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Benefit of Semaglutide in Symptomatic Peripheral Artery Disease by Baseline Type 2 Diabetes Characteristics: Insights From STRIDE, a Randomized, Placebo-Controlled, Double-Blind Trial

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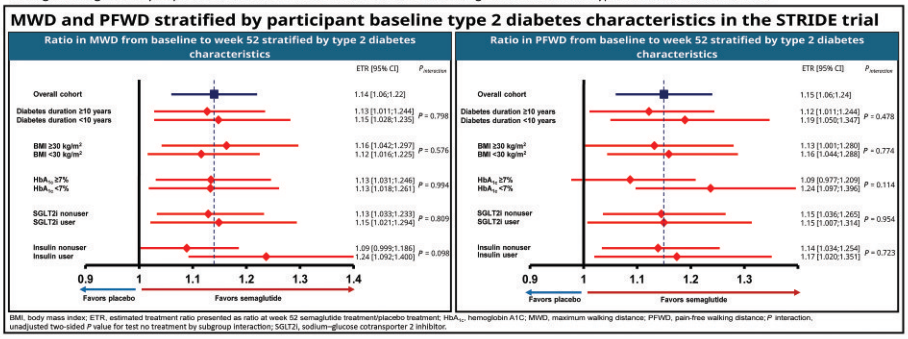
Background:
People living with type 2 diabetes commonly develop peripheral artery disease (PAD), which causes functional impairment, reduced quality of life, and increased morbidity and mortality. The STRIDE trial demonstrated that once-weekly semaglutide 1.0 mg significantly improved functional outcomes, symptoms, and quality of life in people with symptomatic PAD and type 2 diabetes. In the present study, we investigated whether the benefit of semaglutide on functional outcomes in this population was consistent when considering clinically important type 2 diabetes–related characteristics.

Methodology:
- The primary end point, ratio to baseline at week 52 in maximum walking distance (MWD), was measured on a constant load treadmill, as was a selected confirmatory secondary end point, ratio to baseline at week 52 in pain-free walking distance (PFWD).
- These two end points were analyzed by type 2 diabetes duration, body mass index (BMI), HbA_{1c} %, and concomitant SGLT2i or insulin use.
- A mixed model for repeated measurements was used, incorporating treatment, region, and subgroup as fixed factors, along with the treatment-by-subgroup interaction. Baseline values were used as covariates, all nested within each visit.

Results:
Semaglutide significantly improved MWD and PFWD with a consistent benefit regardless of baseline type 2 diabetes characteristics.

MWD and PFWD stratified by participant baseline type 2 diabetes characteristics in the STRIDE trial



BMI, body mass index; ETR, estimated treatment ratio presented as ratio at week 52 semaglutide treatment/placebo treatment; HbA_{1c}, hemoglobin A1C; MWD, maximum walking distance; PFWD, pain-free walking distance; *P* interaction, unadjusted two-sided *P* value for test no treatment by subgroup interaction; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Conclusion:
These findings support the efficacy of semaglutide in patients with symptomatic PAD across the spectrum of type 2 diabetes including participants without obesity and those with HbA_{1c} <7%. The consistent benefits of semaglutide—even in individuals without obesity and those with well-controlled glucose—suggest its effects extend beyond weight loss and glycemic control. These findings support semaglutide's use in a broad range of individuals with symptomatic PAD and type 2 diabetes, highlighting its potential role in comprehensive vascular and metabolic care.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  We aimed to investigate whether the benefits of semaglutide for functional outcomes in people living with symptomatic peripheral artery disease (PAD) and type 2 diabetes were consistent across type 2 diabetes characteristics.

- **What specific questions did we aim to answer?**
  We examined whether semaglutide's beneficial effect on functional outcomes in this population was consistent regardless of duration of type 2 diabetes, degree of glycemic control, and presence of obesity, and whether they were using sodium–glucose cotransporter 2 inhibitors or insulin.

- **What did we find?**
  The beneficial effects of semaglutide on the functional outcomes in people living with PAD were consistent across the spectrum of type 2 diabetes.

- **What are the implications of our findings?**
  These findings support semaglutide's use in a broad range of individuals with PAD and type 2 diabetes.

Benefit of Semaglutide in Symptomatic Peripheral Artery Disease by Baseline Type 2 Diabetes Characteristics: Insights From STRIDE, a Randomized, Placebo-Controlled, Double-Blind Trial

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OBJECTIVE

The Semaglutide and Walking Capacity in People with Symptomatic Peripheral Artery Disease and Type 2 Diabetes (STRIDE) trial (NCT04560998) showed that once-weekly subcutaneous semaglutide 1.0 mg significantly improved functional outcomes, symptoms, and quality of life in individuals with symptomatic peripheral artery disease (PAD) and type 2 diabetes. Whether these benefits are consistent across diabetes-related characteristics remains unclear.

RESEARCH DESIGN AND METHODS

The primary outcome was the ratio to baseline (ETR) in maximum walking distance (MWD), with pain-free walking distance (PFWD) as a key secondary end point. Both were measured at 52 weeks using a constant load treadmill. Subgroup analyses were performed by diabetes duration, BMI, HbA_{1c}, and diabetes medications. A mixed model for repeated measurements was used, incorporating treatment, region, and subgroup as fixed factors, and baseline value as covariate, along with the treatment-by-subgroup interaction.

RESULTS

Among 792 participants (median diabetes duration 12.2 years, HbA_{1c} 7.1%, and BMI 28.7 kg/m^2), 35.1% used sodium–glucose cotransporter 2 inhibitors and 31.7% used insulin. Semaglutide significantly improved MWD regardless of diabetes duration (ETR of 1.15 vs. 1.13 for <10 vs. ≥10 years, $P = 0.80$), BMI (1.12 vs. 1.16 for <30 vs. ≥30 kg/m^2, $P = 0.58$), HbA_{1c} (1.13 for <7% and ≥7%, $P = 0.99$), or medication use. Semaglutide also improved PFWD across subgroups ($P > 0.1$ for all interactions). BMI reduction correlated weakly with MWD improvements and was more pronounced in the control individuals with higher baseline BMI. Safety outcomes were consistent across subgroups.

CONCLUSIONS

Semaglutide improved walking function in people with PAD and type 2 diabetes, including individuals without obesity and those with well-controlled HbA_{1c}. Benefits were consistent across BMI and HbA_{1c} categories, supporting effectiveness beyond weight or glycemic changes.

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Peripheral artery disease (PAD) is a prevalent and early manifestation of cardiovascular disease in individuals with type 2 diabetes (1–4). Lower-extremity PAD is characterized by atherosclerosis of the arteries, leading to impaired perfusion, reduced functional capacity, and an increased risk of major adverse limb events, including amputation. In type 2 diabetes, PAD is associated with greater functional impairment and higher rates of adverse limb events and amputation, largely due to the increased prevalence of below-the-knee small vessel disease and coexisting microvascular complications (5–7).

Functional impairment is often underrecognized in early stages of disease but has significant impact on quality of life (4,8). Early diagnosis presents an important opportunity to improve functional status, enhance quality of life, and potentially alter disease progression—ultimately reducing the need for revascularization, and the risk of the risk of limb-threatening complications (9).

To promote earlier detection, current American Diabetes Association guidelines recommend screening—or at least considering screening—for asymptomatic PAD in people with diabetes who are aged ≥65 years, have had diabetes for ≥10 years, or have known microvascular disease, diabetes-related end-organ damage, or any foot complications (10). Despite these recommendations, testing for PAD is underused for multiple reasons but, in part, because of the paucity of effective therapies to improve function and symptoms in patients with early-stage disease.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) were originally developed to improve glucose metabolism but have since been shown to provide multiple cardiometabolic, kidney, and cardiovascular benefits, including blood pressure reduction, improved lipid profiles, reduced inflammation, and weight loss (11–16). Notably, a previous post hoc analysis reported a reduced risk of amputation in people with type 2 diabetes treated with liraglutide (14). The Semaglutide and Walking Capacity in People with Symptomatic Peripheral Artery Disease and Type 2 Diabetes (STRIDE) trial (NCT04560998) reported significant benefits of semaglutide, a GLP-1 RA, in the functional capacity (as measured by constant load treadmill [CLT]) in individuals with symptomatic PAD and type 2 diabetes (17,18). These results have prompted questions of both mechanisms of action and whether the benefits are consistent in patients with varying metabolic profiles, including baseline glycemic control, body weight, and duration of diabetes.

In this post hoc analysis of the STRIDE trial, we examine the consistency of semaglutide's effect on functional outcome across subgroups defined by baseline diabetes characteristics and body weight.

RESEARCH DESIGN AND METHODS

Trial Design and Participants

The full trial design for the STRIDE trial has been published previously (17). All study activities were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The trial protocol and all related documents were approved by the relevant institutional review boards or independent ethics committees at each participating site prior to study initiation. All participants provided written informed consent before undergoing any study-specific procedures. Briefly, STRIDE was a randomized, double-blind, placebo-controlled trial comparing once-weekly subcutaneous semaglutide 1.0 mg to matched placebo in participants with symptomatic PAD (Fontaine classification IIa) and type 2 diabetes. The trial was multinational, with recruitment conducted in 112 sites across 20 countries (for further details, please see Supplementary Material). Key inclusion and exclusion criteria were being ≥18 years old, being on stable medications, not having another non–PAD-related condition that limits functional capacity (e.g., severe cardiovascular, neurologic, or other disease), and neither having a history of a recent cardiovascular event or arterial revascularization (within 180 days) nor a planned revascularization. In addition, participants had an ankle-brachial index of ≤0.90 or a toe-brachial index of ≤0.70. The primary end point was ratio to baseline at week 52 in maximum walking distance (MWD) on a CLT with a fixed speed of 3.2 kph (2 mph) and fixed inclination of 12%. Confirmatory secondary end points included change in MWD on a CLT test at week 57, change in pain-free walking distance (PFWD) on a CLT test at week 52, and change in patient-reported PAD-specific vascular quality of life score from baseline to week 52.

Post Hoc Analysis and Statistical Approach

The primary outcome and a selected confirmatory end point in STRIDE, ratio to baseline in MWD and PFWD at week 52, respectively, were analyzed by diabetes duration (≥10 vs. <10 years), obesity status as measured by BMI (≥30 vs. <30 kg/m^2), glycemic control as measured by HbA_{1c} percentage (≥7% vs. <7%), and concomitant type 2 diabetes medications (sodium–glucose cotransporter 2 inhibitors [SGLT2i] or insulin). Subgroup definitions were selected based on clinically meaningful thresholds: BMI ≥30 kg/m^2 defined obesity, HbA_{1c} ≥7% reflected standard glycemic targets, and diabetes duration ≥10 years distinguished early from more advanced disease stages. Analyses were performed on all randomized participants using the trial product estimand (hypothetical strategy) based on the on-treatment without rescue therapy observation period. The clinical question of interest addressed by this estimand was to evaluate the treatment effect in all randomized participants who had remained on the randomized treatment and had not initiated rescue therapy (initiation or dose adjustment of cilostazol or pentoxifylline, or lower-limb revascularization procedures). Discontinuation of study medication or initiation of rescue therapy did not result in exclusion from the analysis population; only the data collected after these events were excluded from the analysis. A mixed model for repeated measurements was used, incorporating treatment, region, and subgroup as fixed factors, along with the treatment-by-subgroup interaction. Baseline values were used as covariates, all nested within each visit. The treatment-by-subgroup interaction at week 52 visit was tested using a two-sided α-level of 5%. No multiplicity adjustments were performed, as the tests were exploratory. End points were measured as ratio to baseline and were described by estimated treatment ratio (ETR), a ratio of the estimated geometric means of end points in semaglutide versus placebo groups, along with 95% CI. The unadjusted interaction *P* value was reported for each of the subgroups in the corresponding forest plots. Association between change from baseline in functional capacity end points (MWD and PFWD) and change from baseline in body weight and HbA_{1c} at week 52 were evaluated with Spearman rank correlation (*r*) test.

Data and Resource Availability

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 data sets in a deidentified and anonymized format. Data will be made available after research completion and approval of the product and product use in the European Union and the U.S.

RESULTS

Summary of Baseline Type 2 Diabetes Characteristics

From 1 October 2020 to 12 July 2024, a total of 792 participants were randomized with a full trial participant disposition provided in Bonaca et al. (18).

Among the randomized participants, the median baseline characteristics were as follows: diabetes duration of 12.2 years, HbA_{1c} of 7.1%, and BMI of 28.7 kg/m^2. Duration of diabetes was <10 years in 39% of participants, 44% had an HbA_{1c} of <7%, and most (59%) had BMI <30 kg/m^2. Among this cohort, 35.1% were taking SGLT2i, and 31.7% were taking insulin. The baseline MWD and PFWD in each subgroup have been summarized in Table 1.

After randomization, 57 (14.4%) and 44 (11.2%) participants discontinued study medication in the semaglutide and placebo groups, respectively. Additionally, 10 (2.5%) and 17 (4.3%) participants had rescue therapy in the semaglutide and placebo groups, respectively. As per the prespecified analysis plan, data collected after these events were censored.

Effect of Type 2 Diabetes Characteristics on MWD on CLT Among Participants in the STRIDE Trial

Consistent with prior findings in the overall cohort (18), once-weekly subcutaneous semaglutide 1.0 mg significantly improved MWD across subgroups. Figure 1*A* summarizes the estimated geometric mean ratio to baseline in MWD, while Fig. 1*B* shows the mean (±SE) change in MWD in meters at week 52, comparing semaglutide and placebo within each subgroup.

Overall, semaglutide significantly increased MWD with an ETR of 1.14 (95% CI: 1.06–1.22; P = 0.0005) compared with placebo at week 52 among participants who adhered to treatment without initiation of rescue therapy (Fig. 2*A*). This positive effect on MWD was consistent across subgroups. Semaglutide improved MWD, with an ETR of 1.12 (95% CI: 1.02–1.26) for BMI <30 and 1.16 (95% CI: 1.04–1.23) in those with BMI ≥30 (P = 0.58 for interaction), corresponding to a placebo-subtracted increase of 22.5 and 62.9 m, respectively. Similarly, semaglutide significantly increased MWD regardless of baseline HbA_{1c}, with ETRs of 1.13 (95% CI: 1.02–1.26) and 1.13 (95% CI: 1.03–1.25) for HbA_{1c} <7% and ≥7%, respectively (P = 0.99 for interaction), translating to gains of 27.4 and 48.5 m, respectively. Consistent effects were also observed across subgroups defined by diabetes duration and background diabetes therapies, including insulin and SGLT2i use (Fig. 2*A*).

Effect of Type 2 Diabetes Characteristics on the Pain-Free Treadmill Walking Distance of Participants in the STRIDE Trial

Similar to MWD, PFWD was significantly improved by semaglutide treatment compared with placebo at week 52 (20). Overall, semaglutide increased PFWD, with an ETR of 1.15 (95% CI: 1.06–1.24; P = 0.0007) among participants who adhered to treatment without initiation of rescue (Fig. 2*B*). When stratified by the type 2 diabetes characteristics, semaglutide consistently improved PFWD across all subgroups. The estimated geometric mean ratio to baseline of PFWD and changes in MWD in meters at week 52 in the semaglutide and placebo groups for each type 2 characteristic is summarized in Fig. 1*C* and *D*, respectively. There was no statistically significant difference in treatment effect for each subgroup (Fig. 2*B*). Semaglutide also enhanced PFWD across subgroups. Among participants with BMI <30, the ETR was 1.10 (95% CI: 1.04–1.29), while those with BMI ≥30 had an ETR of 1.13 (95% CI: 1.00–1.28; P = 0.77 for interaction), reflecting placebo-adjusted improvements of 25.5 and 34.1 m, respectively. In analyses stratified by baseline HbA_{1c}, semaglutide was associated with an ETR of 1.24 (95% CI: 1.01–1.40) for HbA_{1c} <7% and 1.09 (95% CI: 0.98–1.21) for HbA_{1c} ≥7% (P = 0.11 for interaction), corresponding to placebo-subtracted increases of 47.4 and 16.3 m. These findings were consistent across other clinically relevant subgroups, including those defined by diabetes duration and concomitant therapies such as insulin and SGLT2i (Fig. 2*B*).

Effect of Semaglutide on Body Weight and HbA_{1c} in Relation to MWD

After 52 weeks of treatment, the estimated treatment difference in body weight change from baseline between semaglutide and placebo was −4.09 kg (95% CI:

Table 1—Baseline MWD and PFWD stratified by type 2 diabetes characteristics

	MWD (m)		PFWD (m)	
	Semaglutide group	Placebo group	Semaglutide group	Placebo group
Diabetes duration ≥10 years	236, 196.2 [0.6]	243, 183.0 [0.5]	236, 118.8 [0.7]	243, 113.6 [0.6]
Diabetes duration <10 years	159, 185.9 [0.6]	153, 193.8 [0.5]	159, 114.7 [0.7]	153, 118.1 [0.7]
BMI ≥30 kg/m^2	165, 193.5 [0.6]	158, 177.7 [0.5]	165, 122.7 [0.7]	158, 113.1 [0.6]
BMI <30 kg/m^2	230, 190.9 [0.6]	238, 196.8 [0.6]	230, 113.3 [0.6]	238, 116.8 [0.6]
HbA_{1c} ≥7%	217, 185.3 [0.6]	224, 188.4 [0.6]	217, 112.7 [0.7]	224, 118.4 [0.6]
HbA_{1c} <7%	178, 200.5 [0.6]	171, 190.0 [0.6]	178, 122.7 [0.6]	171, 111.5 [0.6]
SGLT2i nonuser	249, 190.2 [0.6]	264, 185.7 [0.5]	249, 117.3 [0.6]	264, 112.6 [0.6]
SGLT2i user	146, 195.1 [0.6]	132, 195.6 [0.6]	146, 116.8 [0.7]	132, 120.9 [0.7]
Insulin nonuser	278, 191.4 [0.6]	263, 188.7 [0.6]	278, 116.1 [0.7]	263, 111.3 [0.6]
Insulin user	117, 193.4 [0.6]	133, 189.3 [0.5]	117, 119.5 [0.7]	133, 123.7 [0.7]

Data are presented as number of participants with a baseline measurement, geometric mean [coefficient of variation].

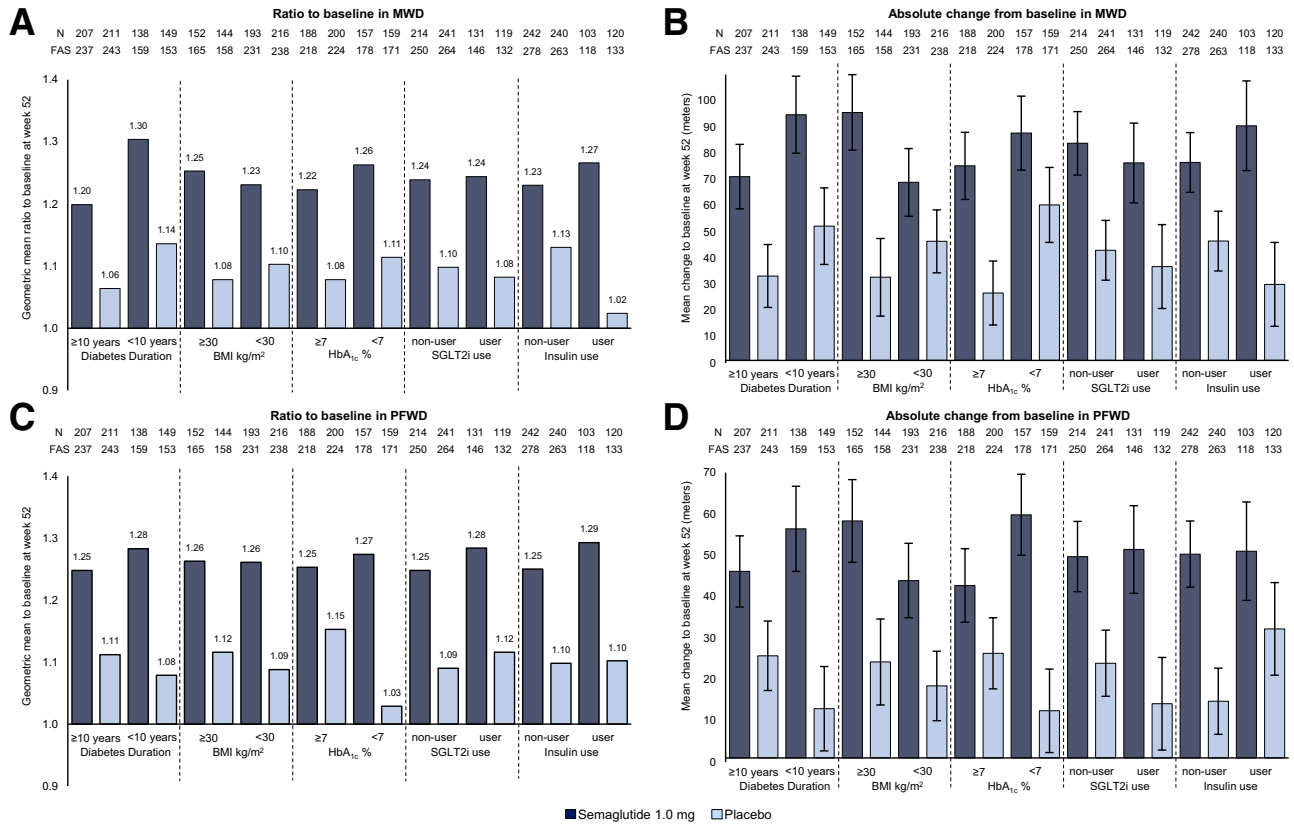

Figure 1—Changes in MWD and PFWD from baseline to week 52 among STRIDE participants. *A*: Geometric mean ratio to baseline in MWD by subgroup. *B*: Mean (±SE) change in MWD from baseline to week 52. *C*: Geometric mean ratio to baseline in PFWD by subgroup. *D*: Mean (±SE) change in PFWD from baseline to week 52 by subgroup. FAS, number of participants in full analysis set; N, number of participants contributing to the analysis (defined as number of participants with a nonmissing baseline value and nonmissing factors and having at least one postbaseline measurement of the end point).

−4.79 to −3.40; $P < 0.0001$) in the overall cohort. Among participants with BMI <30 kg/m^2, body weight reduced by −4.47 kg with semaglutide versus −0.89 kg with placebo, corresponding to a mean reduction of −3.58 kg (95% CI: −4.49 to −2.67). In participants with BMI ≥30 kg/m^2, mean body weight reductions were −6.08 kg vs. −1.44 kg, respectively, corresponding to an estimated treatment difference of −4.64 kg (95% CI: −5.72 to −3.56).

The estimated treatment difference in HbA_{1c} between semaglutide and placebo at week 52 was −0.99% (95% CI: −1.14 to −0.84; $P < 0.0001$) in the overall cohort. Among participants with baseline HbA_{1c} <7%, mean HbA_{1c} changes were −0.63% with semaglutide versus −0.08% with placebo, corresponding to an estimated treatment difference of −0.56% (95% CI: −0.78 to −0.33). In participants with baseline HbA_{1c} ≥7%, mean changes were −0.96% vs. 0.37%, respectively, with an estimated treatment difference of −1.33% (95% CI: −1.53 to −1.14).

In an exploratory analysis, we investigated whether the positive effects of semaglutide on functional capacity were related to weight loss or glycemic improvement. Specifically, we assessed the correlation between changes in MWD from baseline to week 52 and changes in BMI and HbA_{1c}.

In the overall cohort, changes in MWD and BMI were weakly correlated in both the semaglutide ($r = −0.126$; $P = 0.031$) and placebo ($r = −0.141$; $P = 0.014$) groups. No significant correlation was observed between changes in MWD and HbA_{1c} in either the semaglutide ($r = −0.041$; $P = 0.49$) or placebo ($r = 0.067$; $P = 0.25$) groups. These findings suggest that the benefits of semaglutide for functional capacity may extend beyond its effects on weight loss and glycemic control.

To further explore this, we examined the associations within subgroups stratified by baseline BMI and HbA_{1c}, where larger changes were anticipated in participants with higher baseline values. In the BMI <30 kg/m^2 subgroup, no significant correlation was observed between changes in MWD and BMI in either treatment group ($r = −0.085$, $P = 0.282$ and $r = −0.014$, $P = 0.849$ for semaglutide and placebo groups, respectively). In participants with BMI ≥30 kg/m^2, no significant correlation was found in the semaglutide group ($r = −0.134$; $P = 0.126$), whereas a modest correlation was observed in the placebo group ($r = −0.326$; $P < 0.0001$) (Supplementary Fig. 1).

Similarly, changes in MWD were not significantly correlated with changes in HbA_{1c} within either the HbA_{1c} <7% subgroup ($r = −0.159$, $P = 0.071$ and $r = 0.059$, $P = 0.516$ for semaglutide and placebo groups, respectively) or the HbA_{1c} ≥7% subgroup ($r = −0.039$, $P = 0.624$ and $r = 0.066$, $P = 0.389$ for semaglutide and placebo groups, respectively) (Supplementary Fig. 1).

Safety

The rates of adverse events, serious adverse events, gastrointestinal (GI) disorders, and hypoglycemic events during the on-treatment observation period were generally comparable across subgroups.

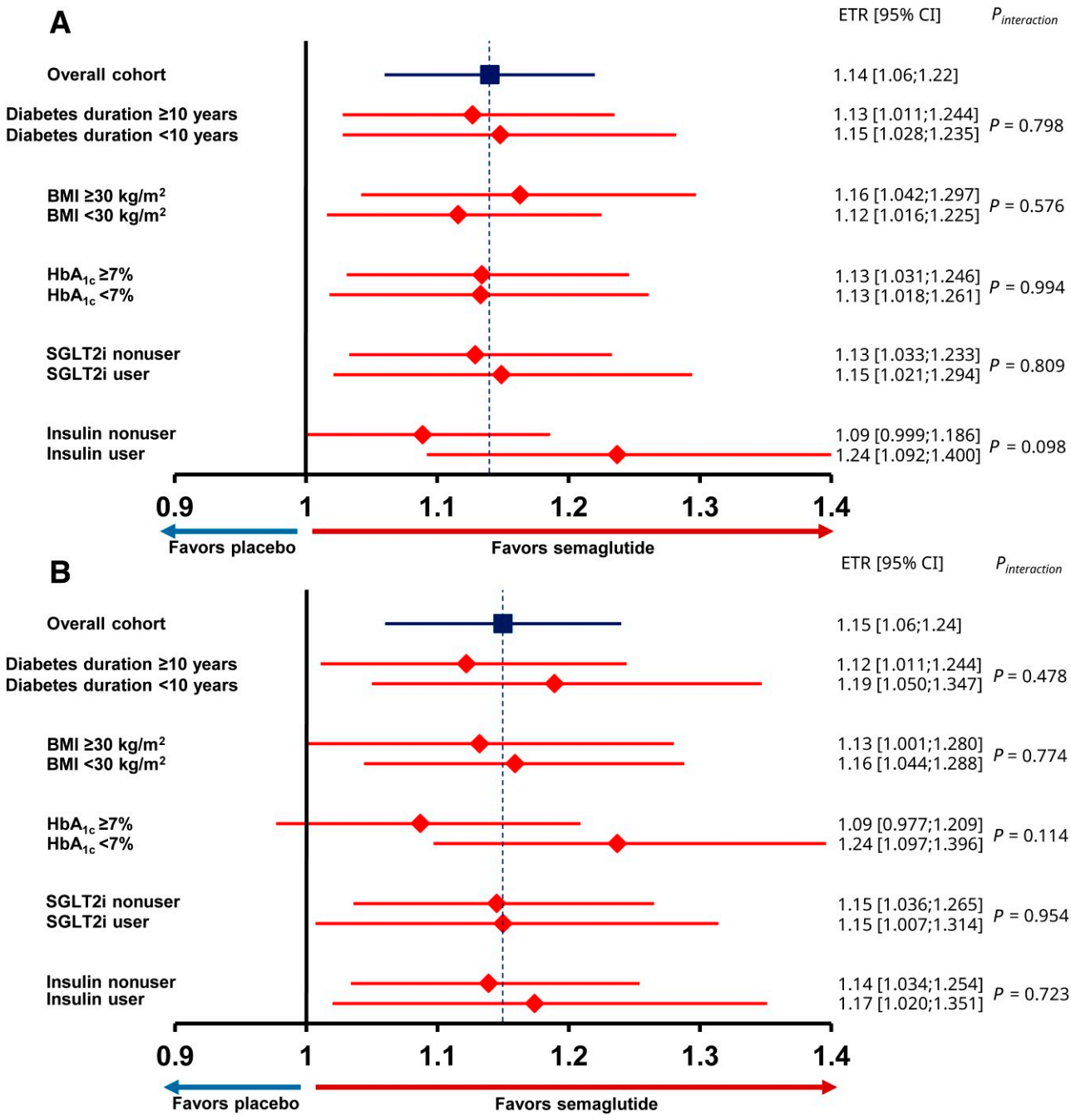

Figure 2—ETR for STRIDE participants. *A*: MWD stratified by participant type 2 diabetes characteristics in the STRIDE trial. *B*: PFWD stratified by participant type 2 diabetes characteristics in the STRIDE trial. ETR is presented as ratio of estimated geometric mean ratio to baseline at week 52 of semaglutide 1.0 mg vs. placebo. The solid line at 1 indicates no treatment effect, and the dashed line indicates the main treatment effect estimate of MWD based on the overall cohort of participants who adhered to treatment without initiation of rescue therapy. *P* interaction denotes unadjusted two-sided *P* value for test of no treatment by subgroup interaction.

A higher percentage of participants in the BMI <30 kg/m^2 subgroup experienced GI disorders (25.1% with semaglutide vs. 4.6% with placebo) compared with the BMI ≥30 kg/m^2 subgroup (12.7% with semaglutide vs. 8.2% with placebo). Most GI events were mild, and the rate of drug discontinuation was similar between subgroups. Rates of hypoglycemia were low and similar between the HbA_{1c} ≥7% and <7% subgroups (Supplementary Table 2).

CONCLUSIONS

The current analysis provides novel insights into the effects of semaglutide in patients with symptomatic peripheral artery disease and their consistency across characteristics of diabetes severity and body weight. It was observed that semaglutide significantly improved both MWD and PFWD by week 52, regardless of diabetes duration, BMI, HbA_{1c} levels, or use of SGLT2i or insulin.

These results have several important implications. First, they suggest that clinicians should not restrict the use of this

therapy to patients with PAD and type 2 diabetes who have elevated HbA_{1c} or high BMI, or who are not already on SGLT2i. Rather, the benefits appear broadly applicable across a range of metabolic profiles. Second, the findings support the hypothesis that the mechanisms underlying the observed improvements in functional capacity are likely independent of glycemic control and weight loss.

PAD significantly impairs mobility and quality of life, and pharmacological treatment options remain limited (4). Our results suggest that semaglutide improves functional capacity across a diverse range of patients, including those with well-controlled glycemia (HbA_{1c} <7%) and a BMI <30 kg/m^2—groups that are often underrepresented in diabetes trials.

Although higher HbA_{1c} levels and obesity are typically linked to greater functional decline in PAD (19,20), semaglutide's effects were consistent across subgroups, suggesting mechanisms beyond glucose lowering and weight loss. Furthermore, when the entire cohort showed modest to no correlation between change in MWD and change in BMI and HbA_{1c}, we considered whether this could be explained by the cohort's characteristics—specifically, 59% had a BMI <30 kg/m^2 and 44% had an HbA_{1c} <7%, where substantial changes in BMI or HbA_{1c} would be less expected. Therefore, we thought it was important to conduct an exploratory analysis to determine whether, among participants with obesity (BMI ≥30 kg/m^2) or poor glycemic control (HbA_{1c} ≥7%), a correlation would emerge. The continued lack of correlation in these subgroups further supports the hypothesis that semaglutide's benefits for walking distance are independent of weight or glucose reductions.

GLP-1 receptor activation improves endothelial function, reduces arterial stiffness, enhances microvascular perfusion, and has anti-inflammatory properties, all of which may contribute to improved walking capacity (21). The consistency in outcomes observed here may suggest a new role for semaglutide within comprehensive vascular and metabolic care strategies for individuals with PAD and type 2 diabetes, offering improvement in functional capacity regardless of baseline BMI and HbA_{1c}, on top of the established cardiovascular and chronic kidney disease benefits (12,22). Beyond enhancing functional capacity, semaglutide's established cardiovascular benefits support its potential as a dual purpose, foundational therapy addressing both functional limitations and cardiovascular risks.

Of note, more than one-third of the cohort were taking SGLT2i. The benefits of semaglutide were independent of SGLT2i use. Similarly, semaglutide's effects were consistent regardless of insulin use—a marker of longer diabetes duration—further supporting its broad applicability in the management of PAD.

The safety analysis showed that the rate of adverse events and drug discontinuation were comparable across subgroups, providing reassurance regarding the use of semaglutide in people with BMI <30 kg/m^2 or HbA_{1c} <7%.

While this study provides valuable insights, some limitations should be acknowledged. The STRIDE trial was not designed to assess semaglutide's interaction with diabetes characteristics, making this a secondary, exploratory analysis. The analyses may be underpowered to detect interaction effects in smaller subgroups, such as insulin users; thus, nonsignificant interaction *P* values should not be interpreted as definitive evidence of uniform treatment effects. Subgroup-specific effect estimates and CIs offer more meaningful insights and should be interpreted with caution. Furthermore, given the exploratory nature of the subgroup analyses, no formal adjustment for multiple comparisons was applied, which increases the risk of type I error. Moreover, these findings are hypothesis-generating and warrant confirmation in future adequately powered studies.

Future research could explore mechanisms beyond glucose lowering and weight reduction that contribute to semaglutide's effects on functional capacity, and dedicated mechanism-of-action trials would provide valuable insight into this therapy's effect on PAD. Additionally, studies should be designed to assess long-term outcomes, including PAD progression and amputation-free survival, and should evaluate the potential benefits of semaglutide in combination with other PAD interventions, such as revascularization and supervised exercise therapy.

Conclusion

This study confirms that once-weekly subcutaneous semaglutide 1.0 mg significantly improves both MWD and PFWD in people with symptomatic PAD and type 2 diabetes, regardless of selected diabetes-related characteristics. These findings support semaglutide's consistent efficacy across the spectrum of type 2 diabetes, including in patients without obesity and those with well-controlled glycemia. Given the lack of effective pharmacological options for PAD, semaglutide represents a promising treatment to enhance mobility and quality of life in this high-risk population.

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