STRIDE

Semaglutide and walking capacity in people with symptomatic peripheral artery disease and type 2 diabetes: A phase 3b, double-blind, randomized, placebo-controlled trial

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Late-Breaking Clinical Trial
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Disclosures

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Silence Therapeutics plc,
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Stealth BioTherapeutics Inc.,
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Background – Peripheral Artery Disease

>230 million individuals with PAD globally[1]

Early and severe CV consequence of T2D[1]

PAD in T2D is more likely to be a small vessel / below knee disease[1]

Functional impairment is significant and the dominant morbidity[1]

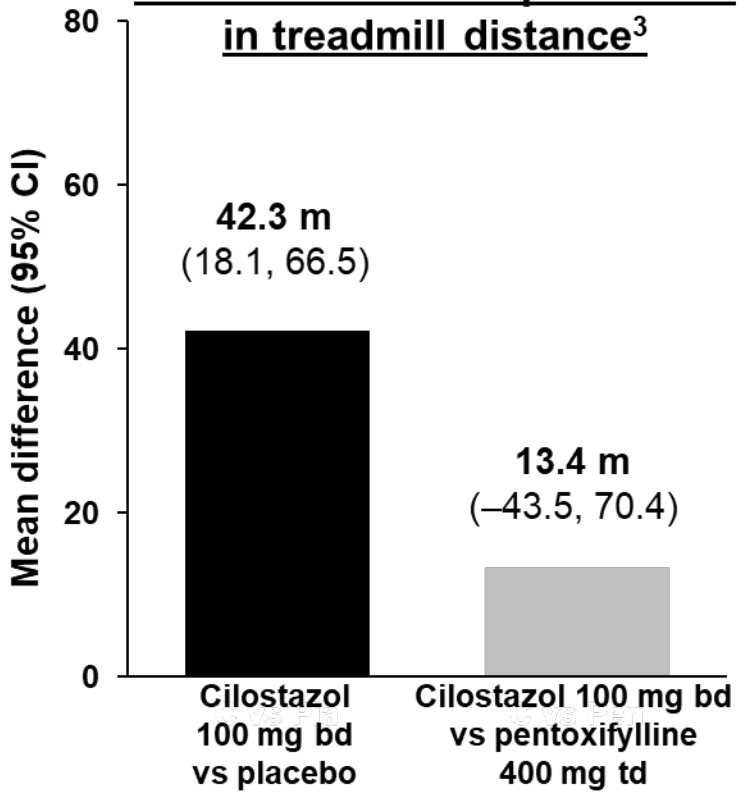
ACC/AHA 2024 PAD guidelines[2]
SGLT2i and GLP-1RA class I for T2D – but no agent is prioritized on the basis of PAD-specific benefits*

Only class I treatment for claudication is cilostazol (approved in 2000)[2,3]

No additional CV benefits

Poorly tolerated, contraindicated in HF

~40-meter mean improvement in treadmill distance[3]



*"Glucagon-like peptide-1 agonists (liraglutide and semaglutide) and SGLT-2i (canagliflozin, dapagliflozin, and empagliflozin) have been demonstrated to reduce MACE in RCTs of people with T2D and CVD, including underlying PAD" (from ACC/AHA)[2]. ACC/AHA, American College of Cardiology/American Heart Association; bd, twice daily; CI, confidence interval; CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; MACE, major adverse cardiovascular events; MWD, Maximum Walking Distance; PAD, peripheral artery disease; PFWD, pain-free walking distance; RCT, randomized controlled trial; SGLT2i, sodium–glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; td, three times a day.

1. Dawson DL. *Am J Cardiol* 2001;87:19–27; **2.** Gornik HL et al. *J Am Coll Cardiol* 2024;83:2497–2604; **3.** Brown T et al. *Cochrane Database Syst Rev* 2021;6:CD003748.

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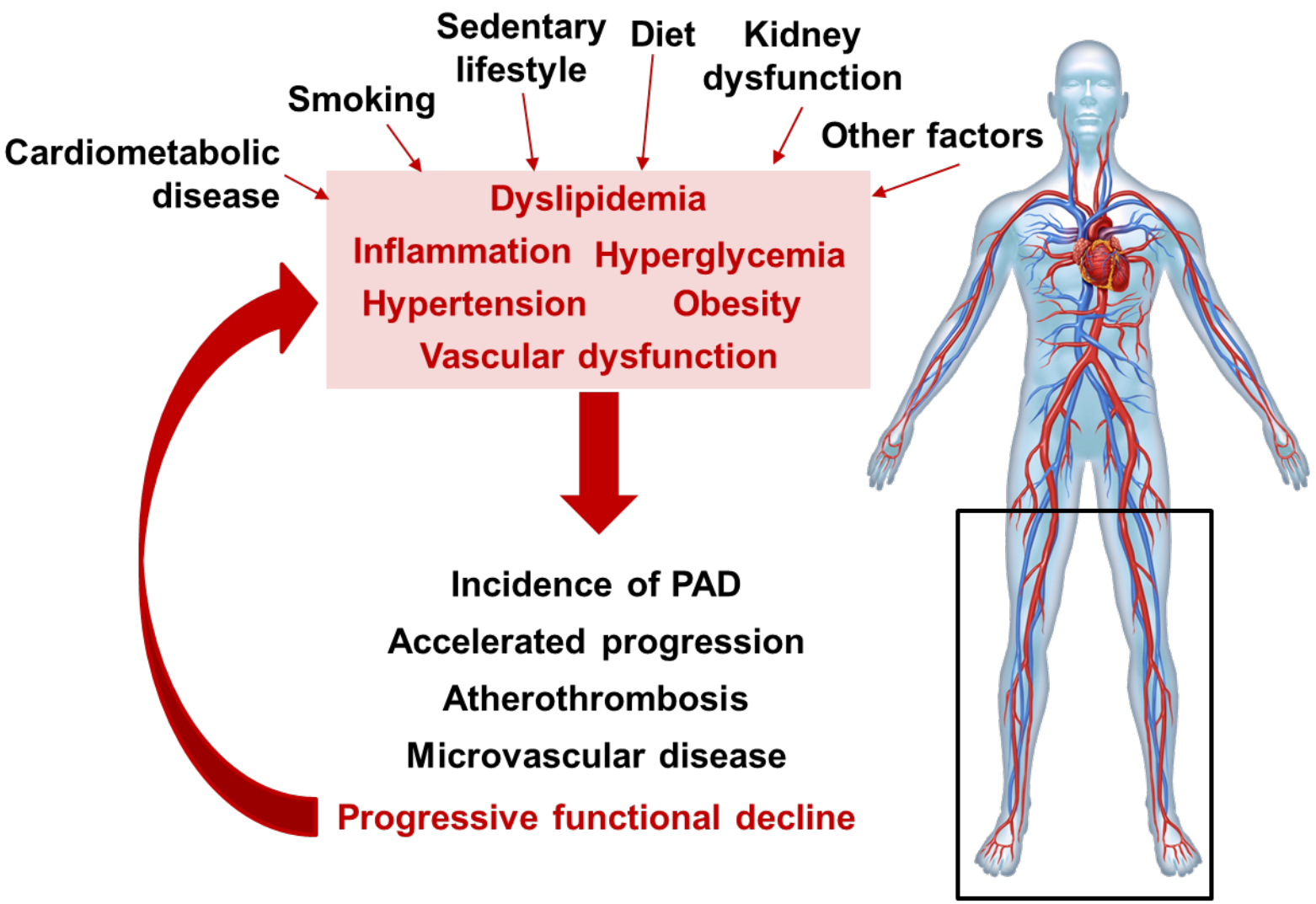
Background – Semaglutide[1–6]



Known benefits:

- ↓ Weight
- ↓ HbA_{1c}
- ↓ Inflammation
- ↓ Blood pressure
- ↓ Cardiometabolic risk
- ↑ Function & ↓ symptoms in HF
- ↓ MACE in ASCVD
- ↓ Kidney complications
- ↓ Amputations *(liraglutide)*

In patients with symptomatic PAD, will semaglutide:

- Improve function?
- Improve symptoms?
- Improve hemodynamics (ABI)?
- Lower rates of rescue therapy? (treatment or revascularization)

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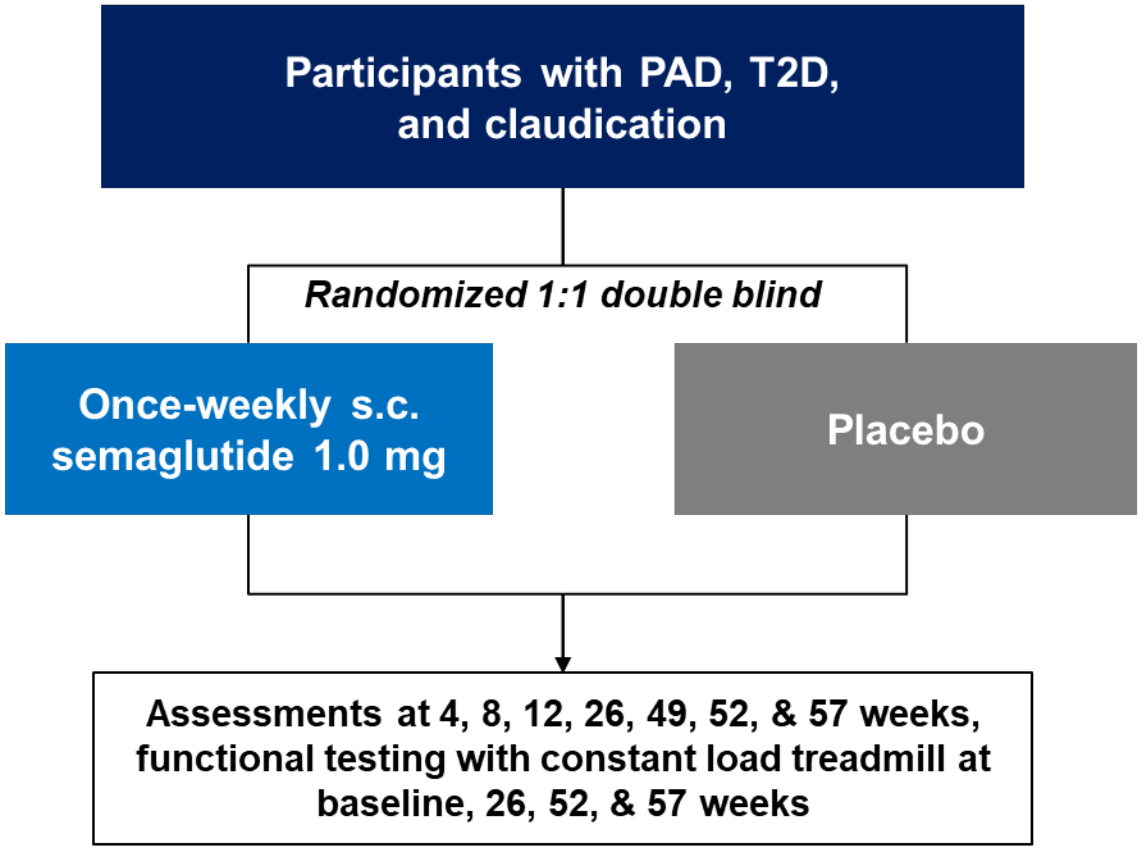
ABI, ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; HbA_{1c}, glycated hemoglobin; HF, heart failure; MACE, major adverse cardiovascular events; PAD, peripheral arterial disease.

1. Marso SP et al. *N Engl J Med* 2016;375:1834–1844; **2.** Wilding JPH et al. *N Engl J Med* 2021;384:989–1002; **3.** Kosiborod MN et al. *N Engl J Med* 2023;389:1069–1084; **4.** Kosiborod MN et al. *Lancet* 2024;404:949–961; **5.** Lincoff AM et al. *N Engl J Med* 2023;389:2221–2232; **6.** Perkovic V et al. *N Engl J Med* 2024;391:109–121.

Objectives and Trial Design

Objective: To demonstrate the effect of once weekly semaglutide 1.0 mg vs. placebo on functional capacity in people with T2D and symptomatic PAD



Inclusion criteria

- Age ≥18 years old
- T2D diagnosis ≥180 days prior to screening
- HbA_{1c} ≤10%
- Early-stage symptomatic PAD (Fontaine stage IIa)
- PFWD ≥200 m (flat treadmill test)
- MWD ≤600 m (constant load treadmill test)
- ABI ≤0.9 or TBI ≤0.7

Exclusion criteria

- Conditions other than PAD that limit walking
- Vascular revascularization ≤180 days prior to screening or planned arterial revascularization
- Heart failure (NYHA Class III–IV)
- MI, stroke, hospitalization for unstable angina, or TIA within 180 days prior to screening

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ABI, ankle-brachial index; HbA_{1c}, glycated hemoglobin; MI, myocardial infarction; MWD, maximum walking distance; NYHA, New York Heart Association; PAD, peripheral artery disease; PFWD, pain-free walking distance; s.c., subcutaneous; T2D, type 2 diabetes; TBI, toe-brachial index; TIA, transient ischemic attack.

Bonaca MP et al. *Eur Heart J Cardiovasc Pharmacother* 2025;10:728–737.

Outcomes

Primary	Change in maximal walking distance (MWD) from baseline to week 52	Function
Confirmatory secondary	Change in MWD from baseline to week 57	Function
	Change in VascuQoL-6 from baseline to week 52	Quality of Life
	Change in pain free walking distance (PFWD) from baseline to week 52	Symptoms
Supportive secondary	Change in PFWD from baseline to week 57	Symptoms
	Change in HbA_{1c}, body weight*, SBP, blood lipids† from baseline to week 52	Mechanism
	Change from screening (week –2) to week 52 in ABI	Mechanism
	Change from baseline to week 52 in SF-36 physical functioning domain	Quality of Life
Exploratory	Anchor measure to assess clinical meaningfulness of observed change in MWD	Clinical Impact
	Clinical outcomes (rescue treatment, major adverse limb events, mortality‡)	Clinical Impact

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*A *post hoc* exploratory analyses evaluated correlations between MWD and BMI. †Total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and triglycerides. ‡Pre-specified data collection with *post hoc* composite for analysis.
ABI, ankle-brachial index; BMI, body mass index; HbA_{1c}, glycated hemoglobin; MWD, maximum walking distance; PFWD, pain-free walking distance; QoL, quality of life; SBP, systolic blood pressure; SF-36, 36-Item Short Form Survey; VascuQoL-6, Vascular QoL Questionnaire-6.

Outcomes

Constant load treadmill[1]

2 mph

12% grade

Time is unlimited, allows participant to walk to maximum – ***distance test***

Regulatory and historical approvals

	Metabolic equivalents at 2 mph ~2× on a 12% grade vs flat walking*
SPEED	
GRADE	
TIME	
RESULT	

6-minute walk test[2]

Generally 1.5–3.0 mph

No grade

Time is limited – ***speed test***

Publications support a 20-meter change as meaningful[3]

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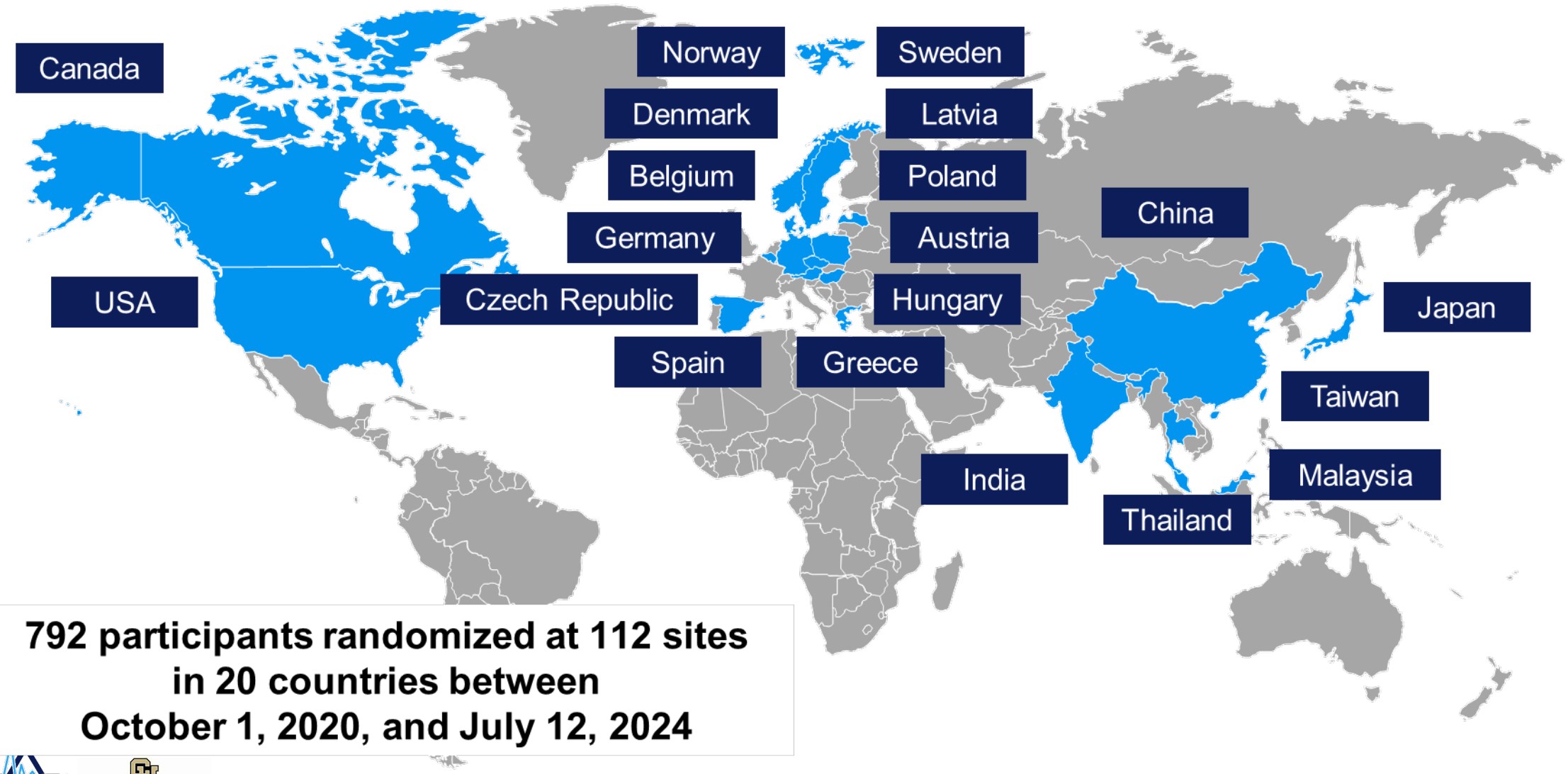
*American College of Sports Medicine (ACSM) equation – special thanks to Dalane Kitzman & Peter Brubaker. EMA, European Medicines Agency.

1. EMA draft guideline on 'Clinical Investigation of Medicinal Products In The Treatment Of Peripheral-Arterial Occlusive Disease'. Available at: https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-peripheral-arterial-occlusive-disease-scientific-guideline Accessed March 26, 2025; **2.** McDermott MM et al. *J Vasc Surg* 2021;73:267–276.e1; **3.** Tew G et al. *J Vasc Surg* 2013;57:1227–1234.

Global Enrollment



792 participants randomized at 112 sites in 20 countries between October 1, 2020, and July 12, 2024

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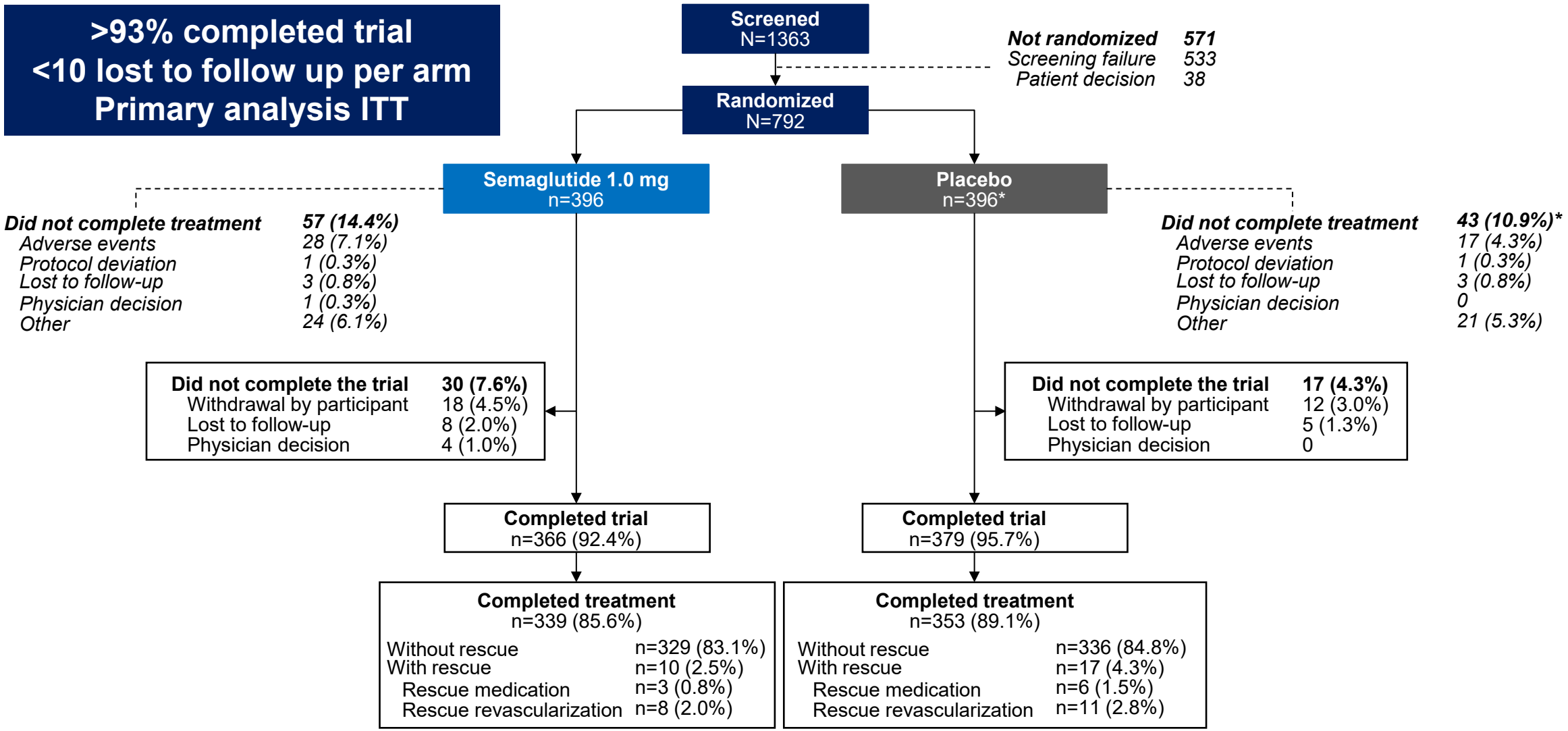
Disposition

>93% completed trial
<10 lost to follow up per arm
Primary analysis ITT



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*One participant was not exposed to treatment.
ITT, intention-to-treat.

Baseline Characteristics

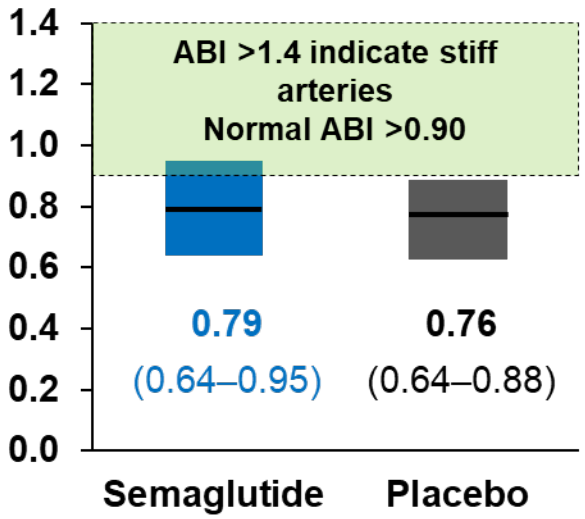
		Semaglutide 1.0 mg (n=396) %	Placebo (n=396) %
	Age – yr – median	68	68
	Female	27	22
	White	65	70
	Asian	33	28
Weight	BMI – kg/m^2 – median	29	28
	<27	37	35
Smoking	Current smoker	24	27
	Previous smoker	45	48
	Hypertension	86	90
	Prior myocardial infarction	15	22
	NYHA Class I–II	14	14
	HbA_{1c} – % – median (IQR)	7.0 (6.5–7.8)	7.2 (6.5–8.1)*
	eGFR – mL/min/1.73 m^2 – median (IQR)	89.0 (70.0–99.0)	87.0 (67.0–98.5)
Medical Therapy	LDL – mg/dL – geometric mean (CV)†	69.2 (0.5)	68.7 (0.5)
	Metformin	80	81
	SGLT2i	37	33
	Insulin	30	34
	Statins	83	82
	Ezetimibe and/or PCSK9i	16	15
	Aspirin or $P2Y_{12}$ inhibitor	73	74
	Direct oral anticoagulants or VKA	13	12
	Cilostazol	11	11

*N=395; †n=381 and n=376 for semaglutide and placebo, respectively. Data shown are percentages unless stated otherwise.
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; NYHA, New York Heart Association; $P2Y_{12}$, purinergic receptor $P2Y_{12}$; PCSK9i, proprotein convertase subtilisin/kexin type 9; SGLT2i, sodium–glucose cotransporter-2 inhibitor; VKA, vitamin K antagonist.

Baseline PAD and Functional Characteristics

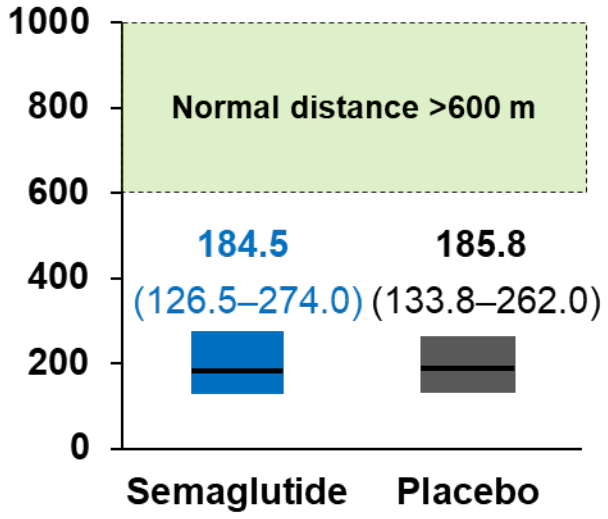
Hemodynamics

Median ABI (IQR)



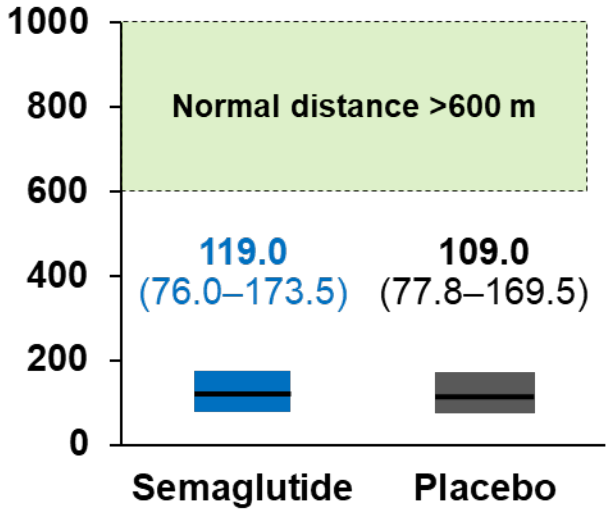
Function

Median MWD (IQR) – meters on constant load treadmill



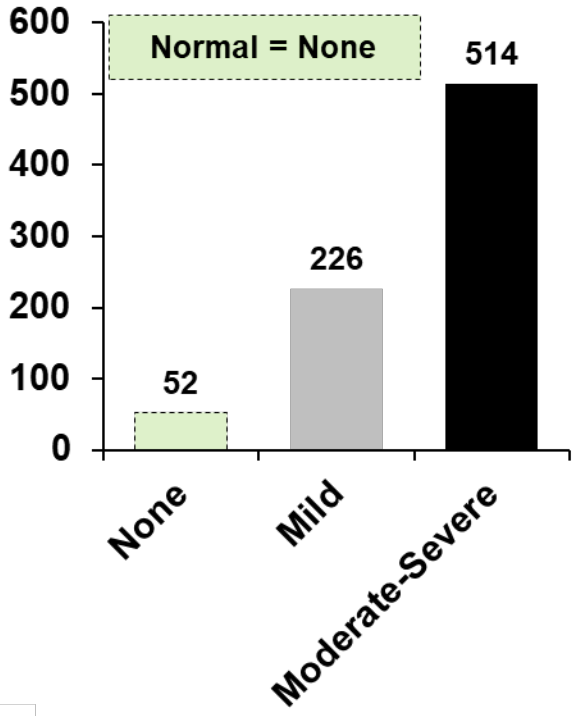
Symptoms

Median PFWD (IQR) – meters on constant load treadmill



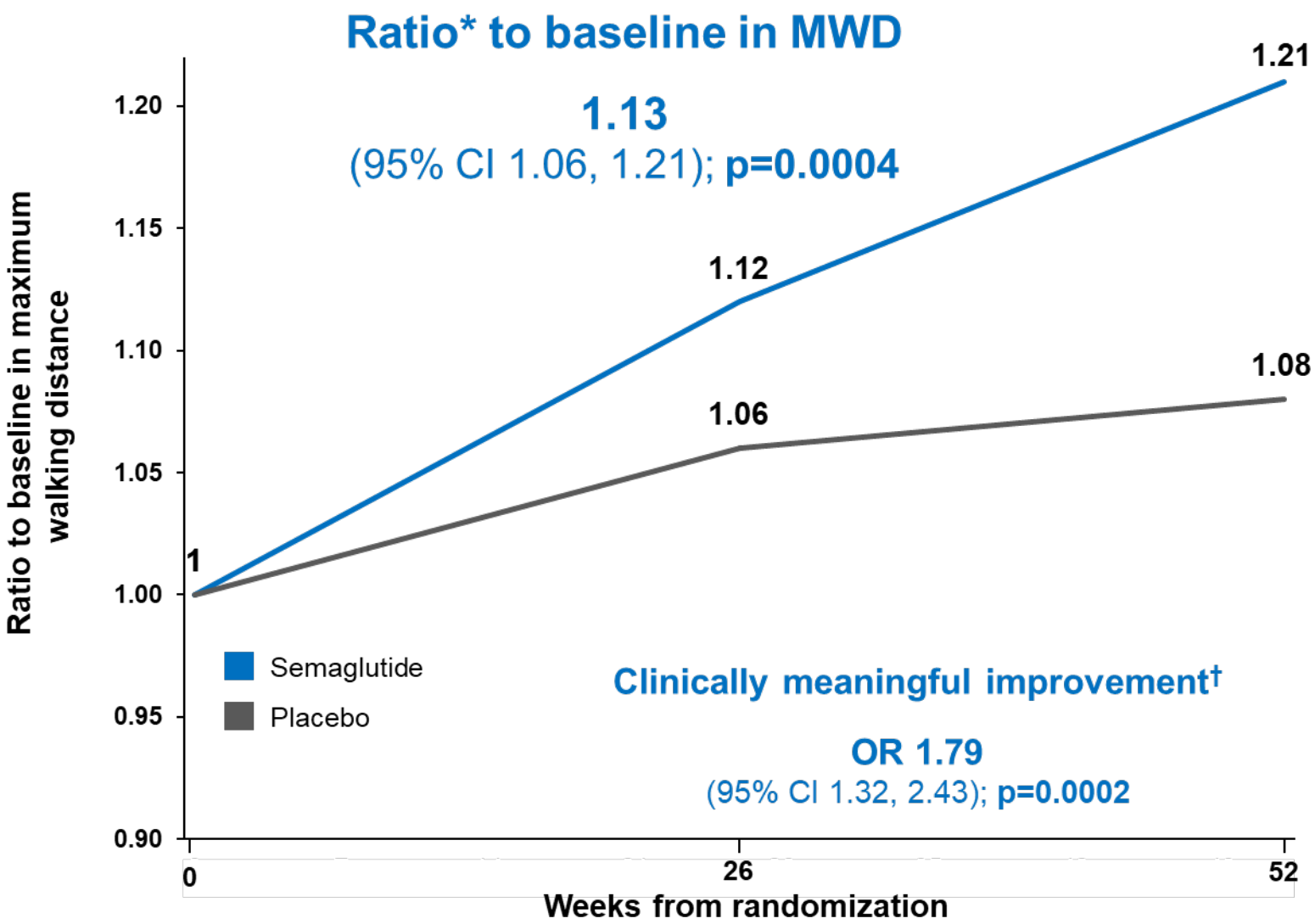
Quality of life

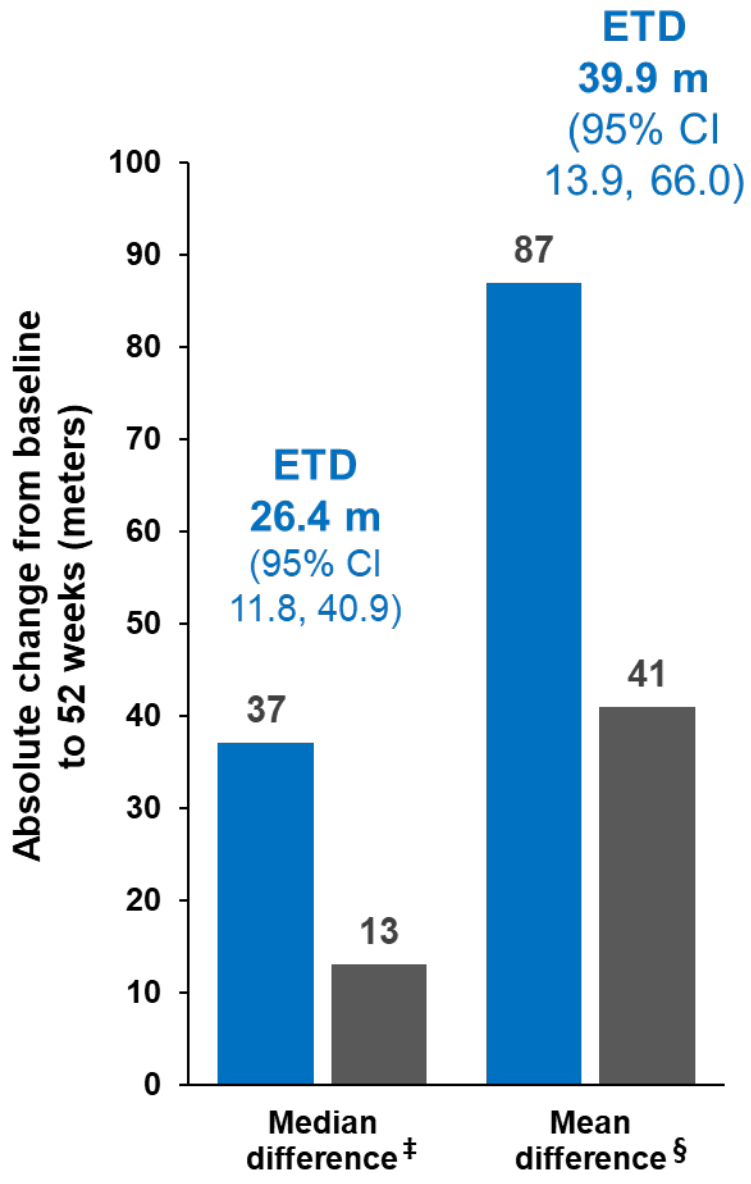
How would you rate your current limitation in walking ability?



Boxes indicate the interquartile range, with horizontal bars showing median values.
ABI, ankle-brachial index; IQR, interquartile range; MWD, maximum walking distance; PAD, peripheral artery disease; PFWD, pain-free walking distance.

Primary Outcome





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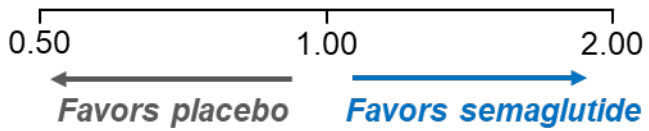
*Estimated treatment ratio; †Using a prespecified anchor measure to assess clinical meaningfulness of change with semaglutide versus placebo; ‡Treatment policy estimand; §Trial product (hypothetical) estimand. Absolute change from baseline to 52 weeks was an exploratory outcome, based on the in-trial observation period for the median difference estimate, and the on-treatment without rescue (revascularization or medication) observation period for the mean difference.
CI, confidence interval; ETD, estimated treatment difference; MWD, maximum walking distance; OR, odds ratio.

Primary Endpoint – Subgroups

Ratio to baseline of the MWD at week 52 measured by the constant load treadmill	Estimated treatment ratio (95% CI)	p value	n/N (semaglutide 1.0 mg; placebo)
Overall	1.13 (1.06, 1.21)	0.0004	338/396; 345/396
Subgroup		p-interaction	
Age — years			
<65	1.18 (1.05, 1.33)	0.35	138/152; 124/133
≥65	1.10 (1.01, 1.21)		207/244; 236/263
Sex			
Female	1.17 (1.02, 1.34)	0.65	98/107; 81/88
Male	1.12 (1.04, 1.22)		247/289; 279/308
Region			
Asia	1.20 (1.05, 1.36)		110/125; 94/106
Europe	1.11 (1.01, 1.22)	0.63	191/220; 213/228
North America	1.11 (0.92, 1.35)		44/51; 53/62
HbA_{1c} — % — median			
<7.1	1.14 (1.03, 1.26)	0.90	176/201; 173/185
≥7.1	1.13 (1.02, 1.25)		169/195; 186/210
BMI — kg/m^2 — median			
<28.6	1.12 (1.01, 1.24)	0.76	162/191; 181/199
≥28.6	1.15 (1.04, 1.26)		182/202; 179/197



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n/N represents the number of participants contributing to the analysis out of the number of participants in the full analysis set.
BMI, body mass index; CI, confidence interval; HbA_{1c}, glycated hemoglobin; MWD, maximum walking distance.

Change in Risk Factors

	Semaglutide	Placebo	Difference (ETD)	p value
Mean (SD) change from baseline in body weight, kg	**n=310 –5.2 (4.8)**	**n=318 –1.2 (4.2)**	**–4.1 kg**	**<0.0001**
	*Spearman's r**	*Spearman's r**		
*Correlation between BMI change and MWD**	*–0.126; p=0.031*	*–0.141; p=0.014*	*r values <0.3 considered a weak correlation*	
Mean (SD) change from baseline in HbA_{1c}, %	**n=304 –0.8 (1.1)**	**n=311 0.2 (1.1)**	**–1.0%**	**<0.0001**
Mean (SD) change from baseline in SBP, mmHg	**n=310 –4.0 (15)**	**n=319 –0.8 (18)**	**–3.2 mmHg**	**0.0042**

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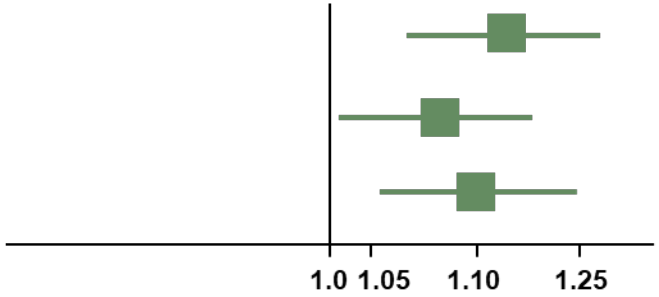
*A *post hoc* analysis.
BMI, body mass index; ETD, estimated treatment difference; HbA_{1c}, glycated hemoglobin; MWD, maximum walking distance; SBP, systolic blood pressure; SD, standard deviation.

Primary and Secondary Outcomes

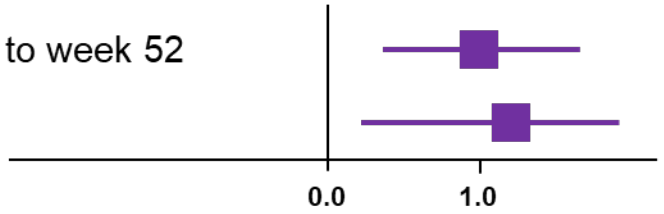
Function

1	Ratio to baseline in MWD at week 52	1.13 (95% CI 1.06, 1.21)	p=0.0004
2	Ratio to baseline in MWD at week 57	1.08 (95% CI 1.00, 1.16)	p=0.0380
2	Ratio to baseline in PFWD at week 52	1.11 (95% CI 1.03, 1.20)	p=0.0046



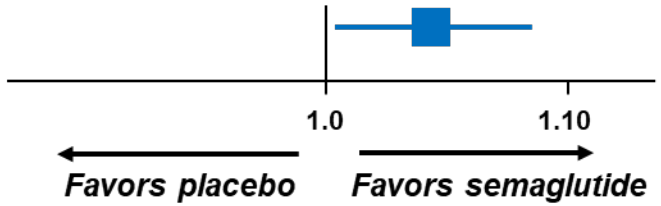
Quality of life

2	Change in VascuQoL-6 total score from baseline to week 52	1.00 (95% CI 0.48, 1.52)	p=0.011
3	Change in SF-36 Physical Functioning Domain	1.25 (95% CI 0.26, 2.24)	p=0.013



Hemodynamics (ABI)

3	Geometric mean ABI ratio to baseline	1.05 (95% CI 1.02, 1.09)	p=0.0037



1 **Primary endpoint**

2 **Confirmatory secondary endpoint**

3 **Supportive secondary endpoint**

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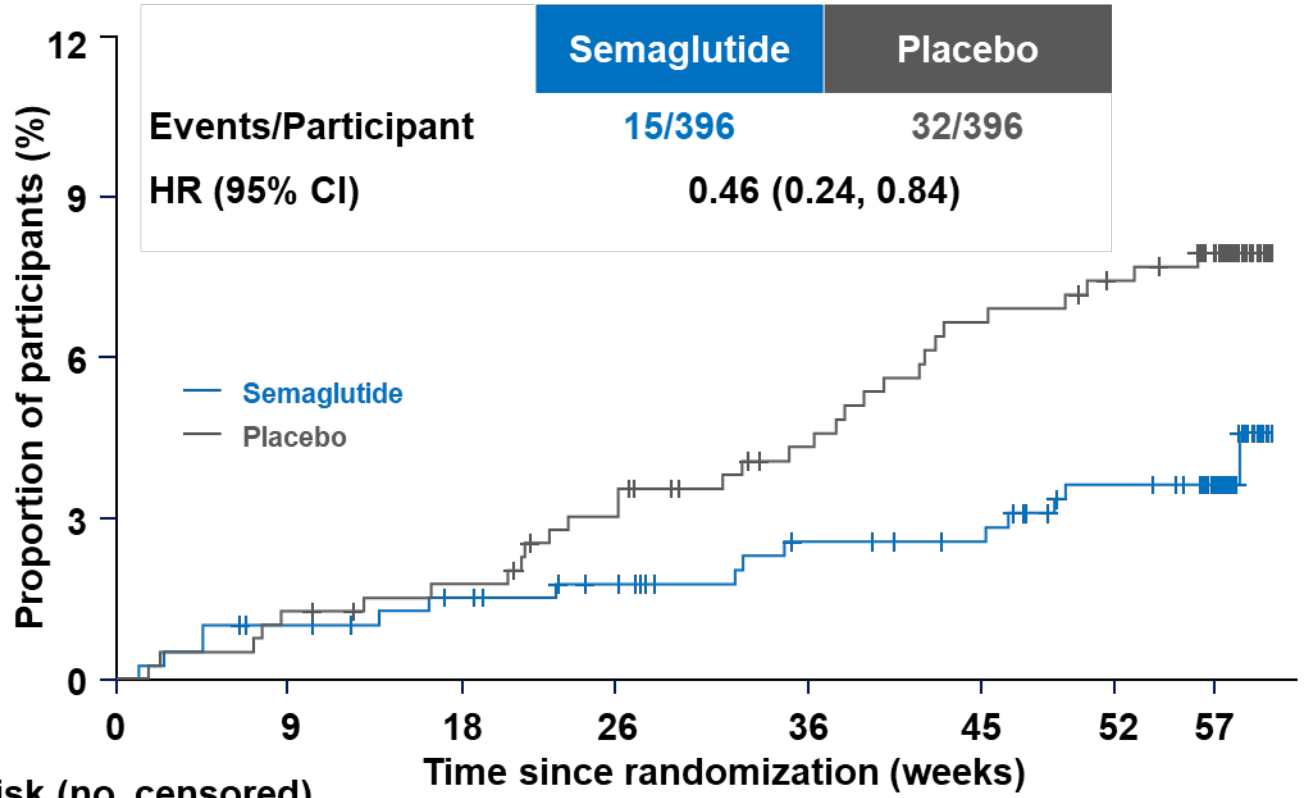
ABI, ankle-brachial index; CI, confidence interval; MWD, maximum walking distance; PFWD, pain-free walking distance; QoL quality of life; SF-36, 36-Item Short Form Survey; VascuQoL-6, Vascular Quality of Life Questionnaire-6.

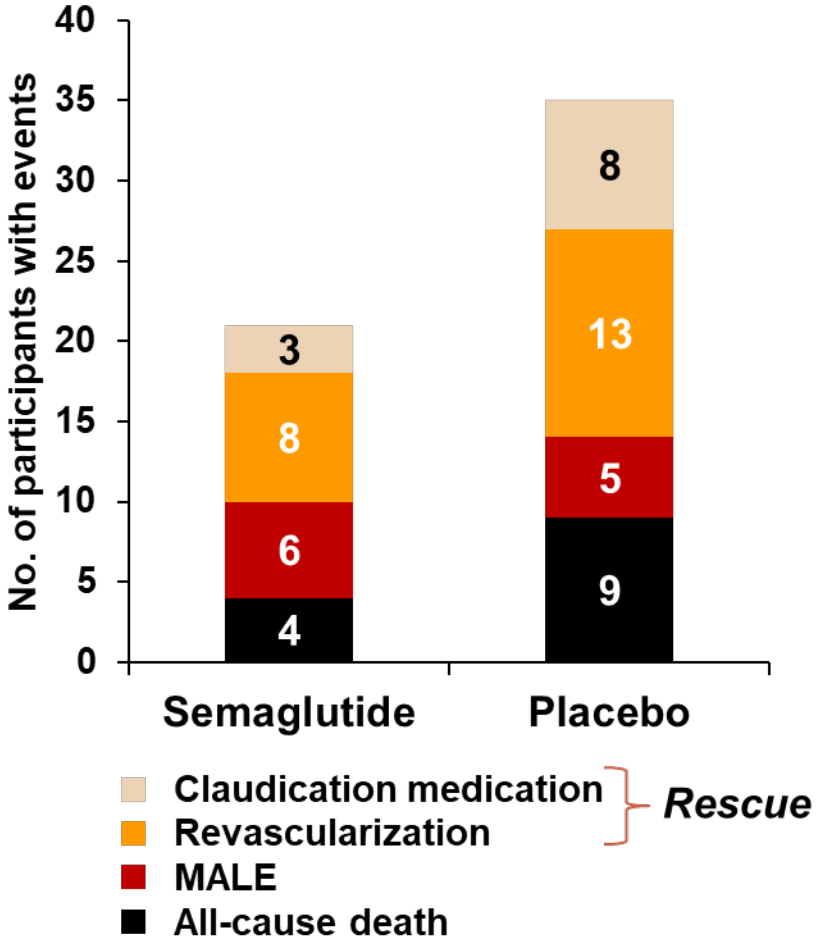
Exploratory Analysis of Progression Outcomes

Composite of rescue initiation, MALE, or all-cause death*



No. at risk (no. censored)

Semaglutide 1.0 mg	396 (0)	390 (2)	385 (3)	380 (5)	371 (5)	368 (3)	359 (5)	342 (21)
Placebo	396 (0)	391 (0)	387 (2)	380 (2)	369 (6)	360 (0)	355 (2)	341 (16)



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*Pre-specified data collection with a *post hoc* exploratory analysis evaluating the composite of rescue initiation, MALE, or all-cause death, and the individual components.
CI, confidence interval; HR, hazard ratio; MALE, major adverse limb events.

Safety

	Semaglutide 1.0 mg (N=396)			Placebo (N=395)		
	Participants, n (%)	Events, n	Events/100 person-yr	Participants, n (%)	Events, n	Events/100 person-yr
Adverse events	210 (53)	490	122.4	182 (46)	409	99.0
Serious adverse events	74 (19)	130	32.5	78 (20)	111	26.9
Leading to death	3 (1)	4	1.0	8 (2)	9	2.2
Selected adverse events						
Gastrointestinal	79 (20)	109	27.2	24 (6)	31	7.5
Decreased appetite	19 (5)	21	5.2	4 (1)	4	1.0
Acute pancreatitis	0 (0)	0	0	1 (0.3)	1	0.2

N represents the number of participants in the safety analysis set.

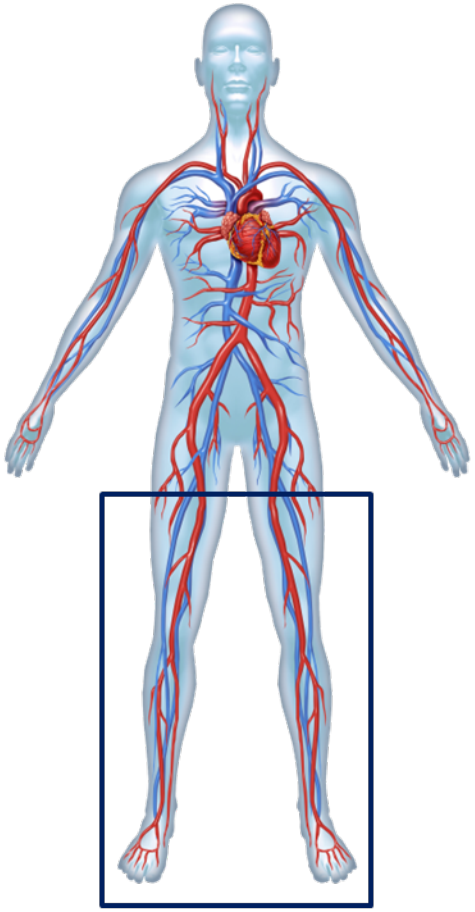
Summary – Semaglutide in Symptomatic PAD

Known benefits of semaglutide[1–5]

- ↓ Weight
- ↓ HbA_{1c}
- ↓ Inflammation
- ↓ Blood pressure
- ↓ Cardiometabolic risk
- ↑ Function & ↓ symptoms in HF
- ↓ MACE in ASCVD
- ↓ Kidney complications

PAD-specific benefits of semaglutide

- ✓ Improves function
- ✓ Improves symptoms
- ✓ Improves hemodynamics (ABI)
- ✓ Lower rates of rescue therapy (treatment or revascularization)



Significantly improved function and met criteria for a clinically meaningful change

Significantly improved symptoms and quality of life

Reduced disease progression

Improved ABI

Safety consistent with previous trials with no unexpected safety findings

ABI, ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; HbA_{1c}, glycated hemoglobin; HF, heart failure; MACE, major adverse cardiovascular events; PAD, peripheral artery disease; T2D, type 2 diabetes.

1. Wilding JPH et al. *N Engl J Med* 2021;384:989–1002; **2.** Kosiborod MN et al. *N Engl J Med* 2023;389:1069–1084; **3.** Kosiborod MN et al. *Lancet* 2024;404:949–961; **4.** Lincoff AM et al. *N Engl J Med* 2023;389:2221–2232; **5.** Perkovic V et al. *N Engl J Med* 2024;391:109–121.

Conclusion

Semaglutide is the first therapy to ↓ MACE, improve cardiometabolic and kidney outcomes…

<u>and improves walking capacity, symptoms, and related quality of life in patients with PAD and T2D</u>

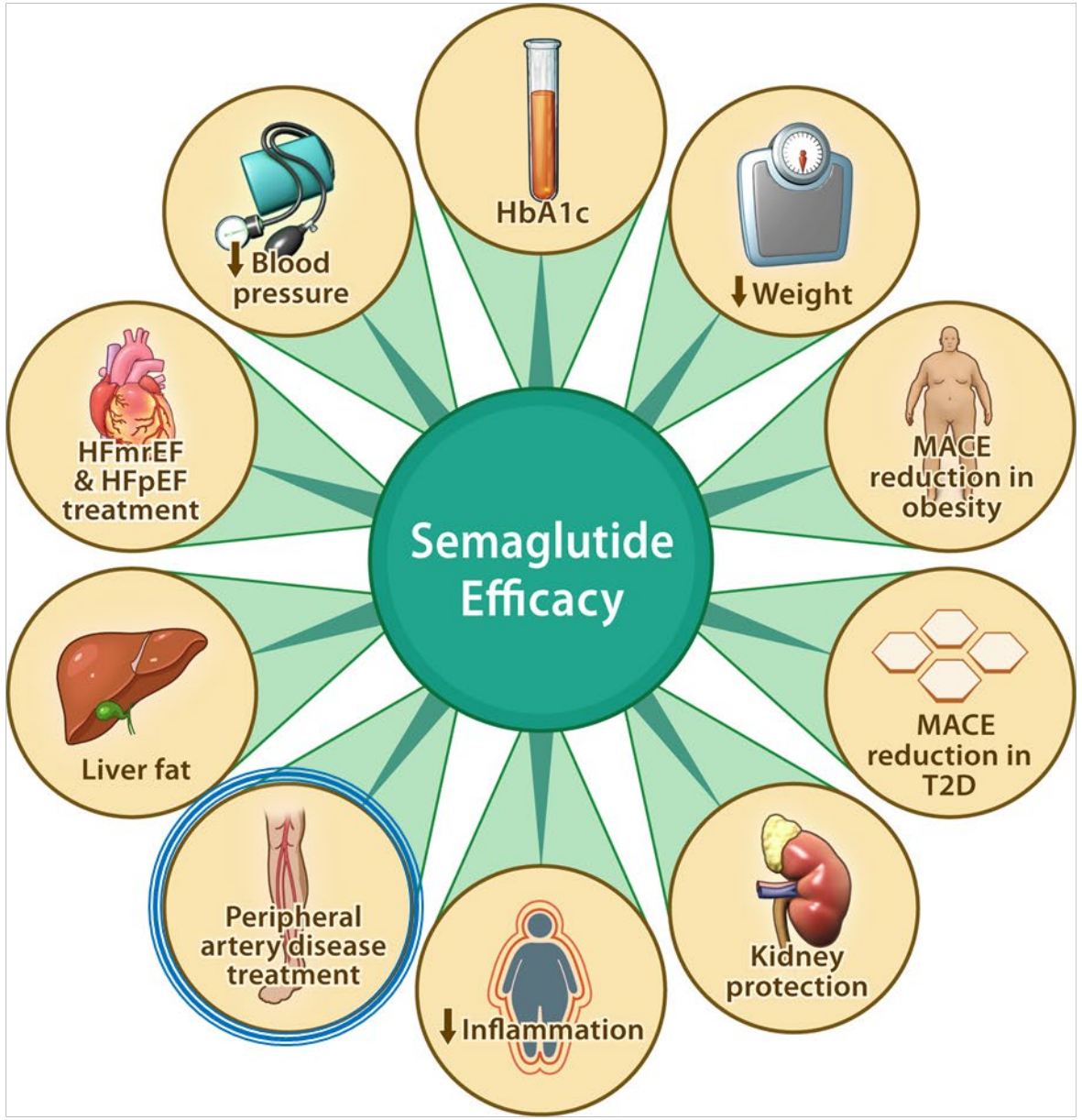


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Figure courtesy of S. Verma.
HbA_{1c}, glycated hemoglobin; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; MACE, major adverse cardiovascular events; PAD, peripheral artery disease; T2D, type 2 diabetes.

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THE LANCET

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

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