Semaglutide and walking capacity in people with symptomatic peripheral artery disease and type 2 diabetes (STRIDE): a phase 3b, double-blind, randomised, placebo-controlled trial

*Marc P Bonaca, Andrei-Mircea Catarig, Kim Houlind, Bernhard Ludvik, Joakim Nordanstig, Chethana Kalmady Ramesh, Neda Rasouli, Harald Sourij, Alex Videmark, Subodh Verma, for the STRIDE Trial Investigators**

Summary

Background: Peripheral artery disease is a highly morbid type of atherosclerotic vascular disease involving the legs and is estimated to affect over 230 million individuals globally. Few therapies improve functional capacity and health-related quality of life in people with lower limb peripheral artery disease. We aimed to evaluate whether semaglutide improves function as measured by walking ability as well as symptoms, quality of life, and outcomes in people with peripheral artery disease and type 2 diabetes.

Methods STRIDE was a double-blind, randomised, placebo-controlled trial done at 112 outpatient clinical trial sites in 20 countries in North America, Asia, and Europe. Participants were aged 18 years and older, with type 2 diabetes and peripheral artery disease with intermittent claudication (Fontaine stage IIa, able to walk >200 m) and an ankle–brachial index of less than or equal to 0·90 or toe–brachial index of less than or equal to 0·70. Participants were randomly assigned (1:1) using an interactive web response system to receive subcutaneous semaglutide 1·0 mg once per week for 52 weeks or placebo. The primary endpoint was the ratio to baseline of the maximum walking distance at week 52 measured on a constant load treadmill in the full analysis set. Safety was evaluated in the safety analysis set. This trial is registered with ClinicalTrials.gov, NCT04560998 and is now completed.

Findings From Oct 1, 2020, to July 12, 2024, 1363 patients were screened for eligibility, of whom 792 were randomly assigned to semaglutide (n=396) or placebo (n=396). 195 (25%) participants were female and 597 (75%) were male. Median age was 68·0 years (IQR 61·0–73·0). The estimated median ratio to baseline in maximum walking distance at week 52 was significantly greater in the semaglutide group than the placebo group (1·21 [IQR 0·95–1·55] *vs* 1·08 [0·86–1·36]; estimated treatment ratio 1·13 [95% CI 1·06–1·21]; p=0·0004). Six serious adverse events in five (1%) participants in the semaglutide group and nine serious adverse events in six (2%) participants in the placebo group were possibly or probably treatment related, with the most frequent being serious gastrointestinal events (two events reports by two [1%] in the semaglutide group and five events reported by three [1%] in the placebo group). There were no treatment-related deaths.

Interpretation Semaglutide increased walking distance in patients with symptomatic peripheral artery disease and type 2 diabetes. Research implications include the need for future studies to further elucidate mechanisms of benefit and to assess the efficacy and safety in patients with peripheral artery disease who do not have type 2 diabetes.

Funding Novo Nordisk.

Copyright © 2025 Elsevier Ltd. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Published Online March 29, 2025 https://doi.org/10.1016/S0140-6736(25)00509-4

See Online/Comment https://doi.org/10.1016/S0140-6736(25)00574-4

*Investigators listed in the appendix (pp 4–10)

CPC Clinical Research, Cardiovascular Division, University of Colorado School of Medicine, Aurora, CO, USA (MP Bonaca MD); **Novo Nordisk, Søborg, Denmark** (A-M Catarig MD; A Videmark MD); **Department of Vascular Surgery, Lillebaelt Hospital, Kolding, Denmark** (Prof K Houlind MD); **Department of Regional Health Research, University of Southern Denmark, Odense, Denmark** (Prof K Houlind); **1st Medical Department and Karl Landsteiner Institute for Obesity and Metabolic Disorders, Landstrasse Clinic, Vienna, Austria** (Prof B Ludvik MD); **Institute of Medicine, Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden** (Prof J Nordanstig MD PhD); **Novo Nordisk India, Bangalore, India** (C K Ramesh MSc); **Division of Endocrinology, Metabolism and Diabetes, University of Colorado School of Medicine, Aurora, CO, USA** (Prof N Rasouli MD); **Interdisciplinary Metabolic Medicine Trials Unit, Division of Endocrinology and Diabetology, Medical University of Graz, Graz, Austria** (Prof H Sourij MD MBA); **Division of Cardiovascular Surgery, St Michael's Hospital, University of Toronto, Toronto, ON, Canada** (Prof S Verma MD PhD)

Introduction

Lower limb peripheral artery disease affects more than 230 million individuals worldwide and its prevalence is increasing due to an ageing population, with a greater burden of cardiometabolic disease including type 2 diabetes.[1–3] People with peripheral artery disease have a heightened risk of major adverse cardiovascular events and major adverse limb events, including amputation; however, the earliest, most common, and most disabling manifestation is functional decline and disability.[4–7]

Functional impairment in people with peripheral artery disease is often unrecognised during early stages despite a severe degree of disability.[2,3,8] Non-specific symptoms and a gradual reduction in activity often mask an important decline in walking ability, and hence physical function, that represents progressive disease.[3] The coexistence of peripheral artery disease with other highly prevalent cardiorespiratory conditions that impair function also further exacerbates overall functional impairment.[9] At later stages, individuals might progress to requiring lower limb revascularisation procedures due

Correspondence to:
Dr Marc Bonaca, CPC Clinical Research, Cardiovascular Division, University of Colorado School of Medicine, Aurora, CO 80045-7120, USA
marc.bonaca@cpcmed.org

See Online for appendix

Research in context

Evidence before this study

Progressive functional decline is the dominant morbidity in patients with lower limb peripheral artery disease, which leads to further morbidity and worsening quality of life, leading to the need for rescue therapies and, in some cases, revascularisation procedures. Functional decline is caused by pain from ischaemia while walking (claudication) as well as chronic changes to the muscle and microvasculature in the setting of chronic hypoxia. The nature of functional limitation is complex in that the core driver is ischaemia from conduit artery obstruction from atherosclerosis; however, a complex set of responses including vasoconstriction, muscle dysfunction, and inflammation might further promote limitation. Supervised exercise therapy improves function; however, access is limited and those who do engage in this therapy remain with substantial impairment despite exercise. There are few medical therapies available to address this functional limitation. Recently, GLP-1 receptor agonists, initially developed for diabetes, have shown broad benefits including weight loss, reduction in the risk of heart attack and stroke, reduction in adverse kidney outcomes, and improvement of walking function as measured by 6-min walk in patients with heart failure. Anti-inflammatory properties, coupled with broad metabolic effects, are believed to result in the direct vascular benefits observed, including reducing myocardial infarction, stroke, and diabetic foot ulcer-related amputation in the LEADER trial. Inflammation is associated with prevalent peripheral artery disease, worsening peripheral artery disease outcomes, and has been highlighted as a potential driver of worsening claudication in these patients. Whether or not GLP-1 receptor agonist therapy has direct benefits in terms of function in peripheral artery disease is not known.

Added value of this study

The STRIDE trial was a large, phase 3, multinational, double-blind, clinical trial that randomly assigned participants with peripheral artery disease and type 2 diabetes to semaglutide or placebo and tested function using a treadmill endpoint of maximum walking distance over 52 weeks of treatment. Semaglutide significantly improved maximum walking distance and anchor measures supported the clinical meaningfulness of the observed changes. In addition, there were statistically significant improvements in all confirmatory secondary endpoints, including pain-free walking distance (symptoms) and quality of life. The observed differences met the prespecified anchor criteria for clinically meaningful change. Safety was consistent with other trials of semaglutide.

Implications of all the available evidence

Semaglutide improved function, symptoms, and quality of life in participants with type 2 diabetes and symptomatic peripheral artery disease. The magnitude of benefit was consistent with previous approved therapies such as cilostazol and naftidrofuryl, and met prespecified criteria for a clinically meaningful change. These benefits coupled with previously described benefits for reducing major adverse cardiovascular events in patients with peripheral artery disease support semaglutide as a novel therapy that improves both function and outcomes in people with diabetes and peripheral artery disease. Our findings could support prescribing and prioritisation among other therapies resulting in improved outcomes for this patient group.

to severe limitations or to prevent tissue loss, often resulting in a subsequent high rate of recurrent procedures and complications.[10–12] However, in the earlier and more prevalent stages of peripheral artery disease, the limited durability of lower limb revascularisation procedures can translate to little or no benefit compared with control treatment beyond 2 years of follow-up.[13]

There are few therapies to address functional impairment in people with peripheral artery disease. Despite strong evidence for supervised exercise therapy, it is underused due to limitations in access, lack of awareness, and relatively poor patient acceptance rates over longer time periods.[14] Despite its benefits, individuals participating in supervised exercise therapy have important residual limitation and access is time-limited.[15] Additionally, home-based programmes that are sufficiently intensive to cause leg pain (claudication) might paradoxically improve function but not health-related quality of life. Although there is broad recognition of unmet need for medical therapies for functional impairment in peripheral artery disease, cilostazol—the only current guideline-recommended medical therapy in the USA—was approved in 1999 and is infrequently used due to side-effects that lead to treatment discontinuation in up to half of all treated patients, black box warnings for heart failure, and a lack of other benefits.[15–18] Another therapy approved for symptoms, pentoxifylline, was found in subsequent studies to have no meaningful effect on function and is not recommended in guidelines. Other therapies such as naftidrofuryl oxalate are noted to have modest or variable benefit and none of these therapies reduce the risk of other cardiovascular outcomes or have other cardiovascular or cardiometabolic benefits beyond reducing symptoms.[1,19]

Over the past decade, GLP-1 receptor agonists have shown a broad range of benefits, including reductions in cardiovascular risk suggesting direct vascular effects.[20–23] People with peripheral artery disease and type 2 diabetes have an indication for GLP-1 receptor agonists, both for their cardiometabolic benefits and for major adverse cardiovascular event reductions, but current practice guidelines do not prioritise GLP-1 receptor agonists over

other therapies with cardiovascular benefits in people with peripheral artery disease, partly due to lack of evidence for specific benefits for morbidity associated with peripheral artery disease.[1,3,11,24] Over the past 5 years, GLP-1 receptor agonists have shown important improvements in function for people with heart failure and preserved ejection fraction through multiple pathways, including reductions in inflammation.[20] Early evidence suggests that the anti-inflammatory effects of GLP-1 receptor agonists extend to the vasculature,[23] and might partly explain the benefits for reducing ischaemic events and a lower rate of amputation observed in one study.[24]

It has been hypothesised that inflammation might play an important role in claudication through effects on shunting, vasoconstriction, and changes in blood viscosity.[25] Additionally, the ischaemia resulting from claudication has been shown to promote inflammation, which has been hypothesised to further promote endothelial dysfunction and adverse effects on the microcirculation and skeletal muscle metabolism, further compromising function.[25] On the basis of these observations, we aimed to evaluate whether semaglutide improves walking ability, symptoms, and patient-reported outcomes in people with peripheral artery disease and type 2 diabetes.[26]

Methods

Study design and participants

STRIDE was a phase 3b, double-blind, randomised, placebo-controlled trial done at 112 outpatient clinical trial sites in 20 countries in North America, Asia, and Europe. The STRIDE trial design has been previously published.[26] Details regarding participating sites and trial organisation are provided in the appendix (pp 4–10).

Briefly, eligible participants were aged 18 years and older, with type 2 diabetes and peripheral artery disease with intermittent claudication (Fontaine stage IIa,[27] able to walk >200 m) and an ankle–brachial index of less than or equal to 0·90 or toe–brachial index of less than or equal to 0·70. Patients with peripheral artery disease who also had type 2 diabetes were selected on the basis of the known benefits in patients with diabetes and potential anti-inflammatory and microvascular benefits observed with liraglutide.[23] Baseline testing using a flat treadmill was required to demonstrate that potential participants had limiting claudication and that their symptoms were consistent with Fontaine stage IIa, which is defined as claudication with a flat walking distance of at least 200 m. The Fontaine classification was chosen instead of the Rutherford classification because the Fontaine classification specifies a walking distance that could be verified at inclusion, whereas the Rutherford classification is more subjective, with no objective distance to distinguish class among those with claudication. Therefore, all eligible participants had a pain-free walking distance of at least 200 m on a flat treadmill with a fixed speed (3·2 km/h [2 miles per h]) in order to confirm their symptoms were consistent with Fontaine stage IIa. Participants also had to demonstrate a limitation due to symptoms consistent with the disease state with a maximum walking distance of less than 600 m on a constant-load treadmill test with fixed speed (3·2 km/h [2 miles per h]) and fixed inclination (12%).[28] Participants could not have a contraindication to semaglutide, another non-peripheral artery disease condition limiting functional capacity (eg, heart failure [New York Heart Association Class III–IV], or musculoskeletal disorder), or a recently completed or planned revascularisation procedure. Participant sex (male, female, or other) was self-reported. Full inclusion and exclusion criteria are described in the appendix (pp 34–35).

All study activities were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent. The trial protocol (appendix pp 57–166) was approved by the applicable independent ethics or institutional review boards in each country and site. A medical monitoring committee comprised of physicians and safety experts reviewed safety data monthly and an independent clinical events committee reviewed events. This trial is registered with ClinicalTrials.gov, NCT04560998, and is completed.

Randomisation and masking

All participants identified by investigators were centrally screened and randomly assigned (1:1) using an interactive web response system to the next available treatment (either semaglutide 1·0 mg or placebo) according to the randomisation schedule. At screening, each participant was assigned a unique six-digit patient number for the duration of the trial, and each site was assigned a three-digit number; all patient numbers started with the site number. STRIDE was a double-blind trial with both participants and investigators masked to treatment. Trial products containing active drug and placebo were visually identical and packaged in a manner to maintain masking, including indications of study product or placebo and approved labelling for each country.

Procedures

Participants received 1·0 mg of semaglutide subcutaneously or a matching placebo injection each week through to 52 weeks. Participants were contacted by the study team to ascertain adherence, dispense medication, and assess for outcome and safety events at 4, 8, 12, 26, 49, 52, and 57 weeks, with functional testing carried out at baseline, 26, 52, and 57 weeks. Details of revascularisation procedures for symptoms (rescue), changes in medical therapy, including those for worsening symptoms (rescue), and all adverse events and clinical outcomes were collected. Rescue medication was defined as starting on cilostazol or pentoxifylline or

increasing the dose of cilostazol or pentoxifylline by ≥20%. Revascularisation was defined as peripheral procedures including both endovascular and open surgical revascularisation, including hybrid procedures (eg, combination of endovascular and open surgical revascularisation). Functional testing (walking on the constant-load treadmill) was carried out by trained site staff using core laboratory-certified equipment as described above. Treadmill assessment, training, and qualification were conducted by The Colorado Prevention Center Clinical Research, a non-profit academic research organisation affiliated with the University of Colorado.

Outcomes

The primary endpoint was the ratio to baseline of the maximum walking distance at week 52 measured by the constant load treadmill with fixed speed (3·2 km/h [2 miles per h]) and fixed inclination (12%). Prespecified confirmatory secondary endpoints (providing supportive evidence to the primary endpoint and adjusted for multiplicity through the hierarchical testing procedure) were the ratio to baseline of maximum walking distance at week 57 (5 weeks after drug discontinuation to evaluate persistence of effect), change in patient-reported peripheral artery disease-specific Vascular Quality of Life Questionnaire-6 (VascuQoL-6) score from baseline to week 52, and the ratio to baseline of pain-free walking distance at week 52.[29,30]

For the **European Medicines Agency draft guideline** see https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-peripheral-arterial-occlusive-disease-scientific-guideline

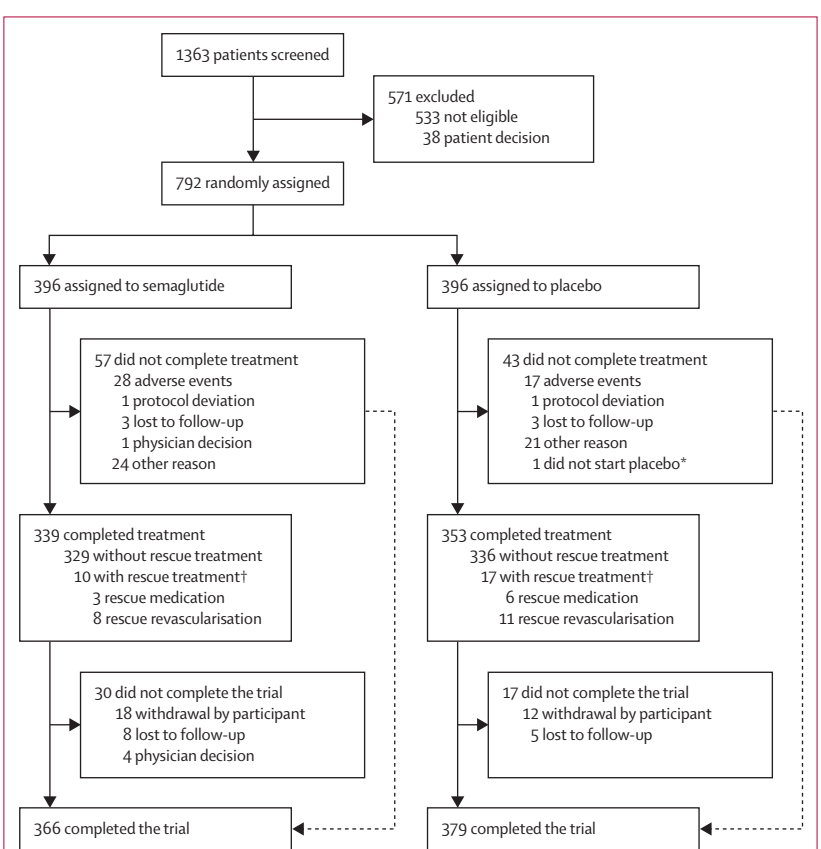

Figure 1: **Trial profile**
*One participant was not exposed to placebo, leaving 395 participants in the safety analysis set. †One participant both received rescue medication and underwent rescue revascularisation.

Supportive secondary endpoints included the physical functioning domain of the Short Form (36) Health Survey (SF-36) change from baseline to week 52, change in ankle–brachial index, change in bodyweight, and change in glycated haemoglobin A_{1C}. Prespecified exploratory analyses included an analysis of time-to-first adjudicated major adverse limb events and an anchor-based measure for assessing the clinical meaningfulness of the change in the primary endpoint. The prespecified exploratory anchor-based methodology employed in this study to derive the thresholds for change in maximum walking distance (ratio) and VascuQoL-6 score that is clinically relevant to the participants from the study population was derived based on data from all randomly assigned participants before database lock and this was regardless of the treatment assignment; clinical relevance was based on a responder analysis of the mean within-patient change thresholds derived from the anchor-based method (appendix pp 36–37).[31] To estimate the treatment effect in meters, exploratory analyses based on the primary and trial product estimand were carried out on both change in maximum walking distance and change in pain-free walking distance in their original scale (meters). Other prespecified exploratory outcomes included adjudicated clinical outcomes (eg, major adverse limb events and mortality; appendix p 36).

The eligibility criteria required a pain-free walking distance of at least 200 m on a flat treadmill test (3·2 km/h [2 miles per h]); for the primary endpoint and all confirmatory secondary endpoints, distances were measured on a constant-load treadmill test with fixed inclination of 12% and a fixed speed of 3·2 km/h (2 miles per h). The treadmill test was chosen on the basis of recommendations by the European Medicines Agency draft guideline on *Clinical Investigation of Medicinal Products In The Treatment Of Peripheral-Arterial Occlusive Disease*, which does not currently include the 6-min walk test, and was also endorsed by the US Food and Drug Administration. Because disease progression and worsening symptoms could lead to use of rescue medication or revascularisation, rescue treatment data were prespecified and collected during the trial (appendix pp 36, 38–41). Although the timing and use of rescue medications and procedures is subjective overall, because the treatment group was randomly assigned and treatment double-blinded, such decisions should not be biased by treatment group.

Adverse events, serious adverse events, and adverse events leading to permanent drug discontinuation were monitored, with cardiovascular and limb outcomes reviewed by an independent, masked, event adjudication committee (appendix p 3). All adverse events were collected with grading of severity, causality, and

seriousness, and were coded using the Medical Dictionary for Regulatory Activities (version 27.0). Full details of outcomes and procedures are described in the protocol (appendix pp 57–166).

Statistical analysis

A sample size of 800 participants was estimated to provide 89% power to detect a 20% improvement in the primary outcome, assuming a coefficient of variation of 0·8 at a two-sided significance level of 0·05. The following hierarchical testing strategy was applied to control the type-I error at an overall two-sided α level of 0·05 across the confirmatory endpoints: (1) superiority of semaglutide 1·0 mg versus placebo on ratio to baseline (week 0) at week 52 in maximum walking distance; (2) superiority of semaglutide 1·0 mg versus placebo on ratio to baseline (week 0) at week 57 in maximum walking distance; (3) superiority of semaglutide 1·0 mg versus placebo on change from baseline (week 0) to week 52 in VascuQoL-6 score; and (4) superiority of semaglutide 1·0 mg versus placebo on ratio to baseline (week 0) at week 52 in pain-free walking distance.

Efficacy endpoints were analysed in the full analysis set (all participants randomly assigned according to the intention to treat). Safety endpoints were summarised descriptively and analysed in the safety population (all participants randomly assigned to trial treatment who received at least one dose of trial product, analysed as treated).

The primary estimand (a mix of treatment policy estimand and composite strategy) evaluated treatment effect in all randomly assigned participants based on the in-trial observation period, regardless of treatment discontinuation or initiation of rescue treatment (revascularisation or starting cilostazol or pentoxifylline) or change in treatment dose. A composite strategy was used to handle intercurrent events of death and physical inability to perform the treadmill test; these intercurrent events were incorporated into the outcome by ascribing them an extreme unfavourable rank. Imputation of missing data at endpoint visit was done using multiple imputation within groups defined by randomly assigned treatment and treatment completion status at week 52. The multiply imputed observations were analysed using a Wilcoxon rank-sum test and results were combined by use of Rubin's rules. The estimated treatment effect, along with the two-sided 95% CIs, was obtained using the Hodges–Lehmann estimate for location shift, and confirmatory statistical testing was based on the two-sided p value of the hypothesis that the distribution of endpoints in both treatment groups was identical, obtained from the Wilcoxon rank-sum test. A tipping point sensitivity analysis supported the robustness of the superiority conclusions for primary and all confirmatory secondary endpoints based on the primary analysis for the primary estimand (data not shown). For the functional capacity endpoints, a worsening from 10% to no change in

	Semaglutide group (n=396)	Placebo group (n=396)
Sex		
Female	107 (27%)	88 (22%)
Male	289 (73%)	308 (78%)
Age, years	68·0 (60·0–73·0)	68·0 (62·0–73·0)
Ethnicity		
Not Hispanic or Latino	388 (98%)	385 (97%)
Hispanic or Latino	7 (2%)	6 (2%)
Not reported	1 (<1%)	5 (1%)
Race		
White	259 (65%)	279 (70%)
Asian	131 (33%)	109 (28%)
Black or African American	4 (1%)	4 (1%)
American Indian or Alaska Native	0	1 (<1%)
Native Hawaiian or other Pacific Islander	1 (<1%)	0
Other	1 (<1%)	3 (1%)
Duration of diabetes, years	12·1 (6·2–18·2)	12·2 (6·7–20·2)
Bodyweight, kg	81·5 (70·8–93·5)	83·1 (71·5–95·4)
BMI, kg/m²		
Median	28·7 (25·6–32·9)	28·5 (25·7–33·1)
<30	231 (58%)	238 (60%)
Systolic blood pressure, mm Hg	134 (124–144)	134 (123–144)
Diastolic blood pressure, mm Hg	76 (69–82)	75 (68–81)
Glycated haemoglobin A_{1c}	7·0% (6·5–7·8)	7·2% (6·5–8·1)*
Estimated glomerular filtration rate, mL/min per 1·73 m²	89·0 (70·0–99·0)	87·0 (67·0–98·5)
Geometric mean LDL, mg/dL (CV)†	69·2 (0·5)	68·7 (0·5)
Smoking status		
Current smoker	96 (24%)	107 (27%)
Previous smoker	178 (45%)	189 (48%)
Never smoker	122 (31%)	100 (25%)
Cardiovascular conditions before screening		
Hypertension	340 (86%)	357 (90%)
Coronary heart disease	162 (41%)	178 (45%)
Coronary revascularisation	122 (31%)	129 (33%)
Myocardial infarction	59 (15%)	89 (22%)
Chronic kidney disease	57 (14%)	68 (17%)
Stroke	21 (5%)	30 (8%)
Chronic heart failure‡	55 (14%)	54 (14%)
NYHA class I	22 (6%)	23 (6%)
NYHA class II	32 (8%)	31 (8%)
Concomitant medication at randomisation	394 (99%)	396 (100%)
Glucose-lowering medication		
Metformin	315 (80%)	319 (81%)
SGLT2 inhibitors	146 (37%)	132 (33%)
Sulfonylurea	87 (22%)	87 (22%)
DPP-4 inhibitors	80 (20%)	64 (16%)
Thiazolidinedione	26 (7%)	12 (3%)
Insulin	118 (30%)	133 (34%)
Lipid-modifying agents		
Statins	329 (83%)	324 (82%)
Ezetimibe	58 (15%)	57 (14%)
PCSK9 inhibitors	5 (1%)	2 (1%)

(Table 1 continues on next page)

	Semaglutide group (n=396)	Placebo group (n=396)
(Continued from previous page)		
Antithrombotic medication	60 (15%)	58 (15%)
Direct oral anticoagulants	50 (13%)	49 (12%)
Vitamin K antagonist	7 (2%)	8 (2%)
Heparin	4 (1%)	1 (<1%)
Platelet aggregation inhibitors	255 (64%)	261 (66%)
P2Y12 inhibitors	85 (21%)	87 (22%)
Acetylsalicylic acid	207 (52%)	207 (52%)
Cilostazol	43 (11%)	43 (11%)
Other cardiovascular-related medication		
Angiotensin converting enzyme inhibitors	137 (35%)	131 (33%)
Angiotensin receptor blockers	149 (38%)	155 (39%)
Functional characteristics		
Ankle–brachial index§¶		
Geometric mean (CV)	0·76 (0·4)	0·75 (0·3)
Median	0·79 (0·64–0·95)	0·76 (0·64–0·88)
Toe–brachial index ¶‖		
Geometric mean (CV)	0·48 (0·4)	0·48 (0·4)
Median	0·53 (0·39–0·64)	0·50 (0·38–0·65)
Maximum walking distance, m**		
Median	184·5 (126·5–274·0)*	185·8 (133·8–262·0)
Geometric mean (CV)	192·0 (0·6)*	188·9 (0·6)
Pain-free walking distance, m**		
Median	119·0 (76·0–173·5)*	109·0 (77·8–169·5)
Geometric mean (CV)	117·1 (0·7)*	115·3 (0·6)
VascuQoL-6 total score		
Median (IQR)	15·0 (12·5–18·0)	15·0 (13·0–17·0)*
Mean	15·2 (3·8)	15·1 (3·6)*

Data are n (%), median (IQR), or mean (SD), except where otherwise specified. The baseline value was defined as the latest predosing value. BMI was calculated based on baseline measurement of bodyweight and height, and estimated glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration 2009 formula.[29] CV=coefficient of variation. NYHA=New York Heart Association. VascuQoL-6=Vascular Quality of Life Questionnaire-6. *n=395. †n=381 in the semaglutide group and n=376 in the placebo group. ‡NYHA class I defined as no symptoms and no limitation in ordinary physical activity; NYHA class II defined as mild symptoms (mild shortness of breath or angina) and slight limitation during ordinary activity, comfortable only at rest. §n=393 for both the semaglutide group and the placebo group. ¶Minimum value of both left and right indices. ‖n=389 in the semaglutide group and n=387 in the placebo group. **The median distance measured on the flat treadmill at screening was 249·0 m (IQR 220·0–267·0) in the semaglutide group and 242·0 m (216·0–267·0) in the placebo group; however, distance was limited in the screening procedure only to demonstrate the ability to walk more than 200 m on a flat treadmill to qualify with Fontaine class IIa symptoms.

Table 1: **Baseline characteristics in the full analysis set**

imputed observations was assumed for the semaglutide 1·0 mg group. For the placebo group, a worsening from 10% to an improvement of 15% in imputed observations was assumed.[32] Superiority of semaglutide 1·0 mg versus placebo was confirmed in the entire grid of penalties. A prespecified hypothetical strategy estimand (a trial product estimand) evaluated treatment effect in all randomly assigned individuals from the on-treatment without rescue medication observation period, had participants adhered to randomly assigned treatment and not received rescue treatment.

Prespecified subgroup analyses were performed for maximum walking distance at week 52 across regions (Europe, North America, and Asia), age groups (<65 years and ≥65 years), and sex (male and female). A prespecified responder analysis was performed for maximum walking distance and VascuQoL-6 total score, based on meaningful within-patient change thresholds.

Post-hoc analyses were performed on two progression-free survival composites (namely rescue or mortality, rescue, mortality, or major adverse limb events) along with their individual components. A Cox proportional hazards model with treatment as a fixed factor was used to analyse (post hoc) time from randomisation to first composite event (all-cause death, or rescue therapy initiation [defined as rescue treatment, or revascularisation procedures]). Kaplan–Meier estimates of proportion of participants experiencing an event were reported. To understand the relationship between change in bodyweight and change in function, an association between change in BMI and maximum walking distance was explored as post-hoc analyses.

Full details of the statistical analyses are in the statistical analysis plan (appendix pp 167–209); statistical hypotheses, multiplicity adjustments, estimand strategies for the primary and secondary objectives, prespecified subgroup analyses, and a prespecified responder analysis are described in the appendix (pp 38–41).

Role of the funding source

The trial protocol was designed by the funder of the study in collaboration with academic scientific advisors. The funder of the study was responsible for data collection, data analysis, and trial conduct which was undertaken in collaboration with academic scientific advisors. The authors were responsible for data interpretation for the manuscript. The manuscript was drafted by the first author and all coauthors contributed to its content.

Results

From Oct 1, 2020, to July 12, 2024, 1363 patients were screened for eligibility (reasons for participants not being eligible are in the appendix pp 46–48), 792 of whom were randomly assigned to semaglutide (n=396) or placebo (n=396; figure 1). 113 (14%) participants were randomly assigned in North America, 231 (29%) in Asia, and 448 (57%) in Europe. 791 participants received at least one dose of treatment, with 100 (13%) of 792 permanently discontinuing study treatment (57 [14%] of 396 in the semaglutide group and 43 [11%] of 396 in the placebo group; figure 1).[26] The representativeness of participants in terms of race and ethnicity was generally consistent with the location of trial sites and their recruitment levels and with the global nature of the study. The risk factors and comorbidities of the population recruited were consistent with those generally seen in this population (appendix p 49). Median follow-up was 13·2 months (IQR 13·2–13·3).

Baseline characteristics are shown in table 1. Median age was 68·0 years (IQR 61·0–73·0), 195 (25%) of

	Semaglutide group (n=396)	Placebo group (n=396)	Estimate (95% CI)	p value
Primary endpoint*				
Median maximum walking distance at week 52, ratio to baseline	338; 1·21 (0·95 to 1·55)	345; 1·08 (0·86 to 1·36)	ETR 1·13 (1·06 to 1·21)	0·0004
Confirmatory secondary endpoints*				
Median maximum walking distance at week 57, ratio to baseline	329; 1·16 (0·92 to 1·48)	333; 1·10 (0·87 to 1·40)	ETR 1·08 (1·00 to 1·16)	0·038
Median VascuQoL-6 total score at week 52, change from baseline	362; 2·0 (0·0 to 4·0)	362; 1·0 (–1·0 to 4·0)	ETD 1·00 (0·48 to 1·52)	0·011
Median pain-free walking distance at week 52, ratio to baseline	338; 1·21 (0·92 to 1·52)	334; 1·10 (0·86 to 1·44)	ETR 1·11 (1·03 to 1·20)	0·0046
Supportive secondary endpoints at week 52				
Geometric mean ankle–brachial index, ratio to baseline†	306; 1·06 (34·0)	315; 1·02 (19·6)	ETR 1·05 (1·02 to 1·09)	0·0037
Mean change from baseline in bodyweight, kg†	310; –5·2 (4·8)	318; –1·2 (4·2)	ETD –4·1 (–4·8 to –3·4)	<0·0001
Mean change from baseline in glycated haemoglobin A_{1c}†	304; –0·8% (1·1)	311; 0·2% (1·1)	ETD –1·0 (–1·1 to –0·8)	<0·0001
Exploratory endpoints at week 52				
Median absolute improvement in maximum walking distance, m*	338; 37 (–8·0 to 109·0)	345; 13 (–26·5 to 70·0)	HL 26·4 (11·8 to 40·9)	..
Mean absolute improvement in maximum walking distance, m†	294; 87 (182)	306; 41 (152)	ETD 39·9 (13·9 to 66·0)	..
Median absolute improvement in pain-free walking distance, m*	338; 22 (–9·0 to 65·5)	344; 12 (–14·0 to 52·8)	HL 13·8 (4·1 to 23·5)	..
Mean absolute improvement in pain-free walking distance, m†	294; 52 (124)	305; 23 (106)	ETD 29·8 (11·6 to 48·0)	..
Composite of rescue treatment, all-cause death, and major adverse limb events‡	15 (4%)	32 (8%)	HR 0·46 (0·24 to 0·84)	..
Composite of rescue treatment and all-cause death‡	14 (4%)	30 (8%)	HR 0·46 (0·24 to 0·85)	..
Rescue treatment§	10 (3%)	21 (5%)	HR 0·48 (0·21 to 0·98)	..
Rescue medication	3 (1%)	8 (2%)	..	..
Rescue revascularisation	8 (2%)	13 (3%)	..	..
All-cause death	4 (1%)	9 (2%)	HR 0·44 (0·12 to 1·34)	..
Major adverse limb events‡ (acute or chronic limb ischaemia requiring hospitalisation)	6 (2%)	5 (1%)	HR 1·21 (0·36 to 4·20)	..

Data are n; median (IQR), n; geometric mean (CV), n; mean (SD), or n (%), except where otherwise stated. CV=coefficient of variation (in %). ETD=estimated treatment difference. ETR=estimated treatment ratio. HL=Hodges–Lehmann estimate for location shift. HR=hazard ratio. VascuQoL-6=Vascular Quality of Life Questionnaire-6. *Treatment policy estimand. Primary and secondary endpoint data were from the in-trial observation period. p values were from the two-sided test of the hypothesis that the distributions were identical, obtained from the Wilcoxon rank-sum test (adjusted for multiplicity). p values <0·05 were considered significant. †Trial product (hypothetical) estimand. Data were from the on-treatment without rescue (medication or revascularisation) period. Postbaseline measurements were analysed using a mixed model for repeated measurements with treatment and region as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix. p values were the unadjusted two-sided p values for test of no difference. ‡Progression-free survival composite (death and rescue treatment) and event adjudication committee-confirmed major adverse limb event data were from the in-trial observation period. Time from randomisation to first event was analysed using a Cox proportional hazards model with treatment as categorical fixed factor. The proportionality of hazards assumption between semaglutide and placebo for each of the time-to-event outcomes were satisfied using Schoenfeld residuals (p>0·05). Participants without events of interest were censored at the end of their in-trial period. §One participant required both rescue medication and revascularisation in the semaglutide group. No p values were generated for exploratory outcomes.

Table 2: **Primary, secondary, and exploratory efficacy endpoints in the full analysis set**

792 participants were female, 597 (75%) were male, and 538 (68%) were White. Duration of diabetes was 10 years or longer in 480 (61%) participants, and 469 (59%) had a BMI of less than 30 kg/m² (median BMI 28·7 kg/m² [IQR 25·6–33·0]).

For baseline severity of peripheral artery disease, geometric mean ankle–brachial index was 0·75 (coefficient of variation 0·3) and toe–brachial index was 0·48 (coefficient of variation 0·4). Although all participants demonstrated the ability to walk more than 200 m on a flat treadmill at screening to show Fontaine class IIa symptoms rather than more severe disease, the median maximum walking distance (185·5 m [IQR 130·0–267·0]) and pain-free walking distance (114·5 m [77·0–171·5]) on the constant load treadmill at baseline were lower due to the addition of the 12% grade. 190 (24%) participants had a history of peripheral lower limb revascularisation. 514 (65%) participants rated current limitations in walking as moderate or severe and 495 (63%) rated the effect of peripheral artery disease on their health-related quality of life as measured by the VascuQoL-6 as moderate or severe, based on Patient Global Impression of Severity questions. Baseline VascuQoL-6 median total score was 15·0 (IQR 13·0–18·0).

Results for the primary, confirmatory secondary, supportive secondary, and exploratory analyses are shown in table 2. The number of participants with missing values for informatively missing intercurrent events for the primary and confirmatory secondary endpoints are shown in the appendix (p 50).

At week 52, the observed median ratio to baseline of maximum walking distance was greater in the semaglutide group than in the placebo group (figure 2A, D, table 2). The on-treatment analysis (participants on treatment without rescue) showed a consistent result with the main analysis (appendix p 51). A higher proportion of participants receiving semaglutide responded to the clinically meaningful within-patient change thresholds from the prespecified anchor based methodology compared with placebo (appendix p 42). In absolute terms, the median improvement in maximum walking distance

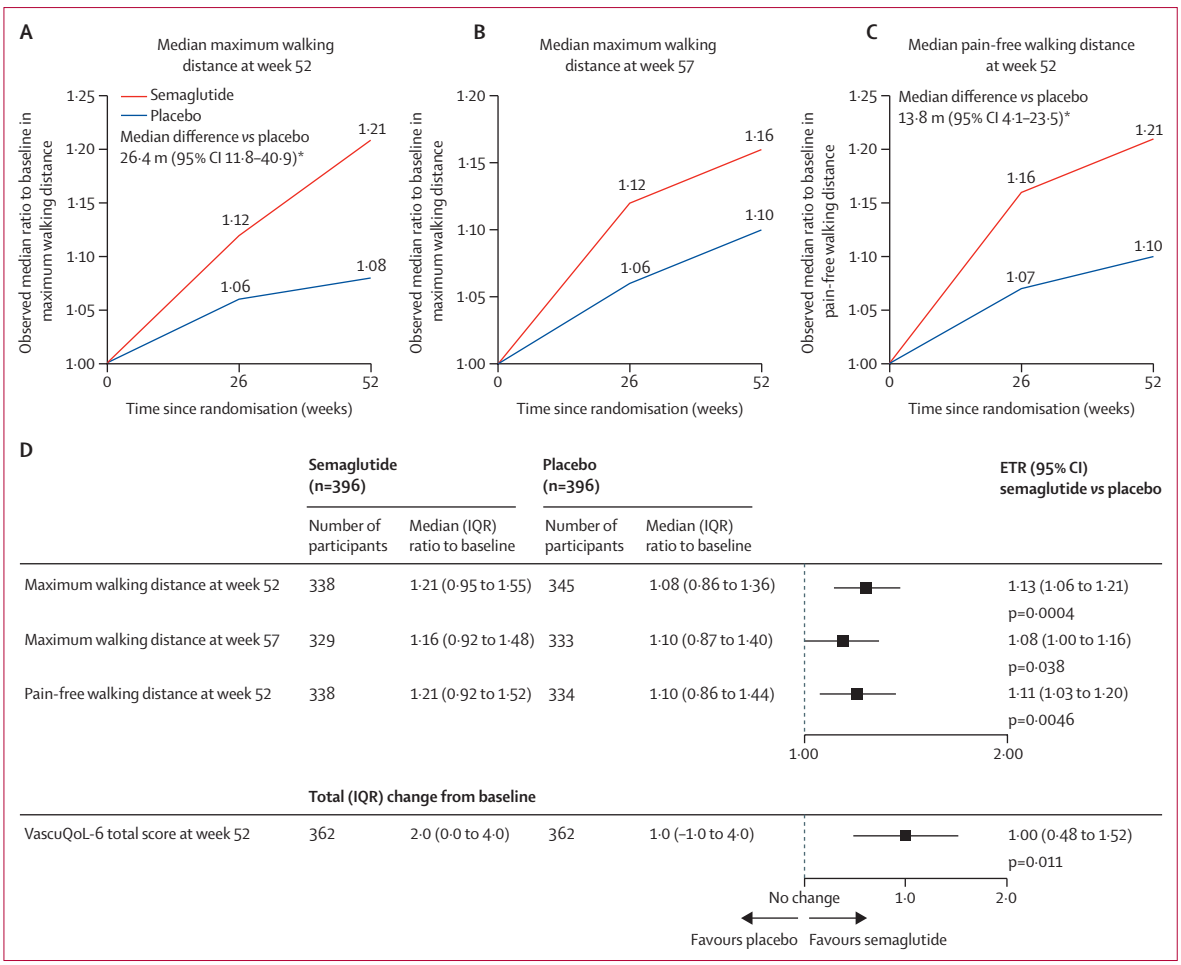

Figure 2: **Primary and confirmatory secondary endpoints (treatment policy estimand; full analysis set)**
(A) Observed median ratio to baseline in maximum walking distance at week 52. (B) Observed median ratio to baseline in maximum walking distance at week 57. (C) The median ratio to baseline in pain-free walking distance at week 52. (D) Improvements estimated from a statistical analysis model and estimated treatment ratios and differences for the primary and confirmatory secondary endpoints. p value: a two-sided test of the hypothesis that the distributions are identical, obtained from the Wilcoxon rank-sum test (adjusted for multiplicity). ETR=estimated treatment ratio. VascuQoL-6=Vascular Quality of Life Questionnaire-6. *Median differences in maximum walking distance and pain-free walking distance for semaglutide versus placebo were derived from an exploratory analysis using the treatment policy estimand.

from baseline to week 52 between the semaglutide and placebo groups was 26·4 m (95% CI 11·8–40·9), and the mean improvement was 39·9 m (95% CI 13·9–66·0). The treatment effect of semaglutide versus placebo was also consistent using the trial product estimand for the primary and confirmatory secondary endpoints (appendix p 51) and across prespecified subgroups (appendix p 43).

The improvement in maximum walking difference was significantly greater in the semaglutide group than the placebo group 5 weeks after treatment cessation (week 57; table 2; figure 2B, D). The improvement in VascuQoL-6 was also significantly greater with semaglutide at week 52 (table 2, figure 2D), increasing to a median of 17·0 (IQR 14·0–20·0) for semaglutide and 16·0 (13·0–19·0) for placebo. Similarly, the improvement at week 52 in pain-free walking distance was significantly greater in the semaglutide group than the placebo group (table 2; figure 2C, D). In the exploratory analysis, the difference between the groups in the median absolute improvement in pain-free walking distance was 13·8 m (95% CI 4·1–23·5) and the difference in the mean absolute improvement was 29·8 m (11·6–48·0; table 2).

In the exploratory post-hoc analysis, a composite of rescue therapy or all-cause death was reported for 14 (4%) of 396 participants in the semaglutide group and 30 (8%) of 396 in the placebo group (hazard ratio 0·46 [95% CI 0·24–0·85]; figure 3), with similar findings for the post-hoc exploratory composite of rescue therapy, all-cause death, or major adverse limb events (table 2). Other limb events occurred in six (2%) participants in the semaglutide group and five (1%) in the placebo group (table 2). At the end of the study, 779 (98%) of 792 participants in follow-up were alive and had not had a major adverse limb event (table 2).

The improvement in the physical functioning domain of the SF-36 was also significantly greater in the semaglutide group versus the placebo group (estimated treatment difference 1·25 [95% CI 0·26–2·24]; p=0·013; appendix p 52). Ankle–brachial index was significantly increased with semaglutide versus placebo (table 2). Participants in both treatment groups lost weight between baseline and week 52: there was a mean change of –5·2 kg (SD 4·8) in the semaglutide group and –1·2 kg (4·2) in the placebo group (estimated treatment difference –4·1 (95% CI –4·8 to –3·4; p<0·0001; table 2). The association between change in BMI and the primary endpoint of maximum walking distance at week 52 was assessed in each treatment group. There was a statistically significant association between BMI change and function in the placebo group; however, the relationship as measured by Spearman's R was weak (–0·1410; p=0·014). Similarly there was a weak relationship in the semaglutide group (Spearman's R –0·1260; p=0·031; appendix p 45).

Safety outcomes are shown in table 3 and the appendix (pp 53–54). 210 (53%) of 396 participants in the semaglutide group and 182 (46%) of 395 in the placebo group had adverse events, respectively, leading to dose reductions in 23 (6%) participants in the semaglutide group and three (1%) in the placebo group. Serious adverse events were reported by 74 (19%) participants in the semaglutide group and 78 (20%) in the placebo group. Six serious adverse events in five (1%) participants in the semaglutide group and nine serious adverse events in six (2%) participants in the placebo group were possibly or probably treatment related (table 3). The most frequent serious adverse events possibly or probably related to treatment were serious gastrointestinal events (two events reported by two [1%] participants in the semaglutide group and five events reported by three [1%] in the placebo group). Serious adverse events leading to permanent treatment discontinuation occurred in 11 (3%) participants in the semaglutide group and 13 (3%) in the placebo group (table 3). Serious adverse events led to the death of three (1%; sudden cardiac death n=1, cardiorespiratory arrest n=1, and asthma and acute coronary syndrome n=1) participants in the semaglutide group and eight (2%; pancreatic carcinoma and septic shock n=1, death n=2, adenocarcinoma of colon n=1, lung adenocarcinoma n=1, metastatic pancreatic

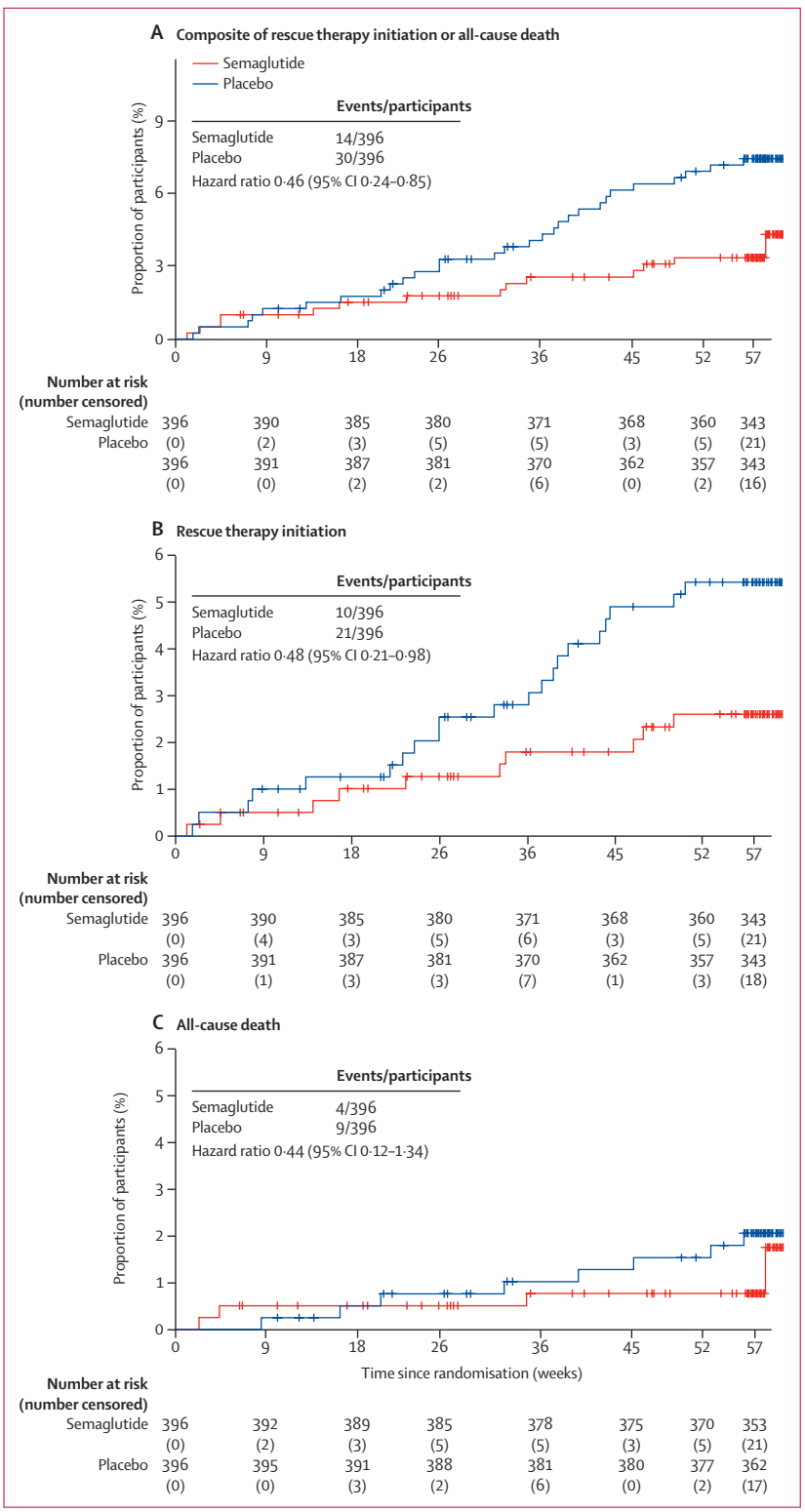

Figure 3: **Post-hoc analysis of time to rescue therapy initiation or all-cause death in the full analysis set**

(A) Time to the composite of rescue therapy or all-cause death. (B) Time to rescue therapy initiation. (C) Time to all-cause death. Rescue medication was defined as starting on cilostazol or pentoxifylline or increasing the dose of cilostazol or pentoxifylline by ≥20%. Revascularisation was defined as peripheral procedures including both endovascular and percutaneous procedures and open surgical revascularisation, including hybrid procedures (eg, combination of endovascular and open surgical revascularisation). Participants without events of interest were censored at their planned in-trial period. The hazard ratio and 95% CI were from a Cox proportional hazards model with treatment as categorical fixed factor. The proportionality of hazards assumption between semaglutide 1·0 mg and placebo for each of the time-to-event outcomes were satisfied using Schoenfeld residuals (p>0·05).

	Semaglutide group (n=396)			Placebo group (n=395)		
	Participants	Events	Events per 100 person-years	Participants	Events	Events per 100 person-years
Adverse events	210 (53%)	490	122·4	182 (46%)	409	99·0
Probably treatment related*	43 (11%)	75	18·7	11 (3%)	14	3·4
Possibly treatment related*	52 (13%)	64	16·0	21 (5%)	33	8·0
Leading to permanent treatment discontinuation	28 (7%)	28	7·0	17 (4%)	17	4·1
Leading to death†	3 (1%)	4	1·0	8 (2%)	9	2·2
Serious adverse events	74 (19%)	130	32·5	78 (20%)	111	26·9
Probably treatment related*	2 (1%)	3	0·7	2 (1%)	3	0·7
Possibly treatment related*	3 (1%)	3	0·7	4 (1%)	6	1·5
Leading to permanent treatment discontinuation	11 (3%)	11	2·7	13 (3%)	13	3·1
Leading to death	3 (1%)	4	1·0	8 (2%)	9	2·2

*As judged by the investigator. †All adverse events leading to death were classed as being serious adverse events. Adverse events based on Medical Dictionary for Regulatory Activities, version 27·0.

Table 3: **Adverse events and serious adverse events during the on-treatment period in the safety analysis set**

carcinoma n=1, urosepsis n=1, and respiratory arrest n=1) in the placebo group. No serious adverse events leading to death were treatment related.

Discussion

People with peripheral artery disease have progressive functional limitation that is often not apparent to the person or their clinicians until their claudication becomes more severe or, in some cases, they progress to chronic limb threatening ischaemia,[2,3,8] missing an opportunity for early medical therapy to improve function. Additionally, in people who are diagnosed with peripheral artery disease there are few treatment options and even those that exist are underused. In STRIDE, people with type 2 diabetes and symptomatic peripheral artery disease including Fontaine class IIa claudication had a median maximum walking distance on a constant load treadmill of 185 m at baseline, which is significantly lower than a normal distance of more than 600 m to 800 m. Our findings show that once-weekly subcutaneous semaglutide 1·0 mg improved maximum walking distance by 13% compared with placebo, with median improvement of 26·4 m and mean improvement of 39·9 m on a graded treadmill (12% incline, corresponding to walking up a steep hill). The benefit in the semaglutide group was apparent early and the separation between groups continued over time, with significant improvements in symptoms (measured by pain-free walking distance), quality of life (as measured by the VascuQoL-6 and SF-36 physical functioning module), and lower rates of rescue treatment than in the placebo group. Overall, safety aligned with previous semaglutide trials.[20–22]

The effect of semaglutide should be considered in the context of the study population and previous studies of functional outcomes in patients with peripheral artery disease.[1,3,14,17,18,33,34] Perhaps the most notable baseline finding is that participants in our study had important disability due to peripheral artery disease, despite having claudication at Fontaine class IIa (consistent with early intermittent claudication). In addition, the population differed from previous trials of semaglutide,[20–22] in that BMI was lower, which is typical of populations with peripheral artery disease who do not tend to have obesity.[35] Coupled with only modest observed weight loss of 4·1 kg with semaglutide versus placebo and improvements in pain-free walking distance and ankle–brachial index, these data suggest a direct vascular benefit of semaglutide rather than benefits mediated solely by weight loss (supported by exploratory data from SELECT[21]). Participants were generally well treated with background therapy (better than most real-world evaluations of treatment for peripheral artery disease[36]) that was substantially different from therapies that existed when pivotal studies for exercise, cilostazol, and revascularisation were performed.[37] Despite these aspects, semaglutide significantly improved the primary endpoint and all confirmatory secondary endpoints compared with placebo.

The benefit of semaglutide for maximum walking distance was apparent at 26 weeks and continued to increase through to 52 weeks, without an apparent plateau, which is relevant because semaglutide would be considered for long-term therapy, and so long-term benefits could prove to be greater. This finding is also relevant for safety as people with peripheral artery disease have muscle atrophy and adverse remodelling in the context of chronic ischaemia.[3] In the context of concerns about sarcopenia from weight loss with GLP-1 receptor agonist therapy,[38] improved function on a graded treadmill suggests that no substantial detrimental effects occurred in the muscle in a highly vulnerable population.

The use of the treadmill to measure and quantify the functional outcome of maximum walking distance is

well established and currently approved medical therapies for claudication have been approved on the basis of treadmill endpoints.[28,39,40] Desirable characteristics include the highly controlled environment, high reproducibility, and low variability, thereby improving precision and the ability to isolate a treatment effect. However, there are important limitations, including an inherent training effect,[40] which might attenuate differences between treatment groups and might attenuate the difference and under-represent the true benefit of an intervention in regular practice. A second limitation noted by some is the challenge of translatability of absolute differences in treadmill improvement into everyday function. However, this should be considered in the context of the test performed. Studies using a 6-min walk test in patients with peripheral artery disease generally report baseline distances of 170–400 m (walking speed of 1–2·5 miles per h). The constant load treadmill used in the current study also had participants walking at 2 miles per h but added a 12% grade, which simulates walking up a hill and allowed the participant to walk for as long as they could, rather than for a fixed duration, both of which are relevant to everyday life. By adding the load of a grade, the constant load treadmill investigates walking performance in the context of greater work. In this context, studies have generally found that improvements in performance on a constant-load treadmill reflect a 2–3-times greater change than what would be observed on a flat surface, for example with the 6-min walk test.[41] The median and mean improvements in maximum walking distance seen in our study with semaglutide compared with placebo on a treadmill then are in a context where a 20 m improvement in a 6-min walking test with no incline has been reported as being clinically relevant in people with peripheral artery disease.[31] However, it is crucial to consider that thresholds for meaningful improvement in walking capacity and quality of life depend on context. Previously published thresholds might therefore not apply universally to populations with peripheral artery disease, as they vary with disease severity, functional demands, and social and recreational life expectations. In addition, historical thresholds were often determined based on physician assessment of clinical improvement and not necessarily the patient's voice. In this regard, within-trial anchor-based methods, as used in this study, are believed to be the most reliable approach to determining clinical relevance, and our findings suggest that a significantly greater proportion of patients in the semaglutide group met this clinically meaningful improvement for the primary endpoint (an input that comes from the participants themselves from the target population).

Although the mechanisms of benefit of GLP-1 receptor agonist therapy have not been completely elucidated, studies show important effects on inflammation, vascular function, and broad cardiometabolic benefits.[20–22,42] In our study, there was a significant association between weight loss and functional improvement of a similar magnitude observed in both groups and a mean net decrease of 4·0 kg with semaglutide versus placebo. The modest weight loss with the dose of semaglutide and the weakness of the association suggest that weight change alone does not explain the benefit observed. The role of inflammation in the pathobiology of claudication and the effects of reducing this inflammation were core to the hypothesis that semaglutide could improve function. The observed increase in ankle–brachial index in the current study coupled with previous studies showing microvascular benefits supports a direct vascular benefit of semaglutide, which might be mediated through its anti-inflammatory effects.[43,44] In addition, some component of benefit could be driven by other effects of semaglutide on broad common disease pathways, and outcomes including weight loss, cardiometabolic effects, kidney benefits, major adverse cardiovascular events benefits, and heart failure.[20–22] These collective clinical findings suggest an effective treatment for functional impairment in peripheral artery disease that has other broad benefits, differentiating semaglutide from therapies such as cilostazol and other cardiometabolic drugs with cardiovascular benefit but without beneficial effects on symptoms in peripheral artery disease.[15,18,33]

The results of STRIDE should be considered in the context of other medical therapies for people with claudication. In the USA, two drugs have been approved for claudication, cilostazol and pentoxifylline, both on the basis of treadmill studies. One randomised trial showed that pentoxifylline provided little benefit relative to placebo, so only cilostazol is class 1 indicated in American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[3] The US label notes that cilostazol improved maximum walking distance by 28% to 100% overall, but this was not net of placebo, which also increased maximum walking distance by up to 41%.[45] Relative effects across trials when controlled for placebo are highly variable, ranging from 0% to more than 50%. Because populations differ, absolute changes might be a more useful construct for comparison. In one key randomised trial cited by the ACC/AHA guidelines that compared both pentoxifylline and cilostazol, each relative to placebo on treadmill walking, cilostazol increased mean maximum walking distance by 107 m, which translated into an improvement versus placebo of 43 m.[19] In comparison, in the current trial, semaglutide increased mean maximum walking distance by 87 m, which translated into a similar improvement versus placebo of 39·9 m. European Medicines Agency draft guidelines do not endorse cilostazol and pentoxifylline as strong recommendations, and note, "…drugs like cilostazol…pentoxifylline are suggested to increase walking distance in patients with intermittent claudication without impacting CV [cardiovascular] health. The additional benefit of these drugs alongside

antithrombotics, antihypertensives, and statins remains unknown."[1] In this context, important differentiations for semaglutide in STRIDE compared with cilostazol are that there are clear additional benefits for cardiovascular health for semaglutide, including benefits for major cardiovascular events in people with peripheral artery disease, and that the results of STRIDE are observed in addition to current therapies (such as statins, antithrombotics, and antihypertensives) and, despite this, benefits for maximum walking distance still appear to be similar in absolute measures to cilostazol.

There are several limitations to the STRIDE trial. First, people without type 2 diabetes were not included and thus benefits for people with peripheral artery disease without type 2 diabetes remain unknown. Second, the effect of semaglutide on major adverse limb events in the long term is unclear as STRIDE evaluated short-term exposure with low event numbers. Fewer rescue treatments in STRIDE, coupled with a favourable trend for major adverse limb events in FLOW[22] support future investigation. Third, the statistically significant, albeit modest, improvement in ankle–brachial index supports future mechanistic studies to better elucidate the effect of semaglutide on lower-extremity artery disease. Fourth, recruitment to the trial was slow, partly due to conduct during the COVID-19 pandemic and the required procedures (in-person treadmill), as well as the challenges in finding participants within the specific criteria of the protocol (eg, with class IIa claudication not planned for revascularisation). Fifth, although the trial was double-blinded, as in other trials of GLP-1 receptor agonists, effects of the drug on weight loss and gastrointestinal effects might have been evident to participants, which could impact patient reports of safety outcomes, symptoms, or quality of life but would be unlikely to modify objective measures such as function, clinical outcomes, or ankle–brachial index. Sixth, as described, the magnitude of the effect observed and its clinical relevance should be interpreted in the context of other available therapies and the included anchor measures and should be noted to have occurred over the 52-week duration of treatment. Finally, the demographics of the trial represent those countries that had greatest enrolment. A greater proportion of Black and Hispanic participants was hoped for, and efforts including a larger number of sites, resourcing, and diversity efforts were undertaken. Nonetheless, eligible participants could not be planned for revascularisation, which is highly variable across countries and posed a frequent reason for ineligibility in the USA. However, there has been no substantial heterogeneity or effect modification for any outcome described for semaglutide on the basis of race and none was hypothesised in STRIDE.

In conclusion, semaglutide significantly improved function, symptoms, and health-related quality of life in people with claudication due to peripheral artery disease and type 2 diabetes. The observed effects met prespecified anchor-based methods for a meaningful improvement and were consistent across major subgroups. Safety was consistent with previous studies of semaglutide. These findings support the use of semaglutide in people with peripheral artery disease and type 2 diabetes and suggest that semaglutide should be prioritised among treatments for this population.

Contributors

A-MC and MPB were involved in the concept and design of the trial. MPB, KH, BL, JN, NR, HS, and SV conducted the trial and collected the data. CKR conducted the statistical analysis. All authors had full access to all the data in the study, and analysed and interpreted the data. MPB and CKR accessed and verified the underlying data. The first draft of the manuscript was prepared by MPB. MPB edited all subsequent drafts and incorporated the input of coauthors along with the senior author. The first draft of the manuscript was reviewed by the trial statistician (CKR). All authors, including those employed by the trial sponsor, were involved in the writing or critical revision of the manuscript, interpreted the data, approved the final draft, had final responsibility for the decision to submit the manuscript for publication, and vouch for the accuracy of the data presented and for the fidelity of the study to the protocol.

Declaration of interests

MPB is the Executive Director of the Colorado Prevention Center, a non-profit academic research organisation affiliated with the University of Colorado, that receives or has received research grant or consulting funding between August, 2021 and the present from: Abbott Laboratories, Agios Pharmaceuticals, Alexion Pharma, Alnylam Pharmaceuticals, Amgen, Angionetics, Anthos Therapeutics, Array BioPharma, AstraZeneca and Affiliates, Atentiv, Audentes Therapeutics, Bayer and Affiliates, Bristol Myers Squibb, Cambrian Biopharma, Cardiol Therapeutics, CellResearch, Cleerly, Cook Regentec, CSL Behring, Eidos Therapeutics, EP Trading, Epizon Pharma, Esperion Therapeutics, Everly Well, Exicon Consulting, Faraday Pharmaceuticals, Foresee Pharmaceuticals, Fortress Biotech, HDL Therapeutics, HeartFlow, Hummingbird Bioscience, Insmed, Ionis Pharmaceuticals, Janssen and Affiliates, Kowa Research Institute, Lexicon Pharmaceuticals, Medimmune, Merck and Affiliates, Nectero Medical, Novartis Pharmaceuticals, Novo Nordisk, Osiris Therapeutics, Pfizer, PhaseBio Pharmaceuticals, Prairie Education and Research Cooperative, Prothena Biosciences, Regeneron Pharmaceuticals, Regio Biosciences, Sanofi-Aventis Group, Silence Therapeutics, Smith & Nephew, Stealth BioTherapeutics, VarmX, and Virta Health Corporation. A-MC is an employee of and owns shares in Novo Nordisk. KH has received payment or honoraria, along with travel support, to give a presentation at a workshop organised by LeMaitre. BL has received consulting fees, payment, or honoraria from Amgen, Bayer, Boehringer Ingelheim, Eli Lilly, and Novo Nordisk; has received travel support from Novo Nordisk, with unpaid roles as a National Leader for the Novo Nordisk ESSENCE trial, a National Leader for the Eli Lilly Triumph-Outcome Study, and an advisor for an advisory board for the Austrian Obesity Society. JN has received payment or honoraria from Novo Nordisk; has received travel support from Philips Medical and Abbott; has served on advisory boards for AstraZeneca, Novo Nordisk, and iThera Medical; and has a research grant from the Swedish Heart and Lung Foundation 2021–26, with unpaid roles as President of the Swedish Society for Vascular Surgery and the Swedish Councillor for the European Society for Vascular Surgery 2020–23. CKR is an employee of and owns shares in Novo Nordisk. NR has served on advisory boards for Eli Lilly and Novo Nordisk, and has received research grants from Eli Lilly, Novo Nordisk, and Soma Scan. HS has received payment or honoraria from Amarin, Amgen, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, and Novo Nordisk; has received travel support from Boehringer Ingelheim, Daiichi Sankyo, and Novo Nordisk; and has served on advisory boards for Eli Lilly and Novo Nordisk, with unpaid roles as a board member of the Austrian Diabetes Association. AV is an employee of Novo Nordisk. SV has received payment or honoraria from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Canadian Medical and Surgical Knowledge Translation Research Group, Eli Lilly, HLS Therapeutics, Humber River Health, Janssen, Novartis, Novo Nordisk,

Pfizer, PhaseBio, S & L Solutions Event Management, Sanofi, and Sun Pharmaceuticals; has served on advisory boards for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, HLS Therapeutics, Janssen, Novartis, Novo Nordisk, and Sanofi; and his institution has received research grants from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, HLS Therapeutics, Merck, Novartis, Novo Nordisk, Pfizer, PhaseBio, and Sanofi.

Data sharing

Data will be shared with bona fide researchers who submit a research proposal approved by the independent review board. Individual patient data will be shared in datasets in a de-identified and anonymised format. Data will be made available after research completion and approval of the product and product use in the EU and the USA. Information about data access request proposals can be found at novonordisk-trials.com.

Acknowledgments

We thank the participants and their families, nurses, trial coordinators, and all investigators involved in STRIDE, without whom the trial would not have been possible. We thank Sebastian Thomas for his assistance in the statistical analysis of the data and for his review of the manuscript. Editorial assistance in the form of drafting tables, redrawing figures, and formatting (but no medical writing support) was provided by Carolyn Bowler of Apollo, OPEN Health Communications, and funded by Novo Nordisk, in accordance with Good Publication Practice guidelines (www.ismpp.org/gpp-2022). KH is currently affiliated to Horsens Regional Hospital, Horsens, Denmark.

References

1 Mazzolai L, Teixido-Tura G, Lanzi S, et al. 2024 ESC guidelines for the management of peripheral arterial and aortic diseases. *Eur Heart J* 2024; **45:** 3538–700.
2 Verma S, Leiter LA, Mangla KK, Nielsen NF, Hansen Y, Bonaca MP. Epidemiology and burden of peripheral artery disease in people with type 2 diabetes: a systematic literature review. *Diabetes Ther* 2024; **15:** 1893–961.
3 Gornik HL, Aronow HD, Goodney PP, et al. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS guideline for the management of lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2024; **83:** 2497–604.
4 Fowkes FG, Aboyans V, Fowkes FJ, McDermott MM, Sampson UK, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol* 2017; **14:** 156–70.
5 McDermott MM, Guralnik JM, Tian L, et al. Associations of borderline and low normal ankle-brachial index values with functional decline at 5-year follow-up: the WALCS (Walking and Leg Circulation Study). *J Am Coll Cardiol* 2009; **53:** 1056–62.
6 McDermott MM, Tian L, Zhang D, et al. Discordance of patient-reported outcome measures with objectively assessed walking decline in peripheral artery disease. *J Vasc Surg* 2024; **79:** 893–903.
7 Beckman JA, Duncan MS, Damrauer SM, et al. Microvascular disease, peripheral artery disease, and amputation. *Circulation* 2019; **140:** 449–58.
8 Sieminski DJ, Gardner AW. The relationship between free-living daily physical activity and the severity of peripheral arterial occlusive disease. *Vasc Med* 1997; **2:** 286–91.
9 Tanaka S, Kamiya K, Masuda T, et al. Low ankle brachial index is associated with the magnitude of impaired walking endurance in patients with heart failure. *Int J Cardiol* 2016; **224:** 400–05.
10 Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med* 2020; **382:** 1994–2004.
11 Bonaca MP, Hamburg NM, Creager MA. Stepping into the future of care for patients with peripheral artery disease. *Circulation* 2024; **149:** 1862–64.
12 Li Q, Birmpili P, Atkins E, et al. Illness trajectories after revascularization in patients with peripheral artery disease: a unified approach to understanding the risk of major amputation and death. *Circulation* 2024; **150:** 261–71.
13 Thanigaimani S, Phie J, Sharma C, et al. Network meta-analysis comparing the outcomes of treatments for intermittent claudication tested in randomized controlled trials. *J Am Heart Assoc* 2021; **10:** e019672.
14 Divakaran S, Carroll BJ, Chen S, Shen C, Bonaca MP, Secemsky EA. Supervised exercise therapy for symptomatic peripheral artery disease among Medicare beneficiaries between 2017 and 2018: participation rates and outcomes. *Circ Cardiovasc Qual Outcomes* 2021; **14:** e007953.
15 Beebe HG, Dawson DL, Cutler BS, et al. A new pharmacological treatment for intermittent claudication: results of a randomized, multicenter trial. *Arch Intern Med* 1999; **159:** 2041–50.
16 Golledge J. Pathology, progression, and emerging treatments of peripheral artery disease-related limb ischemia. *Clin Ther* 2023; **45:** 1077–86.
17 Alameddine D, Damara FA, Pinto Rodriguez P, et al. The use and impact of cilostazol on patients undergoing endovascular peripheral interventions. *Ann Vasc Surg* 2024; **103:** 47–57.
18 Dawson DL, Cutler BS, Meissner MH, Strandness DE Jr. Cilostazol has beneficial effects in treatment of intermittent claudication: results from a multicenter, randomized, prospective, double-blind trial. *Circulation* 1998; **98:** 678–86.
19 Dawson DL. Comparative effects of cilostazol and other therapies for intermittent claudication. *Am J Cardiol* 2001; **87:** 19D–27.
20 Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N Engl J Med* 2023; **389:** 1069–84.
21 Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 2023; **389:** 2221–32.
22 Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med* 2024; **391:** 109–21.
23 Dhatariya K, Bain SC, Buse JB, et al. The impact of liraglutide on diabetes-related foot ulceration and associated complications in patients with type 2 diabetes at high risk for cardiovascular events: results from the LEADER trial. *Diabetes Care* 2018; **41:** 2229–35.
24 Nordanstig J, Behrendt CA, Baumgartner I, et al. Editor's Choice—European Society for Vascular Surgery (ESVS) 2024 clinical practice guidelines on the management of asymptomatic lower limb peripheral arterial disease and intermittent claudication. *Eur J Vasc Endovasc Surg* 2024; **67:** 9–96.
25 Brevetti G, Giugliano G, Brevetti L, Hiatt WR. Inflammation in peripheral artery disease. *Circulation* 2010; **122:** 1862–75.
26 Bonaca MP, Catarig AM, Hansen Y, et al. Design and baseline characteristics of the STRIDE trial: evaluating semaglutide in people with symptomatic peripheral artery disease and type 2 diabetes. *Eur Heart J Cardiovasc Pharmacother* 2025; **10:** 728–37.
27 Aboyans V, Criqui MH, Abraham P, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. *Circulation* 2012; **126:** 2890–909.
28 Degischer S, Labs KH, Aschwanden M, Tschoepl M, Jaeger KA. Reproducibility of constant-load treadmill testing with various treadmill protocols and predictability of treadmill test results in patients with intermittent claudication. *J Vasc Surg* 2002; **36:** 83–88.
29 Morgan MB, Crayford T, Murrin B, Fraser SC. Developing the Vascular Quality of Life Questionnaire: a new disease-specific quality of life measure for use in lower limb ischemia. *J Vasc Surg* 2001; **33:** 679–87.
30 Nordanstig J, Wann-Hansson C, Karlsson J, Lundström M, Pettersson M, Morgan MB. Vascular Quality of Life Questionnaire-6 facilitates health-related quality of life assessment in peripheral arterial disease. *J Vasc Surg* 2014; **59:** 700–07.
31 Tew G, Copeland R, Le Faucheur A, Gernigon M, Nawaz S, Abraham P. Feasibility and validity of self-reported walking capacity in patients with intermittent claudication. *J Vasc Surg* 2013; **57:** 1227–34.
32 McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA* 2004; **292:** 453–61.
33 Bonaca MP, Hess C, Beckman JA. Telmisartan and walking performance in peripheral artery disease. *JAMA* 2022; **328:** 1302–03.
34 Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med* 2000; **109:** 523–30.
35 Heffron SP, Dwivedi A, Rockman CB, et al. Body mass index and peripheral artery disease. *Atherosclerosis* 2020; **292:** 31–36.

36 Hess CN, Cannon CP, Beckman JA, et al. Effectiveness of blood lipid management in patients with peripheral artery disease. *J Am Coll Cardiol* 2021; **77:** 3016–27.

37 Farber A, Menard MT, Bonaca MP, et al. BEST-CLI International Collaborative: planning a better future for patients with chronic limb-threatening ischaemia globally. *Br J Surg* 2024; **111:** znad413.

38 Neeland IJ, Linge J, Birkenfeld AL. Changes in lean body mass with glucagon-like peptide-1-based therapies and mitigation strategies. *Diabetes Obes Metab* 2024; **26:** 16–27.

39 Hiatt WR, Hirsch AT, Regensteiner JG, Brass EP. Clinical trials for claudication. Assessment of exercise performance, functional status, and clinical end points. *Circulation* 1995; **92:** 614–21.

40 Hiatt WR, Rogers RK, Brass EP. The treadmill is a better functional test than the 6-minute walk test in therapeutic trials of patients with peripheral artery disease. *Circulation* 2014; **130:** 69–78.

41 Frans FA, Zagers MB, Jens S, Bipat S, Reekers JA, Koelemay MJ. The relationship of walking distances estimated by the patient, on the corridor and on a treadmill, and the Walking Impairment Questionnaire in intermittent claudication. *J Vasc Surg* 2013; **57:** 720–727.

42 Mosenzon O, Capehorn MS, De Remigis A, Rasmussen S, Weimers P, Rosenstock J. Impact of semaglutide on high-sensitivity C-reactive protein: exploratory patient-level analyses of SUSTAIN and PIONEER randomized clinical trials. *Cardiovasc Diabetol* 2022; **21:** 172.

43 Caruso P, Maiorino MI, Longo M, et al. Liraglutide for lower limb perfusion in people with type 2 diabetes and peripheral artery disease: the STARDUST randomized clinical trial. *JAMA Netw Open* 2024; **7:** e241545.

44 Russell KS, Yates DP, Kramer CM, et al. A randomized, placebo-controlled trial of canakinumab in patients with peripheral artery disease. *Vasc Med* 2019; **24:** 414–21.

45 US Food and Drug Administration. Cilostazol prescribing information. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=a6292311-9cb2-49ff-b8bf-12e2dbd196cd&type=display (accessed March 20, 2025).