SPONZORIRANI ČLANAK / SPONSOR'S ARTICLE

Stručni rad / Professional article

Antitrombocitna terapija: težište na dokazima utemeljenoj terapiji primjenom klopidogrela

Antiplatelet therapy: focus on evidence-based therapy with clopidogrel

Veronika Ljevar, Breda Barbič-Žagar*

Krka, d. d., Novo mesto, Slovenija
Krka, d. d., Novo mesto, Slovenia

SAŽETAK: Akutni koronarni sindromi predstavljaju vodeći uzrok smrtnosti i jedan su od glavnih razloga bolničkog prijma u razvijenim zemljama. Zbog visoke stope smrtnosti i ponovnog infarkta, akutni koronarni sindromi predstavljaju veliki problem javnog zdravstva. Klopidogrel ima čvrstu bazu dokaza koja podupire njegovu uporabu kao učinkovitog i dobro podnošljivog antitrombocitnog lijeka za sekundarnu prevenciju ishemijskih događaja kod bolesnika s različitim kardiovaskularnim stanjima, uključujući akutni koronarni sindrom pa je sveprisutan u kardiološkoj praksi. Nekoliko velikih studija utvrdilo je važnost klopidogrela kod terapije infarkta miokarda bez i sa elevacijom ST-segmenta te kod perkutane koronarne intervencije, gdje je registrirano smanjenje smrtnosti, reinfarkta i neželjenih kardioloških ishoda. Zyllt® (Krkin klopidogrel) također ima formiranu bazu dokaza od mnogih postautorizacijskih kliničkih studija koje potvrđuju njegovu djelotvornost i sigurnost. Ove studije pružaju značajne rezultate i veliku bazu podataka, koja nije dostupna kod bilo kojeg drugog generičkog klopidogrela.

KLJUČNE RIJEČI: medicina utemeljena na dokazima, sekundarna prevencija, akutni koronarni sindrom, klopidogrel.

SUMMARY: Acute coronary syndromes are the leading cause of mortality and one of the main reasons for hospital admissions in the developed nations. Due to high rates of mortality and reinfarction, acute coronary syndromes represent a major public health concern. Clopidogrel has a strong evidence base supporting its use as an effective and well-tolerated antiplatelet agent for the secondary prevention of ischemic events in patients with various cardiovascular conditions, including acute coronary syndrome, and is ubiquitous in cardiology practice. Landmark studies have established the importance of clopidogrel in the treatment of non-ST and ST-segment elevation myocardial infarction and in percutaneous coronary interventions, where it was shown to reduce death, reinfarction, and adverse cardiac events. Zyllt® (Krka's clopidogrel) also has an established evidence base from many post-authorisation clinical studies demonstrating its efficacy and safety. These studies yielded important results and an extensive database, which is not available for any other generic clopidogrel.

KEYWORDS: evidence-based medicine, secondary prevention, acute coronary syndrome, clopidogrel.

CITATION: Cardiol Croat. 2013;8(1-2):74-77.

Kardiovaskularne bolesti su trenutno vodeći uzrok smrtnosti u industrijski razvijenim zemljama te se očekuje da će do 2020. godine takvima postati i u zemljama u razvoju. Najčešća manifestacija ove skupine bolesti je koronarna bolest srca (CAD) koja je povezana s visokim stupnjem smrtnosti i pobola. Kliničke manifestacije CAD uključuju nijemu ishemiju, stabilnu anginu pektoris, nestabilnu anginu pektoris, infarkt miokarda (MI), zatajivanje srca i iznenadnu srčanu smrt.[1] Bolesnici s boli u prsima predstavljaju vrlo značajan dio svih akutnih hospitalizacija u Europi i vodeći su problem javnog zdravstva.[1,2] Jedan od vodećih zadataka zdravstva

Cardiovascular diseases are currently the leading cause of death in industrialised countries and are expected to become so in emerging countries by 2020. Among them, coronary artery disease (CAD) is the most prevalent manifestation and is associated with high mortality and morbidity. The clinical presentations of CAD include silent ischemia, stable angina, unstable angina, myocardial infarction (MI), heart failure, and sudden cardiac death.[1] Patients with chest pain represent a very substantial proportion of all acute medical hospitalisations in Europe and a major public health concern.[1,2] Improvement of outcomes in patients with acute

predstavlja poboljšanje ishoda bolesnika s akutnim koronarnim sindromom (ACS).[2]

Trombociti imaju glavnu ulogu kod aterotromboze, glavnog patološkog supstrata ACS. Jedan od ključnih ciljeva u liječenju ACS je zadovoljavajuća inhibicija agregacije trombocita. Kao ključni mehanizam inhibicije trombocita ustanovljena je blokada P2Y12 komponente adenozin difosfat (ADP) receptora na staničnim membranama trombocita.[2]

Uporaba antitrombocitnih lijekova, a posebno tienopiridina, dio je standardnog zbrinjavanja bolesnika s ACS. Ovi lijekovi ireverzibilno inhibiraju trombocite trajnim vezanjem na P2Y12 receptor na površini i blokiraju vezanje trombocita preko fibrinogena što bi dovelo do agregacije trombocita i formiranja tromba.[3] Oralni tienopiridini započeli su s tiklopidinom, prvom generacijom tienopiridina, za kojeg su utvrđene neželjene nuspojave, iako je bio djelotvoran lijek za ireverzibilno blokiranje trombocitnog receptora P2Y12. Uvođenje klopidogrela, tienopiridina druge generacije, gotovo u potpunosti je zamijenilo tiklopidin kao preferirani P2Y12 inhibitor kod ACS.[3] Trenutno standardno zbrinjavanje oralnim antitrombocitnim lijekovima kod bolesnika s ACS (nestabilna angina, UA; infarkt miokarda bez elevacije ST-segmenta, NSTEMI; infarkt miokarda s elevacijom ST-segmenta, STEMI) i nakon perkutane koronarne intervencije (PCI) s implantacijom stenta, predstavlja kombinaciju acetilsalicilatne kiseline (ASK) i tienopiridinskog P2Y12 inhibitora klopidogrela, što se preporučuje do 1 godine.[4]

Klopidogrel je jedan od najčešće ispitivanih lijekova u kliničkim studijama. Dokazi dobiveni iz velikih randomiziranih istraživanja potvrđuju trajan koristan učinak primjene klopidogrela kod ACS.[5] Klinička učinkovitost klopidogrela je potvrđena kod dvojne terapije s ASK u okruženjima NTSE-ACS, PCI i STEMI i kao samostalna antitrombocitna terapija u sekundarnoj prevenciji.[4]

Klopidogrel se prvi put istraživao u **CAPRIE** studiji. Radilo se o međunarodnoj studiji koja je uključila 19.185 bolesnika. Studija je bila dizajnirana da procijeni relativnu učinkovitost i sigurnost klopidogrela i ASK u smanjenju rizika od moždanog udara, MI ili vaskularne smrti kod bolesnika s nedavnim MI, moždanim udarom ili utvrđenom perifernom vaskularnom bolesti. Iako rezultat pokazuje samo marginalnu superiornost klopidogrela nad ASK, CAPRIE je stvorila osnovu za odobrenje klopidogrela kao terapijskog sredstva za smanjenje trombotskih događaja kod bolesnika s nedavnim MI, nedavnim moždanim udarom ili utvrđenom perifernom vaskularnom bolesti.[5] Budući da je CAPRIE istraživanje objavljeno 1996. godine, brojne studije su ocjenjivale komplementarnost inhibicijskog učinka ASK i klopidogrela u nekoliko okruženja, uključujući i ACS.[6]

Uporaba klopidogrela kod bolesnika s infarktom miokarda bez elevacije ST-segmenta. **CURE** studija predstavlja prospektivno, randomizirano, placebo-kontrolirano istraživanje s uključenih 12.562 bolesnika sa NSTEMI koje je ocjenjivalo učinkovitost i sigurnost klopidogrela kao dodatka ASK.[5] Ovo istraživanje je dokazalo da početna doza od 300 mg klopidogrela (75 mg doza održavanja) s istovremenom terapijom ASK znatno smanjuje rizik od MI i ponovne ishemije u usporedbi sa samostalnom terapijom primjenom ASK.[6] Promatrana superiornost klopidogrela nad placebom u CURE studiji utrla je put rutinskoj uporabi dvojne antitrombocitne terapije u bolesnika s NSTEMI.[5]

Uporaba klopidogrela kod bolesnika s infarktom miokarda s elevacijom ST-segmenta. Dvije novije međunarodne, dvostruko slijepe studije, **CLARITY-TIMI 28** i **COMMIT/CCS-2** istražile su uporabu klopidogrela kod bolesnika s akutnim

coronary syndrome (ACS) is therefore a major healthcare task.[2]

Platelets play a central role in atherothrombosis, the main pathologic substrate in ACS. Sufficient inhibition of platelet aggregation is therefore one of the key targets in the treatment of ACS. Blockade of the P2Y12 subtype of adenosine diphosphate (ADP) receptor on platelet cell membranes has been established as a key mechanism of platelet inhibition.[2]

The use of antiplatelet agents, specifically the thienopyridines, has become a standard of care in the approach to the patient presenting with an ACS. These medicines irreversibly inhibit the platelet by permanently binding to the surface P2Y12 receptor and blocking the downstream fibrinogen cross-linking between platelets, which leads to aggregation and thrombus.[3] Oral thienopyridines began with ticlopidine, a first-generation thienopyridine, which although an effective agent for the irreversible blocking of the platelet P2Y12 receptor, was found to have unfavourable side effects. The use of clopidogrel, a second-generation thienopyridine, almost completely replaced ticlopidine as the preferred P2Y12 inhibitor in ACS.[3] Current standard-of-care oral antiplatelet therapy for patients with ACS (unstable angina, UA; non-ST-elevation myocardial infarction, NSTEMI; ST-segment elevation myocardial infarction, STEMI) and following percutaneous coronary intervention (PCI) with stent implantation is the combination of aspirin and the thienopyridine P2Y12 inhibitor clopidogrel which is recommended for up to 1 year.[4]

Clopidogrel is one of the most studied drugs in clinical trials. Evidence obtained from large randomised trials demonstrated a consistently beneficial effect of using clopidogrel in ACS.[5] The clinical efficacy of clopidogrel has been demonstrated in both add-on therapy to aspirin in the settings of NSTE-ACS, PCI, and STEMI, and single antiplatelet therapy for secondary prevention.[4]

Clopidogrel was first investigated by the **CAPRIE** trial (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events). This was an international trial involving 19,185 patients. It was designed to assess the relative efficacy and safety of clopidogrel and aspirin in reducing the risk of ischemic stroke, MI or vascular death in patients with recent MI, stroke or established peripheral vascular disease. Although the result demonstrated marginal superiority of clopidogrel over aspirin, CAPRIE formed the basis for the approval of clopidogrel as a therapeutic agent for the reduction of thrombotic events in patients with recent MI, recent stroke or established peripheral vascular disease.[5] Since the CAPRIE trial was published in 1996, a number of studies have evaluated the complementary inhibitory properties of aspirin and clopidogrel in several settings, including ACS.[6]

Clopidogrel use in patients with non-ST-elevation myocardial infarction. The **CURE** trial (Clopidogrel in Unstable angina to prevent Recurrent Events) was another prospective randomised, placebo-controlled trial that evaluated the efficacy and safety of clopidogrel when added to aspirin in 12,562 patients presenting acutely with NSTEMI.[5] The CURE trial demonstrated that a 300mg clopidogrel loading dose (75mg maintenance dose) with concomitant aspirin therapy significantly reduced the occurrence of MI and recurrent ischemia compared with aspirin alone.[6] The superiority of clopidogrel over placebo observed in the CURE trial has paved the way for the routine use of dual anti-platelet therapy in patients with NSTEMI.[5]

Clopidogrel use in patients with ST-segment elevation myocardial infarction. Two more recent international, double-

STEMI.[5] Obje studije potvrdile su korist dvojne antitrombocitne terapije kod bolesnika sa STEMI.[4]

U CLARITY studiji, ukupno 3.491 bolesnik s dijagnozom STEMI bio je liječen ASK i fibrinolitičkom terapijom te randomiziran na primjenu klopidogrela (300mg početna doze te 75 mg / doze održavanja) ili placeba. Incidencija primarnog zajedničkog ishoda (okludirana arterija odgovorna za infarkt, smrtni ishod, rekurentni infarkt miokarda prije angiografije) značajno je smanjena kod skupine koja je uzimala klopidogrel s ASK u odnosu na samo ASK (15% naspram 21,7%, P<0,001).[4]

U studiji COMMIT ukupno 45.852 bolesnika sa STEMI liječenih ASK također je uzimalo ili klopidogrel 75 mg ili placebo tijekom 4 tjedna u bolnici ili do otpusta iz bolnice. Kod bolesnika koji su uzimali klopidogrel s ASK značajno se smanjila učestalost zajedničkog složenog ishoda od smrti, ponovljenog infarkta ili moždanog udara u odnosu na bolesnike koji su liječeni samo ASK (9,2% naspram 10,1%, P=0,002). U skupini na klopidogrelu i ASK također je zabilježeno i značajno smanjenje ukupne smrtnosti (dodatni primarni ishod) i to 7,5% naspram 8,1% u odnosu samo na ASK, P=0,03).[4]

Klopidogrel kod bolesnika s perkutanom koronarnom intervencijom. Istraživanje **CREDO** ocjenjivalo je dobrobit 12-mjesečnog liječenja klopidogrelom (75 mg/dnevno) nakon PCI te učinak prethodne početne doze klopidogrela (300mg) kao dodatka terapiji ASK (81-325 mg) u bolesnika liječenih elektivnom PCI. Dvojna antitrombotska terapija bila je povezana sa značajnim, za 27%, relativnim smanjenjen zajedničkog ishoda sastavljenog od smrtnog ishoda, MI i moždanog udara (P=0,02) nakon jedne godine praćenja, u odnosu na terapiju samo primjenom ASK, no nije uočena značajna dobrobit od 300mg početne doze klopidogrela tijekom razdoblja od 28 dana.[4]

Prethodno opisana klinička istraživanja pružaju korisne dokaze uspješne primjene klopidogrela kod bolesnika s ACS.[5] Skupina dokaza sakupljena u proteklih desetak godina čvrsto ukazuje na ulogu dvojne antitrombocitne terapije pomoću ASK i klopidogrela kod kardiovaskularnih bolesnika.[7] Klopidogrel ostaje jedan od najpozornije istraženih antitrombocitnih lijekova, a procjenjuje se da je više od 100.000 bolesnika bilo uključeno u randomizirana istraživanja.[8]

Krkin klopidogrel (Zyllt®) prisutan je na međunarodnom tržištu već više od 7 godina, a zbog svoje kvalitete i povjerenja koje je stekao proteklim godinama, postao je vodeći generički klopidogrel u Europi. Njegova djelotvornost i sigurnost dokazani su u postautorizacijskim studijama koje su potvrdile da se terapija Krkinim klopidogrelom temelji na utvrđenim kliničkim dokazima.[9-15] Ove studije daju značajne rezultate i veliku bazu kliničkih podataka koja nije dostupna kod bilo kojeg drugog generičkog klopidogrela. Visoka djelotvornost, dobra sigurnost te razumna cijena ovog generičkog klopidogrela, zasigurno pridonosi boljoj suradljivosti u liječenju većeg broja bolesnika s ACS.

Received: 21st Jan 2013

*Address for correspondence: Krka d.d., Dunajska 65, SLO-1000 Ljubljana, Slovenija.

Phone: +386-1-4571-339

E-mail: breda.zagar@krka.biz

blind trials, **CLARITY-TIMI 28** (Clopidogrel as Adjunctive Reperfusion Therapy — Thrombolysis In Myocardial Infarction 28) and **COMMIT/CCS-2** (Clopidogrel and Metoprolol in Myocardial Infarction Trial) investigated the use of clopidogrel in patients with acute STEMI.[5] Both trials demonstrated the benefit of dual antiplatelet therapy in patients with STEMI.[4]

In CLARITY, a total of 3,491 patients with STEMI treated with aspirin and fibrinolytic therapy were randomised to receive either clopidogrel (300 mg loading dose followed by 75 mg/day) or placebo. The incidence of the primary efficacy endpoint (composite of an occluded infarct-related artery on angiography or death or recurrent MI before angiography) was significantly reduced in the clopidogrel plus aspirin group versus aspirin alone (15% vs 21.7%, P<0.001).[4]

In COMMIT, a total of 45,852 patients with STEMI treated with aspirin also received either clopidogrel 75 mg or placebo for up to 4 weeks in hospital or until discharge. The rate of the composite endpoint of death, reinfarction, or stroke was significantly lower in patients receiving clopidogrel plus aspirin versus those receiving aspirin alone (9.2% vs 10.1%, P=0.002). A significant reduction in all-cause death (co-primary endpoint) was also noted with clopidogrel plus aspirin (7.5% vs 8.1% with aspirin alone, P=0.03).[4]

Clopidogrel in patients with percutaneous coronary intervention. The **CREDO** (Clopidogrel for the Reduction of Events During Observation) trial evaluated the benefit of 12-month treatment with clopidogrel (75 mg/day) after PCI and the effect of a pre-procedural clopidogrel loading dose (300 mg) in addition to aspirin therapy (81-325 mg) in patients undergoing elective PCI. Dual antiplatelet therapy was associated with a significant 27% relative reduction in the composite endpoint of death, MI, or stroke (P=0.02) at 1 year versus aspirin alone, whereas no significant benefit of the 300 mg loading dose of clopidogrel was apparent at 28 days.[4]

The above outlined clinical trials provide useful evidence of the benefit of clopidogrel in patients with ACS.[5] The body of evidence accumulated over the past decade establishes convincingly the role of dual antiplatelet therapy using aspirin and clopidogrel in a broad spectrum of cardiovascular patients.[7] Clopidogrel remains one of the most carefully studied antiplatelet agents and it is estimated that over 100,000 patients have been enrolled in randomised trials involving clopidogrel.[8]

Krka's clopidogrel (Zyllt®) has been present on the international market for more than 7 years, and due to its quality and trust it has gained over the years it has become the leading generic clopidogrel in Europe. Its efficacy and safety have been proven in post-authorisation safety and efficacy studies which prove that Krka's clopidogrel is a therapy based on well-established clinical evidence.[9-15] These studies yielded important results and an extensive clinical database, which is not available for any other generic clopidogrel. The high efficacy and good safety, as well as the reasonable price of this generic clopidogrel, could undoubtedly contribute to better compliance with the treatment in more patients with ACS.

Literature

1. Sažete smjernice Europskoga kardiološkog društva. Smjernice za dijagnozu I liječenje akutnih koronarnih sindroma u bolesnika bez perzistentne elevacije ST-segmenta. Hrvatsko kardiološko društvo. Zagreb, 2012. http://www.kardio.hr/component/docman/doc_download/256-nste.html

2. Abergel E, Nikolsky E. Ticagrelor: an investigational oral antiplatelet treatment for reduction of major adverse cardiac events in patients with acute coronary syndrome. Vasc Health Risk Manag. 2010;6:963-77.

3. Birkeland K, Parra D, Rosenstein R. Antiplatelet therapy in acute coronary syndromes: focus on ticagrelor. J Blood Med. 2010;1:197-219.

4. Fintel DJ. Oral antiplatelet therapy for atherothrombotic disease: overview of current and emerging treatment options. Vasc Health Risk Manag. 2012;8:77-89.

5. Mudawi TO, Morrison L. Clopidogrel therapy in coronary heart disease: reviewing the evidence and assessing the practice. J R Coll Physicians Edinb. 2008;38:100-7.

6. Raju NC, Eikelboom JW, Hirsh J. Platelet ADP-receptor antagonists for cardiovascular disease: past, present and future. Nat Clin Pract Cardiovasc Med. 2008;5:766-80.

7. Hamdalla H, Steinhubl SR. Clinical efficacy of clopidogrel across the whole spectrum of indications: percutaneous coronary intervention. Eur Heart J Suppl. 2006;8(suppl G):G20-G24.

8. Askari AT, Lincoff AM, eds. Antithrombotic Drug Therapy in Cardiovascular Disease. New York. Springer 2010.

9. Poponina TM, Poponina YS, Kapilevich NA, Efimova E. Current approaches to the prevention of thrombotic complications in patients with acute coronary syndrome without segment elevation ST. Topical issues of heart and vascular diseases. 2009;4:4-9.

10. Grinstein YI, Savchenko EA, Filonenko IV, Grinstein IYu, Savchenko AA. Zyllt in coronary atherosclerosis patients after coronary artery bypass graft surgery. Preliminary results of an open, randomized, comparative ZEUS Study. Kardiovaskularnaya terapija i profilaktika. 2008;7(6):1-7.

11. Osiev AG, Mironenko SP, Koleda NV, Solov'ev ON. Application of antiaggregant treatment for prevention of stent thromboses during percutaneous transluminal balloon coronary angioplasty. Kardiol serdečno-sosud hir. 2010;6:37-9.

12. Sivkov AS, Paukov SV, Balugyan R, Kukes VG, Zhuravleva MV, Sivkov SI, Farafonova TN. Pharmacodynamics and clinical effectiveness of clopidogrel and atorvastatin in patients with acute coronary syndrome and hyperlipidaemia. Kardiovaskularnaya terapija i profilaktika. 2009;8(4):76-83.

13. Sirotkina OV, Bogdanova EV, Bogan'kova N, Stolyarova AN, Vavilova TV, Boldueva SA. Clopidogrel effectiveness in patients with ST elevation myocardial infarction. Kardiovaskularnaya terapija i profilaktika. 2009;8(1):51-5.

14. Jelčaninov AP, Čajkovskij JN, Samorukova EM, Fofanova MA. The influence of antiaggregants on several parameters of haemostasis system in patients with chronic cerebrovascular disease. Aktualnie voprosi boleznej serdca i sosudov. 2008;3:44-8.

15. IMS, Medicube, Pharmexpert, Pharmstandart, Pharmazoom 2011.