Pregledni rad / Review article

Inhibitori ADP-om ovisne agregacije trombocita

Inhibitors of ADP-dependent platelet aggregation

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SAŽETAK: Trombociti imaju središnju ulogu u patogenezi aterotromboze. Trombocitni ADP (adenozindifosfatazni) receptori (P2Y12) imaju ključnu ulogu u agregaciji potencirajući učinak brojnih drugih faktora koji pri njoj sudjeluju. Inhibitori ADP ovisne agregacije trombocita (tiklopidin, klopidogrel, prasugrel, tikagrelor) su skupina lijekova koja povećava antiagregacijski učinak, poglavito u inicijalnoj fazi aktivacije trombocita te time daju značajan doprinos u liječenju aterotrombotskih bolesti, posebice ACS (akutnog koronarnog sindroma). Tiklopidin je prvi uveden u kliničku praksu, no hematološke nuspojave i spor početak učinka brzo su ograničile kliničku primjenu. Klopidogrel uz acetilsalicilatnu kiselinu brzo postaje zlatni standard u antiagregacijskoj terapiji nakon PCI (perkutane koronarne intervencije) i u ACS. No, njegova farmakokinetska i farmakodinamska ograničenja dovode do razvoja novih lijekova. Prasugrel ima jači i brži antiagregacijski učinak, ali uz cijenu više krvarenja. Tikagrelor je zadnji iz ove skupine lijekova s prednošću snažne, efikasne, brze i reverzibilne blokade P2Y12 receptora u odnosu na klopidogrel. Time je prema važećim smjernicama preferirani lijek za PCI u ACS, ali njegov status na Listi lijekova Hrvatskog zavoda za zdravstveno osiguranje za sada ograničava njegovu širu primjenu u Hrvatskoj.

KLJUČNE RIJEČI: antiagregacijska terapija, tiklopidin, klopidogrel, prasugrel, tikagrelor.

SUMMARY: Platelets play a central role in the pathogenesis of atherothrombosis. Platelet adenosine diphosphate (ADP) receptors (P2Y12) have a key role in the aggregation potentiating the effect of many other factors involved in it. Inhibitors of ADP-dependent platelet aggregation (ticlopidine, clopidogrel, prasugrel, ticagrelor) are a group of drugs that increase antiaggregation effect, especially in the initial phase of platelet activation and thereby make a significant contribution to the treatment of atherothrombotic disease, especially ACS (acute coronary syndrome). Ticlopidine was the first that was introduced into clinical practice, but hematologic side-effects and the slow start of effects have quickly limited the clinical application. Clopidogrel with acetylsalicylic acid is fast becoming the gold standard in antiaggregation therapy after PCI (percutaneous coronary intervention) even in ACS. But its pharmacokinetic and pharmacodynamic limitations lead to the development of new drugs. Prasugrel has a more potent and faster antiaggregation effect, but at the expense of more extensive bleeding. Ticagrelor is the last from this group of drugs with the advantage of a potent, efficient, rapid and reversible P2Y12 receptor antagonist over clopidogrel. According to the applicable guidelines, it is a preferred drug for PCI in ACS and its status in the List of the Croatian Health Insurance Fund limits its wider use in Croatia at the moment.

KEYWORDS: antiaggregation therapy, ticlopidine, clopidogrel, prasugrel, ticagrelor.

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Trombociti imaju središnju ulogu u patogenezi aterotromboze. Acetilsalicilatna kiselina (ASK) je temeljni standardni antitrombocitni lijek. Djelovanjem na nastajanje tromboksana A2 dovodi do trajnjeg smanjenja agregacijskih mogućnosti trombocita. Ipak, zbog ograničene uloga tromboksana A2 u agregaciji, ASK je nedostatno djelotvorna u visokorizičnim stanjima kao što su akutni koronarni sindrom (ACS) ili perkutana koronarna intervencija (PCI). Trombocitni ADP (adenozindifosfatazni) receptori (P2Y12) imaju ključnu ulogu u agregaciji potencirajući učinak brojnih drugih faktora koji pri njoj sudjeluju. Inhibitori ADP ovisne agregacije trombocita su skupina lijekova koja povećava antiagregacijski učinkak, poglavito u inicijalnoj fazi aktivacije trombocita te time daju značajan doprinos u liječenju ate-

Platelets play a central role in the pathogenesis of atherothrombosis. Acetylsalicylic acid (ASA) is the basic standard antiplatelet drug. Its action on the formation of thromboxane A2 leads to a permanent reduction in platelet aggregation capabilities. However, due to the limited role of thromboxane A2 in the aggregation, ASA is insufficiently potent in high-risk conditions such as acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI). Platelet adenosine diphosphate (ADP) receptors (P2Y12) have a key role in the aggregation potentiating the effect of many other factors involved in it. Inhibitors of ADP-dependent platelet aggregation are a group of drugs that increase antiplatelet effect, especially in the initial phase of the platelet activation and thereby make a significant contri-

rotrombotskih bolesti, posebice ACS. Intravenski antagonisti GP IIb/IIIa receptora djeluju u završnoj fazi trombocitne agregacije.

U inhibitore P2Y12 receptora spadaju tienopiridinski lijekovi (tiklopidin, klopidogrel i prasugrel) te tikagrelor koji je netienopiridinski lijek.

Tiklopidin

Prvi tienopiridinski lijek koji se počeo koristiti u kliničkoj primjeni je tiklopidin. U početku se je pokazao učinkovitim u dugotrajnoj terapiji nakon ishemijskog moždanog udara i kod klaudikacija, a u placebo kontroliranom ispitivanju u terapiji nestabilne angine pektoris (AP) postignuta je za 46% redukcija u kardiovaskularnoj smrtnosti i infarktu miokarda (IM) u prvih 6 mjeseci[1]. Kombinacija ASK i tiklopidina je olakšala uporabu koronarnih stentova, a u jednoj usporednoj studiji s klopidogrelom nakon elektivnog stenta pokazao je bolji učinak u prvih mjesec dana nakon PCI[2]. Također, to je jedini P2Y12 inhibitor koji ima odobrenu indikaciju primjene nakon elektivnog stenta.

Ipak, njegov kasni početak djelovanja (24 do 48 sati nakon primjene) čini ga nepogodnim u ACS, kao i hematološke nuspojave (osobito trombotična trombociteopenična purpura i aplastična anemija) koje se najčešće javljaju u prva tri mjeseca primjene te zahtjevi za čestom kontrolom krvne slike, ograničili su primjenu ovog lijeka te je on istisnut iz šire uporabe uvođenjem klopidogrela u terapiju. Kako nije dokazana genetska varijabilnost u metabolizmu tiklopidina, a učinkovit je u 96,5% bolesnika s dokazanom rezistencijom na klopidogrel, ostaje kao alterantiva za bolesnike s nepodnošljivošću i neučinkovitošću klopidogrela[3,4].

Klopidogrel

Nakon tiklopidina u terapiju je uveden slijedeći tienopiridin klopidogrel kome je glavna prednost u odnosu na prethodnika bio puno brži farmakodinamski učinak (dva sata nakon "loading" doze od 300-600 mg) što ga je činilo superiornim pri PCI u ACS, a također je imao manje hematoloških nuspojava u odnosu na tiklopidin te bolju gastrointestinalnu toleranciju.

Monoterapija klopidogrelom pokazala se nešto učinkovitija ASK u sekundarnoj prevenciji ishemijskog događaja u bolesnika s perifernom vaskularnom bolešću, ishemijskim moždanim udarom i IM u CAPRIE studiji[5]. Ipak, nije zamjenio ASK zbog visoke cijene u odnosu na njega te se u monoterapiji primjenjuje kao alternativa ASK kod njegova nepodnošenja.

Brojna ispitivanja u ACS i nakon PCI pokazala su superiornost kombinacije klopidogrela i ASK u odnosu na samu ASK tijekom jednogodišnje primjene tako da je to postala standardna terapija u bolesnika s ACS te nakon implantacije stenta[6-10].

Glavne mane klopidogrela su još uvijek relativno sporiji nastup djelovanja, velike interindividualne razlike u učinku te ireverzibilan učinak na agregaciju trombocita. Za prve dvije odgovoran je proces aktivacije klopidogrela koji se provodi u dvije faze, a uključuje velik broj citokrom P450 enzima koji su osjetljivi na interakcije lijekova te genski polimorfizam. Bolesnici s genskim polimorfizmom nemaju ili imaju ograničen metabolizam klopidogrela te time i rezistenciju na njegov učinak[11].

bution to the treatment of atherothrombotic disease, especially ACS. Intravenous GP IIb/IIIa receptor antagonists have an action in the final stage of platelet aggregation.

The P2Y12 receptor inhibitors include thienopyridine drugs (ticlopidine, clopidogrel and prasugrel) and ticagrelor which is a non-thienopyridine drug.

Ticlopidine

Ticlopidine is the first thienopyridine drug that started to be used in the clinical practice. It first proved to be efficient in the long-term therapy after ischemic stroke even in case of claudication and a 46% reduction was achieved in cardiovascular mortality and myocardial infarction (MI) in the first six months in the placebo-controlled study for the treatment of unstable angina pectoris (AP)[1]. The combination of ASA and ticlopidine has facilitated the use of coronary stents, and in one comparative study with clopidogrel after elective stenting, it showed a better effect in the first month after PCI[2]. It is also the only P2Y12 inhibitor that has an approved indication for application after the elective stent.

However, its delayed onset of action (24 to 48 hours after administration) makes it unsuitable in ACS, as well as hematological side-effects (especially thrombotic thrombocytopenic purpura and aplastic anemia), which usually occur in the first three months of application and requirements for frequent blood count control have limited the administration of this drug, and it has been squeezed out from the wider use at the time of introducing clopidogrel in the therapy. Since genetic variability has not been proved in the metabolism of ticlopidine and it is effective in 96.5% of patients with proved resistance to clopidogrel, it remains to be an alternative for patients who do not tolerate clopidogrel and in whom it is inefficent[3,4].

Clopidogrel

After ticlopidine, the following thienopyridine clopidogrel was introduced in the therapy which had a major advantage over its predecessor which was much faster pharmacodynamic effect (two hours after the "loading" dose of 300-600 mg) which made it superior when performing PCI in ACS, and it also had less hematological side effects than ticlopidine and better gastrointestinal tolerance.

Clopidogrel monotherapy proved to be somewhat more effective ASA in secondary prevention of ischemic events in patients with peripheral vascular disease, ischemic stroke and MI in the CAPRIE study[5]. However, it has not replaced ASA due to the high cost compared to it, and it is used as an alternative to ASA in the monotherapy in case of its intolerance. Numerous tests in ACS and after PCI have shown the superiority of the combination of clopidogrel and ASA compared to ASA alone during one-year application, so that it has become a standard therapy in patients with ACS and after stent implantation[6-10].

The main disadvantages of clopidogrel are still relatively slow onset of action, high inter-individual differences in the effect of the irreversible effect on platelet aggregation. Clopidogrel activation process is responsible for the first two ones that is carried out in two phases, and includes a large number of cytochrome P450 enzymes that are susceptible to drug interactions and genetic polymorphisms. Patients with the genetic polymorphism have no or limited metabolism of clopidogrel and thus resistance to its effect[11].

Pokušaji da se predvidi učinak klopidogrela mjerenjem agregacije trombocita nisu se do sada pokazali učinkovitim (npr. nedavno ARCTIC ispitivanje[12] u kome je prilagođena antiagregacijska terapija uspoređivana sa standardnom nakon PCI) tako da nema smisla određivati agregaciju trombocita za određivanje djelotvornosti klopidogrela, a u ovom trenutku i ostalih antiagregacijskih lijekova[13].

Također pitanje interakcije klopidogrela s inhibitorima protonske pumpe (o čemu je puno diskutirano zadnjih godina), ima više teoretsko, nego praktično značenje[14,15].

Prasugrel

Najnoviji u klasi tenopiridina je učinkovitiji od tiklopidina i klopidogrela, primarno zbog bržeg i učinkovitijeg metabolizama (samo u jednoj fazi) tako da na trombocit djeluje više aktivnog metabolita. Ima brži početak djelovanja i jači antiagregacijski učinak od klopidogrela. U usporedbi s njim pokazuje manju varijabilnost u učinku, a nema dokaza da genski polimorfizam u CYP izoenzimima utječe na njegov metabolizam. U TRITON TIMI 38 ispitivanju u bolesnika s AKS pokazao se superiornijim klopidogrelu u smanjenju ishemijskih događaja (posebice u bolesnika sa STEMI ili dijabetesom), ali uz cijenu nešto većeg rizika od krvarenja, poglavito fatalnog (21 prasugrel: 4 klopidogrel). Učinak je bio vidljiv svih 15 mjeseci koliko je trajalo prosječno praćenje bolesnika u studiji. Također je za 50% smanjena in-stent tromboza, kako kod BMS tako i kod DES. Rizik krvarenja bio je povećan u bolesnika starijih od 75 godina, manje tjelesne mase te preboljelim moždanim udarom, tako da se tim bolesnicima ne preporuča primjena lijeka (CVI kontraindikacija), odnosno ako je primjena neophodna treba im dati reduciranu dozu od 5 mg. Također je rizik krvarenja bio viši za 4 puta u bolesnika koji su bili podvrgnuti aortokoronarnom premoštenju (CABG) nego u skupini koja je primala klopidogrel, a povećan je i kod drugih operacija prvih tjedan dana nakon prestanka uzimanja lijeka[16].

U TRILOGY studiji uspoređivan je prasugrel u odnosu na klopidogrel u bolesnika s AKS, ali koji su bili liječeni medikamentozno. Tu se nije pokazala statistički značajna razlika između dva lijeka, ali u skupini bolesnika s angiografski dokumentiranom koronarnom bolesti srca prasugrel je bio bolji od klopidorela u smanjenju ishemijskih događaja (12,8 naspram 16,5%, p=0,001)[17].

Tikagrelor

Tikagrelor je prvi predstavnik nove skupne inhibitora P2Y12 receptora tzv. ciklopentiltrazolpirimidina. Nastao je u procesu traženja mimetika oralno aktivnog ATP, prirodnog antagonista P2Y12 receptora. Tikagrelor se reverzibilno veže uz receptor uz jači i brži antitrombocitni učinak od klopidogrela. U PLATO studiji pokazao je u odnosu na klopidogrel relativnu redukciju za 16% rizika primarnog cilja studije (zbir kardiovaskularne smrtnosti, MI i moždanog udara) uz nesignifikantno povećanje rizika od velikih krvarenja[18]. U podstudiji PLATO-INVASIVE dokazana je statistički značajna redukcija ishemijskih događaja (uključivo tromboza stenta), ali bez povećanja velikih krvarenja u odnosu na klopidogrel[19].

Također je bio sigurniji u bolesnika koji su bili podvrgnuti CABG, premda su krvarenja u bolesnika koji nisu operirani bila nešto češća. Dok klopidogrel i prasugrel nisu pokazali redukciju mortaliteta, tikagrelor je imao za 22% manji mortalitet usprkos snažnom antitrombocitnom učinku[20].

The attempts to predict the effect of clopidogrel by measuring platelet aggregation have not proved effective so far (e.g. the recent ARCTIC trial[12] in which the adjusted antiplatelet therapy was compared to standard therapy after PCI), so there is no sense to determine platelet aggregation for determining the efficacy of clopidogrel, and other antiplatelet drugs at this moment[13].

The question as to the interaction of clopidogrel with proton pump inhibitors (which has been much discussed in recent years), has more theoretical than practical significance[14,15].

Prasugrel

Being most recent one in the thienopyridine class, it is more effective than ticlopidine and clopidogrel, primarily due to a faster and more efficient metabolism (only in one phase), so that the platelets are affected by several active metabolites. It has a faster onset of action and a stronger antiaggregation effect than clopidogrel. Compared to it, it shows less variability in effect, and there is no evidence that genetic polymorphism in the CYP isoenzymes affects its metabolism. In TRITON TIMI 38 trial in patients with ACS it has proven to be superior to clopidogrel in reducing ischemic events (particularly in patients with STEMI or diabetes), but at the expense of a slightly higher risk of bleeding, especially fatal one (21 prasugrel versus 4 clopidogrel). The effect was visible in all 15 months as long as an average follow-up of patients lasted in the study. The in-stent thrombosis was reduced by 50%, both in BMS and DES. The risk of bleeding was increased in patients over 75 years of age, with less weight and previous stroke, so administration of the medicine was not recommended in these patients (stroke contraindication), or if the administration is necessary, they should be given a reduced dose of 5 mg. The risk of bleeding was higher by four times in patients who underwent the coronary artery bypass grafting than in the group receiving clopidogrel and it was also increased in other operations in the first week after they stopped taking the medicine[16].

The study TRILOGY compared prasugrel vs. clopidogrel in patients with ACS, but who were treated pharmacologically. There was no statistically significant difference between the two drugs, but in patients with angiographically documented coronary artery disease, prasugrel was superior to clopidogrel in reducing ischemic events (12.8% vs. 16.5%, p = 0.001)[17].

Ticagrelor

Ticagrelor is the first representative of a new group of P2Y12 receptor inhibitors, the so-called cyclopen-tyltriazolo-pyrimidines. It was created in the process of searching orally active mimetic ATP, the natural P2Y12 receptor antagonist. Ticagrelor reversibly binds with the receptor with a more potent and more rapid antiplatelet effect of clopidogrel. In the PLATO study it showed, compared to clopidogrel, a relative reduction by 16% of risk-primary endpoint (the composite of cardiovascular mortality, myocardial infarction and stroke) with an insignificant increase in the risk of major bleeding[18]. A statistically significant reduction of ischemic events (including stent thrombosis) was proved in the substudy PLATO-INVASIVE, but with no increase in major bleeding as compared to clopidogrel[19].

It was also safer in patients who underwent coronary artery bypass grafting, although bleeding was more extensive in patients who did not undergo the surgery. While clopidogrel and prasugrel showed no reduction in mortality, ticagrelor

Relativno kratak poluživot lijeka te uzimanje dvaput dnevno zahtjeva dobru suradljivost bolesnika na kojoj treba trajno inzistirati. Također treba biti oprezan u bolesnika s velikim rizikom od krvarenja i komorbiditetom.

Premda je lijek još 2011. registriran u EU i SAD te uvršten u smjernice za liječenje AKS Europskog kardiološkog društva i engleskog NICE, serija članaka objavljenih 2013. dovode u pitanje rezultate i metodologiju PLATO studije, tako da je u rujnu 2013. god. Ministarstvo pravosuđa SAD započelo istragu o provođenju studije (čije rezultate još čekamo). Interesantno je spomenuti da je regulatorni status lijek usprkos toj istrazi, nepromjenjen[21,22].

Klinička istraživanja novih antiagregacijskih lijekova

U kliničkim ispitivanjima je još nekoliko antiagregacijskih lijekova koji djeluju različitim mehanizmima,a od njih je najbliži kliničkoj uporabi voraksapar koji inhibira aktivaciju trombocita preko trombinskih PAR-1 receptora. U ovom trenutku je u tijeku njegova registracija u indikaciji sekundarne prevencije IM, dok je negativan sigurnosni profil (nepovoljan odnos prevencije ishemijskih događaja u odnosu na krvarenja) isključio ovaj lijek u liječenju AKS[23].

Antiagregacijski lijekovi u smjernicama

Smjernice ESC za liječenje AKS, poglavito u bolesnika koji idu na PCI, preferiraju tikagrelor i prasugrel nad klopidogrelom, gdje je lijek prvog izbora tikagrelor. Klopidogrel se navodi kao mogućnost liječenja ako su prva dva lijeka nedostupna ili kontraindicirana. Dualnu terapiju treba provoditi 12 mjeseci nakon PCI[24,25].

Američke smjernice za PCI u AKS u istu razinu preporuke stavljaju: klopidogrel, prasugrel i tikagrelor uz preporuku da ih se daje u dvojnoj terapiji s ASK još 12 mjeseci.

Kod PCI koja nije povezana s AKS, jedini blokator P2Y12 receptora koji se preporuča je klopidogrel uz preporuku da se nakon BMS daje minimalno u dvojnoj terapiji mjesec dana (optimalno godinu), a nakon DES obvezno godinu dana uz mogućnost daljnjeg produženja[26].

Engleske NICE smjernice za sekundarnu prevenciju infarkta miokarda preporučavaju klopidogrel za dvojnu antiagregacijsku terapiju u onih bolesnika kojima je indicirana trajna antikoagulacijska terapija. Dužina primjene dvojne antikoagulacije terapije nakon AKS i PCI, odnosno elektivne PCI je sukladna već navedenim smjernicama. Izričito navode da se tikagrelol i prasugrel ne preporučaju davati uz varfarin, a također ne preporučaju niti primjenu novih oralnih antikoagulansa (dabigatran, rivaroksoban i apiksaban) uz dvojnu antiagregacijsku terapiju[27,28].

Zaključak

U nas su registrirana sva četiri inhibitora P2Y12 receptora koji se spominju u ovom članku,a sva četiri su i na Listi lijekova HZZO. Od toga dva nova (Efient® — prasugrel i Brilique® — tikagrelor) s relativno velikom nadoplatom od 214 i 324 kune po kutiji lijeka. To bitno ograničava njihovu primjenu sukladno hrvatskim smjernicama za liječenje AKS.

Premda u literaturi postoje mišljenja da njihova prednost nad klopidogrelom i nije tako velika da bi opravdala razliku u cijeni[29], ipak bi njihovo uvrštenje na Osnovnu Listu lijekova HZZO-a (bez nadoplate) omogućilo bolje liječenje naših

had a 22% lower mortality despite the potent antiplatelet effect[20].

The relatively short half-life of the drug and taking the drug twice a day requires good patient compliance which should be permanently insisted on. You should be cautious in patients with a high risk of bleeding and comorbidity.

Although the drug was registered in the European Union and the United States of America in 2011, and is included in the guidelines of the European Society of Cardiology (ESC) for the treatment of ACS, as well as in the British NICE guidelines, a series of articles published in 2013 has raised doubts about the results and methodology of the PLATO study, so that in September 2013 the U.S. Department of Justice began an investigation on the implementation of the study (which results are still awaited). It is interesting to note that the regulatory status of the drug has remained unchanged in spite of that investigation[21,22].

New antiplatelet drugs in clinical trials

There are several antiplatelet drugs included in the clinical trials whose action is enabled by various mechanisms, whereas voraxapar is one of them being closest to the clinical use and inhibiting activation of platelets via thrombin PAR-1 receptors. At this point, its registration in the indication of secondary prevention of myocardial infarction is underway, while the negative safety profile (negative ratio of prevention of ischemic events vs. bleeding) excluded this drug in the treatment of ACS[23].

Antiplatelet drugs in the guidelines

ESC Guidelines for the treatment of ACS, especially in patients undergoing PCI, prefer ticagrelor and prasugrel to clopidogrel, where ticagrelor is the drug of choice. Clopidogrel is mentioned as a treatment option, if the first two drugs are unavailable or contraindicated. Dual therapy should be conducted 12 months after PCI[24,25].

American guidelines for PCI in ACS place the below specified drugs in the same level of the recommendation: clopidogrel, prasugrel and ticagrelor thereby recommending that they should be administered in the dual therapy with ASA in the further 12 months' period.

In case when PCI is not associated with ACS, the only P2Y12 receptor antagonist that is recommended is clopidogrel with a recommendation, that after BMS it should be administered in dual therapy for at least one month (one year optimally), and after DES it should be administered mandatory for one year with the possibility of further extension of this term[26].

The English NICE guidelines for secondary prevention of myocardial infarction recommend clopidogrel for dual antiplatelet therapy in those patients with indicated permanent anticoagulation therapy. The length of administering dual antiplatelet therapy after ACS and PCI, that is, elective PCI, is consistent with mentioned guidelines. They explicitly state that ticagrelol and prasugrel are not to be administered together with warfarin, and also do not recommend the administration of new oral anticoagulants (dabigatran, rivaroxoban and apixaban) with dual antiplatelet therapy[27,28].

Conclusion

All four P2Y12 receptor inhibitors discussed in this article are registered in Croatia, and all four of them are listed in the

koronarnih bolesnika, poglavito u AKS, ali je pitanje koliko je to u ovom ekonomskom trenutku realno.

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List of the Croatian Health Insurance Fund. Out of these new drugs, there are two new ones (Efient® — prasugrel and Brilique® — ticagrelor) with a relatively high surcharge ranging from HRK 214 to HRK 324 per box of the drug. This is the reason why their use is greatly limited in accordance with Croatian guidelines for the treatment of ACS.

Although the literature mentions some opinions according to which their advantage over clopidogrel is not so great to justify the difference in price[29], their listing in the List of Essential Medicines of the Croatian Health Insurance Fund (without a surcharge) would allow a better treatment for our coronary patients, especially in ACS, but the question is how viable it is in this hard economic situation.

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