

Treatment with Once-Weekly Semaglutide 2.4 mg Improves Cardiometabolic Risk Factors in Adults with Overweight/Obesity and Type 2 Diabetes: STEP 2 Post-hoc Analysis

Lorraine Albon¹; Robert F Kushner²; Melanie Davies³; John E Deanfield⁴; W Timothy Garvey⁵; Ole Kleist Jeppesen⁶; Usman Khalid⁶; Mikhail Kosiborod⁷; Peter Norkjaer Laursen⁶; Domenica M Rubino⁸; Subodh Verma⁹

Aim

- To further explore the effect of semaglutide 2.4 mg vs 1.0 mg and placebo on cardiometabolic risk factors in the Semaglutide Treatment Effect in People with obesity (STEP) 2 trial.
- Post-hoc analyses were conducted to explore whether the magnitude of weight loss affected cardiometabolic risk factors.

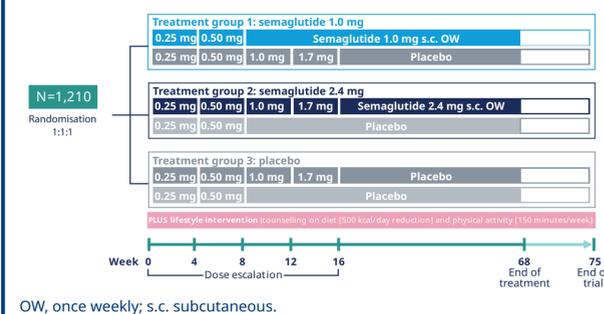
Introduction

- Over 90% of people with type 2 diabetes (T2D) have overweight/obesity.¹
- Weight loss has been shown to improve glycaemic control and reverse diabetes progression in people with established disease.²
- The glucagon-like protein-1 receptor agonist (GLP-1RA) subcutaneous (s.c.) semaglutide at a dose of 2.4 mg dose is being investigated for obesity pharmacotherapy in the STEP programme.³
- The STEP 2 trial evaluated the efficacy and safety of once-weekly s.c. semaglutide 2.4 mg vs 1.0 mg and placebo for weight management in adults with overweight/obesity and T2D.⁴

Methods

- Eligibility criteria for STEP 2 participants included:
 - Male or female aged ≥18 years old, with body mass index ≥27 kg/m² and HbA_{1c} 7–10% (53–86 mmol/mol).
 - T2D diagnosis ≥180 days prior to screening.
 - T2D managed with diet and exercise, or with stable dose of ≤3 oral glucose-lowering agents (metformin, sulphonylureas, sodium-glucose co-transporter 2 inhibitors, or thiazolidinediones).
 - ≥1 self-reported unsuccessful dietary effort to lose weight.
- Patients were randomised to semaglutide 1.0 mg, 2.4 mg, or placebo for 68 weeks (Figure 1).

Figure 1: STEP 2 design: a randomised, double-blind, multicentre, placebo-controlled trial



¹Western Sussex Hospitals NHS Foundation Trust, St Richards Hospital, Chichester, UK; ²Division of Endocrinology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; ³Diabetes Research Centre, Department of Health Sciences, University of Leicester, Leicester, UK; ⁴NIHR Leicester Biomedical Research Centre, Leicester, UK; ⁵Institute of Cardiovascular Science, University College London, London, UK; ⁶Department of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, AL, USA; ⁷Novo Nordisk A/S, Søborg, Denmark; ⁸Department of Cardiovascular Disease, Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA; ⁹Washington Center for Weight Management and Research, Arlington, VA, USA; ¹⁰Division of Cardiac Surgery, Li Ka Shing Knowledge Institute of St Michael's Hospital, Unity Health Toronto, Toronto, ON, Canada. This trial was sponsored by Novo Nordisk A/S and is registered with ClinicalTrials.gov (NCT03552757). Presenter Lorraine Albon reports honoraria from Mylan, Novo Nordisk and Lilly. The authors acknowledge the medical writing assistance of Paul Barlass of Axis, a division of Spirit Medical Communications Group Limited; and editorial updates by Ashfield Health. Presented at the Association of British Clinical Diabetologists (ABCD), 14 October 2021, virtual meeting.

- To mitigate risk of hypoglycaemia, patients on sulphonylureas were to reduce the dose by approximately 50% at treatment start, at the investigator's discretion. Patients could intensify glucose-lowering therapy as judged by the investigator. Insulin was permitted only in cases of persistent hyperglycaemia.
- Change from baseline to week 68 was assessed for the following cardiometabolic endpoints: waist circumference, HbA_{1c}, fasting plasma glucose (FPG), fasting serum insulin (FSI), systolic and diastolic blood pressure (SBP and DBP), lipids (triglycerides, non-high-density lipoprotein [HDL] cholesterol [post-hoc analysis], low-density lipoprotein [LDL] cholesterol), and C-reactive protein.
- The effect on cardiometabolic risk was evaluated in the overall population (primary analysis), and in those who achieved <10% and ≥10% weight loss (post-hoc analysis).

Results

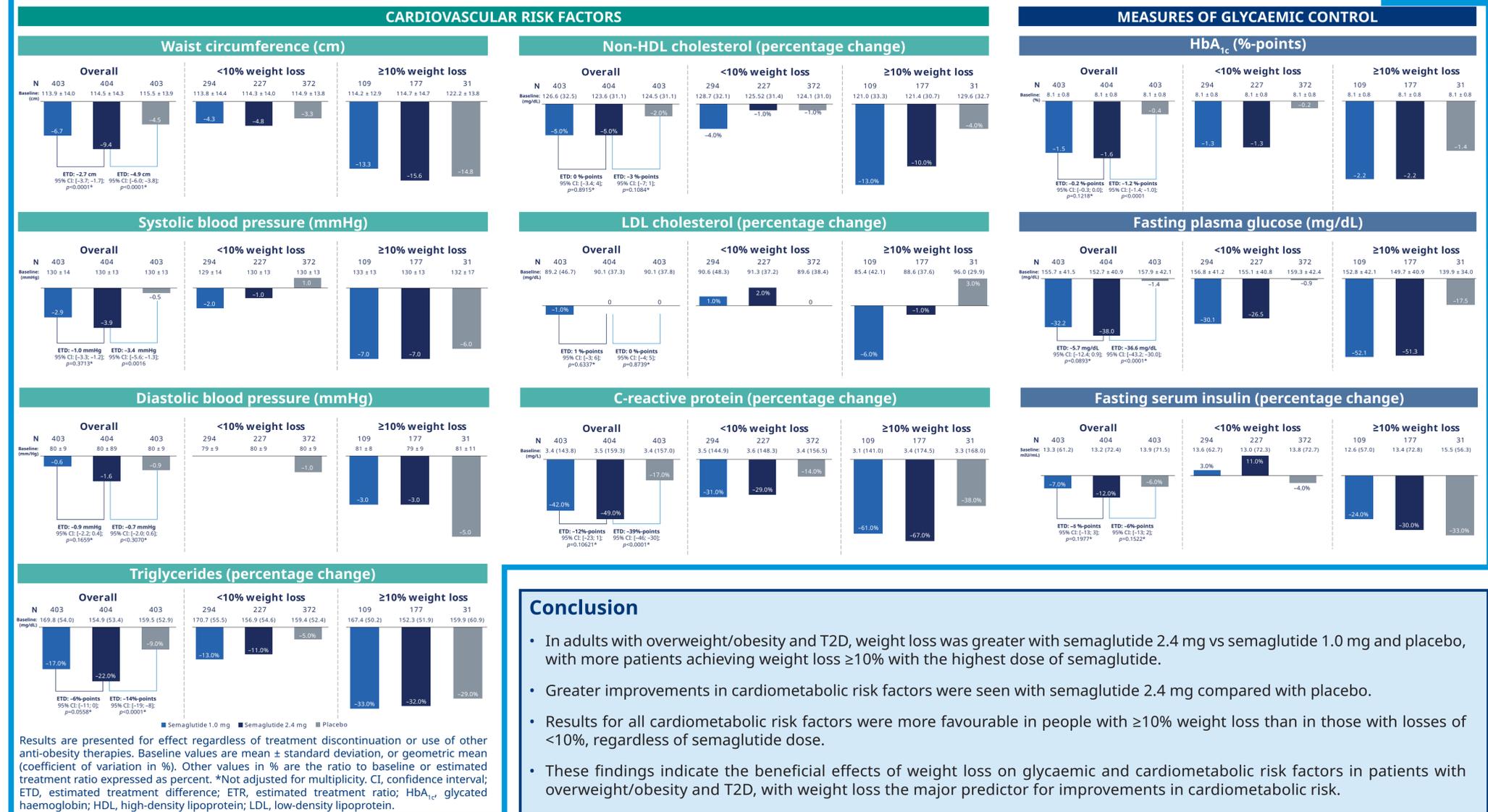
- At baseline, patients had a mean age of 55 years, body weight of 99.8 kg, HbA_{1c} of 8.1%, and diabetes duration of 8 years (Table 1); 88% were on 1–2 oral antihyperglycaemic drugs.
- Mean percentage change in body weight from baseline to week 68 was significantly greater with semaglutide 2.4 mg (–9.6%) vs placebo (–3.4%) and vs semaglutide 1.0 mg (–7.0%) (estimated treatment difference [ETD] vs placebo: –6.2 %-points; ETD vs semaglutide 1.0 mg: –2.7 %-points; both *p*<0.0001).
- Semaglutide 2.4 mg significantly improved cardiometabolic risk factors vs placebo from baseline to week 68, including for waist circumference, HbA_{1c}, SBP, triglycerides, C-reactive protein and FPG (all *p*<0.01) (Figure 2).
- Improvements in cardiometabolic risk factors were similar with semaglutide 2.4 mg and 1.0 mg, except for change in waist circumference, which favoured semaglutide 2.4 mg (Figure 2).
- For all cardiometabolic risk factors, improvements were greater in those patients who achieved ≥10% weight loss from baseline to week 68 than in those with weight losses of <10% (Figure 2).

Table 1: Demographics and baseline characteristics

	Total population (N=1,120)
Sex, female, %	50.9
Mean age, years	55
Race, %	
White	62.1
Asian	26.2
Other*	11.7
Mean HbA _{1c} , % (mmol/mol)	8.1 (65.3)
Mean duration of diabetes, years	8
Mean body weight, kg (lbs)	99.8 (220.0)
Mean BMI, kg/m ²	35.7
Mean waist circumference, cm (inches)	114.6 (45.1)

*Includes not applicable, American Indian or Alaskan Native, Black or African American, Native Hawaiian or other Pacific Islander, and other. BMI, body mass index; HbA_{1c}, glycated haemoglobin.

Figure 2: Change from baseline to week 68 in cardiometabolic risk factors



Conclusion

- In adults with overweight/obesity and T2D, weight loss was greater with semaglutide 2.4 mg vs semaglutide 1.0 mg and placebo, with more patients achieving weight loss ≥10% with the highest dose of semaglutide.
- Greater improvements in cardiometabolic risk factors were seen with semaglutide 2.4 mg compared with placebo.
- Results for all cardiometabolic risk factors were more favourable in people with ≥10% weight loss than in those with losses of <10%, regardless of semaglutide dose.
- These findings indicate the beneficial effects of weight loss on glycaemic and cardiometabolic risk factors in patients with overweight/obesity and T2D, with weight loss the major predictor for improvements in cardiometabolic risk.

References:
 (1) Bramante CT, et al. Diabetes Spectr. 2017;30:237–43; (2) Wilding JP. Int J Clin Pract. 2014;68:682–91; (3) Kushner RF, et al. Obesity (Silver Spring). 2020;28:1050–61; (4) Davies M, et al. Lancet. 2021;397:971–84.