 (1.2) |
| Peripheral artery stenosis ≥50%, *n* (%)[a] | 733 (4.2) | 212 (3.6) | 252 (4.1) | 269 (4.8) |
| Hypertension, *n* (%) | 14,388 (81.7) | 4754 (80.5) | 4950 (81.3) | 4680 (83.4) |
| Chronic heart failure, *n* (%) | 4274 (24.3) | 1315 (22.3) | 1505 (24.7) | 1453 (25.9) |
| Subclass[b] | | | | |
| HFpEF | 2268 (12.9) | 710 (12.0) | 797 (13.1) | 761 (13.6) |
| HFrEF | 1341 (7.6) | 373 (6.3) | 490 (8.0) | 477 (8.5) |
| Unknown | 662 (3.8) | 232 (3.9) | 217 (3.6) | 213 (3.8) |
| NYHA class, *n* (%) [percentage of those with CHF, %][c] | | | | |
| NYHA class I | 1368 (7.8) [32.0] | 449 (7.6) [34.1] | 484 (8.0) [32.2] | 435 (7.8) [29.9] |
| NYHA class II | 2534 (14.4) [59.3] | 761 (12.9) [57.9] | 893 (14.7) [59.3] | 879 (15.7) [60.5] |
| NYHA class III | 362 (2.1) [8.5] | 104 (1.8) [7.9] | 128 (2.1) [8.5] | 130 (2.3) [8.9] |
| Unknown | 10 (<0.1) [0.2] | 1 (<0.1) [<0.1] | 0 (0) [0] | 9 (0.2) [0.6] |
| Obesity-related comorbidities | | | | |
| Chronic kidney disease, *n* (%) | 1947 (11.1) | 603 (10.2) | 710 (11.7) | 633 (11.3) |
| Knee osteoarthritis, *n* (%) | 2849 (16.2) | 967 (16.4) | 989 (16.2) | 891 (15.9) |
| Hip osteoarthritis, *n* (%) | 1323 (7.5) | 467 (7.9) | 450 (7.4) | 406 (7.2) |
| Nonalcoholic fatty liver, *n* (%) | 1451 (8.2) | 424 (7.2) | 521 (8.6) | 505 (9.0) |
| Nonalcoholic steatohepatitis, *n* (%) | 115 (0.7) | 41 (0.7) | 43 (0.7) | 31 (0.6) |
| Sleep apnea syndrome, *n* (%) | 2542 (14.4) | 850 (14.4) | 879 (14.4) | 812 (14.5) |
| Asthma, *n* (%) | 1187 (6.7) | 413 (7.0) | 419 (6.9) | 354 (6.3) |

(Continues)

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**TABLE 2** (Continued)

| | Overall ($n = 17,605$) | $HbA_{1c}$ <5.7% ($n = 5904$) | $HbA_{1c}$ ≥5.7% to <6.0% ($n = 6087$) | $HbA_{1c}$ ≥6.0% to <6.5% ($n = 5609$) |
|---|---|---|---|---|
| Chronic obstructive pulmonary disease, *n* (%) | 1466 (8.3) | 429 (7.3) | 496 (8.1) | 541 (9.6) |
| Gout, *n* (%) | 1532 (8.7) | 521 (8.8) | 501 (8.2) | 510 (9.1) |

*Note*: CV history was based on the participant's medical records and the investigator's discretion. Obesity-related comorbidities were based on the participant's medical records and the investigator's discretion. For CV history, the subclassifications listed may not total the full number of patients with the relevant CV history, as investigators were not required to provide information about the relevant subclassification; furthermore, for coronary revascularization, stroke, and myocardial infarction, the electronic case report form was designed to collect only the subclassifications for the most recent event.
Abbreviations: CHF, chronic heart failure; CV, cardiovascular; $HbA_{1c}$, glycated hemoglobin; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association.
[a]Number of responses <90%; percentage is calculated using *n* for the relevant (sub-)population. For coronary artery stenosis, carotid artery stenosis, and peripheral artery stenosis, number of responses was ≥80% of the total population.
[b]Chronic heart failure subclass was not reported for some participants ($n = 3$; <0.1%).
[c]NYHA class was unknown in 10 participants (1 in the $HbA_{1c}$ <5.7% group and 9 in the $HbA_{1c}$ ≥6.0% to <6.5% group).

(SBP) was 131.0 (15.4) mm Hg, whereas baseline diastolic blood pressure was 79.3 (10.0) mm Hg. Despite nearly 90% reporting use of lipid-lowering medications, the low-density lipoprotein cholesterol (LDL-C) plasma level was above the guideline recommended level of 1.8 mmol/L, with a median of 2.02 mmol/L (Table 1) [23].

## Characteristics of the population grouped by $HbA_{1c}$ value

The baseline characteristics classified by the subgroups of the population defined by baseline $HbA_{1c}$ are shown in Table 1. Key CV risk factors were increasingly prevalent and more severe in the higher $HbA_{1c}$ groups, including age, BMI, waist to height ratio, high-sensitivity C-reactive protein (hsCRP), triglycerides, very low-density lipoprotein cholesterol, lower high-density lipoprotein cholesterol, and current smoking (Table 1). Several comorbidities were also more prevalent in patients with higher $HbA_{1c}$ at baseline, including hypertension, CHF (especially for NYHA class II and III subgroups, including both heart failure with preserved ejection fraction and heart failure with reduced ejection fraction), and nonalcoholic fatty liver disease (Table 2). The use of all classes of CV pharmacotherapy, including lipid-lowering drugs, diuretics, platelet aggregation inhibitors, and/or antithrombotic agents, was also higher in those with higher $HbA_{1c}$ (Table 3), which may underlie the trend for lower total cholesterol and LDL-C and similar blood pressure readings across the $HbA_{1c}$ groups (Table 1). Patient-reported outcomes, measured using the weight-related sign and symptom scale as well as EuroQoL 5 Dimensions and the EuroQoL Visual Analog Scale, showed slightly worse scores with higher $HbA_{1c}$ (Table 1).

## Characteristics of the population grouped by prior CV event

Supporting Information Table S1 lists participant characteristics for the subgroups defined by qualifying CVD criteria. Although those enrolled based on a prior MI had a strong male predominance (78.6%), gender distribution was closer to equal in those who qualified based on prior stroke or PAD. Geographic differences existed in the distribution of prior qualifying events, with relatively more North American and European participants having prior PAD versus prior MI or stroke, whereas prior MI was more prevalent in enrollees from South America and Asia. Such differences were also noted across race and ethnicity, with a higher relative prevalence of prior MI in the Asian and Hispanic populations, higher prior stroke in the Black population, and higher prior PAD in the White population.

Those with a prior diagnosis of PAD, and no prior MI or stroke, were most likely to be current smokers, and had the highest hsCRP, total cholesterol and LDL-C levels, and SBP, compared with all other groups. This group also had a high prevalence of hypertension (86.1%); it also had the lowest overall rate of use of CV pharmacotherapy (82.1%) and lipid-lowering drugs (72.7%). Those with a prior stroke only had the lowest $HbA_{1c}$ across groups. The prior-stroke-only group also had a lower eGFR and higher ACR and a high rate of hypertension compared with the prior-MI- or PAD-only groups. Like the PAD group, the prior -stroke group also had a lower rate of use of concomitant CV agents versus the prior-MI group and those with ≥2 CV comorbidities. Notably, those in the "prior-stroke-only" group had a worse self-reported health status (EuroQoL 5 Dimensions index score) compared with those with "prior MI" or "PAD only."

The group with a prior MI only was more likely to have concomitant CHF compared with those with stroke and PAD only, and overall CV medication use was high (94.2%) for this group.

The group that had multiple prior events was older, had the highest $HbA_{1c}$, and the lowest eGFR across the groups. This group also had the lowest EuroQoL Visual Analog Scale score. Notably, this group was more likely to have preexistent CHF, chronic kidney disease, chronic obstructive pulmonary disease, and gout.

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**TABLE 3** Concomitant CV- and weight-related medications ongoing at randomization in the overall population and by baseline $HbA_{1c}$ value

| | Overall ($n = 17,605$) | $HbA_{1c}$ <5.7% ($n = 5904$) | $HbA_{1c}$ ≥5.7% to <6.0% ($n = 6087$) | $HbA_{1c}$ ≥6.0% to <6.5% ($n = 5609$) |
|---|---|---|---|---|
| *CV-related medication* | | | | |
| CV medications, *n* (%) | 16,168 (91.8) | 5274 (89.3) | 5624 (92.4) | 5265 (93.9) |
| Beta blockers | 12,329 (70.0) | 3898 (66.0) | 4315 (70.9) | 4113 (73.3) |
| ACE inhibitors | 7915 (45.0) | 2523 (42.7) | 2723 (44.7) | 2666 (47.5) |
| Angiotensin receptor blockers | 5259 (29.9) | 1721 (29.1) | 1849 (30.4) | 1688 (30.1) |
| Calcium channel blockers | 4706 (26.7) | 1508 (25.5) | 1638 (26.9) | 1559 (27.8) |
| Angiotensin receptor-neprilysin inhibitor | 254 (1.4) | 85 (1.4) | 90 (1.5) | 79 (1.4) |
| Lipid-lowering drugs, *n* (%) | 15,804 (89.8) | 5173 (87.6) | 5512 (90.6) | 5114 (91.2) |
| Statins | 15,369 (87.3) | 5014 (84.9) | 5339 (87.7) | 5011 (89.3) |
| Ezetimibe | 2314 (13.1) | 664 (11.2) | 812 (13.3) | 838 (14.9) |
| Fibrates | 477 (2.7) | 161 (2.7) | 146 (2.4) | 170 (3.0) |
| PCSK-9 inhibitors | 335 (1.9) | 117 (2.0) | 132 (2.2) | 86 (1.5) |
| Other[a] | 330 (1.9) | 135 (2.3) | 104 (1.7) | 91 (1.6) |
| Diuretics, *n* (%) | 5861 (33.3) | 1757 (29.8) | 1997 (32.8) | 2104 (37.5) |
| Loop diuretics | 2207 (12.5) | 660 (11.2) | 719 (11.8) | 827 (14.7) |
| Thiazides | 2010 (11.4) | 614 (10.4) | 681 (11.2) | 714 (12.7) |
| Aldosterone antagonists | 1808 (10.3) | 510 (8.6) | 628 (10.3) | 670 (11.9) |
| Thiazide-like diuretics | 1014 (5.8) | 283 (4.8) | 362 (5.9) | 368 (6.6) |
| Other potassium sparring diuretics | 61 (0.3) | 21 (0.4) | 16 (0.3) | 24 (0.4) |
| Platelet aggregation inhibitors, *n* (%) | 15,130 (85.9) | 4996 (84.6) | 5276 (86.7) | 4853 (86.5) |
| Acetylsalicylic acid | 13,691 (77.8) | 4511 (76.4) | 4780 (78.5) | 4396 (78.4) |
| P2Y12 inhibitors | 5912 (33.6) | 1961 (33.2) | 2103 (34.5) | 1847 (32.9) |
| Other[b] | 179 (1.0) | 57 (1.0) | 49 (0.8) | 73 (1.3) |
| Antithrombotic medications, *n* (%) | 2220 (12.6) | 717 (12.1) | 773 (12.7) | 730 (13.0) |
| DOAC | 1510 (8.6) | 497 (8.4) | 530 (8.7) | 483 (8.6) |
| Vitamin K antagonists | 670 (3.8) | 209 (3.5) | 229 (3.8) | 232 (4.1) |
| Heparin-related agents | 47 (0.3) | 13 (0.2) | 16 (0.3) | 18 (0.3) |
| Antianginal agents, *n* (%) | 3487 (19.8) | 1127 (19.1) | 1199 (19.7) | 1160 (20.7) |
| Antiarrhythmic agents, *n* (%) | 584 (3.3) | 214 (3.6) | 172 (2.8) | 198 (3.5) |
| *Weight-related medication, n (%)*[c] | 26 (0.1) | 12 (0.2) | 7 (0.1) | 7 (0.1) |

Abbreviations: ACE, angiotensin converting enzyme; CV, cardiovascular; DOAC, direct oral anticoagulant; $HbA_{1c}$, glycated hemoglobin; PCSK-9, proprotein convertase subtilisin kexin-9.

[a]The category "Other" includes other omega-3 triglycerides, eicosapentaenoic acid ethyl ester, omega-3-acid ethyl ester, bile acid sequestrants, and bempedoic acid.

[b]The category "Other" includes dipyridamole, indobufen, sarpogrelate hydrochloride, triflusal, vorapaxar, and vorapaxar sulfate.

[c]Use of glucagon-like peptide-1 receptor agonist for any indication within 90 days before screening was an exclusion criterion [18].

## Characteristics of the population grouped by waist to height ratio

Across the waist to height ratio subgroups, there were notable differences in the distribution of several CV risk factors (Supporting Information Table S2). In the lowest waist to height ratio tertile group, there was a greater male predominance and higher prevalence of prior MI, whereas PAD and stroke were more prevalent in the highest tertile group.

With increasing tertiles of waist to height ratio, eGFR was lower, and hsCRP, total cholesterol, LDL-C, triglycerides, free fatty acids, very low-density lipoprotein cholesterol levels, ACR, and SBP all increased. Interestingly, although the use of CV medications and diuretics increased across the waist to height ratio groups, the use of lipid-lowering agents was lower in the highest waist to height ratio group. The prevalence of hypertension, CHF (both heart failure with preserved ejection fraction and heart failure with reduced ejection fraction, and especially class II and III), and all obesity-related

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comorbidities increased across the subgroups of increasing waist to height ratio tertiles. All patient-reported outcome scores worsened across these groups.

## DISCUSSION

We present a comprehensive report of the baseline characteristics of the SELECT study population. The SELECT trial, which is one of the largest CVOTs in the field of obesity, will answer the important question of whether subcutaneous semaglutide 2.4 mg once weekly reduces the risk of adverse CV outcomes in persons with overweight or obesity but without diabetes. In addition, SELECT will show the long-term effect of semaglutide on multiple cardiometabolic and other obesity-related end points. SELECT is the only CVOT study thus far designed to evaluate the superiority of weight-lowering pharmacotherapy and will provide definitive data regarding the role of the GLP-1RA semaglutide 2.4 mg once weekly and the weight loss it induces on CVD and 3-point MACE reduction [18]. As such, it is important that the population enrolled in the study closely reflects the population toward which such intervention is geared, and the results for the total SELECT population will be the primary objective of this trial.

On average, the population of SELECT has similar characteristics to those enrolled in the other CVOTs in the fields of diabetes or obesity, with the exception that SELECT does not include persons with established diabetes (Supporting Information Table S3 includes citations to these studies), suggesting good representation of the underlying population intended for study. Across the CVOTs in these fields, SELECT has a relatively low average age (61.6 years; range for all studies 60-66 years) and a relatively high male predominance (72.3%; range for all studies 45.5%-77.0%) but is still well within the overall range observed in these studies (Supporting Information Table S3). The average BMI in the SELECT population (33.3) was comparable with those in the other obesity CVOTs, but higher than in the diabetes CVOTs. In the SELECT population, one of the lowest baseline mean LDL-C levels was encountered, compared with other CVOT studies, possibly reflecting temporal trends to greater lipid-lowering drug use and more intensive LDL-C targets, although such trends may also reflect clinician recognition of the CV risk of the typical SELECT enrollee. The SELECT population also has a high smoking rate (16.8%, as compared with other recent CVOTs [9.2%-15.7%]; Supporting Information Table S3), which will enable the evaluation of the effect of semaglutide on smoking habits, a prespecified exploratory end point. SELECT is the only CVOT study to exclude those with established diabetes, whereas in other obesity CVOTs, 56.8% to 83.6% of participants had diabetes.

A central defining characteristic of CVOTs in the fields of diabetes and obesity is whether they enroll only those participants with prior CVD. SELECT only enrolled participants with prior CV events or PAD, whereas, in other CVOTs, up to two-thirds of the enrolled population did not have prior CV events. Specifically, across the obesity CVOTs, SELECT is the only study to our knowledge that only enrolled participants with established CVD, whereas in the other obesity CVOTs, 24.9% to 50.5% of participants had no prior events [5–8]. As such, it is anticipated that SELECT will have the highest event rates versus previously published obesity CVOTs, but lower event rates compared with the diabetes CVOTs.

We report the characteristics of the SELECT population grouped by several potential determinants of CV risk, including glycemia as measured by $HbA_{1c}$, tertiles of adiposity as measured by waist to height ratio, and type of prior CV event. Prespecified analyses will evaluate the CV and metabolic benefits of semaglutide across subgroups with distinct CVD phenotypes, as well as across the obesity and diabetes disease continuum, providing insights into both the CV protective mechanisms and the ability to define populations who observe the greatest benefit [18]. For example, the $HbA_{1c}$ subgroups will contribute to our understanding of glucose-mediated risk of CV events in people with overweight or obesity and no diabetes. It is notable that two-thirds of the population had an abnormal $HbA_{1c}$ (>5.7%) at baseline. This finding highlights the high prevalence of dysglycemia among those with established CVD and allows us to investigate whether any effect of semaglutide on 3-point MACE is mediated through improvements in glycemic status. The waist to height tertiles will allow us to quantify the CV benefits across various degrees of obesity. Importantly, it also allows us to explore the degree to which weight loss, as opposed to the other effects of semaglutide, mediates any CV benefits. The subgroups with different CVD phenotypes will provide further understanding of the effect of semaglutide in different disease subtypes. Of particular note is the enrollment of patients with PAD, which reflects a subpopulation of patients that has been relatively under investigated.

One of the study population limitations is the disproportionately smaller number of females and some ethnic/race groups, which will limit our ability for subgroup analyses. For example, the Black population, which has a higher prevalence of obesity as well as CVD, is under represented. As comorbidities were ascertained through medical records and investigator discretion is a limitation, the prevalence of comorbidities that were not directly measured has been underestimated. Reporting of comorbidities may also vary by race and/or country. Additionally, only those with preexistent CV events or PAD were eligible; thus, the study will provide no information on those with lower CV risk. SELECT will evaluate the CV outcomes of semaglutide-mediated weight loss, and thus, it would not be possible to extrapolate the results to weight loss achieved through other methods, including lifestyle interventions. Furthermore, semaglutide might have direct cardioprotective effects independent of weight loss; thus, the results should not be extrapolated to other weight-lowering pharmacotherapies either.

## CONCLUSION

In conclusion, to our knowledge, SELECT is the first CVOT in people with overweight or obesity and established CVD but

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without diabetes. The study uses standard-of-care preventive measures along with semaglutide 2.4 mg subcutaneous once-weekly treatment, which has been demonstrated to provide significant and sustained mean weight loss of up to 16% [10–13, 24, 25], significant CV risk factor improvements, and proven CV benefit in patients with diabetes and prior CV events [16, 26]. If SELECT does demonstrate CV event reduction with semaglutide, we anticipate that this may have an impact on treatment recommendations for GLP-1RAs and guidelines for people with obesity and established CVD. Furthermore, if SELECT demonstrates a protective effect, it would be the first randomized controlled trial to demonstrate the benefits of significant and sustained semaglutide-mediated weight loss on CV events; previous evidence, even in the bariatric field, is only observational. The study population in SELECT represents the general population with atherosclerotic CVD as encountered internationally and also includes a broad range of patients across relevant risk categories and thus will provide important insights into the CV and metabolic benefits of this GLP-1RA intervention.O

## AUTHOR CONTRIBUTIONS

Ildiko Lingvay wrote the first draft of the manuscript and incorporated all authors' feedback in subsequent versions. Ildiko Lingvay and Steven P. Marso contributed to acquisition of data. Sille Esbjerg performed the statistical analysis of data. All authors contributed to the conception and design of the research, contributed to interpretation of data and results, revised the manuscript critically for important intellectual content, and gave final approval of the version to be published. Ildiko Lingvay and Donna H. Ryan are the guarantors of this work and take responsibility for the integrity of the data.

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## CONFLICT OF INTEREST

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## CLINICAL TRIAL REGISTRATION

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## ORCID

*Ildiko Lingvay* https://orcid.org/0000-0001-7006-7401
*Robert F. Kushner* https://orcid.org/0000-0002-1380-3705

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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