Reumatizam 2021;68(2):69–85
https://doi.org/10.33004/reumatizam-68-2-2

REVIEW PAPER PREGLEDNI RAD

ANTICOAGULATION: AN OVERVIEW OF PHARMACOLOGICAL AGENTS AND THERAPEUTIC IMPLICATIONS IN RHEUMATOLOGY

ANTIKOAGULACIJA: PREGLED FARMAKOLOŠKIH SREDSTAVA I TERAPIJSKIH IMPLIKACIJA U REUMATOLOGIJI

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Received / Primljeno: 26th November 2021 / 26. 11. 2021.
Accepted / Prihvaćeno: 23rd December 2021 / 23. 12. 2021.

Abstract

The use of anticoagulant therapy is a part of the daily work of clinicians and a reason for fear, primarily due to the risk of bleeding. The use of anticoagulant drugs in rheumatology remains a challenge. First, a large number of clinicians consider rheumatic conditions as a hypercoagulable state, which often leads to wrong decisions. Second, the use of drugs in the treatment of rheumatic diseases may be associated with an increased risk of venous thromboembolism (VTE), and they can have effect on dose of anticoagulant agent. The aim of this paper is to present the properties of anticoagulant therapy through the prism of rheumatological pathology.

Keywords: Anticoagulants, Rheumatology, Treatment

Sažetak

Primjena antikoagulantne terapije dio je svakodnevnog rada kliničara i postupak koji izaziva strah, prvenstveno zbog opasnosti od krvarenja. Primjena antikoagulantnih lijekova u reumatologiji i dalje je izazovan postupak. Kao prvo, velik broj kliničara smatra reumatska stanja hiperkoagulabilnim stanjima, što često dovodi do donošenja pogrešnih odluka. Kao drugo, primjena lijekova u liječenju reumatskih bolesti može biti povezana s povećanim rizikom od venske tromboembolije (VTE) te lijekovi mogu utjecati na dozu antikoagulansa. Cilj je ovog rada prikazati svojstva antikoagulantne terapije kroz prizmu patologije reumatskih bolesti.

Ključne riječi: antikoagulansi, reumatologija, liječenje

INTRODUCTION

Anticoagulant treatment in rheumatology is a field that still remains unexplored, primarily due to the risk of bleeding (1). However, the risk (and fear) of bleeding should not be a reason not to include anticoagulant therapy (1,2). The CHADS2 score (established in 2010) and then the revised CHA2DS2-VASc score (in 2012) have been used in practice since the first guidelines for

UVOD

Antikoagulantna terapija u reumatologiji još je uvijek neistraženo područje, prvenstveno zbog rizika od krvarenja (1). Međutim, rizik (i strah) od krvarenja ne bi trebao biti razlog da se antikoagulantna terapija ne uvede u liječenje (1,2). Bodovni sustav CHADS2 (uspostavljen 2010.), a potom i revidirani bodovni sustav CHA2DS2-VASc (uspostavljen 2012.) u praksi se upo-

the treatment of atrial fibrillation (AF), and they serve to assess the risk of stroke in patients with non-rheumatic AF, common and severe cardiac arrhythmias associated with thromboembolic stroke, and to determine whether or not treatment with anticoagulant therapy or anti-aggregation therapy is required (3,4). Assessing the risk of bleeding (HAS-BLED, ATRIA, ABC, ORBIT, HEMORR2HAGE score) is an important part of deciding on a therapeutic modality, but it should not be an eliminatory step in the initiation of anticoagulant therapy (5). Scores are a simple and indispensable tool in optimizing the therapeutic modality of patients with AF, along with imperative knowledge of the pharmacodynamic and pharmacokinetic properties of the pharmacological agent (5). The literature states that in the case of adequate thromboprophylaxis, about 185,255 cases of venous thromboembolism (VTE) per year worldwide could be prevented (6). In 70% of cases, deep vein thrombosis (DVT) occurs in patients hospitalized for acute medical conditions such as acute myocardial infarction, acute heart failure, oncological pathology, or pneumonia (6). A risk assessment in accordance with the PADUA score is recommended (as well as the IMPROVE-DD score), as well as a bleeding risk assessment according to the IMPROVE score (7). All hospitalized patients over 40 years of age with active pathology and reduced mobility, and one of the associated comorbidities (acute heart failure, respiratory disease, active malignancy, acute infectious condition, thrombophilia, rheumatic disease, ischemic stroke, acute myocardial infarction) are candidates for thromboprophylaxis, both in rheumatology and complete internal medicine (7). It is crucial to take into account the patient's medical history (positive family history for coagulopathy or coagulation-related gene polymorphism) and any additional data that could predispose to VTE (electrocardiogram (ECG) Holter monitoring findings, if not indicative of atrial fibrillation, but verifies a great number of supraventricular extrasystoles, is also alarming regarding anticoagulation) (8).

AIM

The aim of this paper is to present the properties of anticoagulant therapy through the prism of rheumatological pathology.

ANTICOAGULANT AGENTS

Pharmacological anticoagulants are differentiated into heparin (low molecular weight, unfractionated), warfarin derivatives (vitamin K antagonists), new oral anticoagulants (NOACs), and fondaparinux (9). According to the method of administration, they are divided into parenteral and oral. The use of anticoagu-

trebljavaju od pojave prvih smjernica za liječenje atrijske fibrilacije (AF), a služe za procjenu rizika od moždanog udara u bolesnika s nereumatskom AF, uobičajenim i teškim srčanim aritmijama povezanim s tromboembolijskim moždanim udarom te kako bi se utvrdilo je li potrebno liječenje antikoagulantnom terapijom ili antiagregacijskom terapijom (3,4). Procjena rizika od krvarenja (bodovni sustavi HAS-BLED, ATRIA, ABC, ORBIT, HEMORR2HAGE) važan je dio odlučivanja o terapijskom modalitetu, ali ne smije biti eliminacijski korak u započinjanju antikoagulantne terapije (5). Bodovni su sustavi, uz obavezno poznavanje farmakodinamičkih i farmakokinetičkih svojstava farmakološkog sredstva, jednostavan i nezaobilazan alat u optimizaciji terapijskog modaliteta bolesnika s AF (5). U literaturi se navodi da bi se, primjenom odgovarajuće tromboprofilakse, godišnje u svijetu moglo spriječiti oko 185.255 slučajeva venske tromboembolije (VTE) (6). U 70% slučajeva duboka venska tromboza (DVT) javlja se u bolesnika hospitaliziranih zbog akutnih zdravstvenih stanja kao što su akutni infarkt miokarda, akutno zatajenje srca, onkološka patologija ili upala pluća (6). Preporučuje se procjena rizika prema bodovnom sustavu PADUA, to jest, The Padua Prediction Score (kao i prema bodovnom sustavu IMPROVE-DD) te procjena rizika od krvarenja prema bodovnom sustavu IMPROVE (7). Kandidate za tromboprofilaksu, kako u reumatologiji, tako i u internoj medicini, predstavljaju svi hospitalizirani bolesnici stariji od 40 godina s aktivnom patologijom i smanjenom pokretljivošću te jednim od pridruženih komorbiditeta (akutno zatajenje srca, respiratorna bolest, aktivna maligna bolest, akutno infektivno stanje, trombofilija, reumatska bolest, ishemijski moždani udar, akutni infarkt miokarda) (7). Ključno je uzeti u obzir bolesnikovu anamnezu (pozitivna obiteljska anamneza na koagulopatiju ili polimorfizam gena povezan s koagulacijom) i sve dodatne podatke koji bi mogli predstavljati predispoziciju za VTE (nalazi Holter elektrokardiograma [EKG] također su alarmantni u pogledu antikoagulacije ako ne ukazuju na atrijsku fibrilaciju, ali potvrđuju velik broj supraventrikulskih ekstrasistola) (8).

CILJ

Cilj je ovog rada prikazati svojstva antikoagulantne terapije kroz prizmu patologije reumatskih bolesti.

ANTIKOAGULANTNA SREDSTVA

Farmakološki antikoagulansi dijele se na heparin (niskomolekularni, nefrakcionirani), derivate varfarina (antagonisti vitamina K), nove oralne antikoagulanse (NOAK) i fondaparinuks (9). Prema načinu primjene dijele se na parenteralne i oralne. Primjena antikoagulantne terapije indicirana je u profilaksi venske

Table 1. Properties of unfractionated heparin and LMWH (10)
Tablica 1. Svojstva nefrakcioniranog heparina i NMH-a (10)

Heparin	Advantages / Prednosti	Disadvantages / Nedostatci
Unfractionated / Nefrakcionirani	Rapid onset, greater flexibility for the dose titration, as well as the discontinuation of therapy, the ability to monitor the effect through monitoring aPTT and anti-factor Xa activity, activated platelet aggregation time, usage independent of renal function, the presence of antidotes in the form of protamine sulfate. / Brz početak djelovanja, veća fleksibilnost za titraciju doze, kao i prekid terapije, mogućnost praćenja učinka praćenjem APTV-a i antifaktora Xa aktivnosti, aktivirano vrijeme agregacije trombocita, uporaba neovisna o funkciji bubrega, prisutnost antidota u obliku protamin sulfata.	Short plasma half-life, need for continuous infusion administration, the requirement of frequent activity monitoring through laboratory parameters, higher incidence of HIT, skin reactions or osteoporosis with prolonged use, increased risk of bleeding. / Kratko poluvrijeme eliminacije u plazmi, potreba za kontinuiranom primjenom infuzije, potreba za čestim praćenjem aktivnosti kroz laboratorijske parametre, veća učestalost trombocitopenije izazvane heparinom (HIT), kožnih reakcija ili osteoporoze kod produljene primjene, povećan rizik od krvarenja.
LMWH / Niskomolekularni heparin (NMH)	Greater bioavailability, easy administration, longer effect compared to the unfractionated, possibility of faster dose adjustment, lower risk of HIT, lower incidence of osteoporosis. / Bolja bioraspoloživost, laka primjena, dulji učinak u odnosu na nefrakcionirani heparin, mogućnost bržeg prilagođavanja doze, manji rizik od trombocitopenije izazvane heparinom (HIT), manja pojavnost osteoporoze.	The effect appears after 20–30 minutes, slower ability to stop bleeding due to the longer action, protamine sulfate has less effect on LMWH, prolonged plasma half-life in renal insufficiency (especially enoxaparin) / Učinak se javlja nakon 20 do 30 minuta, sporija sposobnost zaustavljanja krvarenja zbog duljeg djelovanja, slabiji učinak protamin sulfata na NMH, produljeno poluvrijeme eliminacije u plazmi kod bubrežne insuficijencije (osobito pri primjeni enoksaparina).

aPTT / APTV – activated Partial Thromboplastin Time / aktivirano parcijalno tromboplastinsko vrijeme; HIT – heparin-induced thrombocytopenia / trombocitopenija izazvana heparinom; LMWH / NMH – Low Molecular Weight Heparin / niskomolekularni heparin

lant therapy is indicated in the prophylaxis of venous thromboembolism (VTE), in the treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE), in the treatment of acute coronary syndrome, for the prevention of ischemic stroke or transient ischaemic attack (TIA), in the pediatric population (VTE, DVT, PE, cerebral venous thrombosis), during pregnancy, under neuraxial anesthesia, and perioperatively, postoperatively and during hospitalization in the form of thromboprophylaxis (10,11).

The choice of the appropriate pharmacological agent should be in accordance with the indication and the characteristics of the patient himself, taking into account the pharmacodynamic and pharmacokinetic properties of the drug.

Table 1 shows the characteristics of parenteral anticoagulant therapy. Heparin, used in clinical practice, has been isolated from the intestines of pigs or cows (11,12). Low molecular weight heparin (LMWH; enoxaparin, dalteparin, nadroparin, bemiparin, certoparin, tinzaparin) is obtained by enzymatic or chemical depolymerization of unfractionated heparin (15 segments in the form of polysaccharides) (11). The mechanism of action of heparin is binding to antithrombin and thus inactivating factor Xa (10). The difference between unfractionated heparin and LMWH is that, in theory, it is a much more effective thrombin inhibitor (direct intravenous thrombin inhibitors such as argatroban and bivalirudin are also used in practice) (10). Unfractionated heparin is metabolized through

tromboembolije (VTE), u liječenju i prevenciji duboke venske tromboze (DVT) i plućne embolije (PE), u liječenju akutnog koronarnog sindroma, u prevenciji ishemijskog moždanog udara ili tranzitorne ishemijske atake (TIA), u pedijatrijskoj populaciji (VTE, DVT, PE, cerebralna venska tromboza), tijekom trudnoće, u neuraksijalnoj anesteziji, te perioperativno, postoperativno i tijekom hospitalizacije u obliku tromboprofilakse (10,11).

Odabir odgovarajućeg farmakološkog sredstva treba biti u skladu s indikacijom i karakteristikama samog bolesnika, uzimajući u obzir farmakodinamička i farmakokinetička svojstva lijeka.

U tablici 1 prikazane su karakteristike parenteralne antikoagulantne terapije. Heparin, koji se primjenjuje u kliničkoj praksi, izoliran je iz crijeva svinja ili krava (11,12). Niskomolekularni heparin (NMH; enoksaparin, dalteparin, nadroparin, bemiparin, certoparin, tinzaparin) dobiva se enzimskom ili kemijskom depolimerizacijom nefrakcioniranog heparina (15 segmenata u obliku polisaharida) (11). Mehanizam djelovanja heparina vezanje je na antitrombin, čime se postiže inaktivacija faktora Xa (10). Razlika između nefrakcioniranog heparina i niskomolekularnog heparina (NMH) u tome je što je prvi navedeni, u teoriji, učinkovitiji inhibitor trombina (u praksi se također primjenjuju i direktni intravenski inhibitori trombina kao što su argatroban i bivalirudin) (10). Nefrakcionirani heparin metabolizira se kroz retikuloendotelni sustav i jetru, a izlučuje se urinom (10). Što se tiče terapijskih

the reticuloendothelial system and liver, and it is excreted through urine (10). In terms of therapeutic doses, renal function does not affect elimination (13,14). The maximum effect of heparin, whether administered intravenously or subcutaneously, is two to four hours, and the plasma half-life is 45 minutes to one hour. Heparin cannot be administered intramuscularly or orally (10,13,14). LMWH is metabolized in the liver, and the excretion itself is through the kidneys. Renal clearance is between 10 to 40%. Peak plasma values are reached three to five hours after subcutaneous administration and two hours after intravenous administration (10,13,14). The plasma half-life is three to seven hours. The therapeutic effect can be monitored by activated partial thromboplastin time (aPTT) and antifactor Xa activity, and it is recommended to use any available test (10). APTT values greater than 1.5 to 2.5 times the upper reference limit are accepted in clinical practice (10).

WARFARIN DERIVATIVES (VITAMIN K ANTAGONISTS)

Vitamin K antagonists (warfarin, acenocoumarol, phenprocoumon, fluindione) are anticoagulant drugs for oral use (10,15). The indications for using vitamin K antagonists are atrial fibrillation (for stroke prevention), acute coronary syndrome, heart failure, mechanical valve implantation, DVT treatment, PTE prevention, PE treatment, and antiphospholipid syndrome. Their mechanism of action is blocking the vitamin K epoxide reductase complex subunit 1 (encoded by vitamin K epoxide reductase complex subunit 1 – VKORC1 gene) (10,16). They block proteins C and S and inhibit coagulation factors II, VII, IX, and X (17).

Warfarin is rapidly and completely absorbed from the intestine after oral administration. It has a small volume of distribution and is strongly bound to plasma albumin. The peak plasma concentration of warfarin is achieved after one hour, while acenocoumarol reaches it after one to three hours. It is metabolized by the CYP2C9 enzyme. The bioavailability of warfarin and acenocoumarol is 99.4% and 60%, respectively (Table 2) (10).

Their advantages are that they still represent the first and only option after mechanical valve implantation, in case of left ventricular apex aneurysm and thrombotic mass, low cost, the possibility of reversibility of effect (vitamin K, fresh frozen plasma, prothrombin concentrated complex (PCC)) (10). Its disadvantages are that the metabolism of the drug is individually dependent, the level of the drug depends on comorbidities, and frequent controls of PV and INR are required, which are dependent even on the type of diet. Foods rich in vitamin K will impair the values, and the value of INR is also affected by the use of alcohol, smoking,

doza, bubrežna funkcija ne utječe na njegovu eliminaciju (13,14). Maksimalni je učinak heparina, bilo da se primjenjuje intravenski ili supkutano, dva do četiri sata, a poluvrijeme eliminacije u plazmi iznosi 45 minuta do jedan sat. Heparin se ne može primijeniti intramuskularno ili oralno (10,13,14). NMH se metabolizira u jetri, a izlučuje se putem bubrega. Bubrežni klirens iznosi između 10% i 40%. Vršne vrijednosti u plazmi postižu se tri do pet sati nakon supkutane primjene i dva sata nakon intravenske primjene (10,13,14). Poluvrijeme eliminacije u plazmi iznosi tri do sedam sati. Terapijski učinak može se pratiti pomoću aktiviranoga parcijalnog tromboplastinskog vremena (APTV) i antifaktora Xa aktivnosti, a preporučuje se upotreba bilo kojeg dostupnog testa (10). U kliničkoj praksi prihvaćene su vrijednosti APTV-a koje su od 1,5 do 2,5 puta veće od gornje referentne granice (10).

DERIVATI VARFARINA (ANTAGONISTI VITAMINA K)

Antagonisti vitamina K (varfarin, acenokumarol, fenprokumon, fluindion) predstavljaju antikoagulanse za oralnu primjenu (10,15). Indikacije za primjenu antagonista vitamina K su sljedeće: atrijska fibrilacija (za prevenciju moždanog udara), akutni koronarni sindrom, zatajenje srca, implantacija mehaničke valvule, liječenje duboke venske tromboze (DVT), prevencija plućne tromboembolije (PTE), liječenje plućne embolije (PE) i antifosfolipidni sindrom. Njihov mehanizam djelovanja uključuje blokiranje podjedinice 1 vitamin K epoksid reduktaza kompleksa (kodirane podjedinicom 1 kompleksa vitamin K epoksid reduktaze – VKORC1 gen) (10,16). Oni blokiraju proteine C i S i inhibiraju faktore koagulacije II, VII, IX i X (17).

Varfarin se nakon oralne primjene brzo i potpuno apsorbira iz crijeva. Ima mali volumen distribucije i snažno se veže za albumin, protein krvne plazme. Vršna koncentracija varfarina u plazmi postiže se nakon jednog sata, a acenokumarola nakon jednog do tri sata. Metabolizira ga enzim CYP2C9. Bioraspoloživost varfarina iznosi 99,4%, a acenokumarola 60% (tablica 2) (10).

Prednosti su im što još uvijek predstavljaju prvu i jedinu opciju nakon implantacije mehaničke valvule, u slučaju aneurizme vrha lijeve klijetke i tromba, niska cijena, mogućnost reverzibilnosti učinka (vitamin K, svježe smrznuta plazma, koncentrat protrombinskog kompleksa [PCC]) (10). Njihovi su nedostatci što je metabolizam lijeka individualno ovisan, razina lijeka ovisi o komorbiditetima, a potrebne su i česte kontrole u obliku protrombinskog vremena (PV) i internacionalnog normaliziranog omjera (INR), koje ovise čak i o načinu prehrane. Hrana bogata vitaminom K narušit će vrijednosti, a na vrijednost INR-a utječe i konzumacija alkohola, pušenje, pa čak i upotreba vitaminskih

Table 2. Pharmacokinetic differences between warfarin and acenocoumarol (10)
Tablica 2. Farmakokinetičke razlike između varfarina i acenokumarola (10)

	Warfarin / Varfarin	Acenocoumarol / Acenokumarol
Route of administration / Način primjene	oral / oralno	oral / oralno
Monitoring / Praćenje	PT / PV (INR)	PT / PV (INR)
Peak plasma concentration / Vršna koncentracija u plazmi	4 hours / sata	1–3 hours / 1 do 3 sata
Plasma half-time / Poluvrijeme eliminacije u plazmi	30–80 hours / 30 do 80 sati	10.9 hours / 10,9 sati
Duration of action / Trajanje djelovanja	2–5 days / 2 do 5 dana	2 days / 2 dana
Elimination / Eliminacija	renal 92% / renalna 92%	renal 60% / renalna 60%
Dependency on the CYP2C9 metabolism / Ovisnost o enzimu CYP2C9 u metabolizmu lijekova	++	+
Antidote / Antidot	vitamin K1, prothrombin complex concentrate, fresh or frozen plasma / vitamin K1, koncentrat protrombinskog kompleksa, svježa ili smrznuta plazma	vitamin K1
Preganancy / Trudnoća	contraindicated / kontraindiciran	contraindicated / kontraindiciran

PT / PV – prothrombin time / protrombinsko vrijeme; INR – international normalized ratio / internacionalni normalizirani omjer

and even the use of vitamin supplements. Warfarin is a less compelling option than new oral anticoagulants (NOACs) for the prevention of ischemic stroke, as well as the prophylaxis and treatment of PTE itself (10). However, due to its low cost, it is still the most commonly used option for anticoagulant therapy in Bosnia and Herzegovina. The development of pharmacogenetics, especially the understanding of CYP2C9 and VKORC1 gene polymorphisms, has developed different schemes of therapy initiation but also made it known that control of therapeutic modality by warfarin derivatives is challenging.

Therapeutic values of INR are usually in the range of 2.0 to 3.0, and after implantation of the mechanical valve, that range is between 3.0 and 4.0 (18). The plasma half-life of warfarin is 36 to 42 hours, acenocoumarol 8 to 11 hours, phenprocoumon 3 to 5 days, and fluindione 69 hours, which additionally complicates the decision on urgent surgical procedures and causes problems in the field of pharmacokinetic interactions (10). The INR values can be affected by drugs including cotrimoxazole, metronidazole, macrolides, fluorokinolones and drugs metabolized by CYP2C9 enzyme (fluconazole, amiodarone, sulfamethoxazole), acetaminophen, as well as drugs binding to albumin. Concomitant use of nonsteroidal anti-inflammatory drugs (and acetylsalicylic acid) or certain alkaloids may increase the risk of bleeding, while all drugs inducing CYP2C9 enzyme may decrease the anticoagulant effect (10).

In case of life-threatening bleeding, it is necessary to discontinue warfarin therapy, administer vitamin K1 and treat the patient with fresh frozen plasma or prothrombin complex concentrate (PCC) (25 to 50 units per kilogram of body weight) (10).

Novi oralni antikoagulansi (NOAK)

Novi oralni antikoagulansi (NOAK) uključuju pet predstavnika, od kojih su četiri izravni inhibitori faktora Xa (rivaroksaban, apiksaban, edoksaban i betriksaban), a peti je izravni inhibitor trombina (dabigatran). Betriksaban nije odobren za uporabu u Europi, ali ga je odobrila Agencija za hranu i lijekove Sjedinjenih Američkih Država (FDA) (10).

U kliničkim studijama, u kojima se predstavila upotreba NOAK-a, navodi se da su novi oralni antikoagulansi (NOAK) jednako učinkoviti kao varfarin i njegovi derivati u prevenciji moždanog udara kod pacijenata s nevalvularnom atrijskom fibrilacijom i za liječenje VTE, te da su sigurniji za upotrebu zbog nižih stopa intrakranijalnog krvarenja (10). Odabir određene primjene NOAK-a trebao bi se temeljiti na individualnim karakteristikama pacijenata, kao i na farmakološkim svojstvima same tvari.

indione 69 hours, which additionally complicates decisions about urgent surgical procedures, as well as complicates the story of pharmacokinetic interactions (10). INR values may be affected by drugs including cotrimoxazole, metronidazole, macrolides, fluoroquinolones, and drugs that metabolize CYP2C9 (fluconazole, amiodarone, sulfamethoxazole), acetaminophen, as well as drugs that bind to albumin. The use of nonsteroidal antirheumatic drugs (and acetylsalicylic acid) or certain alkaloids may increase the risk of bleeding, whereas all drugs that induce CYP2C9 may reduce the anticoagulant effect (10).

In case of life-threatening bleeding, it is necessary to discontinue warfarin use, administer ampullary vitamin K1, and treat the patient with fresh frozen plasma or PCC (25–50 units per kilogram of body weight) (10).

New oral anticoagulants (NOAC)

New oral anticoagulants (NOACs) include five representatives, four of which are direct inhibitors of factor Xa (rivaroxaban, apixaban, edoxaban, and betrixaban), and the fifth is a direct thrombin inhibitor (dabigatran). Betrixaban is not approved for use in Europe, while it is approved by U.S. Food and Drug Administration (FDA) (10).

Clinical studies that have established the use of NOAC state that NOACs are as effective as warfarin and its derivatives in stroke prevention in patients with non-valvular atrial fibrillation and for the treatment of VTE, and are safer to use due to lower rates of intracranial hemorrhage (10). The choice of particular NOAC use should be based on the individual characteristics of the patients, as well as the pharmacological properties of the substance itself.

The first representative of this group to emerge was dabigatran, with the initial study "Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)" (19). Dabigatran achieves peak plasma values within two hours after administration. It inhibits free thrombin, fibrin-bound thrombin, and thrombin-induced platelet aggregation. Its bioavailability is about 6.5%, and the elimination half-life is between 12 and 14 hours (19). It is eliminated by the kidneys, and about 80% of the drug is excreted as unchanged (19).

Rivaroxaban has been established in clinical practice with two studies, "Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF)" and "Xarelto on Prevention of Stroke and Non- Central Nervous System Embolism in Patients with Non-Valvular and Atrial Fibrillation (XANTUS)" (20,21). Rivaroxaban is the most frequently prescribed NOAC in Bosnia and Herzegovina. Peak plasma value is reached between 2 to 4 hours after ingestion. It is a selective, direct, and re-

Prvi predstavnik ove skupine koji se pojavio bio je dabigatran, čije je djelovanje opisano u početnoj studiji Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) (19). Primjenom dabigatrana postižu se vršne vrijednosti u plazmi unutar dva sata nakon primjene lijeka. On inhibira slobodni trombin, trombin vezan na fibrin i agregaciju trombocita induciranu trombinom. Bioraspoloživost mu je oko 6,5%, a poluvrijeme eliminacije između 12 i 14 sati (19). Eliminacija se vrši putem bubrega, a oko 80% lijeka izlučuje se nepromijenjeno (19).

Rivaroksaban je u kliničkoj praksi predstavljen u dvije studije: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) i Xarelto on Prevention of Stroke and Non- Central Nervous System Embolism in Patients with Non-Valvular and Atrial Fibrillation (XANTUS) (20,21). Rivaroksaban je NOAK koji se najčešće propisuje u Bosni i Hercegovini. Njegova vršna vrijednost u plazmi postiže se između 2 i 4 sata nakon ingestije. On je selektivni, izravni i reverzibilni inhibitor faktora Xa, koji sprječava i unutarnje i vanjske putove koagulacije, čime inhibira stvaranje trombina i sam razvoj tromba (10). Poluvrijeme eliminacije iz plazme je oko 9 sati u mlađih osoba i između 11 i 13 sati u starijih osoba. Dvije trećine lijeka metabolički se razgrađuje, jedna polovica se eliminira putem bubrega, a druga putem crijeva. Preostala jedna trećina lijeka izlučuje se izravno putem bubrega u mokraću kao nepromijenjena djelatna tvar. Tjelesna težina, dob i spol ne utječu na farmakodinamička svojstva lijeka (10). Rivaroksaban je klinički ispitan u dozi od 2,5 mg za primarnu i sekundarnu prevenciju kardiovaskularnih događaja, kao i za liječenje bolesti perifernih arterija (22).

U kliničkim studijama Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) i Apixaban for Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First Line Therapy (AMPLIFY) predstavljena je primjena apiksabana u kliničkoj praksi (23,24). Nakon 3 do 4 sata od ingestije, lijek će postići maksimalnu vrijednost u plazmi, s dominantnim hepatičkim klirensom. Studije navode da je apiksaban najsigurniji NOAK u smislu rizika od krvarenja, iako je teško donijeti takav zaključak s obzirom na neujednačenost uzorka u početnim studijama. On je selektivni, reverzibilni inhibitor faktora Xa koji sprječava stvaranje trombina (10). Oko 87% apiksabana veže se na proteine plazme. Njegovo poluvrijeme eliminacije iznosi otprilike 12 sati, dok se 27% lijeka eliminira putem bubrega, a 63% putem fecesa (10).

Primjena edoksabana u kliničkoj praksi predstavljena je u kliničkoj studiji Effective Anticoagulation with

versible factor Xa inhibitor, interrupting both intrinsic and extrinsic coagulation pathways, thus inhibiting thrombin formation and thrombus development itself (10). The plasma elimination half-life is about 9 hours in younger individuals and between 11 and 13 hours in the elderly. Two-thirds of the drug is degraded metabolically, with one-half eliminated by the kidneys and the other by the gut. The remaining one-third is excreted directly by the kidneys into the urine as an unchanged active substance. Bodyweight, age, and sex do not affect the pharmacodynamic properties of the drug (10). Rivaroxaban has been tested in clinical studies at a dose of 2.5 mg for both primary and secondary prevention of cardiovascular events, as well as in the treatment of peripheral arterial disease (22).

The clinical studies "Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)" and "Apixaban for Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY)" established apixaban in clinical practice (23,24). After 3 to 4 hours of ingestion, it will achieve a maximum value in plasma, with a dominant hepatic clearance. Studies state that apixaban is the safest NOAC in terms of bleeding risk, although it is difficult to draw this type of conclusion given the non-uniformity of the sample in initiation studies. It is a selective, reversible factor Xa inhibitor that prevents thrombin formation (10). About 87% of apixaban binds to plasma proteins. Its elimination half-life is approximately 12 hours, whereas 27% of it is eliminated through the kidneys and 63% through the feces (10).

The clinical study "Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48)" established edoxaban in clinical practice. It reaches peak plasma concentration in 1–2 hours after the ingestion (25). Edoxaban is a selective inhibitor of factor Xa. Its bioavailability is about 62%, and the plasma half-life is about 10 to 14 hours (25).

The only NOAC to receive an indication for use in an acute endangered patient is betrixaban, with the study "Acute Medical Ill VTE (Venous Thromboembolism) Prevention with Extended Duration Betrixaban (APEX)". Its bioavailability is approximately 34%, and the plasma half-life is between 19 to 27 hours, with the lowest renal clearance (26).

Regarding antidotes, idarucizumab is used to reverse the effect of dabigatran, while andexanet alfa is used for rivaroxaban and apixaban (10). Aripazine is under ongoing investigation for use as a factor Xa inhibitor. In the absence of options, the use of PCC or activated PCC is meaningful (10). Dosage and pharmacological properties of NOAC are listed in Table 3, effects on Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48). Vršna koncentracija lijeka u plazmi postiže se 1 do 2 sata nakon ingestije (25). Edoksaban je selektivni inhibitor faktora Xa. Bioraspoloživost mu je oko 62%, a poluvrijeme eliminacije u plazmi između 10 i 14 sati (25).

Jedini NOAK koji je indiciran za primjenu kod akutno ugroženih pacijenata je betriksaban, čija je primjena predstavljena u studiji Acute Medical Ill VTE (venous Thromboembolism) Prevention with Extended Duration Betrixaban (APEX). Bioraspoloživost mu je oko 34%, a poluvrijeme eliminacije u plazmi između 19 i 27 sati, s najnižim bubrežnim klirensom (26).

Što se tiče antidota, idarucizumab se upotrebljava za poništavanje učinka dabigatrana, dok se andeksanet alfa upotrebljava za rivaroksaban i apiksaban (10). U tijeku je ispitivanje aripazina za upotrebu kao inhibitora faktora Xa. U nedostatku drugih opcija, smislenom se smatra upotreba koncentrata protrombinskog kompleksa (PCC) ili aktiviranog PCC-a (10). Doziranje i farmakološka svojstva NOAK-a navedeni su u tablici 3, učinci na laboratorijske parametre navedeni su u tablici 4, dok je doziranje u različitim indikacijama objašnjeno u tablici 5. Ne savjetuje se uporaba NOAK-a u slučaju implantiranih mehaničkih valvula ili umjerene i teške mitralne stenoze. Nadalje, nema dovoljno podataka za primjenu NOAK-a u bolesnika s teškom aortnom stenozom, perkutanom transluminalnom aortnom valvuloplastikom ili transkateterskom implantacijom aortnog zalistka. Za bolesnike kod kojih je antikoagulantna terapija kontraindicirana treba razmotriti postavljanje filtera u donju šuplju venu. Indicirana je u bolesnika s rekurentnom plućnom embolijom (PE) unatoč primjeni antikoagulantne terapije, te u bolesnika s plućnom hipertenzijom i zatajenjem srca. Njihova se primjena može razmotriti u bolesnika s trombima u području zdjelice ili donje šuplje vene s pokretnim dijelovima, u rekurentnoj DVT prije planiranog kirurškog zahvata, prije plućne trombendarterektomije i u bolesnika s rekurentnim embolijama kojima je dijagnosticiran rak.

Odluka o tome koje sredstvo upotrebljavati ovisi o riziku od krvarenja. U literaturi su primijećene veće stope gastrointestinalnog krvarenja u bolesnika koji su uzimali rivaroksaban (3,2 na 100 pacijent-godina liječenja) nego s drugim lijekovima (2,5 za apiksaban i 1,9 za dabigatran, možda zbog primjene doze lijeka jednom dnevno) (27). U budućnosti će se vjerojatno pojaviti sredstva koja će inhibirati faktor XI. Milveksian (milvexian) je ispitivani NOAK koji cilja faktor XI, a pri ispitivanju lijeka za određivanje doze, stope postoperativne VTE bile su niže pri primjeni milveksiana u usporedbi sa standardnom profilaktičkom dozom

Table 3. The NOACs in clinical practice (according to reference No.10)
Tablica 3. Novi oralni antikoagulansi u kliničkoj praksi (u skladu s literaturom br. 10)

New oral anticoagulant / Novi oralni koagulans	Dabigatran	Rivaroxaban / Rivaroksaban	Apixaban / Apiksaban	Edoxaban / Edoksaban	Betrixaban / Betriksaban
Initial clinical study / Početna klinička studija	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE-AF	APEX
Pharmacological mechanism of action / Farmakološki mehanizam djelovanja	Direct thrombin inhibitor / Izravni inhibitor trombina	Factor Xa inhibitor / Inhibitor faktora Xa	Factor Xa inhibitor / Inhibitor faktora Xa	Factor Xa inhibitor / Inhibitor faktora Xa	Factor Xa inhibitor / Inhibitor faktora Xa
Bioavailability (%) / Bioraspoloživost (%)	6,5	80 – 100	50	62	34
Half-life (hours) / Poluvrijeme eliminacije (u satima)	12 – 14	5 – 13	8 – 15	9 – 11	19 – 27
Dose (mg) / Doza (mg)	110; 150	2,5; 10; 15; 20	2,5; 5	30; 60	40; 20
Dosing regimen / Doziranje	BID	OD	BID	OD	BID
CYP450 metabolism / CYP450 u metabolizmu lijekova	No / Ne	Yes / Da	Yes / Da	Yes / Da (<10 %)	No / Ne (<1 %)
CYP3A4/5	–	Yes / Da	Yes / Da	Yes / Da (<10 %)	–
CYP2J2	–	Yes / Da	Yes / Da	–	–
Renal clearance (%) / Bubrežni klirens (%)	85	66	27	50	17,8
CrCl 30 – 50 ml/min	2 x 110 mg once a day / 2 x 110 mg jedanput na dan	15 mg once a day / 15 mg jedanput na dan	2.5 mg twice a day or 5 mg twice a day / 2,5 mg dvaput na dan ili 5 mg dvaput na dan	30 mg once a day / 30 mg jedanput na dan	40 mg once a day / 40 mg jedanput na dan
CrCl 15 – 29 ml/min	Contraindicated / Kontraindiciran	15 mg once a day / 15 mg jedanput na dan	2.5 mg twice a day / 2,5 mg dvaput na dan	30 mg once a day / 30 mg jedanput na dan	40 mg once a day / 40 mg jedanput na dan
CrCl < 15 ml/min	Contraindicated / Kontraindiciran	Contraindicated / Kontraindiciran	Contraindicated / Kontraindiciran	Contraindicated / Kontraindiciran	Contraindicated / Kontraindiciran

CrCl – creatine clearance / kreatininski klirens; OD: once a day / jedanput na dan; BID: twice a day / dvaput na dan

laboratory parameters are mentioned in Table 4, while dosage in different indications is explained in Table 5. NOACs are not advised to be used in case of implanted mechanical valves or moderate and severe mitral stenosis. Moreover, insufficient data is available for the use of NOACs in patients with severe aortic stenosis, percutaneous transluminal aortic valvuloplasty, or transcatheter aortic valve implantation. For patients in whom anticoagulant therapy is contraindicated, the use of inferior vena cava filters should be considered. It is indicated in patients with recurrent PE attacks, despite anticoagulant therapy, in patients with pulmonary hypertension and heart failure. Their use may be considered in patients with pelvic or inferior vena cava thrombi with mobile parts, in recurrent DVT before planned surgery, prior to pulmonary thrombendarterectomy, and in patients with recurrent emboli who are diagnosed with cancer.

enoksaparina (28). Uz to, abelacimab, monoklonsko antitijelo koje sprječava aktivaciju faktora XI, smanjilo je stopu postoperativne VTE na učinkovitiji način od NMH (29).

ANTIKOAGULANSI U REUMATSKIM BOLESTIMA

Bolesnici s reumatoidnim artritisom (RA) imaju povećan rizik od VTE koji je vjerojatno povezan s osnovnom upalom, dok kliničari često gledaju na reumatske bolesti kao na stanja hiperkoagulacije (30–36). Rizik od pojave VTE kod sistemskih autoimunih bolesti prikazan je u tablici 6. Indikacije za primjenu antagonista vitamina K prikazane su u tablici 7. Indikacije u kojima bi se novi oralni antikoagulansi (NOAK) trebali upotrebljavati kao prva opcija prikazane su u tablici 8. Stanja u kojima antikoagulantna terapija nije korisna prikazana su u tablici 9. Interakcije lijek – lijek između

Table 4. Laboratory monitoring of NOACs and their effect on certain parameters (according to reference No.10)
Tablica 4. Laboratorijsko praćenje NOAK-a i njihov učinak na određene parametre (u skladu s literaturom br. 10)

	Dabigatran	Apixaban / Apiksaban	Edoxaban / Edoksaban	Rivaroxaban / Rivaroksaban
Prothrombin time (PT) / Protrombinsko vrijeme (PV)	+	(+)	+ (+)	++ (+)
Activated partial thromboplastin time (aPTT) / Aktivirano parcijalno tromboplastinsko vrijeme (APTV)	++ (+)	(+)	+	+
Activated clotting time (ACT) / Aktivirano vrijeme zgrušavanja (AVZ)	+ (+)	+	+	+
Thrombin time (TT) / Trombinsko vrijeme (TV)	+++	–	–	–

Table 5. Dosing of NOACs according to indications (according to reference No.10)
Tablica 5. Doziranje NOAK-a prema indikacijama (u skladu s literaturom br. 10)

Dabigatran
1. Stroke prevention in atrial fibrillation – 150 mg BID (after PCI in dual therapy with clopidogrel without dose reduction) / Prevencija moždanog udara kod atrijske fibrilacije – 150 mg BID (nakon perkutane koronarne intervencije (PCI) u dvojnoj terapiji klopidogrelom bez smanjenja doze) 2. VTE prophylaxis – 220 mg OD / Profilaksa venske tromboembolije (VTE) – 220 mg OD 3. VTE treatment – after initial parenteral therapy / Liječenje VTE – nakon inicijalne parenteralne terapije 4. Patients aged ≥ 80 years or having eGFR of 30–50 mL/min – 110 mg BID / Bolesnici u dobi od ≥ 80 godina ili s procijenjenom brzinom glomerularne filtracije (eGFR) u rasponu od 30 – 50 ml/min – 110 mg BID
Rivaroxaban / Rivaroksaban
1. Stroke prevention in atrial fibrillation – 20 mg OD (after PCI in triple therapy 15 mg OD) / Prevencija moždanog udara kod atrijske fibrilacije – 20 mg OD (nakon perkutane koronarne intervencije (PCI) u trojnoj terapiji u dozi od 15 mg OD) 2. VTE treatment – 15 mg BID for 3 weeks, then 20 mg OD up to 6 months, after that, consider 10 mg OD / VTE prophylaxis – 10 mg OD / Profilaksa venske tromboembolije (VTE) – 10 mg OD 3. Liječenje VTE – 15 mg BID tijekom 3 tjedna, zatim 20 mg OD u trajanju do 6 mjeseci, nakon toga razmotriti dozu od 10 mg OD 4. Reduction of risk of MACE (CV death, MI, and stroke) in chronic CAD or PAD – 2.5 mg BID (with an antiaggregant drug) / Smanjenje rizika od velikih kardiovaskularnih događaja (MACE) (KV smrt, MI i moždani udar) kod kronične koronarne bolesti srca (KBS) ili bolesti perifernih arterija (BPA) – 2,5 mg BID (s antiagregacijskim lijekom) 5. Patients aged ≥ 80 years or eGFR 15–49 mL/min – 15 mg OD / Bolesnici u dobi od ≥ 80 godina ili s procijenjenom brzinom glomerularne filtracije (eGFR)u rasponu od 15 – 49 ml/min – 15 mg OD
Apixaban / Apiksaban
1. Stroke prevention in atrial fibrillation – 5 mg BID / Prevencija moždanog udara kod atrijske fibrilacije – 5 mg BID 2. VTE prophylaxis – 2.5 mg BID / Profilaksa venske tromboembolije (VTE) – 2,5 mg BID 3. VTE treatment – 10 mg BID for 7 days, then 5 mg BID for at least 6 months / Liječenje VTE – 10 mg BID tijekom razdoblja od 7 dana, zatim 5 mg BID tijekom razdoblja od najmanje 6 mjeseci 4. Two of three criteria present in a patient: age ≥ 80 years, weight ≤ 60 kg, and Cr ≥ 1.5 mg/dL – 2.5 mg BID / U bolesnika su prisutna dva od tri kriterija: dob ≥ 80 godina, težina ≤ 60 kg i koncentracija kreatinina (Cr) ≥ 1,5 mg/dl – 2,5 mg BID
Edoxaban / Edoksaban
1. Stroke prevention in atrial fibrillation – 60 mg OD / Prevencija moždanog udara kod atrijske fibrilacije – 60 mg OD 2. VTE prophylaxis – 60 mg OD (only proven in Asia) / Profilaksa venske tromboembolije (VTE) – 60 mg OD (dokazano samo u Aziji) 3. VTE treatment – after initial parenteral therapy / Liječenje VTE – nakon inicijalne parenteralne terapije 4. ≥ 1 of 3 criteria – concomitant use of potent P-gp inhibitors, body weight ≤ 60 kg, CrCl 30–50 mL/min – 30 mg OD / Ako je prisutno ≥ 1 od 3 kriterija – istodobna primjena snažnih inhibitora P-glikoproteina (P-gp), tjelesna težina ≤ 60 kg, kreatininski klirens (CrCl) 30 – 50 ml/min – 30 mg OD
Betrixaban / Betriksaban
1. VTE prophylaxis – 80 mg OD for 35–42 days / Profilaksa venske tromboembolije (VTE) – 80 mg OD tijekom razdoblja od 35 do 42 dana 2. VTE treatment – 160 mg OD / Liječenje venske tromboembolije (VTE) – 160 mg OD

Legend / Legenda: AF: atrial fibrillation / atrijska fibrilacija; OD: once a day / jedanput dnevno; BID: twice a day / dva puta dnevno; VTE: venous thromboembolism / venska tromboembolija; eGFR: estimated glomerular filtration rate / procijenjena brzina glomerularne filtracije; PCI: percutaneous coronary intervention / perkutana koronarna intervencija; MACE: major adverse cardiac events / veliki kardiovaskularni događaji; CV: cerebrovascular / kardiovaskularni; MI: myocardial infarction / infarkt miokarda; CAD / KBS: coronary artery disease / koronarna bolest srca; PAD / BPA: peripheral artery disease / bolest perifernih arterija; P-gp: P-glycoprotein / P-glikoprotein

Table 6. Risk of VTE in rheumatological diseases (according to references No. 30, 36)
Tablica 6. Rizik od venskog tromboembolizma (VTE) u reumatskim bolestima (u skladu s literaturom br. 30 i 36)

Disease / Bolest	Risk of VTE (%) / Rizik od venskog tromboembolizma (VTE) (%)
Rheumatoid arthritis / Reumatoidni artritis	1,17 – 1,91
Ankylosing spondylitis / Ankilozantni spondilitis	1,16 – 1,93
Systemic lupus erythematosus / Sistemski eritemski lupus	1,23 – 3,71
Systemic sclerosis / Sistemska skleroza	1,61 – 1,97
Polymyositis/dermatomyositis / Polimiozitis/dermatomiozitis	3,04 – 3,36
Sjögren syndrome / Sjögrenov sindrom	2,02 – 2,19
Polymyalgia / Polimialgija	1,91
Polyarteritis nodosa / Nodozni poliarteritis	2,57 – 3,53
Behçet disease / Behçetov sindrom	1,68

VTE – venous thromboembolism / venski tromboembolizam

Deciding on which agent to use depends on the risk of bleeding. In literature, higher rates of gastrointestinal bleeding were observed in patients taking rivaroxaban (3.2 per 100 patient-years) than with the other agents (2.5 for apixaban and 1.9 for dabigatran, perhaps due to once-daily dosing) (27). The future is likely to bring agents that will inhibit factor XI. Milvexian is an investigational NOAC that targets factor XI, and in a dose-finding trial, rates of postoperative VTE were lower with milvexian compared to standard prophylactic enoxaparin (28). Also, abelacimab, a monoclonal antibody that prevents activation of factor XI, reduced the rate of postoperative VTE more effectively than LMWH (29).

ANTICOAGULANTS IN RHEUMATOLOGICAL DISEASES

Patients with rheumatoid arthritis (RA) have an increased risk of VTE likely related to underlying inflammation, while clinicians often view rheumatic diseases as a hypercoagulable condition (30–36). The risk of VTE in systemic autoimmune diseases is presented in Table 6. Indications for using vitamin K antagonists are presented in Table 7. Indications in which NOACs should be used as the first option are presented in Table 8. Conditions where anticoagulant therapy is without benefit, are shown in Table 9. Drug interactions between anticoagulant therapy and drugs that are used in the treatment of rheumatological diseases are shown in Table 10.

Table 7. Indications for using vitamin K antagonists
Tablica 7. Indikacije za primjenu antagonista vitamina K

Antiphospholipid syndrome (acetylsalicylic acid is not enough) / Antifosfolipidni sindrom (acetilsalicilna kiselina nije dovoljna)	First VTE (INR 2–3, recurrent 3–4) / Prva pojava VTE (INR 2–3, rekurentna 3–4)
Pulmonary artery hypertension resulting from Systemic sclerosis / Plućna arterijska hipertenzija koja je posljedica sistemske skleroze	For treatment of pulmonary arterial hypertension / Za liječenje plućne arterijske hipertenzije
Kawasaki disease / Kawasakijeva bolest	Indicated / Indicirana
Polyarteritis nodosa / Nodozni poliarteritis	Indicated (along with antiphospholipid syndrome) / Indiciran (uz antifosfolipidni sindrom)

VTE – venous thromboembolism / venski tromboembolizam, INR – international ratio / internacionalni normalizirani omjer

antikoagulansa i lijekova koji se upotrebljavaju u liječenju reumatskih bolesti prikazane su u tablici 10.

Dvojbena je primjena inhibitora Janus kinaze (JAK) i rizik od VTE. Značajno veća incidencija PE zabilježena je u liječenju tofacitinibom (10 mg dva puta dnevno) u usporedbi s tofacitinibom u dozi od 5 mg ili inhibitorima faktora nekroze tumora (31). Dokazana je neravnoteža u incidenciji VTE za dnevnu dozu od 4 mg baricitiniba u odnosu na placebo, dok nema povezanosti s velikim kardiovaskularnim događajima (MACE), arterijskim trombotičkim događajima ili kongestivnim zatajenjem srca (31).

O mjerama profilakse VTE treba odlučiti unutar 24 sata od prijema u bolnicu, uz procjenu rizika (zajedno s kontraindikacijama za profilaksu). Ako se upotrebljava profilaksa VTE, enoksaparin je indiciran za primjenu u liječenju (nema indikacija za NOAK). Kontraindikacije za primjenu NOAK-a uključuju mehaničku protetičku valvulu, umjerenu do tešku mitralnu stenozu (obično reumatskog podrijetla), dok je dvojbena primjena NOAK-a u blagim do umjerenim drugim valvularnim bolestima (ograničeni podatci), teškoj aortalnoj stenozi (ograničeni podatci), hipertrofičnoj kardiomiopatiji (nema prospektivnih podataka) i perkutanoj aortnoj valvuloplastici i transkateterskoj implantaciji aortnog zalistka (ali nema prospektivnih podataka; može zahtijevati kombinaciju s jednostrukom ili dvostrukom antitrombotskom terapijom; razmotriti rizik od krvarenja) (10). Nakon popravka mitralnog zalistka i bioprostetičkog zalistka prihvatljiva je primjena NOAK-a, osim u razdoblju od prva tri mjeseca nakon operacijskog zahvata.

Čimbenici koji povećavaju hiperkoagulabilnost kod reumatskih poremećaja uključuju povećanu ekspresiju tkivnog faktora, povećane mikročestice (povišene su

Table 8. Indications in which NOACs can be used (should be the first option if we have indications for it)
Tablica 8. Indikacije u kojima se mogu upotrebljavati novi oralni antikoagulansi (NOAK) (trebali bi biti prva opcija ako za to postoje indikacije)

Rheumatoid arthritis (psoriatic) / Reumatoidni artritis (psorijatični)
Ankylosing spondylitis / Ankilozantni spondilitis
Polymyositis / Polimiozitis
Dermatomyositis / Dermatomiozitis
Polymyalgia rheumatica / Reumatska polimialgija
Sjögren syndrome / Sjögrenov sindrom
Sarcoidosis / Sarkoidoza
Systemic sclerosis / Sistemska skleroza
Systemic lupus erythematosus / Sistemski eritemski lupus
Retroperitoneal fibrosis with venous thrombosis / Retroperitonealna fibroza s venskom trombozom

Table 9. Conditions where we do not have indications for anticoagulant treatment
Tablica 9. Bolesti u kojima ne postoje indikacije za antikoagulantnu terapiju

ANCA-associated vasculitis – non-beneficial anticoagulant treatment / Vaskulitis povezan s ANCA protutijelima – beskorisno liječenje antikoagulansima
Behcet syndrome – non-beneficial anticoagulant treatment (corticosteroids and azathioprine (venous thromboembolism), cyclophosphamide or cyclosporin A (arterial involvement)) / Behçetov sindrom – beskorisno liječenje antikoagulansima (kortikosteroidi i azatioprin [venska tromboembolija], ciklofosfamid ili ciklosporin A [zahvaćenost arterija])
Giant Cell Arteritis (GCA) and Takayasu arteritis (TA) – marginal benefit of using anticoagulation together with corticosteroids in the treatment of venous thromboembolism; in TA there is a benefit of acetylsalicylic acid in the ischemia stroke prevention) / Arteritis velikih stanica (GCA) i Takayasuov arteritis (TA) – marginalna korist primjene antikoagulacijske terapije zajedno s kortikosteroidima u liječenju venske tromboembolije; u TA korisna je primjena acetilsalicilne kiseline u prevenciji ishemijskog moždanog udara
Henoch-Schönlein purpura – no indication (extremely rare incidence of venous thromboembolism) / Henoch-Schönleinova purpura – nema indikacija (izuzetno rijetka incidencija venske tromboembolije)

Janus kinase (JAK) inhibitors and the risk of VTE are questionable. A significantly higher incidence of PE was reported in treatment with tofacitinib (10 mg twice daily) compared with tofacitinib 5 mg or tumor necrosis factor inhibitors (31). Imbalance in the incidence of VTE for a 4-mg daily dose of baricitinib versus placebo was proved, while there is no link with major adverse cardiovascular events, arterial thrombotic events, or congestive heart failure (31).

VTE prophylaxis measures should be decided within 24 hours of hospital admission, with a risk assessment (along with contraindications for prophylaxis). If VTE prophylaxis is used, enoxaparin is indicated (there is no indication for NOACs). Contraindications for NOACs include mechanical prosthetic valve, moderate to severe mitral stenosis (usually of rheumatic origin), while dubious use is in mild to moderate other valvular diseases (limited data), severe aortic stenosis (limited data), hypertrophic cardiomyopathy (no prospective data) and percutaneous aortic valvuloplasty and transcatheter aortic valve implantation (but no prospective data; may require combination with single or double antiplatelets; consider bleeding risk) (10). After mitral valve repair and bioprosthetic valve, NOACs are eligible, except for the first three months postoperatively.

Factors increasing hypercoagulability in rheumatic disorders encompass increased tissue factor expression, increased microparticles (levels of platelet-derived microparticles are elevated), platelet activation, increased fibrinogen level through inflammation, hypercoagulability via complement activation and interaction with coagulation factors, reduced thrombomodulin, as well as increased plasminogen activator inhibitor-1 (PAI-1) (33–35).

razine mikročestica izvedenih iz trombocita), aktivaciju trombocita, povećanu razinu fibrinogena koja nastaje kao odgovor na upalu, hiperkoagulabilnost putem aktivacije komplementa i interakcije s faktorima koagulacije, smanjene razine trombomodulina, kao i povećani inhibitor aktivatora plazminogena-1 (PAI-1) (33–35).

Zanimljiva je činjenica da se u Behçetovom sindromu uzrokom DVT-a smatra vaskulitis, a ne hiperkoagubilnost. Cerebralna venska tromboza koja se javlja u ovih bolesnika treba se liječiti visokim dozama kortikosteroida, nakon čega slijedi smanjenje doze (metilprednizolon treba davati na dnevnoj bazi u obliku parenteralnih pulseva od 1000 mg tijekom 3 do 5 dana, nakon čega slijedi oralna primjena prednizona, počevši s dozom od 1 mg/kg dnevno, dok se doza kortikosteroida za održavanje [koji se daju oralnom primjenom] treba smanjivati tijekom 2 do 3 mjeseca, a antikoagulansi se mogu uvesti kratkotrajno) (36). Zbog toga je primjena antikoagulansa (iako je u različitim studijama utvrđeno da je njihova uloga u Behçetovom sindromu diskutabilna) dopuštena tijekom prijelaznog razdoblja, ali tek nakon što se isključi aneurizma plućne arterije i procijeni rizik od krvarenja. Primjena antikoagulantne terapije preporučuje se i u slučajevima Budd-Chiarijevog sindroma, u slučajevima odgovarajuće imunosupresivne terapije za liječenje rekurentne tromboze, kada su u pitanju drugi uzroci trombofilije: faktor V Leiden ili mutacija gena za protrombin, nedo-

Table 10. Interactions of anticoagulants drugs with drugs that are used in rheumatology (according to references No. 31,32)
Tablica 10. Interakcije antikoagulansa s lijekovima koji se upotrebljavaju u reumatologiji (u skladu s literaturom br. 31, 32)

	Warfarin / Varfarin	Dabigatran	Rivaroxaban / Rivaroksaban	Apixaban / Apiksaban	Edoxaban / Edoksaban
Methotrexate / Metotreksat	P-gp competition; no relevant interaction anticipated / P-gp kompeticija; bez očekivane relevantne interakcije	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena
Rituximab, / Rituksimab	No relevant interaction assumed / Bez pretpostavke relevantne interakcije	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena
Cyclosporine / Ciklosporin	Strong-to-moderate P-gp inhibitiion, moderate CYP3A4 inhibition; CYP3A4/P-gp competition / Snažna do umjerena inhibicija P-gp-a, umjerena inhibicija CYP3A4; CYP3A4/P-gp kompeticija	Contraindicated / Kontraindiciran	Caution required, especially in case of polypharmacy or in the presence of >_2 bleeding risk factors / Potreban oprez, osobito u slučaju polifarmacije ili u prisutnosti >_2 čimbenika rizika od krvarenja	Caution required, especially in case of polypharmacy or in the presence of >_2 bleeding risk factors / Potreban oprez, osobito u slučaju polifarmacije ili u prisutnosti >_2 čimbenika rizika od krvarenja	+73% AUC (dose reduction to 30 mg once daily by label) / +73% u područjima ispod krivulje (AUC) (smanjenje doze na 30 mg jednom dnevno prema uputama)
Dexamethasone / Deksametazon	Moderate CYP3A4 induction; CYP3A4 competition / Umjerena indukcija CYP3A4; CYP3A4 kompeticija	No clinical significance / Bez klinički značajnih promjena	Caution required, especially in case of polypharmacy or in the presence of >_2 bleeding risk factors / Potreban oprez, osobito u slučaju polifarmacije ili u prisutnosti >_2 čimbenika rizika od krvarenja	Caution required, especially in case of polypharmacy or in the presence of >_2 bleeding risk factors / Potreban oprez, osobito u slučaju polifarmacije ili u prisutnosti >_2 čimbenika rizika od krvarenja	No clinical significance / Bez klinički značajnih promjena
Prednisone / Prednizon	Moderate CYP3A4 induction; CYP3A4 competition / Umjerena indukcija CYP3A4; CYP3A4 kompeticija	No clinical significance / Bez klinički značajnih promjena	Caution required, especially in case of polypharmacy or in the presence of >_2 factors that can reduced NOAC plasma levels. / Potreban oprez, osobito u slučaju polifarmacije ili u prisutnosti >_2 čimbenika koji mogu smanjiti razinu NOAK-a u plazmi	Caution required, especially in case of polypharmacy or in the presence of >_2 factors that can reduced NOAC plasma levels. / Potreban oprez, osobito u slučaju polifarmacije ili u prisutnosti >_2 čimbenika koji mogu smanjiti razinu NOAK-a u plazmi	No clinical significance / Bez klinički značajnih promjena
Tofacitinib / Tofacitinib	Risk or severity of bleeding can be increased / Rizik ili jačina krvarenja mogu se povećati	Risk or severity of bleeding can be increased / Rizik ili jačina krvarenja mogu se povećati	Risk or severity of bleeding can be increased / Rizik ili jačina krvarenja mogu se povećati	Risk or severity of bleeding can be increased / Rizik ili jačina krvarenja mogu se povećati	Risk or severity of bleeding can be increased / Rizik ili jačina krvarenja mogu se povećati
Baricitinib	The metabolism of baricitinib can be increased when combined with warfarin. / Metabolizam baricitiniba može se povećati kada se upotrebljava u kombinaciji s varfarinom	The serum concentration of baricitinib can be increased when it is combined with dabigatran. / Serumska koncentracija baricitiniba može se povećati kada se upotrebljava u kombinaciji s dabigatranom	may decrease the excretion rate, which could result in a higher serum level / Može smanjiti brzinu izlučivanja, što može rezultirati višom serumskom koncentracijom	may decrease the excretion rate, which could result in a higher serum level / Može smanjiti brzinu izlučivanja, što može rezultirati višom serumskom koncentracijom	The serum concentration of Baricitinib can be increased when it is combined with Edoxaban. / Serumska koncentracija baricitiniba može se povećati kada se upotrebljava u kombinaciji s edoksabanom
Leflunomide / Leflunomid	Concentration can be decreased. / Koncentracija se može smanjiti	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena	No clinical significance / Bez klinički značajnih promjena
Sulfasalazine / Sulfasalazin	Increased risk of bleeding. / Povećan rizik od krvarenja	Increased risk of bleeding. / Povećan rizik od krvarenja	Increased risk of bleeding. / Povećan rizik od krvarenja	Increased risk of bleeding. / Povećan rizik od krvarenja	Increased risk of bleeding. / Povećan rizik od krvarenja

Interestingly, in Behçet's disease, vasculitis, and not hypercoagulability, is thought to be the cause of DVT. Cerebral venous thrombosis occurring in these patients should be treated with high doses of corticosteroids followed by tapering (methylprednisolone should be given as daily parenteral pulses of 1000 mg for 3–5 days followed by oral prednisone starting at 1 mg/kg daily, oral maintenance corticosteroids should be tapered over 2–3 months, while anticoagulants may be added for a short duration) (36). On that account, even though the role of anticoagulation in Behçet's disease is debatable among different studies, their use is allowed transiently, but only after a pulmonary artery aneurysm has been ruled out and the risk of bleeding has been assessed; they are also recommended in Budd-Chiari syndrome, in cases of recurrent thrombosis appropriate immunosuppressive therapy, when other causes of thrombophilia are involved – Factor V Leiden or prothrombin gene mutation, protein C, proteins S, and antithrombin III deficiencies, as well as the presence of antiphospholipid (APL) antibodies (41,42,43).

Systemic lupus erythematosus is an independent risk factor for both arterial and venous thrombotic events and is particularly associated with the presence of aPL antibodies; such patients may also use anticoagulation during high-risk periods such as pregnancy and puerperium, postoperatively or if immobilized (42,43,44). One of the manifestations of systemic lupus erythematosus is acute pericarditis, primarily related to high disease activity as well as high D-dimer, and for which NSAIDs are the mainstay of the therapy. Additionally, concurrent use of heparin with another anticoagulant is frequently regarded as a risk factor for hemorrhagic pericardial effusion, leading to cardiac tamponade in SLE patients manifesting pericarditis.

Systemic sclerosis is yet another rheumatic disease characterized by pulmonary hypertension, peripheral arterial disease, positive anti-Scl-70, and aPL antibodies, which all represent risk factors for VTE. However, anticoagulation is not indicated in scleroderma-associated pulmonary hypertension because of the unfavorable risk-to-benefit ratio due to an increased gastrointestinal bleeding rate (45). Anticoagulation, on the other hand, is beneficial in SSc patients with positive aPL antibodies. In other autoimmune rheumatic diseases, namely rheumatoid arthritis, ankylosing spondylitis, polymyositis/dermatomyositis, Sjögren syndrome, and sarcoidosis, which also lead to an increased incidence of DVT and VTE, prophylactic anticoagulation is recommended in cases with a high risk of thrombosis (45). Risk assessment of such patients is based on the Padua Prediction Score, whereby patients with a score ≥ 4 are identified as candidates who would benefit from thromboprophylaxis.

statak proteina C, proteina S i antitrombina III, kao i prisutnost antifosfolipidnih (aPL) protutijela (41,42,43).

Sistemski eritemski lupus neovisni je čimbenik rizika i za arterijske i za venske tromboze i posebno je povezan s prisutnošću aPL protutijela. U tih pacijenata također je moguća primjena antikoagulantne terapije tijekom visokorizičnih razdoblja kao što su trudnoća i puerperij, postoperativno ili ako su imobilizirani (42,43,44). Jedna od manifestacija sistemskog eritemskog lupusa jest akutni perikarditis, prvenstveno povezan s visokom aktivnošću bolesti kao i visokim D-dimerom, a za koji su nesteroidni protuupalni lijekovi glavni oslonac terapije. Osim toga, istodobna primjena heparina s drugim antikoagulansom često se smatra čimbenikom rizika za hemoragični perikardijalni izljev, što uzrokuje tamponadu srca u pacijenata sa sistemskim eritemskim lupusom u kojih se javljaju manifestacije perikarditisa.

Sistemska skleroza još je jedna reumatska bolest koju karakteriziraju plućna hipertenzija, bolest perifernih arterija, pozitivna anti-Scl-70 i aPL protutijela, a sve prethodno navedene karakteristike predstavljaju čimbenike rizika za VTE. Međutim, antikoagulacija nije indicirana kod plućne hipertenzije povezane sa sklerodermijom zbog nepovoljnog omjera rizika i koristi zbog povećane stope gastrointestinalnog krvarenja (45). Antikoagulacija je, s druge strane, korisna u bolesnika sa sistemskom sklerozom s pozitivnim aPL protutijelima. Kod drugih autoimunih reumatskih bolesti, poput reumatoidnog artritisa, ankilozantnog spondilitisa, polimiozitisa/dermatomiozitisa, Sjögrenovog sindroma i sarkoidoze, koje također dovode do povećane incidencije DVT i VTE, preporučuje se profilaktička antikoagulanta terapija u bolesnika s visokim rizikom od tromboze (45). Procjena rizika takvih bolesnika temelji se na bodovnom sustavu Padua (Padua Prediction Score), pri čemu se bolesnici s rezultatom ≥ 4 identificiraju kao kandidati koji bi imali koristi od tromboprofilakse.

Bolesnici s vaskulitisom povezanim s aktivnim antineutrofilnim citoplazmatskim protutijelima (ANCA) u stanju su hiperkoagulacije i imaju vrlo visok rizik od razvoja VTE. Ovaj rizik vjerojatno ostaje povišen, iako u puno manjim razmjerima, tijekom remisije (38). Ne postoje dostupne određene smjernice za liječenje VTE i/ili plućne embolije u bolesnika s vaskulitisom povezanim s ANCA protutijelima (AAV) (38). U bolesnika s apsolutnim kontraindikacijama za antikoagulantnu terapiju preporučuje se postavljanje filtera u donju šuplju venu (36). Antitrombotska / antikoagulantna terapija prije dijagnoze arteritisa velikih stanica (GCA) nije bila povezana sa smanjenjem teških ishemijskih komplikacija (36). U Takayasuovom arteritisu (TA) čini se da primjena antitrombotske terapije ima zaštitni učinak protiv ishemijskih događaja, dok izgleda da niti

Patients with active antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis are in hypercoagulable states and have a very high risk of VTE. This risk probably remains elevated, although to a much lower degree, during remission (38). No specific guidelines are available for VTEs and/or pulmonary embolism treatment in ANCA-Associated Vasculitis (AAV) patients (38). Insertion of vena cava filter is recommended in patients with absolute contraindications for anticoagulation therapy (36). Antiplatelet/anticoagulant therapy prior to the diagnosis of Giant cell arteritis (GCA) was not associated with a reduction in severe ischemic complications (36). In Takayasu's Arteritis (TA), the use of antiplatelet treatment appears to have a protective effect against ischemic events, while neither anticoagulants nor corticosteroids/immunosuppressive drugs seem to be able to prevent cardiovascular events (36).

Rheumatic heart disease (RHD), specifically rheumatic mitral stenosis, is often complicated by AF, and in these patients, oral anticoagulant therapy is imperative regardless of the stenosis severity and the CHA2DS2-VASc score (37). In rheumatic mitral stenosis patients, permanent or paroxysmal AF is a Class I indication for anticoagulation using vitamin K antagonists. Conversely, non-vitamin K antagonist oral anticoagulants (NOACs) are not recommended in patients with moderate-to-severe mitral stenosis (IIIC) owing to the scarcity of data but are now considered in guidelines for patients who develop AF on aortic valve diseases or mitral regurgitation due to rheumatic disease (37,38,39). Individuals with RHD who have a history of stroke or another cardioembolic complication are at increased risk for experiencing recurrent episodes and should be anticoagulated (37).

Indications for rheumatic heart disease anticoagulation include a history of cardioembolic complications such as ischemic stroke, AF, left atrial spontaneous contrast or thrombus in left appendage on echocardiography, mechanical valve implantation, as well as transiently following postoperative valve repair or bioprosthetic implantation (37,38,39).

Efficacy, risk of bleeding, safety, reversibility, and pregnancy suitability are all essential factors to be accounted for when choosing an anticoagulant agent and managing RHD patients. Essentially, warfarin remains the cornerstone of anticoagulation in RHD, owing to the limited evidence of other drugs' efficacy. Warfarin is the treatment of choice for preventing valve thrombosis and thromboembolic complications following mechanical valve implantation.

Anticoagulation requisite in pregnancy due to mechanical valve replacement or AF can be attained with warfarin or heparin (40). Unfractionated or LMWH is mainly reserved for individuals who need anticoagula-

antikoagulansi niti kortikosteroidi / imunosupresivni lijekovi ne mogu spriječiti kardiovaskularne događaje (36).

Reumatska bolest srca, točnije reumatska mitralna stenoza, često se javlja uz komplikacije zbog atrijske fibrilacije (AF), te je u ovih bolesnika oralna antikoagulantna terapija obvezna bez obzira na težinu stenoze i CHA2DS2-VASc bodovanje (37). U bolesnika s reumatskom mitralnom stenozom, trajna ili paroksizmalna AF indikacija je klase I za antikoagulaciju uz upotrebu antagonista vitamina K. Suprotno tomu, oralni antikoagulansi (NOAK) koji nisu antagonisti vitamina K ne preporučuju se u bolesnika s umjerenom do teškom mitralnom stenozom (stadij IIIC) zbog nedostatka podataka, ali se sada razmatraju u smjernicama za bolesnike koji razviju AF zbog bolesti aortnog zalistka ili mitralnu regurgitaciju zbog reumatske bolesti (37,38,39). Bolesnici s reumatskim bolestima srca koji u anamnezi imaju moždani udar ili neku drugu kardioembolijsku komplikaciju izloženi su povećanom riziku od rekurentnih epizoda bolesti i trebaju uzimati antikoagulantnu terapiju (37).

Indikacije za primjenu antikoagulantne terapije u bolesnika s reumatskim bolestima srca uključuju anamnezu kardioembolijskih komplikacija kao što su ishemijski moždani udar, AF, spontani kontrast lijevog atrija ili tromb u artikuli lijevog atrija na ehokardiografiji, implantacija mehaničke valvule, kao i prijelazno razdoblje nakon postoperativnog popravka zalistka ili implantacije bioprotetskog zalistka (37,38,39).

Učinkovitost, rizik od krvarenja, sigurnost, reverzibilnost i prikladnost za primjenu u trudnoći ključni su čimbenici koje treba uzeti u obzir pri odabiru antikoagulansa i liječenju bolesnika s reumatskim bolestima srca. Zbog ograničenih dokaza o učinkovitosti drugih lijekova, varfarin ostaje temeljni antikoagulans za primjenu u liječenju reumatskih bolesti srca. Varfarin je lijek koji je prvi odabir u prevenciji tromboze zalistaka i tromboembolijskih komplikacija nakon implantacije mehaničke valvule.

Antikoagulacijska terapija potrebna u trudnoći zbog zamjene valvule mehaničkom valvulom ili AF može se postići primjenom varfarina ili heparina (40). Nefrakcionirani heparin ili NMH uglavnom je rezerviran za bolesnike kojima je potrebna antikoagulacijska terapija tijekom trudnoće ili kada je potrebna brza reverzibilnost u perioperativnom razdoblju ili u slučaju krvarenja. Međutim, iznimka se odnosi na bolesnice s mehaničkim srčanim valvulama, kod kojih se antagonisti vitamina K (VKA) mogu razmatrati kao opcija za primjenu tijekom trudnoće jer, za razliku od heparina, imaju manju vjerojatnost za razvoj tromboze zalistka i manju vjerojatnost da će doći do smrti majke (40). Paralelno, prema preporuci klase I, pacijentice s mehaničkim srčanim valvulama trebaju uzimati male doze

tion during pregnancy or when quick reversibility is required in the perioperative period or the case of bleeding. However, an exception applies to patients with mechanical heart valves, in whom VKAs may be considered an option during pregnancy because, as opposed to heparins, they carry a lesser likelihood of valve thrombosis and maternal death (40). In parallel, by Class I recommendation, patients with MHV should take low-dose aspirin (75–100 mg per day) during the second and third trimesters of pregnancy, in addition to VKAs. LMWH should therefore not be used in pregnant women with rheumatic heart disease and ensuing mechanical heart valves unless weekly monitoring of anti-Xa levels and dose adjustments of LMWH are made, as renal clearance is increased during pregnancy.

In antiphospholipid syndrome (APS) patients presenting with VTE, unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) is the standard first-line therapy, followed by VKA with INR target range 2.0–3.0. Anticoagulation for APS patients with unprovoked VTE ought to be long-term because of the high risk of thrombosis recurrence after discontinuation (41,42,43,44). Recurrent thrombosis with VKA treatment at therapeutic INR is a noted complication of APS, but it can be controlled by increasing the INR target range, switching to LMWH, or adding low-dose aspirin. To prevent pregnancy complications in women with obstetrical APS, a combination of prophylactic dose of LMWH (or prophylactic dose of UFH) and low-dose aspirin is commonly indicated (41,42,43,44). It is noteworthy to mention that, for isolated microhemorrhages, anticoagulant therapy could be a confounding factor because of microvascular damage in APS patients and aPL carriers.

Furthermore, Coronavirus disease (COVID-19) has affected a wide range of rheumatological patients, including those diagnosed with systemic lupus erythematosus, juvenile idiopathic arthritis, Still's disease, as well as catastrophic antiphospholipid syndrome (CAPS), mainly through mechanisms related to the cytokine release syndrome. Thereupon, anticoagulation is invaluable in the management of complicated and severely ill patients due to the uncontrolled release of pro-inflammatory mediators, and in particular, COVID-19 patients with catastrophic antiphospholipid syndrome (CAPS) should be handled with thromboprophylaxis or full-dose therapeutic anticoagulation. Moreover, if COVID-19 patients were on antithrombotic medications for a previously diagnosed thrombotic disease, their treatment should continue as prescribed. If there are no contraindications, patients on vitamin K antagonists who have not had recent stable INRs, and are unable to undergo INR testing, should be transitioned to NOACs; if NOACs are neither ap-

aspirina (75 – 100 mg dnevno) tijekom drugog i trećeg tromjesečja trudnoće, uz primjenu antagonista vitamina K (VKA). NMH se stoga ne smije primjenjivati u trudnica s reumatskom bolešću srca i posljedičnim mehaničkim srčanim valvulama osim ako se ne vrši tjedno praćenje razine anti-Xa aktivnosti i prilagodba doze NMH, budući da je bubrežni klirens povećan tijekom trudnoće.

U bolesnika s antifosfolipidnim sindromom (APS) koji imaju VTE, nefrakcionirani heparin (UFH) ili niskomolekularni heparin (NMH) predstavlja standardnu prvu liniju terapije, nakon čega slijedi primjena antagonista vitamina K (VKA) s ciljnim rasponom INR 2,0 – 3,0. Antikoagulantna terapija za bolesnike s antifosfolipidnim sindromom (APS) i neprovociranim venskim tromboembolizmom (VTE) trebala bi biti dugotrajna zbog visokog rizika od recidiva tromboze nakon prekida terapije (41,42,43,44). Rekurentna tromboza s liječenjem antagonistima vitamina K (VKA) pri terapijskom INR-u poznata je komplikacija APS-a, ali se može kontrolirati povećanjem ciljnog raspona INR-a, prelaskom na terapiju NMH ili uvođenjem niske doze aspirina. Kako bi se spriječile komplikacije u trudnoći kod žena s opstetričkim APS-om, obično je indicirana kombinacija profilaktičke doze NMH (ili profilaktičke doze UFH) i niske doze aspirina (41,42,43,44). Bitno je spomenuti da za izolirana mikrokrvarenja antikoagulantna terapija može biti zbunjujući čimbenik zbog mikrovaskularnih oštećenja u bolesnika s APS-om i nositelja aPL protutijela.

Nadalje, koronavirus (COVID-19) je utjecao na bolesnike koji pate od raznih reumatskih bolesti, uključujući one kojima je dijagnosticiran sistemski eritemski lupus, juvenilni idiopatski artritis, Stillova bolest, kao i katastrofalni antifosfolipidni sindrom (CAPS), uglavnom putem mehanizama povezanih sa sindromom otpuštanja citokina. Stoga je antikoagulantna terapija od neprocjenjive važnosti u liječenju kompliciranih i teško bolesnih pacijenata zbog nekontroliranog otpuštanja proupalnih medijatora, a posebice u slučaju bolesnika oboljelih od COVID-19 s katastrofalnim antifosfolipidnim sindromom (CAPS) koje treba liječiti tromboprofilaksom ili terapijom uz primjenu pune doze antikoagulansa. Nadalje, ako su pacijenti oboljeli od COVID-19 uzimali antitrombotike za prethodno dijagnosticiranu trombotičku bolest, njihovo liječenje treba nastaviti na propisani način. Ako ne postoje kontraindikacije, pacijente koji se liječe primjenom antagonista vitamina K, koji nedavno nisu imali stabilne INR-ove i ne mogu se podvrgnuti INR testiranju, treba prebaciti na liječenje novim oralnim antikoagulansima (NOAK). Ako NOAK nisu niti odobreni niti dostupni, kao alternativna opcija može se primijeniti NMH (enoksaparin 40 mg/dan) (10,11,46).

proved nor available, LMWH (enoxaparin 40 mg/day) can be used as an alternativ (10,11,46).

CONCLUSION

Decision-making on the choice of anticoagulation relies heavily on risk assessment of patients as well as the type of disease, its activity and severity, and comorbidities, with special consideration given to possible drug-drug interactions. The use of NOAC should be based on an individual approach to the patient. Occasionally, circumstances require the use of NOAC in different spheres where there was no primary indication. There are recommendations for treating rheumatological patients, owing to the occurrence of thromboembolic events, which could be attributed to inadequate dosing, monitoring, and poor patient adherence resulting in subtherapeutic anticoagulation. The inclusion of anticoagulants in the treatment of rheumatology patients represents a challenging issue but with considerable space for scientific research.

Conflict of interest statement: The authors declare no conflict of interest.

ZAKLJUČAK

Donošenje odluke o izboru antikoagulansa uvelike ovisi o procjeni rizika bolesnika kao i o vrsti bolesti, njezinoj aktivnosti i težini te komorbiditetima, s posebnim osvrtom na moguće interakcije lijek – lijek. Primjena novih oralnih antikoagulansa (NOAK) treba se temeljiti na individualnom pristupu svakom bolesniku. Povremeno okolnosti zahtijevaju primjenu NOAK-a u različitim sferama u kojima nije bilo primarne indikacije. Postoje preporuke za liječenje reumatoloških bolesnika, zbog pojave tromboembolijskih incidenata koji se mogu pripisati neadekvatnom doziranju, praćenju i slaboj adherenciji bolesnika, što rezultira subterapijskom primjenom antikoagulansa. Uvođenje antikoagulansa u liječenje reumatoloških bolesnika predstavlja velik izazov, ali to je i tema koja ima velik potencijal u znanstvenom istraživanju.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

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