VIA MEDICA

REVIEW ARTICLE

Journal of Transfusion Medicine
2022, vol. 15, no. 2, 150–153
DOI: 10.5603/JTM.2022.0012

ISSN 1689-6017
eISSN 2080-1505

DOAC — not for everyone, and sometimes at different dose

Jacek Musiał

II Department of Internal Medicine, Jagiellonian University, Medical College, Krakow

Summary

Direct oral anticoagulants (DOACs) are used in Europe over a decade. One of their favourable properties is a stable prophylactic or therapeutic drug dose. Sometimes, however, it is preferred to use older antithrombotic drugs (vitamin K antagonists, heparins) or — in some clinical situations — to modify the standard recommended drug dose.

Key words: direct oral anticoagulant inhibitors, treatment, atrial fibrillation, antiphospholipid syndrome, kidney disease, venous thromboembolism

J. Transf. Med. 2022; 15: 150–153

Introduction

Direct oral anticoagulants (DOACs) were approved worldwide for prevention and treatment of thrombotic disorders in 2010. In Europe, the first new oral anticoagulant — dabigatran, was approved on August 5th, 2011, followed by rivaroxaban registered at the end of the same year. The former is a direct inhibitor of thrombin, the latter — of the activated factor X (Xa). The latter group of drugs also includes apixaban and edoxaban (unavailable in Poland) which were approved at a later date. In 2018, the European Agency for the Evaluation of Medicinal Products (EMEA) refused to register yet another drug of this group, namely betrixaban which demonstrated no marked clinical benefit compared with enoxaparin (low molecular weight heparin, LMWH) as well as higher bleeding frequency.

In long-term prophylaxis and management of thromboembolic complications, the advantages of DOAC over the classical heparins or vitamin K antagonists are as follows: comparable efficacy, oral route of administration, standard dosage, no need for monitoring, limited interactions with other drugs, and a lower incidence rate of serious adverse reactions.

There are currently two main indications for long-term use of DOACs. The first is prevention of thromboembolic complications in atrial fibrillation, the second is treatment and secondary prophylaxis of venous thromboembolism [1, 2]. Due to their efficacy and safety profile, DOACs are gradually replacing vitamin K antagonists [2, 3] the dosage of which is troublesome and requires laboratory monitoring.

There are however, clinical settings/situations in which the use of DOACs is either not recommended, or the dosage requires modification.

Vitamin K antagonists still preferable over DOAC

Antiphospholipid syndrome (APS) is an autoimmune disorder in which antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, and anti-beta2-glycoprotein I antibodies) coexist with venous or arterial thrombosis (mostly ischemic stroke). APS is also associated with obstetric failures. In prevention of thrombosis in APS, attempts to replace vitamin K antagonists

Correspondence address: prof. dr hab. n. med. Jacek Musiał, II Department of Internal Medicine, Jagiellonian University, Medical College, Krakow, Skawinska Street 8, 31–066 Krakow, e-mail: jacek.musial@uj.edu.pl

Translation: mgr Krystyna Dudziak

with DOACs (rivaroxaban and apixaban) have not proved successful [4, 5]. In two larger randomized trials of patients treated with DOAC against warfarin, a markedly higher frequency of thrombotic events was reported and — what makes it more dangerous — these were solely episodes of arterial thrombosis, ischemic stroke included. In two smaller trials with thrombotic APS patients, the incidence rate for recurrent thrombosis was higher after rivaroxaban than following administration of warfarin [6, 7]. As a result, most international societies do not recommend DOAC for preventing recurrence of thrombotic complications in patients with a history of arterial thrombosis or for individuals with the presence of all three types of antiphospholipid antibodies (triple positivity) and exceptionally high risk of thrombotic complications [8]. In such situations, warfarin is the drug of a first-choice. Warfarin is also preferred in other APS patients but if DOACs are to be considered for a patient with thrombotic APS and poor INR control or serious adverse reactions following vitamin K antagonists, the possible health benefits/ /risks should be discussed with the patient and drug administered with utmost caution [8].

According to the Summary of Product Characteristics, DOACs are contraindicated for patients with **chronic kidney disease** (end-stage kidney disease, creatinine clearance as estimate of glomerular filtration: < 15 ml/min/1.73 m^2 for rivaroxaban and apixaban and < 30 ml/min/1.73 m^2 for dabigatran) and for chronic dialysis patients. Such patients were not enrolled in the randomized phase III clinical trials and for them warfarin should still be considered as the drug of first choice. DOACs are eliminated by the kidneys to various extent. Dabigatran has the highest degree of elimination and is associated with higher bleeding frequency and mortality as compared to warfarin in atrial fibrillation patients on hemodialysis [9]. On the other hand, apixaban with minimal degree of renal elimination [10], may be administered to hemodialysis patients and the bleeding risk may even be reduced as compared to warfarin [11, 12]. Based on observational studies, rivaroxaban place is somewhere in between [11, 12].

Aortic valve implantation (either biological or mechanical) is an indication for using warfarin in long-term prophylaxis of thromboembolic complications [13]. Life-long thromboprophylaxis with vitamin K antagonists is an absolute indication for patients with mechanical heart valves. Unsuccessful attempts at using dabigatran versus warfarin for this indication (higher frequency of ischemic strokes) have practically eliminated DOACs as antithrombotic prevention in patients with mechanical heart valves [14].

Further studies are required [11] to determine if DOACs could find place in patients with biological heart valves and individuals after transcatheter aortic valve replacement (TAVR).

Smaller doses of DOACs in specific clinical situations

DOAC doses used in most patients, with either atrial fibrillation or VTE episodes, are defined by their dosage used in the phase III clinical trials [15, 16]. Table 1 presents these DOAC doses used in patients with atrial fibrillation. Standard doses were reduced when the bleeding risk was higher due to older age, low body weight, impaired renal function, or concurrent administration of p-glycoprotein inhibitors.

Sometimes the physician reduces DOAC doses also in other situations ("off label") mostly due to unwarranted fear of excessive bleeding. In everyday practice, too much caution is not uncommon and usually leads to higher risk of thromboembolic complications and death [17].

Apart from the situations presented in Table 1, it seems that the reduction of DOAC doses ought

Table 1. Recommended DOAC dosage in atrial fibrillation

Drug	Standard dosage	Criteria for dose reduction
Dabigatran	150 mg twice daily	**ACC/AHA:** 75 mg twice daily at CrCl 15–30 mL/min ESC: 110 mg twice daily, if: age ≥ 80, verapamil, or increased bleeding risk
Rivaroxaban	20 mg once daily	**ACC/AHA:** 15 mg once daily at CrCl 15–50 mL/min ESC: 15 mg once daily at CrCl 15–49 mL/min
Apixaban	5 mg twice daily	**ACC/AHA:** 2.5 mg twice daily, if ≥ 2 of 3 criteria: age ≥ 80 weight ≤ 60 kg, or creatinine concentration > 133 μmol/L

Recommendations: ACC/AHA (American College of Cardiology/American Heart Association); ESC (European Society of Cardiology); CrCl (creatinine clearance)

to be considered also in other cases. Not only cardiologists, but also specialists in hematology, angiology and internal medicine may be confronted with such a problem [18].

Let us consider an example of an elderly patient (89 years old) with permanent atrial fibrillation who presented recurrent gastrointestinal bleeding at recommended DOAC doses [18]. Here the reduction of the DOAC dose may obviously be warranted. Moreover, such dose reductions may be considered in other specific situations, such as:

1. recurrent gastrointestinal bleeding, with no specific cause precluding effective therapy (e.g. vascular lesions in the gastrointestinal tract);
2. high risk factors for life-threatening bleeds that cannot be eliminated (e.g. colon diverticulosis with contraindications for surgery);
3. post-radiation hemorrhagic bladder infection;
4. nose bleeding that requires hospitalization and blood transfusion;
5. high risk factors for life-threatening bleeding:

— esophageal and gastric varices with a high risk of bleeding despite other preventive methods (beta-blockers, bands);
— previous bleeding into the central nervous system with control of risk factors, eg. hypertension/high blood pressure;
— moderate thrombocytopenia (25,000–50,000/ /mm^3).

However, it is not recommended to reduce DOAC doses merely because of old age, tendency to fall or minor bleeding [18].

Re-initiation of anticoagulant therapy and drug selection following gastrointestinal bleeding in the course of DOAC therapy may be a challenge [19]. As a rule, re-initiation of treatment is associated with expected lower risk of thrombosis and death, but at the same time with the higher risk of recurrent bleeding. Careful consideration of the benefits and risks is crucial [20].

The situation is somewhat different when reduced DOAC doses are used in the secondary prophylaxis of venous thromboembolism. Two studies (AMPLIFY-EXT and EINSTEIN CHOICE) have demonstrated that after 6–12 months of VTE treatment with apixaban at 2 × 5 mg or rivaroxaban at 1 × 20 mg, respectively, the therapy can be continued at the same doses, or at reduced dose of both drugs (apixaban 2 × 2.5 mg, or rivaroxaban once daily 10 mg) — with no difference to efficacy and safety [21, 22]. Such extended anticoagulant therapy is indicated for all patients with unprovoked venous thromboembolism. Smaller doses of DOAC reduce the risk of unwanted bleeding and should be recommended for most patients. The question however remains; should lower DOAC doses be used in all patients or only in some.

Let us consider the case of a 66-year-old woman (BMI = 42 kg/m^2, unprovoked pulmonary embolism) who is now eligible for extended anticoagulation therapy [18]. Her risk of relapse is high and standard DOAC doses are rather justified. Currently it is suggested [18] to use standard doses of DOAC for extended anticoagulant therapy in patients with no serious risk of bleeding and with:

— other indications for anticoagulant therapy (e.g. atrial fibrillation);
— VTE recurrence following DOAC therapy at reduced doses;
— life-threatening VTE episode (hemodynamic response to pulmonary embolism; phlegmasia cerulea dolens);
— chronic thromboembolic pulmonary hypertension;
— severe post-thrombotic syndrome;
— active cancer;
— at body weight > 120 kg, BMI > 40 kg/m^2.

Other patients may use reduced DOAC doses indefinitely. Check-up at least once a year is recommended.

The above considerations indicate that modification of DOAC doses may be recommended in justified cases and go beyond the existing recommendations ("off label"). The extended use of reduced DOAC doses which is extremely convenient and safe, requires however a critical approach and focus on conditions in which standard DOAC doses are more preferrable. A common, somewhat annoying standard is nowadays to add a remark to some experts' suggestions/recommendations, that they require validation in large randomized clinical trials. In an overwhelming number of cases, such expert recommendations refer to such small patients' subgroups that no funds could be raised to conform their validity.

Conflict of interest: none declared

References

1. Jame S, Barnes G. Stroke and thromboembolism prevention in atrial fibrillation. Heart. 2020; 106(1): 10–17, doi: 10.1136/heartjnl-2019-314898, indexed in Pubmed: 31533990.
2. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020; 4(19): 4693–4738, doi: 10.1182/bloodadvances.2020001830, indexed in Pubmed: 33007077.

3. Bayer V, Kotalczyk A, Kea B, et al. Global Oral Anticoagulation Use Varies by Region in Patients With Recent Diagnosis of Atrial Fibrillation: The GLORIA-AF Phase III Registry. J Am Heart Assoc. 2022; 11(6): e023907, doi: 10.1161/JAHA.121.023907, indexed in Pubmed: 35243870.
4. Woller SC, Stevens SM, Kaplan D, et al. Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: a randomized trial. Blood Adv. 2022; 6(6): 1661–1670, doi: 10.1182/bloodadvances.2021005808, indexed in Pubmed: 34662890.
5. Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood. 2018; 132(13): 1365–1371, doi: 10.1182/blood-2018-04-848333, indexed in Pubmed: 30002145.
6. Martinelli I, Abbattista M, Bucciarelli P, et al. Recurrent thrombosis in patients with antiphospholipid antibodies treated with vitamin K antagonists or rivaroxaban. Haematologica. 2018; 103(7): e315–e317, doi: 10.3324/haematol.2017.185132, indexed in Pubmed: 29519861.
7. Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, et al. Rivaroxaban versus vitamin K antagonist in antiphospholipid syndrome: a randomized noninferiority trial. Ann Intern Med. 2019; 171(10): 685–694, doi: 10.7326/M19-0291, indexed in Pubmed: 31610549.
8. Pastori D, Menichelli D, Cammisotto V, et al. Use of direct oral anticoagulants in patients with antiphospholipid syndrome: a systematic review and comparison of the international guidelines. Front Cardiovasc Med. 2021; 8: 715878, doi: 10.3389/fcvm.2021.715878, indexed in Pubmed: 34414220.
9. Chan KE, Edelman ER, Wenger JB, et al. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation. 2015; 131(11): 972–979, doi: 10.1161/CIRCULATIONAHA.114.014113, indexed in Pubmed: 25595139.
10. Wang X, Tirucherai G, Marbury TC, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. J Clin Pharmacol. 2016; 56(5): 628–636, doi: 10.1002/jcph.628, indexed in Pubmed: 26331581.
11. Wadsworth D, Sullivan E, Jacky T, et al. A review of indications and comorbidities in which warfarin may be the preferred oral anticoagulant. J Clin Pharm Ther. 2021; 46(3): 560–570, doi: 10.1111/jcpt.13343, indexed in Pubmed: 33393699.
12. Cheung CYS, Parikh J, Farrell A, et al. Direct oral anticoagulant use in chronic kidney disease and dialysis patients with venous thromboembolism: a systematic review of thrombosis and bleeding outcomes. Ann Pharmacother. 2021; 55(6): 711–722, doi: 10.1177/1060028020967635, indexed in Pubmed: 33073581.
13. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017; 135(25): e1159–e1195, doi: 10.1161/CIR.0000000000000503, indexed in Pubmed: 28298458.
14. Eikelboom JW, Connolly SJ, Brueckmann M, et al. RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013; 369(13): 1206–1214, doi: 10.1056/NEJMoa1300615, indexed in Pubmed: 23991661.
15. Connolly S, Ezekowitz M, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med . 2009; 361(12): 1139–1151, doi: 10.1056/nejmoa0905561, indexed in Pubmed: 19717844.
16. Connolly S, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011; 364(9): 806–817, doi: 10.1056/nejmoa1007432, indexed in Pubmed: 21309657.
17. Camm A, Cools F, Virdone S, et al. Mortality in patients with atrial fibrillation receiving nonrecommended doses of direct oral anticoagulants. J Am Coll Cardiol. 2020; 76(12): 1425–1436, doi: 10.1016/j.jacc.2020.07.045, indexed in Pubmed: 32943160.
18. Carlin S, Eikelboom JW. Direct oral anticoagulant dose selection: Challenging cases. J Thromb Haemost. 2021; 19(11): 2680–2686, doi: 10.1111/jth.15536, indexed in Pubmed: 34558172.
19. Bingzheng X, Jingnan R, Ligang B, et al. The effects of anticoagulant therapy re-initiation after gastrointesitinal bleeding: a systematic review and meta-analysis. J Clin Pharm Ther. 2021; 46(6): 1509–1518, doi: 10.1111/jcpt.13442 , indexed in Pubmed: 34101229.
20. Xu Y, Siegal DM. Anticoagulant-associated gastrointestinal bleeding: Framework for decisions about whether, when and how to resume anticoagulants. J Thromb Haemost. 2021; 19(10): 2383–2393, doi: 10.1111/jth.15466, indexed in Pubmed: 34273241.
21. Agnelli G, Buller HR, Cohen A, et al. AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013; 368(8): 699–708, doi: 10.1056/NEJMoa1207541, indexed in Pubmed: 23216615.
22. Weitz J, Lensing A, Prins M, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. N Engl J Med . 2017; 376(13): 1211–1222, doi: 10.1056/nejmoa1700518, indexed in Pubmed: 28316279.