# KRVARENJE UDRUŽENO SA PRIMENOM DIREKTNIH ORALNIH ANTIKOAGULANSA

# HEMORRHAGIC COMPLICATIONS ASSOCIATED WITH THE USE OF DIRECT ORAL ANTICOAGULANTS

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## SAŽETAK

Ključ lečenja i prevencije venskog tromboembolizma (VTE) predstavlja primena antikoagulantne terapije. Dugi niz godina, kamen temeljac je predstavljala primena antagonista vitamina K (VKA) koja je bila povezana sa mnogobrojnim preprekama i komplikacijama. Uvođenjem nove generacije direktnih oralnih antikoagulantnih lekova (DOAK) neke od prepreka, kao što su brzina postizanja terapijskog efekta, fiksna doza, inhibicija manjeg broja koagulacionih faktora, manji broj interakcija sa lekovima su prevaziđene, uz zadržavanje adekvatnog bezbedonosnog profila. Stoga su se DOAK vrlo brzo našli u preporukama za lečenje i prevenciju VTE, kao i za prevenciju ishemijskih komplikacija kod pacijenata sa atrijalnom fibrilacijom bez mehaničke valvule. Ipak, primenom antikoagulantne terapije, narušava se homeostaza, te lečenjem ili sprečavanjem VTE sa jedne strane, povećavamo rizik od krvarenja sa druge. Brojne studije, kako randomizovane kliničke, tako i retrospektivne su analizirale rizik od krvarenja nakon primene DOAK u poređenju sa VKA, kao i između DOAK međusobno. Nedvosmisleno je pokazano da je rizik od intrakranijalne hemoragije manji sa DOAK u poređenju sa VKA, dok je većina studija pokazala da je i rizik od major krvarenja isti ili čak i manji sa DOAK. Upravo veća bezbednost, efikasnost, kao i jednostavna primena DOAK su dovela do toga da se sve češće primenjuju u svakodnevnoj kliničkoj praksi, te se čini da će VKA postepeno postati deo istorije, odnosno da će se koristiti samo u određenoj, jasno definisanoj populaciji.

**Ključne reči:** krvarenje, venski tromboembolizam, antikoagulansi

## ABSTRACT

The milestone of treating and preventing venous thromboembolism (VTE) is the application of anticoagulants. For many years the cornerstone was the use of vitamin K antagonists (VKAs), but it was associated with numerous obstacles and complications. With the introduction of a new generation of direct oral anticoagulants (DOAC), some of the difficulties, such as delayed onset/offset of the action, individual dose modifications, inhibition of several coagulation factors, need for frequent monitoring of prothrombin time, multiple drug interactions, have been overcome, while maintaining an adequate safety profile. Therefore, DOACs have rapidly replaced VKAs as a standard of care in the treatment and prevention of VTE, as well as in the prevention of ischemic complications in patients with non-valvular atrial fibrillation. However, the expected consequence of the use of anticoagulant drugs is increased bleeding risk. Several randomized and retrospective studies have analyzed the risk of bleeding associated with the use of DOACs compared to VKAs and between DOACs. It has been clearly shown that intracranial hemorrhage risk is decreased with DOAC compared to VKA, while most studies have shown that the risk of major bleeding is the same or even lower with DOAC. Considering DOAC's efficacy, excellent safety, and simple application compared with VKAs, it does not surprise their increasingly frequent application in everyday clinical practice. Will VKAs gradually become a part of history, or will their use be limited to a specific, clearly defined population? The time has to show.

**Keywords:** bleeding risk, venous thromboembolism, anticoagulants

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## UVOD

Antagonisti vitamina K (VKA) su kamen temeljac u prevenciji i lečenju venske tromboembolije (VTE) više od pola veka. Međutim, njihova upotreba takođe ima brojne poteškoće, kao što su odloženi početak/prestanak delovanja, individualna varijabilnost doze, brojne interakcije lekova i hranljivih materija i potreba za čestim praćenjem terapijskog opsega [1]. Sve navedeno je dovelo do stvaranja novih lekova, direktnih oralnih antikoagulanasa (DOAK), koji blokiranjem faktora IIa (dabigatran) ili faktora Xa (rivaroksaban, edoksaban, apiksaban) postižu željeni antikoagulantni efekat [2]. DOAK, kao klasa lekova, efikasni su i bezbedni, barem kao VKA, sa fiksnim rasporedom doza, manjim brojem interakcija lek-lek i bez potrebe za praćenjem [2]. Navedene prednosti dovele su do toga da su DOAK u velikoj meri zamenili VKA, pa se sada sve više koriste u prevenciji i lečenju VTE, kao i u prevenciji ishemijskog moždanog udara kod pacijenata sa ne-valvularnom atrijalnom fibrilacijom (NVAF) [2,3]. Međutim, VKA su i dalje poželjna opcija kod pacijenata sa valvularnom AF i antifosfolipidnim sindromom [4]. Prirodna posledica antikoagulantnog dejstva i VKA i DOAK je krvarenje, koje može biti teško i ponekad opasno po život. Lečenje krvarenja povezanih sa DOAK može biti izazovno iz nekoliko razloga: rutinski testovi koagulacije ne pokazuju antikoagulacionu aktivnost, reverzibilni agensi često nisu dostupni, a u nekim slučajevima mogu biti čak i protrombotični [5]. Sa kliničke tačke gledišta, ključno je utvrditi koliko često se može očekivati krvarenje povezano sa upotrebom DOAK i koji su prediktivni faktori za ovu komplikaciju. Na osnovu toga bi se mogle napraviti dalje strategije i planovi lečenja.

## RIZIK OD KRVARENJA KOD PACIJENATA SA AKUTNOM VTE

Nekoliko randomizovanih kontrolisanih studija (RCT) uporedilo je efikasnost i bezbednost različitih DOAK sa VKA ili heparinom niske molekularne težine (LMVH) kod pacijenata sa akutnom VTE [6]. U okviru pomenutih studija praćena je incidencija major i non-major krvarenja (Tabela 1). Major krvarenje je definisano kao klinički teško krvarenje udruženo sa smanjenjem nivoa hemoglobina za > 20 g/L, potrebom za transfuzijom ≥ 2 jedinice koncentrovanih eritrocita, krvarenje u "kritične" lokalizacije (npr. intrakranijalana, retroperitonealna) ili fatalno krvarenje. Sva druga krvarenja od kliničkog značaja okarakterisana su kao non-major krvarenja [7]. U RE-COVER studiji, koja je upoređivala bezbednost dabigatrana i varfarina, rizik od major kraveranja bio je sličan u obe grane (HR 0,82; 95% CI, 0,45-1,48, $p$ = 0,38), dok je rizik od bilo kakvog krvare-

## INTRODUCTION

Vitamin K antagonists (VKAs) have been a cornerstone in preventing and treating venous thromboembolism (VTE) for over half a century. However, their use also has numerous difficulties, such as a delayed onset/offset of action, individual dosage variability, numerous drug and nutrient interactions, and the need for frequent monitoring of the therapeutic range [1]. All of the above led to the generation of new medicines, direct oral anticoagulants (DOACs), which, by blocking Factor IIa (dabigatran) or Factor Xa (rivaroxaban, edoxaban, apixaban), achieve the desired anticoagulant effect [2]. DOACs, as a class of drugs, are effective and safe, at least as VKAs, with fixed-dose schedules, fewer drug-drug interactions, and no need for monitoring [2]. The mentioned benefits have led to the fact that DOACs have largely replaced VKAs, so they are now increasingly used in the prevention and treatment of VTE, as well as in the prevention of ischemic stroke in patients with non-valvular atrial fibrillation (NVAF) [2,3]. However, VKAs are still a preferable option in patients with valvular AF and antiphospholipid syndrome [4]. The natural consequence of the anticoagulant effect of both VKA and DOAC is bleeding, which can be severe and sometimes life-threatening. Management of DOACs associated with bleeding can be challenging for several reasons: routine coagulation tests do not demonstrate anticoagulation activity, reversible agents are often not available, and in some cases, they can even be prothrombotic [5]. From a clinical point of view, it is crucial to establish how frequently bleeding associated with DOAC use could be expected and what the predictive factors are for this complication. According to this, further strategies and treatment plans could be made.

## BLEEDING RISK IN PATIENTS WITH ACUTE VTE

Several randomized controlled trials (RCT) have compared the efficacy and safety of different DOACs with VKA or low molecular weight heparin (LMWH) in patients with acute VTE [6]. Within the mentioned studies, the incidence of major and non-major bleeding was monitored (Table 1). Bleeding was defined as major if it was clinically overt and if it was associated with a fall in the hemoglobin level of at least 20 g per liter, resulted in the need for transfusion of 2 or more units of red cells, involved a critical site (e.g., intracranial, retroperitoneal), or was fatal. All other hemorrhages of clinical importance were characterized as non-major bleedings [7]. In the RE-COVER study, which compared the safety of dabigatran versus warfarin, the risk of major bleeding was similar in both arms (HR 0.82; 95% CI, 0.45-1.48, $p$ = 0.38), while the

nja bio niže u grani tretiranoj dabigatranom (HR 0,71, 95% CI, 0,59-0,85, $p < 0,001$) [8]. Dve studije, EINSTEIN-PE i EINSTEIN-DVT, i njihova objedinjena analiza, upoređivale su bezbednost rivaroksabana u poređenju sa enoksabanom ili varfarinom. Pokazalo se da je rizik od major krvarenja u grani lečenoj sa rivaroksabanom značajno manji u odnosu na standardnu terapiju (HR 0,54, 95% CI, 0,37-0,79, $p = 0,002$), a apsolutni rizik od krvarenja smanjen je za 0,8% u korist rivaroksabana [9-11]. Podaci iz studije AMPLIFY pokazali su superiornost apiksabana u odnosu na varfarin kada su major krvarenja u pitanju (HR 0,31, 95% CI, 0,17-0,55, $p < 0,001$), dok je Hokusai-VTE studija pokazala da je incidencija major krvarenja slična između konvencionalne terapije i edoksabana (HR 0,84, 95% CI, 0,59-1,21, $p = 0,35$) [12,13]. Sve gore pomenute studije su pokazale da je učestalost intrakranijalnog krvarenja kod pacijenata lečenih sa DOAK, bez obzira na specifičnu vrstu korišćenog DOAK-a, niža od one sa varfarinom. Što se tiče gastrointestinalnog krvarenja, učestalost je bila nešto veća sa dabigatranom, manja sa apiksabanom, a ista sa rivaroksabanom i edoksabanom [8-13].

Iako rezultati navedenih randomizovanih studija govore u prilog DOAK, podaci iz RWE (*Real Worl Evidence*) studija su drugačiji. Tri velike RWE studije iz Sjedinjenih Američkih Država (SAD) koje su upoređivale apiksaban i varfarin, pokazale su da je učestalost major krvarenja manja kod pacijenata lečenih apiksabanom (HR 0,67-0,76). Štaviše, učestalost non-major klinički značajnog krvarenja je takođe bila niža sa apiksabanom (HR 0,77) tokom perioda praćenja od 6 meseci [14-16]. Studija sprovedena u Francuskoj na 10 440 pacijenata sa VTE lečenih sa apiksabanom i 36 922 pacijenta lečena rivaroksabanom, pokazala je da je rizik od major krvarenja manji pod apiksabanom u poređenju sa varfarinom (10 775 pacijenata), dok je sličan kod pacijenata lečenih rivaroksabanom i varfarinom tokom šestomesečnog praćenja [17]. Do sličnog zaključka kada je rivaroksaban u pitanju, došli su i autori XALIA studije u kojoj je rizik od major krvarenja pod rivaroksabanom i standardnom terapijom (enoksaban/varfarin) gotovo identičan [18]. GARFIELD-VTE opservaciona studija nije pokazala statistički značajnu razliku u pojavi bilo major ili bilo kog drugog krvarenja kod pacijenata sa VTE lečenih DOAK i VKA [19].

Rezultati i RCT i RWE studija su pokazali da većina DOAK ima identičan ili manji rizik od krvarenja kod pacijenata sa akutnom VTE u poređenju sa standardnom terapijom. Ipak, pitanje je kolika je učestalost krvarenja ukoliko se porede različiti lekovi iz DOAK grupe. Poredeći međusobno rizik od krvarenja kod pacijenata na rivaroksabanu i apiksabanu, Jin i saradnici su pokazali da je učestalost ne-intrakranijalnog krvarenja manja u

risk of any bleeding was lower in dabigatran treated arm (HR 0.71, 95% CI, 0.59-0.85, $p < 0.001$) [8]. Two studies, EINSTEIN-PE and EINSTEIN-DVT, and their pooled analysis compared the safety of rivaroxaban to enoxaban or warfarin. It was shown that the risk of major bleeding in the rivaroxaban arm was significantly lower compared to standard therapy (HR 0.54, 95% CI, 0.37-0.79, $p = 0.002$), and the absolute risk of bleeding was reduced by 0.8% in favor of rivaroxaban [9-11]. Data from the AMPLIFY study showed apixaban superiority compared to warfarin for major bleeding (HR 0.31, 95% CI, 0.17-0.55, $p < 0.001$), while the Hokusai-VTE study showed that the incidence of major bleeding was similar between edoxaban and conventional therapy (HR 0.84, 95% CI, 0.59-1.21, $p = 0.35$) [12,13]. All of the studies mentioned above demonstrated that the frequency of intracranial hemorrhage in DOAC-treated patients, despite the type of DOAC used, is lower than that of warfarin. Regarding gastrointestinal bleeding, it was slightly more familiar with dabigatran, less common with apixaban, and the same with rivaroxaban and edoxaban [8-13].

Although the results of the RCTs speak in favor of DOAC, data from RWE (Real World Evidence) studies are different. Three large RWE studies from the United States of America (USA) comparing apixaban and warfarin showed that the frequency of major bleeding was lower in patients treated with apixaban (HR 0.67-0.76). Furthermore, the frequency of non-major clinically significant bleeding was also lower with apixaban (HR 0.77) during the follow-up period of 6 months [14-16]. A study in France on 10,440 patients with VTE treated with apixaban and 36,922 patients treated with rivaroxaban reported that the risk of major bleeding was lower with apixaban than with warfarin (10,775 patients), while it was similar in patients treated with rivaroxaban and warfarin during a 6-month follow-up [17]. Regarding rivaroxaban, the authors of the XALIA study came to a similar conclusion, confirming that the risk of major bleeding was almost identical between rivaroxaban and standard therapy (enoxaban/warfarin) [18]. The GARFIELD-VTE observational study showed no statistically significant difference in the occurrence of either major or any other bleeding in patients with VTE treated with DOAC and VKA [19].

Results from both RCT and RWE studies have demonstrated that most DOACs have an identical or lower risk of bleeding in patients with acute VTE compared with standard therapy. Yet, it remains a question: are the bleeding risks associated with the use of different DOAC drugs comparable? Evaluating the risk of bleeding in patients on rivaroxaban and apixaban,

**Tabela 1.** Poređenje rizika od krvarenja između varfarina i DOAK kod pacijenata sa akutnim VTE, rezultati odabranih studija

**Table 1.** Results of selected studies comparing the risk of bleeding between DOACs and warfarin in acute VTE setting

| Studija / *Study* | Vrsta krvarenja / *Type of bleeding* | Lek / *Drug* | Rezultati / *Results* |
|---|---|---|---|
| **AMPLIFY (12) / *AMPLIFY (12)*** | Bilo koje krvarenje / *Any bleeding* | apiksaban / *apixaban* | HR 0.31, 95% CI, 0.17-0.55, $p < 0.001$ |
| **Hokusai-VTE (13) / *Hokusai-VTE (13)*** | Bilo koje krvarenje / *Any bleeding* | edoksaban / *edoxaban* | HR 0.84, 95% CI, 0.59-1.21, $p = 0.35$ |
| **RE-COVER (8) / *RE-COVER (8)*** | Major krvarenje / *Major bleeding* | dabigatran / *dabigatran* | HR 0.82; 95% CI, 0.45-1.48, $p = 0.38$ |
| **RE-COVER (8) / *RE-COVER (8)*** | Bilo koje krvarenje / *Any bleeding* | dabigatran / *dabigatran* | HR 0.71, 95% CI, 0.59-0.85, $p < 0.001$ |
| **EINSTEIN-PE and EINSTEIN-DVT* (9,10,11) / *EINSTEIN-PE and EINSTEIN-DVT* (9,10,11)*** | Major krvarenje / *Major bleeding* | rivaroksaban / *rivaroxaban* | HR 0.54, 95% CI, 0.37-0.79, $p = 0.002$ |
| **RWE studije SAD (14,15,16) / *RWE studies USA (14,15,16)*** | Major krvarenje / *Major bleeding* | apiksaban / *apixaban* | HR 0.67-0.76, $p < 0.05$ |
| **RWE studije SAD (14,15,16) / *RWE studies USA (14,15,16)*** | Bilo koje krvarenje / *Any bleeding* | apiksaban / *apixaban* | HR 0.77, $p < 0.05$ |
| **RWE studija Francuska (17) / *RWE study France (17)*** | Major krvarenje / *Major bleeding* | apiksaban / *apixaban* | Niži / *lower* |
| **RWE studija Francuska (17) / *RWE study France (17)*** | Bilo koje krvarenje / *Any bleeding* | rivaroksaban / *rivaroxaban* | sličan rizik / *similar risk* |
| **XALIA* (18) / *XALIA* (18)*** | Major krvarenje / *Major bleeding* | rivaroksaban / *rivaroxaban* | Sličan rizik / *similar risk* |

* u poređenju sa varfarinom i edoksabanom
RWE - Real World Evidence (Dokazi iz kliničke prakse)

** compared to warfarin and edoxaban*
*RWE - Real World Evidence*

grani lečenoj apiksabanom [20]. Novija meta-analiza potvrdila je manju učestalost major krvarenja sa apiksabanom u poređenju sa rivaroksabanom, dok nisu uočene razlike između apiksabana i dabigatrana ili dabigatrana i rivaroksabana [21].

## RIZIK OD KRVARENJA KOD PACIJENATA SA EKSTENDIRANOM PRIMENOM DOAK NAKON VTE

Lečenje VTE se zasniva na primeni antikoagulantne terapije, a prema važećim smernicama, primarno lečenje obično traje 3-6 meseci. Kod pacijenata sa VTE izazvanim prolaznim faktorima rizika (hirurškim ili nehirurškim) terapija se završava u primarnoj fazi [22]. S druge strane, poseban oprez je potreban kod pacijenata sa hroničnim faktorima rizika ili kod onih koji su imali neprovociranu VTE, te vodiči u ovoj grupi predlažu ekstendiranu, sekundarnu terapiju i primenu antikoagulanasa sa ciljem prevencije rekurentnih VTE

Jin et al. showed that the incidence of non-intracranial bleeding was lower in the apixaban-treated arm [20]. A more recent meta-analysis confirmed a lower frequency of major bleeding with apixaban compared to rivaroxaban, while they found no differences between apixaban and dabigatran or dabigatran and rivaroxaban [21].

## BLEEDING RISK IN PATIENTS WITH EXTENDED VTE TREATMENT

The treatment of VTE is based on the use of anticoagulant therapy, and according to the current guidelines, primary treatment usually lasts 3-6 months. In patients with VTE provoked by transient risk factors (surgical or non-surgical), therapy is completed in the primary phase [22]. On the other hand, particular concerns are needed in patients with unprovoked VTE or those exposed to chronic risk factors. The guidelines in this group suggest extended secondary therapy and the

[22]. Studija EPSTEIN- Extended, koja je analizirala bezbednost i efikasnost ekstendirane primene rivaroksabana u poređenju sa placebom tokom 6-12 meseci, pokazala je da je rizik od ponovnog VTE smanjen za 82% u grani koja je primala rivaroksaban u kojoj je zabeleženo 0,7% major krvarenja, odnosno 5,4% klinički relevantnih non-major krvarenja [9]. Apiksaban, bilo u terapijskoj dozi (5 mg) ili u dozi za tromboprofilaksu (2,5 mg), značajno je smanjio rizik od ponovnih VTE događaja u poređenju sa placebom, bez povećanja rizika od velikog krvarenja (0,5% u placebo grupi, 0,2% u apiksaban u grupi od 2,5 mg i 0,1% u grupi sa 5 mg apiksabana) [23]. Meta-analiza koja je uključila 16 RTC i 22 000 pacijenata pokazala je da je upotreba bilo kog oralnog antikoagulansa (VKA ili DOAK) značajno redukovala rizik od retromboza u poređenju sa placebom ili Aspirinom, dok je veća incidencija major krvarenja zabeležena samo u grani lečenoj VKA u poređenju sa Aspirinom/placebom [24]. Novija meta-analiza (14 RTC i 13 kohortnih studija), upoređujući produženu upotrebu DOAK ili VKA tokom još tri meseca kod pacijenata sa prvom neprovociranom trombozom, pokazala je da dugoročni rizik od major krvarenja u obe ispitivane grupe nije zanemarljiv [25].

Na osnovu ovih zapažanja, biće potrebne dodatne analize i podaci iz svakodnevne kliničke prakse da bi se doneo definitivan zaključak o bezbednosti dugoročne primene DOAK.

## RIZIK OD KRVARENJA KOD PACIJENATA SA NEVALVULARNOM AF

Direktni oralni antikoagulansi se koriste za prevenciju ishemijskog moždanog udara i sistemske embolizacije kod pacijenata sa NVAF [2,3]. Nekoliko RTC (ROCKET AF, RE-LY, ENGAGE AF-TIMI 48, ARISTOTLE) upoređivalo je rizik od krvarenja između DOAK i standardne terapije VKA (Tabela 2).

Rizik od major krvarenja bio je manji kod pacijenata lečenih dabigatranom u dozi od 110 mg (HR 0,80), apiksabanom (HR 0,69) i niskom/visokom dozom edoksabana (HR 0,47/0,80) u poređenju sa varfarinom. Sa druge strane, rizik je bio sličan u granama lečenim primenom dabigatrana u dozi od 150 mg i rivaroksabana u poređenju sa varfarinom. Rizik od intrakranijalnog krvarenja je značajno smanjen upotrebom DOAK, dok je rizik od gastrointestinalnog krvarenja bio veći sa rivaroksabanom, dabigatranom 150 mg i visokim dozama edoksabana u poređenju sa varfarinom [26-29]. Meta-analiza na 94 656 pacijenata pokazala je da apiksaban 5 mg/12h, dabigatran 110 mg/12h, edoksaban 30 mg/dan i edoksaban 60 mg/dan dovode do značajno nižeg rizika od major krvarenja u poređenju sa varfarinom. Rizik od major krvarenja bio je veći sa dabigatranom 150 mg/12h nego sa apiksabanom 5 mg/12h, sa rivaroksabanom 20 mg/12h u poređenju sa

use of anticoagulants to prevent recurrent VTE [22]. The EPSTEIN-Extended study, which analyzed the safety and efficacy of extended use of rivaroxaban compared to placebo for 6-12 months, showed that the risk of recurrent VTE was reduced by 82% in the rivaroxaban arm, with 0.7% incidence of major bleeding, and 5.4% of clinically relevant non-major bleeding [9]. Apixaban, either in the therapeutic dose (5mg) or in the thromboprophylaxis dose (2.5 mg), significantly reduced the risk of recurrent VTE events compared to placebo, without increasing the risk of major bleeding (0.5% in the placebo group, 0.2% in the apixaban 2.5mg group and 0.1% in the apixaban 5mg group) [23]. A meta-analysis that included 16 RTCs and 22,000 patients showed that the use of any oral anticoagulant (VKAs or DOACs) significantly reduced the risk of new thromboembolism compared to placebo or Aspirin. The higher incidence of major bleeding was noted only in the VKA arm compared to Aspirin/placebo [24]. A more recent meta-analysis (14 RTC and 13 cohort studies), comparing the extended use of DOACs or VKAs for another three months in patients with first unprovoked thrombosis, described that the long-term risks and outcomes of anticoagulant-related major bleeding were significant with both VKAs and DOACs [25].

Based on these observations, additional analyses and data from RWE will be needed to reach a definitive conclusion on the safety of long-term use of DOACs.

## BLEEDING RISK IN PATIENTS WITH NON-VALVULAR AF

Direct oral anticoagulants are used to prevent ischemic stroke and systemic embolization in patients with NVAF [2,3]. Several RTCs (ROCKET AF, RE-LY, ENGAGE AF-TIMI 48, ARISTOTLE) compared bleeding risks between DOACs and standard VKA therapy (Table 2).

The risk of major bleeding was lower in patients treated with dabigatran 110 mg (HR 0.80), apixaban (HR 0.69), and low/high dose edoxaban (HR 0.47/0.80) compared to warfarin. In comparison, the risk was similar in the dabigatran 150 mg and rivaroxaban arm compared to warfarin. The risk of intracranial hemorrhage was significantly decreased by using DOACs than VKAs. The risk of gastrointestinal bleeding was higher with rivaroxaban, dabigatran 150mg, and high-dose edoxaban compared to warfarin [26-29]. A meta-analysis of 94,656 patients showed that apixaban 5 mg/12h, dabigatran 110 mg/12h, edoxaban 30 mg/day, and edoxaban 60 mg/day lead to a significantly lower risk of major bleeding compared to warfarin. The risk of major bleeding was higher with dabigatran 150 mg/12h than with apixaban 5 mg/12h, with rivaroxaban 20 mg/12h compared to

**Tabela 2.** Različiti sistemi bodovanja za procenu verovatnoće krvarenja kod pacijenata sa AF

**Table 2.** Risk assessment models to evaluate bleeding probability in patients with AF

| | HAS-BLED | OBRI | ATRIA | ORBIT | ABC | NBP | HEMORR2HAGES |
|---|---|---|---|---|---|---|---|
| **Hipertenzija / *Hypertension*** | √ | | √ | | | √ | √ |
| **Abnormalna funkcija bubrega/jetre / *Abnormal renal/liver function*** | √ | | | | | | √ |
| **Moždani udar / *Stroke*** | √ | √ | √ | | | | √ |
| **Istorija krvarenja ili predispozicija / *Bleeding history or predisposition*** | √ | | | √ | √ | √ | √ |
| **Krvarenje iz GI trakta / *GI tract bleeding*** | | √ | | | | | |
| **Labilan iNR / *Labile iNR*** | √ | √ | | | | | |
| **Starost / *Age*** | √ | √ | √ | √ | √ | | √ |
| **Lekovi (NSAID)/alkohol / *Drugs (NSAID)/Alcohol*** | √ | | | | | | √ |
| **Ozbiljni komorbiditet / *Serious comorbidity*** | | √ | | | | | |
| **Pol / *Sex*** | | | √ | | | √ | |
| **Dijabetes Melitus / *Diabetes Mellitus*** | | | √ | | | | |
| **Hronična srčana insuficijencija / *Chronic Heart Failure*** | | | √ | | | | |
| **Proteinurija / *Proteinuria*** | | | √ | | | | |
| **eGFR** | | | √ | √ | | √ | |
| **Anemija / *Anaemia*** | | | | √ | √ | √ | √ |
| **Antiplatelet th / *Antiplatelet th*** | | | | √ | | √ | √ |
| **GDF-15** | | | | | √ | | |
| **cTn-hs** | | | | | √ | | |
| **Trombocitopenija / *Thrombocytopenia*** | | | | | | √ | √ |
| **Rizik od pada / *Fall risk*** | | | | | | √ | √ |
| **Serumski holesterol / *Serum cholesterol*** | | | | | | √ | |
| **Istorija maligniteta / *Malignancy history*** | | | | | | | √ |
| **Genetski faktori / *Genetic factors*** | | | | | | | √ |

GI – gastrointestinalni, iNR – internacionalni normalizovani odnos, NSAID – nesteroidni antiinflamatorni lekovi, eGFR – procenjena glomerulska filtracija, CDF-15 – Faktor diferencijacije rasta 15, cTn-hs – visokosenzitivni troponin

*GI – gastrointestinal, iNR - International normalized ratio, NSAID - Non-steroidal anti-inflammatory drugs, eGFR - Estimated glomerular filtration rate, CDF-15 - Growth differentiation factor 15, cTn-hs - High-sensitivity cardiac troponin*

tranom 150 mg/12 h nego sa apiksabanom 5 mg/12 h, sa rivaroksabanom 20 mg/12 h u poređenju sa apiksabanom 5 mg/12 h i sa rivaroksabanom 20 mg/12h u poređenju sa edoksabanom 60 mg/dan. Ipak, rizik od intrakranijalnog krvarenja je bio nizak, sa skoro svim DOAK u svim dozama [30].

Novija meta-analiza, koja je uključivala veliki broj retrospektivnih kohortnih studija i skoro pola miliona pacijenata iz Evrope sa NVAF, upoređujući bezbednost DOAK u odnosu na VKA, zaključila je da ne postoji veći rizik od major krvarenja sa DOAK u odnosu na VKA (HR 0,94, 95% CI, 0,87–1,02). Nasuprot tome, uočene su razlike između različitih DOAK. Tako su, na primer, pacijenti na rivaroksabanu imali nešto veću učestalost krvarenja od VKA, dok je učestalost kod dabigatrana i apiksabana u poređenju sa VKA bila niža [31]. Pored toga, rezultati drugih studija potvrdili su da rizik od

apixaban 5 mg/12h, and with rivaroxaban 20 mg/12h compared to edoxaban 60 mg/day. However, the risk of intracranial bleeding was low, with almost all DOACs at all doses [30].

A more recent meta-analysis, which included a large number of retrospective cohort studies and almost half a million patients from Europe with NVAF, comparing the safety of DOACs versus VKAs concluded that there is no greater risk of major bleeding with DOACs versus VKAs (HR 0.94, 95% CI, 0.87–1.02). Conversely, the differences were observed between different DOACs. Thus, for example, patients on rivaroxaban had a slightly higher bleeding frequency than VKAs, while the frequency with dabigatran and apixaban compared to VKAs was lower [31]. Additionally, the results of other studies confirmed that the risk of bleeding and effectiveness vary within different DOACs. The

krvarenja i efikasnost variraju unutar različitih DOAK. Nemačka studija je primetila da je edoksaban efikasniji u smanjenju rizika od ishemijskog moždanog udara i sistemske embolizacije u poređenju sa drugim DOAK i VKA, uz manji rizik od krvarenja u poređenju sa rivaroksabanom i VKA, odnosno isti kao apiksaban [32]. Upoređujući DOAK, nekoliko studija je naglasilo da je apiksaban bezbedniji kada se uzme u obzir rizik od major krvarenja i gastrointestinalnog/intrakranijalnog krvarenja u poređenju sa rivaroksabanom, pa čak i dabigatranom, dok je njegova efikasnost u poređenju sa drugim DOAK još uvek predmet rasprave [33,34].

## PREDIKTIVNI FAKTORI ZA RAZVOJ KRVARENJA

Između 2-4% pacijenata sa AF na terapiji VKA godišnje razvije krvarenje, a od toga njih 0,61% intrakranijalno krvarenje. U slučaju VTE, veliko krvarenje se javlja kod 7,22/100 pacijenata godišnje, sa stopom mortaliteta od 9% [35]. Imajući u vidu navedene rizike, jasno je da je neophodno identifikovati i određene prediktivne faktore za razvoj hemoragijskih komplikacija.

Prethodno krvarenje u anamnezi je najvažniji faktor rizika povezan sa major krvarenjem kod pacijenata na terapiji antikoagulansima. Pored navedenog, drugi relevantni faktori rizika su starija životna dob, bolesti jetre ili bubrega, maligniteti, trombocitopenija, istovremena primena antiagregacione terapije i prekomerna antikoagulacija usled neadekvatno visokih doza DOAK ili loše kontrolisanog INR (Internationa Normalized Ratio). Ne treba zanemariti ni postojanje minimalnih lezija sluzokože u gastrointestinalnom ili urinarnom traktu [6].

Sa namerom da se identifikuju pacijenti sa povećanim rizikom od krvarenja, danas postoje brojni sistemi bodovanja. Među najčešće korišćenim i potvrđenim kod pacijenata sa AF je HAS-BLED („Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly ≥ 65, Drugs (NSAID)/alcohol“), koji stratifikuje pacijente u tri grupe rizika (nizak, umeren i visok). Pacijenti sa visokim rizikom od krvarenja prema HAS-BLED skoru ≥ 3 imaju godišnju stopu major krvarenja > 3,74% [36]. Takođe, postoje i drugi sistemi bodovanja za pacijente sa AF: OBRI, ATRIA, ORBIT, ABC, NBP, HEMORR$_2$HAGES [6]. Slično, kod pacijenata sa VTE na oralnoj antikoagulansnoj terapiji, postoje različiti sistemi bodovanja (RIETE, *Registro Informatizado de Enfermedad TromboEmbo´lica;* ACCP, *American College of Chest Physician;* VTE-BLEED) koji kombinuju starost, stepen anemije, prethodna krvarenja, funkciju jetre/bubrega, trombocitopeniju, konkomitantnu terapiju, druge komorbiditete, postojanje kancera da bi se pacijent stratifikovao u odgovarajuću grupu rizika (Tabela 3) [6].

German study observed that edoxaban is more effective in reducing the risk of ischemic stroke and systemic embolization compared to other DOACs and VKAs, carrying a lower risk of bleeding compared to rivaroxaban and VKAs, and the same as apixaban [32]. Comparing DOACs, several studies have emphasized that apixaban is safer when considering the risk of both major bleeding and gastrointestinal/intracranial bleeding compared to rivaroxaban and even dabigatran, while its efficacy compared to other DOACs is still a subject of debate [33,34].

## PREDICTORS OF BLEEDING

Anticoagulant therapy has an annual rate of bleeding between 2-4% among patients receiving VKA, and the annual risk of intracranial hemorrhage is 0.61%. In the case of VTE, major bleeding occurs in 7.22/100 patients/year, with a mortality rate of 9% [35]. Therefore, it is crucial to identify certain predictive factors for hemorrhagic complications and to stratify patients into risk groups.

History of previous bleeding is the most important risk factor associated with major bleeding in patients on anticoagulant therapy. In addition to the above, other relevant risk factors are older age, liver or kidney diseases, malignancies, thrombocytopenia, concomitant use of antiplatelet therapy, and excessive anticoagulation due to inadequately high doses of DOACs or poorly controlled INR (International Normalized Ratio). The existence of minimal mucosal lesions in the gastrointestinal or urinary tract should not be ignored either [6].

Intending to identify those patients at increased bleeding risk, there are numerous scoring systems available today. Among the most used and validated in patients with AF is HAS-BLED (“Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly ≥ 65, Drugs (NSAID)/alcohol”), which stratifies patients into three risk groups (low, moderate and high). Patients with a high risk of bleeding according to HAS-BLED score ≥ 3 have an annual rate of significant bleeding > 3.74% [36]. Also, other scoring systems exist for patients with AF: OBRI, ATRIA, ORBIT, ABC, NBP, HEMORR$_2$HAGES [6]. Similarly, in patients with VTE on oral anticoagulant therapy, there are different scoring systems (RIETE, Registro Informatizado de Enfermedad TromboEmbólica; ACCP, American College of Chest Physician; VTE-BLEED) combining age, severity of anemia, previous bleeding, liver/kidney function, platelet count, concomitant therapy, other comorbidities, existence of cancer to stratify the patient into the appropriate risk group (Table 3) [6].

**Tabela 3.** Različiti sistemi bodovanja za procenu verovatnoće krvarenja kod pacijenata sa VTE

**Table 3.** Risk assessment models to evaluate bleeding probability in patients with VTE

| Faktor rizika / *Risk factor* | *RIETE* | *ACCP* | *VTE-BLEED* |
|---|---|---|---|
| Abnormalna funkcija bubrega / *Abnormal renal function* | √ | √ | √ |
| Istorija krvarenja ili predispozicija / *Bleeding history or predisposition* | √ | √ | √ |
| Starost / *Age* | √ | √ | √ |
| Anemija /*Anaemia* | √ | √ | √ |
| Abnormalna funkcija jetre / *Abnormal liver function* | | √ | |
| Istorija moždanog udara/TIA / *History of stroke/TIA* | | √ | |
| Lekovi (NSAID)/Alkohol / *Drugs (NSAID)/Alcohol* | | √ | |
| Ozbiljni komorbiditet / *Serious comorbidity* | | √ | |
| Dijabetes Melitus / *Diabetes Mellitus* | | √ | |
| Česti padovi / *Frequent falls* | | √ | |
| Nedavna operacija / *Recent surgery* | | √ | |
| Trombocitopenija / *Thrombocytopenia* | | √ | |
| Antitrombocitna terapija / *Antiplatelet therapy* | | √ | |
| Loša kontrola antikoagulansa / *Poor anticoagulant control* | | √ | |
| Metastatski karcinom / *Metastatic cancer* | | √ | |
| Aktivni malignitet / *Active malignancy* | | √ | √ |
| Pacijent sa hipertenzijom / *Male patient with hypertension* | | | √ |
| Istorija maligniteta / *Malignancy history* | √ | | |
| Klinički očigledna plućna embolija / *Clinically overt pulmonary embolism* | √ | | |

NSAID – nesteroidni antiinflamatorni lekovi; TIA – Tranzitorni ishemijski napad; VTE – venska tromboembolija

*NSAID - Non-steroidal anti-inflammatory drugs; TIA - Transient ischemic attack; VTE - Venous thromboembolism*

Na osnovu svega navedenog, najvažnija je klinička procena, adekvatna evaluacija svih faktora rizika za krvarenje kod datog pacijenta, te na osnovu toga proceniti rizik i korist od antikoagulantne terapije i mogućnosti krvarenja usled korišćenja iste.

## NASTAVAK ANTIKOAGULANTNE TERAPIJE NAKON KRVARENJA

Ponovno započinjanje antikoagulantne terapije nakon povlačenja krvarenja je izazovna klinička odluka, koju je potrebno doneti individualno za svakog pacijenta, a često uz pomoć multidiscilinarnog tima sačinjenog od specijaliste za hemostazu, kardiologa, gastroenterologa, neurologe i specijaliste intenzivne nege [37]. S jedne strane, prerano ponovno uvođenje može povećati rizik od ponovnog krvarenja, dok sa druge strane, kasniji nastavak antikoagulantne terapije povećava rizik od tromboembolijskih događaja i smrti [38]. Podaci u vezi sa ponovnim uvođenjem DOAK kod pacijenata koji su doživeli krvarenje su oskudni. Kohortna studija Tapaskara i saradnika pokazala je da je ponovno uvođenje varfarina povezano sa povećanim rizikom od rekurentnog gastrointestinalnog krvarenja (HR, 2,12;

Therefore, careful evaluation of individual patient bleeding risk factors and clinical judgment remains the best approach to minimizing the personal risk of bleeding during anticoagulant treatment.

## RESUMING ANTICOAGULATION THERAPY AFTER BLEEDING

Restarting anticoagulation therapy after the resolution of bleeding is a challenging clinical decision. It should be made individually for every patient, usually by a multidisciplinary team, including hemostasis specialists, cardiologists, gastroenterologists, neurologists, and intensive care specialists [37]. On the one hand, early restart can increase the risk of rebleeding, while on the other hand, later continuation of anticoagulation therapy increases patients' risk of thromboembolic events and mortality [38]. Data regarding restarting DOACs in patients who experienced bleeding are scarce. A cohort study by Tapaskar et al. showed that the restart of warfarin was associated with an increased risk of recurrent gastrointestinal bleeding (HR, 2.12; 95% CI, 1.43–3.14; $p < 0.001$), while DOAC resumption was not associated with recurrent bleed-

95% CI, 1,43–3,14; $p < 0,001$), dok nastavak DOAK nije bio povezan sa ponovnim krvarenjem (HR, 1,43; 95% CI, 0,81–2,52; $p = 0,22$). Ipak, ista studija je pokazala da je rivaroksaban jedini DOAK povezan sa rekurentnim gastrointestinalnim krvarenjem (HR, 2,73; 95% CI, 1,43–5,20; $p = 0,002$) [39]. Kada je reč o intrakranijalnom krvarenju, Poli i saradnici su pokazala da pacijenti koji uzimaju varfarin imaju veći rizik od rekurentnog intrakranijalnog krvarenja u poređenju sa pacijentima na terapiji DOAK (OR 1,9; 95% CI 0,7–6,7). Međutim, u DOAK kohorti je bila primećena veća učestalost rekurentnog ne-cerebralnog krvarenja [40]. Na drugom kraju spektra, nastavak primene antikoagulanasa je bio povezan sa manjim brojem tromboembolijskih događaja i smanjenim mortalitetom [41,42]. Nakon otklanjanja krvarenja, određivanje pravog vremena za ponovno uvođenje DOAK je najizazovnije pitanje. Sengupta et al. pokazali su da ponovno uvođenje DOAK u roku od 30 dana nakon krvarenja nije povezano sa tromboembolijom u roku od 90 dana (HR, 0,98; 95% CI, 0,37-2,21) ili rekurentnim gastrointestinalnim krvarenjem (HR, 1,44; 95% CI 0,72-436). Prema BSG/ESGE smernicama, ponovno uvođenje DOAK što je pre moguće do sedmog dana nakon njihovog prekida može biti razumno u većini slučajeva [44]. Međutim, treba napomenuti da je ovaj zaključak donet na osnovu podataka sa varfarinom, a podaci iz randomizovanih kontrolisanih studija nedostaju.

## ZAKLJUČAK

U poređenju sa VKA, DOAK su bar jednako efikasni u lečenju i prevenciji VTE kao i u prevenciji ishemijskog insulta i sistemskih embolizacija kod pacijenata sa AF, a sve to uz potvrđeno značajno manji rizik od intrakranijalnog krvarenja. Takođe, većina studija je pokazala da je rizik od major krvarenja manji kada se koriste DOAK, dok je rizik od gastrointestinalnog krvarenja varijabilan i zavisi od vrste DOAKa.

Razvijeni su brojni sistemi bodovanja koji pomažu objektivizaciji, jasnoj stratifikaciji i identifikaciji pacijenata sa većim rizikom od krvarenja. Međutim, individualno profilisanje rizika od krvarenja i izbor odgovarajućih DOAK-a na osnovu komorbiditeta, starosti, prethodnog krvarenja, opšteg stanja i interakcija lekova mogu dodatno smanjiti rizik od hemoragijskih komplikacija. Takođe, intenzivnije i češće praćenje bilo bi važno kod pacijenata sa visokim rizikom od krvarenja. Na osnovu navedenog, postavlja se pitanje da li će DOAK zameniti VKA kao prihvatljiviji oblik prevencije i lečenja VTE u većini kliničkih indikacija posle više od jednog veka.

**Sukob interesa:** Nije prijavljen.

ing (HR, 1.43; 95% CI, 0.81–2.52; $p = 0.22$). However, the same study showed that rivaroxaban was the only individual DOAC associated with recurrent gastrointestinal bleeding (HR, 2.73; 95% CI, 1.43–5.20; $p = 0.002$) [39]. When the word is about intracranial hemorrhage, Poli et al. showed that patients taking warfarin were at higher risk of intracranial hemorrhage recurrence than patients taking DOACs (OR 1.9;95% CI 0.7–6.7). However, non-cerebral major re-bleeding was more common in the DOAC cohort [40]. On the other end of the spectrum, resuming anticoagulants was associated with fewer thromboembolic events and decreased mortality [41,42]. After resolving the bleeding, determining the right timing for DOAC restart is the most challenging question. Sengupta et al. showed that reintroducing DOACs within 30 days after bleeding was not associated with thromboembolism within 90 days (HR, 0.98; 95% CI, 0.37-2.21) or recurrent gastrointestinal bleeding (HR, 1.44; 95% CI 0.72-2.68) [43]. According to BSG/ESGE guidelines, restarting DOACs as soon as possible by day seven after their interruption could be reasonable in most cases [44]. However, it should be noted that this conclusion was made in parallel with warfarin, and data from randomized controlled trials are lacking.

## CONCLUSION

Compared to VKA, DOACs are at least as effective in treating and preventing VTE as in preventing ischemic insult and systemic embolization in patients with AF, with a confirmed significantly lower risk of intracranial bleeding. Also, most studies showed that the risk of major bleeding is lower when using DOACs, while the risk of gastrointestinal bleeding is variable and depends on the type of DOACs.

Numerous scoring systems have been developed to help objectify, clearly stratify, and identify patients at higher risk of bleeding. However, individual bleeding risk profiling and selection of the appropriate DOACs based on the patient's comorbidities, age, previous bleeding, general condition, and drug interactions can further reduce the risk of hemorrhagic complications. Also, more intensive and frequent monitoring would be important in patients at high risk of bleeding. Based on the above, the question arises whether DOACs will replace VKAs as a more acceptable form of VTE prevention and treatment in most clinical indications after over a century.

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