MOŽEMO LI SMANJITI KARDIOVASKULARNI RIZIK KOD PRETILIH BOLESNIKA?

Jasmina Ćatić[1,2], Dijana Bešić[1,2], Marin Viđak[1], Šime Manola[1,3], Ivana Jurin[1]

[1] Klinika za bolesti srca i krvnih žila, Klinička bolnica Dubrava, Zagreb, Hrvatska
[2] Medicinski fakultet Sveučilišta Josipa Jurja Strossmayera u Osijeku, Osijek, Hrvatska
[3] Medicinski fakultet Sveučilišta u Zagrebu, Zagreb, Hrvatska
e-mail: jcjasmina@gmail.com

Uvod: Značajan uspjeh cjelokupne medicinske struke u smanjenju kardiovaskularnog mortaliteta u posljednja dva desetljeća umanjen je gotovo trostrukim porastom kardiovaskularne smrtnosti povezane s prekomjernom tjelesnom masom i pretilošću. Također, ne čudi da su upravo kardiovaskularne bolesti uzrok smrti u 70% ovih bolesnika. U kontekstu ovih podataka, prijeko potrebna promjena paradigme pristupu kardiovaskularnim bolestima obuhvaća i liječenje pretilosti i prekomjerne tjelesne mase kao neovisnih rizičnih čimbenika za razvoj kardiovaskularnih oboljenja, poput koronarne bolesti srca, cerebrovaskularnih bolesti i zatajivanja srca. Stoga ne čudi da su u trenutnom središtu zanimanja kliničke studije koje ispituju utjecaj glukagonu sličnih peptida 1 (skr. GLP-1) receptora agonista, poput semaglutida, na ishode u visokorizičnih bolesnika i onih s kardiovaskularnim bolestima. Rasprava: Međunarodna, interkontinentalna SELECT (skr. od *Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity*) studija konstruirana je kao dvostruko slijepo, placebo-kontrolirano istraživanje koje je ispitivalo superiornost ranije spomenutog GLP-1 receptor agonista semaglutida u bolesnika dobne skupine ≥ 45 godina, s prekomjernom tjelesnom masom i pretilošću, odnosno indeksom tjelesne mase (skr. ITM) ≥ 27 kg/m2, te dokazanim kardiovaskularnim oboljenjem (preboljeli infarkt miokarda i/ili cerebrovaskularni inzult ≥ 60 dana od datuma uključenja u istraživanje, ili simptomatska periferna arterijska bolest). Prethodna anamneza šećerne bolesti, to jest vrijednosti glikiranog hemoglobina (skr. HbA1c) ≥ 6,5%, bila je isključni kriterij, kao i bolesnici klasificirani u New York Heart Association (skr. NYHA) funkcionalnu klasu IV. Ukupno 17605 ispitanika koji su ispunjavali uključne kriterije bilo je randomizirano u intervencijsku skupinu koja je primala semaglutid u dozi od 2,4 mg jedanput tjedno, te kontrolnu skupinu koja je primala palcebo, u omjeru 1:1. Tijekom prosječnog vremena praćenja od otprilike 40 mjeseci istraživanje je uspoređivalo pojavu velikih štetnih kardiovaskularnih događaja (engl. *major cardiovascular adverse events,* MACE), uključujući nefatalni infarkt miokarda, nefatalni cerebrovaskularni inzult i smrt od kardiovaskularnog uzroka, između dvije navedene skupine. Rezultati su pokazali da semaglutid u usporedbi s placebom statistički značajno smanjuje relativni rizik za pojavu MACE-a za 20% (omjer opasnosti – engl. *hazard ratio,* HR 0,80 [0,72–0,90]), p < 0,001. Relativni rizik mortaliteta od bilo kojeg uzroka smanjen je za 19% u odnosu

na placebo (HR 0,81 [0,71–0,93]), a razvoj kronične bubrežne bolesti (KBB) i šećerne bolesti relativno je smanjen, za 22%, odnosno 73%. Potreba za perkutanom koronarnom intervencijom bila je također statistički značajno manja u skupini ispitanika koji su primali semaglutid (HR 0,77 [0,68; 0,87]). Potrebno je napomenuti da je kod ispitanika koji su bili liječeni semaglutidom trend smanjenja relativnog rizika za MACE započeo i prije nego što su ispitanici postigli maksimalnu redukciju tjelesne mase: statistički značajni rezultati zabilježeni su već 3 mjeseca (za ishod kompozitnog MACE-a), odnosno 6 mjeseci (za ishode kardiovaskularne smrti, pogoršanja zatajivanja srca i ukupnog mortaliteta) nakon početka randomizacije. Navedeno signalizira mogućnost da je povoljan učinak na kardiovaskularne ishode ovog GLP-1 receptor agonista neovisan o pozitivnim učincima redukcije tjelesne mase. Nadalje, u STEP HFpEF (skr. *Semaglutide Treatment Effect in People with Obesity and Heart Failure with Preserved Ejection Fraction,* HFpEF) studiji, koja je obuhvaćala bolesnike sa zatajivanjem srca s očuvanom istisnom frakcijom lijeve klijetke i pretilošću, semaglutid je značajno smanjio simptome zatajivanja srca i fizičke limitacije ovih bolesnika. Rezultati ovih studija ispitivani su i u stvarnom svijetu u sklopu SCORE programa (skr. *Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity in the Real World*), iz kojeg je proizašla retrospektivna opservacijska studija u kojoj je semaglutid bio povezan sa značajnim smanjenjem rizika pojave MACE-a u bolesnika s prekomjernom tjelesnom masom ili pretilošću i aterosklerotskom kardiovaskularnom bolesti, u odnosu na placebo. S druge strane, GLP-1 receptor agonist tirzepatid bio je uspoređen sa semaglutidom u STEER (engl. *Semaglutide and Tirzepatide Effects on Cardiovascular Outcomes in People with Overweight or Obesity in the Real World*) studiji iz stvarnog svijeta. Kod bolesnika s prekomjernom tjelesnom masom ili pretilosti i aterosklerotskom kardiovaskularnom bolesti bez anamneze šećerne bolesti, semaglutid je bio povezan s manjom učestalošću MACE-a u odnosu na tirzepatid. Ovim rezultatom semaglutid je izdvojen kao specifičan GLP-1 receptor agonist, čiji povoljni učinci ne mogu biti pripisani ostalim GLP-1 receptor agonistima na tržištu. Zaključak: Zahvaljujući rezultatima navedenih studija i registara iz stvarnog svijeta, koji jasno pokazuju povoljne učinke primjene semaglutida u bolesnika s vrlo visokim kardiovaskularnim rizikom, GLP-1 receptor agonisti zaslužili su mjesto u smjernicama Europskog kardiološkog društva (engl. *European Society of Cardiology*, ESC), uključujući smjernice za zbrinjavanje kroničnog koronarnog sindroma (KKS) iz 2024. godine, prvenstveno za primjenu u bolesnika sa KKS-om i šećernom bolešću tip 2, neovisno o inicijalnim ili ciljnim vrijednostima HbA1c i konkomitantnoj hipoglikemijskoj terapiji, a s ciljem redukcije neželjenih kardiovaskularnih događaja. Semaglutid je kao jedini GLP-1 receptor agonist okrunjen i klasom preporuke IIa i levela dokaza B, za primjenu u KKS bolesnika s prekomjernom tjelesnom masom ili pretilošću, bez konkomitantne šećerne bolest tip 2, a u svrhu redukcije kardiovaskularne smrti, infarkta miokarda i moždanog udara. Sukladno navedenim smjernicama, jasno je da je upravo semaglutid neizostavni dio standardnog farmakološkog liječenja bolesnika s kardiovaskularnim oboljenjima sa šećernom bolesti tip 2, prekomjernom tjelesnom masom

i pretilošću. Ranije navedene studije signaliziraju proširenje indikacija GLP-1 agonista i semaglutida u skorijoj budućnosti i na bolesnike sa zatajivanjem srca, prvenstveno HFpEF bolesnike s fenotipom pretilosti, što bi svakako bio dobrodošao korak prema naprijed u liječenju ove heterogene i zahtjevne skupine.

Ključne riječi

pretilost, GLP-1 receptor agonist, semaglutid

CAN WE REDUCE CARDIOVASCULAR RISK IN PATIENTS WITH OBESITY?

1. Department of Cardiovascular Diseases, Dubrava University Hospital, 10000 Zagreb, Croatia
2. School of Medicine, Josip Juraj Strossmayer University of Osijek, 31000 Osijek, Croatia
3. University of Zagreb School of Medicine, 10000 Zagreb, Croatia

Introduction: The significant success of the medical profession in reducing cardiovascular mortality over the past two decades has been partly offset by an almost threefold increase in cardiovascular mortality associated with overweight and obesity. It is therefore not surprising that cardiovascular diseases account for approximately 70% of deaths in these patients. In this context, a necessary paradigm shift in the management of cardiovascular diseases includes treating overweight and obesity as independent cardiovascular risk factors for conditions such as coronary artery disease, cerebrovascular disease, and heart failure. Accordingly, clinical studies investigating the impact of glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide, on outcomes in high-risk patients and those with cardiovascular disease have become a major focus of interest. Discussion: The international, intercontinental SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial was designed as a double-blind, placebo-controlled study evaluating the superiority of the GLP-1 receptor agonist semaglutide in patients aged ≥45 years with overweight or obesity (body mass index ≥27 kg/m²) and established cardiovascular disease (prior myocardial infarction and/or cerebrovascular event ≥60 days before enrollment, or symptomatic peripheral arterial disease). A history of diabetes mellitus, defined as glycated hemoglobin (HbA1c) ≥6.5%, was an exclusion criterion, as were patients classified as New York Heart Association (NYHA) functional class IV. A total of 17,605 eligible participants were randomized 1:1 to receive either semaglutide 2.4 mg once weekly or placebo. Over a mean follow-up of approximately 40 months, the study assessed the occurrence of major adverse cardiovascular events (MACE), including nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. Semaglutide significantly reduced the relative risk of MACE by 20% compared with placebo (hazard ratio [HR] 0.80 [0.72–0.90]; p<0.001). All-cause mortality was reduced by 19% (HR 0.81 [0.71–0.93]), while the relative risk of chronic kidney disease and incident diabetes was reduced by 22% and 73%, respectively. The need for percutaneous coronary intervention was also significantly lower in the semaglutide group (HR 0.77 [0.68–0.87]). Importantly, the reduction in relative MACE risk began before participants achieved maximal weight

loss, with statistically significant differences observed as early as 3 months for the composite MACE endpoint and 6 months for cardiovascular death, worsening heart failure, and all-cause mortality. This suggests that the cardiovascular benefits of semaglutide may be partly independent of weight reduction. Furthermore, in the STEP HFpEF (Semaglutide Treatment Effect in People with Obesity and Heart Failure With Preserved Ejection Fraction) study involving patients with obesity-related HFpEF, semaglutide significantly improved heart failure symptoms and physical limitations. These findings have also been examined in real-world settings within the SCORE program (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity in the Real World), where retrospective observational data showed a significant reduction in MACE risk among overweight or obese patients with atherosclerotic cardiovascular disease treated with semaglutide compared with placebo. In contrast, the GLP-1 receptor agonist tirzepatide was compared with semaglutide in the real-world STEER study (Semaglutide and Tirzepatide Effects on Cardiovascular Outcomes in People with Overweight or Obesity in the Real World). Among overweight or obese patients with atherosclerotic cardiovascular disease and no history of diabetes, semaglutide was associated with a lower incidence of MACE compared with tirzepatide. These findings highlight semaglutide as a single GLP-1 receptor agonist whose cardiovascular benefits may not necessarily be extrapolated to all agents in the same class. Conclusion: Based on the results of these trials and real-world registry data demonstrating clear cardiovascular benefits of semaglutide in patients at very high cardiovascular risk, GLP-1 receptor agonists have been incorporated into the European Society of Cardiology (ESC) guidelines, including the 2024 ESC guidelines for the management of chronic coronary syndromes. Their use is primarily recommended in patients with chronic coronary syndromes and type 2 diabetes, regardless of baseline or target HbA1c levels and irrespective of concomitant glucose-lowering therapy, with the aim of reducing adverse cardiovascular events. Semaglutide is currently the only GLP-1 receptor agonist with a class IIa recommendation and level of evidence B for use in patients with chronic coronary syndromes who are overweight or obese without concomitant type 2 diabetes, to reduce cardiovascular death, myocardial infarction, and stroke. Accordingly, semaglutide is becoming an integral component of standard pharmacological therapy for patients with cardiovascular disease and either type 2 diabetes, overweight, or obesity. Emerging evidence also suggests a potential expansion of indications for GLP-1 receptor agonists, particularly semaglutide, to the patients with heart failure—especially those with HFpEF and an obesity phenotype—which would represent an important advance in managing this heterogeneous and challenging patient population.

Keywords

obesity, GLP-1 receptor agonist, semaglutide

References

1. GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377(1):13-27. doi:10.1056/NEJMoa1614362.
2. Raisi-Estabrach Z, et al. Association of adiposity with cardiovascular outcomes: insights from large-scale cohort analysis. J Am Heart Assoc. 2023;12:e028409. doi:10.1161/JAHA.123.028409.
3. Koskinas KC, et al. Semaglutide and cardiovascular outcomes in patients with obesity: a randomized clinical trial. Eur Heart J. 2024;45:ehae508. doi:10.1093/eurheartj/ehae508.
4. Ryan DH, et al. Design and baseline characteristics of the SELECT trial: semaglutide effects on cardiovascular outcomes in people with overweight or obesity. Am Heart J. 2020;229:61-69. doi:10.1016/j.ahj.2020.08.012.
5. Lingvay I, et al. Effects of semaglutide in patients with overweight or obesity: pooled analysis of randomized trials. Obesity (Silver Spring). 2023;31:111-122. doi:10.1002/oby.23600.
6. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al; SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389(24):2221-2232. doi:10.1056/NEJMoa2307563.
7. Butler J, et al. Semaglutide in patients with heart failure and obesity. Lancet. 2024;403(10437):1635-1648. doi:10.1016/S0140-6736(24)00489-1.
8. Kosiborod MN, et al. Semaglutide in patients with obesity-related heart failure with preserved ejection fraction. Lancet. 2024;404(10456):949-961. doi:10.1016/S0140-6736(24)01421-3.
9. Zhao Z, et al. Cardiovascular outcomes with semaglutide in obesity: results from real-world evidence. Presented at: American College of Cardiology Scientific Session; 2025 Mar 29–31; Chicago, IL.
10. Vrints C, et al; ESC Scientific Document Group. 2024 ESC guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45:3615-3726. doi:10.1093/eurheartj/ehae177.