Management of bleeding in patients on direct oral anticoagulants in Sri Lanka

Karunathilaka H G C S¹, Gooneratne L V²

Journal of the Ceylon College of Physicians, 2019, 50, 72-76

Abstract

Direct oral anticoagulants (DOACs) are being used increasingly in Sri Lanka. However, the specific antidotes for the reversal of DOACs are not currently available in Sri Lanka. Although DOACs have a predictable dose response they may cause bleeding, including major bleeds such as intracranial and gastrointestinal bleeds. Most of the available algorithms providing guidance for management of bleeding in patients on DOACs contain laboratory tests and therapeutic agents that are not available in Sri Lanka. Therefore, it is timely to have an evidence-based guide for managing patients who develop bleeding while on a DOAC in Sri Lanka.

Key words: direct oral anticoagulants, warfarin, bleeding risk

Introduction

DOACs act by directly inhibiting coagulation serine proteases. They are more convenient to use, and at least as safe and effective as vitamin K antagonists (VKA)¹². Although DOACs are yet to be registered in Sri Lanka, physicians increasingly encounter patients who are prescribed these medications. The most frequently encountered DOACs are the direct thrombin inhibitor dabigatran and direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban. DOACs are more convenient to use than VKA because they have a predictable dose response, therefore, do not require routine monitoring and have fewer food and drug interactions. However, unlike warfarin, they are approved only for specific indications and are superior or at least as effective as VKA in stroke prevention in non-valvular atrial fibrillation (NVAF), treatment and prophylaxis of venous thrombo-embolism (VTE)⁴⁻⁹. The use of rivaroxaban in combination with anti-platelets is licensed for secondary prevention of acute coronary syndrome (ACS) in the absence of atrial fibrillation (AF)⁶. Many clinical trials show DOACs are non-inferior to VKA and low molecular weight heparin (LMWH) in prophylaxis and treatment of cancer associated VTE¹⁰⁻¹¹.

When bleeding risk is considered, DOACs have less risk of intracranial haemorrhage (ICH) than VKA but gastrointestinal (GI) bleeding risk is higher with rivaroxaban, dabigatran and edoxaban compared to warfarin¹⁻³. DOACs may also cause major bleeds, most commonly GI followed by ICH. Specific antidotes for DOACs such as idarucizumab for factor IIa inhibitors and adexanet alpha for factor Xa inhibitors have been approved for clinical use. Controlling of bleeding associated with DOACs is challenging in Sri Lanka because of the unavailability of the specific antidotes and their prohibitive cost. A 100mg vial of Andexanet Alpha is about $2750 (a single dose is 400mg) and idarucizumab 5g kit is $3500 to 4200 (Table 1).

Monitoring of the anticoagulant effect of DOACs

Routine monitoring of anticoagulant effect is not recommended for patients on DOACs. Monitoring of drug levels are indicated in the following circumstances¹¹⁻¹⁴.
Pre-operatively or prior to invasive procedures if drug has been taken within 24 hours
If patient is bleeding
Taken an overdose
Renal impairment
To establish the optimal dose in patients with extremes of body weight
If the patient develops thrombosis while on treatment.

Quantitative assessment of drug levels using liquid chromatography/tandem mass spectrometry (LC-MS/MS) is the gold standard to monitor drug levels. However, due to the limited availability of LC-MS/MS, adaptations of more widely available coagulation tests are used to monitor coagulation activity of DOACs. Calibrated Xa assay for factor Xa inhibitors and modified diluted plasma thrombin time (dTT) or Ecarin clotting time (ECT) for factor IIa inhibitors are some of them. Qualitative tests such as prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT) may give some indication of whether the anticoagulant effect is supra-therapeutic, therapeutic or sub-therapeutic. Dabigatran causes prolongation of APTT and TT and a normal TT indicates a very low level of dabigatran. Rivaroxiban and edoxaban cause prolongation of PT, but PT and APTT are usually insensitive to apixaban.

Management of bleeding in patients on DOACs
Management options depend on the type of anticoagulant, site and severity of bleeding. Initial non-pharmacological management is most important and is common to all types of anticoagulant associated bleeding. Specific pharmacological management depends on the type of DOAC and severity of bleeding.

1) Initial non-pharmacological measures.
- Stop the drug
- Document the time and dose of the last drug dose and other concomitant medications.
- Document presence of pre-existing renal or hepatic impairment and other comorbidities.
- Estimate the half-life (Table 1).
- Assess the source of bleeding.
- Request FBC, PT, APTT, TT, fibrinogen level, serum creatinine.
- If available, specific laboratory test to measure the anticoagulant effect of the drug: diluted TT for dabigatran and calibrated anti Xa assay for factor Xa inhibitors.
- Intravenous fluid resuscitation and red cell concentrate (RCC) transfusions to maintain haemodynamic stability.

### Table 1. Characteristics of DOACs

|                  | **Apixaban** | **Edoxaban** | **Rivaroxaban** | **Dabigatran** |
|------------------|--------------|--------------|-----------------|----------------|
| **Target**       | Factor Xa    | Factor Xa    | Factor Xa       | Factor IIa     |
| **Time to peak effect (hours)** | 1-3          | 1-2          | 2-4             | 1-3            |
| **Half-life (hours)** | 12           | 6 -10        | 5-9             | 12-17          |
| **Dosing regimen** | Twice daily  | Once daily   | Once daily      | Twice daily    |
| **Renal clearance (%)** | 25%          | 50%          | 33%             | 80%            |
| **Dosing in acute VTE treatment** | 10 mg BID for 7 days, then 5mg BID | 60 mg OD after 5 days of parenteral anticoagulation | 15 mg BID for 21 days, then 20 mg OD | 150 mg BID after 5 days of parenteral anticoagulation |
| **Prophylactic dose for VTE prevention** | 5 mg BID | 60 mg OD | 20 mg OD | 150 mg BID |

Dosing regimen
- Twice daily
- Once daily
- Twice daily

Renal clearance
- 25%
- 50%
- 33%
- 80%

Dosing in acute VTE treatment
- 10 mg BID for 7 days, then 5mg BID
- 60 mg OD after 5 days of parenteral anticoagulation
- 15 mg BID for 21 days, then 20 mg OD
- 150 mg BID after 5 days of parenteral anticoagulation

Prophylactic dose for VTE prevention
- 5 mg BID
- 60 mg OD
- 20 mg OD
- 150 mg BID
Clinical Practice

- Mechanical compression to control bleeding, e.g. for superficial wounds, epistaxis.
- Endoscopic, radiological or surgical measures to control bleeding.

2) Adjunct treatment

Antifibrinolytics: Tranexamic acid and e-aminocaproic acid have not been specifically studied for their therapeutic effect in DOAC associated bleeding. They stabilize the clot by inhibiting fibrinolysis. Therefore, they can be considered in moderate to severe bleeding\(^1\),\(^17\).

Desmopressin: Has not been specifically studied in DOACs associated bleeding. It increases the secretion of VWF from endothelial cells and increases plasma VWF and promotes haemostasis. Therefore, it can be considered in DOACs associated bleeding\(^1\),\(^17\).

3) Specific treatment

3.1 Factor IIa inhibitors (Dabigatran)

If the patient presents within 2 hours of the last dose of dabigatran, activated charcoal is effective for prevention of further drug absorption. Dabigatran can be effectively cleared from plasma by haemodialysis, haemofiltration and charcoal haemoperfusion because of its low plasma protein binding ability\(^16\).

Minor bleeds can effectively be managed with non-pharmacological measures. Major bleeds and minor bleeds not responding to non-pharmacological methods need a reversal agent. Andexanet alpha is the specific antidote for factor Xa inhibitors, which is catalytically inactivated recombinant factor Xa. It binds and sequestrates factor Xa inhibitors. When andexanet alpha is not available the next option is four factor PCC. Other less effective options are rFVIIa, aPCC and fresh frozen plasma (FFP)\(^2\),\(^13\),\(^16\)-\(^19\).

In Sri Lanka the available first option is four factor PCC and if it’s not available rFVIIa, aPCC or FFP can be used.

Peri-operative management of patients on DOACs

Treatment interruption is required prior surgery, usually 24-48 hours before surgery depending on renal function and the bleeding risk of surgery\(^20\).

Table 2. Pre-operative interruption of DOACs

| Drug       | Minor surgery | Major surgery |
|------------|---------------|---------------|
| Apixaban\(^1\),\(^18\),\(^19\) | 24 h          | 48 h          |
| Edoxaban\(^1\),\(^18\)       | 24 h          | 48 h          |
| Rivaroxaban\(^18\),\(^19\)   | 24 h          | 48 h          |
| Dabigatran\(^1\),\(^18\),\(^19\) |              |               |
| CrCl >80 mL/min            | 24 h          | 48 h          |
| CrCl 50-80 mL/min          | 36 h          | 72 h          |
| CrCl 30-50 mL/min          | 48 h          | 96 h          |

If the patient needs an urgent invasive procedure or surgery it should be delayed for at least 12 hours after the last dose of DOAC, if possible. If it cannot be delayed, use of reversal agents is suggested. (refer step 5 of algorithm I).

DOACs can be restarted at a therapeutic dose 24 hours after “low bleeding risk” procedures and 48-72 hours after “high bleeding risk” procedures, if adequate haemostasis has been achieved. If the patient has high thromboembolic risk, starting a low dose of dabigatran (75mg bd), rivaroxaban (10mg bd), apixaban (2.5mg bd) or low molecular weight heparin (LMWH) 6-8 hours after surgery once haemostasis has been achieved can be considered\(^20\),\(^21\).
Algorithm I – Treatment algorithm for bleeding in patients on DOACs in Sri Lanka

Step 1
✓ Stop the drug
✓ Assess the bleed
✓ FBC, PT, APTT, TT, S.fibrinogen, S.Cr, LFT, grouping and DT
✓ Anti FXa level and/OR diluted TT (if available)

Step 2
✓ Fluid resuscitation and RCC transfusion

Step 3
✓ Local haemostasis
  • Local measures – eg direct pressure for superficial wounds, epistaxis
  • Early referral – endoscopic, interventional radiology procedures or surgical measures to control bleeding

Step 4
✓ Adjunct treatment – antifibrinolytic agents/desmopressin
✓ Patient on Dabigatran – consider activated charcoal if last dose is within 2 hours

Step 5

**Factor IIa inhibitors –**
- haemodialysis or haemofiltration
- aPCC 50IU/kg single dose
  - If no response
  - rFVIIa 90μg/kg IV single dose or 4-factor or 3-factor PCC 50IU/kg IV single dose

**Factor Xa inhibitors – Apixaban Rivaroxaban Edoxaban**
- 4-factor PCC 50IU/kg IV one
  - If no response
  - rFVIIa 90μg/kg IV single dose or aPCC 50IU/kg IV single dose or FFP 15-20ml/kg

If no response OR WHO grade 3 or 4 bleeding score
References

1. Baglin T, Keeling D. Antithrombotic Agents. In: A Victor Hoffbrand, Doulas R Higgs, David M Keeling, Atul B Mehta, editors. Postgraduate Haematology; 7th ed, Weley Blackwell 2016: 820-9.

2. Levy JH, Douketis J, Weitz JI. Reversal agents for non-Vitamin K antagonist oral anticoagulants. Nature Reviews Cardiology 2018; 15: 273-81.

3. Undas A, Goralczyk T. Direct oral anticoagulants in patients with thrombophilia: Challenges in diagnostic evaluation and treatment. Advances in Clinical and Experimental Medicine 2016; 25(6): 1321-30.

4. Czuprynska J, Patel JP, Arya R. Current challenges and future prospects in oral anticoagulant therapy. British Journal of Haematology 2017; 178(6): 838-51.

5. Granger CB, Alexander JH, McMurray J, et al. Apixaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine 2011; 365: 981-92.

6. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New England Journal of Medicine 2011; 365: 883-91.

7. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal of Medicine 2009; 361: 1139-51.

8. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine 2013; 368: 2093-2104.

9. Shah S, Norby FL, Datta YH, et al. Comparative effectiveness of direct oral anticoagulants and warfarin in patients with cancer and atrial fibrillation. Blood Advances 2018; 2(3): 200-9.

10. Kraaijpoel N, Carrier M. How I treat cancer-associated venous thromboembolism. Blood 2019; 133(4): 291-8.

11. Ay C, Beyer-Westendorf J, Pabinger I. Treatment of cancer-associated venous thromboembolism in the age of direct oral anticoagulants. Annals of Oncology. 2019; 30: 897-907.

12. Green L, Tan J, Morris JK, et al. A three-year prospective study of the presentation and clinical outcomes of major bleeding episodes associated with oral anticoagulant use in the UK (Orange study). Haematologica 2018; 103(4): 738-45.

13. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. American Journal of Hematology 2019; 94: 697-709.

14. Lee LH. DOACs — advances and limitations in real world. Thrombosis Journal. 2016; 14(1): 133-63.

15. Connors JM. Testing and monitoring direct oral anticoagulants. Blood 2018; 132(19): 2009-15.

16. Makris M, Van Veen JJ, Tait CR, Mumford AD, Laffan M. Guideline on the management of bleeding in patients on antithrombotic agents. British Journal of Haematology 2012; 160: 35-46.

17. Shih AW, Crowther MA. Reversal of direct oral anticoagulants: A practical approach. Hematology 2016; 1: 612-19.

18. Baumann Kreuziger LM, Keenan JC, Morton CT, Dries DJ. Management of the Bleeding Patient Receiving New Oral Anticoagulants: A Role for Prothrombin Complex Concentrates. Bio Med Research International 2014; 2014: 583794: 1-7.

19. Frank Peacock W, Gearhart MM, Mills RM. Emergency management of bleeding associated with old and new oral anticoagulants. Clinical Cardiology 2012; 35(12): 730-7.

20. Dubois V, Dincq AS, Douxfils J, Ickx B, Samama CM, Dogné JM, et al. Perioperative management of patients on direct oral anticoagulants. Thrombosis Journal 2017; 15(14): 2-17.

21. Lai A, Davidson N, Galloway SW, Thachil J. Perioperative management of patients on new oral anticoagulants. British Journal of Surgery 2014; 101: 742-9.