

КЛИНИЧКИ ИСТРАЖУВАЊА

## ДИРЕКТНИ ОРАЛНИ АНТИКОАГУЛАНСИ - БАЛАНС ПОМЕГУ ТРОМБОЗА И КРВАВЕЊЕ - НАРАТИВЕН ПРЕГЛЕД

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**Цитирање:** Лазарова Трајковска Е. Директни орални антикоагуланси-баланс помеѓу тромбоза и крвавење. Арх Ј Здравје 2020;12(2):32-36DOI: <https://doi.org/10.3889/aph.2020.5192>**Клучни зборови:** крвавење, ДОАК, антидоти**\*Кореспонденција:** Емилија Лазарова Трајковска, Универзитетска клиника за кардиологија, Скопје, Република Северна Македонија. E-mail: emilaztra@gmail.com**Примено:** 31-ное-2019; **Ревидирано:** 3-мај-2020; **Прифатено:** 20-мај-2020; **Објавено:** 15-јун-2020**Печатарски права:** ©2020 Емилија Лазарова Трајковска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналните автор(и) и изворот.**Конкурентски интереси:** Авторот изјавува дека нема конкурентски интереси.

Крвавењето е чест несакан ефект од употребата на антикоагулантни лекови. Повеќето од крвавечките компликации не се животозагрозувачки и можат да се третираат конзервативно. Прв чекор во решавање на значајно крвавење е привремено да се прекине антикоагулансот. Целта на овој труд беше да се одреди соодветната стратегија за акутно крвавење на пациент на ДОАК. Директните орални антикоагуланси (ДОАК) се нашироко употребувани во третманот на венски тромбоемболизам (ВТЕ) и се препорачани како прва линија пред витамин К антагонисти (ВКА) кај ВТЕ која не е асоцирана со рак. До скоро, супортивна терапија и инфузија на фактори на коагулација беа единствените достапни опции за пресврт на дејството на ДОАК. Во последните 4 години одобрувањето на специфични антидоти ја зголемија надежта за подобар исход на крвавењата асоцирани со употреба на ДОАК, но сè уште постојат ограничувања како што се цената, достапноста и податоци од клиничката пракса. При тешки, животозагрозувачки крвавења, се препорачува употреба на неспецифични (пр. ПСС) и специфични (idarucizumab, andexanet alpha) агенси. Но, потребни се понатамошни искуства и податоци за споредба на исходот помеѓу двете стратегии во однос на бенефитот и економичноста.

CLINICAL SCIENCE

## DOACS- BALANCE BETWEEN THROMBOSIS AND BLEEDING - NARATIVE REVIEW

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## Abstract

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Bleeding is a common side effect of anticoagulant use. However, the majority of bleeding events are not life-threatening and can be managed conservatively. The first step in managing any significant bleeding event is to temporarily stop using the anticoagulant. The aim of this review was to determine the appropriate management strategy for an acutely bleeding patient on DOACs. Direct oral anticoagulants (DOACs) are now widely used in treatment of venous thromboembolism (VTE) and are recommended first-line over vitamin K antagonists (VKAs) in non-cancer associated VTE. Until recently, supportive measures and infusion of clotting factors were the only available options for reversal of DOACs. Within the last 4 years, approval of specific antidotes has led to hopes for improved outcomes in DOAC-related acute bleeding, however limitations remain including cost, availability and „real-world“ data. In severe and life-threatening bleeding events, use of non-specific (e.g. PCC) or specific (e.g. idarucizumab, andexanet alpha) reversal agents are recommended. However, further data is needed to compare outcomes between these two management strategies and identify the cost-effectiveness of these various strategies.

## Introduction

Bleeding is a common side effect of anticoagulant use. However, the majority of bleeding events are not life-threatening and can be managed conservatively.<sup>1</sup> To assess the severity of an anticoagulant-related bleeding event, clinicians should identify the source (if possible) and location of bleeding, evaluate laboratory studies (including blood counts and coagulation studies), and closely monitor vital signs. The first step in managing any significant bleeding event is to temporarily stop using the anticoagulant. Local measures, such as manual compression, can be useful in the case of skin-bleeds and epistaxis. Transfusion of blood products may be needed for more significant bleeding events. Ultimately, the decision to reverse an anticoagulant should be made based on the location of bleeding, time since last use of the anticoagulant, and patient's hemodynamic stability. The decision to reverse an anticoagulant is largely the same for patients with atrial fibrillation and venous thromboembolism. But the strategies for reversal differ based on the specific anticoagulant. The decision to restart the anticoagulant after bleeding has been controlled may differ based on indication.

Direct oral anticoagulants (DOACs) are now widely used in treatment of venous thromboembolism (VTE) and are recommended first-line over VKAs in non-cancer associated VTE<sup>2</sup>. While routine assessment of anticoagulant effect is unnecessary, it can be helpful in determining the appropriate management strategy for an acutely bleeding patient. Unlike VKAs, standard coagulation tests such as activated partial thromboplastin time (aPTT) and prothrombin time (PT)/INR are unreliable

markers of anticoagulant effect in DOAC-treated patients. Time since last dose and end-organ function affecting DOAC clearance should be used to guide the decision on need for reversal of the DOAC. Availability of drug specific assays or use of a low-molecular weight heparin calibrated anti-Xa level can be useful to determine activity but should not delay treatment in those known to have DOAC on board.

The aim of this review was to determine the appropriate management strategy for an acutely bleeding patient on DOACs. Comparing non-specific with specific reversal agents in severe and life-threatening bleeding, we want to determine outcomes between these two management strategies and identify the cost-effectiveness of these various strategies.

## Material and methods

This review was conducted to provide an overview and update on direct oral anticoagulants and their reversal agents. A literature search was conducted using PubMed, Medline, Cochrane Library, Medscape, UpToDate and databases for original studies, case reports, clinical guidelines, and clinical trial reports on DOACs and their reversal agents using relevant search terms and the combinations, including bleeding, DOACs and reversal agents. The reference list of review papers was also used to identify relevant publications. Inclusion was limited to publications available in English. The research period extended between 2011-2019, and there were 20 studies that were selected as relevant references.

**Results**

Until recently, supportive measures and infusion of clotting factors were the only available options for reversal of DOACs. Initial animal models evaluating activated PCC (aPCC) [FEI-BA], 4-factor PCC, and recombinant factor VII demonstrated mixed and inconsistent effects on coagulation parameters, bleeding time, and hemostatic efficacy.<sup>3-7</sup> Additionally, high dose 4F-PCC (50 units/kg) in healthy subjects reversed abnormal coagulation tests from rivaroxaban but not dabigatran.<sup>8</sup> The use of aPCC in dabigatran-associated acute bleed-

ing suggests good hemostatic efficacy as compared to historical controls<sup>9</sup> and specific antidote trials<sup>10</sup>. In apixaban and rivaroxaban patients, two observational cohort reports have described 4F-PCC use with hemostasis rates of 70-80% and low rates of thromboembolism<sup>11-12</sup>.

Within the last 4 years, approval of specific antidotes has led to hopes for improved outcomes in DOAC-related acute bleeding, however limitations remain including cost, availability (andexanet alfa), and „real-world“ data.

**Table 1.** Specific Reversal Agents for Direct Oral Anticoagulants <sup>20</sup>

Од 18 до 29 месеци	Idarucizumab	Andexanet Alpha	Ciraparantag
Drug reversed	Dabigatran	Rivaroxaban Apixaban Edoxaban (non-FDA) LMWH (non-FDA)	Dabigatran Xa inhibitors LMWH UFH
Mechanism	Monoclonal Ab binds Dabigatran with high affinity	Recombinant human factor Xa protein acts as a decoy	Noncovalent bonding and charge-charge interactions
Published Clinical Studies	Healthy volunteers; bleeding patients; emergent reversal	Healthy volunteers; bleeding patients;	Healthy volunteers
FDA approval	Approved	Approved	Not approved

A majority of patients in both trials demonstrated normalization of thrombin activity and reduction in unbound drug concentration. In REVERSE-AD, unbound dabigatran levels were suppressed for 12 hours at which point 23% of patients had re-elevation of levels.<sup>15</sup> In ANNEXA-4, unbound apixaban and rivaroxaban levels returned to that of the placebo group two hours after the end of

the 2-hour infusion, however endogenous thrombin potential remained normalized.<sup>14</sup> Hemostasis was reported in a majority of patients in both trials. Use of agent specific antidotes is recommended over non-specific reversal agents for DOAC-associated life-threatening bleeding or bleeding at a critical site. If agent specific antidotes are not available, based on observational data, aPCC (25-50 units/

kg) is recommended for reversal of dabigatran and 4F-PCC (25-50 units/kg) is recommended for reversal of oral anti-Xa inhibitors.<sup>1,2,14,15</sup>

## Discussion

The acute management of anticoagulant-related bleeding in patients with VTE should also include an assessment for restarting anticoagulation once bleeding has been resolved. This is of particular importance for patients with VTE, who remain at elevated risk for recurrence. In fact, the majority of thromboembolic events and deaths occurring in the ANNEXA-4 study occurred after bleeding had been controlled but before anticoagulation had been resumed.<sup>14</sup> Among patients with atrial fibrillation who experienced an anticoagulant-related bleeding, data suggests lower rates of ischemic stroke and death when the anticoagulant is restarted.<sup>17</sup> The same is likely to be true for patients with VTE. Recent guidelines recommend resuming anticoagulation within 90 days if the patient is at moderate-high risk for VTE recurrence and the risk of recurrent bleeding is adequately low.<sup>18,19</sup>

## Conclusion

Bleeding is a common complication of chronic anticoagulant therapy. Most bleeding events can be managed conservatively, usually by omitting a few doses of the anticoagulant. In severe and life-threatening bleeding events, use of non-specific (e.g. PCC) or specific (e.g. idarucizumab, andexanet alpha) reversal agents are recommended. However, further data is needed to compare outcomes between these two management strategies and identify the cost-effectiveness of these various strategies. Once

bleeding has been controlled, clinicians and patients should discuss the appropriateness of resuming anticoagulant therapy to prevent potentially life-threatening future thrombotic events.

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