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WHAT'S NEW IN INTENSIVE CARE

Ten things ICU specialists need to know about direct oral anticoagulants (DOACs)

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Anticoagulation is the cornerstone in the treatment of thromboembolic disorders. In the intensive care unit (ICU), anticoagulation is often challenging as the balance between bleeding and thrombosis is subtle, and anticoagulation-induced bleeding is associated with adverse outcome [1]. In this paper, we outline ten important things ICU specialists need to know about patients treated with direct oral anticoagulants (DOACs)

1. Indications for using DOACs

The main indication for DOACs is as an alternative to warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, where they reduce the risk of stroke, bleeding and all-cause mortality [2]. DOACs are also used in venous thromboembolism, where they are non-inferior to warfarin with a potentially lower risk of bleeding [3]. DOACs are characterised by the rapid onset of action, a relatively short half-life, a predictable anticoagulant effect in patients with normal organ function, and the lack of need for therapeutic monitoring.

2. Types of DOACs

The available drugs include dabigatran, a selective anti-factor II_a molecule functioning as a direct thrombin inhibitor, and three direct anti-factor X_a inhibitors, i.e. apixaban, edoxaban and rivaroxaban, which inhibit the factor X_a activity of the prothrombinase complex [4] (Fig. 1).

3. Half-life and mode of elimination

DOACs exhibit more predictable pharmacokinetic and pharmacodynamic profiles than warfarin when they are used in patients without organ failure, i.e. outside the ICU. The half-life of dabigatran is about 15 h with 80% eliminated via the renal route and 20% via the hepatic route, whereas the half-life of the direct anti-factor X_a inhibitors is about 10 h with 30–40% eliminated via the renal route and 60–70% via the hepatic route [4].

4. DOACs and organ failure

In patients with organ failure, there is an inherent risk of bleeding because of accumulation of the DOACs. Acute kidney injury with a reduction in creatinine clearance (CrCl) to less than 15 mL/min doubles the half-life of dabigatran to more than 30 h, whereas the half-life of the direct anti-factor X_a inhibitors is increased around 50% to 15–17 h, as they are mainly eliminated hepatically [4]. In hepatic failure, little is known about the activity and elimination of DOACs; however, in cirrhotic patients the anticoagulant effect differs substantially from healthy individuals [5].

5. Reduced absorption and enterohepatic recirculation

Administration of activated charcoal early after drug ingestion (2–6 h) or in case of hepatic failure has been suggested as a means to reduce absorption and enterohepatic recirculation [4].

6. Monitoring of DOACs

ICU patients are prone to develop clinically important coagulopathy, which can be assessed by both conventional coagulation testing and viscoelastic haemostatic assays (VHAs) [6, 7]. It is important to monitor the effect of DOACs in ICU patients, in order to evaluate

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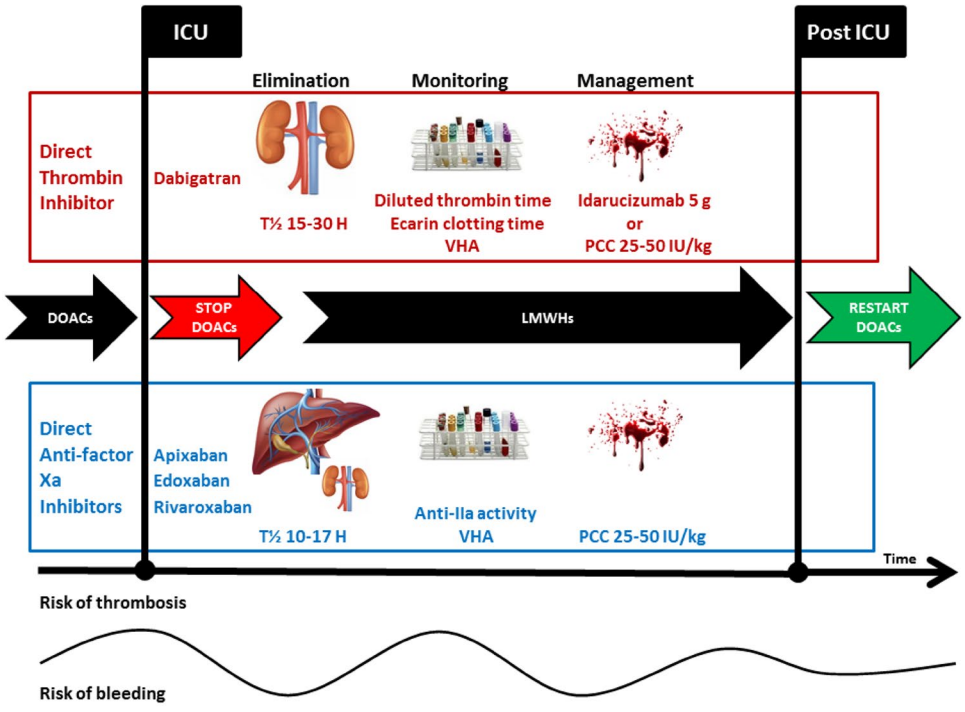

DOACs: direct oral anticoagulants
H: hour
ICU: intensive care unit
IU: international units
Kg: kilograms
LMWHs: low-molecular-weight heparins
PCC: prothrombin complex concentrate
T½: half-live
VHA: viscoelastic haemostatic assay

Fig. 1 Key points ICU specialists need to know about direct oral anticoagulants (DOACs). H hour, ICU intensive care unit, IU international units, kg kilograms, LMWHs low molecular weight heparins, PCC prothrombin complex concentrate, T½ half-life, VHA viscoelastic haemostatic assay

the activity and risk of bleeding. Unfortunately, many global clotting tests such as the international normalised ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (aPTT) are affected by a non-specific increase if any [4], which is why monitoring of the activity of DOACs in ICU patients prone to coagulopathy is complex. The specialised assays available, including dilute thrombin time and ecarin clotting time for dabigatran, and anti-IIa activity for the direct anti-factor Xa inhibitors assays [4] can be considered, but they have not yet been validated in patients with coagulopathy or bleeding, which is why there are concerns about the interpretation in ICU patients [8]. VHAs in patients on DOACs will display an increased time to clotting, both by thromboelastometry/ROTEM® (longer clotting time) and by thromboelastography/TEG® (longer reaction time), and they seem promising [9, 10].

7. Reversal of DOACs

Most bleedings in patients on DOACs can be managed conservatively by withholding the drug and supporting organ function, including the kidneys [4, 11]. In situations with major haemorrhage, fresh frozen plasma does not reverse the anticoagulation effect of DOACs, but it can be used according to general indications in resuscitation. Immediate DOAC reversal may be needed in major bleeding, and partial reversal of the antithrombotic activity and restoration of the thrombin generation can be achieved by prothrombin complex concentrate (PCC) 50 IU/kg [4, 11]. However, a risk of overshoot in thrombin generation and a resulting increased risk of thromboembolic complications may exist [12]. Consequently, a titrated or repeated dose regimen of 25 IU/kg according to the clinical condition is recommended.

In 2015, the monoclonal antibody fragment idarucizumab was approved as a specific dabigatran antidote in

severe haemorrhage and in emergency procedures on the basis merely of observational data [13]. Importantly, a 7% increased risk of thromboembolic complications and a 19% increased risk of 30-day mortality have recently been reported in patients treated with idarucizumab [13].

8. Management of major bleeding in ICU patients on DOACs

Major bleeding in ICU patients on DOACs should in general follow the standard protocol for treatment of bleeding with special attention to early surgical control. Specific management includes (1) stopping the drug, (2) avoiding additional absorption and enterohepatic recirculation by using activated charcoal early after drug ingestion (up to 6 h) [14], (3) monitoring anticoagulation activity, (4) normalising elimination, and (5) considering reversal with PCC 25–50 IU/kg or idarucizumab in case of life-threatening bleeding [4, 11] (Fig. 1). Use of intermittent haemodialysis or continuous renal replacement therapy to increase the elimination of DOACs in uremic patients has been advocated; however, the effect is unclear [15], and routine use of any form of renal replacement therapy to increase elimination is not recommended. Tranexamic acid does not reverse the effect of DOACs, but should be considered in major bleeding according to indications and contraindications, including disseminated intravascular coagulation [16].

9. DOACs in ICU patients

There is a paucity of data on use of DOACs in ICU patients. On the basis of current knowledge about DOACs, they should be avoided in ICU patients because of uncertain activity and elimination, risk of accumulation due to organ failure (kidney and liver), risk of bleeding, and a risk of surgery in many patients. Standard of care in ICU patients with an indication for anticoagulation should continue to be low molecular weight heparins (LMWHs) [17]. Additional research on monitoring and management of DOACs in ICU patients is warranted.

10. Resuming DOACs

Adequate anticoagulation is paramount in patients at risk of thromboembolic complications, including ICU patients. When control of bleeding has been achieved, anticoagulation should likely be restarted as early as in the first 24 h after bleeding [4]. As a result of the subtle balance between the risk of bleeding and the risk of thrombosis in ICU patients, use of LMWHs is recommended over DOACs during ICU stay, whereas DOACs can be resumed in a more stable phase after discharge from ICU, when the risk of bleeding and thrombosis is lower (Fig. 1).

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Compliance with ethical standards

Conflicts of interest
Authors declare that they have no competing interest.

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References

1. Hunt BJ (2014) Bleeding and coagulopathies in critical care. N Engl J Med 370:847–859
2. Lopez-Lopez JA, Sterne JAC, Thom HHZ, Higgins JPT, Hingorani AD, Okoli GN, Davies PA, Bodalia PN, Bryden PA, Welton NJ, Hollingworth W, Caldwell DM, Savovic J, Dias S, Salisbury C, Eaton D, Stephens-Boal A, Sofat R (2017) Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ 359:j5058
3. Sterne JA, Bodalia PN, Bryden PA, Davies PA, Lopez-Lopez JA, Okoli GN, Thom HH, Caldwell DM, Dias S, Eaton D, Higgins JP, Hollingworth W, Salisbury C, Savovic J, Sofat R, Stephens-Boal A, Welton NJ, Hingorani AD (2017) Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis. Health Technol Assess 21:1–386
4. Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, Florido R, Hucker W, Mehran R, Messe SR, Pollack CV Jr, Rodriguez F, Sarode R, Siegal D, Wiggins BS (2017) 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Task Force on expert consensus decision pathways. J Am Coll Cardiol 70:3042–3067
5. Potze W, Arshad F, Adelmeijer J, Blokzijl H, van den Berg AP, Meijers JC, Porte RJ, Lisman T (2014) Differential in vitro inhibition of thrombin generation by anticoagulant drugs in plasma from patients with cirrhosis. PLoS One 9:e88390
6. Lyons PG, Micek ST, Hampton N, Kollef MH (2018) Sepsis-associated coagulopathy severity predicts hospital mortality. Crit Care Med. https://doi.org/10.1097/CCM.0000000000002997
7. Johansson PI, Stensballe J, Vindelov N, Perner A, Espersen K (2010) Hypocoagulability, as evaluated by thrombelastography, at admission to the ICU is associated with increased 30-day mortality. Blood Coagul Fibrinolysis 21:168–174
8. Jensen KOF, Hansen SH, Goetze JP, Jesting A, Stensballe J, Hansen H (2017) Preliminary report: measurement of apixaban and rivaroxaban in plasma from bleeding patients. Eur J Haematol 99:431–436
9. Solbeck S, Jensen AS, Maschmann C, Stensballe J, Ostrowski SR, Johansson PI (2018) The anticoagulant effect of therapeutic levels of dabigatran in atrial fibrillation evaluated by thrombelastography (TEG®), hemoclot thrombin inhibitor (HTI) assay and ecarin clotting time (ECT). Scand J Clin Lab Invest 78:25–30
10. Dias JD, Norem K, Doorneweerd DD, Thurer RL, Popovsky MA, Omert LA (2015) Use of thromboelastography (TEG) for detection of new oral anticoagulants. Arch Pathol Lab Med 139:665–673
11. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Georg HK, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbuchel H (2018) The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. Europace. https://doi.org/10.1093/europace/euy054

12. Marlu R, Hodaj E, Paris A, Albaladejo P, Crackowski JL, Pernod G (2012) Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban. A randomised crossover ex vivo study in healthy volunteers. Thromb Haemost 108:217–224
13. Pollack CV Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kam CW, Kamphuisen PW, Kreuzer J, Levy JH, Royle G, Sellke FW, Stangier J, Steiner T, Verhamme P, Wang B, Young L, Weitz JI (2017) Idarucizumab for dabigatran reversal - full cohort analysis. N Engl J Med 377:431–441
14. Wang X, Mondal S, Wang J, Tirucherai G, Zhang D, Boyd RA, Frost C (2014) Effect of activated charcoal on apixaban pharmacokinetics in healthy subjects. Am J Cardiovasc Drugs 14:147–154
15. Stangier J, Rathgen K, Stahle H, Mazur D (2010) Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet 49:259–268
16. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K (2011) Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 16(3):001886
17. Beitland S, Sandven I, Kjaervik LK, Sandset PM, Sunde K, Eken T (2015) Thromboprophylaxis with low molecular weight heparin versus unfractionated heparin in intensive care patients: a systematic review with meta-analysis and trial sequential analysis. Intensive Care Med 41:1209–1219