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Uloga klopidogrela i atorvastatina u liječenju akutnog koronarnog sindroma

Role of clopidogrel and atorvastatin in the treatment of acute coronary syndrome

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SAŽETAK: *Akutni koronarni sindrom (ACS) uključuje niz stanja povezanih sa ishemijom miokarda. Cilj liječenja svih pacijenta s ACS su minimiziranje ishemijskog oštećenja, ponovna uspostava koronarnog protoka i poboljšanje preživljavanja. Sadašnje europske i hrvatske smjernice za liječenje ACS-a predlažu strategije liječenja za akutnu fazu, kao i za dugotrajnije liječenje. Preporučena farmakoterapija uključuje antitrombocitnu terapiju i hipolipemike. Objavljene kliničke studije dokazuju da klopidogrel i atorvastatin značajno poboljšavaju ishode pacijenata sa ACS.*

KLJUČNE RIJEČI: *akutni koronarni sindrom, antitrombocitna terapija, statini, klopidogrel, atorvastatin.*

ABSTRACT: *Acute coronary syndrome (ACS) includes a spectrum of conditions associated with myocardial ischemia. The goals of therapy for all ACS patients are to minimize ischemic damage, re-establish coronary flow and improve survival. The current European and Croatian guidelines for the treatment of ACS recommend treatment strategies for the acute phase as well as for longer-term treatment. Recommended pharmacotherapy includes antiplatelet and lipid lowering therapy. Published clinical studies proved that clopidogrel and atorvastatin significantly improve outcomes in patients with ACS.*

KEYWORDS: *acute coronary syndrome, antiplatelet therapy, statins, clopidogrel, atorvastatin.*

Kardiovaskularne bolesti predstavljaju vodeći uzrok preuranjene smrti u industrijaliziranim zemljama te se očekuje da će to postati i u zemljama u razvoju do 2020. godine. Među njima je prevladavajuća koronarna bolest srca (CHD, prema engl. *coronary heart disease*) koja se povezuje sa visokim mortalitetom i morbiditetom[1,2].

Akutni koronarni sindrom (ACS, prema engl. *acute coronary syndrome*) uključuje niz stanja povezanih s ishemijom miokarda, uključujući nestabilnu anginu (UA, prema engl. *unstable angina*), infarkt miokarda bez elevacije ST-segmenta (NSTEMI, prema engl. *non-ST-segment elevation myocardial infarction*) te infarkt miokarda s elevacijom ST-segmenta (STEMI, prema engl. *ST-segment elevation myocardial infarction*). Sva ova stanja dijele zajedničku fiziologiju rupture aterosklerotskog plaka i koronarne tromboze, što ima za posljedicu nedostatak opskrbe miokarda kisikom[2,3]. Zbog heterogene naravi ACS, za identifikaciju pacijenata sa STEMI potrebno je rano učiniti 12-kanalni elektrokardiogram. Svim pacijentima s ACS neophodno je i stupnjevati rizik temeljem životne dobi, srčane frekvencije, vrijednosti sistoličkog tlaka, prisustva depresije ST-segmenata, stupnja zatajivanja srca i povišenih vrijednosti biljega nekroze (kao što su troponin T ili I), itd[2,4,5].

Sadašnje europske[2] i hrvatske[5] smjernice za liječenje ACS podrazumijevaju strategije liječenja ne samo za akutnu fazu, već i za dugotrajno liječenje. Cilj liječenja svih pacijenta s ACS je minimiziranje ishemijskog oštećenja, ponovna uspostava koronarnog protoka i poboljšanje preživljavanja. Ovo se često postiže kombinacijom invazivnih metoda liječenja i farmakoterapije[2,4]. Pacijenti s ACS, unatoč danas dostupnih modernih metoda liječenja, nakon početne faze zadržavaju rizik od ponavljanja ishemijskih epizoda. Stoga je aktivna sekundarna prevencija neophodan element dugotrajnog liječenja[2]. Dugotrajno liječenje ACS podrazumijeva promjene životnog stila i liječenje lijekovima, što također uključuje antitrombocitnu terapiju i terapiju snižavanja lipida[1,2].

Cardiovascular diseases are presently the leading cause of premature death in industrialized countries and are expected to become so in developing countries by 2020. Among these, coronary heart disease (CHD) is the most prevalent manifestation and is associated with high mortality and morbidity[1,2].

Acute coronary syndrome (ACS) includes a spectrum of conditions associated with myocardial ischemia, including unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). All these conditions share the common physiology of atherosclerotic plaque rupture and coronary thrombosis, which typically deprive the heart muscle of sufficient oxygen[2,3]. Because of the heterogeneous nature of ACS, early 12-lead electrocardiogram is necessary to identify patients with STEMI. It is also essential that patients with ACS undergo further risk categorization based on features such as age, heart rate, systolic blood pressure, ST-segment depression, signs of heart failure and increased cardiac biomarkers (like troponin T or I), etc[2,4,5].

The current European[2] and Croatian[5] guidelines for the treatment of ACS imply the treatment strategies for ACS with the requirements for the acute phase as well as for longer-term treatment. The goals of therapy for all ACS patients are to minimize ischemic damage, re-establish coronary flow and improve survival. This is often achieved through a combination of invasive approaches and pharmacotherapy[2,4]. Patients with ACS after the initial phase carry a high risk of recurrence of ischaemic events in spite of modern treatment, which is available nowadays. Therefore, active secondary prevention is an essential element of long-term management[2]. Long-term management of ACS implies lifestyle changes and drug treatment, which includes also antiplatelet and lipid lowering therapy[1,2].

Antitrombocitna terapija je postala okosnica liječenja ACS. Aktivacija trombocita igra ključnu patofiziološku ulogu u UA/NSTEMI. Zbog toga je antitrombocitna terapija neophodna ne samo za akutne epizode, već i za kasniju terapiju održavanja[2,4]. Čvrsti dokazi potvrđuju klopidogrel kao učinkovito i dobro podnošljivo antitrombocitno sredstvo za sekundarnu prevenciju ishemijskih epizoda kod pacijenata s različitim kardiovaskularnim stanjima, uključujući i one s ishemijskim moždani udarom ili ACS. Prema CAPRIE ispitivanju dugotrajno davanje klopidogrela je povezano s blagom, no statistički značajnom dobrobiti prema acetilsalicilnoj kiselini (ASA, prema engl. *acetylsalicylic acid*) u sniženju nepovoljnih kardiovaskularnih ishoda kod pacijenata s utvrđenom kardiovaskularnom bolesti[6]. Dobrobit primjene klopidogrela u odnosu na ASA pri prijemu i kontinuirano tijekom daljnjeg liječenja dokazana je u pacijenata s ACS u mnogim kliničkim studijama. CURE studija je pokazala da je ova kombinacija znatno učinkovitija u smanjenju značajnih kardiovaskularnih epizoda u roku od 30 dana i 12 mjeseci (maksimalno) od same ASA. Kod ACS (NSTEMI) pacijenata podvrgnutih PCI-u, predliječenje s klopidogrelom i ASA je, u odnosu na ASA, u dva značajna ispitivanja (PCI-CURE i CREDO) smanjilo relativan rizik od značajnih kardiovaskularnih događaja za otprilike 30%. U COMMIT istraživanju su u pacijenata koji su 24 sata nakon početka STEMI-a primili klopidogrel i ASA, u odnosu na one liječenih samo ASA, registrirani znatno manja učestalost smrtnosti i neželjenog zajedničkog ishoda (smrt, infarkt miokarda i moždanog udara)[4,6].

Dugo je poznato da su statini učinkoviti za primarnu i sekundarnu prevenciju CHD[7]. Nekoliko randomiziranih kontroliranih studija pokušalo je razjasniti imaju li statini dodatne dobrobiti ukoliko se kod pacijenata sa ACS-om propišu rano i u velikim dozama. Nedavna meta-analiza 13 randomiziranih kontroliranih kliničkih studija koja je uključivala 17.963 pacijenta hospitaliziranih zbog ACS-a liječenih primjenom rane intenzivne statinske terapije pokazala je da takva terapija znatno smanjuje kardiovaskularnu smrt i recidiv ishemije nakon ACS-a tijekom idućih 6 mjeseci. Ovaj pozitivan učinak je ostao značajan u trajanju od dvije godine[8]. Učinkovitost i sigurnost atorvastatina je naročito dobro dokazana kod pacijenata s ACS-om. Studija MIRACL provedena je primjenom 80 mg atorvastatina i pružila je prvi klinički dokaz da intenzivna statinska terapija započeta rano nakon ACS-a umanjuje povratne ishemijske epizode. U PROVE IT-TIMI 22 studiji[7] je dodatno dokazano da rano primjena 80 mg atorvastatina (unutar 30 dana), ravnomjerno i kontinuirano poboljšava kliničke ishode. Pretpostavlja se da su rani učinci statina povezani sa njihovim o dozi ovisnim pleiotropnim učincima koji ne snižavaju lipide i redukcijom C-reaktivnog proteina (CRP), dok je dugoročna korist povezana s smanjenjem LDL-kolesterola i CRP-a. Dokazano je da je s visokim dozama statina moguće zaustaviti ili čak umanjiti aterosklerotske nakupine[7]. Na temelju rezultata kliničkih studija, preporučljivo je da se kod pacijenata s ACS-om u bolnici započne te dalje nastavi dugotrajna intenzivna terapija statinom[7,9].

Zaključak: ***Objavljene studije su dokazale da klopidogrel, ako se daje zasebno ili u kombinaciji s ASA, te intenzivna terapija atorvastatinom znatno poboljšavaju ishode kod pacijenata s ACS-om, što bi se stoga trebalo razmotriti kao dio terapije AKS.***

Antiplatelet therapy has emerged as a cornerstone in the management of ACS. Platelet activation plays a key pathophysiological role in UA/NSTEMI. This is why antiplatelet therapy is necessary for the acute event as well as for the subsequent maintenance therapy[2,4]. Strong evidence base has established clopidogrel as an effective and well tolerated antiplatelet agent for the secondary prevention of ischaemic events in patients with various cardiovascular conditions, including those with ischaemic stroke or ACS. Long-term administration of clopidogrel was associated with a modest but statistically significant advantage over acetylsalicylic acid (ASA) in reducing adverse cardiovascular outcomes in patients with established cardiovascular disease in the CAPRIE trial[6]. In ACS patients, the benefit of adding clopidogrel to ASA on admission and continued long term was established in many clinical studies. The CURE study has shown that the combination was significantly more effective than ASA alone in reducing major cardiovascular events at 30-day and 12-month (maximum) follow-up. In ACS (NSTEMI) patients undergoing PCI, pretreatment with clopidogrel and ASA, compared with ASA alone, reduced the relative risk of a major cardiovascular event by approximately 30% in two major trials, PCI-CURE and CREDO. In COMMIT, patients presenting within 24 hours of onset of STEMI who received clopidogrel plus ASA had significantly lower rates of death and the composite of death, MI or stroke than those who received ASA alone[4,6].

Statins have long been known to be effective for primary and secondary prevention of CHD[7]. Several randomized controlled studies have sought to clarify whether statins have additional benefits if prescribed early and at high dose in patients with ACS[8]. A recent meta-analysis of 13 randomized controlled clinical studies involving 17.963 patients who were hospitalized for ACS and were receiving early intensive statin therapy showed that such therapy did significantly decrease cardiovascular death and recurrent ischemia following ACS after six months of treatment. This positive effect remained significant for two years[8]. Efficacy and safety of atorvastatin is especially well established in patients with ACS. The MIRACL study conducted with atorvastatin 80 mg provided actually the first clinical evidence that intensive statin therapy started early after ACS reduced recurrent ischemic events. Noticeable early (within 30 days), sustained and continued improvement in clinical outcomes by atorvastatin 80 mg has been additionally shown in PROVE IT-TIMI 22 study[7]. It is suggested that early effects of statins might be related to their non-lipid lowering dose-dependent pleiotropic effects and reduction in C-reactive protein (CRP), while long-term benefits are related to reductions in LDL-cholesterol and CRP. It has been shown that it is possible to halt or even reverse atherosclerosis plaque burden with high dose of statins[7]. Based on results from clinical studies it is recommended that patients with ACS should be started in hospital and continued long term on intensive statin therapy[7,9].

Conclusion: ***Published studies proved that clopidogrel, given alone or in combination with ASA, and intensive atorvastatin therapy significantly improve outcomes in patients with ACS, they should, therefore, be considered as part of overall ACS therapy.***

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