Era tikagrelora

The Ticagrelor Era

Krešimir Štambuk*[1,2]

[1]Klinika za kardiovaskularne bolesti Magdalena Medicinskog fakulteta Sveučilišta u Osijeku, Krapinske Toplice, Hrvatska
[2]Fakultet za dentalnu medicinu i zdravstvo Sveučilišta u Osijeku, Osijek, Hrvatska

[1]Magdalena Clinic for Cardiovascular Diseases, Faculty of Medicine, University of Osijek, Krapinske Toplice, Croatia
[2]Faculty of Dental Medicine and Health, University of Osijek, Osijek, Croatia

SAŽETAK: Koronarna bolest srca jedan je od vodećih uzroka smrtnosti u zemljama razvijenoga svijeta. U posljednja tri desetljeća učinjen je velik iskorak u njezinu liječenju, i to prije svega akutnoga koronarnog sindroma (AKS). Takvi su rezultati posljedica uvođenja strategije perkutane koronarne intervencije i dvojne antiagregacijske terapije. Posljednjih deset godina obilježilo je uvođenje potentnijih antiagregacijskih lijekova kao što su tikagrelor i prasugrel. Danas slobodno možemo reći da je dvojna kombinacija acetilsalicilatne kiseline i tikagrelora jedna od temeljnih kombinacija u liječenju bolesnika s AKS-om, bilo da su liječeni koronarnom intervencijom bilo konzervativno. Tikagrelor je s vremenom proširio lepezu indikacija tako se danas može uključiti u liječenje bolesnika s visokim ishemijskim rizikom i nakon godinu dana od izvedene intervencije ili inicijalnoga akutnoga koronarnog događaja. Bitno je istaknuti da u svim provedenim istraživanjima, iako je rizik od krvarenja bio nešto viši u usporedbi s klopidogrelom, krvarenja nisu uzrokovala smanjenje klinički pozitivnog učinka tikagrelora. Iako nema velikih istraživanja s primjenom tikagrelora u bolesnika s kroničnim koronarnim sindromom (KKS), smjernice daju preporuku da se tikagrelor može uvesti u terapiju bolesnika s KKS-om i visokim rizikom od ishemijskog događaja. Posljednjih je deset godina tikagrelor duboko ušao u kliničku praksu i postao temelj dvojne antiagregacijske terapije u većine bolesnika s AKS-om, kao i u dijela bolesnika s KKS-om.

SUMMARY: Coronary heart disease is still one of the leading causes of mortality in developed counties. In the last three decades, a significant step forward has been achieved in its treatment, primarily for acute coronary syndrome (ACS). These results are the consequence of the introduction of a treatment strategy based on percutaneous coronary interventions and dual antiplatelet therapy. The last decade was also marked by the introduction of more potent antiplatelet medications such as ticagrelor and prasugrel. We can now confidently say that dual combination of aspirin and ticagrelor is one of the fundamental combinations for the treatment of patients with ACS, whether they were treated with percutaneous coronary intervention or with conservative treatment. Over time, ticagrelor has expanded its scope of indications and can today be included in the treatment of patients with high ischemic risk even one year after an intervention or the initial acute coronary event. It is important to emphasize that although the risk of bleeding in all the studies was somewhat higher compared with clopidogrel, the bleeding did not cause a reduction in the clinical benefits of ticagrelor. While there are no large studies on the application of ticagrelor in patients with chronic coronary syndrome (CCS), guidelines recommend the introduction of ticagrelor to the treatment of patients with CCS and high risk of ischemic events. Over the last decade, ticagrelor has embedded itself deeply in clinical practice and become the basis of dual antiplatelet therapy in most patients with ACS as well as some patients with CCS.

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

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

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***ADDRESS FOR CORRESPONDENCE**: Krešimir Štambuk, Odjel kardiologije, Klinika Magdalena, Ljudevita Gaja 2, HR-49217 Krapinske Toplice, Croatia. / Phone: +385-98-743-779 / E-mail: kresimir.stambuk@gmail.com

ORCID: Krešimir Štambuk, https://orcid.org/0000-0002-9107-6187

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Uvod

Dobro je poznato da su kardiovaskularne bolesti najčešći uzrok smrtnosti u visokorazvijenim zemljama pa tako i u Republici Hrvatskoj. To je

Introduction

It is a well-known fact that cardiovascular diseases are the most common cause of mortality in highly developed countries, including the Re-

i jedan od osnovnih razloga zašto je izrazito puno uloženo, ali i postignuto u prevenciji i liječenju te skupine bolesti, i to prije svega koronarne bolesti srca (KBS). Jedan od najbitnijih pomaka bilo je uvođenje perkutane koronarne intervencije u akutnom infarktu miokarda (primarna PCI) koja je promijenila sliku preživljavanja i komplikacija u bolesnika nakon preboljelog infarkta. Usporedo s razvojem tehnologije dolazi i do velikog iskoraka u poznavanju patofiziologije KBS-a, a pogotovo akutnoga koronarnog sindroma (AKS). Aterotrombotski događaj prepoznat je kao osnovni patološki mehanizam nastanka i progresije akutnoga, ali i kroničnoga koronarnog sindroma (KKS). Postalo je jasno da trombociti imaju središnju ulogu u nastanku koronarne tromboze na bazi rupturiranoga plaka, a antiagregacijski lijekovi postaju temelj liječenja AKS-a, ali i ishemijskih komplikacija povezanih s perkutanom koronarnom intervencijom (PCI). Pivotalne su studije dvojnu antiagregacijsku terapiju (DAPT) s acetilsalicilatnom kiselinom (ASK) i klopidogrelom postavile kao osnovu terapije u kontekstu AKS-a i PCI-ja. Usprkos dokazanoj učinkovitosti DAPT-a, i dalje relativno česti neželjeni ishemijski događaji potaknuli su razvoj novih, potentnijih antiagregacijskih lijekova prasugrela i tikagrelora. Od tih dvaju lijekova u Hrvatskoj je donedavno dostupan bio samo tikagrelor i možemo reći da i danas još traje „era tikagrelora".

Farmakodinamika i farmakokinetika tikagrelora

Tikagrelor je peroralni antiagregacijski lijek koji uz klopidogrel i prasugrel pripada grupi inhibitora P2Y12 receptora. Za razliku od spomenutih dvaju lijekova koji su po kemijskom sastavu tienopiridini, tikagrelor je ciklopentiltriazolopirimidin i zahvaljujući drukčijim kemijskim svojstvima postoje dvije bitne razlike u njegovoj farmakodinamici u usporedbi s tienopiridinima – veže se reverzibilno za P2Y12 receptor dok se prasugrel i klopidogrel vežu ireverzibilno i, za razliku od tienopiridina, tikgrelor nije predlijek te nije potrebna bioaktivacija, već ima izravan antiagregacijski učinak. Također je i sam mehanizam djelovanja tikagrelora različit jer ne sprječava vezanje ADP-a na P2Y12 receptor, nego reverzibilno inhibira ADP-om induciranu promjenu receptora i aktivaciju G-proteina vežući se na različito mjesto od mjesta vezanja ADP-a, odnosno ostalih antiagregacijskih lijekova. To je bitno jer receptor ostaje u neaktivnome stanju, a nakon otpuštanja tikagrelora ADP može brzo reaktivirati receptor. S kliničkoga gledišta ova dva svojstva objašnjavaju brz i siguran početak djelovanja (neovisan o bioaktivaciji), kao i relativno brz oporavak agregacije trombocita i smanjenje rizika od krvarenja. Enzim CYP3A4/5 brzo metabolizira tikagrelor u jetri, a glavni metabolit razgradnje tikagrelora gotovo je jednako učinkovit u inhibiciji P2Y12 receptora. Zahvaljujući opisanim farmakokinetskim svojstvima, u usporedbi s klopidogrelom, tikagrelor ima mnogo brži početak djelovanja, mnogo višu razinu inhibicije trombocita i brži prestanak farmakodinamičkoga djelovanja.

Danas se zna da postoje učinci tikagrelora neovisni o inhibiciji P2Y12 receptora. Većina je tih učinaka posljedica povećanja koncentracije adenozina koji dodatno djeluje na mikrocirkulaciju i pretpostavlja se da smanjuje reperfuzijsku ozljedu miokarda. Također se smatra da je adenozin jedan od glavnih mehanizama nastanka nuspojava tikagrelora – zaduhe i, rjeđe, bradikardije.

public of Croatia. This is also one of the main reasons why so much has been invested and achieved in both prevention and treatment of this disease group, especially for coronary heart disease (CHD). One of the major shifts was the introduction of percutaneous coronary intervention in acute myocardial infarction (primary PCI), which transformed the prognosis of survival and complications in post-infarction patients. Simultaneously with the development of new technology, there was a large step forward in our understanding of the pathophysiology of CHD, especially acute coronary syndrome (ACS). Atherothrombotic events were recognized as the basic pathological mechanism of the development and progression of both acute and chronic coronary syndromes. It has become clear that platelets have a central role in the development of coronary thrombosis based on ruptured plaque, and antiaggregation agents became fundamental for the treatment of ACS as well as ischemic complications associated with percutaneous coronary intervention (PCI). In pivotal studies, dual antiplatelet therapy (DAPT) with aspirin and clopidogrel was established as the basis of therapy in the context of ACS and PCI. Despite the proven effectiveness of DAPT, undesirable ischemic events remained relatively frequent and have encouraged the development of newer, more potent antiaggregation agents, namely prasugrel and ticagrelor. Out of these two, only ticagrelor was available in Croatia until recently, and one could argue that "the ticagrelor era" still continues today.

Pharmacodynamics and pharmacokinetics of ticagrelor

Ticagrelor is an oral antiaggregation agent that, along with clopidogrel and prasugrel, belongs to the class of P2Y12 receptor inhibitors. Unlike these two agents, which are classified as thienopyridines according to their chemical compositions, ticagrelor is a cyclopentyl triazolopyrimidine, and there are two important differences in its pharmacodynamics compared to thienopyridines due to its different chemical properties – it reversibly binds to P2Y12 receptor, while prasugrel and clopidogrel bind irreversibly, and, unlike thienopyridine, ticagrelor is not a prodrug and does not require bioactivation. It instead has a direct antiaggregation effect. Ticagrelor's mechanism of action is different as well, because it does not preclude the binding of ADP to P2Y12 receptor. Instead, it reversibly inhibits the ADP-induced change in the receptor and activation of G-protein by binding to a site different then the ADP binding site or the binding sites of other antiaggregation agents. This is important because the receptor remains in its inactive state, and the receptor can be quickly reactivated by ADP after releasing ticagrelor. From a clinical aspect, these two properties explain the quick and safe onset of action (independent of bioactivation), as well as the relatively quick recovery of platelet aggregation and reduction in bleeding risk. Ticagrelor is quickly metabolized in the liver by the CYP3A4/5 enzyme, and the main metabolite of ticagrelor breakdown is almost equally effective in inhibiting the P2Y12 receptor. Due to the pharmacokinetic properties described above, ticagrelor has a much faster onset of action, a significantly higher level of platelet inhibition, and a quicker cessation of pharmacodynamic activity compared with clopidogrel.

We now know that there are effects of ticagrelor that are independent of P2Y12 receptor inhibition. Most of these effects are a consequence of increased concentration of adenosine, which has an additional effect on microcirculation and is presumed to reduce myocardial reperfusion injury. Adenosine is also thought to be one of the main mechanisms behind the adverse effects of ticagrelor – dyspnea and, less commonly, bradycardia.

Indikacijski spektar i trajanje terapije tikagrelorom

Indikacija za primjenu i izbor antiagregacijske terapije, pa tako i tikagrelora, ovisi o više različitih čimbenika koji se mogu zajedno prikazati kao odnos ishemijskog rizika i rizika od krvarenja. Ishemijski rizik prije svega ovisi samoj dijagnozi i zna se da je mnogo viši kod AKS-a nego u bolesnika s KKS-om. Nadalje, značajne su činjenice je li u bolesnika provedeno intervencijsko liječenje i je li ugrađen stent ili je pak provedeno samo medikamentno liječenje. Donedavno je razliku činila i vrsta ugrađenog stenta, ali se danas praktički koristimo samo stentovima s otpuštanjem lijeka. Na indikaciju također utječe i odabrana kombinacija antiagregacijskih lijekova, odnosno primjenjujemo li lijekove kao monoterapiju ili DAPT, a u bolesnika na antikoagulantnoj terapiji i trojnu terapiju. Također treba spomenuti i različito trajanje antiagregacijske terapije koja se u bolesnika s visokim rizikom od krvarenja pokušava maksimalno skratiti, a u onih s visokim ishemijskim rizikom i niskim rizikom od krvarenja produljiti i do doživotne terapije. U svjetlu navedenoga indikacijski spektar tikagrelora prije svega treba gledati imajući na umu bolesnike s AKS-om i one s jednim od KKS-a.

Akutni koronarni sindrom

Današnje smjernice za liječenje bolesnika s AKS-om s elevacijom ST-segmenta ili bez nje preporučuju dvojnu antiagregacijsku terapiju s ASK-om i tikagrelorom ili prasugrelom, i to u trajanju od dvanaest mjeseci[1] (**tablica 1**). Tikagrelor treba uz ASK dati u udarnoj dozi od 180 mg i nastaviti dozom 2 x 90 mg. U usporedbi s prasugrelom, tikagrelor ima nekoliko prednosti – indiciran je neovisno o strategiji liječenja, što znači i u bolesnika koji su liječeni intervencijski (PCI), kao i u onih koji su liječeni samo medikamentnom terapijom. Nadalje, tikagrelor možemo relativno sigurno primijeniti u standardnoj dozi u bolesnika koji u terapiji već imaju klopidogrel, kao i u onih koji su niske tjelesne težine (<60 kg) i visoke životne dobi (>75 godina). Tikagrelor je ušao u svakodnevnu kliničku praksu u liječenju AKS-a 2009. godine, kada su objavljeni rezultati za tikagrelor ključnog istraživanja *PLATO*[2]. Riječ je bila o randomiziranoj, multicentričnoj, dvostruko slijepoj studiji koja je ispitivala učinkovitost tikagrelora (180 mg udarna doza, 2 x 90 mg doza održavanja) u usporedbi s dotadašnjim zlatnim standardom klopidogrelom (300 – 600 mg udarna doza / 75 mg doza održavanja). Terapija tikagrelorom pokazala se mnogo učinkovitijom u redukciji kombiniranog ishoda smrti i ishemijskih događaja nakon 30 dana (4,8 *vs.* 5,4 %; P = 0,045), a superiornost tikagrelora održala se i nakon 12 mjeseci s relativnom redukcijom rizika od 16 % (9,8 *vs.* 11,7 %, P <0.001). Bitno je istaknuti da je u istraživanju *PLATO* bilo nešto više velikih krvarenja uz tikagrelor, ali nije bilo razlike u kritičnim krvarenjima između dvaju lijekova. S kliničkoga stajališta vrlo je zanimljiv podatak da nije bilo razlike u velikim krvarenjima u bolesnika u kojih je izvedeno aortokoronarno premoštenje uz napomenu da je tikagrelor prekinut 24 – 72 sata prije operacije, dok je klopidogrel izostavljen 5 dana prije zahvata. To je bio izravan dokaz farmakokinetske prednosti tikagrelora, odnosno njegova bržeg prestanka djelovanja. *Jedan od najbitnijih rezultata istraživanja PLATO jest znatno smanjenje smrtnosti povezano s terapijom tikagrelorom.* Još jednom treba istaknuti da je antiishemijska učinkovitost tikagrelora u odnosu prema klopidogrelu bila neovisna o strategiji lije-

Indication range and duration of ticagrelor therapy

Indications for the use and choice of antiaggregation therapy, including ticagrelor, depend on several different factors that can collectively be described as a relationship between ischemic risk and the risk of bleeding. Ischemic risk depends primarily on the diagnosis itself and is known to be significantly higher in ACS than in chronic coronary syndrome (CCS). Furthermore, it matters whether a patient has undergone interventional treatment and had a stent implanted or has only had medication treatment. Until recently, the type of stent implanted also made a difference, but today we practically only use drug-eluting stents (DES). Indications are also influenced by the chosen combination of antiaggregation agents, in particular on whether the medications are administered as monotherapy or dual antiaggregation therapy, or even triple therapy in patients receiving anticoagulant treatment. Different duration of antiaggregation therapy is also relevant, since we normally try to make it as short as possible in patients with high bleeding risk, therapy is long-term or even life-long whereas in patients with high ischemic risk and low bleeding risk. In light of the above, ticagrelor's indication range should be primarily viewed through patients with ACS and those with one of the CCS.

Acute coronary syndrome

Current guidelines for the treatment of patients with ST-elevation and non-ST-elevation ACS recommend DAPT with aspirin and ticagrelor or prasugrel for twelve months[1] (**Table 1**). Ticagrelor should be given with aspirin at a loading dose of 180 mg and then continued at a dosage of 2x90 mg. Compared with prasugrel, ticagrelor has several advantages – it is indicated regardless of the treatment strategy, including both patients undergoing interventional treatment (PCI) and patients receiving only medication treatment. Furthermore, the standard dose of ticagrelor can be used relatively safely in patients who are already receiving therapy with clopidogrel, as well as in those with low body weight (<60 kg) and advanced age (>75 years). Ticagrelor became a part of daily clinical practice of treating ACS in 2009, when the results of PLATO, a pivotal study with ticagrelor, were published.[2] PLATO was a randomized, multicentric, double-blind study on the efficacy of ticagrelor (180 mg loading dose, 2x90 mg maintenance dose) versus clopidogrel as the current gold standard (300-600 mg loading dose/75 mg maintenance dose). Ticagrelor therapy was demonstrated to be significantly more effective in reducing the combined outcome of death and ischemic events after 30 days (4.8 vs. 5.4%; P = 0.045), and ticagrelor superiority was maintained even after 12 months, with a relative risk reduction of 16% (9.8 vs. 11.7%, P <0.001). It should be noted that slightly higher rates of major bleeding were observed with ticagrelor in the PLATO study, but there was no difference in critical bleeding between these two agents. From a clinical point of view, it is very interesting that there was no difference in major bleeding between patients who underwent coronary artery bypass grafting, noting that ticagrelor was discontinued 24-72 hours before the surgery, while clopidogrel was omitted 5 days before the procedure. This directly demonstrated the pharmacokinetic advantage of ticagrelor, specifically, its quicker cessation of effect. One of the most important results of the PLATO study was a significant reduction in mortality associated with ticagrelor therapy. It should again be emphasized that ticagrelor's anti-ischemic efficacy vs. clopidogrel was independent of the chosen treatment strategy, whether the treatment was interventional or conservative. Based on this result,

čenja, bilo da se radilo o intervencijskom ili konzervativnom liječenju. Ovakav je rezultat tikagrelor u svim smjernicama pozicionirao kao antiagregacijski lijek prvog izbora u DAPT-u za bolesnike s AKS-om koji su liječeni samo medikamentnom terapijom (**tablica 1**).

Treba istaknuti da je u istraživanju *PLATO* primjena tikagrelora bila povezana s češćim nuspojavama, od kojih je najčešća bila zaduha – pojavljivala se do u oko 15 % bolesnika tijekom prvog tjedna liječenja, ali najčešće blagog stupnja te zbog nje najčešće nije bio potreban prekid terapije. Danas nakon više od deset godina kliničkog iskustva s tikagrelorom možemo reći da se zaduha najčešće pojavljuje tijekom prvih 48 sati nakon primjene lijeka i popušta unutar nekoliko dana. Taj simptom ne smijemo podcijeniti jer može biti riječ i o ekvivalentu angine, odnosno eventualnoj trombozi u stentu pa u takvih bolesnika svakako treba snimiti kontrolni EKG.

all guidelines listed ticagrelor as the antiaggregation agent of choice for DAPT in patients with ACS only receiving medication treatment (**Table 1**).

It is worth noting that ticagrelor was associated with more frequent adverse effects in the PLATO study, the most common of which was dyspnea – occurring in up to 15% of patients during the first week of treatment, in most cases in mild form and not requiring treatment discontinuation. Today, after more than ten years of clinical experience with ticagrelor, we can say that dyspnea most commonly occurs during the first 48 hours post-administration and subsides within a few days. Dyspnea as a symptom must not be underestimated because it could also be equivalent to angina, i.e., a potential in-stent thrombosis, which is why a follow-up ECG should be performed in these patients.

TABLE 1. Indication range of ticagrelor.

Indication	ESC guidelines	Study
Indication range of ticagrelor in DAPT		
NSTE-ACS – PCI	I B	PLATO
NSTE-ACS – conservative	I B	PLATO
STEMI – PCI	I A	PLATO
Long-term DAPT in high risk (>12 months)	IIa A	PEGASUS, THEMIS-PCI
Long-term DAPT in moderate risk (>12 months)	IIb A	
Complex PCI (up to 12 months)	IIb C	
Indication range of ticagrelor as monotherapy		
Instead of DAPT in case of aspirin intolerance	IIb C	
High ischemic risk (>3 months)	IIa B	TWILIGHT

NSTE-ACS = non-ST elevation-acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction; DAPT = dual antiplatelet therapy.

Kronični koronarni sindrom

Kako je navedeno u uvodu, KKS u odnosu prema AKS-u ima mnogo niži ishemijski, odnosno trombotski rizik pa je zato i primjena potentnijih antiagregacijskih lijekova rjeđa. Indikacijski spektar tikagrelora u bolesnika s KKS-om može se podijeliti u tri strategije (**tablica 1**): (1) produljena (>12 mjeseci) primjena DAPT-a koja uključuje tikagrelor kod visokog ishemijskog rizika, (2) primjena tikagrelora u sklopu DAPT-a unutar 12 mjeseci od izvedene PCI i (3) primjena tikagrelora kao monoterapije.

(1) Produljena primjena tikagrelora u sklopu DAPT-a – Objavljeni su rezultati više istraživanja koji su pokazali pozitivan učinak kombinacije tikagrelora i ASK-a u produljenoj terapiji, odnosno nakon 12 mjeseci od AKS-a ili učinjene PCI. Prvo i temeljno takvo istraživanje jest *PEGASUS TIMI 54* koje je bolesnike s anamnezom preboljelog infarkta (većina ih je liječena PCI-jem) randomiziralo na ASK s tikagrelorom 2 x 60 mg ili tikagrelorom 2 x 90 mg u odnosu prema ASK-u i

Chronic coronary syndrome

As mentioned in the introduction, CCS carries a significantly lower ischemic or thrombotic risk compared with ACS, so potent antiplatelet agents are used less frequently. The indication range of ticagrelor in patients with CCS can be divided into three zones (**Table 1**) – (1) long-term (>12 months) use of ticagrelor in DAPT in high ischemic risk, (2) use of ticagrelor as part of DAPT within 12 months of PCI, and (3) ticagrelor monotherapy.

(1) Long-term use of ticagrelor in DAPT – The results of several studies have demonstrated a positive effect of combining ticagrelor and aspirin in long-term therapy, i.e., 12 months after ACS or after PCI. The first and fundamental study was PEGASUS TIMI 54, which randomized patients with a previous infarction (most of them had undergone PCI) to aspirin with either ticagrelor 2x60 or ticagrelor 2x90 vs. aspirin and placebo.[3] After an average follow-up period of 33 months, the ticagrelor group had a significantly lower rate of cardiovascu-

placebu[3]. Nakon prosječnog praćenja od 33 mjeseca skupina liječena tikagrelorom je imala mnogo manje kardiovaskularnih i cerebralnih događaja, ali na račun povećane incidencije krvarenja. Grupa liječena nižom dozom tikagrelora 2 x 60 mg imala je mnogo manje krvarenja u usporedbi s višom dozom lijeka. Treba napomenuti da ni u jednoj od triju grupa nije bilo razlike u učestalosti intrakranijalnih i kritičnih krvarenja. To je istraživanje izuzetno bitno jer je pokazalo učinkovitost produljene DAPT u bolesnika visokog ishemijskog rizika. Slične rezultate dobili smo i iz istraživanja *THEMIS-PCI* koje je pokazalo da dugotrajna terapija tikagrelorom uz ASK može biti učinkovita u redukciji ishemijskih događaja u bolesnika s dijabetesom i stanjem nakon PCI-ja. Smjernice Europskog kardiološkog društva (ESC)[4] na temelju rezultata istraživanja *PEGASUS*[3] i *THEMIS-PCI*[5] donose preporuku da se DAPT s tikagrelorom 2 x 60 mg može produljiti na više od 12 mjeseci u bolesnika nakon preboljelog infarkta miokarda ili u onih s visokim ishemijskim rizikom.

(2) Primjena tikagrelora u sklopu DAPT-a unutar 12 mjeseci od izvedene PCI – Iako nema velikih randomiziranih istraživanja, Smjernice ESC-a jasno navode da se može razmotriti primjena tikagrelora u specifičnim visokorizičnim situacijama kod elektivne PCI kao što je primjerice suboptimalna pozicija stenta ili druga obilježja procedure povezane s visokim rizikom od tromboze u stentu, kompleksni „left main" ili stentiranje višežilne bolesti[4].

(3) Primjena tikagrelora kao monoterapije – U bolesnika s intolerancijom na ASK nakon učinjene PCI, ako se primijeni samo klopidogrel, postoji povećani rizik od tromboze u stentu. Zbog toga nam Smjernice ESC-a daju mogućnost primjene tikagrelora kao monoterapije kako bi se postigao potentniji antiagregacijski učinak.[4] Istraživanje *TWILIGHT* objavljeno 2019. otvara nam mogućnost još jedne antiagregacijske strategije – u bolesnika s izvedenom PCI u kojih postoji visok ishemijski rizik i visok rizika od krvarenja, nakon tri mjeseca DAPT-a s tikagrelorom nastavak monoterapije tikagrelorom do 12 mjeseci pokazao je znatnu redukciju krvarenja za 44 %, a bez povećanja rizika od ishemijskih događaja[6].

Zaključak

U posljednjih deset godina tikagrelor je postao temelj dvojne antiagregacijske terapije u bolesnika s AKS-om s elevacijom ST-segmenta ili bez nje, bez obzira na strategiju liječenja. Može se primijeniti i u bolesnika s kompleksnim PCI-jem tijekom 12 prvih mjeseci, a u bolesnika s visokim ishemijskim rizikom i nakon 12 mjeseci dugoročno u reduciranoj dozi.

lar and cerebral events, but at the expense of increased incidence of bleeding. The group receiving the lower 2x60 mg dosage of ticagrelor had significantly lower rates of bleeding vs. the group receiving the higher dosage. It should be noted that there were no differences among the three groups in the incidence of intracranial and critical bleeding. This study is extremely important as it demonstrated the efficacy of long-term DAPT in patients with high ischemic risk. Similar results were observed in THEMIS-PCI, a study that demonstrated that long-term therapy with ticagrelor and aspirin can effectively reduce ischemic events in patients with diabetes and post-PCI status. Guidelines of the European Society of Cardiology (ESC) recommend that DAPT with ticagrelor 2x60 mg can be prolonged for more than 12 months in post-myocardial infarction patients or those with high ischemic risk[4], based on the results of PEGASUS[3] and THEMIS-PCI[5].

(2) Use of ticagrelor as part of DAPT within 12 months of PCI – Although no large-scale randomized studies have been performed, ESC guidelines clearly state that the use of ticagrelor can be considered in specific high-risk situations involving elective PCI, such as suboptimal stent position or other characteristics of the procedure associated with a high risk of in-stent thrombosis, complex "left main", or stenting in multivessel disease.[4]

(3) Ticagrelor monotherapy – If clopidogrel is administered alone in post-PCI patients with aspirin intolerance, there is an increased risk of in-stent thrombosis. This is why ESC guidelines provide the option of ticagrelor as monotherapy in order to achieve a more potent antiaggregation effect.[4] The TWILIGHT study, published in 2019, provided the option of another antiaggregation therapy – in post-PCI patients with high ischemic risk and high bleeding risk, after three months of DAPT with ticagrelor, continued ticagrelor monotherapy lasting up to 12 months demonstrated a significant reduction in bleeding by 44%, without any increase in the risk of ischemic events.[6]

Conclusion

In the past decade, ticagrelor has become the basis of dual antiaggregation therapy in patients with ST-elevation and non-ST-elevation acute coronary syndrome, regardless of the treatment strategy. It can also be used in patients with complex PCI during the first 12 months, and used in patients with high ischemic risk even longer than 12 months, or used long-term at a reduced dose.

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