CPC Clinical Research

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University of Colorado Anschutz Medical Campus

STRIDE

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

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American College of Cardiology Scientific Sessions 2025

Late-Breaking Clinical Trial

March 29, 2025

Disclosures

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- **Dr Bonaca is the Executive Director of CPC, a non-profit academic research organization affiliated with the University of Colorado, that receives or has received research grant/consulting funding between August 2021 and present from: Abbott Laboratories, Agios Pharmaceuticals, Inc., Alexion Pharma, Alnylam Pharmaceuticals, Inc., Amgen Inc., Angionetics, Inc., Anthos Therapeutics, Array BioPharma, Inc., AstraZeneca and Affiliates, Atentiv LLC, Audentes Therapeutics, Inc., Bayer and Affiliates, Bristol-Myers Squibb Company, Cambrian Biopharma, Inc., Cardiol Therapeutics Inc., CellResearch Corp., Cleerly Inc., Cook Regentec LLC, CSL Behring LLC, Eidos Therapeutics, Inc., EP Trading Co. Ltd., Epizon Pharma, Inc., Esperion Therapeutics, Inc., Everly Well, Inc., Exicon Consulting Pvt. Ltd., Faraday Pharmaceuticals, Inc., Foresee Pharmaceuticals Co. Ltd., Fortress Biotech, Inc., HDL Therapeutics Inc., HeartFlow Inc., Hummingbird Bioscience, Insmed Inc., Ionis Pharmaceuticals, Janssen and Affiliates, Kowa Research Institute, Inc., Lexicon Pharmaceuticals, Inc., Medimmune Ltd., Merck and Affiliates, Nectero Medical Inc., Novartis Pharmaceuticals Corp., Novo Nordisk, Inc., Osiris Therapeutics Inc., Pfizer Inc., PhaseBio Pharmaceuticals, Inc., Prairie Education and Research Cooperative, Prothena Biosciences Limited, Regeneron Pharmaceuticals, Inc., Regio Biosciences, Inc., Sanofi-Aventis Groupe, Silence Therapeutics PLC, Smith & Nephew plc, Stealth BioTherapeutics Inc., VarmX, Virta Health Corporation**

Background – Peripheral Artery Disease

> 230 million with PAD globally

Early and severe CV consequence of T2DM

PAD in T2DM more likely to be small vessel/below knee disease

<u>Functional Impairment</u> is significant and the dominant morbidity

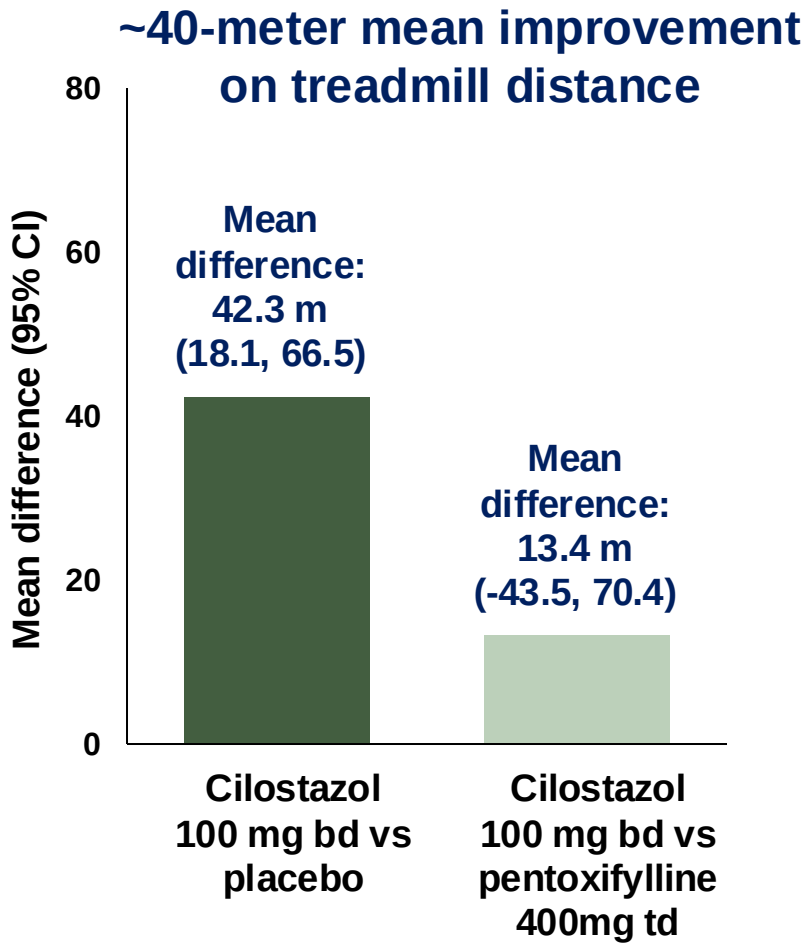
ACC/AHA 2024 GL
SGLT2i and GLP-RA class I for T2D – but no agent is prioritized on the basis of PAD-specific benefits*

Only Class I treatment for claudication is cilostazol (approved in 2000)

~40-meter mean improvement on treadmill distance

No additional CV benefits

Poorly tolerated, contraindicated in HF



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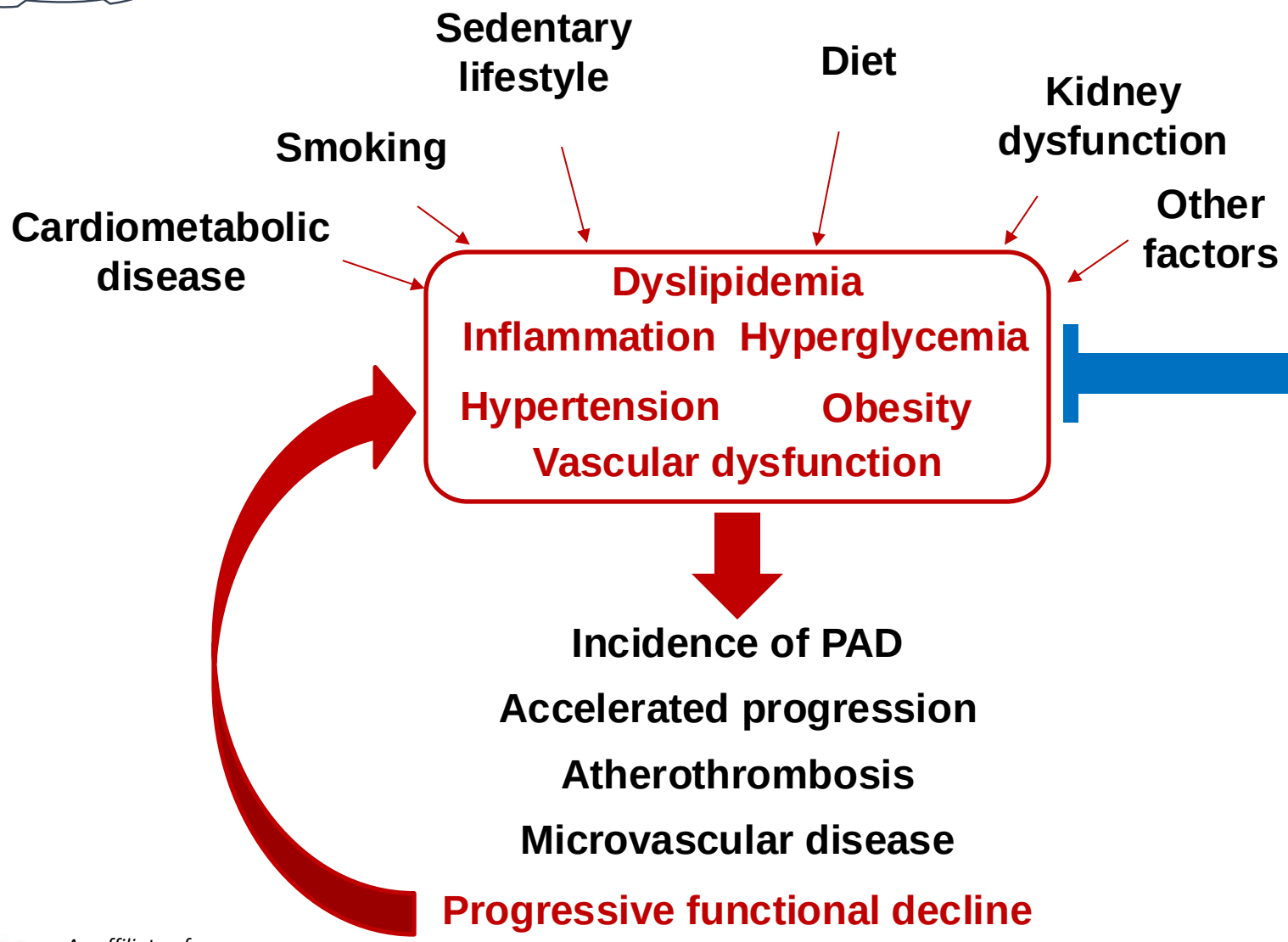
Gornik HL et al. *J Am Coll Cardiol* 2024;83(24):2497–2604.
Dawson DL. *Am J Cardiol* 2001;87(12):19–27.
Brown T, et al. *Cochrane Database Syst Rev*. 2021;6(6):CD003748..

Glucagon-like peptide-1 agonists (liraglutide and semaglutide) and SGLT-2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) have been demonstrated to reduce MACE in RCTs of patients with type 2 diabetes and CVD, including underlying PAD" (from ACC/AHA)*

Potential Mechanisms of GLP-1RA Benefit in PAD



GLP-1 Receptor Agonists

- ↓ HbA_{1c}
- ↓ Weight
- ↓ Inflammation
- ↓ Blood pressure
- ↓ Kidney Complication
- ↓ Macro & Micro Vascular Benefits

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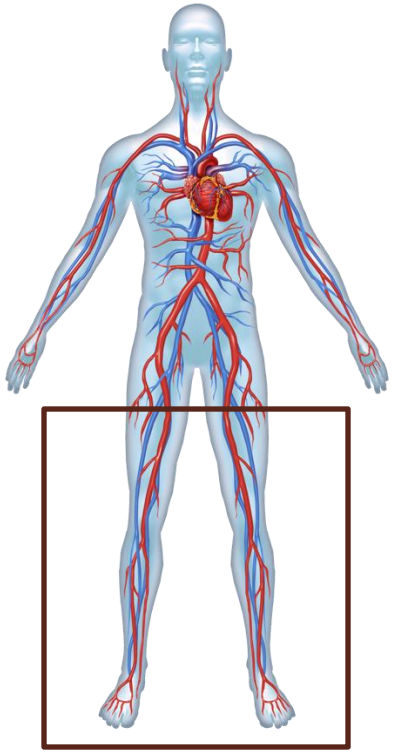
Ridker et al. Circulation 1998; Brevetti et al. Circulation 2010; Dhatariya et al. Diabetes Care 2018.

Background – GLP-1 Receptor Agonists

↓ Weight

↓ Cardiometabolic risk

↑ Function & ↓ symptoms in HF



↓Obstructive sleep apnea

↓ MACE in ASCVD

↓ Kidney outcomes (sema)

Semaglutide & GLP1r-a

In patients with symptomatic PAD

Improve function ?

Improve symptoms ?

Improve hemodynamics ?

Reduce progression → rescue (e.g. revascularization) ?

- ↓ HbA_{1c}
- ↓ Weight
- ↓ Inflammation
- ↓ Blood pressure
- ↓ Kidney Complication
- ↓ Macro & Micro Vascular Benefits

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Wilding JPH, et al. N Engl J Med. 2021;384(11):989-1002; Kosiborod MN, et al N Engl J Med 2023; 389(12): 1069-84; Lincoff AM, et al. N Engl J Med 2023; 389(24): 2221-32; Perkovic V, et al. N Engl J Med 2024; 391(2): 109-21; Li M, et al. Sleep, 2024;zsae280. Online ahead of print. doi:10.1093/sleep/zsae280.

Objectives

In patients with symptomatic peripheral artery disease and type 2 diabetes with functional limitation

- Test whether once-weekly semaglutide 1.0 mg (titrated) improves function
  - Clinically meaningful change
  - Improves symptoms
  - Improves quality of life

- To evaluate the safety of once-weekly semaglutide 1.0 mg vs. placebo

Trial Design NCT04560998

Patients with peripheral artery disease and type 2 diabetes with claudication

Randomized 1:1 double blind

Semaglutide 1.0 mg SC weekly

Placebo

Visits at 4, 8, 12, 26, 49, 52, and 57 weeks, with functional testing at baseline, 26, 52, and 57 weeks

Primary endpoint: Ratio to baseline of the Maximum Walking Distance (MWD) at week 52 measured by the constant load treadmill

Confirmatory Secondary endpoints: MWD at 57 weeks, VascuQoL-6 at 52 weeks, Pain-Free Walking Distance (PFWD) at 52 weeks

Inclusion and Exclusion Criteria

Inclusion criteria

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

Exclusion criteria

- Conditions other than PAD that limit walking
- Planned orthopedic leg surgery or surgery affecting walking ability
- Vascular revascularization within 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
- Current or previous treatment with any GLP-1RA within 90 days prior to screening
- eGFR <30 mL/min/1.73 m^2 measured within the previous 6 months

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Bonaca MP, et al. *Eur Heart J Cardiovasc Pharmacother* 2025;10(8):728–737.

Outcomes

Function **Quality of Life** **Symptoms**

PRIMARY ENDPOINT

Change in maximum walking distance on a constant load treadmill from baseline to week 52

SECONDARY CONFIRMATORY ENDPOINTS

Change in **maximum walking distance** on a constant load treadmill from baseline to **week 57**

Change in **Vascular QoL Questionnaire-6** from baseline to week 52

Change in **pain-free walking distance** on constant load treadmill from baseline to week 52

SUPPORTIVE SECONDARY ENDPOINTS

Change from baseline to end of follow-up (week 57) in Pain-free walking distance (constant load treadmill)

Change from baseline to week 52 in:

- **HbA_{1c}**
- **SBP**
- **Body weight**
- **Blood lipids***

Change from screening (week –2) to week 52 in Ankle Brachial Index (ABI)

Change from baseline to week 52 in SF-36 physical functioning domain

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***Anchor** measure to assess **clinical meaningfulness** of observed change in MWD*

*Total cholesterol, low-density lipoprotein-cholesterol; high-density lipoprotein-cholesterol and triglycerides.

Outcomes

Metabolic equivalents at 2 mph ~2x on at 12% grade vs flat walking*

Constant load treadmill		6-minute walk test
2 mph		Generally 1.5-3.0 mph
12% grade		No grade
Time unlimited, allows participant to walk to maximum – *distance test*		Time limited – *speed test*
EMA/regulatory approval Cilostazol (class I in guidelines) with 40-meter mean improvement		Publications support a 20-meter change as meaningful

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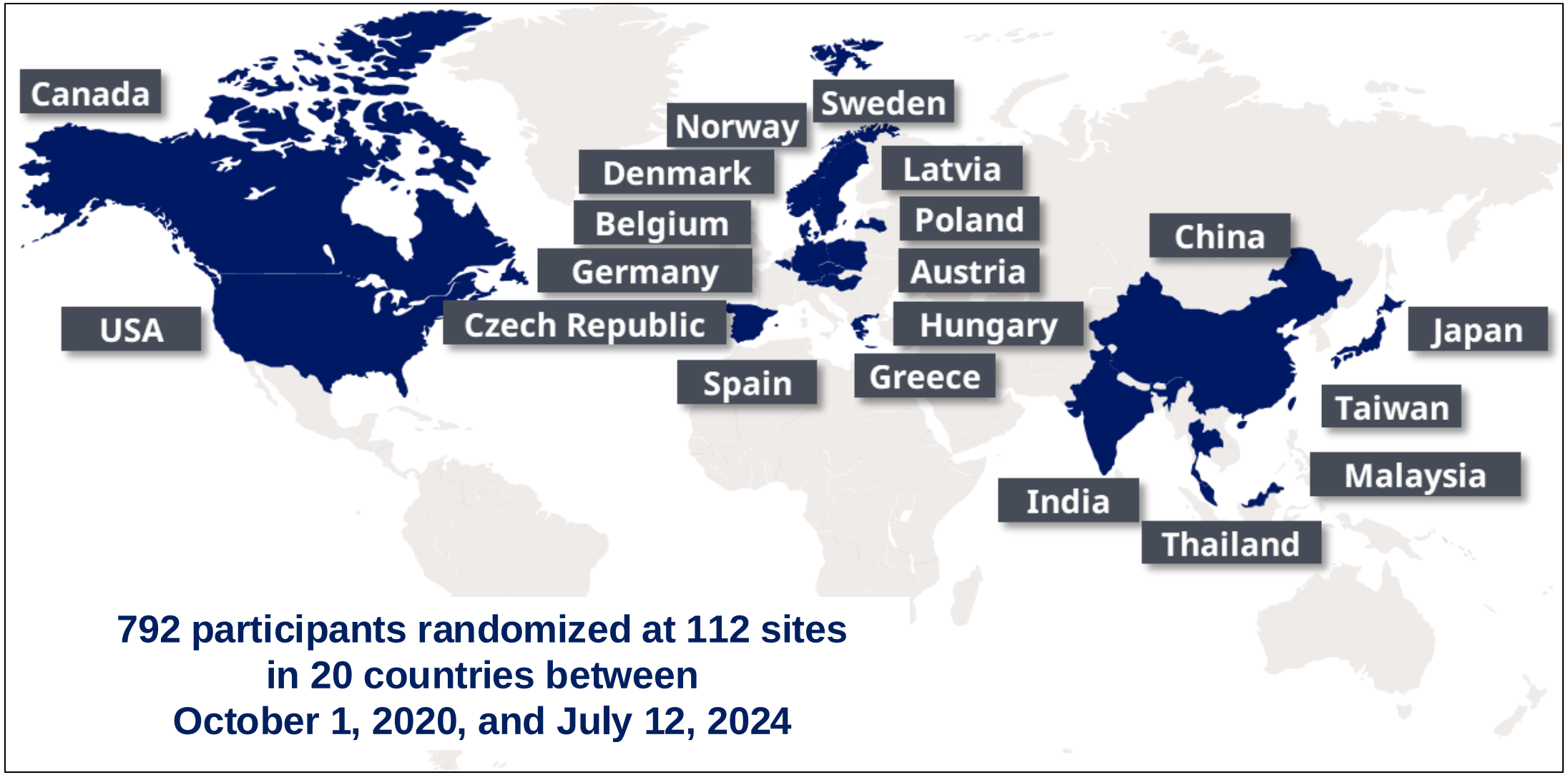
**American College of Sports Medicine (ACSM) equation – special thanks to Dalane Kitzman & Peter Brubaker.*
Tew G et al. *J Vasc Surg* 2013;57(5):1227–1234?

Global Enrollment



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

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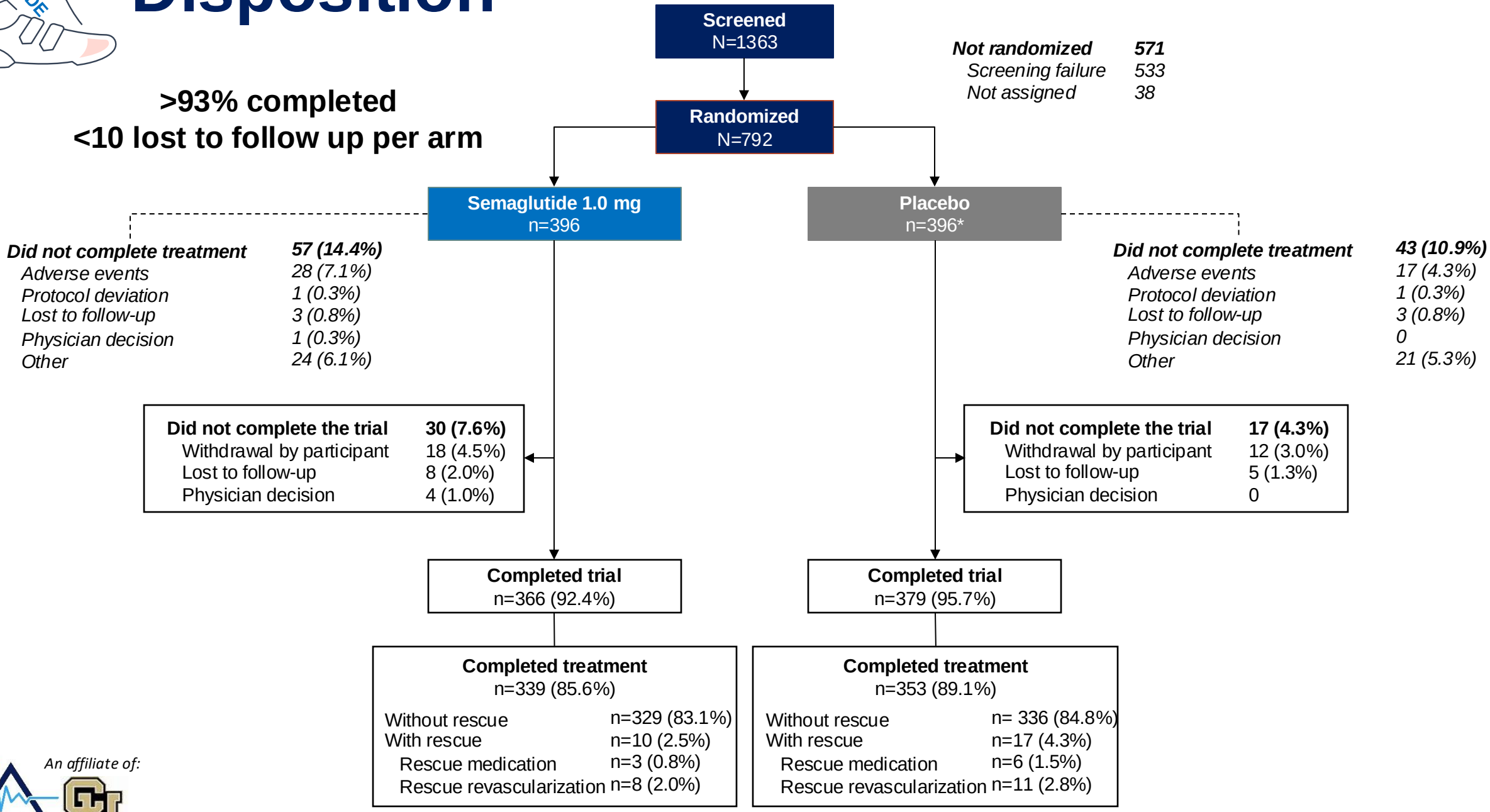
Disposition

>93% completed
<10 lost to follow up per arm



Baseline Characteristics

	Semaglutide 1·0 mg (n=396), %	Placebo (n=396), %
Age — yr — median (IQR)	68.0 (60.0–73.0)	68.0 (62.0–73.0)
Female	27	22
White	65	70
Asian	33	28
BMI — kg/m^2 – median (IQR)	28.6 (25.6–32.9)	28·5 (25.7–33.1)
≥30	42	40
>27–30	58	60
Current smoker	24	27
Previous smoker	45	48
Hypertension	86	90
Myocardial infarction	15	22
Prior stroke	5	8
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)	53.0 (47.6–55.8)	55.2 (47.6–65.0)
LDL — mg/dL – geometric mean (CV)†	69.2 (0.5)	68.7 (0.5)
Metformin	80	81
SGLT2 inhibitors	40	33
Insulin	30	34
Statins	83	82
Ezetimibe and/or PCSK9i	16	15
Acetylsalicylic acid	52	52
$P2Y_{12}$ inhibitors	21	22
Direct oral anticoagulants or VKA	13	12
Cilostazol	11	11

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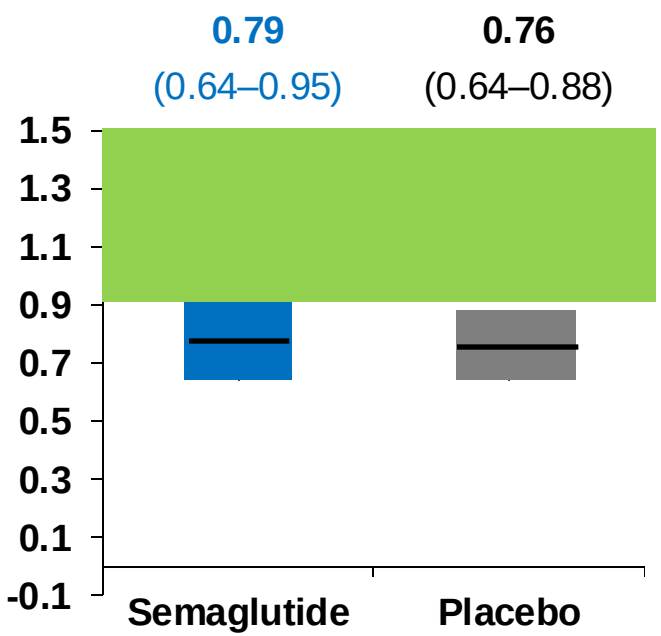
*N=395; †n=381 and n=376 for semaglutide and placebo, respectively.

Baseline PAD and Functional Characteristics

Hemodynamics

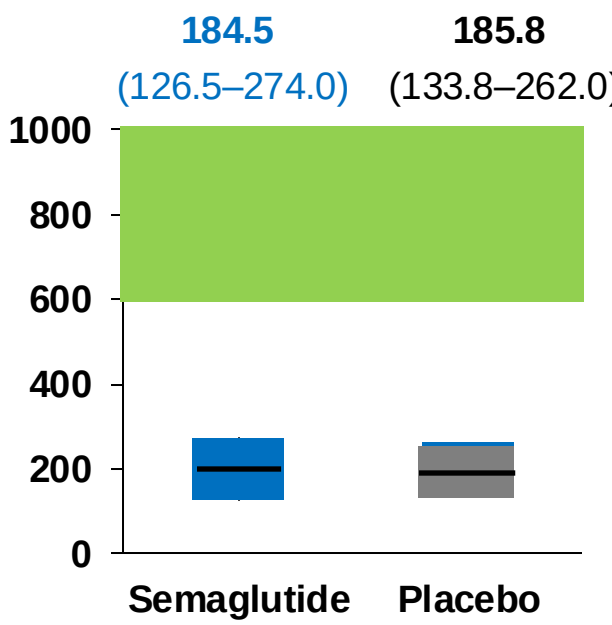
Normal ABI >0.90



Function

Normal distance > 600 m

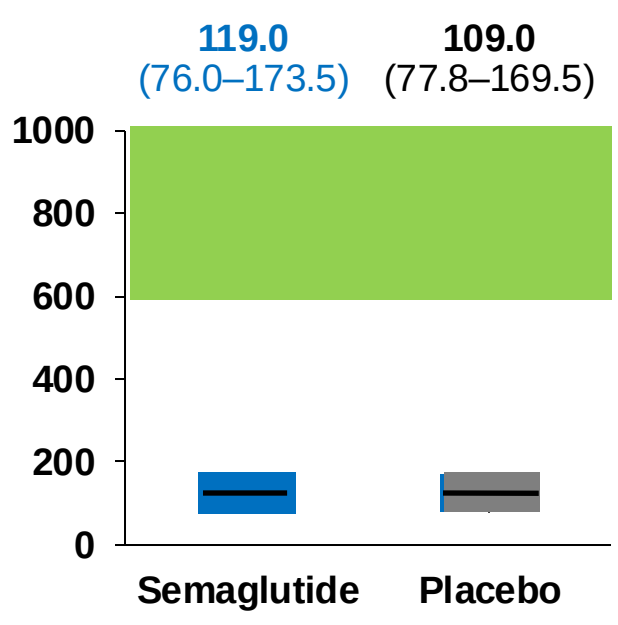
MWD — meters on CLT



Symptoms

Normal distance > 600 m

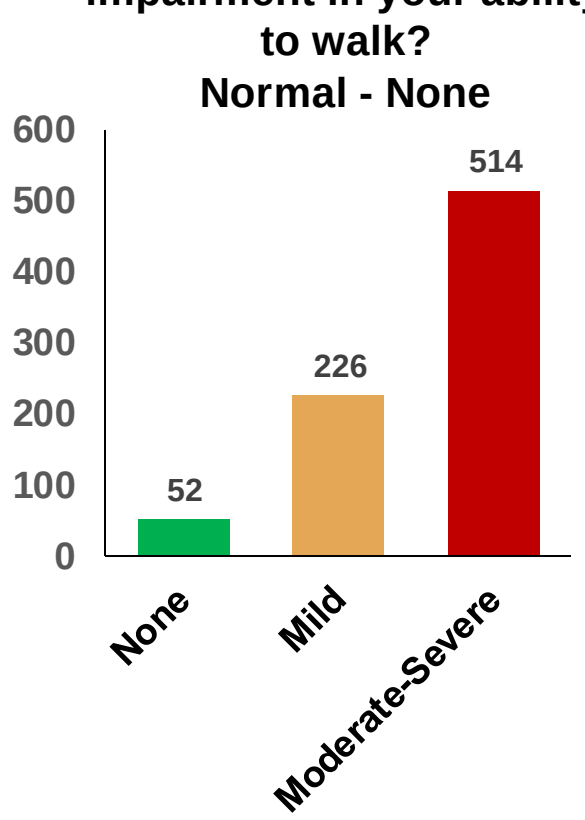
PFWD — meters



Quality of Life

VascuQol 6 – How would you rate your current impairment in your ability to walk?

Normal - None



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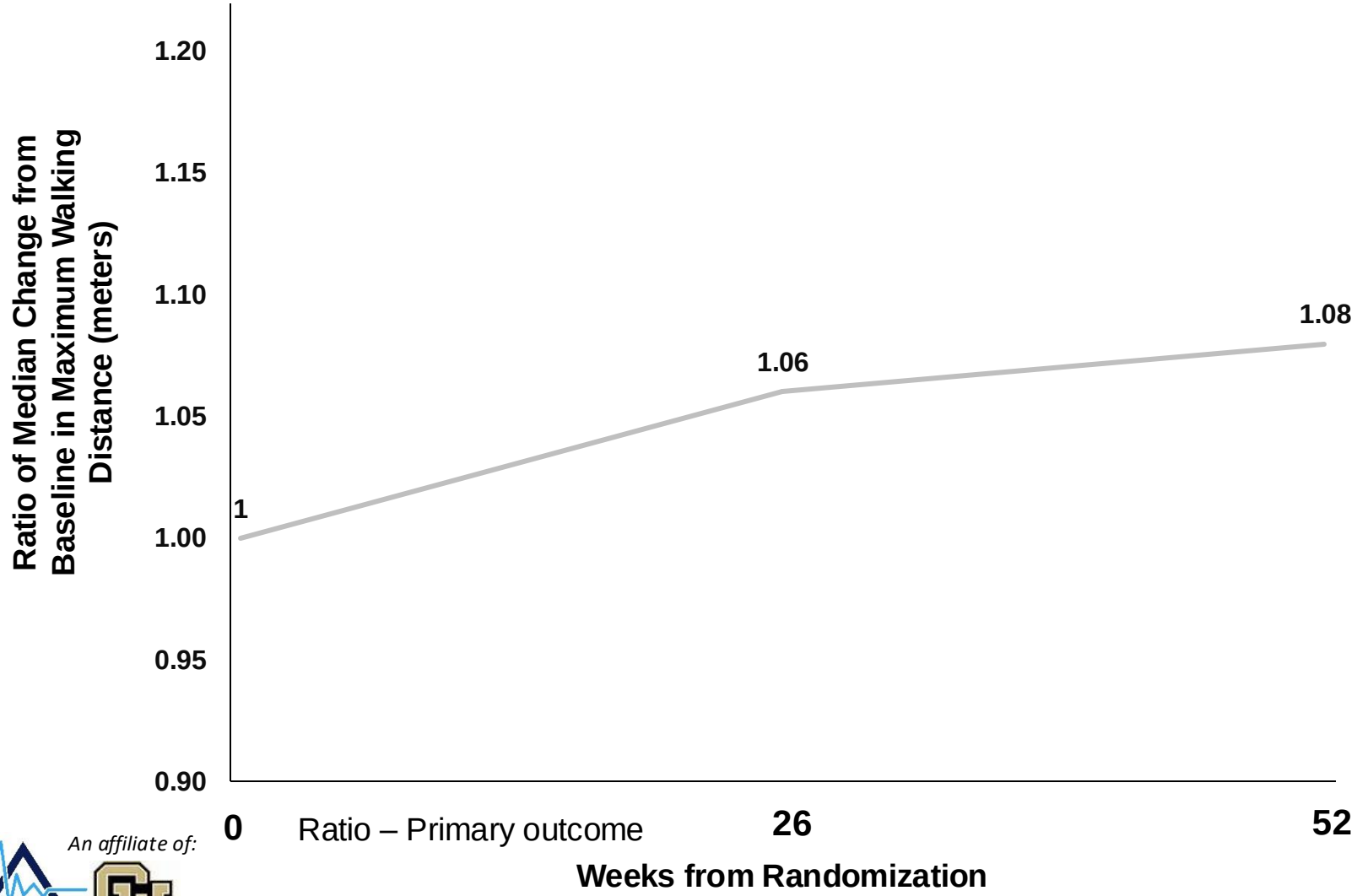
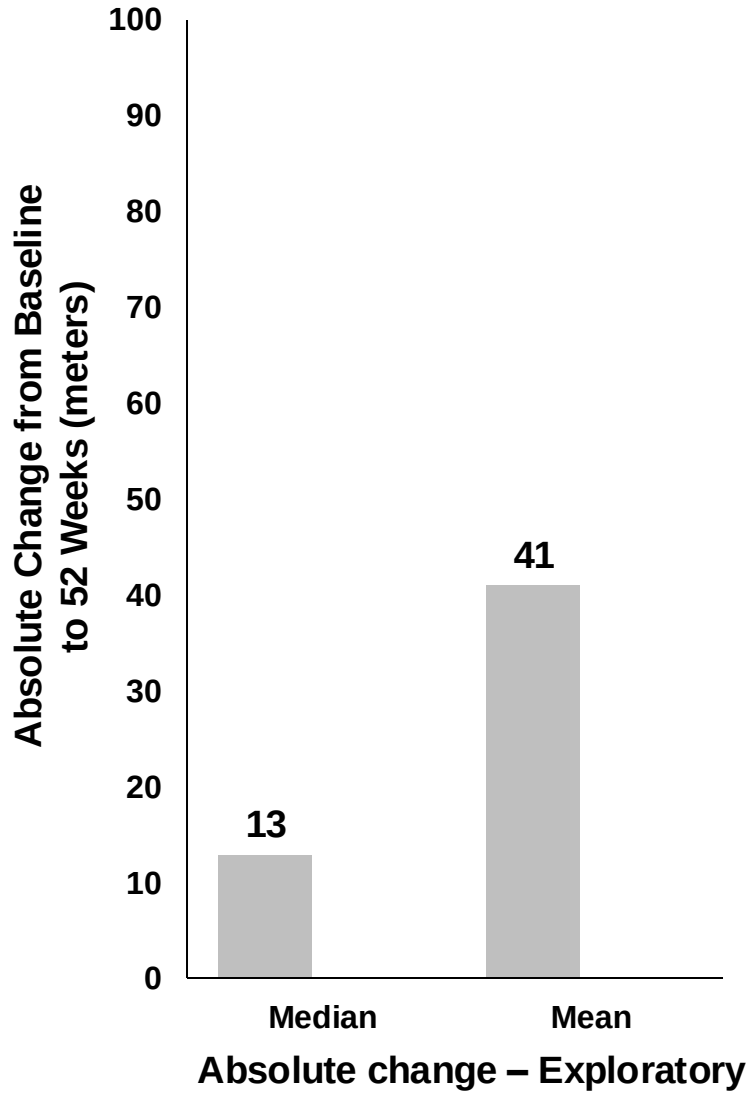
Boxes indicate the interquartile range, with horizontal bars showing median values.

Bonaca MP, et al. *Eur Heart J Cardiovasc Pharmacother* 2025;10(8):728–737.

Primary Outcome

Placebo





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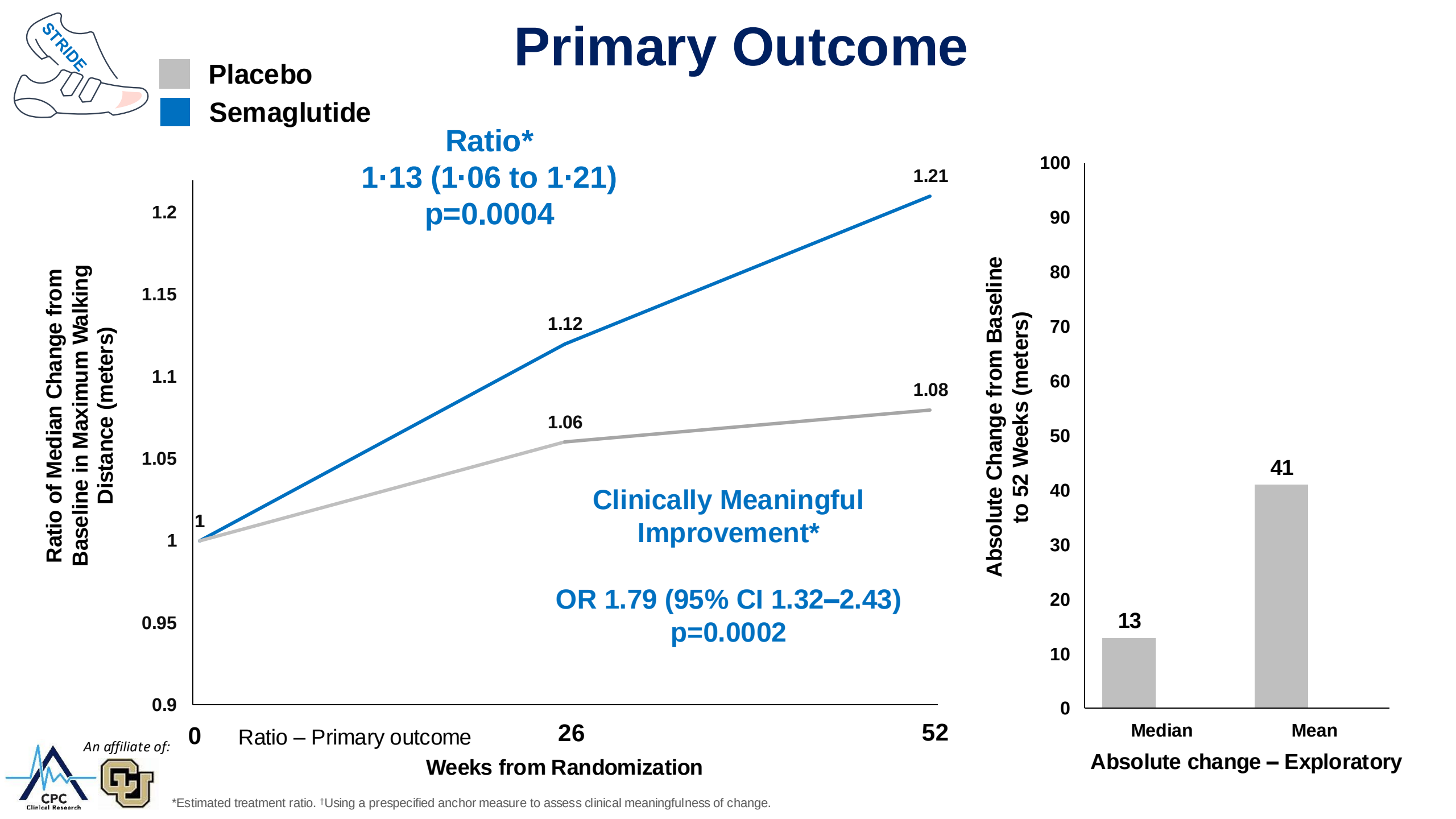
*Estimated treatment ratio. †Using a prespecified anchor measure to assess clinical meaningfulness of change.

Primary Outcome



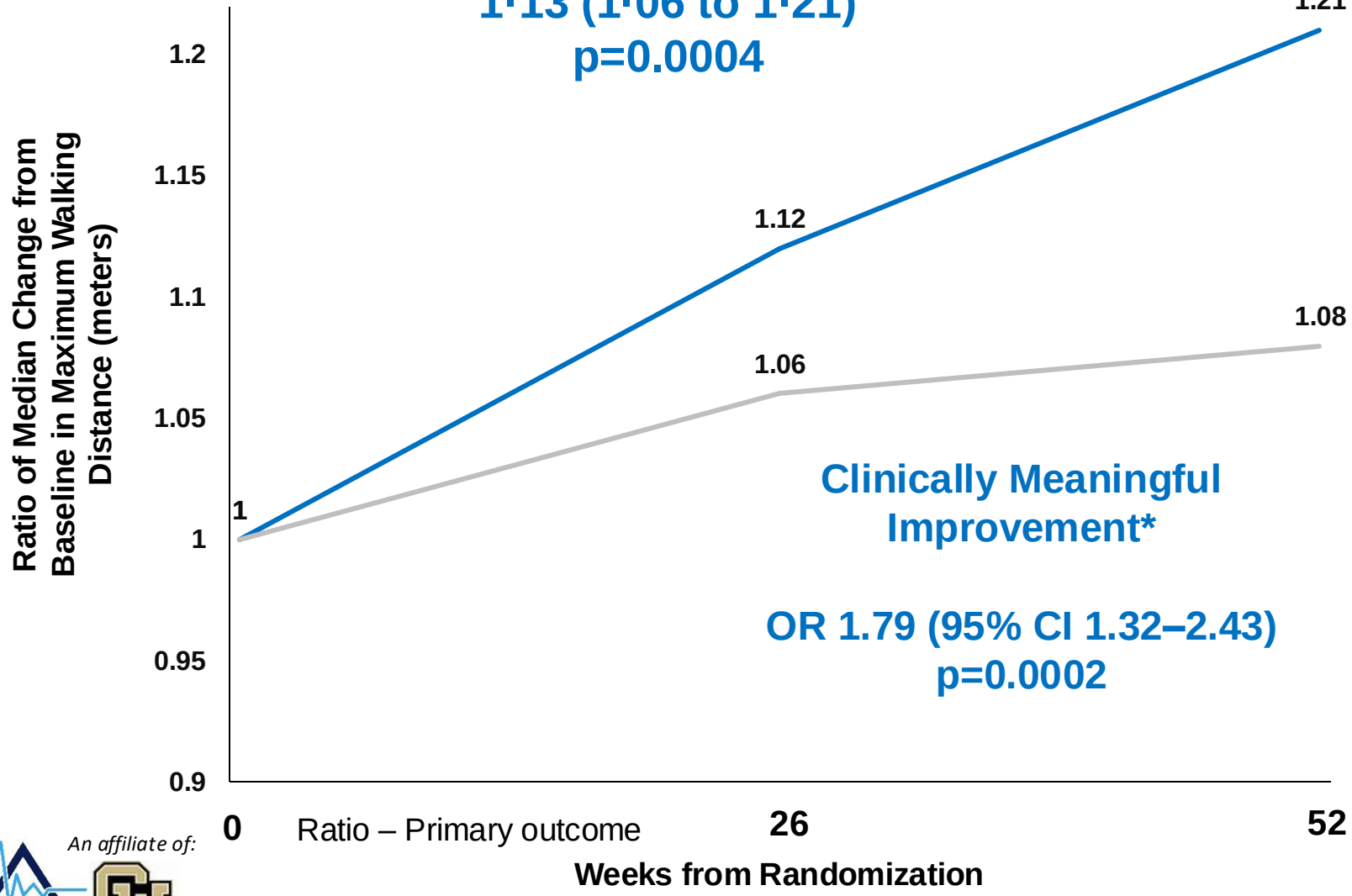
An affiliate of:

*Estimated treatment ratio. †Using a prespecified anchor measure to assess clinical meaningfulness of change.

Primary Outcome

Placebo
Semaglutide

Ratio*
1·13 (1·06 to 1·21)
p=0.0004

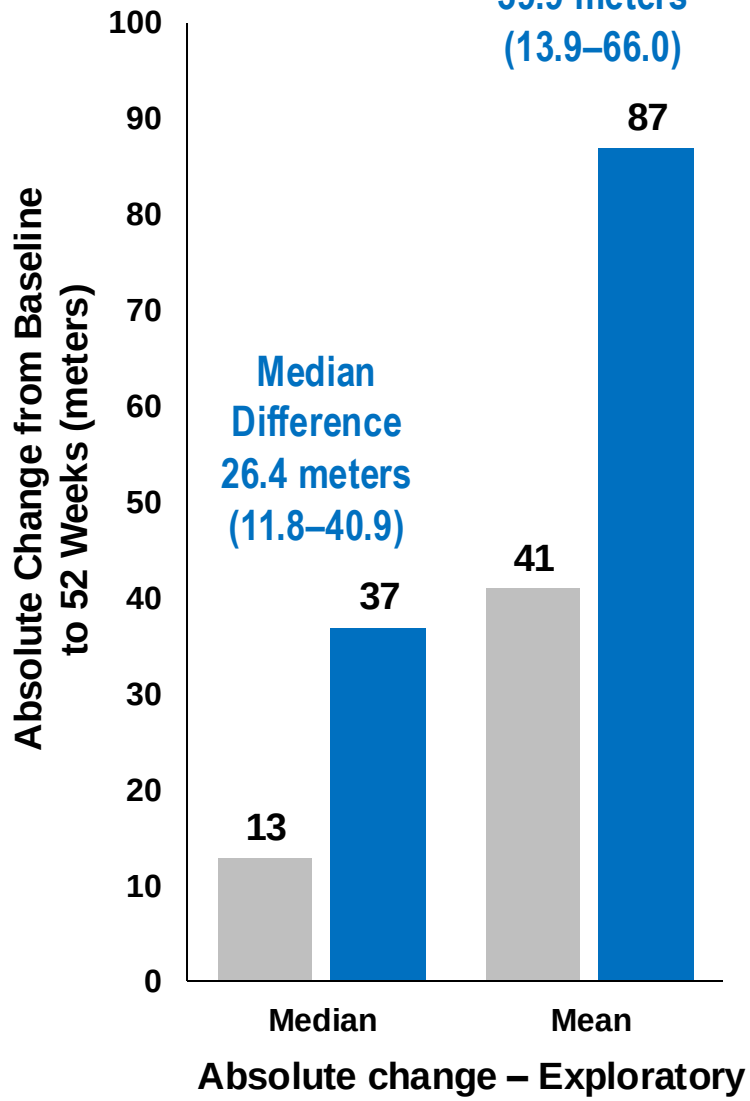


Clinically Meaningful Improvement*

OR 1.79 (95% CI 1.32–2.43)
p=0.0002

Mean Difference 39.9 meters (13.9–66.0)

Median Difference 26.4 meters (11.8–40.9)

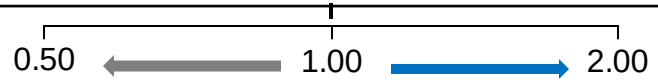


An affiliate of:

*Estimated treatment ratio. †Using a prespecified anchor measure to assess clinical meaningfulness of change.

Primary Endpoint - Subgroups

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



Favors Placebo **Favors Semaglutide**

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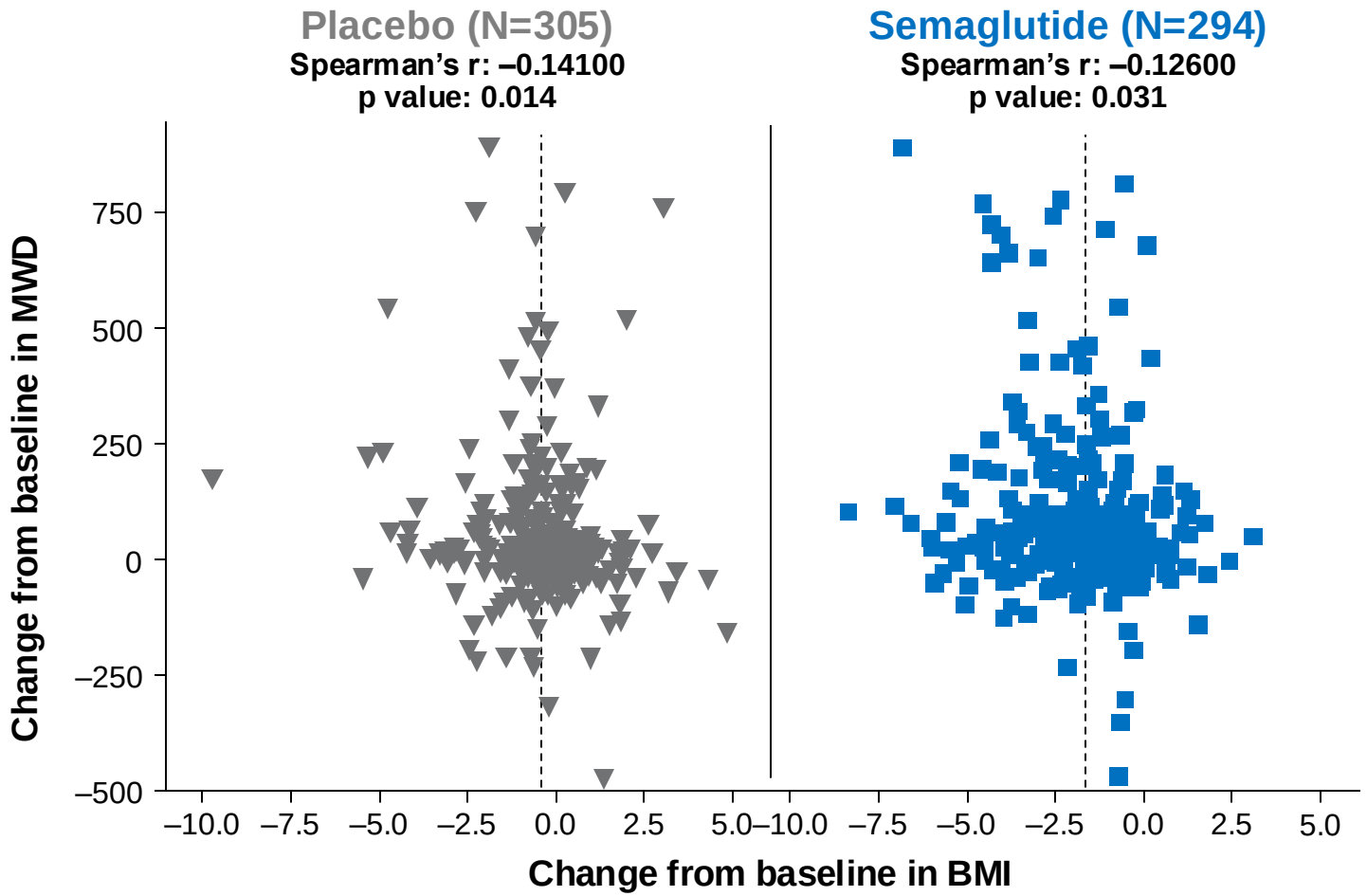
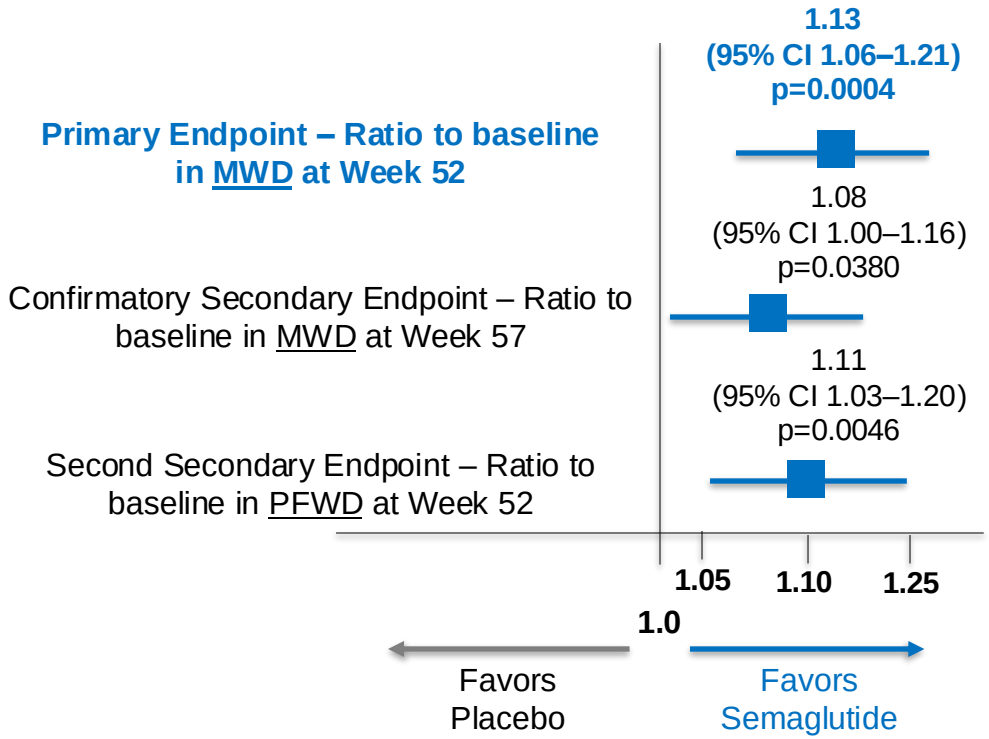
Change in Risk Factors

	Semaglutide	Placebo	ETD	p value
Mean change from baseline in body weight — kg (SD)	n=310; **–5.2** (4.8)	n=318; **–1.2** (4.2)	**–4.1 kg**	<0.0001
Mean change from baseline in HbA_{1c} — % (SD)	n=304; **–0.8** (1.1)	n=311; **0.2** (1.1)	**–1.0%**	<0.0001
Mean change from baseline in SBP — mmHg (SD)	n=310; **–4.0** (0.8)	n=319; **–0.8** (0.8)	**–3.2 mmHg**	0.0042

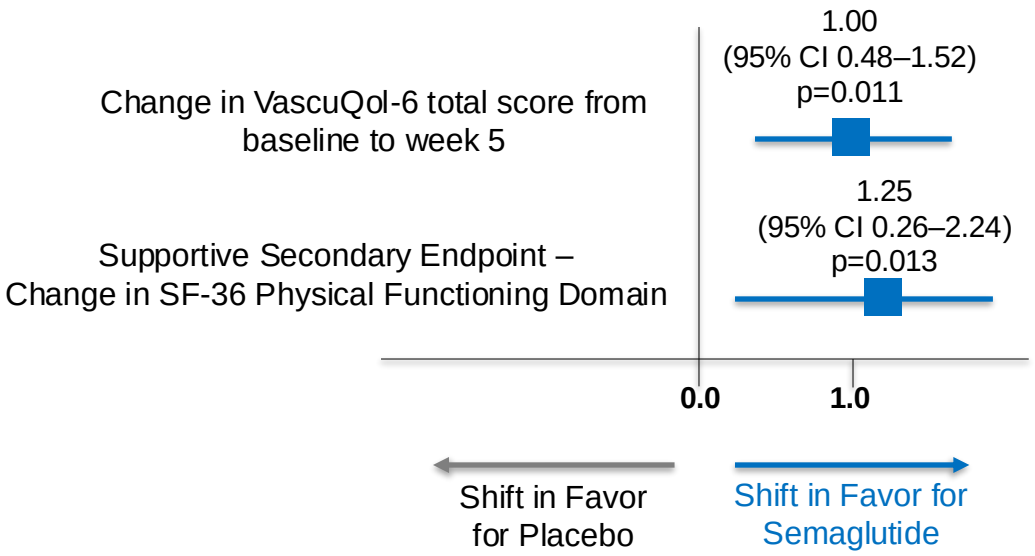


Secondary and Exploratory Outcomes

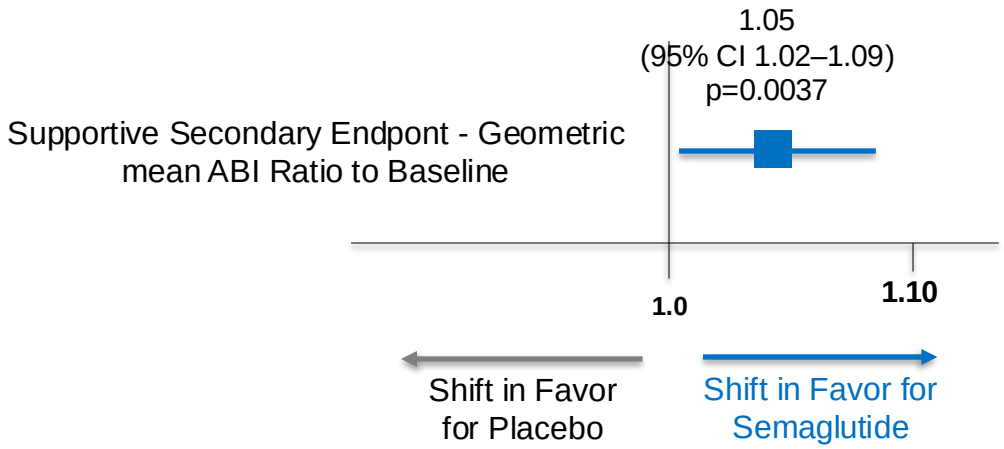
Function



Quality of Life



Hemodynamics



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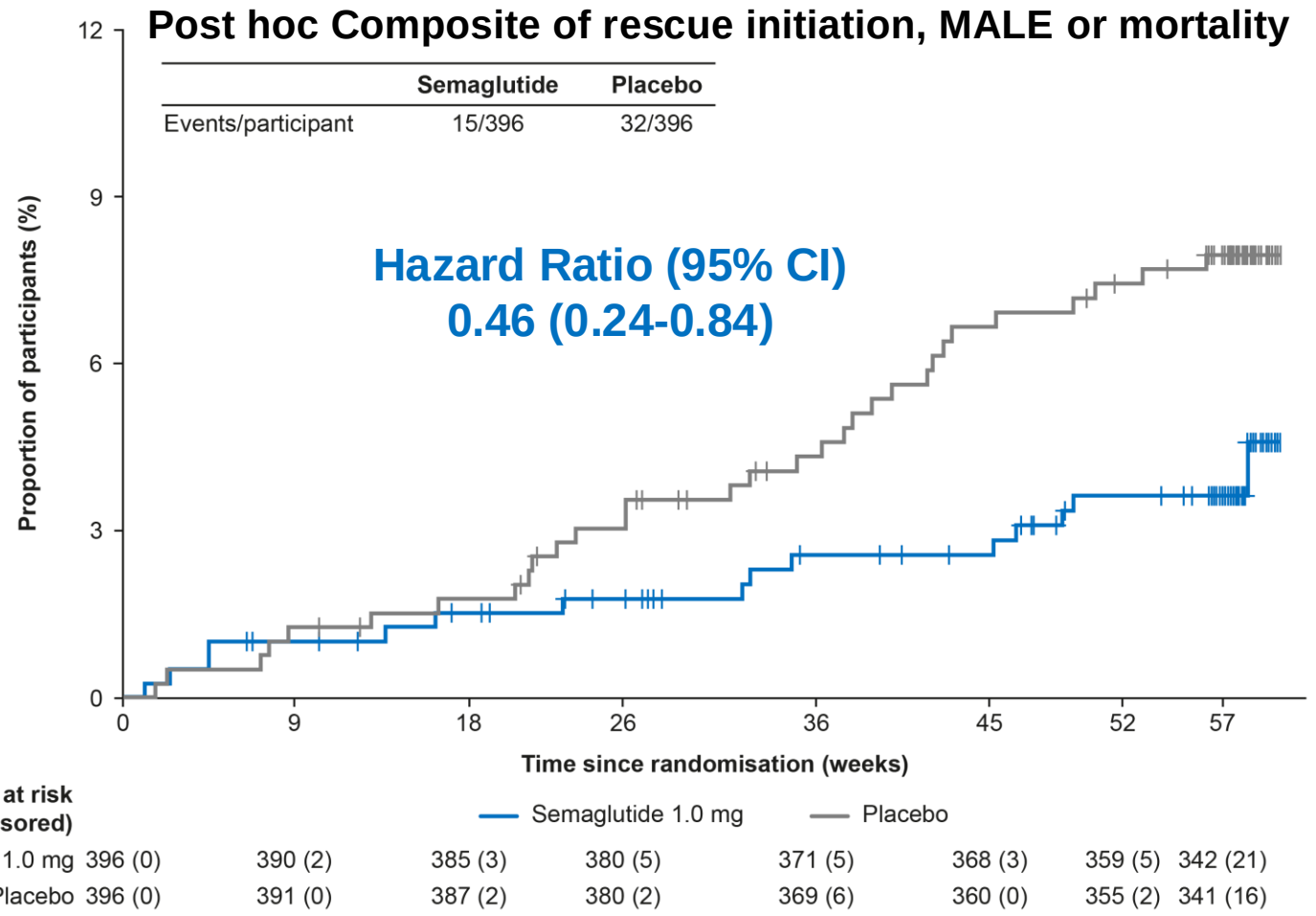
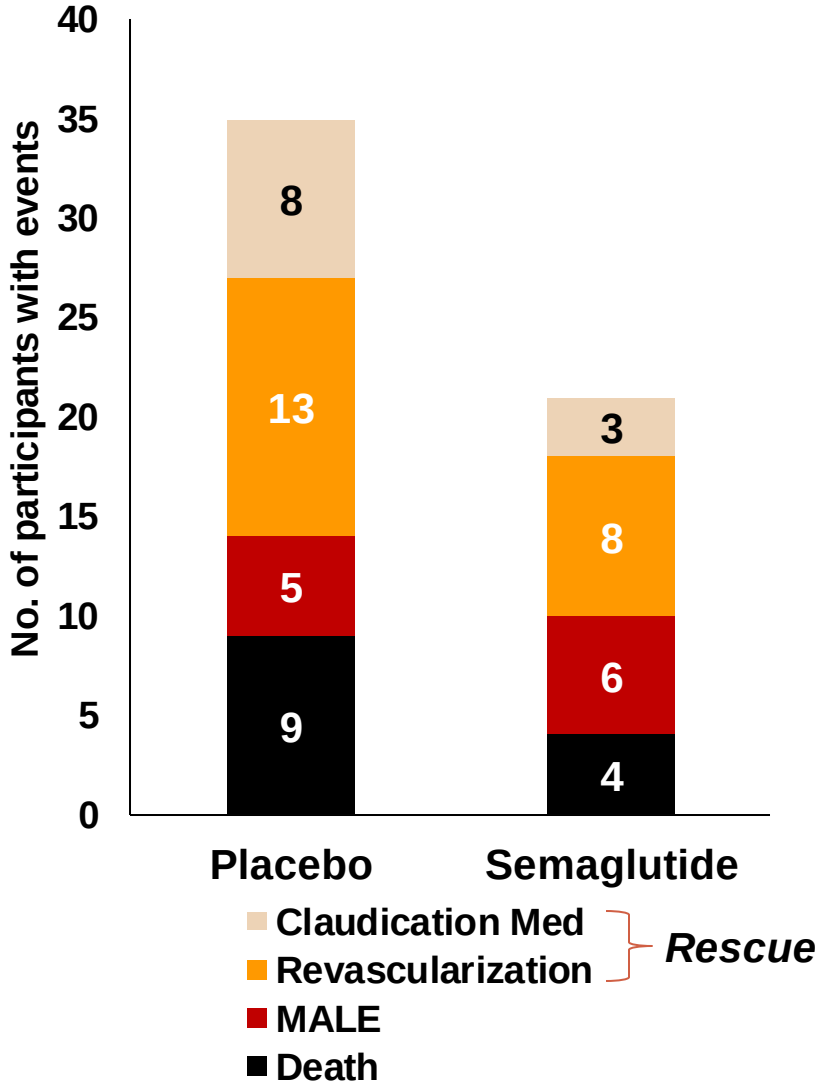
Exploratory Clinical Analysis





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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
Probably treatment related*	2 (1)	3	0·7	2 (1)	3	0·7
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
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	0 (0)	0	0

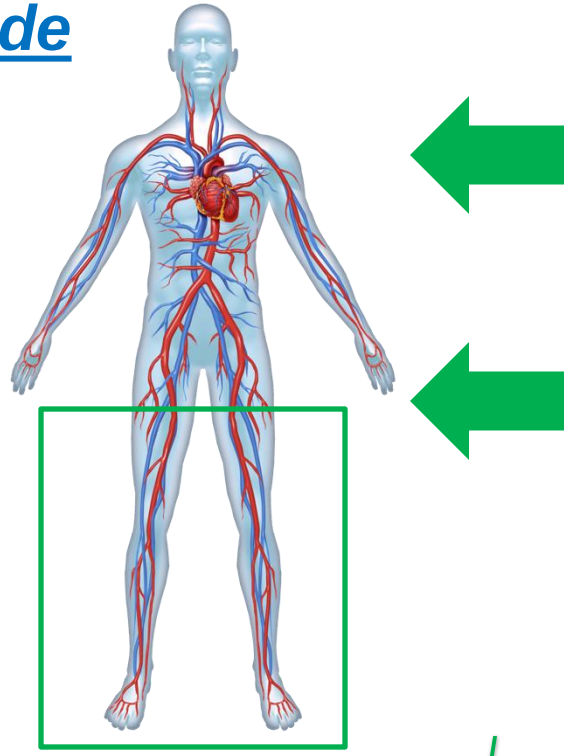
Summary

Semaglutide

↓ Weight

↓ Cardiometabolic risk

↑ Function & ↓ symptoms in HF



↓ MACE in ASCVD

↓ Kidney outcomes

Improves function √

Improves symptoms √

Improves hemodynamics √

Reduces progression → rescue (e.g. revascularization) √

- Significantly improved MWD and PFWD, similar in magnitude to cilostazol (class I) and met prespecified criteria for a clinically meaningful change
- Significantly improved in all supportive secondary outcomes including two QOL measures
- Reduced in progression requiring rescue treatment
- Improved in ABI
- Limitation: patients without T2DM were not included and should be studied in future trials

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Wilding JPH et al. *N Engl J Med* 2021;384(11):989–1002; Kosiborod MN et al. *N Engl J Med* 2023;389:1069–1084; Lincoff AM et al. *N Engl J Med* 2023;389(24):2221–2232; Perkovic V et al. *N Engl J Med* 2024;391(2):109–121; Li M et al. Sleep, 2024;zsae280. Online ahead of print. doi:10.1093/sleep/zsae280.

Conclusion

Semaglutide is the first therapy to ↓MACE, improve cardiometabolic and kidney outcomes, and improve walking capacity and related quality of life in Patients with PAD and Type 2 Diabetes

We have a new treatment for PAD!

Simultaneous Publication

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