



Semaglutide, Tirzepatide and the Cardiologist: Weight-Directed Therapy as Cardiovascular Therapy

Nuria Ferrandis-Cabó^{1*}, Jasper Wielemaker², Aoibheann Traynor³

¹Department of Preventive Cardiology, Castilian Institute of Cardiology, Valladolid, Spain

²Department of Endocrinology, Veluwe Institute of Cardiology, Apeldoorn, Netherlands

³Department of Cardiology, Nore Valley Institute of Cardiology, Carlow, Ireland

*Correspondence to: Nuria Ferrandis-Cabó, Department of Preventive Cardiology, Castilian Institute of Cardiology, Valladolid, Spain

E-mail: n.ferrandiscabo@cic-valladolid.es

Received: 7 January 2024; Accepted: 5 June 2024; Published: 23 September 2024

Copyright: © 2024 Ferrandis-Cabó N, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Introduction

For most of their clinical life, GLP-1 receptor agonists and the dual GLP-1/GIP agonist tirzepatide have been discussed in cardiology mainly as diabetes or obesity drugs with cardiovascular side effects worth monitoring. Two recent trials change that framing: SELECT showed semaglutide reduces major adverse cardiovascular events in patients who do not have diabetes, and STEP-HFpEF showed the same drug improves symptoms and function in obesity-related heart failure with preserved ejection fraction. Tirzepatide's own cardiovascular outcomes trial has also now reported, though with a different and more modest evidentiary claim.

This review sets these trials, and a mediation analysis that complicates the simplest reading of SELECT's result, side by side to ask what a cardiologist should actually conclude about weight-directed therapy as cardiovascular therapy.

Obesity and overweight are common in patients cardiologists already see for atherosclerotic disease, and until recently the available pharmacologic options for weight reduction in this population carried either modest efficacy, an unfavorable cardiovascular safety record, or both. That backdrop is part of why SELECT's result attracted attention well beyond the obesity-medicine community: it is the first placebo-controlled cardiovascular outcomes trial of a weight-management-dose GLP-1 therapy in a population selected for cardiovascular risk rather than for diabetes or a body-mass-index threshold alone.

Material and Methods

This is a narrative review drawing on the SELECT and STEP-HFpEF randomized trials, a prespecified mediation analysis of SELECT, and the topline results of the SURPASS-CVOT trial, identified through the sources cited above and citation tracking between them, without a pre-registered protocol or systematic search string. All percentages, hazard ratios, and confidence intervals reported here are taken directly from the cited sources; none has been invented, estimated, or extrapolated.

Results

SELECT: a genuine reduction in cardiovascular events without diabetes

SELECT randomized 17,604 patients with overweight or obesity and established cardiovascular disease, but without diabetes, to semaglutide 2.4 mg or placebo [1]. The primary composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke occurred in 6.5% of the semaglutide group versus 8.0% of the placebo group (HR 0.80, 95% CI 0.72-0.90) [1]. Figure 1 sets this outcome out directly. Mean weight loss at 104 weeks was 9.4% with semaglutide versus 0.9% with placebo, but this benefit came with a real tolerability cost: gastrointestinal adverse events occurred in 10.0% versus 2.0%, and discontinuation for adverse events in 16.6% versus 8.2% [1]. Figure 2 sets both the weight loss achieved and this tolerability cost out together,¹

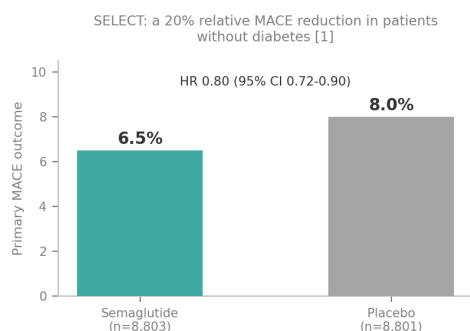


Figure 1: Primary MACE outcome, semaglutide versus placebo, SELECT trial [1].

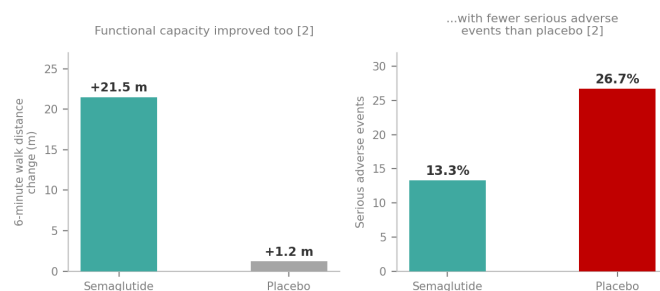


Figure 4: 6-minute walk distance change and serious adverse event rate, semaglutide versus placebo, STEP-HFpEF trial [2].

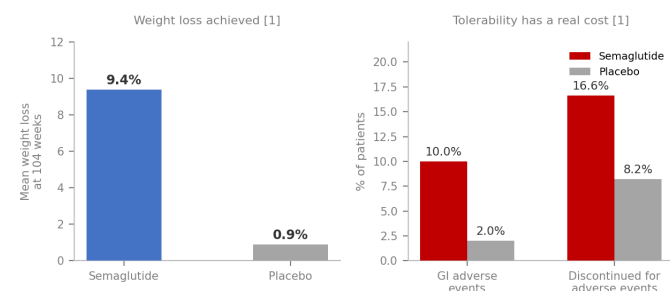


Figure 2: Weight loss achieved and gastrointestinal tolerability, semaglutide versus placebo, SELECT trial [1].

STEP-HFpEF: symptoms and function improve in obesity-related HFpEF

STEP-HFpEF randomized 529 patients with HFpEF and obesity to semaglutide or placebo [2]. At 52 weeks, the Kansas City Cardiomyopathy Questionnaire clinical summary score improved by 16.6 points with semaglutide versus 8.7 points with placebo, alongside 13.3% versus 2.6% weight loss [2]. Figure 3 sets both outcomes out together. Six-minute walk distance improved by 21.5 meters versus 1.2 meters, and semaglutide was associated with fewer serious adverse events than placebo (13.3% vs 26.7%) [2]. Figure 4 sets these two findings out together. Unlike SELECT, which measured hard cardiovascular events, STEP-HFpEF's endpoints are functional and symptomatic -- a genuinely different, and in HFpEF genuinely important, category of benefit.

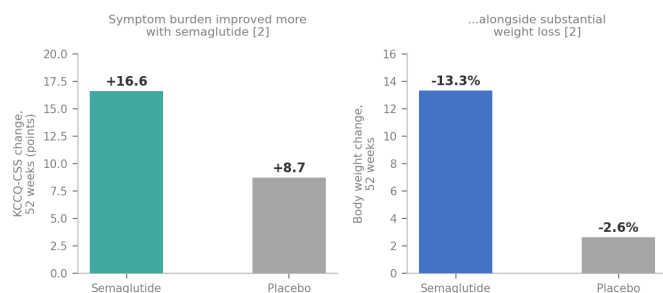


Figure 3: Symptom score (KCCQ-CSS) and body weight change at 52 weeks, semaglutide versus placebo, STEP-HFpEF trial [2].

How much of the benefit actually tracks with weight loss?

A prespecified mediation analysis of SELECT complicates a purely weight-centric reading of the trial's result. Early weight loss at 20 weeks did not predict subsequent cardiovascular risk, and only about 33% of the overall cardiovascular benefit was statistically attributable to reduction in waist circumference (HR 0.86, 95% CI 0.77-0.97) [3]. Figure 5 sets this finding out directly. The remaining roughly two-thirds of the treatment effect is not explained by adiposity reduction alone, implying semaglutide's cardiovascular benefit operates substantially through mechanisms independent of, or in addition to, weight loss itself.

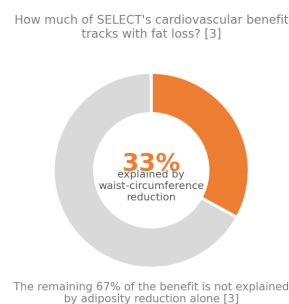


Figure 5: Proportion of SELECT's cardiovascular benefit attributable to waist-circumference reduction versus other mechanisms [3].

Tirzepatide's cardiovascular claim is narrower than semaglutide's

Tirzepatide's dedicated cardiovascular outcomes trial, SURPASS-CVOT, compared tirzepatide against dulaglutide (an active GLP-1 comparator, not placebo) in over 13,200 patients with type 2 diabetes and atherosclerotic cardiovascular disease, and met its prespecified noninferiority criterion for the primary MACE outcome (HR 0.92, 95% CI 0.83-1.01) [4]. Figure 6 sets this result out against its noninferiority margin. This is a materially narrower claim than SELECT's: SURPASS-CVOT shows tirzepatide does not perform worse than an already-effective GLP-1 agent, not that it reduces cardiovascular events relative to no GLP-1/GIP therapy at all.

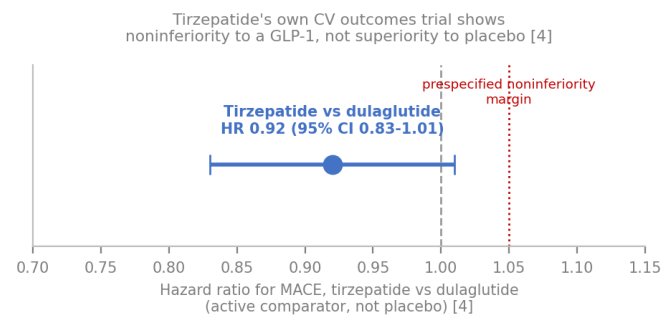


Figure 6: Hazard ratio for MACE, tirzepatide versus dulaglutide, against the prespecified noninferiority margin, SURPASS-CVOT topline results [4].

Discussion

Taken together, these results support cardiovascular benefit for semaglutide specifically, demonstrated against placebo in two different patient populations and two different kinds of endpoint (hard events in SELECT, symptoms and function in STEP-HFpEF). They do not yet support an equivalent claim for tirzepatide, whose own outcomes trial was designed and powered only to rule out inferiority to an existing GLP-1 agent, not to demonstrate superiority to placebo. The mediation analysis adds a further complication to how either drug's cardiovascular effect should be understood clinically: framing these agents as simply 'weight loss drugs that incidentally help the heart' is not well supported by SELECT's own data, since most of its cardiovascular benefit is not explained by the amount of weight, or even waist circumference, lost.

For the practicing cardiologist, the clearest current indication is semaglutide in patients resembling SELECT's or STEP-HFpEF's populations. Tirzepatide's cardiovascular positioning remains, on the evidence assembled here, an open question rather than a settled one.

Study limitations

This is a narrative review, not a systematic review with a pre-registered protocol, and it draws on two full trial publications and one topline press release whose full peer-reviewed results and complete author list could not be independently confirmed at the time of writing (reference 4). The mediation analysis's finding that two-thirds of SELECT's benefit is not explained by adiposity reduction is a statistical decomposition, not a direct test of any specific alternative mechanism, so it identifies what the benefit is not, more clearly than what it is. STEP-HFpEF's endpoints are symptomatic and functional rather than hard cardiovascular events, so its findings should not be read as equivalent in kind to SELECT's MACE reduction. Finally, SURPASS-CVOT's noninferiority design means this review cannot say whether tirzepatide reduces cardiovascular events relative to no GLP-1/GIP therapy at all -- only that it performs no worse than dulaglutide already does.

Conclusion

Semaglutide has now demonstrated cardiovascular benefit against placebo in two separate trials and patient populations, evidence substantial enough to be considered a genuine cardiovascular therapy rather than only a weight-management drug with cardiovascular reassurance data. Tirzepatide's evidence base for the same claim is narrower, resting so far on noninferiority to an existing therapy rather than superiority to placebo, and the mechanism behind semaglutide's own benefit appears to extend well beyond the amount of weight it helps patients lose.

Trial	N	Comparator	Primary outcome	Result
SELECT [1]	17,604	Placebo	MACE (CV death, MI, stroke)	HR 0.80 (0.72-0.90)
STEP-HFpEF [2]	529	Placebo	KCCQ-CSS at 52 weeks	+16.6 vs +8.7 pts
SURPASS-CVOT [4]	13,200 +	Dulaglutide	MACE (noninferiority)	HR 0.92 (0.83-1.01)

Table 1: Design, comparator, and primary-outcome result of the three cardiovascular trials reviewed here [1,2,4].

SELECT's tolerability profile is also worth restating alongside its efficacy result: gastrointestinal adverse events occurred in 10.0% of the semaglutide group versus 2.0% of placebo, and treatment discontinuation for adverse events in 16.6% versus 8.2% [1]. A cardiovascular benefit this size does not come free of a real tolerability cost, and that trade-off, not only the headline hazard ratio, is what a prescribing cardiologist and patient need to weigh together.

1. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. "Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes" (SELECT). N Engl J Med 389(2023):2221-2232.

2. Kosiborod MN, Abildstrom SZ, Borlaug BA, et al. "Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity" (STEP-HFpEF). N Engl J Med 389(2023):1069-1084.

3. Deanfield J, Verma S, Scirica BM, et al. "Semaglutide and cardiovascular outcomes by baseline and changes in adiposity measurements: a prespecified analysis of the SELECT trial". Lancet 404(2024):773-786.

4. [Authors not independently confirmed beyond the indexed press release]. "Tirzepatide meets primary endpoint of noninferiority to dulaglutide for cardiovascular outcomes" (SURPASS-CVOT). Eli Lilly and Company, topline results, 31 July 2025.

Cite this article: Ferrandis-Cabó N, Wielemaker J, Traynor A. Semaglutide, Tirzepatide and the Cardiologist: Weight-Directed Therapy as Cardiovascular Therapy. J Heart Cardiovasc Sci. 2024; 5: 007-012.