

Rosuvastatin i ezetimib za učinkovitu prevenciju aterosklerotskih kardiovaskularnih bolesti

Rosuvastatin and Ezetimibe for Effective Prevention of Atherosclerotic Cardiovascular Disease

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SAŽETAK: Aterosklerotske kardiovaskularne bolesti (ASCVD) globalan su javnozdravstveni izazov s potencijalno fatalnim posljedicama. Ključni čimbenik u prevenciji ASCVD-a jest kontrola razine LDL kolesterola (LDL-C). Prikazujemo dva važna lijeka za snižavanje povišenih vrijednosti LDL-C-a: rosuvastatin i ezetimib. Rosuvastatin je snažan inhibitor HMG-CoA reduktaze koji znatno smanjuje LDL-C, povećava HDL kolesterol i smanjuje vrijednost triglicerida. Ezetimib, s druge strane, inhibira apsorpciju kolesterola u crijevima. Kombinacija tih lijekova omogućuje postizanje ciljanih razina kolesterola. Iako su statini temeljna terapija za snižavanje LDL-C-a, često je potrebna kombinacija s ezetimibom, osobito u bolesnika s visokim rizikom. Istraživanja pokazuju da takva kombinacija može znatno smanjiti rizik od kardiovaskularnih događaja. Unatoč smjernicama, postizanje ciljanih razina LDL-C-a u praksi je često izazovno. Kombinacija statina i ezetimiba može biti ključna u postizanju ciljeva i poboljšanju zdravlja srca. Kontrola razine LDL-C-a ključna je u prevenciji ASCVD-a. Integrirani pristup, koji uključuje pravilnu prehranu, tjelesnu aktivnost i farmakološku terapiju, ključan je za borbu protiv ovoga globalnoga javnozdravstvenog izazova.

SUMMARY: Atherosclerotic cardiovascular diseases (ASCVD) present a global public health challenge with potentially fatal consequences. The key factor in the prevention of ASCVD is the control of LDL cholesterol (LDL-C) levels. Herein we present two important agents for the reduction of elevated LDL-C levels: rosuvastatin and ezetimibe. Rosuvastatin is a potent HMG-CoA reductase inhibitor that considerably lowers LDL-C, increases HDL cholesterol, and reduces triglyceride levels. Ezetimibe, on the other hand, inhibits the intestinal absorption of cholesterol. The combination of these drugs enables achieving target cholesterol levels. Although statins are the cornerstone therapy for LDL-C reduction, they often need to be combined with ezetimibe, especially in high-risk patients. Research shows that this combination can significantly reduce the risk of cardiovascular events. Despite the guidelines, achieving target LDL-C levels is often challenging in practice. A statin/ezetimibe combination may be key to achieving set targets and improving cardiac health. Control of LDL-C levels is key in the prevention of ASCVD. An integrated approach, including healthy diet, exercise, and pharmacotherapy, is crucial in fighting this global public health challenge.

KLJUČNE RIJEČI: rosuvastatin, ezetimib, aterosklerotska kardiovaskularna bolest.

KEYWORDS: rosuvastatin, ezetimibe, atherosclerotic cardiovascular disease.

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Uvod

Aterosklerotske kardiovaskularne bolesti (ASCVD) ozbiljan su globalan javnozdravstveni izazov s potencijalno fatalnim posljedicama. Međutim, mnoge od tih bolesti mogu se učinkovito prevenirati kontrolom i smanjenjem čimbenika rizika, a jedan od ključnih čimbenika jest razina LDL kolesterola (LDL-C) u krvi. Vrijednost LDL-C-a ima središnju ulogu u razvoju ASCVD-a, a ta je činjenica potvrđena mnogobrojnim znanstvenim istraživanjima.

Introduction

Atherosclerotic cardiovascular diseases (ASCVD) present a serious global public health challenge with potentially fatal consequences. However, many of these diseases can be effectively prevented by controlling and reducing the risk factors, and one of the key risk factors is LDL cholesterol (LDL-C). LDL-C value plays a central role in the development of ASCVD, which is a fact that has been confirmed in numerous scientific studies.

Osnovna obilježja rosuvastatina i ezetimiba

Rosuvastatin je jedan od najjačih inhibitora HMG-CoA reduktaze koji je dostupan i može smanjiti vrijednost LDL-C-a za do 55 %. Dodatni korisni utjecaji na profil kolesterola uključuju povećanje HDL kolesterola (HDL-C) za otprilike 6 % i smanjenje vrijednosti triglicerida (TG) za 15 % ili više, kao i smanjenje sadržaja kolesterola u aterosklerotskim plakovima¹. Rosuvastatin također ima pleiotropne učinke, uključujući protuupalne učinke, zaštitu endotela i antioksidativne učinke. Prednosti rosuvastatina u usporedbi s drugim statinima uključuju njegovu hidrofilnost, koja je povezana s vrlo niskim stopama miopatije i rhabdomiolize, kao i njegovo dugotrajno djelovanje koje mu omogućuje da se uzima bilo kad tijekom dana^{1,2}. Osim toga, samo otprilike 10 % lijeka transformira se s pomoću enzima citokrom P450, dok se preostalih 90 % izlučuje preko bilijarnih puteva, što dovodi do vrlo malo interakcija lijekova^{2,3}.

Ezetimib je jedini lijek u svojoj klasi i djeluje inhibicijom NPC1L1, što dovodi do smanjenja apsorpcije kolesterola za do 67 %, što rezultira smanjenjem LDL-C-a za otprilike 15 – 20 %. Utjecaj na HDL-C jest povećanje od otprilike 3 % bez utjecaja na TG. Osim njegovih protuupalnih učinaka, kombinacija ezetimiba i statina smanjuje visoko osjetljiv CRP otprilike 10 % više nego monoterapija statinima. Ezetimib se metabolizira glukuronidacijom i stoga ima minimalne interakcije s lijekovima, poput rosuvastatina³.

Kombinacija rosuvastatina i ezetimiba

Kombinacija rosuvastatina i ezetimiba dostupna je u dozama 10/10 mg, 20/10 mg i 40/10 mg. Oni djeluju preko komplementarnih mehanizama djelovanja, omogućujući manje doze svakoga pojedinog agensa da bi se postigle iste promjene u lipidnom profilu. Kada statini ostvaruju svoje djelovanje snižavanja lipida smanjenjem endogene sinteze kolesterola u jetri, tijelo odgovara povećanjem apsorpcije kolesterola, što može smanjiti učinkovitost statina. Stoga dodatak ezetimiba može pružiti dodatnu korist blokiranjem apsorpcije kolesterola, poboljšavajući tako sposobnost statina da smanje LDL-C^{3,4}.

Statini, skupina lijekova koji djeluju inhibirajući proizvodnju kolesterola u jetri, dugoročno su bili i ostaju temeljna terapija za snižavanje razine LDL kolesterola^{5,6}. Njihova učinkovitost i sigurnost dokazane su u brojnim istraživanjima, a svako apsolutno sniženje LDL-C za 1 mmol/L terapijom statinima smanjuje rizik od velikih kardiovaskularnih (KV) događaja za impresivna 22 %. Statini su prva crta obrane, često se kombiniraju s promjenama prehrane da bi se postigle preporučene ciljane vrijednosti LDL-C-a.

Preporuke Europskoga kardiološkog društva (ESC) i Europskoga društva za aterosklerozu (EAS) iz 2019. godine jasno upućuju na ključnu ulogu smanjenja razine LDL-C-a u prevenciji kardiovaskularnih bolesti. Prema tim smjernicama, ciljana razina LDL-C-a trebala bi biti <1,8 mmol/L za bolesnike s visokim rizikom, te <1,4 mmol/L uz ≥50 %-tno smanjenje s obzirom na početne vrijednosti kod onih s vrlo visokim rizikom. Smanjenje rizika od ASCVD-a pokazuje se proporcionalnim smanjenjem razine LDL-C-a^{5,6}.

Treba napomenuti da postizanje ciljanih razina LDL-C-a nije uvijek jednostavno, kao što se čini na prvi pogled. Bolesnici s akutnim koronarnim sindromom (ACS), porodičnom

Basic characteristics of rosuvastatin and ezetimibe

Rosuvastatin is one of the most potent HMG-CoA reductase inhibitors available and can reduce LDL-C levels by up to 55%. Additional beneficial effects on the cholesterol profile include an increase in HDL cholesterol (HDL-C) by around 6% and a decrease in triglyceride (TG) levels by 15% or more, as well as a reduction of cholesterol in atherosclerotic plaques¹. Rosuvastatin also has pleiotropic effects, including anti-inflammatory effects, protective effects on the endothelium, and antioxidant effects. Advantages of rosuvastatin in comparison with other statins include its hydrophilic nature that is connected with very low rates of myopathy and rhabdomyolysis, as well as its long-term effect that enables it to be taken at any point during the day^{1,2}. In addition, only about 10% of the drug is transformed by cytochrome P450, while the remaining 90% undergoes biliary excretion, leading to very few drug interactions^{2,3}.

Ezetimibe is the only drug in its class and acts by inhibiting NPC1L1, leading to a reduction in cholesterol absorption by up to 67%, resulting in a reduction of LDL-C by approximately 15-20%. Consequently, HDL-C increases by approximately 3%, without impacting TG. In addition to its anti-inflammatory effects, the combination of ezetimibe with a statin reduces high-sensitivity CRP by approximately 10% more than statin monotherapy. Ezetimibe is metabolized by glucuronidation and therefore has minimal drug interactions, just like rosuvastatin³.

Combination of rosuvastatin and ezetimibe

The rosuvastatin/ezetimibe combination is available in dosages of 10/10 mg, 20/10 mg, and 40/10 mg. Their complementary mechanisms of action enable the use of lower doses of individual agents for achieving the same changes in the lipid profile. When statins exhibit their lipid-lowering effects by reducing the endogenous synthesis of cholesterol in the liver, the body responds by increasing cholesterol absorption, which may reduce the effect of statins. Therefore, the addition of ezetimibe can provide an additional benefit by blocking cholesterol absorption, thereby improving the LDL-C-lowering capacity of statins^{3,4}.

Statins, a class of drugs that act by inhibiting the production of cholesterol in the liver, have long been and still remain the cornerstone therapy for LDL cholesterol reduction^{5,6}. Their efficacy and safety have been demonstrated in numerous studies, and each absolute reduction in LDL-C by 1 mmol/L through statin therapy reduces the risk of major cardiovascular (CV) events by an impressive 22%. Statins are the first line of defense and are often combined with dietary changes in order to achieve the recommended target values of LDL-C.

The 2019 Guidelines of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) clearly indicate the key role that LDL-C lowering plays in the prevention of cardiovascular diseases. According to the Guidelines, the LDL-C target level should be <1.8 mmol/L for high-risk patients, and <1.4 mmol/L with ≥50% reduction from baseline for very high-risk patients. A reduction in ASCVD risk is reflected in a proportional reduction of LDL-C levels^{5,6}.

It should be noted that achieving target LDL-C levels is not always as simple as it might seem. Patients with acute coronary syndrome (ACS), familial hypercholesterolemia, and

hiperkolesterolemijom i drugim visokim KV rizicima možda neće postići ciljeve samo terapijom statinima⁴. Ovdje dolazi do izražaja važnost kombiniranja terapije statinima s drugim lijekovima za snižavanje kolesterola, kao što je ezetimib.

Opservacijska istraživanja, kao što je *DA VINCI*, pokazuju da samo manji udio bolesnika s visokim rizikom i vrlo visokim rizikom postiže ciljane vrijednosti prema smjernicama iz 2019. godine. Primjena statina visokog intenziteta i ezetimiba također ostaje ispod željenih standarda, upućujući na potrebu za smanjenjem jaza između preporučenih ciljnih razina LDL-C i stvarno postignutih vrijednosti^{5,7}.

Ezetimib, inhibitor apsorpcije kolesterola u crijevima, pokazao se kao vrijedan dodatak terapiji statinima. U istraživanju koja je obuhvatilo bolesnike nakon ACS-a, dodatak ezetimiba statinskoj terapiji rezultirao je znatnim smanjenjem razine LDL-C-a i smanjenjem rizika od novih KV događaja⁸. Spomenuto istraživanje upućuje na važnost snižavanja vrijednosti LDL-C-a preko kombinirane terapije, a ne samo načina postizanja tih vrijednosti.

Unatoč jasnim smjernicama i dokazima o učinkovitosti, postizanje preporučenih ciljnih razina LDL-C-a u kliničkoj je praksi često izazovno. U tom je kontekstu ključno prepoznati da kombinacija terapije statinima i ezetimibom može biti od vitalnoga značenja, osobito u bolesnika s najvećim rizikom⁸. Istraživanja pokazuju da je učestalost primjene spomenutih lijekova još uvijek nedostatna i da postoji jasna potreba za smanjenjem razine rizika.

U istraživanju iz 2015. godine, Cannon *i sur.* istraživali su učinak dodavanja ezetimiba statinskoj terapiji ACS-a. Studija je uključivala bolesnike s ACS-om koji su već primali statinsku terapiju. Ezetimib dodan terapiji statinima smanjuje razine LDL-C-a za dodatnih 21 – 27 % u usporedbi s placeboom u bolesnika s hiperkolesterolemijom s utvrđenim koronarnom bolešću srca ili bez nje. U bolesnika koji prije toga nisu primali statine, kombinirana terapija ezetimibom i statinima rezultirala je oko 15 %-tnim većim smanjenjem vrijednosti LDL-C-a u usporedbi s istim statinima i dozama u monoterapiji⁸.

U drugim je istraživanjima opisana kombinacija također znatno poboljšala smanjenje razine LDL-C-a u usporedbi s udvostručenjem doze statina (13 – 20 %) i nakon prelaska s monoterapije statinima na kombiniranu terapiju ezetimibom i statinima (11 – 15 %).⁶ Dodatak ezetimiba terapiji statinima u istraživanju *IMPROVE-IT* rezultirao je mnogo manjim rizikom od KV događaja. Rezultati su pokazali da dodatak ezetimiba statinskoj terapiji znatno smanjuje razinu LDL-C-a, što je rezultiralo smanjenjem rizika od ponovnih KV događaja. Spomenuto istraživanje dodatno potvrđuje važnost kontrole razine LDL-C-a u bolesnika nakon ACS-a i upućuje na korist od dodatka ezetimiba statinskoj terapiji⁹.

Studija objavljena 2022. godine donosi nove uvide u pristup liječenju visokih razina LDL-C-a. Rezultati istraživanja upućuju na to da kombinacija ezetimiba i rosuvastatina može biti učinkovitija u postizanju ciljanih razina LDL-C-a u usporedbi s primjenom tih lijekova pojedinačno. Ovakav pristup otvara nove mogućnosti u liječenju bolesnika s dislipidemijom i upućuje na potrebu za daljnjim istraživanjem ove kombinirane terapije¹⁰.

Ray *i sur.* istraživali su strategiju kombinirane terapije snižavanja lipida kao prvi izbor u visokorizičnih bolesnika. Objavljeno 2022. godine, spomenuto istraživanje istražuje al-

other high CV risks may not necessarily reach their target values with statin therapy alone⁴. This is where the importance of combining statin therapy with other cholesterol-lowering drugs, such as ezetimibe, becomes evident.

Observational studies, such as *DA VINCI*, demonstrate that only a minor proportion of high-risk and very high-risk patients achieve their target levels according to the 2019 Guidelines. Use of high-intensity statins and ezetimibe also remains below the desired standards, suggesting the need to reduce the gap between the recommended target LDL-C and the actual achieved values^{5,7}.

Ezetimibe, an inhibitor of intestinal absorption of cholesterol, has proven to be a valuable addition to statin therapy. In a study on post-ACS patients, addition of ezetimibe to statin therapy resulted in significant reduction of LDL-C levels and a lower risk of new CV events⁸. This study highlights the importance of lowering LDL-C levels using combination therapy, not only the method of reaching the values.

Despite the clear guidelines and evidence of efficacy, achieving recommended target LDL-C levels is often quite challenging in clinical practice. In this context, it is crucial to recognize that the combination of statin therapy with ezetimibe may be of vital importance, especially in patients who are most at risk⁸. Research shows that the frequency of using these drugs is still inadequate and that there is a clear need to reduce the risk levels.

In a 2015 study, Cannon *et al.* examined the effect of adding ezetimibe to statin therapy for ACS. The study involved patients with ACS who were already on statin therapy. Ezetimibe added to statin therapy reduced LDL-C levels by an additional 21-27% vs. placebo in patients with hypercholesterolemia with or without confirmed coronary heart disease. In statin-naïve patients, the combination of ezetimibe with statins resulted in approximately 15% higher reduction in LDL-C values vs. the same statins and doses in monotherapy⁸.

In other studies, this combination also significantly enhanced the reduction of LDL-C levels vs. doubling statin dosage (13-20%) and after switching from statin monotherapy to combination therapy with ezetimibe and statins (11-15%)⁶. The addition of ezetimibe to statin therapy in the *IMPROVE-IT* study resulted in a greatly reduced risk of CV events. The results of the study demonstrated that ezetimibe added to statin therapy significantly lowered LDL-C levels, leading to lower risks of recurrent CV events. This study also confirmed the importance of controlling LDL-C levels in post-ACS patients and indicated the beneficial effects of adding ezetimibe to statin therapy⁹.

A study published in 2022 provided new insights in the approach to treatment of elevated LDL-C levels. The study results suggested that the combination of ezetimibe and rosuvastatin may be more effective in reaching target LDL-C levels than using the drugs individually. This approach opens up new possibilities for the treatment of patients with dyslipidemia and indicates a need for further studies of this combination therapy¹⁰.

Ray *et al.* examined combination lipid-lowering therapy as first-line strategy in high-risk patients. Published in 2022, this study examined an alternative approach to treating patients with high risk of CV disease. The results showed that a combination of lipid-lowering drugs as first-line therapy may be

ternativan pristup liječenju bolesnika s visokim rizikom od KV bolesti. Rezultati pokazuju da bi kombinacija lijekova za snižavanje lipida, kao prva linija terapije, mogla biti korisna u postizanju ciljanih razina LDL-C-a i u smanjenju rizika od ozbiljnih KV događaja¹¹.

Katzmann *i sur.* istraživali su primjenu statina i ezetimiba u fiksnoj dozi u usporedbi s primjenom spomenutih lijekova u odvojenim tabletama u bolesnika s vrlo visokim rizikom. Ta studija, objavljena 2022. godine, donosi nove uvide u praktičnost i učinkovitost različitih pristupa terapiji. Rezultati pokazuju da fiksna doza statina i ezetimiba može biti jednostavnija i jednako učinkovita opcija za bolesnike s visokim rizikom¹².

Prospektivno istraživanje o procjeni malignosti u velikog broja bolesnika koji su bili randomizirani na primanje ezetimiba ili placeba, objavljeno 2020. godine, istraživalo je moguću povezanost između primjene ezetimiba i rizika od malignosti. Rezultati nisu pronašli povećan rizik od malignih bolesti povezan s primjenom ezetimiba, pružajući dodatne informacije o sigurnosti ovog lijeka u kontekstu terapije snižavanja lipida¹³.

Zaključak

Kontrola razine LDL-C-a ima ključnu ulogu u prevenciji ASCVD-a, čime se smanjuje rizik od ozbiljnih KV događaja i poboljšava kvaliteta života bolesnika. Smjernice ESC-a i EAS-a jasno preporučuju ciljane vrijednosti LDL-C-a kao ključan cilj terapije. Statini ostaju osnovna terapija, ali dodatak ezetimiba, inhibitora apsorpcije kolesterola u crijevima, može znatno poboljšati kontrolu razine LDL-C-a, posebno u bolesnika s visokim rizikom. Unatoč dokazanoj učinkovitosti ovakvog liječenja, postoje izazovi u postizanju preporučenih ciljnih razina LDL-C-a u kliničkoj praksi. Opservacijska istraživanja upućuju na nisku stopu postizanja ciljeva, što naglašava potrebu za boljom primjenom smjernica i boljim pristupom primjene liječenja statinima i ezetimibom. Važno je kontinuirano raditi na poboljšanju svijesti među bolesnicima i liječnicima o važnosti kontrole razine LDL-C-a te na razvoju strategija koje će poboljšati adherenciju. Kombinacija statina i ezetimiba može biti ključna u postizanju ciljanih vrijednosti LDL-C-a, posebno u bolesnika s visokim rizikom od ASCVD-a. Ovo će imati pozitivan utjecaj na zdravlje srca i kvalitetu života te će smanjiti rizik od smrtnosti povezane s ovakvim bolestima. U konačnici, sve napore treba usmjeriti prema integriranom pristupu u prevenciji ASCVD-a koji će kombinirati pravilnu prehranu, tjelesnu aktivnost i farmakološku terapiju kako bi se postigli ciljevi u kontroli razine LDL-C-a i smanjio teret ove ozbiljne javnozdravstvene prijetnje.

useful for achieving target LDL-C levels and reducing the risk of serious CV events¹¹.

Katzmann *et al.* investigated the use of fixed-dose statin/ezetimibe compared with separate pills of the drugs in very high-risk patients. This study, published in 2022, provided new insights into the practicality and effectiveness of different therapeutic approaches. The results showed that a fixed-dose combination of statin and ezetimibe may be a simpler and equally effective option in high-risk patients¹².

A prospective study evaluating malignancy in a large number of patients, randomized to either ezetimibe or placebo, was published in 2020 and examined a possible connection between the use of ezetimibe and the risk of malignancy. The results did not identify increased risk of malignant diseases connected with ezetimibe therapy, thus providing additional information on the safety of this drug in the context of lipid-lowering therapy¹³.

Conclusion

Control of LDL-C levels plays a key role in the prevention of ASCVD, which reduces the risk of serious CV events and improves the quality of life in patients. ESC/EAS Guidelines clearly recommend target LDL-C values as the key therapeutic goal. Statins remain the cornerstone therapy, but adding ezetimibe, an inhibitor of intestinal absorption of cholesterol, can significantly improve the control of LDL-C levels, especially in high-risk patients. Despite the proven efficacy of this treatment, there are challenges in achieving the recommended target LDL-C levels in clinical practice. Observational studies indicate low rates of reaching target values, highlighting the need for better implementation of the guidelines and a better treatment approach with statins and ezetimibe. It is important to continually work on raising awareness of the importance of controlling LDL-C levels, both among patients and medical professionals, and on developing strategies for improving adherence. The statin/ezetimibe combination may be key for achieving target LDL-C levels, especially in patients with high risk of ASCVD. This will positively impact cardiac health and quality of life and will reduce the risk of mortality connected with these diseases. Ultimately, all efforts should be directed towards an integrated approach to ASCVD prevention that will combine healthy diet, exercise, and pharmacotherapy in order to achieve the goals of LDL-C control and to lessen the burden of this serious threat to public health.

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