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Editorial

Bleeding Management for Patients Under Direct Oral Anticoagulant Treatment

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Atrial fibrillation (AF) is an important cause of stroke, heart failure, cardiovascular morbidity and mortality worldwide. 20 - 30% of the stroke cases also have AF diagnosis and death caused by stroke can be mostly prevented by anticoagulation [1]. Warfarin has been used for a very long time for stroke prevention in AF patients. But it is a difficult medication for both patients and physicians. Warfarin's dose regimen is not standard for every patient. Also it is affected by dietary intake, commonly used drugs like antibiotics, etc. Because of these facts after the use of direct oral anticoagulants (DOAC), physicians tend to change the treatment from warfarin to DOACs. Of course for patients with prosthetic valves, moderate or severe mitral stenosis and abnormal kidney function (glomerular filtration rate < 30) DOACs are contraindicated but for other patients, these drugs are a new hope [2]. But like every new drug, at first we didn't know how to cope with complications like bleeding. Phase 3 studies showed that DOACs cause less intracranial or life-threatening bleeding than warfarin. Also bleeding cases caused by DOACs have better outcomes than warfarin cases [3-8]. But there are always questions about DOACs; because good or bad, warfarin is a long-time friend of the physicians. This text will be a summary of what to do in case of bleeding caused by DOACs.

Prevention from Bleeding

First of all dosing is very important for prevention from bleeding. Basically if creatinine clearance (CrCl) is between 30 - 50 ml/min, dabigatran 110 mg, rivaroxaban 15 mg and edoxaban 30 mg should be used. If CrCl > 50 ml/min, higher doses can be used. But in case of apixaban you should use apixaban 5 mg if CrCl > 30 ml/min. Dose modification is not necessary for this drug [8].

If the patient has high risk of gastrointestinal bleeding dabigatran 110 mg twice daily, apixaban 2.5 mg or 5 mg twice daily, rivaroxaban 15 mg once daily or edoxaban 30 mg twice daily should be used.

HAS-BLED [hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (.65 years), drugs/alcohol concomitantly (1 point each)] scoring system can be used to determine the bleeding risk of AF patients. It is important to detect the modifiable risk factors. In this scoring system; hypertension, labile INR, alcohol intake and medications other than anticoagulants like antiplatelets or non-steroidal anti-inflammatory drugs can be modified by the patients or the doctor [2]. For example when a patient's blood pressure is regulated with an antihypertensive drug; one point from the HAS-BLED score will be diminished.

Nuisance and Minor Bleeding

Nuisance and minor bleeding is important because patients may stop using DOACs totally or temporarily which may cause stroke at the end. The patients must know the risks and if such an event occurs, they should directly see their physician. Nuisance bleeding can be stopped by delaying a dose or withholding one dose of the treatment. Minor bleeding should be managed by removing the origin of the bleeding. For example epistaxis can be managed by local anti-fibrinolytics or peptic ulcers by proton pump inhibitors. The dosing should be checked. If CrCl is reduced, the dosing should be changed. Or another DOAC with a different bleeding profile should be used [8].

Moderate Bleeding

Elimination half-life of DOACs change between 5-9 hours to 17 hours (For dabigatran, 12 - 17 hours; for apixaban, 12 hours; for edoxaban, 10 - 14 hours; for rivaroxaban 5 - 9 hours for young and 11 - 13 hours for elderly) [9-12]. Mostly bleeding should be controlled by supportive measures. We should apply mechanical compression. Fluid or blood transfusion should be done if necessary. Homeostasis is expected within 12 hours but it should be delayed according to CrCl values. Cause of the bleeding should be eliminated (e.g. gastroscopy). If the intake of the NOAC is recent, charcoal can also be applied [2]. Renal clearance of dabigatran is 80% so diuresis is especially important for dabigatran. Dialysis is very effective for dabigatran but it is less effective on apixaban, rivaroxaban and edoxaban [8].

Severe Bleeding

Antithrombotic effect of the DOACs should be eliminated immediately in case of severe bleedings. It should always be kept in mind that evaluation of the patient is very important. Symptomatic treatment should be given; fluid replacement blood transfusion should be applied. The origin of the bleeding should be eliminated if possible. Specific antidote should be considered if available [2].

Idarucizumab is an antidote for dabigatran and approved in 2015. It binds dabigatran rapidly and reverses the effects of dabigatran within minutes [13]. Idarucizumab should be applied in two 2.5g bolus doses and the duration between them should not be more than 15 minutes. After the administration, clinical and laboratory follow-up is important because this dose may not neutralize all the dabigatran if the drug concentration is high [8]. We only have antidote against dabigatran but antidote for Factor Xa antagonists is under evaluation for approval. Andexanet alpha is not approved yet but it is a modified recombinant factor Xa which reverses the anticoagulant activity of factor Xa antagonists [14].

If antidotes are not available, platelet substitution should be considered if patient is thrombocytopenic, fresh frozen plasma may be given as plasma expander. Fresh frozen plasma may not be useful as a reversal agent like warfarin overdose cases but it may help to stabilize the patients. Tranexamic acid may be considered or desmopressin may be given if the patient has coagulopathy or thrombopathy. Also prothrombin complex concentrate 50 U/kg (+25U/kg if indicated) or activated prothrombin complex 50 U/kg (max 200 U/kg/day) may be useful [8].

In conclusion, DOACs seems to be safer than warfarin in terms of intracranial bleedings and life-threatening bleedings. They have shorter half-life so homeostasis is maintained faster even without specific treatment. But in cases of major bleedings, only dabigatran has a specific antidote. And this is a major advantage for now. But we should keep in mind that every DOAC has specific advantages and disadvantages.

Bibliography

1. Kotecha D., *et al*. "Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis". *The Lancet* 384.9961 (2014): 2235-2243.

2. Kirchhof., *et al*. "2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS". *European Heart Journal* 37.38 (2016): 2893-2962.

3. Hylek EM., *et al*. "Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes". *Journal of the American College of Cardiology* 63.20 (2014): 2141-2147.

4. Piccini JP., *et al*. "Management of major bleeding events in patients treated with rivaroxaban vs. warfarin: results from the ROCKET AF trial". *European Heart Journal* 35.28 (2014):1873-1880.

5. Kawabori M., *et al*. "Characteristics of symptomatic intracerebral hemorrhage in patient receiving direct oral anticoagulants: comparison with warfarin*". Journal of Stroke Cerebrovascular Diseases* 27.5 (2018): 1338-1342.

6. Wilson D., *et al*. "Outcome of intracerebral hemorrhage associated with different oral anticoagulants". *Neurology* 88.18 (2017):1693-1700.

7. Inohara T., *et al*. "Association of intracerebral hemorrhage among patients taking non-vitamin K antagonist vs vitamin K antagonist oral anticoagulants with in-hospital mortality". *The Journal of the American Medical Association* 319.5 (2018): 463-473.

8. Steffel J,. *et al*. "The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation". *European Heart Journal* 39.16 (2018): 1330-1393.

9. Blech S., *et al*. "The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans". *Drug Metabolism and Disposition* 36.2 (2008): 386-399.

10. Raghavan N., *et al*. "Apixaban metabolism and pharmacokinetics after oral administration to humans". *Drug Metabolism and Disposition* 37.1 (2009): 74-81.

11. Ogata K*,. et al*. "Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers". *The Journal of Clinical Pharmacology* 50.7 (2010):743-753.

12. Mueck W., *et al*. "Rivaroxaban: population pharmacokinetic analyses in patients treated for acute deep-vein thrombosis and exposure simulations in patients with atrial fibrillation treated for stroke prevention". *Clinical Pharmacokinetics* 50.10 (2011): 675-686.

13. Pollack CV Jr., *et al*. "Idarucizumab for Dabigatran Reversal". *New England Journal of Medicine* 373.6 (2015): 511-520.

14. Connolly SJ., *et al*. "Andexan*et al*fa for acute major bleeding associated with factor Xa inhibitors". *New England Journal of Medicine* 375.12 (2016): 1131-1141.

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