Content available at: https://www.ipinnovative.com/open-access-journals

IP Indian Journal of Neurosciences

Journal homepage: https://www.ijnonline.org/

Review Article

DOACs/vitamin K antagonists induced hemorrhagic adverse effects; How to bridge therapy before procedures

Ajith Cherian[1], **Naveen Kumar Paramasivan**[1], **Divya KP**[1,*]

[1] *Dept. of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India*

ARTICLE INFO

Article history:
Received 24-05-2023
Accepted 30-06-2023
Available online 28-07-2023

Keywords:
Anticoagulation
Oral direct thrombin inhibitor
Oral factor Xa inhibitors
Pharmacotherapy

ABSTRACT

Direct oral anticoagulants (DOACs) are emerging as attractive alternatives to vitamin K antagonist which have long been the standard of care in anticoagulation. DOACs are indicated for both prevention and treatment. DOACs have emerged as more effective, safe, and convenient treatment options in thromboembolic settings. With the availability of a gamut of DOACs, clinicians are faced with challenging decisions relating to its hemorrhagic adverse effects. This review will provide an overview on how to manage the hemorrhagic adverse effects of DOACs/vitamin K antagonists and act as a practical guide for clinicians to optimize DOAC use in such challenging scenarios. Topics addressed include transitioning between anticoagulant regimens known as the bridge therapy.

1. Introduction

Direct oral anticoagulants (DOACs) have quickly become attractive alternatives to the long-standing standard of care in anticoagulation, vitamin K antagonist. DOACs are indicated for both prevention and treatment. DOACs have emerged as more effective, safe, and convenient treatment options in thromboembolic settings. With the expanding role of DOACs, clinicians are faced with increasingly complex decisions relating to its hemorrhagic adverse effects. This review will provide an overview on how to manage the hemorrhagic adverse effects of DOACs/vitamin K antagonists and act as a pragmatic guide for clinicians to optimize DOAC use in such challenging scenarios. This review addresses the transitioning between anticoagulant regimens known as the bridge therapy.

2. When is Anticoagulation Reversal Indicated?

Anticoagulation reversal is indicated only in instances of major bleeding in a critical site or in instances where urgent invasive procedure is being contemplated in patients taking anticoagulation, when the procedure cannot be safely delayed. The 2019 guidelines of the anticoagulation forum suggest reversal when there is a concern of clinically relevant plasma concentration of Direct acting Oral Anticoagulants(DOACs).[1] Although various definitions have been put forth to define a major bleed, the one proposed by The International Society on Thrombosis and Hemostasis (ISTH) is the most accepted,[2] which defines major bleeding as:

1. Fatal bleeding and/or,
2. Symptomatic bleeding in critical sites or organs such as intracerebral, intraspinal, intraocular, pericardial, retroperitoneal, intra-articular or intramuscular hemorrhages with compartment syndrome and/or,
3. Massive bleeding causing a drop in Hemoglobin of ≥2g/dL or requiring two units of whole blood or

* *Corresponding author*.
E-mail address: drdivyakp01@gmail.com (Divya KP).

https://doi.org/10.18231/j.ijn.2023.013

packed red cell transfusions.

Before considering reversal, it is important to know the type of anticoagulation the patient was on and understand the pharmacokinetics of the drugs. Of the oral anticoagulants commonly in use, DOACs have a favorable side effect profile with no requirement for monitoring of activity. A meta-analysis of more than 100000 patients from 13 randomised controlled trials reported that DOACs have 47% lesser bleeding risk compared to Vitamin K antagonists (VKAs).[3] Regarding DOACs, their shorter half-life and predictable pharmacokinetics, favorable safety profile compared to VKAs have favored the use of supportive measures alone (such as discontinuation of the offending drug and antiplatelets, compression or procedure directed at bleeding site if feasible, transfusion support and volume resuscitation) without any reversal agents in the pre-antidote era.[1]

Reversal agents may be specific (Idarucizumab for Dabigatran and Andexenat alpha for rivaroxaban/apixaban) or non-specific [Prothrombin Complex Concentrates (PCC), activated Prothrombin Complex Concentrates, Vitamin K, Fresh frozen plasma (FFP)].

1. For reversal of VKA associated bleeding PCC with vitamin K are the drugs of choice.
2. Protamine sulphate is the agent of choice for reversal of heparin.
3. For reversal of DOAC associated bleeding, specific reversal agents are recommended. When such reversal agents are not available, PCC may be used as an alternative.

Patients with overdose of DOAC without bleeding manifestations are to be managed as that of any other drug poisoning with supportive care. For those with VKA overdose, it is prudent to monitor the INR and treat them only when there are bleeding manifestations, depending on INR values. When there are no bleeding manifestations and INR is <4, omitting the next dose of VKA may be sufficient, while for those with INR >4 but <10 and bleeding risk is low, parentral vitamin K alone is sufficient without the need for PCC of FFP.

Dabigatran is the only DOAC for which hemodialysis may be used for reversal due to its low plasma protein binding, although the technical feasibility is limited especially when patients present with acute severe bleeding. Activated charcoal is another nonspecific therapeutic strategy that may be used within 3 hours of intake of dabigatran and upto 6 hours in case of apixaban.[4] Ciraparantag (PER977) is a novel agent that can bind to heparin, low molecular weight heparin, direct thrombin inhibitors as well as Xa inhibitors, and is being touted as an universal reversal agent that is still in clinical trials.[5]

Reversal agents have adverse effects such as thromboembolic events especially in the initial days after reversal. It is important to consider the degree of anticoagulation, the time interval since the last dose and the extent to which the anticoagulant could contribute to the bleeding. The benefits of reversal should always be weighed against the risk of thromboembolic complications and anticoagulation should be resumed soon afterwards.

The following situations may be taken as examples wherein anticoagulation reversal is not indicated and alternative supportive measures may be deemed enough:[1]

1. Mucosal bleeding (epistaxis, uterine bleeding, hematuria) that is mild with no significant drop in hemoglobin
2. Superficial skin abrasions with minor oozing
3. Peripheral venous injuries that are amenable to compression
4. Occult blood positive in stools
5. Trauma without bleeding
6. Overdose of anticoagulant without bleeding manifestations
7. Surgical procedures that can be safely delayed in patients on anticoagulation
8. Minor surgical procedures such as cataract surgery, upper gastrointestinal endoscopy without biopsy, minor dental or dermatological procedures with minimal bleeding risk may be performed with the patient on anticoagulation. Surgery may be performed when the INR is <1.5 in patients on VKA.

The PAUSE study found that patients on DOACs may be subjected to surgery by delaying the procedure based on the associated bleeding risk. For surgical procedures with mild bleeding risk, anticoagulation was withheld a day before, while for those with higher bleeding risk it was withheld 2 days before and even longer for patients on dabigatran with creatinine clearance less than 50ml/min.[6] When there is a pressing need for an urgent surgery and the PAUSE protocol cannot be adhered to, it is recommended to assess the DOAC level in blood. Alternatively factor Xa assays or thrombin time may be performed, for Xa inhibitors and dabigatran respectively.

In patients taking VKA requiring non emergent surgery, further doses may be withheld and the procedure may be done when INR <1.5. In patients with INR >1.5 and in whom an urgent surgery may be delayed for 6-12 hours, it may be reasonable to give Vitamin K. For those requiring emergency surgery that cannot be delayed, anticoagulation reversal with both vitamin K and PCC may be considered.

3. Methods to Bridge Therapy

Assessment of the thromboembolic risk to the patient with atrial fibrillation versus the risk of perioperative bleeding has to be made before deciding on the need for bridging therapy, which can be done using the CHA2DS2VASc (congestive heart failure, hypertension,

Table 1: Risk stratification of thromboembolic potential

Thromboembolic risk category	Atrial fibrillation	Mechanical heart valves	Venous thromboembolism (VTE)
High risk (annual risk >10%)	CHADS2 score ≥5, Recent stroke/TIA within 3 months, Rheumatic valvular heart disease,	Mechanical mitral valve, Older aortic mechanical valve (caged ball, tilting disk), recent stroke/TIA within 3 months	Recent VTE within 3 months, High risk thrombophilia (deficiency of protein C, protein S, antithrombin, antiphospholipid syndrome, homozygous factor V Leiden or prothrombin gene mutation)
Moderate risk (annual risk 5-10%)	CHADS2 score 3 or 4	Bileaflet aortic valve prosthesis with ≥1 risk factor(age ≥75, atrial fibrillation, congestive heart failure, diabetes mellitus, hypertension, stroke or TIA)	VTE within 3-12 months, moderate risk thrombophilia (heterozygous mutations in factor V Leiden or prothrombin gene), recurrent VTE, active cancer (metastatic or treated within past 6 months)
Low risk (annual risk <5%)	CHADS2 score 0-2	Bileaflet aortic valve prosthesis with no risk factors	VTE >12 months ago

Table 2: List of low and high bleeding risk procedures

Low bleeding risk procedures	High bleeding risk procedures
Cataract surgery	Cardiac surgeries
Dental extraction and minor dental procedures like endodontics, prosthetic fitting, restoration	Intracranial and intraspinal surgeries
Upper and Lower gastrointestinal endoscopies without biopsies	Major orthopedic surgeries
Dermatological procedures	Surgery in highly vascular organs (liver, spleen, kidney)
Bronchoscopies	Intra-abdominal or intra-thoracic surgeries (eg. Visceral organ or lung resection, cancer surgeries)
Intra-articular injections	Polpectomies
Carpal tunnel surgery	Biopsies of kidney, prostrate
Cardiac catheterization (with or without percutaneous coronary intervention)	Vascular surgeries (aneurysm repair, vascular bypass)
Any surgical procedure lasting < 1 hour	Permanent pacemaker or internal defibrillator insertion
	Any surgical procedure lasting ≥1 hour

age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female))scores and HAS-BLED (Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage) scores respectively.[7] HAS-BLED has been shown to reliably predict post-operative bleeding in the BORDER study.[8] Bridging therapy is substitution of a long-acting oral anticoagulant with a short acting anticoagulant (usually heparin or low molecular weight heparin) so as to minimize the duration the patient is out of therapeutic anticoagulation.[9] Recent evidence do not favor bridging therapy as it has been shown to increase bleeding risk with no significant differences in the thromboembolic risks when comparing patients with and without bridging therapy respectively[10–12] (although conditions with high bleeding risks were not adequately represented in some). Despite this, bridging therapy is used in high risk conditions with thromboembolic potential, some of which are mentioned below:

1. Prosthetic mitral valve, prosthetic aortic valve with additional risk factors such as prior stroke, TIA, or in-situ thrombus in the heart, more than 2 prosthetic valves
2. Recent history (within 3 months) of stroke, TIA or venous thromboembolism.
3. Recent coronary stenting (within 3 months).
4. Those who had thromboembolic events while on anticoagulation or when anticoagulation was temporarily withheld.
5. Those with atrial fibrillation and a CHA2DS2VASc score >5 with additional cardiovascular risk factors.

Risk stratification of thromboembolic potential to decide on the need for bridging therapy as suggested by BRIDGE investigators[13] (Table 1)

The protocol used in the BRIDGE study is the one that is commonly used for bridging therapy.[12]

1. Stop VKA 5 days prior to surgery.

2. Start low molecular weight heparin (LMWH) 3 days prior to surgery.
3. Check INR 24 hours prior to surgery, if INR >1.8, then administer vitamin K. If INR 1.5-1.8, then vitamin K is optional.
4. Restart VKA on the same evening or next day of procedure.
5. Restart LMWH by 12- 24 hours after surgery for low bleeding risk procedures and by 48-72 hours for high bleeding risk procedures.
6. Stop LMWH when INR reaches therapeutic levels.

A suggested classification of low and high bleeding risk procedures may be used for deciding on the timing of restarting bridging therapy. For low bleeding risk procedures bridging may be started 24 hours after surgery while for high bleeding risk procedures it is reasonable to wait for 48-72 hours.[14] (Table 2)

A patient with a high bleeding risk will benefit from anticoagulation interruption in situations such as major surgeries with high risk of perioperative bleeding. For patients on DOACs, a minimum interruption time of at least 2 half-lives (~24 hours) is recommended for patients with low bleeding risks, and maximum of 72 hours for those with high bleeding risks. The duration of interruption is extended to a maximum of 120 hours for those on dabigatran with creatinine clearance <30ml/min.[14]

Reversal of anticoagulation needs to be applied to clinical scenarios of major bleeding or where urgent surgery is required. It is not to be used injudiciously in alternative scenarios where supportive management is often enough. With current evidence not favouring bridging therapy in view of elevated bleeding risks and no differences in thromboembolic potential, bridging therapy may be considered only in instances of high thromboembolic risks.

4. Conflict of Interest

None.

5. Source of Funding

None.

References

1. Cuker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott E, et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. *Am J Hematol*. 2019;94(6):697–709.
2. Schulman S, Kearon C. Scientific the SOCOAOT, Thrombosis SC of the ISO, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692–4. doi:10.1111/j.1538-7836.2005.01204.x.
3. Chai-Adisaksopha C, Hillis C, Isayama T, Lim W, Iorio A, Crowther M, et al. Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials. *J Thromb Haemost*. 2015;13(11):2012–20.
4. Shih AW, Crowther MA. Reversal of direct oral anticoagulants: A practical approach. *Hematology*. 2016;(1):612–9.
5. Ansell J, Laulicht BE, Bakhru SH, Burnett A, Jiang X, Chen L, et al. Ciraparantag, an anticoagulant reversal drug: mechanism of action, pharmacokinetics, and reversal of anticoagulants. *Blood*. 2021;137(1):115–25.
6. Douketis JD, Spyropoulos AC, Anderson JM, Arnold DM, Bates SM, Blostein M, et al. The Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) Study for Patients on a Direct Oral Anticoagulant Who Need an Elective Surgery or Procedure: Design and Rationale. *Thromb Haemost*. 2017;117(12):2415–24.
7. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, et al. AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2009;74(1):104–32.
8. Omran H, Bauersachs R, Rübenacker S, Goss F, Hammerstingl C. The HAS-BLED score predicts bleedings during bridging of chronic oral anticoagulation. Results from the national multicentre BNK Online bRiDging REgistRy (BORDER). *Thromb Haemost*. 2012;108(1):65–73.
9. Tafur A, Douketis J. Perioperative management of anticoagulant and antiplatelet therapy. *Heart*. 2018;104(17):1461–7.
10. Siegal D, Yudin J, Kaatz S, Douketis JD, Lim W, Spyropoulos AC, et al. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation*. 2012;126(13):1630–9.
11. Douketis JD, Healey JS, Brueckmann M, Eikelboom JW, Ezekowitz MD, Fraessdorf M, et al. Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients who had an elective surgery or procedure. *Thromb Haemost*. 2015;113(3):625–32.
12. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. *N Engl J Med*. 2015;373(9):823–33.
13. The BRIDGE investigators, Bridging Anticoagulation. *Circulation*. 2012;125:496–8.
14. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL, Ortel TL, Saxonhouse SJ, et al. ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation. *J Am Coll Cardiol*. 2017;69(7):871–98. doi:10.1016/j.jacc.2016.11.024.

Author biography

Ajith Cherian, Additional Professor https://orcid.org/0000-0001-8743-9793

Naveen Kumar Paramasivan, Post Doctoral Fellow https://orcid.org/0000-0002-2185-4385

Divya KP, Associate Professor https://orcid.org/0000-0002-4695-8842

Cite this article: Cherian A, Paramasivan NK, Divya KP. DOACs/vitamin K antagonists induced hemorrhagic adverse effects; How to bridge therapy before procedures. *IP Indian J Neurosci* 2023;9(2):66-69.