Pregledni rad / Review article

Nove perspektive i strategije u liječenju tromboembolijskih bolesti

New perspectives and strategies in the treatment of thromboembolic diseases

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SAŽETAK: U prevenciji tromboembolijskih događaja različite etiologije, a stoga i kod pacijenata s fibrilacijom atrija (FA) te pacijenata s akutnim koronarnim sindromom (AKS) konvencionalno se primjenjuje acetilsalicilatna kiselina, heparini te antagonisti vitamina K. Ovisno o indikaciji različite prednosti i nedostatci svake od ovih kategorija lijekova usmjeravaju ili ograničavaju njihovu uporabu. Njihovom primjenom postignut je znatan napredak u liječenju, međutim kako ipak imaju neke neželjene karakteristike, a prevalencija trombotskih događaja generalno je još uvijek vrlo visoka, javila se potreba za razvojem novih protuzgrušavajućih lijekova. U zadnjih nekoliko godina na tržištu je predstavljena nova generacija protuzgrušavajućih lijekova čije je djelovanje usmjereno na inhibiciju trombina ili aktiviranog faktora X. Rezultati provedenih kliničkih istraživanja istakli su potencijal direktnog inhibitora trombina dabigatrana te anti-Xa lijeka rivaroksabana u liječenju i prevenciji duboke venske tromboze te moždanog udara povezanog s FA. Odnedavna je u mnogim zemljama njihova primjena odobrena za navedene indikacije, a preliminarna istraživanja kod pacijenata s AKS su ukazala na to da bi primjena pojedinih lijekova nove generacije mogla biti dobra alternativa za akutno zbrinjavanje ili blagotvorna u sekundarnoj prevenciji ishemije. Ovdje dan kratak pregled spoznaja o farmakologiji novih lijekova, rezultatima kliničkih ispitivanja kod pacijenata s FA i AKS, kao i mogućnostima njihovog monitoringa.

KLJUČNE RIJEČI: akutni koronarni sindrom, fibrilacija atrija, tromboza, oralni antikoagulansi.

SUMMARY: In the prevention of tromboembolic events of different etiology and therefore in patients with atrial fibrillation (AF) and patients with acute coronary syndrome (ACS) aspirin, heparins and vitamin K antagonists are traditionally applied. Depending on the indication, various advantages and disadvantages of each of these categories of drugs direct or restrict their use. Their application has achieved considerable progress in the treatment, but as some of them show undesired characteristcs and considering that general prevalence of thrombotic events is generally still very high, a development of new antithrombotic drugs has been considered. In the last few years, a new generation of antithrombotic drugs with effects directed on the inhibition of thrombin (FIIa) or activated factor X (FXa) has been developed and introduced in the market. The results of the conducted clinical trials have demonstrated the potential of these drugs in the treatment and prevention of deep venous thrombosis and AF related stroke. In many countries their application for the above mentioned indications has been recently approved, while the preliminary trials in patients with ACS have showed that the use of particular new generation drugs could be a good alternative for the acute management or could be beneficial in the secondary prevention of ischemia. Here, we have presented a short overview of insights about pharmacology, results of clinical trials and possibilities of monitoring of new antithrombotic drugs.

KEYWORDS: acute coronary syndrome, atrial fibrillation, thrombosis, antithrombotic drugs.

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Uvod

Tromboembolijske bolesti su veliki javnozdravstveni problem i jedan od glavnih uzroka pobola i smrtnosti u razvijenim zemljama[1,2]. Procjenjuje se da u svijetu godišnje ima 32 milijuna srčanih i moždanih udara od čega 12,5 milijuna završava smrću. Udio osoba umrlih zbog kardiovaskularnih bolesti (KVB) u Hrvatskoj u ukupnom mortalitetu 2011. godine iznosio je 48,7%, a vodeće dijagnostičke podskupine

Introduction

Thromboembolic diseases are a major public health problem and one of the major causes of morbidity and mortality in developed countries[1,2]. It is estimated that there are 32 millions of myocardial infarction and strokes on an annual basis worldwide, of which 12.5 millions end up in death. The rate of deaths due to cardiovascular diseases (CVD) in Croatia with regard to overall mortality in 2011 was 48.7%;

su i dalje ishemijska bolest srca (IBS) s udjelom od 21,3% te cerebrovaskularne bolesti s udjelom u ukupnom mortalitetu od 14,7%[2]. Pozitivan je pokazatelj to što je ovo treća godina za redom u kojoj je smanjen udio KVB u ukupnom mortalitetu. Prema istraživanjima provedenim u različitim populacijama, čak 44-76% smanjenja smrtnosti od IBS pripisuje se prevenciji i promjeni rizičnog ponašanja, dok se 23-47% smanjenja smrtnosti pripisuje terapijskim intervencijama[2]. U prevenciji trombotskih komplikacija kod visoko rizičnih pacijenata do nedavno su u uporabi bile isključivo dvije kategorije protuzgrušavajućih lijekova: heparini (visoko- i nisko- molekulski) i antagonisti vitamina K (VKA), dok se u smislu antiagregacijske terapije primjenjivala acetilsalicilatna kiselina (ASK)[3,4]. Dakako, ovisno o indikaciji različite prednosti i nedostaci svake od ovih kategorija lijekova usmjeravaju ili ograničavaju njihovu uporabu. Primjenom ovih lijekova postignut je znatan napredak u liječenju, međutim, zbog nekih njihovih ograničenja poput odgođenog djelovanja, interakcije s drugim lijekovima, potrebe za čestim laboratorijskim slijedom i titracijom doze, slabim odgovorom, hiperosjetljivosti ili nuspojavama poput krvarenja te još uvijek visoke prevalencije trombotskih događaja javila se potreba za razvojem novih protuzgrušavajućih lijekova s poboljšanim farmakokinetskim i farmakodinamskim profilom[5,6]. U zadnjih nekoliko godina osim nove generacije antiagregacijskih lijekova, razvijena je i na tržištu predstavljena nova generacija protuzgrušavajućih lijekova čije je djelovanje usmjereno na inhibiciju trombina (FIIa) ili faktora X (FXa). Za razliku od VKA, nova klasa protuzgrušavajućih lijekova selektivna je za jedan specifični faktor zgrušavanja, a središnja karakteristka im je poboljšan farmakokinetski i farmakodinamski profil. Primjena direktnog inhibitora trombina dabigatrana te anti-Xa lijeka rivaroksabana odnedavna je u mnogim zemljama odobrena u svrhu prevencije duboke venske tromboze (DVT) kod odraslih pacijenata koji su podvrgnuti elektivnom kirurškom zahvatu ugradnje kuka ili koljena te moždanog udara (MU) i sistemskog embolizma povezanog s fibrilacijom atrija (FA)[4-6]. Preliminarna istraživanja kod pacijenata s akutnim koronarnim sindromom (AKS) su ukazala na to da bi primjena pojedinih lijekova nove generacije mogla biti alternativa za akutno zbrinjavanje ili blagotvorna u sekundarnoj prevenciji ishemije[6,7],. Ovdje dan kratak pregled spoznaja o farmakologiji novih lijekova, rezultatima kliničkih ispitivanja kod pacijenata s FA i AKS te mogućnostima njihovog monitoringa.

Farmakologija i mehanizam djelovanja novih protuzgrušavajućih lijekova

Nova generacija protuzgrušavajućih lijekova je razvijana u smislu specifične inhibicije određenog dijela ili enzima u koagulacijskoj kaskadi. Djelovanje im je usmjereno na inhibiciju FIIa ili aktiviranog FXa. Trombin predstavlja atraktivan cilj zbog svoje središnje uloge u sustavu zgrušavanja u smislu pretvorbe fibrinogena u fibrin te aktivacije brojnih drugih supstrata poput trombocitnih receptora koji se aktiviraju proteazama te faktora V, VIII, XI i XIII. S druge strane, pozicija na početku tvz."zajedničkog puta" koagulacije čini FXa također vrlo atraktivnim ciljem[4,8]. Osnovne karakteristike pojedinih novih lijekova su prikazane u **Tablici 1**.

the leading diagnostic subgroups were ischemic heart diseases (IHD) and cerebrovascular diseases with mortality rates of 21.3% and 14.7%, respectively[2]. It is a positive indicator that this is the third consecutive year in which the frequency of total CVD mortality has been decreased. According to the trials conducted in different populations, even 44-76% of reduction in mortality from IHD is attributed to the prevention and changes in risk behavior, while 23-47% of reduction in mortality is attributed to therapeutic interventions[2]. In the prevention of thrombotic complications in high-risk patients, until recently, only two categories of antithrombotic drugs were in the use: heparins (high- and low-molecular weight heparins) and vitamin K antagonists (VKA), while regarding the antiplatelet therapy, aspirin was applied[3,4]. So, depending on the indication, various advantages and disadvantages of each of these categories of drugs direct or restrict their use. The administration of these drugs has resulted in a significant progress in the treatment, however, due to some of their limitations such as a delayed effect, interactions with other drugs, the need for frequent laboratory monitoring and titration of dose, low responsiveness, hypersensitivity or adverse events such as bleeding as well as due to still very high prevalence of thrombotic events a need for the development of new antithrombotic drugs with improved pharmacokinetic and pharmacodynamic profile has occurred[5,6]. In the last few years, beside a new generation of antiaggregation drugs, a new generation of antithrombotic drugs with effects directed on the inhibition of thrombin (FIIa) or factor X (FXa) has been developed and introduced in the market. Thus, unlike VKA, a new class of antithrombotic drugs is selective for one specific clotting factor, while the central characteristic is their improved pharmacokinetic and pharmacodynamic profile. Recently, in many countries, the application of the direct thrombin inhibitor dabigatran and anti-Xa drug rivaroxaban has been approved for the prevention of deep venous thrombosis (DVT) in adult patients who undergo elective surgery of the hip or knee replacement as well as for the stroke and systemic embolism related with atrial fibrillation (AF)[4-6]. Preliminary trials in patients with acute coronary syndrome (ACS) have showed that the use of particular new generation drugs could be an alternative solution for the acute management or could be beneficial in the secondary prevention of ischemia[6,7]. Here we have given a short overview of insights about pharmacology of new drugs, the results of clinical trials in patients with AF and ACS, as well as their influence on routine coagulation tests and possibilities of their monitoring.

Pharmacology and mechanism of the action of new antithrombotic drugs

A new generation of antithrombotic drugs has been developed by means of specific inhibition of particular phase or enzyme in the coagulation cascade. Their action is directed on the inhibition of thrombin or activated coagulation FX. Thrombin is an attractive target due to its central role in the coagulation system in terms of conversion of fibrinogen to fibrin and the activation of many other substrates such as platelet receptors that are activated by proteases of factors V, VIII, XI and XIII. On the other hand, the position at the beginning of the so called 'common pathway' of coagulation makes FXa also a very attractive target[4,8]. Some basic features of particular new drugs are shown in **Table 1**.

Table 1. *Main pharmacokinetic and pharmacodynamics properties of new anticoagulant agents.*

Property	*Dabigatran*	*Rivaroxaban*	*Apixaban*	*Edoxaban*	*Otamixaban*
Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa	Factor Xa
Approved indication	Prevention of stroke and embolism in nonvalvular AF; VTE prophylaxis	Prevention of stroke and embolism in nonvalvular AF; VTE prophylaxis	Not yet FDA approved	Under investigation	Under investigation
Route	Oral	Oral	Oral	Oral	Intravenous
Dosing and frequency	150 mg BID	FA: 20 mg/daily VTE prophylaxis: 10 mg/daily	5 mg BID	Once/day	Bolus + infusion
Renal dosage adjustment	75 -110 mg	15 mg/daily	2.5 mg	—	—
Prodrug	Dabigatran is active metabolite of dabigatran etexilate	No	No	No	No
Bioavailability (%)	6-7	80	66	45	NR
Protein binding (%)	35	> 90	87	40-59	NR
Tmax (hrs)	1-2	2-4	3	4	3 min
Half-life (hrs)	9-13h (GFR>80ml/min) Until 18h (GFR30-50ml/min)	Healthy: 5-9 Elderly: 9-13	8-15	9-11	Initial: 30 min Effective: 2-3 hrs
Mode of excretion (%)	~80 renal ~20 fecal	~66 renal ~34 feces	~75 feces ~25 renal	~65 feces ~35 urine	~25 urine ~75 biliary
Substrate of CYP enzymes	No	Yes: CYP3A4, CYP2J2 (major drug interactions)	Yes: CYP3A4 (minor drug interactions)	Yes: CYP3A4	NR
Substrate of P-gp	Yes	Yes	Yes	Yes	NR
Adverse effect other than bleeding	Dyspepsia	Elevated hepatic GGT	Nausea	—	—
Antidote	No known	No known	NR	NR	NR

Dabigatran eteksilat je kompetitivni direktni inhibitor trombina koji se hidrolizira u jetri, a djelovanjem esteraza se brzo i u potpunosti pretvara u svoju aktivnu formu, dabigatran[3,4,9]. Bioraspoloživost dabigatrana je mala, otprilike 6-7% i stoga mu je neophodna kisela sredina za efikasnu resorpciju. Maksimalna koncentracija lijeka u plazmi se postiže ~3 sata nakon primjene, a poluvrijeme izlučivanja je od 9-13 sati, što omogućuje njegovu primjenu jednom ili dva puta dnevno. Oko 80% lijeka izlučuje se nepromijenjeno putem bubrega, a oko 20% putem žuči nakon konjugacije u aktivne metabolite. Dabigatran stupa u relativno mali broj interakcija obzirom da njegov metabolizam nije ovisan o sustavu citokroma P450 (CYP). Dabigatran eteksilat je međutim supstrat za P-glikoprotein (P-gp), membranski transporter koji je prisutan u tankom crijevu i bubrezima. Stoga je potreban oprez pri istovremenoj primjeni dabigatrana s lijekovima koji inhibiraju P-gp transporter, obzirom da mogu uzrokovati povećanje njegove koncentracije u plazmi, a specifičan antidot koji bi neutralizirao njegovo djelovanje ne postoji. Primjena dabigatrana također je kontraindicirana kod pacijenata s teškom insuficijencijom bubrega, kao i kod pacijenata s teškom insuficijencijom jetre unatoč tome što ne posto-

Dabigatran etexilate is a competitive direct thrombin inhibitor that is hydrolyzed in the liver, whereas by means of action of esterases it is rapidly and completely converted to its active form, dabigatran[3,4,9]. The bioavailability of dabigatran is low, approximately 6-7%, and therefore it requires acidic environment for efficient absorption. Maximum drug concentration in plasma is achieved ~3 hours after its administration, and the elimination half-life is between 9-13 hours, which enables its administration once or twice a day. About 80% of the drug is excreted unchanged by the kidneys, whereas about 20% in the bile after conjugation into the active metabolites. Dabigatran comes in a relatively small number of interactions, as its metabolism is independent of the cytochrome P450 (CYP). Dabigatran etexilate is a substrate for P-glycoprotein (P-gp), a membrane transporter that is present in the small intestine and kidneys. Therefore, the caution is required while co-administering dabigatran with drugs that inhibit P-gp transporter, because its concentration in plasma may increase and there is no specific antidote that could neutralize its effect. In patients with severe renal insufficiency and in those with severe hepatic insufficiency, the use of dabigatran is contraindicated, although there is no evidence of its

je dokazi o njegovoj hepatotoksičnosti. U slučaju predoziranja može se provesti dijaliza koja efikasno uklanja oko 60% lijeka iz krvi tijekom 2-3 sata.

Rivaroksaban je specifični, direktni inhibitor FXa. Primjenjuje se oralno, brzo se resorbira, a za njegovu aktivaciju nije potrebno prisutstvo kofaktora[3,4,10]. Maksimalnu koncentracija lijeka u plazmi postiže za 2-4 sata, a poluvrijeme života mu iznosi 7-11 sati. U metabolizam rivaroksabana uključen je CYP3a4, a obzirom da je lijek također i supstrat za P-gp transporter, istovremena primjena snažnih inhibitora CYP3a4 (npr. ketokonazol) ili P-gp je kontraindicirana, obzirom da može uzrokovati povećanje koncentracije lijeka u plazmi. Zahvaljujući svojim farmakokinetskim i farmakodinamskim osobinama, rivaroksaban se može primjeniti u fiksnim dozama kod odraslih osoba bez potrebe za rutinskom kontrolom koagulacije.

Apiksaban je visokoselektivni reverzibilni direktni inhibitor FXa[3,11]. Maksimalna koncentracija lijeka u plazmi postiže se 3-4 sata nakon njegove primjene. Poluvrijeme života mu je 8-15 sati, a za doze više od 10mg bioraspoloživost lijeka je oko 50%. Apiksaban se metabolizira u jetri putem CYP3A4-ovisnih i neovisnih mehanizama, a oko 25% lijeka se izlučuje nepromjenjeno.

Edoksaban je također direktni inhibitor FXa. Primjenjuje se oralno, poluvrijeme života mu je 9-11 sati, a metabolizira se u jetri putem CYP3A4.

Otamiksaban je parenteralni direktni inhibitor FXa kojeg karakterizira brzo djelovanje, predvidljiv antikoagulantni učinak i kratak poluživot u plazmi, što ga čini pogodnim kandidatom za zamjenu heparina kod pacijenata s AKS.

Novi antikoagulansi i fibrilacija atrija

Fibrilacija atrija (FA) predstavlja najučestaliju srčanu aritmiju, koju prema procjenama ima šest milijuna osoba u Europi, a odgovorna je za oko 15-20% svih MU[12-14]. FA se smatra jednom od najvažnijih indikacija za primjenu VKA, međutim odabir vrste antitrombotske terapije će dakako ovisiti o procjeni rizika od tromboembolijskih komplikacija[13-14].

U početnom istraživanju o primjeni direktnog inhibitora trombina dabigatrana, studiji RE-LY (*Randomized Evaluation of Long-Term Anticoagulation Therapy Y*) primjena dabigatrana u dvije različite doze 110 mg i 150 mg dva puta dnevno uspoređena je s primjenom varfarina kod 18.113 ispitanika s FA[11,15,16]. RE-LY je bilo multicentrično randomizirano istraživanja otvorenog tipa. Prosječna dob ispitanika uključenih u istraživanje iznosila je 71 godinu, dok je udio muških ispitanika iznosio 63,6%. Prema bodovnom sustavu CHADS prosječni rizik u istraživanju je iznosio 2,1, a ispitanici su praćeni tijekom dvije godine. Rezultati su pokazali da je u usporedbi s varfarinom primjena 150 mg dabigatrana povezana s nižom incidencijom MU, ali i sličnim rizikom od većih krvarenja, dok je primjena doze od 110 mg povezana sa sličnom incidencijom MU i embolije, ali i manjom incidencijom velikih krvarenja. Na temelju ovog istraživanja dabigatran je odobren kao alternativa za varfarin u prevenciji nevalvularne FA u mnogim zemljama diljem svijeta.

Primjena rivaroksabana je testirana u istraživanju RECORD (*Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation*)[17]. Istraživanje je provedeno na visokorizičnoj populaciji, a primjena rivaroksabana u prevenciji MU se pokazala efikasnom kao i ona varfarinom, ali uz nešto manji rizik krvarenja. U dvostruko

hepatotoxicity. In case of an overdose, the dialysis which effectively removes about 60% of the drug from the blood during 2-3 hours can be performed.

Rivaroxaban is a specific and direct inhibitor of FXa. It is applied orally and is rapidly reabsorbed. Its activation does not require the presence of cofactors[3,4,10]. The maximum plasma concentration is achieved within 2-4 hours, while its half-life is 7-11 hours. The metabolism of rivaroxaban includes CYP3a4, and, since it is also a substrate for P-gp transporter, the co-administration with strong CYP3aA4 (e.g. ketoconazole) or P-gp inhibitors is contraindicated, as it may cause increased drug levels in plasma. Owing to its pharmacokinetic and pharmacodynamic properties, rivaroxaban can be administered in fixed doses in adults without the need for routine coagulation testing.

Apixaban is highly selective reversible direct inhibitor of FXa[3,11]. Maximum plasma concentration is achieved 3-4 hours following the administration. Its half-life ranges from 8 to 15 hours, while the bioavailability of the drug is around 50% for doses exceeding 10mg. Apixaban is metabolized in the liver via CYP3A4-dependent and independent mechanisms, while about 25% is excreted unchanged.

Edoxaban is also the oral direct inhibitor of FXa. Its half-life ranges from 9 to 11 hours, and is metabolized in the liver via CYP3A4.

Otamixaban is a parenteral direct FXa inhibitor, which is characterized by fast action, predictable anticoagulant effect and short plasma half-life, which makes it a suitable replacement for heparin in patients with ACS.

New anticoagulants and atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia, which affects about 6 million people in Europe and it is accountable for about 15-20% of all strokes[12-14]. AF is considered to be one of the most important indications for VKA; however, selection of the antithrombotic therapy type in AF depends on the assessment of the thromboembolic risk[13-14].

In the initial trial on the application of the direct thrombin inhibitor dabigatran, the RE-LY study (Randomized Evaluation of Long-Term Anticoagulation Therapy Y) the administration of dabigatran in two different doses of 110 mg and 150 mg twice a day was compared to the application of warfarin in 18,113 subjects suffering from AF[11,15,16]. RE-LY was a multicentre, randomized, open type study. The mean age of the patients included into the study was 71 years, whereas the frequency of males was 63.6%. According to the CHADS scoring system, the average risk in the trial was 2.1, and the subjects were followed-up for two years. The results showed that in comparision with warfarin, the application of 150 mg dabigatran is associated with a lower incidence of stroke and a similar risk of major bleeding, while the application of 110 mg was associated with a similar incidence of stroke and embolism, but with lower bleeding incidence. Based on this study, dabigatran has been approved as an alternative to warfarin in the prevention of non-valvular AF in many countries around the world.

The application of rivaroxaban was tested in the RECORD study (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)[17]. The study was conducted in high-risk population and the application of rivaroxaban in prevention of stroke proved to be as effective as the application of warfarin, but with lower risk of

slijepom multicentričnom randomiziranom istraživanju ROCKET AF, (*Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation*) sudjelovalo je 14.264 ispitanika s umjerenim do visokim rizikom MU, a rivaroksaban je primjenjen u dvije doze: 20mg dnevno ili 15 mg za pacijente s klirensom kreatinina 30-49 mL/min[18-19]. Udio muških ispitanika u istraživanju je iznosio 60,3%, a prosječna dob svih ispitanika 73 godine. Ispitanici su praćeni u prosjeku 1,9 godine, a prema bodovnom sustavu CHADS oko 87% pacijenata je pokazalo rizik najmanje 3 (u prosjeku 3,5). Razlika u primjeni rivaroksabana i varfarina u smislu redukcije MU i/ili tromboembolizma kod ispitanika nije se pokazala statistički značajnom.

Prvi objavljeni rezultati o efikasnosti apiksabana, inhibitora FXa, u prevenciji MU kod pacijenata s FA došli su iz istraživanja AVERROES (*Apixaban VERsus acetylsalycilic acid to pRevent strOkE in atrial fibrillation patientS who have failed or are unsuitable for vitaminK antagonist treatment*). U istraživanje su bili uključeni pacijenti s nevalvularnom FA i bar još jednim čimbenikom rizika, ali koji nisu bili kandidati za primjenu varfarina ili ga nisu htjeli uzimati. Istraživanje je pokazalo da u usporedbi s ASK primjena apiksabana značajno smanjuje rizik MU ili sistemskog embolizma bez značajnog porasta rizika većeg i/ili intrakranijalnog krvarenja. Drugo veliko provedeno istraživanje o primjeni apiksabana je istraživanje ARISTOTLE (*Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation*)[20]. ARISTOTLE je bilo multicentrično randomizirano, dvostruko slijepo istraživanje provedeno na 18.201 ispitanika s prosječnim rizikom od 2,1 prema bodovnom sustavu CHADS. Prosječna dob uključenih ispitanika iznosila je 70 godina, a udio muškaraca među ispitanicima je iznosio 64,7%. Apiksaban je primjenjen u dozi 5 mg 2 x dnevno te u dozi od 2,5 mg kod starijih ispitanika ili ispitanika s renalnom insuficijencijom. Ispitanici su praćeni prosječno oko 1.8 godinu, a prema rezultatima primjena apiksabana se pokazala superiornom nad varfarinom u smislu smanjenja incidencije MU, smrtnosti te rizika krvarenja.

Prema rezultatima provedenih istraživanja sva tri oralna antikoagulansa novije generacije pokazala su u najmanju ruku jednaku efikasnost kao i VKA, sa sličnim profilom neželjenih nuspojava. Unatoč tome što se ovi lijekovi kod pacijenata s ne-valvularnom FA smatraju atraktivnom alternativom VKA ili ASK treba imati na umu da se radi o rezultatima treće faze ispitivanja ovih lijekova te da rezultati dugotrajnog slijeda još nisu objavljeni. Vrlo je teško odgovoriti na pitanje koji od ovih lijekova je bolji obzirom da do danas nije provedeno istraživanje u kojem se direktno uspoređuje njihovo djelovanje. Pretpostavlja se da bi direktna usporedba u smislu procjene efikasnosti ovih lijekova trebala uključiti oko 50.000 pacijenata. Na temelju provedenih istraživanja usporedbu nije jednostavno napraviti prvenstveno zbog razlike u njihovom dizajnu[21]. Istraživanja RE-LY i ARISTOTLE su izvršena na umjereno rizičnoj populaciji za razliku od ROCKET AF gdje je uz to bila prisutna i nešto starija populacija, a vrijeme optimalnog terapijskog raspona u smislu primjene varfarina je bilo nešto manje. U istraživanjima su sudjelovali ispitanici različite etničke pripadnosti, a razlike postoje i u vremenskom slijedu te definiciji krajnje točke ovih istraživanja. Indirektna usporedba efikasnosti ovih lijekova provedena je od strane dvije skupine istraživača, *Mantha i sur.*[22] te *Lip i sur.*[23]. Oba istraživanja se slažu u tome da je malo argumenata koji bi istakli primjenu jednog lijeka nad drugim u smislu efikasnosti, međutim zbog nešto manjeg broja zabilježenih nuspojava favorizirana je uporaba apiksabana i dabigatrana u dozi

bleeding. In a double-blind randomized multicentre ROCKET AF (*Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation*) study, rivaroxaban was administered in 14,264 patients with moderate to high risk of stroke in two doses of 20mg or 15mg a day for patients with creatinine clearance 30-49mL/min[18-19]. The frequency of male patients included in the study was 60.3%, and the mean age of all patients was 73 years. The median follow-up of patients was 1.9 years and according to the CHADS scoring system approximately 87% of patients showed a risk of minimum 3 (on average 3.5). Difference in the application of rivaroxaban and warfarin did not reach a statistically significance in terms of reduction of stroke and/or thromboembolism in subjects.

The first published results of the efficacy of apixaban as the FXa inhibitor for the prevention of stroke in patients with AF derived from the AVERROES study (*Apixaban VERsus acetylsalycilic acid to pRevent strOkE in atrial fibrillation patientS who have failed or are unsuitable for vitaminK antagonist treatment*). The study included patients with non-valvular AF and at least one additional risk factor, but who were not candidates for VKA application or did not want to take it. The trial has shown that apixaban significantly reduces the risk of stroke or systemic embolism compared with aspirin, with no significant increase in risk of major or intracranial hemorrhage. Another large trial conducted on apixaban administration was the ARISTOTLE study (*Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation*)[20]. ARISTOTLE was a multicenter, randomized, double-blind trial in 18,201 patients with an average risk of 2.1 according to the CHADS scoring system. The mean age of included patients was 70 years with 64.7% of male patients. Apixaban was administered at a dose of 5 mg b.i.d. and 2.5 mg in elderly patients or those with renal insufficiency. Median follow-up of patients was 1.8 years and according to the findings, the application of apixaban seems to be superior to warfarin regarding lower incidence of stroke, mortality and the bleeding risk.

According to the results of the conducted trials, all three oral anticoagulants of a new generation showed at least equal efficacy as VKA with a similar profile of side effects. Although considered to be attractive alternatives to VKA or aspirin in patients with non-valvular AF, one should keep in mind that these are the results of Phase III trials of these drugs and that long-term results have not yet been published. It is difficult to answer the question as to which of these drugs is better since to date no trial on direct comparison of efficacy of these drugs has been conducted. It is assumed that the direct comparison of these drugs should include about 50,000 patients. According to existing trials, it is not easy to make a comparison mainly due to their different design[21]. The RE-LY and ARISTOTLE studies were conducted on moderate risk population unlike the ROCKET AF study which included some older population, with less time within optimal therapeutic range in terms of application of warfarin. The trials also included subjects from different ethnic groups, and were different in the time line as well as in definition of the trial end point. Indirect comparison of efficacy of these drugs was conducted by two groups of researchers, *Mantha et al*[22] and *Lip et al*[23]. The both trials agree that there are few arguments that emphasize the superiority of application of one drug over another in terms of efficacy, but due to a smaller number of side effects the application of apixaban and dabigatran at a dose of 110 mg is preferred, which

od 110 mg, a što se mora naravno promatrati i u kontekstu tolerancije, cijene lijeka i slično.

Novi antikoagulansi i akutni koronarni sindrom

Akutni koronarni sindrom definira raspon ishemijskih stanja miokarda koja uključuju nestabilnu anginu i infarkt miokarda (IM) s elevacijom ST-segmenta (STEMI) ili bez elevacije ST-segmenta (NSTEMI), a najčešće su posljedica akutne koronarne tromboze. Pacijenti s AKS visoko su rizični, a brza dijagnoza i primjena adekvatne terapije može znatno poboljšati ishod gledajući kratkoročno i dugoročno. Zbrinjavanje AKS znatno je poboljšano zadnjih godina s predstavljanjem intervencijskih terapijskih strategija, potentnih lijekova inhibitora trombocita i režimom liječenja u smislu sekundarne prevencije[7,24]. Unatoč znatnom smanjenju mortaliteta i morbiditeta, rizik opetovanih ishemijskih događaja i dalje je visok.

Antiagregacijska terapija važna je sastavnica prevencije AKS[6,24-27]. Unatoč dokazanom učinku ASK i klopidogrela u liječenju AKS, jedan dio liječenih ne odgovara na primjenjenu terapiju i razvija trombotske komplikacije. Učestalost neadekvatnog odgovora za ova dva lijeka kreće se u rasponu od 1-45%, a razlog je nedostatak definicije kojom se procjenjuje odgovor na terapiju i razlike u laboratorijskim testovima (koncentracije agonista te (ne)definiranih "cut off" vrijednosti). Dosadašnja istraživanja su pokazala da su promjene vezane za COX-1, nedostatna količina lijeka na potrebnom mjestu djelovanja npr. zbog slabije apsorpcije lijeka ili velikog obrtaja trombocita u određenim bolestima značajke rezistencije ASK[28]. U odnosu na ASK, mehanizam djelovanja klopidogrela je različit. Njegov aktivni metabolit, ireverzibilni inhibitor trombocitnog P2Y12 ADP receptora nastaje u dvostupanjskom procesu koji uključuje sustav enzima citokroma P450. Sve je više podataka o tome da je uzrok varijabilnosti odgovora na terapiju mehanizam pretvorbe klopidogrela u aktivni metabolit. Prema tome, odluka o njegovoj primjeni u liječenju bi se trebala donijeti nakon što se ispita trombocitna funkcija, a dodatne informacije u smislu rezistencije bi se mogle dobiti genotipizacijom pojedinih izoenzima CYP sustava koji su odgovorni za pretvorbu klopidogrela u aktivni metabolit. Za sada nema preporuke za svakodnevnu praksu jer tek treba pronaći idealni laboratorijski test koji bi dao odgovor na osnovno pitanje o kliničkoj koristi primjene klopidogrela.

Novija klinička istraživanja su pokazala superiornu efikasnost primjene CYP12 antagonista prasugrela i tikagrelora uz ASK kod pacijenata koji prolaze koronarnu revaskularizaciju te poboljšanu inhibiciju trombocita ex-vivo kod pacijenata koji ne odgovaraju na primjenu klopidogrela. Međutim, kako su tijekom liječenja pojedine podgrupe pacijenata pokazale razliku u smislu efikasnosti terapije, željenog ishoda i nuspojava poput krvarenja, kod odluke o njihovoj primjeni u suspektnom AKS u obzir bi trebalo uzeti pacijentov rizik za trombozu (STEMI, prethodna stent tromboza), potrebni zahvat (npr. kompleksna PCI, ugrušak in-situ) i čimbenike koji mogu utjecati na sigurnost (dob, težina, prethodni MU, vjerojatnost kirurške revaskularizacije). Stavljajući u fokus individualni omjer rizika i koristi za pacijenta uz odgovarajuću procjenu funkcije trombocita kada je to indicirano te nastavak istraživanja učinka prasuagrela i tikagrelora trebale bi biti ključne strategije u smislu primjene dvojne antitrombocitne terapije. Lijekovi iz skupine VKA se rjeđe primjenjuju kod pacijenata s AKS jer je slijed terapije vrlo opsežan. U

of course must be observed in the context of the patient's tolerance, price etc.

New anticoagulants and acute coronary syndrome

Acute coronary syndrome defines the range of myocardial ischemic conditions that include unstable angina and myocardial infarction (MI) with ST-segment elevation (STEMI) or non ST-segment elevation (NSTEMI), and are commonly a result of acute coronary thrombosis. Patients with ACS are high risk patients, and a rapid diagnosis and application of appropriate therapy can improve the short and long term outcome[7,24]. The management of ACS has been significantly improved in recent years with the introduction of therapeutic intervention strategies, potent platelet inhibitors and the treatment regime in terms of secondary prevention[7,24]. Despite a significant reduction in mortality and morbidity, the risk of recurrent ischemic events still remains high.

Antiaggregation therapy is an important component of prevention of ACS[6,24-27]. Despite the proven effect of aspirin and clopidogrel in the treatment of ACS, one part of the treated patients does not respond to the therapy and develop thrombotic complications. The frequency of inadequate response to these two drugs ranges from 1 to 45%, and the reason is the lack of definition used to assess the response to the therapy and differences in the laboratory tests (concentration of agonist and (non)defined "cut off" value). Previous trials have shown that the changes are attributable to COX-1, insufficient amount of the drug at the required point of action, for instance as a result of poor absorption of the drug or a high platelet turnover in certain diseases, ASC resistance features[28]. Compared to aspirin the mechanism of clopidogrel action is different. Its active metabolite, irreversible inhibitor of the platelet P2Y12 ADP receptor occurs in a two-step process involving the cytochrome P450 enzyme system. There is an increasing number of information claiming that the cause of the variability of response to the therapy is the mechanism of conversion of clopidogrel into its active metabolite. Accordingly, the decision on its application in the treatment should be made after the platelet function has been tested, while some additional information regarding the resistance could be obtained by genotypization of specific CYP isoenzymes that are responsible for the conversion of clopidogrel into its active metabolite. Certainly for the time being, there is no recommendation for the daily practice, because we should find an ideal laboratory test that would give an answer to the basic question about the clinical benefit of application of clopidogrel.

Recent clinical trials have demonstrated the superior efficacy of CYP12 administration and antagonists such as prasugrel and ticagrelor with aspirin in patients undergoing the coronary revascularization and improved platelet inhibition *ex-vivo* in patients who do not respond to clopidogrel administration. However, during the time of treatment, specific subgroups of patients showed a difference in the treatment efficacy, the desired outcome and side effects such as bleeding, the patient's risk for thrombosis (STEMI, previous stent thrombosis), required surgery (e.g. complex PCI, clot in-situ) and factors that may affect the safety (age, weight, previous stroke, the likelihood of surgical revascularization) should consider when making a decision on their administration in suspected ACS. Focusing on the individual risk-benefit ratio for the patient with an appropriate assessment of the platelet function when indicated and continuation of the investigation of the effects of prasuagrel and tickagrelor should be the crucial strategies for the application of dual antiplatelet therapy.

tom smislu novi antikoagulansi možda mogli pružiti unaprijeđenje u liječenju AKS[25,26].

Novi antikoagulansi u sekundarnoj prevenciji akutnog koronarnog sindroma

Kako bi se utvrdilo je li primjena dabigatrana, rivaroksabana, apiksabana te dareksabana kod ispitanika s NSTEMI i STEMI učinkovita u smislu smanjenja ponovnih ishemijskih događaja provedena je faza II kliničkih istraživanja[6,7,25].

U istraživanju RE-DEEM (*Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome*) kod pacijenata s AKS su primjenjene iste doze dabigatrana kao i u istraživanjima s FA (110 i 150 mg) pri čemu je, ovisno o dozi, zabilježena veća učestalost krvarenja iz gastrointestinalnog trakta, ali ne i značajan rezultat u smislu ishoda[29].

U studiji ATLAS ACS-TIMI 46 (*Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With Acute Coronary Syndromes-Thrombolysis In Myocardial Infarction*) kod ispitanika s AKS primjenom rivaroksabana su zabilježene klinički značajne komplikacije krvarenja kod pacijenata koji su istovremeno primali ASK ili dvojnu antiagregacijsku terapiju[30]. U usporedbi s primjenom placeba nešto manji omjer rizika zabilježen je primjenom rivaroksabana u kontekstu ishoda, MU ili ponovne ishemije koja zahtjeva revaskularizaciju. U trećoj fazi istraživanja (ATLAS ACS-TIMI 51) sa srednjim vremenom primjene rivaroksabana od 13,1 mjeseci, u dozi od 2,5 i 5 mg u usporedbi s placebom zabilježena je značajno manja incidencija kardiovaskularne smrti, IM i MU[31].

Primjena apiksabana u istraživanju APPRAISE (*Apixaban for Prevention of Acute Ischemic and Safety Events*) također je pokazala o dozi ovisan povećan rizik krvarenja kada se govori o dozama od 2,5 i 10 mg, a istraživanja s dozama većim od 10mg nisu nastavljena. Incidencija u smislu kardiovaskularne smrti, IM, ponovne ishemije koja zahtjeva revaskularizaciju ili ishemijskog MU nije bila značajno manja pri primjeni 2,5 ili 10 mg apiksabana u odnosu na placebo. Međutim faza tri istraživanja, tj. APPRISE-2 je brzo prekinuta zbog nuspojava poput klinički značajnog subkutanog krvarenja, a bez dokazane koristi primjene lijeka.

Istraživanje RUBY-1 (*Study Evaluating Safety, Tolerability and Efficacy of YM150 in Subjects With Acute Coronary Syndromes*) dalo je obećavajuće rezultate u smislu primjene dareksabana u prevenciji ishemijskih događaja u AKS, međutim njegova primjena zajedno s dvojnom antiagregacijskom terapijom u odnosu na placebo pokazala je o dozi ovisno krvarenje, bez dodatnih izmjena u smislu sigurnost njegove primjene, ali ni koristi[32].

Djelovanje jedinog novog parenteralnog antikoagulansa ispitano je u istraživanju SEPIA-ACS1 TIMI 42 (*Otamixaban for the treatment of patients with non-ST-elevation acute coronary syndromes*). Uspoređeno je djelovanje 5 različitih doza otamiksabana primjenom bolusa 0,08 mg/kg, a nakon toga infuzije od 0,035, 0,070, 0,105, 0,140 ili 0,175 mg/kg/h) kod 3.241 visokorizičnog pacijenta s AKS bez ST-elevacije[33]. Za procjenu efikasnosti tijekom sedam dana praćena je pojava ukupnog mortaliteta, ponovnog IM, ishemije koja je zahtijevala hitnu revaskularizaciju ili tromboembolijske komplikacije kod PCI. Ispitivanje s najmanjom dozom otamiksabana je prekinuto zbog neadekvatnog protuzgrušavajućeg djelovanja, a primjena bolusa otamiksabana u dozi 0,08 mg/kg, uz nastavak infuzija od 0,105 ili 0,140 mg/kg/h je

Drugs from the VKA group are administered more rarely in patients with ACS, because the therapy monitoring is very comprehensive. It is believed that in this sense the new anticoagulants may provide improvement in the treatment of ACS[25,26].

New anticoagulants in secondary prevention of ACS

Phase II of clinical trail was conducted as to determine whether the application of dabigatran, rivaroxaban, and apixaban and darexaban in patients with NSTEMI and STEMI is effective in reducing recurrent ischemic events[6,7,25].

In the RE-Deem study (*Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome*) the same doses of dabigatran were applied as in AF trials (110 and 150 mg) which resulted in a higher frequency of dose-dependent gastrointestinal bleeding, but not in a significant result in terms of the outcome[29].

In the ATLAS ACS-TIMI 46 study (*Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With Acute Coronary Syndromes-Thrombolysis In Myocardial Infarction*) the dose-dependent bleeding was also recorded in ACS patients receiving Rivaroxaban who simultaneously received aspirin or dual therapy for platelet inhibition[30]. Compared with placebo, a slightly lower risk ratio has been recorded by rivaroxaban administration regarding the outcome, stroke or recurrent ischemia that requires revascularization. In the third phase of the study (ATLAS ACS-TIMI 51) mean time of applying rivaroxaban was 13.1 months, and in comparisons of administration of drug dose of 2.5 and 5 mg with placebo, a significantly lower incidence of cardiovascular death, MI and stroke was recorded[31].

The application of apixaban in the APPRAISE study (*Apixaban for Prevention of Acute Ischemic and Safety Events*) also showed a dose-dependant increased risk of bleeding when talking about the 2.5 and 10 mg doses, while the trials with doses greater than 10 mg were discontinued. The incidence regarding the cardiovascular death, MI, recurrent ischemia requiring revascularization, or ischemic stroke was not significantly lower while administering 2.5 or 10 mg apixaban compared to placebo. However, phase three study, i.e. APPRISE-2 was prematurely discontinued as a consequence of side effects such as extensive subcutaneous bleeding, without any proven benefit.

The RUBY-1 study (*Study Evaluating Safety, Tolerability and Efficacy of YM150 in Subjects With Acute Coronary Syndromes*) has shown promising results in respect of the darexaban application in the prevention of ischemic events in ACS, but its application with dual antiplatelet therapy has shown a dose-dependant bleeding compared to placebo, without additional changes related to safety of its application and no benefits as well[32].

The efficacy of the only new parenteral anticoagulant was tested in SEPIA-ACS1 TIMI 42 study (*Otamixaban for the treatment of patients with non-ST-elevation acute coronary syndromes*). The study compared the efficacy of 5 different doses of otamixaban by using bolus of 0.08 mg/kg, followed by infusion of 0.035, 0.070, 0.105, 0.140, or 0.175 mg/kg/h) in 3,241 high-risk patients with non ST-segment elevation ACS[33]. The combined end-point of total mortality, recurrent MI, ischemia requiring urgent revascularization, or thromboembolic complications in PCI were followed up to estimate the efficacy during the seven days' period. The investigation with the lowest dose of otamixaban was early terminated because of its inadequate antithrombotic efficacy, while the application of the otamixaban bolus in a dose of 0.08mg/kg,

pokazala najbolji omjer efikasnosti i sigurnosti, te smanjenje mortaliteta i ishemijskih komplikacija za 40% u usporedbi s heparinom. Istraživanje navedenih doza ušlo je u treću fazu ispitivanja.

Sva navedena istraživanja o djelovanju novih antikoagulanasa u AKS dizajnirana su tako da se procjeni sigurnost primjene jedne do dvije doze dnevno ovih lijekova u razdoblju od šest mjeseci. U većini slučajeva, pacijenti su primali i dvojnu antiagregacijsku terapiju (ASK i klopidogrel), što je rezultiralo trendom porasta krvarenja kod ovih pacijenata. Prema važećim smjernicama Europskog kardiološkog društva u liječenju AKS bez elevacije ST-segmenta u kombinaciji s ASK preferira se primjena P2Y12 inhibitora prasugrela i tikagrelora[7,26]. Dugotrajno liječenje prasugrelom ili tikagrelorom je povezano s smanjenjem neželjenih događaja u usporedbi s primjenom klopidogrela (tikagrelor i s nižim mortalitetom) te relativno malim porastom rizika (30%) velikog krvarenja u usporedbi s rizikom objavljenim za inhibitore FXa. Stoga, uporaba bilo kojeg od ovih antotrombocitnih lijeka uz inhibitore FXa čini se bolja od primjene klopidogrela. Dakako, kod pacijenata s AKS pri dodavanju inhibitora FXa trenutnoj antitrombocitnoj terapiji treba razmišljati i o mogućem neželjenom krvarenju. Nije dokazano mogu li niže doze bilo kojeg od novih oralnih antikoagulansa biti korisne u prisutnosti bilo kojeg od navedenih antitrombocitnih lijekova. Trenutne spoznaje o djelovanju inhibitora FXa u AKS za sada neće rezultirati promjenama u kliničkoj praksi. One ipak, otvaraju novi put za istraživanje zbog dokaza da mogu reducirati ishemijske događaje kod pacijenata s koronarnom bolesti srca. U budućnosti, izazov će biti identificirati kombinaciju antitrombotika čija će primjena uz manju incidenciju krvarenja smanjiti broj trombotskih događaja.

Laboratorijski slijed novih antikoagulanasa

Neovisno o tome primjenjuje li se kod pacijenta terapija varfarinom ili heparinom, zbog prilagodbe doze lijeka i činjenice da prekomjerna koagulacija može povećati rizik tromboze, a preslaba rizik krvarenja ona se mora redovno pratiti. Danas je njihov monitoring rutinski u smislu uporabe jednostavnih laboratorijskih testova poput protrombinskog vremena/internacionalnog normalizirajućeg omjera (PV/INR) ili aktiviranog parcijalnog tromboplastinskog vremena (APTV).

Novi protuzgrušavajući lijekovi smatraju se lijekovima koji ne zahtjevaju monitoring zbog svoje stabilne i reproducibilne kinetike[34]. Stoga su i klinička ispitivanja s novim lijekovima uglavnom dizajnirana tako da su lijekovi primjenjivani u fiksnoj dozi bez laboratorijskog monitoringa. Međutim, kako će brojni pacijenti koji prolaze koagulacijski probir koristiti ove lijekove, neophodno je znati kako i do kojeg je stupnja koagulacija odgođena u smislu korištenja rutinskih koagulacijskih testova. Nadalje, brojni su slučajevi u kojima treba znati je li i u kojoj mjeri aktivni agens prisutan npr. kod hospitalizacije pacijenta bez svijesti radi krvarenja ili zbog hitne operacije gdje prisutnost aktivnih antikoagulanasa može utjecati na rizik kirurškog krvarenja, u slučaju tromboze ili hemoragije dok je pacijent na antikoagulantnoj terapiji kako bi se procijenila pogreška terapije te kod prelaska s jednog na drugi antikoagulans ili identifikacije interakcija lijekova[35,36]. Sve ovo ipak sugerira moguću korisnost slijeda terapije u specifičnim kliničkim situacijama[37,38]. Spoznaje o monitoringu za sada nisu velike, a najbolja strategija kontrole terapije tek treba biti utvrđena. Kako bi se izbjegla pogrešna interpretacija rezultata rutinskih koagulacijskih testova (PV, APTV,

followed by an infusion of 0.105 or 0.140mg/kg/h showed the best efficacy and safety ratio, as well as reduction of mortality and ischemic complications by 40% in comparison with heparin. The investigation of the above doses was included in the third phase of the investigation.

All of the investigations conducted in patients with ACS were designed in the manner to assess the safety of receiving one to two doses of a drug daily throughout a period of 6 months. Most of the patients received dual anti-aggregation therapy (aspirin and clopidogrel) that consequently has resulted an upward trend in bleeding. According to the guidelines of the European Society of Cardiology in the management of non ST-segment elevation ACS, more effective P2Y12 inhibitors prasugrel and ticagrelor are preferred antiplatelet drugs in combination with aspirin[7,26]. Prolonged treatment with prasugrel or ticagrelor is associated with a reduction of undesired events compared with clopidogrel (ticagrelor also with decreased mortality) and a relatively small increase (30%) in the risk of major bleeding compared with that published for FXa inhibitors. Therefore, the administration of any of these new antiplatelet agents instead of clopidogrel seems to be better if we add them to FXa inhibitors. Certainly, when FXa inhibitors are added to the current antiplatelet therapy in patients with ACS, the possibility of undesirable bleeding should be kept in mind. It has not been proven whether lower doses of any of the new anticoagulants may be useful in concomitant presence of any of the new, more effective anti-platelet drugs. The current results on the effect of FXa inhibitors in ACS will not result in a change of the clinical practice for the time being. They however, open a new path for the investigation due to the evidence that they can reduce ischemic events in patients with coronary heart disease. The challenge for the future investigation will be to identify the combination of antithrombotic drugs that are aimed at reduction of thrombotic events with a low risk of bleeding.

Laboratory monitoring of new anticoagulants

Irrespective of whether a therapy with heparin or warfarin is applied in a patient, it must be regularly monitored due to dose adjustment and the fact that excessive coagulation increases the risk of thrombosis, while the low level of coagulation increases the risk of bleeding. Today their monitoring is a routine procedure owing to the use of simple laboratory tests such as prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (APTT).

Due to stable and reproducible kinetics, the new anticoagulant drugs are considered to be the drugs that do not require monitoring[34]. Therefore, clinical trials of new drugs were designed in a manner that drugs were applied in a fixed dose without a laboratory monitoring. However, given that many patients who undergo coagulation screening will take these drugs, it has to be known to what extent the coagulation is delayed by means of the use of routine coagulation tests. Furthermore, there are numerous cases when we have to know whether the active agent is present e.g. in case of hospitalization of a fainted patient with bleeding symptoms or urgent surgery where the presence of active anticoagulants may affect the risk of surgical bleeding, in case of thrombosis or hemorrhage while taking anticoagulation therapy in order to estimate the error of the therapy, when switching from one anticoagulant to another or identifying drug interactions[35,36]. All of this suggests a potential benefit of the therapy monitoring in some specific clinical situations[37,38]. Current insights regarding monitoring are scarce, and the best strategy to control new drugs is to be revealed. In order to

TV i fibrinogen), potrebno je znati i na koji način novi antikoagulansi djeluju na navedene testove.

Utjecaj novih antikoagulanasa na rutinske koagulacijske testove

Utjecaj dabigatrana i rivaroksabana na rezultate rutinskih koagulacijskih testova je otkriven pomoću in vitro istraživanja dodajući u plazmu normalnih uzoraka određenu koncentraciju aktivne komponente lijeka ili prikupljanjem plazme ispitanika (volontera/pacijenata) kod kojih je primjenjen lijek. Ex vivo je istražen i utjecaj novih lijekova na globalne testove zgrušavanja, a iako spoznaje nisu velike, izgleda da se neki globalni i specifični testovi mogu upotrijebiti za procjenu njihovog učinka[37,38,39].

Inhibitori trombina i FXa utječu na test PV i to na način da produžuju vrijeme u sekundama te povećavaju INR ovisno o primjenjenoj dozi lijeka. Istraživanja s rivaroksabanom i dabigatranom su pokazala da je test PV osjetljiviji na primjenu rivaroksabana nego dabigatrana, ali u oba slučaja produženje PV ovisi o upotrebljenom reagensu/tromboplastinu. Za razliku od primjene VKA gdje se osjetljivost različitih tromboplastina rješava primjenom INR, ovdje to nije moguće. Iako se vrijednost PV može koristiti kao relativno dostupan test za procjenu relativnog stupnja antikoagulacije kod pacijenata koji primaju rivaroksaban, on nije dovoljno osjetljiv u smislu detekcije klinički relevantnih promjena u koncentraciji lijeka. In vitro studije su pokazale da i apiksaban produžuje PV, međutim mjerenje inhibicije aktivnosti FXa dalo je bolji uvid u koncentracije apibaxana u plazmi od PV testa[5,36,37].

Primjena direktnih inhibitora faktora Xa ili inhibitora trombina također dovodi do produženja vrijednosti APTV. Rezultati istraživanja su pokazali da je kod pacijenata koji dobivaju 110-150 mg dabigatrana dva puta dnevno u piku koncentracije omjer APTV otprilike 1,4-1,8x veći od kontrole. Rezultati dakako ovise primjenjenom reagensu te pripadajućem aktivatoru tj. sadržaju fosfolipida. Potrebne su daljne studije kako bi se ustanovila relativna osjetljivost APTV na dabigatran i razvile preporuke o tome koji bi reagens bilo bolje primjeniti. Rivaroksaban također pokazuje o dozi ovisan odgovor na APTV. Njegova primjena u dozi od 20 mg kod zdravih muškaraca uzrok je porasta APTV za otprilike 1,5-1,8x u odnosu na kontrolnu vrijednost. Izgleda da je pri primjeni niskih koncentracija rivaroksabana i dabigatrana test osjetljiviji na dabigatran. U zdravih volontera, primjena apixabana u dozi od 50 mg uzrokovala je produženje APTV od oko 1,2x u odnosu na kontrolu, a produženo APTV je pokazalo korelaciju s koncentracijama apixabana određenim u plazmi.

Inhibitori FXa nemaju utjecaja na test trombinskog vremena (TV), međutim inhibitori trombina, direktni i indirektni, mogu uzrokovati njegovo produženje. TV se može koristiti za slijed terapije dabigatranom. Dakako, rezultat ovisi o primjenjenom reagensu, a većina testova je preosjetljiva. Stoga se TV može koristiti kao osjetljiva metoda za određivanje prisutnosti minimalnih koncentracija lijeka, a prisutnost lijeka se može sa sigurnošću isključiti ako je TV normalno. Kako je TV vrlo osjetljivo na ove inhibitore za slijed terapije argatrobana te dabigatrana razvijena je i modifikacija testa nazvana HemoClot[5,36,37].

Inhibitori FXa ne utječu na određivanje fibrinogena metodom po Claussu koja se bazira na dodatku suviška trombina plazmi. Međutim, inhibitori trombina mogu uzrokovati

prevent misinterpretation of the results of routine coagulation tests (PT, APTT, TT, and fibrinogen) it is important to know influence of the new anticoagulants to these tests.

The impact of new anticoagulants on routine coagulation tests

The impact of dabigatran and rivaroxaban on the results of routine coagulation tests is discovered by in vitro studies by adding a certain concentration of the drug active component to plasma of normal samples or by collecting the plasma from subjects (volunteers or patients) who take these drugs. Influence of the new oral anticoagulants on the global coagulation tests has been also investigated ex vivo after the administration of these drugs and although the insights are not extensive, it seems that some global and specific tests can be used to assess their effect[37,38,39].

Inhibitors of thrombin and FXa affect PT, by means of the prolongation of time in seconds and increase in the INR value, dependently on the applied dose. Investigations with rivaroxaban and dabigatran has shown that PT is more sensitive to the rivaroxaban than on to dabigatran administration, but in both cases prolongation of PT depends on used reagents/thromboplastin. Unlike the application of VKA where the sensitivity of various thromboplastins is solved by applying INR, here it is not possible. Although the PT can be used as a relatively available test for the determination of relative intensity of anticoagulation due to rivaroxaban, it is not a sufficiently sensitive test that could detect clinically relevant changes in the drug concentration. In vitro studies have shown that apixaban also prolongs PT, however, measuring of the inhibition of the FXa activity provides a better insight into the concentrations of apibaxan in plasma than the PT test[5 36,37].

With the use of the direct factor Xa inhibitors and thrombin inhibitors prolongation of APTT has also occurred. Some studies have shown that administration of 110 or 150 mg of dabigatran b.i.d. at maximum of plasma concentration prolongs APTV ratio approximately 1.4-1.8x. Certainly, the result depends on used reagents, with corresponding activator and certain content of phospholipids. However, further studies are warranted in order to reveal relative sensitivity of APTT due to dabigatran and to develop recommendations by means of the use of appropriate reagent. Rivaroxaban has also influence on APTT prolongation in a dose dependent manner. The administration of 20mg of rivaroxaban in healthy men has resulted in approximately 1.5-1.8x increase of APTT ratio. It seems that at administration of low concentrations of dabigatran and rivaroxaban APTT is much more sensitive to a dabigatran. In healthy volunteers, administration of 50mg dose of apixaban has resulted in an increase APTT to approximately 1.2x and the prolonged APTT correlated with concentrations of apixaban determined in the plasma.

The FXa inhibitors have no effect on the thrombin time (TT), however thrombin inhibitors, direct and indirect ones cause its prolongation. TT can be used for a monitoring of thrombin inhibitors such as dabigatran. However, result depends on used reagents, and in most cases it is too sensitive to these inhibitors. Therefore, TT can be used as relatively sensitive test for the determination of relative low concentrations of drug in the plasma. Presence of the dabigatran in the plasma could be excluded if TT is normal. As TT is very sensitive to these inhibitors, a test modification named HemoClot has been developed for the argatroban and dabigatran therapy monitoring[5,36,37].

lažno negativno smanjenje koncentracije fibrinogena s nekim testovima[5,36,37].

Utjecaj novih antikoagulanasa na globalne i kromogene testove zgrušavanja

Tromboelastografija je globalni test zgrušavanja čija se potencijalna uporaba kod novih antikoagulanasa tek istražuje. Dosadašnji rezultati su pokazali dobru povezanost koncentracije lijeka i produženog vremena zgrušavanja za nekoliko antikoagulansa, i stoga se uskoro očekuju i smjernice za njezinu primjenu. U smislu monitoringa dabigatrana vrlo dobre rezultate pokazao je test Ekarinskog vremena zgrušavanja (ECT). Dabigatran produžuje ECT ovisno o primjenjenoj dozi, a test je moguće i kalibrirati prema koncentracijama dabigatrana. Prema svom mehanizmu djelovanja za rivaroksaban se ne očekuje da će utjecati na ECT, dok utjecaj apiksabana nije ispitan ili o tome nema objavljenih rezultata.

Kromogeni test koji mjeri anti-Xa aktivnost upotrebljava se za procjenu terapijskog učinka LWMH pri primjeni lijeka kod pacijenata s renalnom insuficijencijom, pretilih osoba i trudnica. Primjena rivaroksabana također može utjecati ovisno o koncentraciji na ove testove, a nadalje je razvijena i varijanta istog testa koja je specifična za rivaroksaban tj. pogodna za mjerenje širokog raspona njegovih koncentracija (20-660 ng/L) u plazmi.

Kromogeni test za mjerenje anti-IIa aktivnosti tj. dabigatrana je u razvitku, a varijanta ovog testa za procjenu aktivnosti hirudina i argatrobana može se već neko vrijeme naći na tržištu.

Preporuke za monitoring novih antikoagulanasa

Podaci o monitoringu novih lijekova i njihovom utjecaju na postojeće testove su ograničeni, a stoga još uvijek nisu razvijene opće smjernice. Na temelju ograničenih podataka British Comitee for Standards in Hematology je napravio preporuke za procjenu antikoagulacijskog učinka dabigatrana i rivaroksabana[39]. Smatra se da bi svaki laboratorij koji sudjeluje u procjeni njihovog učinka trebao uzeti u obzir osjetljivosti koagulacijskih testova koje koristi. Za relativnu procjenu antikoagulacijskog učinka dabigatrana može se koristiti APTV. APTV se ne smije koristiti za procjenu koncentracije lijeka u plazmi, a u tom smislu normalno TV bi značilo da je njegova količina u plazmi izrazito niska. U smislu procjene učinka dabigatrana može se koristiti i ECT-test ili modificirani test TV, HemoClot. Za relativnu procjenu antikoagulacijskog učinka rivaroksabana može se koristiti PV, obzirom da je nešto osjetljivije na ovaj lijek u odnosu na APTV. Nadalje, u oba slučaja i kod PV i APTV preporuka je da se rezultati izraze kao omjer vremena izmjerenog u pacijentovoj plazmi prema onome u normalnoj standardnoj plazmi. Što se vrijednosti INR tiče, može se uzeti u obzir isključivo ako je validiran za lijek koji se testira. Međutim, ako je INR validiran prema VKA ne uzima se u obzir jer pokazuje dramatično nereproducibilne rezultate i varijabilnost ovisnu o primjenjenom reagensu[5,39]. U smislu procjene koncentracije lijeka može se koristiti visokotlačna tekućinska kromatografija ili masena spektrometrija.

Inhibitors of FXa do not affect the determination of fibrinogen by Clauss method, which is based on the addition of excess thrombin to the plasma. However, thrombin inhibitors may lead to false negative reduction of concentration in some tests[5,36,37].

The impact of new anticoagulants on the global and chromogenic coagulation tests

Thromboelastography is a global coagulation test and its potential use with new anticoagulants is still under investigation. The results obtained so far have showed a good correlation between the concentration and prolonged clotting time for several anticoagulants and in that sense the recommendations are expected. In sense of dabigatran monitoring, the Ecarin clotting time (ECT) test has shown satisfactory results. Dabigatran prolongs ECT in the way dependant on the applied dose, and the test can be calibrated according to the dabigatran concentration. Due to its mechanism of action, rivaroxaban is not expected to affect the ECT, whereas the impact of the apixaban has not been tested yet or at least there are no published results.

Chromogenic test that measures anti-Xa activity is used to measure the effect of LWMH if applied in patients with renal insufficiency, obese people and pregnant women. Administration of rivaroxaban also exerts concentration dependant effect on these tests, and furthermore specific modification of the test in order to measure effect of rivaroxaban in a wide concentration span (20-660 ng/L) in plasma has been developed.

Chromogenic test for measuring anti-IIa activity of dabigatran is under investigation, whereas specific variant of the anti-FIIa activity test has been developed in order to assess the activity of hirudin and argatroban.

Recommendations for monitoring new anticoagulants

The data related to the monitoring of new anticoagulants are limited, and therefore general guidelines do not exist. Owing to a limited data, British Committee for Standards in Hematology has gave recommendation for monitoring the effect of the dabigatran and rivaroxaban[39]. Considering it, every laboratory that participated in evaluation of their effect has to take into account sensitivity of the reagents in use. For the determination of relative intensity of anticoagulation due to dabigatran APTT could be used. APTT should not be used for the determination of the drug concentrations in the plasma, and in that sense TT could be helpful by means that normal TT mean that drug concentration is very low. In terms of the assessment of the dabigatran effect, ECT or modification of TT test known as HemoClot could be used. For the determination of relative intensity of anticoagulation due to rivaroxaban PT could be used, since it has higher sensitivity on this drug in comparison to APTT. Furthermore, considering both of the tests, PT and APTV, recommendation is to express results as a ratio of the clotting time in the patient plasma according to clotting time in normal plasma. Considering INR values, the result could be taken into account only if INR was validated for the appropriate anticoagulants. If this is not a case, and INR is validated according to VKAs it should not be used as it dramatically shows non-reproducible results and the variability among the test reagents[5,39]. In order to assess concentration of particular drug, a high performance liquid chromatography or mass spectrometry could be used.

Diskusija i zaključci

Predstavljanjem novih protuzgrušavajućih lijekova napravljen je važan je korak prema jednostavnijem, efikasnijem i sigurnijem liječenju tromboze. U odnosu na konvencionalne, novi lijekovi poboljšanog su farmakokinetskog i farmakodinamskog profila[5], a trenutno dostupni podaci ukazuju na njihovu različitu efikasnost i sigurnosni profil kod različitih kliničkih indikacija.

Primjena novih lijekova započela je u smislu prevencije venskog tromboembolizma nakon ortopedskih zahvata, a za navedenu indikaciju kao i prevenciju MU kod pacijenata s FA njihova primjena odobrena je u mnogim zemljama. Rezultati istraživanja su pokazali da su ovi lijekovi u najmanju ruku efikasni kao VKA i/ili heparin. Međutim, iako dostupnost alternative terapije predstavlja veliki napredak, potrebno je više informacija o tome koji pacijenti imaju najveću korist od primjene ovih lijekova. Više informacija potrebno je i o tranziciji između dva lijeka te prekidu postupka liječenja i/ili indiciranog zahvata te njihovog doziranja kod bubrežnih bolesnika. Zbog kratkog vremena poluživota novih oralnih antikoagulanasa, prestankom njihovog uzimanja pacijenti mogu biti pod većim rizikom sistemskog embolizma u razdoblju relativno kraćem u onosu na prestanak uzimanja varfarina. Također kod prelaska npr. s dabigatrana na VKA, varfarin bi se trebao primjeniti otprilike 3 dana prije prestanka uzimanja dabigatrana uz pretpostavku da pacijent ima normalni klirens kreatinina[40,41]. Nadalje treba imati na umu i moguće interakcije ovih lijekova s drugim lijekovima što je važno za njihovu primjenu u dugotrajnim indikacijama[40]. Svi induktori ili inhibitori CYP3A4 (npr. makrolidni antibiotici ili blokatori kalcijskih kanala) ili P-glikoproteina (imunosupresivi, blokatori kalcijskih kanala...) moraju se primjeniti s velikim oprezom ili treba izbjeći njihovu istovremenu primjenu s inhibitorima FXa.

Novi antikoagulansi su na tržištu su predstavljeni kao lijekovi koji ne zahtjevaju monitoring. Iako se to marketinški navodi kao njihova velika prednost, ovakav nedostatak može postati vrlo važan kod pacijenata koji dožive ishemijski događaj zbog pogreške terapije. Kako nisu razvijani kao lijekovi koji zahtjevaju monitoring laboratorijski testovi za mjerenje njihovog protuzgrušavajućeg djelovanja tek se trebaju standardizirati. Za sada, niti jedan od postojećih testova nije validiran kao optimalan test za mjerenje njihovog djelovanja. Također više informacija je potrebno i o tome kako slijediti pacijenta s krvarenjem u smislu toksičnosti lijeka, obzirom da nema specifičnog antidota za bilo koji od ovih lijekova[40,41]. Za sada, u slučaju predoziranja, sugerira se suportivna terapija svježom smrznutom plazmom ili uporaba koncentrata FVII, kao i protrombinskog kompleksa. Nedavno provedena istraživanja su pokazala da protrombin kompleks može djelomice neutralizirati utjecaj rivaroksabana, ali ne i dabigatrana. Hemodijaliza može biti efikasna u otklanjanju oko 60% dabigatrana iz krvi tijekom 2-3h što se može iskoristiti u smislu njegove toksičnosti[40,41].

Očekivanja od nove terapije su velika. Iako potreba za njihovim monitoringom može biti manja u odnosu na onu za VKA, sve dok je na antikoagulantnoj terapiji broj posjeta pacijenta liječniku se ne može smanjiti, a povremena procjena pacijentovog stanja u smislu isključenja anemije, trombocitopenije, jetrene ili bubrežne bolesti kako bi se izbjegle komplikacija krvarenja je neophodna. Osim toga, jedan od ograničavajućih koraka u uporabi ovih lijekova je i njihova cijena. U EU je procijenjeno da se godišnje po pacijentu s FA potroši otprilike 1.500-3.200 EUR, a prema sistemskoj anali-

Debate and conclusions

By introducing new antithrombotic drugs, an important step towards a simpler, more efficient and safer treatment of thrombosis has been made. Compared to conventional drugs, new oral anticoagulants have improved pharmacokinetic and pharmacodynamic profile[5], and currently available data suggests their different efficacy and safety profile for different clinical indications.

The current application of these new drugs began with an aim to prevent venous thromboembolism after orthopedic surgical procedures, and they have been approved in many countries for these indications and prevention of stroke in patients with AF. The results at least showed that these drugs are as efficient as VKA and/or heparin for approved indications. However, although the availability of an alternative therapy represents a major breakthrough, we still need more information about what are the patients that mostly benefit from the new drugs. More information is also needed on the transition between the two drugs and discontinuation of the treatment procedure and/or surgical procedure and dosing in kidney patients. Due to a shorter half-life of new oral anticoagulants, the patients who stop taking them may be at an increased risk for systemic embolism in a shorter period relative to the one when warfarin effects stop to be effective. Also when switching e.g. from dabigatran to VKA, warfarin should be administered approximately 3 days before a patient stops taking dabigatran under the assumption that the patient has normal creatinine clearance[40,41]. Besides, one must keep in mind any potential interactions of these drugs with some other drugs which proved to be important for the application in long term indications[40]. All inducers or inhibitors of CYP3A4 (e.g. macrolide antibiotics or calcium channel blockers) or P-glycoprotein (immunosuppressants, calcium channel blockers ...) have to be applied with a great caution in patients receiving FXa inhibitors or their simultaneous administration should be avoided.

The new anticoagulant drugs are introduced as drugs that do not require monitoring. Although this is considered to be a marketing advantage of these drugs, this disadvantage can become very important for patients who experience an ischemic event due to an error made in the therapy. As they were not developed as drugs that require monitoring, the laboratory tests for measuring their anticoagulant effect or drug level in the serum still have to be standardized. Currently, none of the tests has been validated as the optimal test to measure their efficacy. More information is also warranted on how to follow up patients with bleeding because there are no specific antidote for any of these new agents[40,41]. So far, supportive therapy by the fresh frozen plasma, and the use of FVII concentrate, as well as the prothrombin complex is recommended. Recently conducted trials have shown that prothrombin complex can reverse the effect of rivaroxaban, but not those of dabigatran. In case of dabigatran, the hemodialysis may be effective in eliminating as much as 60% of dabigatran from the blood during the period of 2-3 hours which can be exploited in terms of its toxicity[40,41].

Expectations of the new therapy are great. Although monitoring of the new drugs in comparison to warfarin can be reduced, the number of patient's visits can not be reduced, while a periodic assessment of his/her condition by means of the exclusion of anemia, thrombocytopenia, liver or kidney disease as to avoid the bleeding complications is necessary as long as the patient receives the therapy. Additionally, high price of these drugs is certainly one of the

zi najveći udio troškova otpada na hospitalizacije[42]. Tijekom zadnjih dekada troškovi i broj hospitalizacija zbog FA su u porastu zbog sve starije populacije, a za očekivati je da će primjena novih antikoagulanasa povećati ove troškove. Godišnja cijena terapije dabigatranom se procjenjuje na otprilike 1.680 EUR, dok godišnji troškovi terapije s VKA iznose otprilike 50-150 EUR tj. točnije 12 EUR za lijek, a ostalo ovisi o učestalosti mjerenja INR. Američko istraživanje troškovne učinkovitosti metodom po Markovu je pokazalo da u određenim slučajevima dabigatran može biti korisniji od varfarina, npr. primjena dabigatrana u dozi od 150 mg dva puta dnevno je korisnija kod pacijenata čiji INR nije idealan, a stariji su od 65 god. te su visokorizični za MU (CHADS2 Score ≥1), kao i onih s visokim rizikom hemoragije i MU (CHADS2 Score ≥3). Međutim, kod umjereno rizičnih pacijenata primjena varfarina je korisnija, iako INR nije idealan. U Hrvatskoj, na osnovnoj listi lijekova HZZO registrirane su tablete rivaroksaban 10 mg u pakiranju od 30x10 mg i 10x10 mg čija cijena prema zadnjim iznosi informacijama iznosi 874,80 kn tj. 291,60 kn te tablete dabigatrana 75 mg u pakiranju od 30x75 mg po cijeni 441,63 kn te tablete 110mg u pakiranju 10x110 mg po cijeni 153,36 kn. Odluka o tome koji će se protuzgrušavajuči lijek prepisati ovisi o očekivanoj koristi, riziku, troškovima te pacijentovim sklonostima, a omjer rizika i koristi njihove primjene za pacijente u Hrvatskoj tek bi se trebao izračunati. Za pacijente kod kojih se ne postiže efikasnost u liječenju primjenom VKA, ovi lijekovi mogu biti alternativni izbor. Međutim, pacijenti s nestabilnim INR ne moraju biti idealni kandidati za nove lijekove. Stoga je potrebno pričekati proširenje spoznaja kako bi se ovi lijekovi mogli primjenjivati i izvan klinika, a u međuvremenu, njihova primjena će ovisiti o čimbenicima vezanim za nuspojave, doziranju i cijeni te eventualnom zahtjevu za dodatnim testovima. Za sada, primjena varfarina u svakom slučaju je jeftinija čak i kada se uzmu u obzir regularni troškovi monitoringa.

Velike promjene se očekuju u slijedećih nekoliko godina. Novi antikoagulansi su dobrodošli u smislu nadilaženja nedostataka tradicionalne protuzgrušavajuće terapije, a pažljivo provedena faza IV kliničkih studija osnova je za optimizaciju pozitivnih i negativnih dokaza iz faze III kliničkih studija. Spoznaje o sigurnosnom profilu novih lijekova će se proširiti kako se bude širila njihova uporaba, a pri tome je velika odgovornost na liječnicima u smislu objave očekivanih i neočekivanih podataka o primjeni novih lijekova. Pri tome se mora razmišljati i u smislu razvoja lokalnih i globalnih preporuka za specijalne situacije koje zahtjevaju monitoring ovih lijekova.

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reasons why their administration is limited. In EU, it is estimated that approximately EUR 1,500-3,200 is spent per patient with AF on an annual basis, and according to the recent systematic analysis the hospitalizations are accountable for the largest portion of costs[42]. Costs and hospitalizations for AF have increased over the last decade due to the aging population, and we could expect that the application of new anticoagulants will cause an increase in these costs. The annual cost of the therapy with dabigatran is estimated at approximately EUR 1,680, while the annual costs of treatment with VKA are estimated at approximately EUR 50-150, that is, EUR 12 for the drug, while the remaining amount depends on INR measurement. An American investigation of the cost effectiveness by applying the Markov model has shown that in certain cases dabigatran can be more useful than warfarin (e.g. in patients older than 65 who are at high risk for stroke (CHADS2 Score ≥1) and those with a high risk for hemorrhage and stroke (CHADS2 Score ≥3), whereas dabigatran at a 150 mg dose b.i.d. has a greater benefit for patients whose INR is not ideal. However, in patients with moderate-risk, the administration of warfarin is beneficial, although the INR is not ideal. The rivaroxaban 10 mg tablets in 30x10 mg packs and 10x10 mg packs are registered on the Croatian list of essential drugs which according to the latest information are priced at HRK 874.80 or HRK 291.60 and the abigatran 75 mg tablets in 30x75 mg packs are priced at HRK 441.63, while 110 mg tablets in 10x110 mg packs are priced at HRK 153.36. The clinical decision on which anticoagulant drug will be prescribed depends on the expected benefit, risk, costs and patients' preferences, and the risk-benefit ratio for the Croatian patients still have to be calculated. These drugs may be an alternative choice for patients in whom the efficacy is not achieved in the therapy by applying VKA. However, the patients with unstable INR may not be the ideal candidates for new drugs. Therefore, it will be necessary to wait for the more comprehensive insights in order to apply them outside of the clinic and in the mean time, their administration will depend on side effects-related factors, dosing and pricing by the time as well as on demands for some additional testing. So, far the administration of warfarin is definitively cheaper even when taking into account ordinary monitoring costs.

Major changes are expected to be made in the next few years. New anticoagulants are welcome for the purpose of overcoming deficiencies of traditional anticoagulant therapy, while carefully conducted Phases IV of clinical trials are the basis for the optimization of positive and negative evidence obtained from the Phase III of the clinical trials. The insights about the safety profile of the new drugs will broaden parallel with the expansion of their administration, whereas physicians will assume a great responsibility to report expected and unexpected data on the application of the new drugs. In this sense, it is necessary to develop local and global recommendations for special situations that require monitoring of these drugs.

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