Antiagregacijska terapija prasugrelom i tikagrelorom u liječenju bolesnika s akutnim koronarnim sindromom

Antiplatelet Therapy with Prasugrel and Ticagrelor in the Treatment of Patients with Acute Coronary Syndrome

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SAŽETAK: Dvojna antiagregacijska terapija (DAPT) osnova je liječenja svih bolesnika koji su podvrgnuti perkutanoj koronarnoj intervenciji (PCI) i bolesnika s akutnim koronarnim sindromom (AKS). Prasugrel i tikagrelor potentni su inhibitori $P2Y_{12}$ receptora, koji su u višestrukim kliničkim ispitivanjima pokazali superiornost u odnosu prema klopidogrelu u bolesnika s AKS-om. Prema nedavnom randomiziranom kliničkom istraživanju *ISAR REACT 5*, prasugrel je statistički značajno reducirao ishemijske ishode, bez povećanja krvarećih komplikacija u usporedbi s tikagrelorom. Slični su rezultati prikazani i u naknadnoj metaanalizi. S obzirom na navedeno, prasugrel je, prema postojećim smjernicama za AKS bez elevacije ST-segmenta, $P2Y_{12}$ inhibitor izbora u liječenju bolesnika koji su podvrgnuti PCI-ju. S druge strane, tikagrelor je lijek izbora u situacijama kada je prasugrel kontraindiciran. Ipak, u određenim populacijama bolesnika (stariji od 75 godina života i lakši od 60 kilograma) i kliničkim scenarijima (odgođena invazivna obrada) ne može se jasno preporučiti terapija zbog nedostatka adekvatnih dokaza. Oba su lijeka indicirana i u situacijama kada je potrebna produljena DAPT, pri čemu tikagrelor ima prednost. Završno, randomizirana istraživanja o monoterapiji $P2Y_{12}$ inhibitorom, koja je nastavljena nakon provedene PCI i 1 – 3 mjeseca primjene DAPT-a, upućuju na redukciju krvarećih komplikacija, a bez znatnog porasta u ishemijskim komplikacijama u usporedbi s klasičnim DAPT-om. Ipak, u tom su području potrebna daljnja istraživanja prije eventualne promjene svakodnevne kliničke prakse.

SUMMARY: Dual antiplatelet therapy (DAPT) forms the basis for the treatment of all patients undergoing percutaneous coronary intervention (PCI) and patients who suffered acute coronary syndrome (ACS). Prasugrel and ticagrelor are potent $P2Y_{12}$ receptor inhibitors that have demonstrated their superiority in patients with ACS in comparison with clopidogrel in multiple clinical trials. In a recent randomized clinical trial called ISAR REACT 5, prasugrel provided a statistically significant reduction in the rate of ischemic outcomes without an increase in bleeding complications, in comparison with ticagrelor. Similar results were also presented in a subsequent meta-analysis. Considering the above and according to current guidelines for non-ST elevation ACS, prasugrel is the $P2Y_{12}$ inhibitor of choice in the treatment of patients undergoing PCI. On the other hand, ticagrelor is the treatment of choice in cases when prasugrel is contraindicated. However, in some patient populations (patients older than 75 and weighing less than 60 kg) and clinical scenarios (delayed invasive treatment), no clear recommendations can be made regarding therapy or treatment of choice due to inadequate evidence. Both agents are also indicated in situations when prolonged DAPT is required, although ticagrelor is the preferred choice. Finally, randomized studies on $P2Y_{12}$ inhibitor monotherapy after 1 to 3 months of DAPT following PCI indicate a reduction in bleeding complications, but without any significant increase in ischemic complications, compared with classic DAPT. However, additional research is required in this area before introducing any changes to everyday clinical practice.

KLJUČNE RIJEČI: prasugrel, tikagrelor, dvojna antiagregacijska terapija, akutni koronarni sindrom.

KEYWORDS: prasugrel, ticagrelor, dual antiplatelet therapy, acute coronary syndrome.

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Uvod

Dvojna antiagregacijska terapija (DAPT) osnova je liječenja svih bolesnika koji su podvrgnu-

Introduction

Dual antiplatelet therapy (DAPT) forms the basis for the treatment of all patients undergoing

ti perkutanoj koronarnoj intervenciji (PCI) i bolesnika koji su preboljeli akutni koronarni sindrom (AKS)[1-3]. Višestruka klinička ispitivanja konzistentno pokazuju da godinu dana uzimanja DAPT-a, sastavljenog od acetilsalicilatne kiseline (ASK) i inhibitora $P2Y_{12}$ receptora, smanjuje rizik od budućega aterotrombotskog događaja nakon AKS-a[4-7]. Nadalje, terapija potentnijim $P2Y_{12}$ inhibitorima, prasugrelom ili tikagrelorom, pruža bolju zaštitu od ishemijskog događaja, ali uz veću učestalost krvarećih komplikacija u usporedbi s klopidogrelom[5,6]. Upravo su zbog toga prasugrel i tikagrelor $P2Y_{12}$ inhibitori izbora u liječenju bolesnika bez velikog rizika od krvarenja s akutnim infarktom miokarda s elevacijom ST-segmenta (STEMI) i AKS-om bez ST-elevacije[2,3].

Prasugrel

Prasugrel je tienopiridinski inhibitor $P2Y_{12}$ receptora, brzog početka djelovanja[8,9]. Jednako kao i kod klopidogrela, prije iskazivanja antiagregacijskog učinka prasugrela potrebna je njegova konverzija u aktivnu supstanciju preko intestinalne esteraze te putem citokroma P-450[10]. Za razliku od klopidogrela, navedena aktivacija nastupa bitno brže, već unutar 15 minuta. Nadalje, prasugrelov put aktivacije preko citokroma P-450 razlikuje se od puta klopidogrela, te je bitno manje ovisan o pridruženoj terapiji i genskim varijantama citokroma[9]. Zbog svega navedenog prasugrel u usporedbi s klopidogrelom dovodi do konzistentnije i pouzdanije inhibicije agregacije trombocita.

TRITON TIMI 38 prvo je veliko, randomizirano, dvostruko slijepo, kliničko istraživanje koje je uspoređivalo prasugrel s klopidogrelom[5]. Studija je uključivala bolesnike s AKS-om u kojih je u 99 % slučajeva bila izvedena PCI. U predmetnoj studiji terapija prasugrelom dovela je do redukcije skupnog velikog neželjenog kardiovaskularnog događaja (MACE) sastavljenog od kardiovaskularne smrti, infarkta miokarda i moždanog udara (9,9 % prema 12,1 %, omjer rizika (OR) 0,81, 95 % CI 0,73 – 0,90, p < 0,001)[5]. S druge strane, terapija prasugrelom uzrokovala je i veću incidenciju krvarećih komplikacija koje nisu bila povezane s kardiokirurškom revaskularizacijom (2,4 % prema 1,8 %, OR 1,32, 95 % CI 1,03 – 1,68, p = 0,03)[5]. Naknadnim subanalizama definirane su tri skupine bolesnika u kojih je rizik od krvarenja posebno visok: 1) bolesnici s anamnestičkim podatcima o preboljelom moždanom udaru, 2) bolesnici stariji od 75 godina života, 3) bolesnici s tjelesnom težinom manjom od 60 kilograma[5]. Iz navedenog proizlaze valjane kliničke preporuke da je prasugrel kontraindiciran u bolesnika s anamnestičkim podatcima o preboljelom moždanom udaru i tranzitornoj ishemijskoj ataci, dok je u bolesnika starijih od 75 godina i onih s manje od 60 kilograma preporučeno prepoloviti dozu održavanja s uobičajenih 10 mg na 5 mg[1,3]. Potrebno je naglasiti da spomenute preporuke o smanjenju doze proizlaze iz farmakokinetskih istraživanja, odnosno da klinička učinkovitost u randomiziranom kliničkom istraživanju nije potvrđena[11,12]. Kliničko istraživanje *ACCOAST*, koje je uključivalo bolesnike s AKS-om bez elevacije ST-segmenta, pokazalo je da primjena prasugrela prije utvrđivanja koronarne anatomije ne utječe na kliničke i angiografske ishode u usporedbi s grupom bolesnika kojima je udarna doza prasugrela (60 mg) ordinirana nakon koronarografije[13]. S druge strane, bolesnici kojima je prasugrel ordiniran prije koronarografije (odmah nakon postavljanja dijagnoze AKS-a) imali su mnogo veću učestalost krvarenja (OR, 1,90; 95 % CI, 1,19 prema 3,02; P = 0,006)[13]. Iz navedenog su proizašle preporuke da je prasugrel u bolesnika s AKS-om bez elevacije ST-segmenta

percutaneous coronary intervention (PCI) and patients who suffered acute coronary syndrome (ACS)[1-3]. Multiple clinical trials consistently show that one year of DAPT, consisting of aspirin and a $P2Y_{12}$ receptor inhibitor, lowers the risk of a future atherothrombotic event after ACS[4-7]. Furthermore, therapy with more potent $P2Y_{12}$ inhibitors, prasugrel or ticagrelor, provides better protection from ischemic events but with a higher frequency of bleeding complications than with clopidogrel[5,6]. This is why prasugrel and ticagrelor are the $P2Y_{12}$ inhibitors of choice when treating patients without a high risk of bleeding with acute ST elevation myocardial infarction (STEMI) and non-ST elevation ACS[2,3].

Prasugrel

Prasugrel is a thienopyridine $P2Y_{12}$ receptor inhibitor with a rapid onset of action[8,9]. Just like clopidogrel, prasugrel requires conversion into active substance by intestinal esterase and by cytochrome P-450 before it can demonstrate its antiplatelet effect[10]. Unlike with clopidogrel, this activation happens significantly sooner, already within 15 minutes. Moreover, prasugrel's activation path through cytochrome P-450 is different from that of clopidogrel and is significantly less dependent on concomitant therapy and genetic variants of the cytochrome[9]. Because of the above, prasugrel, when compared with clopidogrel, leads to more consistent and more reliable inhibition of platelet aggregation.

TRITON TIMI 38 was the first large, randomized, double-blind clinical study to compare prasugrel and clopidogrel[5]. The study included patients with ACS, 99% of whom had undergone PCI. In the study, therapy with prasugrel led to a reduction in overall major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, and stroke (9.9% vs. 12.1%, hazard ratio (HR) 0.81, 95% CI 0.73-0.90, p < 0.001)[5]. On the other hand, prasugrel treatment also caused a higher incidence of bleeding complications that were not associated with cardiac surgical revascularization (2.4% vs. 1.8%, HR 1.32, 95% CI 1.03-1.68, p = 0.03)[5]. In subsequent subanalyses, three groups of patients with especially high risk of bleeding were identified: 1) patients with a history of stroke, 2) patients older than 75 years of age, 3) patients with body weight under 60 kg[5]. In accordance with the above and under current clinical recommendations, prasugrel is contraindicated in patients with a history of stroke and transient ischemic attack, whereas in patients older than 75 and patients with body weight under 60 kg it is advisable to reduce the maintenance dose by half, from the standard 10 mg to 5 mg[1,3]. It should be noted that the above-mentioned recommendations concerning dose reduction are the result of pharmacokinetic studies, i.e. that clinical efficacy has not been confirmed in a randomized clinical study[11,12]. The ACCOAST clinical study, which included patients with non-ST elevation ACS, showed that using prasugrel before identifying coronary anatomy had no effect on the clinical or angiographic outcomes compared with the group of patients in whom the loading dose of prasugrel (60 mg) was administered after coronarography[13]. On the other hand, patients in whom prasugrel was administered before coronarography (immediately after diagnosing ACS) had a significantly higher frequency of bleeding (HR, 1.90; 95% CI, 1.19 to 3.02; p = 0.006)[13]. Based on this, prasugrel is indicated in patients with non-ST elevation ACS only after identifying coronary pathology or after decid-

indiciran tek nakon utvrđivanja koronarne patologije, odnosno nakon odluke o PCI-ju[3]. Budući da u kliničkom istraživanju *TRILOGY-ACS*, u koje su uključeni bolesnici s AKS-om, ali koji nisu podvrgnuti revaskularizaciji, nije bilo značajne redukcije MACE-a između klopidogrela i prasugrela, terapija prasugrelom nije indicirana ako se ne planira PCI[14]. Terapiju prasugrelom, u sklopu DAPT-a, moguće je nastaviti i nakon godine dana na temelju rezultata *DAPT* istraživanja[15]. U navedenom je istraživanju od ukupno gotovo 10 000 ispitanika njih 32 % imalo AKS te su nakon godine dana DAPT-a (ako su ga tolerirali bez znatnih nuspojava) randomizirani na nastavak liječenja terapijom ili klopidogrelom ili prasugrelom uz ASK, ili samo ASK-om uz placebo[15]. Rezultati su u cijeloj skupini utvrdili statistički značajno nižu incidenciju tromboze stenta i infarkta miokarda, ali uz veći rizik od krvarenja te statistički granično značajnu višu ukupnu smrtnost u skupini na produljenom DAPT-u. Nakon analize podskupina bolesnici s preboljelim AKS-om imali su više koristi od produljenog DAPT-a[15].

Tikagrelor

Tikagrelor je netienopiridinski, direktni reverzibilni inhibitor $P2Y_{12}$ receptora s brzim početkom djelovanja od 30 minuta[8,16]. Za razliku od prasugrela, tikagrelor ne zahtijeva konverziju u aktivnu supstanciju. U registracijskom istraživanju *PLATO* tikagrelor je, u usporedbi s klopidogrelom, doveo do znatne redukcije MACE-a (9,8 % prema 11,7 %; OR 0,84; 95 % CI 0,77-0,92, P < 0,001) i sveukupne smrtnosti kao zasebnog ishoda (OR 0,78; 95 % CI 0,69 – 0,91, p < 0,001) s obzirom na klopidogrel[6]. U skupini ispitanika liječenih tikagrelorom zabilježena je veća učestalost krvarenja koja nije povezana s kardiokirurškom revaskularizacijom (4,5 % prema 3,8 %, p = 0,03), ali nije utvrđena statistički značajna razlika u velikim krvarenjima[6]. U istraživanje su uključeni bolesnici neovisno o načinu liječenja AKS-a (invazivno ili konzervativno), zbog čega je tikagrelor indiciran i u slučajevima isključivo medikamentne terapije[1,6]. Drugo istraživanje tikagrelora koje znatno utječe na kliničku praksu jest *PEGASUS-TIMI 54*, u kojemu je više od 21 000 bolesnika s preboljelim infarktom miokarda randomizirano na: 1) tikagrelor u punoj dozi (2 x 90 mg), 2) tikagrelor u smanjenoj dozi (2 x 60 mg) ili 3) placebo[17]. Svi su bolesnici trajno uzimali terapiju ASK-om. Nakon trogodišnjega praćenja zabilježena je značajna redukcija MACE-a u objema skupinama liječenima tikagrelorom (7,85 % prema 7,77% prema 9,04%; OR 0,85, 95 % CI 0,75 – 0,96 i 0,84, 95 % CI 0,74 – 0,95)[17]. Nadalje, incidencija velikih krvarenja bila je mnogo veća u skupinama liječenih tikagrelorom, ali bez razlike u fatalnim ili intrakranijskim krvarenjima[17]. Na temelju te studije, u postojećim smjernicama stoji da je nastavak primjene tikagrelora u dozi 2 x 60 mg moguć u odabranih bolesnika s preboljelim AKS-om nakon godine dana „klasične" DAPT[3].

Potrebno je naglasiti da su bolesnici za koje se smatralo da imaju visok rizik od krvarenja unaprijed isključeni iz svih navedenih istraživanja obaju lijekova.

Prasugrel u usporedbi s tikagrelorom

Istraživanje *ISAR REACT 5* jest dosad najveća (uključeno više od 4 000 bolesnika) randomizirana studija koja je izravno uspoređivala prasugrel i tikagrelor u bolesnika s AKS-om predviđenih za intervencijsko liječenje[18]. Ispitanicima koji su imali STEMI odmah je ordinirana udarna doza obaju lijekova (tikagrelor 180 mg, prasugrel 60 mg). Ako je inicijalna dijagnoing to perform PCI[3]. Considering that the TRILOGY-ACS study, which included patients with ACS who had not undergone revascularization, found no significant reduction in MACE between clopidogrel and prasugrel, therapy with prasugrel is not indicated if PCI is not planned[14]. Prasugrel therapy as a part of DAPT, can be continued even after one year, based on the results of the DAPT study[15]. In it, out of almost 10.000 subjects in total, 32% had ACS, and after one year of DAPT (if they were able to tolerate it without significant adverse effects), they were randomized to continue treatment with either clopidogrel or prasugrel with aspirin or just aspirin with placebo[15]. The results in the overall population confirmed statistically significantly lower incidence of stent thrombosis and myocardial infarction, but with a higher risk of bleeding and statistically borderline significantly higher overall mortality in the group receiving prolonged DAPT. After subgroup analysis, patients who had suffered ACS benefited more from the prolonged DAPT[15].

Ticagrelor

Ticagrelor is a non-thienopyridine, direct, reversible $P2Y_{12}$ receptor inhibitor with a rapid onset of action of 30 minutes[8,16]. Unlike prasugrel, ticagrelor does not require conversion to active substance. In the PLATO registration study, there was a significant reduction in MACE (9.8% vs. 11.7%; HR 0.84; 95% CI 0.77-0.92, p < 0.001) and overall mortality as a separate outcome (HR 0.78; 95% CI 0.69-0.91, p < 0.001) with ticagrelor compared with clopidogrel[6]. The group of patients treated with ticagrelor had a higher frequency of bleeding not associated with cardiac surgical revascularization (4.5% vs. 3.8%, p = 0.03), but there was no statistically significant difference in major hemorrhages[6]. The study included patients regardless of which ACS treatment method was used (invasive or conservative), which is why ticagrelor is also indicated in cases where only medication therapy is used[1,6]. PEGASUS-TIMI 54 was another ticagrelor study with a significant influence on clinical practice, where over 21,000 patients with a history of myocardial infarction were randomized to receive: 1) ticagrelor at full dosage (2 × 90 mg), 2) ticagrelor at reduced dosage (2 × 60 mg) or 3) placebo[17]. All patients were receiving ongoing therapy with aspirin. After three years of follow-up, a significant reduction in MACE was reported in both groups treated with ticagrelor (7.85% vs. 7.77% vs. 9.04%; HR 0.85, 95% CI 0.75-0.96 and 0.84, 95% CI 0.74-0.95)[17]. Moreover, major hemorrhage incidence was significantly higher in the ticagrelor groups, without any differences in fatal or intracranial hemorrhage[17]. Based on this study, current guidelines state that ticagrelor at 2 × 60 mg can potentially be continued in selected patients post ACS after one year of "classic" DAPT[3].

It should be noted that patients who were considered to have high risk of bleeding were excluded in advance from all of the above-mentioned studies for both agents.

Prasugrel vs. ticagrelor

ISAR REACT 5 is the largest (over 4.000 patients) randomized study to date to directly compare prasugrel and ticagrelor in patients with ACS scheduled for intervention treatment[18]. Subjects presenting with STEMI were immediately treated with the saturation dose for both agents (ticagrelor 180 mg, prasugrel 60 mg). If their initial diagnosis was non-ST eleva-

za bila AKS bez elevacije ST-segmenta, odmah je ordinirana udarna doza tikagrelora, dok je prasugrel ordiniran tek nakon učinjene koronarografije[18]. Iz navedenog je proizašla hipoteza o superiornosti tikagrelora (zbog ranijeg ordiniranja) u usporedbi s prasugrelom u MACE-u nakon godine dana. U suprotnosti s hipotezom, rezultati su upozorili na jasnu redukciju MACE-a u skupini s prasugrelom (6,9 % prema 9,3 %, OR 1,36, 95 % CI 1,09 – 1,70, p = 0,006) bez značajne razlike u krvarećim komplikacijama[18]. Iz ispitivanja su bili isključeni bolesnici s anamnestičkim podatcima o moždanom udaru (jer je kod njih prasugrel kontraindiciran), dok je bolesnicima starijima od 75 godina života (oko 24 % u objema skupinama) te onima s manje od 60 kg tjelesne težine (oko 5 % u objema skupinama) ordinirana doza prasugrela manja od 5 mg[18]. Subanaliza navedenih podskupina upozorila je na prednost prasugrela (što je u skladu s glavnim rezultatima), ali bez postizanja statističke značajnosti[18]. U nedavno objavljenoj metaanalizi koja je uključila više od 145 000 bolesnika, iz ukupno 14 randomiziranih istraživanja ili velikih prospektivnih registara uspoređivani su prasugrel, tikagrelor i klopidogrel u liječenju AKS-a[7]. Prema rezultatima metaanalize, prasugrel je superioran tikagreloru i klopidogrelu u redukciji MACE-a i ukupne smrtnosti nakon 30 dana, dok je tikagrelor smanjio ukupnu smrtnost s obzirom na klopidogrel[7]. Nadalje, prasugrel je znatno smanjio incidenciju tromboze stenta, ali bez značajne razlike u incidenciji infarkta miokarda u usporedbi s tikagrelorom. Nije bilo statistički značajne razlike u krvarenjima nakon 30 dana praćenja. Ipak, nakon godine dana nije bilo razlike u MACE-u između svih triju ispitivanih $P2Y_{12}$ inhibitora[7]. S druge strane, tikagrelor i prasugrel doveli su do znatne redukcije ukupne smrtnosti u usporedbi s klopidogrelom. Brojčano gledano, uz prasugrel je bilo manje smrtnih ishoda nego uz tikagrelor, ali bez postizanja statističke značajnosti[7]. Ni nakon godine dana praćenja nije utvrđena statistički značajna razlika u krvarećim komplikacijama[7].

Uzevši u obzir sve navedeno, oba inhibitora $P2Y_{12}$ receptora, prasugrel i tikagrelor, ispravna su opcija za liječenje bolesnika s AKS-om bez velikog rizika od krvarenja. Ipak, s obzirom na istraživanje *ISAR REACT 5*, kao i metaanalizu, prasugrel ima prednost u odnosu prma tikagreloru. Navedeno je prepoznato i u postojećim smjernicama za liječenje AKS-a bez elevacije ST-segmenta, a slične je preporuke moguće očekivati i u budućim smjernicama za STEMI[3]. Nadalje, prasugrel je lijek izbora i u liječenju bolesnika (podvrgnutih PCI-ju), a koji su inicijalno liječeni tikagrelorom te se u njih razvila zaduha neovisno o naporu. Naime, spomenuta nuspojava perzistira u oko 4 % bolesnika na tikagreloru nakon 7 dana terapije[8,19]. S druge strane, u određenih skupina bolesnika i u kliničkim scenarijima prednosti prasugrela nisu toliko jasne. Prije svega to su bolesnici s preboljelim moždanim udarom u kojih je prasugrel kontraindiciran, odnosno u kojih je tikagrelor jedina ispravna opcija (ako se procijeni da ukupan rizik od krvarenja nije visok). Slično tomu, ako je riječ o bolesnicima s AKS-om u kojih se planira medikamentno liječenje, a oni nemaju visok rizik od krvarenja, tikagrelor je bolja opcija od klopidogrela. Nadalje, tikagrelor ima prednost i u kliničkim scenarijima kada se planira odgođena invazivna dijagnostika, odnosno liječenje. Naime, u smjernicama za AKS bez elevacije ST-segmenta više se ne preporučuje ordiniranje $P2Y_{12}$ inhibitora bez poznavanja koronarne anatomije ako se planira rano invazivno liječenje, vremenski definirano unutar 24 sata od postavljanja dijagnoze[3]. Kao napomena, u istraživanju *ACCOAST* prosječno vrije-

tion ACS, they were immediately treated with a saturation dose of ticagrelor, while prasugrel was administered only after coronarography (in line with the recommendations for administering these medications)[18]. This generated the hypothesis that ticagrelor (due to its earlier administration) would be superior to prasugrel in MACE after one year. Contrary to the hypothesis, the results showed a clear reduction in MACE in the prasugrel group (6.9% vs. 9.3%, HR 1.36, 95% CI 1.09-1.70, p = 0.006) without any significant differences in bleeding complications[18]. Patients with a history of stroke were excluded from the study (since prasugrel is contraindicated in these patients), while patients above the age of 75 (approximately 24% in both groups) and those with body weight below 60 kg (approximately 5% in both groups) were given a low dose of prasugrel of 5 mg[18]. A subanalysis of these subgroups suggested the superiority of prasugrel (which is in line with the main results), but without statistical significance[18]. A recently published meta-analysis of over 145,000 patients from a total of 14 randomized studies or large prospective registries compared prasugrel, ticagrelor, and clopidogrel in ACS[7]. The results of this meta-analysis indicated that prasugrel was superior to ticagrelor and clopidogrel in reducing MACE and overall mortality after 30 days, while ticagrelor reduced overall mortality in comparison with clopidogrel[7]. In addition, prasugrel significantly reduced the incidence of stent thrombosis, but without a significant difference in the incidence of myocardial infarction in comparison with ticagrelor. There were no statistically significant differences in bleeding after 30 days of follow-up. However, after one year there were no differences in MACE among the three studied $P2Y_{12}$ inhibitors[7]. On the other hand, ticagrelor and prasugrel lead to a significant reduction in overall mortality compared with clopidogrel. In terms of numbers, prasugrel had fewer fatal outcomes than ticagrelor, but without statistical significance[7]. Even after one year of follow-up, no statistically significant difference was reported in bleeding complications[7].

Considering all of the above, both $P2Y_{12}$ receptor inhibitors, prasugrel and ticagrelor, are appropriate options for treating patients with ACS without high risk of bleeding. Nevertheless, considering the ISAR REACT 5 study and the meta-analysis, prasugrel is preferred to ticagrelor. This has also been recognized in the current guidelines for the treatment of non-ST elevation ACS, and similar recommendations can be expected in the future guidelines for STEMI[3]. In addition, prasugrel is the treatment of choice for patients (undergoing PCI) who were initially treated with ticagrelor or who developed non-exertional dyspnea. Specifically, this adverse effect persists in approximately 4% of patients on ticagrelor after 7 days of therapy[8,19]. On the other hand, the advantages of prasugrel are not as clear in certain patient populations and clinical scenarios. This primarily refers to patients who suffered a stroke, in whom prasugrel is contraindicated, i.e. in whom ticagrelor is the only right option (if the estimated total bleeding risk is not high). Similarly, in patients with ACS in whom medication treatment is intended and who do not have high bleeding risk, ticagrelor is a better option than clopidogrel. In addition, ticagrelor is also preferred in clinical scenarios when delayed invasive diagnostics or treatment is planned. Namely, guidelines for non-ST elevation ACS no longer recommend using $P2Y_{12}$ inhibitors without being familiar with coronary anatomy if early invasive treatment is planned, defined as occurring within 24 hours of diagnosis[3]. It should be noted that

me do PCI-ja iznosilo je 4,3 sata[13]. Ipak, same smjernice navode mogućnost primjene $P2Y_{12}$ inhibitora u situacijama kada rizik od krvarenja nije visok, a ne planira se rano invazivno liječenje[3]. U takvim situacijama, prema rezultatima opisanih istraživanja, tikagrelor ima prednost pred klopidogrelom. Završno, ostaje pitanje što činiti sa skupinom bolesnika koji su kandidati za dozu prasugrela manju od 5 mg (stariji od 75 godina života i lakši od 60 kilograma). Kao što je prije opisano, iako je učinkovitost navedene doze opisana u farmakokinetskim istraživanjima, nema jasnih kliničkih dokaza o superiornosti prasugrela nad tikagrelorom u tih skupina bolesnika. Kad je riječ o produljenoj DAPT (nakon godine dana), smjernice za liječenje AKS-a bez elevacije ST-segmenta s relativno snažnom preporukom razine IIa (razina dokaza A) preporučuju prolongiranu primjenu DAPT-a u bolesnika s procijenjenim visokim rizikom od ishemijskog incidenta, a niskim rizikom od krvarenja, odnosno razinom IIb (razina dokaza A) za bolesnike s umjerenim rizikom od ishemijskog događaja i niskim rizikom od krvarenja[3]. U takvim kliničkim slučajevima kao prva opcija liječenja preporučuje se tikagrelor u reduciranoj dozi (2 x 60 mg) na temelju opisanog istraživanja *PEGASUS-TIMI 54*, dok su prasugrel (ili klopidogrel) drugi izbor na temelju DAPT studije[3,17].

Prasugrel i tikagrelor kao monoterapija

Zahvaljujući napretku u dizajnu stentova, a u svrhu smanjenja prije svega krvarećih komplikacija DAPT-a nakon PCI-ja, provođena su istraživanja s ranijim ukidanjem $P2Y_{12}$ inhibitora te nastavkom monoterapije ASK-om[20,21]. Posljednjih se godina razvija sličan pristup, ali u kojem se ukida terapija ASK-om nakon inicijalna 1 – 3 mjeseca DAPT-a, a nastavlja terapija $P2Y_{12}$ inhibitorom[22]. Naime, teza u vezi s navedenim jest da ASK kao inhibitor enzima cikloksigenaza 1, osim toga što inhibira agregaciju trombocita, štetno djeluje na gastrointestinalnu sluznicu, a upravo su gastrointestinalna krvarenja najčešći uzrok krvarećih komplikacija[20]. Nadalje, farmakodinamska su istraživanja pokazala ograničen utjecaj antiagregacijskog djelovanja ASK-a ako je bolesnik na terapiji potentnim $P2Y_{12}$ inhibitorom[20,23,24]. Konačno, rizik od tromboze stenta s modernim DES najveći je unutar prvih mjesec dana[25-29].

Do sada je objavljeno pet randomiziranih studija u kojima je terapija DAPT-om prekinuta nakon 1 – 3 mjeseca od PCI-ja prema shemi da je ukinuta terapija ASK-om, a nastavljena terapija $P2Y_{12}$ inhibitorom (u trima studijama riječ je bila o tikagreloru, a u dvjema o raznim $P2Y_{12}$ inhibitorima, ponajprije klopidogrelu)[30-34]. U većini navedenih istraživanja, kao i u dvjema metanalizama, utvrđena je redukcija ozbiljnih krvarećih komplikacija od 31 do 71 % u skupini „kratkog" DAPT-a[25,30-35]. Ni u jednom istraživanju nije ustanovljena statistički značajna razlika u ishemijskim komplikacijama, MACE-u ili smrtnosti. Rezultati su bili konzistentni neovisno o kliničkim okolnostima PCI-ja – akutni ili kronični koronarni sindrom; bolesnici visokog rizika ili kompleksna PCI[26,36-38]. Na temelju navedenih rezultata smjernice za liječenje AKS-a bez elevacije ST-segmenta već dopuštaju primjenu DAPT-a (ASK-a i tikagrelora) tijekom 3 mjeseca, nakon čega se nastavlja monoterapija tikagrelorom u punoj dozi u bolesnika s niskim rizikom od krvarenja[3].

Nedavno su objavljeni rezultati *ASET* pokusnog istraživanja[39]. Riječ je se o multicentričnoj, opservacijskoj studiji u koju je bio uključen 201 ispitanik podvrgnut nekompliciranoj elektivnoj PCI[39]. Ispitanicima je na sam dan PCI-ja ordinirana

the average time to PCI was 4.3 hours in ACCOAST[13]. Nevertheless, the guidelines themselves include the option of using $P2Y_{12}$ inhibitors in situations when the risk of bleeding is not high and early invasive treatment is not planned[3]. In such situations, according to the results of these studies, ticagrelor is preferred to clopidogrel. Finally, the question remains what to do with the group of patients who are candidates for a lower dose of prasugrel of 5 mg (older than 75 and below 60 kg). As stated previously, although the efficacy of this dose has been described in pharmacokinetic investigations, there is no clear clinical evidence of the superiority of prasugrel over ticagrelor in these patient groups. In case of prolonged DAPT (after one year), guidelines for treating non-ST elevation ACS recommend prolonged DAPT with a relatively strong level IIa recommendation (evidence level A) in patients with an estimated high risk of ischemic incidents and low risk of bleeding and provide a level IIb (evidence level A) recommendation for patients with moderate risk of ischemic events and low risk of bleeding[3]. In such clinical cases, the recommended first treatment option is ticagrelor at a reduced dose (2 × 60 mg) based on the previously described PEGASUS-TIMI 54 study, while prasugrel (or clopidogrel) are second-choice agents based on the DAPT study[3,17].

Prasugrel and ticagrelor as monotherapy

Thanks to advancements in stent design and with the goal of reducing primarily bleeding complications of DAPT after PCI, studies have been conducted with earlier discontinuation of $P2Y_{12}$ inhibitors and continued monotherapy with aspirin[20,21]. A similar approach has been in development in recent years, but it involves discontinuing therapy with aspirin after the initial 1-3 months of DAPT and continuing therapy with a $P2Y_{12}$ inhibitor[22]. The premise behind this approach is that, besides inhibiting platelet aggregation, aspirin has a harmful effect on the gastrointestinal mucosa as a cyclooxygenase 1 inhibitor; gastrointestinal bleeding being the most common cause of bleeding complications[20]. Furthermore, pharmacodynamics studies demonstrated limited influence of the anti-aggregation effect of aspirin if the patient was on a potent $P2Y_{12}$ inhibitor[20,23,24]. Finally, the risk of stent thrombosis with a modern DES is highest during the first month[25-29].

Five randomized studies have been published to date in which DAPT was discontinued after 1-3 months post PCI, which involved discontinuing therapy with aspirin and continuing therapy with a $P2Y_{12}$ inhibitor (three studies involved ticagrelor and two involved various $P2Y_{12}$ inhibitors, primarily clopidogrel)[30-34]. Most of these studies, as well as two meta-analyses, identified a reduction in serious bleeding complications from 31 to 71% in the "short" DAPT group[25,30-35]. No study found statistically significant differences in ischemic complications, MACE, or mortality. The results were consistent regardless of the clinical circumstances of the PCI – acute or chronic coronary syndrome, high-risk patients, or complex PCI[26,36-38]. Based on these results, guidelines for treating non-ST elevation ACS already allow using DAPT (aspirin and ticagrelor) for 3 months, after which monotherapy with ticagrelor is continued at a full dose in patients with low risk of bleeding[3].

The results of the ASET pilot study were recently published[39]. ASET was a multicentric, observational study involving 201 subjects undergoing non-complicated elective PCI[39]. On the day of their PCI, the subjects were given their last dose

posljednja doza standardne terapije DAPT-om (klopidogrel i ASK), koja je potom ukinuta te nastavljena monoterapija prasugrelom tijekom sljedećih triju mjeseci, koliko je trajalo praćenje. U navedenom je razdoblju zabilježen jedan slučaj (0,5 %) kombiniranog ishemijskog i krvarećeg ishoda[39]. Na temelju navedenih rezultata u planu je prospektivno istraživanje u kojemu će svi bolesnici biti isključivo na monoterapiji prasugrelom te praćeni godinu dana.

Zaključak

Potentni $P2Y_{12}$ inhibitori, prasugrel ili tikagrelor, sastavni su dio DAPT-a u bolesnika s AKS-om bez visokog rizika od krvarećih komplikacija, liječenih PCI-jem. Prema dosadašnjim istraživanjima, terapija prasugrelom u odabranim skupinama bolesnika pruža veću zaštitu od potencijalnih ishemijskih ishoda, bez povećanja rizika od krvarenja u usporedbi s tikagrelorom te je stoga prva terapija izbora. S druge strane, tikagrelor je lijek izbora u bolesnika s medikamentno liječenim AKS-om. Usprkos obećavajućim rezultatima istraživanja s reduciranim trajanjem DAPT-a od tri mjeseca uz nastavak terapije $P2Y_{12}$ inhibitorom, potrebna su daljnja istraživanja, ponajprije u skupini bolesnika s AKS-om, prije eventualne promjene dosadašnje kliničke prakse.

of standard therapy with DAPT (clopidogrel and aspirin) which was then discontinued and replaced by prasugrel monotherapy for the next 3 months of the follow-up period. During this time, one case (0.5%) of a combined ischemic and bleeding outcome was reported[39]. Based on these results, plans are being made for a prospective study in which all the patients will exclusively receive prasugrel monotherapy during the study and the one-year follow-up.

Conclusion

Potent $P2Y_{12}$ inhibitors, prasugrel or ticagrelor, are an integral part of DAPT in patients with ACS who underwent PCI and who do not have a high risk of bleeding complications. According to present studies, the protection provided by prasugrel therapy compared with ticagrelor is greater than the potential ischemic outcomes in selected groups of patients, without increased risk of bleeding, and is therefore the first treatment of choice. On the other hand, ticagrelor is the treatment of choice in patients with ACS treated with medication. In spite of the promising results of the studies involving reduced 3-month DAPT followed by continued therapy with a $P2Y_{12}$ inhibitor, additional studies are required, primarily in patients with ACS, before introducing any changes to the current clinical practice.

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