

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

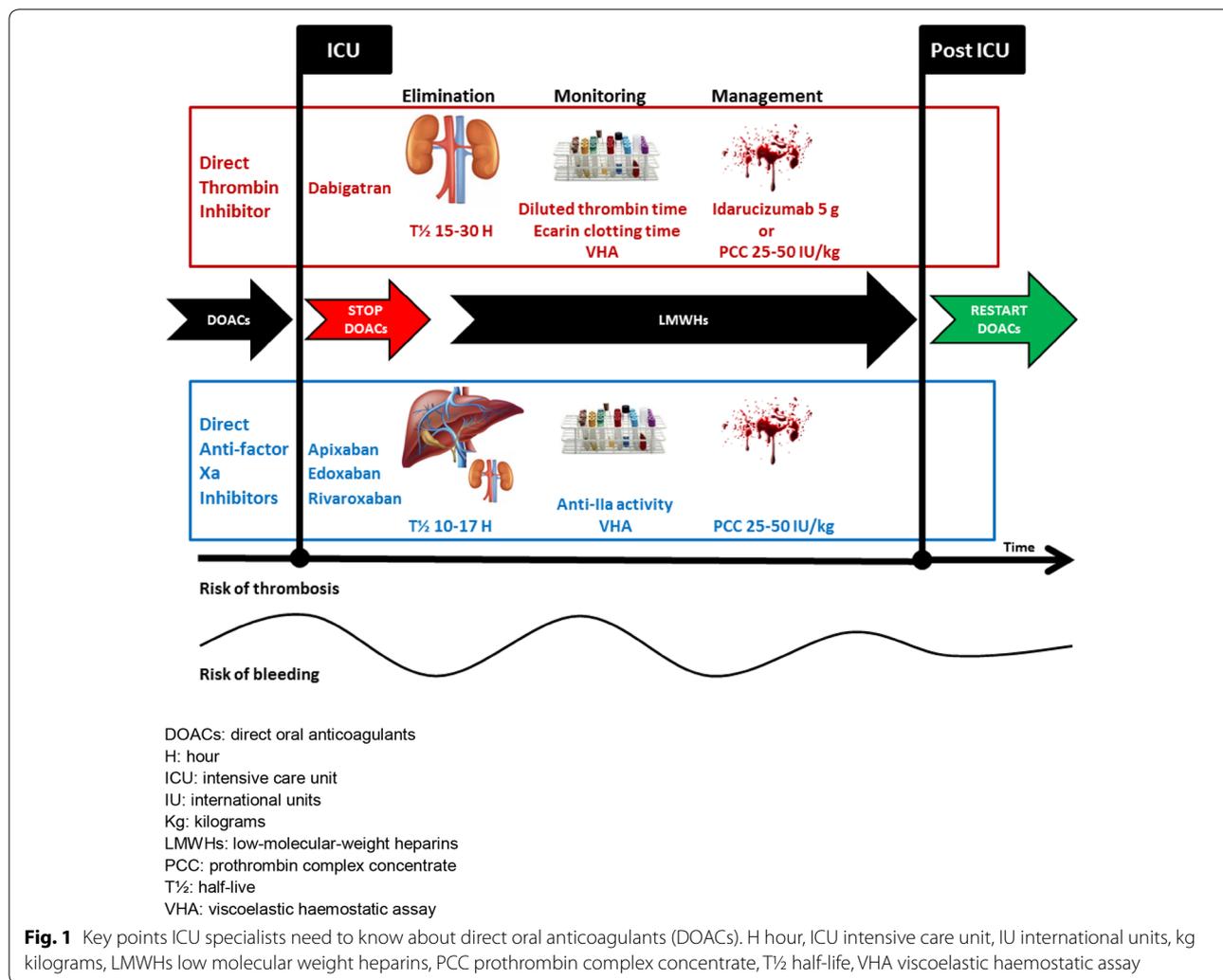
Administration of activated charcoal early after drug ingestion (2–6 h) or in case of hepatic failure has been suggested as a means to reduce absorption and enterohepatic recirculation [4].

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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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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