High Blood Pressure & Cardiovascular Prevention
https://doi.org/10.1007/s40292-024-00626-4

EDITORIAL

Obesity and Overweight: The "Elephant in the Room" That We can No Longer Ignore: Time to SELECT Treatments

Armando Ferrera[1] · **Giovanna Gallo**[1] · **Massimo Volpe**[1,2]

Received: 4 January 2024 / Accepted: 17 January 2024

In the last decades the prevalence of obesity and overweight show an unrelenting trend to increase in all age and sex groups, irrespective of geographical areas, ethnicity, or socioeconomic conditions. In May 2022, the World Health Organization (WHO) released a study on the state of the obesity pandemic in Europe, indicating that 60% of European inhabitants are either overweight or obese. The Global Burden of Disease estimates that more than 600 million people worldwide are obese [1]. Nearly one-third of the world's population is predicted to be overweight or obese in developed countries within the next few years [2].

Obesity has negative health effects, and it is directly involved in the development of cardiovascular disease (CVD) through different pathophysiological mechanisms, mostly a state of chronic low-grade inflammation, as well as indirectly through the development of cardiometabolic (CV) risk factors, such as high blood pressure, pre-diabetes or diabetes and atherogenic dyslipidemia. Despite the impressive advances in the therapeutic management of CV risk factors, patients with established CVD and obesity continue to be at considerable increased risk [3]. In this view, it seems of paramount importance to recognize obesity in clinical practice as well as to increase and intensify the efforts to reduce obesity-related cardiometabolic risk in order to diminish the current burden of CV disease in large segments of the population [4–6].

In this regard, international guidelines have been so far rather shy and have frequently issued marginal recommendations on the need to treat obesity mostly based on generic life-style advice. The latest European Society of Cardiology guidelines on CVD prevention in clinical practice recommend that obese and overweight people "should" aim for a reduction in weight to improve their CV risk profile [7]. This general attitude has not really encouraged individual physicians to take action to fight body weight excess and its consequences. Recently, large trials and meta-analyses have shown the favorable effects of pharmacological interventions on body weight loss, blood pressure reduction, glycemic control and CV mortality, compared with lifestyle intervention alone [8]. New compounds such as liraglutide and semaglutide, two Glucagon Like peptide-1 receptor agonists (GLP-1RA), originally developed to treat diabetes, have been successfully used to treat obesity achieving persistent weight loss in diabetic and non-diabetic individuals [9–12].

Most recently, a significant gap in knowledge about the potential CV benefits of a GLP-1RA compound was filled by the results of a large study performed in non-diabetic high CV risk patients, the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial [13], published in the New England Journal of Medicine in November 2023.

The SELECT trial extends the findings of Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6) trial and other GLP-1 RAs trials, which have demonstrated CV benefits in diabetic population with high CV risk [11].

The SELECT trial is a company-funded, multicenter, double-blind, randomized, placebo-controlled, event-driven superiority trial in which 17,604 patients were randomly assigned (1:1) to receive once weekly subcutaneous semaglutide 2.4 mg or placebo. The primary objective was to demonstrate that semaglutide added to standard of care lowered the incidence of major adverse cardiovascular events (MACE) in participants with established CV disease and overweight or obesity. Secondary objectives were to compare the effects of semaglutide 2.4 mg vs placebo on mortality, CV risk factors, glucose metabolism and body weight.

Main inclusion criteria were adult male or female individuals aged ≥ 45 years; Body Mass Index (BMI) ≥ 27 kg/m^2;

✉ Massimo Volpe
massimo.volpe@uniroma1.it

[1] Department of Clinical and Molecular Medicine, University of Rome Sapienza, Rome, Italy

[2] IRCCS San Raffaele Rome, Rome, Italy

Published online: 04 February 2024

prior myocardial infarction (MI), prior stroke, or symptomatic peripheral arterial disease (PAD).

Key exclusion criteria were history of diabetes mellitus (DM) or hemoglobin A1c (HbA1c) $\geq 6.5\%$, treatment with glucose-lowering agents within the past 90 days and heart failure in New York Heart Association (NYHA) class IV.

Seventy-one percent of the participants were obese (mean BMI of the study population 33.3 kg/m^2), 66% had prediabetes (HbA1c 5.7–6.4%) and 88% of patients were on statin therapy.

After about 40 months of follow-up, once-weekly dose of subcutaneous semaglutide, during a mean exposure period of 33 months, resulted in a 20% reduction of the composite outcome of death from CV causes, nonfatal MI, or nonfatal stroke, with a consistent trend to reduction seen for each component of the composite outcome as well as for death from any cause which was also reduced by about 20%. The Kaplan–Meier curves revealed an early separation of the event trends observed in the semaglutide and placebo group, suggesting a prompt benefit of the active treatment. Semaglutide led to a mean change in body weight of -9.4%; the steady state of body weight reduction was achieved in about 10 weeks and it was sustained throughout the follow up of the trial. Even in the context of widespread concurrent statin treatment, the benefit was recorded.

Study drug discontinuation was more common with semaglutide than with placebo and was primarily due to gastrointestinal intolerance (10.0% vs. 2.0%), a known side effect of GLP-1 RAs [14], although serious adverse events were similar or less common with semaglutide.

The cardioprotective effects of GLP-1 RAs are not fully understood and most likely recognize a multifactorial nature. The larger reductions observed in both systolic blood pressure and incidence of DM in the treatment arm may have played a role. The latter is significant because of the prevalence of pre-diabetes in the study cohort as well as the associated interaction on exploratory subgroup analysis. Also, the reductions observed with semaglutide in LDL-cholesterol and C-reactive protein, as a biomarker of chronic inflammation, are to be considered as potential contributory factors. Altogether, these results, beside the possible GLP1-RA-linked direct mechanistic actions, reveal that subcutaneous semaglutide may play a specific role in secondary CVD prevention in overweight/obese patients without DM.

In this perspective, several noteworthy findings from this trial may need to be highlighted. First, major strengths of the study are the large and representative population and the three-year follow-up, that in addition to a realistic sample size calculation, preserved the planned statistical power of the study. Secondly, the effects of semaglutide were independent of the baseline BMI range and were observed also in overweight patients with a BMI below 30. Third, on average, semaglutide treatment led to a substantial reduction in body weight of 9.4% in the study group. In such a context, it is still unknown whether the extent of these findings depends on weight loss, concurrent reductions in risk factors, or other beneficial mechanisms of GLP-1 RAs. Indeed, in SUSTAIN-6, semaglutide reduced the risk of CV events in patients with diabetes by 26%, even though the reduction in body weight was only 4 to 5% with the use of lower doses [11]. Fourth, in the SELECT trial, semaglutide consistently improved total CV risk profile as it had a favorable impact on lipid profile, inflammatory markers, and blood pressure. Finally, and most importantly, the fact these benefits of semaglutide were obtained in a large study performed in non-diabetic patients opens a new clinical scenario in relation to the clinical indications of GLP1-RA.

The main limitations of the study included the underrepresentation of women (28% of the participants), Black, Asian, and Hispanic or Latino populations, and the fact that the trial was not powered to analyze statistical significance for mortality. Future analyses may help to clarify the pathophysiological mechanisms of GLP1-RA benefits in CVD and to extend the results of the study in clinical practice.

Although the SELECT trial may offer a much-needed treatment option for million patients worldwide, especially those with a persistently high residual risk of atherosclerotic CVD despite an adequate control of the major CV risk factors [11], the current results need to be interpreted with caution in terms of public health strategies to fight obesity and its relations with raised CV risk. Semaglutide, in fact, is expensive for both patients and healthcare systems at the current GLP-1RAs pricing, rendering this treatment substantially unaffordable for many people. In addition, the estimated number needed to treat to prevent a CVD event in the high-risk population of SELECT reveals that a relatively limited proportion of patients may achieve the greatest benefit from the treatment. Finally, the safety profile of Semaglutide at this dosage in the long-term may need to be consolidated with further long-term observations.

In spite of these considerations, obesity definitely represents an underestimated clinical problem in the practice of cardiologists [15] and a prompt revision of its contemporary management needs to be undertaken also in the light of the impressive results of SELECT with the aim to consider this condition as a preventable and treatable chronic disease [16, 17].

SELECT, in fact, throws two important messages on the working table of the management of obesity and overweight: (1) The study provides a convincing proof that, at least in the high-risk clinical context, body weight reduction achieved with drug treatment is highly beneficial, is well tolerated and safe (also in view of the reduction of all-cause mortality); (2) Treatment with semaglutide at the dosage used in the study prevents non-fatal myocardial infarction in secondary prevention and

this provides a new therapeutic weapon to be considered in designing future strategies of CVD prevention.

Intensive lifestyle interventions and bariatric surgery are useful but often problematic and underutilized options along the obesity treatment continuum, especially in under-resourced populations that are disproportionately affected by obesity. The approach based on implementing lifestyle changes or by addressing patients to surgery has quite likely discouraged effective virtuous clinical behaviors in the clinical practice, even at the level of cardiologists in both recognizing and treating obesity [18].

A final word must be said on the fact that a major objective should be to prevent obesity before it starts. This is a complex issue which involves economic, environmental, and psychological factors contributing to incident obesity. Thus, equity-focused obesity prevention and treatment initiatives are needed to address obesity at multiple integrated levels to achieve this goal.

In conclusion, the SELECT trial shows that GLP-1 receptor agonists improve CVD outcomes in the absence of diabetes in patients with atherosclerotic CVD who are overweight or obese. Semaglutide joins the list of proven therapies useful to reduce the burden of CVD. According to the researchers, in the SELECT trial for the first-time a pharmacological treatment has been proven to reduce CV events in adults with overweight or obesity without DM. Until now, obesity was a chronic disease without an effective therapy. Now, a new efficacious and safe weapon that can complement lifestyle changes and reduce CV events has become available. After this trial we are entering a new era of treating obesity and cardiometabolic risk and we have less excuses to ignore this condition in our clinical practice.

Acknowledgements The present work has been endorsed by the Italian Society of Cardiovascular Prevention (SIPREC).

Data availability Not applicable.

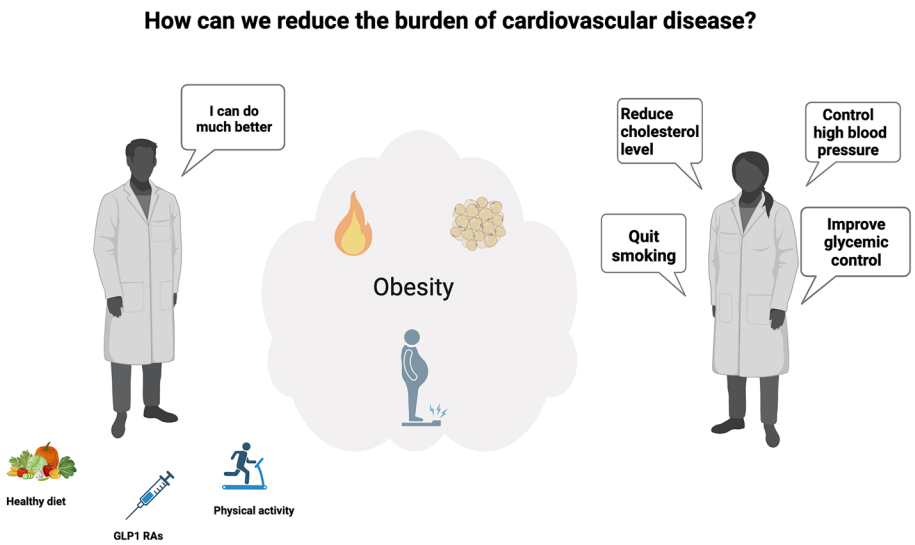
Declarations

Funding None.

Conflict of interest Authors have no conflict of interest to disclose with the contents of the present manuscript.

Ethical approval This article does not contain any studies with human participants.

Central figure How can we reduce the burden of cardiovascular disease? (created by Biorender).



References

1. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism. 2022;133: 155217.
2. Koliaki C, Dalamaga M, Liatis S. Update on the obesity epidemic: after the sudden rise, is the upward trajectory beginning to flatten? Curr Obes Rep [Internet]. 2023. https://doi.org/10.1007/s13679-023-00527-y.
3. Bovet P, Chiolero A, Gedeon J. Health effects of overweight and obesity in 195 countries. N Engl J Med. 2017;377:1495–6.
4. Volpe M, Gallo G, Modena MG, Ferri C, Desideri G, Tocci G, et al. Updated recommendations on cardiovascular prevention in 2022: an executive document of the Italian Society of Cardiovascular Prevention. High Blood Press Cardiovasc Prev Off J Ital Soc Hypertens. 2022;29:91–102.
5. Volpe M, Gallo G. Obesity and cardiovascular disease: an executive document on pathophysiological and clinical links promoted by the Italian Society of Cardiovascular Prevention (SIPREC). Front Cardiovasc Med [Internet]. 2023. https://doi.org/10.3389/fcvm.2023.1136340.
6. Obesità: da amplificatore di rischio a malattia cronica [Internet] [cited 2023 Nov 21]. https://www.siprec.it/siprec-flipbook/DOCUMENTO-SIPREC-2022/.
7. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42:3227–337.
8. Kane JA, Mehmood T, Munir I, Kamran H, Kariyanna PT, Zhyvotovska A, et al. Cardiovascular risk reduction associated with pharmacological weight loss: a meta-analysis. Int J Clin Res Trials [Internet]. 2019. https://www.graphyonline.com/archives/IJCRT/2019/IJCRT-131/index.php?page=abstract.
9. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med. 2015;373:11–22.
10. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384:989–1002.
11. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834–44.
12. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387:205–16.
13. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389:2221–32.
14. Wharton S, Davies M, Dicker D, Lingvay I, Mosenzon O, Rubino DM, et al. Managing the gastrointestinal side effects of GLP-1 receptor agonists in obesity: recommendations for clinical practice. Postgrad Med. 2022;134:14–9.
15. Ferrera A, Battistoni A, Lanza O, Rossi C, Tocci G, Volpe M. Low perception of obesity as a pathological condition among Italian cardiologists. High Blood Press Cardiovasc Prev Off J Ital Soc Hypertens. 2023;30:351–6.
16. Volpe M, Borghi C, Cameli M, Cianflone D, Cittadini A, Maggioni AP, et al. How cardiologists can manage excess body weight and related cardiovascular risk. An expert opinion. Int J Cardiol. 2023;381:101–4.
17. Volpe M, Borghi C, Cameli M, Cianflone D, Cittadini A, Maggioni AP, et al. Eight reasons why cardiologists should not overlook the problem "obesity". Expert opinion for clinical practice. G Ital Cardiol. 2023;24:677–91.
18. Ferrera A, Battistoni A, Volpe M. Obesity who? An often-disregarded player in cardiology practice and the need for an action. Eur Heart J. 2024. https://doi.org/10.1093/eurheartj/ehad875.