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Editorial

Rational use of direct oral anticoagulants

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Direct oral anticoagulants (DOACs) are oral antithrombotic agents gaining popularity in clinical practice due to their rapid onset of action, fixed dosing, predictable pharmacokinetics, reduced need for frequent laboratory monitoring and less interactions with diet and medications when compared with oral vitamin K antagonists.

There are two major classes of DOACs; direct thrombin inhibitors and factor Xa inhibitors. Dabigatran is a direct thrombin inhibitor and was the first DOAC to receive Food and Drug Administration (FDA) approval in 2010 while rivaroxaban, apixaban, edoxaban, and betrixaban are factor Xa inhibitors which were approved subsequently[1].

Since the use of DOACs is increasing among the healthcare professionals, some important facts on the correct use of these therapeutic agents are discussed below.

DOACs in venous thromboembolism (VTE): Chest Guidelines 2021 recommends the use of a DOAC (apixaban, rivaroxaban, dabigatran or edoxaban) for the treatment phase (initial 3 months) of VTE and for the extended phase when indicated[2].

Rivaroxaban is initiated at a dose of 15 mg twice daily for 21 days followed by 20 mg daily. Apixaban can be started at a dose of 10 mg twice a day for 7 days followed by 5 mg twice a day. For patients who are offered extended phase anticoagulation, rivaroxaban 10 mg once a day or apixaban 2.5 mg twice a day are recommended.

DOACs for VTE prophylaxis in surgical and medical patients: Rivaroxaban can be given for primary prophylaxis in total hip arthroplasty (THA), total knee arthroplasty (TKA) and acutely ill medical patients at a dose of 10 mg once daily for 35 days, 12 days and 31 to 39 days respectively[3].

Apixaban can be given at a dose of 2.5 mg twice daily for 12-14 days in TKA and around 30 days in THA[4].

DOACs for cancer associated venous thrombosis (CAT): BSH guidelines 2024 recommends direct oral factor Xa inhibitors or low molecular weight heparin (LMWH) for CAT (other than catheter-related) for 6 months initially. DOACs can be considered in the absence of luminal gastrointestinal (GI)/ urothelial or intracranial malignancies, GI tract impairment, severe renal impairment (CrCl<30 mL/min) and for patients with possible drug to drug interactions. Continuation of anticoagulation beyond six months is recommended in patients with CAT and active cancer[5].

DOACs in thrombosis at unusual sites: Dabigatran and factor Xa inhibitors can be considered in place of warfarin in adults with cerebral venous thrombosis (CVT) after an initial period of treatment with heparins. DOACs can be used as alternatives to warfarin in splanchnic vein thrombosis and upper limb deep vein thrombosis. For superficial vein thrombosis of the lower limb that require anticoagulation, rivaroxaban 10 mg daily over 45 days can be used in place of LMWH or fondaparinux[6].

DOACs in atrial fibrillation (AF): Based on large phase 3 randomized controlled trials, ROCKET AF, ARISTOTLE, ENGAGE AF TIMI and RE-LY, FDA approval has been granted for dabigatran, rivaroxaban, apixaban and edoxaban, in the prevention of thromboembolic disease in NVAF.

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Rivaroxaban is recommended at a dose of 20 mg once a day (15 mg once a day when the CrCl is 15-50 mL/min). Recommended dose of apixaban is 5 mg twice a day (or 2.5 mg twice a day in patients with 2 or more of the criteria; age >80 years, body weight ≤60 kg, serum creatinine level of ≥1.5 mg/dL)[7].

DOACs in peripheral arterial disease (PAD): Rivaroxaban 2.5 mg twice a day with low dose aspirin can be considered for those with stable PAD, at low risk of bleeding and high risk of major thrombotic vascular events including after recent lower extremity revascularization[3,12].

Use of DOACs in inherited thrombophilia: A study involving 597 patients with inherited thrombophilia and VTE has shown that the efficacy of DOACs is comparable to warfarin/ heparin in prevention of VTE recurrences, residual vein thrombosis and post thrombotic syndrome. Although the incidence of clinically relevant non major bleeding episodes were higher among those who were on DOACs, there were no major bleeding[8].

Role of DOACs in heparin induced thrombocytopenia (HIT): BSH guidelines 2023 suggests the use of DOACs as an oral anticoagulant in clinically stable HIT. It is suggested either as the initial therapy in selected hemodynamically stable patients or after initial treatment with a parenteral non heparin anticoagulant once the platelet count is normalized[4,12]. The duration of anticoagulation in HIT complicated with thrombosis is three months while in HIT without thrombosis, anticoagulation therapy for four weeks or until platelet count is more than $150x10^9$/L, whichever later, is indicated. In the presence of arterial thrombosis DOACs are not recommended[9].

DOACs in antiphospholipid syndrome (APLS): BSH guidelines 2020 recommends not to initiate DOACs for treatment or secondary prophylaxis in patients with venous thrombosis in known triple positive APLS. It further suggests against the initiation of DOACs in non-triple positive APLS. DOACs are not recommended for those with APLS and arterial thrombosis.

Other contraindications and warnings for DOACs: DOACs are contraindicated in mechanical prosthetic heart valves and AF in moderate to severe mitral stenosis (valvular AF).

DOACs should not be used in pregnancy. Some available data suggest that there is a high possibility of fetal loss and fetal abnormalities with its use in pregnancy compared to LMWH[11]. Use of DOACs in lactation is not generally recommended due to lack of safety data.

Drug to drug interactions: Even though, DOACs impart a lower risk of drug-to-drug interaction, when compared with warfarin, they still show significant interactions with some agents. Some of the recommendations include, to avoid the concomitant use of rivaroxaban and apixaban with strong CYP3A4 inhibitors + p-gp inhibitors (e.g. ketoconazole, itraconazole, ritonavir), strong CYP3A4 inducers (e.g. phenytoin) and p-gp inducers (e.g. rifampicin). Use of both agents with moderate CYP3A4 inhibitors + p-gp inhibitors (e.g. clarithromycin, diltiazem) should be avoided in severe renal impairment[1].

Use of DOACs in renal and hepatic disease: For rivaroxaban and apixaban, no dose adjustment is needed for the treatment and prophylaxis of VTE in mild to moderate renal impairment (CrCl>30 mL/min)[12,13]. There is no clinical data on the use of rivaroxaban in patients with severe renal impairment (CrCl<15 mL/min) including those on dialysis, for above indications. Hence it is advised to avoid its' use[3].

Manufacturer suggests the use of apixaban for the treatment and prophylaxis of VTE with caution in patients with severe renal impairment (CrCl 15-29 mL/min) while it is not recommended in patients with CrCl<15 mL/min and on haemodialysis due to lack of safety data[13]. Some experts avoid use of apixaban in all indications if CrCl <25 mL/min until robust data are available[4].

All five DOACs can be used in mild hepatic impairment (Child-Pugh A) without dose adjustments whereas all of them are contraindicated in severe hepatic impairment (Child-Pugh C). In moderate disease (Child-Pugh B) only dabigatran, apixaban and edoxaban can be used with caution whereas rivaroxaban and betrixaban need to be avoided.

Use of DOACs in extremes of body weight: Standard doses of any DOAC can be considered for patients with VTE, up to BMI 40 kg/m^2 and weight 120 kg while standard doses of apixaban and rivaroxaban are considered beyond this weight limit[14].

A review on use of DOACs at extremes of body weight in the context of NVAF, showed that standard doses used for non-obese individuals appear safe for obese patients[15].

A large Korean study has concluded that four DOACs (rivaroxaban, apixaban, edoxaban and dabigatran) have shown better effectiveness and safety profiles than warfarin in underweight patients <60 kg with NVAF and results with reduced dosage was comparable to the regular dose[16].

Management of bleeding: In case of major bleeding, gastric lavage or activated charcoal can be considered if the last dose of DOACs is between 2-6 hours. Dabigatran action can be reversed with idaruzucimab. If it is not available, haemodialysis can be considered especially in renal failure. Andexanet alpha has been FDA and NICE approved as the reversal agent for rivaroxaban and apixaban. If specific reversal agents are not available pro-thrombin complex concentrates (PCC) or activated factor VII can be used to control the bleeding[17].

Procedural management: DOACs have been found to give false positive results in aPTT and dRVVT tests for lupus anticoagulants (LA) even with low concentrations. Therefore, if feasible withholding DOACs for 48 hours (or longer in renal impairment) is generally indicated[18].

Discontinuing rivaroxaban and apixaban for 24 hours (48 hours if CrCl <30 mL/min) before low-bleed-risk procedures and 48 hours before high-risk bleeding procedures (72 hours if CrCl<30 mL/min) is indicated[19]. For neuraxial interventions guidelines recommend to discontinue apixaban and rivaroxaban 72 hours prior to the procedure (Horlocker 2018)[4,12].

Reintroduction is generally indicated 6-12 hours following low bleeding risk procedures if haemostasis is fully achieved and 48 hours after high bleeding risk procedures.

Monitoring of therapy: Routine coagulation tests such as PT, aPTT are not useful for the monitoring of DOAC therapy because of high variability of their sensitivity.

Thrombin time is very sensitive to dabigatran, and hence normal values suggest that the plasma drug level is clinically insignificant.

In well-resourced settings rivaroxaban/apixaban assays based on chromogenic anti Xa methods with the use of appropriate calibrators and controls, provide accurate drug levels. These tests are not suitable during emergencies as the turnaround time (TAT) is longer. For emergency assessments, heparin assays using anti-Xa activity may be useful[20].

Switching between anticoagulants: DOACs show immediate onset of action, hence bridging with unfractionated heparin/ LMWH is not indicated at the initiation.

Switching from warfarin to a DOAC involves stopping warfarin with daily monitoring of INR and to start dabigatran/apixaban when INR is <2, edoxaban when INR is ≤2.5 and rivaroxaban when INR is <3[3,21]. If a DOAC (apixaban/ rivaroxaban) to be replaced with warfarin, continuation of the former concomitantly with warfarin until the target INR is reached is indicated due to the slow onset of action of warfarin. Alternatively withholding DOAC, initiation of LMWH at the due time for DOAC with warfarin and to discontinue LMWH once target INR is reached is advised[1]. If switching between a DOAC and LMWH or two DOACs is needed, the second agent can be administered at the time of the next scheduled dose without any overlap.

Use of DOACs in children: FDA recently approved rivaroxaban (from birth to 18 years of age) and dabigatran (from 3 months to 17 years of age) for the treatment and prevention of VTE. There are some safety concerns on limited availability of therapeutic monitoring and lack of approved reversal agents in this population. Despite these limitations the use of DOACs in children is rapidly increasing. It is recommended to follow dose nomogram when prescribing DOACs for these age groups[22].

References

1. Chen A, Stecker E, A Warden B. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *J Am Heart Assoc.* 2020; **9**(13): e017559. PMID: 32538234; PMCID: PMC7670541.
2. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. *Chest.* 2021; **160**(6): e545-e608. PMID: 34352278.
3. Xarelto package insert; Janssen pharmaceuticals inc, 2022.
4. Apixaban: Drug information; UpToDate; Topic 85642 Version 331.0
5. Alikhan R, Gomez K, Maraveyas A, Noble S, Young A, Thomas M. British Society for Haematology. Cancer-associated venous thrombosis in adults (second edition): A British Society for Haematology Guideline. *Br J Haematol.* 2024; 25. doi: 10.1111/bjh.19414. PMID: 38664942.
6. Riat R, Gomez K; British Society for Haematology Haemostasis and Thrombosis Taskforce. Addendum to guidelines on the investigation and management of venous thrombosis at unusual sites. *Br. J. Haematol.* 2012; **159**: 28-38. Use of Direct Oral Anticoagulants. *Br J Haematol.* 2022; **198**(1): 46-9. PMID: 35389508.
7. Joglar et al. Peer Review Committee Members. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2024; **149**(1): e1-e156.
8. Campello E, Spiezia L, Simion C, Tormene D, Camporese G, Dalla Valle F, et al. Direct Oral Anticoagulants in Patients with Inherited Thrombophilia and Venous Thromboembolism: A Prospective Cohort Study. *J Am Heart Assoc.* 2020; **9**(23): e018917. PMID: 33222589; PMCID: PMC7763770.
9. Arachchillage DJ, Thachil J, Anderson JAM, Baker P, Poles A, Kitchen S, Laffan M. BSH Committee. Diagnosis and management of heparin-induced thrombocytopenia: Third edition. *Br J Haematol.* 2024; **204**(2): 459-75. PMID: 38153164.
10. Arachchillage DRJ, Gomez K, Alikhan R, Anderson JAM, Lester W, Laffan M. British Society for Haematology Haemostasis and Thrombosis Taskforce. Addendum to British Society for Haematology Guidelines on Investigation and Management of Antiphospholipid syndrome. *Br. J. Haemato*l. 2012; **157**: 47-58. use of direct acting oral anticoagulants. *Br J Haematol.* 2020; **189**(2): 212-15. PMID: 31943138.
11. Areia AL, Mota-Pinto A. Experience with direct oral anticoagulants in pregnancy – a systematic review. *J Perinat Med.* 2022; **50**(4): 457-61. PMID: 35073471.
12. Rivaroxaban; Drug information. UpToDate; Topic 9498 Version 379.
13. Apixaban package insert; Zydus Lifesciences Limited.
14. Martin KA, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. *J Thromb Haemost.* 2021; **19**(8): 1874-82. PMID: 34259389.
15. Talerico R, Pola R, Klok FA, Huisman MV. Direct-Acting Oral Anticoagulants in patients at extremes of body weight: a review of pharmacological considerations and clinical implications. *TH Open.* 2024; **8**(1): e31-e41. PMID: 38197017; PMCID: PMC10774013.
16. Lee SR, Choi EK, Park CS, Han KD, Jung JH, Oh S, Lip GYH. Direct Oral Anticoagulants in Patients with Nonvalvular Atrial Fibrillation and Low Body Weight. *J Am Coll Cardiol.* 2019; **73**(8): 919-31. PMID: 30819360.
17. Suvash Shrestha, On Chen, Robert Frankel, Yisachar Greenberg, Felix Yang, Direct oral anticoagulants: A user's guide, Consultant 360 April 2017; **57**(4).
18. Devreese KMJ, de Groot PG, de Laat B, Erkan D, Favaloro EJ, Mackie I, et al. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis: Update of the guidelines for lupus anticoagulant detection and interpretation. *J Thromb Haemost.* 2020; **18**(11): 2828-39. PMID: 33462974.
19. Keeling D, Tait RC, Watson H. British Committee of Standards for Haematology. Peri-operative management of anticoagulation and antiplatelet therapy.

Br J Haematol. 2016; **175**(4): 602-13. doi: 10.1111/bjh.14344. Epub 2016 Oct 7. PMID: 27714755.

20. Sarode R. Direct oral anticoagulant monitoring: what laboratory tests are available to guide us? Hematology Am Soc Hematol Educ Program. 2019; **2019**(1): 194-7. PMID: 31808890; PMCID: PMC6913449
21. Switching between oral anticoagulants; UpToDate; Graphic 120639 Version 4.0
22. Bhat RV, Young G, Sharathkumar AA. How I treat pediatric venous thromboembolism in the DOAC era. *Blood.* 2024; **143**(5): 389-403. PMID: 37390311; PMCID: PMC10862368