Effects of semaglutide on functional capacity in patients with type 2 diabetes and peripheral arterial disease: rationale and design of the STRIDE trial

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Background/Introduction: Lower extremity peripheral arterial disease (PAD) is a severe form of atherosclerotic cardiovascular (CV) disease. The classical symptom is intermittent claudication (IC), associated with limited walking ability and poor health-related quality of life (QoL). Type 2 diabetes (T2D) is one of the leading causes of PAD; ∼30% of patients with PAD have T2D. While anti-atherosclerotic drugs and lifestyle changes are recommended, there are no effective drugs to specifically improve functional outcomes in PAD and T2D. Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA) approved as an adjunct to diet and exercise for glycaemic control in patients with T2D. In the T2D SUSTAIN clinical trial programme, once-weekly (OW) subcutaneous semaglutide 0.5 and 1.0 mg was superior for glycaemic control and weight loss vs placebo and a range of approved antidiabetic drugs. In SUSTAIN 6, a dedicated CV outcomes trial, OW semaglutide resulted in a 26% reduction in three-point major adverse CV events (MACE) compared with placebo in patients with T2D at high CV risk, leading to its approval for MACE risk reduction in those with T2D and CV disease in the USA. Evidence suggests this may be partly attributable to the anti-inflammatory and anti-atherosclerotic effects of semaglutide, which may also apply to PAD.

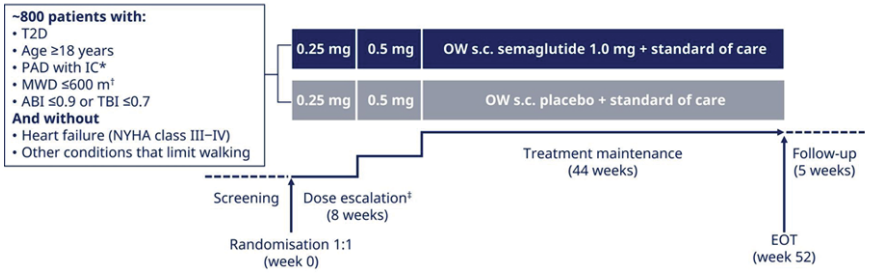
Purpose: The STRIDE trial will demonstrate the effect of OW semaglutide 1.0 mg vs placebo on walking ability in patients with T2D and PAD with IC.

Methods: STRIDE is a 52-week, randomised, double-blind, placebo-controlled, phase 3b trial. Trial design and eligibility criteria are shown in the Figure; ∼800 patients will be randomised 1:1 to OW semaglutide 1.0 mg or placebo, both added to standard of care. The primary endpoint is change in maximum walking distance on a constant load treadmill test from baseline to week 52. Secondary confirmatory endpoints include changes in pain-free walking distance and PAD-specific, health-related patient-reported outcomes (Vascular QoL Questionnaire-6) from baseline to week 52.

Results: The trial started in October 2020 and is currently recruiting, with ∼120 sites in ∼20 countries across Asia, Europe, and North America.

Conclusion: STRIDE is the first and only dedicated PAD outcomes trial with a GLP-1RA and thus presents a unique trial design. While major adverse limb events typically occur in the later stages of PAD, STRIDE instead measures the effect of OW semaglutide on functional outcomes such as walking ability and QoL, which affect everyday living in patients with PAD and IC. STRIDE data will provide important clinical insights regarding the role of OW semaglutide in patients with T2D and PAD.

Figure: trial design



*Fontaine stage IIa ≥3 months. †On a graded treadmill test. ‡Semaglutide dose escalation from a starting dose of 0.25 mg, doubled every 4 weeks until maintenance dose achieved. ABI, ankle–brachial index; EOT, end of treatment; IC, intermittent claudication; MWD, maximum walking distance; NYHA, New York Heart Association; OW, once-weekly; PAD, peripheral artery disease; s.c., subcutaneous; T2D, type 2 diabetes; TBI, toe–brachial index.