Diagnosis, treatment and long-term effects of venous thromboembolism
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Chapter 8

Management of bleeding complications in patients treated with direct oral anticoagulants: the present and future

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Summary

Contrary to vitamin K antagonists (VKA), there is no specific reversal agent for direct oral anticoagulants (DOACs). It is therefore feared that the mortality and morbidity of bleeding or invasive emergency procedures is higher in patients treated with DOACs than in VKA treated patients. Yet, the outcome of bleeding in patients with atrial fibrillation and venous thromboembolism included in the phase III trials was similar. The efficacy of non-specific prohaemostatic agents such as prothrombin complex concentrates and recombinant factor VIIa has been studied in healthy human volunteers and in animal bleeding models. Despite some conflicting conclusions, both inactive and activated prothrombin complex concentrates could be beneficial. Since none of these agents have been studied in patients with bleeding, it is uncertain if these non-specific agents can improve patient outcome. Specific antidotes for dabigatran and factor Xa inhibitors are in development with promising first results. Until such agents become available in daily practice, optimal management remains challenging. Due to the relatively short elimination half-life of DOACs, supportive measures and local source control will often be sufficient and non-specific prohaemostatic agents should probably be reserved for the most severe cases. Based on the best available, yet scarce, evidence several practical guidance documents provide useful treatment suggestions in case of a DOAC-associated bleeding.
DOAC-associated bleeding complications

Introduction

After six decades during which vitamin K antagonists (VKA) were the only available oral anticoagulants, a new class of oral anticoagulants has been developed. The direct thrombin inhibitor dabigatran etexilate and the direct factor Xa inhibitors rivaroxaban and apixaban have now been approved for prevention and treatment of venous thromboembolism (VTE) and stroke prevention in patients with atrial fibrillation (AF). Rivaroxaban is also approved for secondary prevention after acute myocardial infarction. Based on recent phase III studies it is likely that edoxaban, another factor Xa inhibitor will also be registered for both indications of stroke prevention in patients with AF and VTE treatment. Since two years the three approved DOACs are reimbursed to patients with AF and patients undergoing orthopaedic surgery but not yet to patients with an indication for VTE treatment.

DOACs have a more stable pharmacokinetic profile and therefore are prescribed in a fixed dose regimen, once or twice daily without the need for frequent monitoring which is required for treatment with VKA. This simplifies the long term treatment with anticoagulants and increases user convenience of anticoagulants. Since surveillance of the Thrombosis Services for frequent INR monitoring is not necessary, the near future will show whether this affects the adherence of patients to DOAC treatment. Phase III AF studies showed that DOACs were at least as effective as VKAs in stroke prevention. In terms of bleeding complications, all DOACs showed a risk reduction of 30-70% of intracranial haemorrhages (ICH) and this reduction was independent of the quality of VKA treatment. On the other hand, the risk of gastro-intestinal bleeding complications is higher for rivaroxaban and the high dose of dabigatran (150 mg twice daily).

Although both VKA and DOACs are very effective in treatment of VTE and stroke prevention in AF patients, use of anticoagulants leads to an increased risk of bleeding. The incidence of major bleeding in the phase III trials that compared DOACs with VKA in AF patients ranged from 2.0-3.5 per 100 patient-years. Oral anticoagulant therapy consistently ranks on top of the list of drugs of which the adverse effects lead to hospital admission and it is unlikely that the introduction of DOACs will substantially change this. The risk of bleeding is considered acceptable for most individual patients, as it is opposed to 70% reduction of ischemic stroke with anticoagulants compared to no treatment. However, as in the Netherlands 400,000 patients are being treated with anticoagulants, anticoagulant-associated major bleeding, both intracranial and extracranial, remains a frequently encountered medical emergency which highlights the importance of optimal management strategies in bleeding patients.

A potential drawback of DOACs is the lack of a specific agent that neutralises the anticoagulant effects of these drugs, whereas administration of prothrombin complex concentrate (PCC) immediately reverses the anticoagulant
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effects of VKA. This implies, at least theoretically, that the outcome of bleeding could be worse in patients treated with DOACs than in patients treated with VKA. In this overview, we discuss the relevance of a reversal agent for DOACs, the currently available treatment options for major bleeding and look ahead at the future options.

The relevance of a reversal agent for DOACs

The goal of reversing effects of anticoagulants should be to reduce mortality and long-term morbidity of bleeding complications. Mortality of VKA-associated intracranial haemorrhage (ICH) is about 45-50% and at least half of the survivors remain severely disabled.10,11 Mortality of extracranial haemorrhage is about 5%.11 Substitution of vitamin K dependent clotting factors with PCC rapidly restores haemostasis but its effect on the clinical outcome of bleeding is uncertain.

There are no randomised studies that demonstrate improvement in clinical outcome of bleeding complications managed with PCC. The absence of high quality evidence is explained by the logistical challenges of performing a randomised trial in patients with life-threatening conditions, as well as the ethical issues involved in randomising patients to withhold potentially life-saving treatment. Some studies suggest efficacy of PCC in patients with VKA-associated ICH by a reduction of surrogate endpoints such as haematoma growth.12,13 However, this evidence is weak due to the small number of included patients, retrospective design and lack of randomisation of treatment. Moreover, similar studies failed to show any benefit of PCC.14,15

Phase III trials of patients with major DOAC- and VKA-associated bleeding provide important insights. Recently the results of major bleeding from the RE-LY study (dabigatran versus VKA in patients with AF) and the EINSTEIN studies (rivaroxaban versus VKA in the treatment of VTE) were published.16,17 Of the 18,000 included patients in the RE-LY study, 741 of the dabigatran-treated (6.1%) and 421 warfarin-treated patients (7.0%) had a major bleeding. De 30-days mortality of dabigatran-associated bleeding complications was 9.1% and this was significant lower than the mortality of warfarin-associated bleeding complications, despite the lack of an antidote for dabigatran (odds ratio 0.56, 95% confidence interval 0.36-0.86, adjusted for age, sex, body weight, renal function, and co-medication with anti-platelet agents).17 In the EINSTEIN studies, more than 8,000 patients were treated for VTE; 40 had a rivaroxaban-associated major bleeding and 72 patients had a VKA-associated major bleeding. The mortality of major bleeding complications did not differ between the groups (7.5% and 11.1% respectively).16 Although these studies suggest that the lack of a reversal agent for DOACs may not lead to worse outcome of the bleeding, it is doubtful whether patients with VKA-associated major bleeding were treated optimally. Only a minority of warfarin-treated
patients with major bleeding received vitamin K (27%) or PCC (1.2%). Despite the fact that the efficacy of vitamin K and PCC is not established, these numbers are not in line with Dutch clinical practice. Secondly, the majority of the major bleeding did not seem to require an antidote. Major bleeding was life-threatening in 10-30% with a need for extensive interventions such as factor concentrate (PCC and recombinant activated factor VII) and endoscopic, radiologic, or surgical interventions to stop the bleeding. This was less than 1% of the total number of patients included in these studies.

Since a specific antidote is not needed in most patients with major bleeding and due to the uncertainties about the efficacy of the antidote for VKA, is it unjustified to consider the lack of the antidote as reason to not prescribe DOACs. The potential drawback of the lack of an antidote should be weighed against the advantages of user convenience and reduction of ICH risk. Nevertheless, it seems desirable to have a fast-acting reversal agent that is able to reverse the anticoagulant effect of DOACs in case of major bleeding or emergency invasive procedures.

**Current treatment options for patients with DOAC-associated bleeding**

In the absence of a reversal agent for DOACs, the initial approach to patients with bleeding should consist of local haemostatic options such as compression, or endoscopic and radiologic interventions combined with supportive measures including haemodynamic support and maintaining adequate diuresis to ensure continued renal clearance. These supportive measures will be sufficient in the majority of patients with DOAC-associated bleeding complications.

In case of life-threatening bleeding or necessity of immediate surgical intervention, alternative options should be considered.

Two types of in vivo studies have explored the effects of non-specific prohaemostatic agents as reversal agents for DOACs. The first evaluated the effects on ex-vivo coagulation assays in healthy human volunteers treated with DOACs. It is unclear however, whether correction of these coagulation tests leads to improvement of bleeding outcomes. Coagulation assays such as the prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time only partly reflect in vivo human haemostasis, especially local haemostasis at the site of injury. The second type of studies are those in standardised animal bleeding models in which potential reversal agents are administered to DOAC-treated animals. Although this type of study allows evaluation of the effects on actual bleeding, differences between animals and humans with respect to haemostasis and pharmacokinetics limit the applicability of the study results.
**Prothrombin complex concentrate (PCC)**

In a study by Eerenberg, 50 IU/kg of four-factor PCC was given to healthy volunteers treated with rivaroxaban or dabigatran etexilate. Rivaroxaban-induced prolongation of PT and decrease in endogenous thrombin potential (ETP) was corrected by PCC, whereas dabigatran-induced prolongation of APTT and ecarin clotting time (ECT) was not. Another study with lower PCC dosages (25EH/kg and 37.5 EH/kg) showed partial reversal of the anticoagulation assays. Similar studies with three-factor PCC (containing factors II, IX, X) and other DOACs showed comparable results.

Studies in dabigatran-treated mice (ICH bleeding model), rats (tail bleeding), and rabbits (kidney bleeding) suggest reduced blood loss after treatment with PCC at dosages of 25-100 IU/kg as compared to placebo, without significant effects on coagulation assays. Studies with PCC in rivaroxaban-treated animals have also shown reduced blood loss. These studies indicate that four-factor PCC at a dose of 25-50 IU/kg may be a reasonable treatment option in case of severe, life-threatening bleeding complications in DOAC-treated patients. However, the use of PCC has been associated with an increased risk of thromboembolic events.

Activated PCC (aPCC) contains factors II, VII, IX, and X which are activated during the manufacturing process, and was developed as a bypassing agent for haemophiliac patients with factor VIII and IX inhibitors. Studies in dabigatran and rivaroxaban-treated rats have demonstrated reduction of bleeding at a dose of 50 or 100 IU/kg.

**Recombinant activated factor VII (rVIIa)**

Like aPCC, rVIIa was developed for treatment of haemophiliac patients with inhibitors to factor VIII or IX. There is ample experience with rVIIa as potential treatment for life-threatening bleeding complications with mixed results. Importantly, rVIIa doubles the risk of arterial thromboembolism compared with placebo (4.5% vs. 2.0%). In human volunteers treated with melagatran, a direct thrombin inhibitor of which further development was discontinued, a single dose of 90 ug/kg of rVIIa did not correct the effects on coagulation assays. In an ICH model where mice were treated with dabigatran or rivaroxaban, rVIIa reduced haematoma expansion. Combined, these studies suggest that rVIIa should only be considered as a last resort treatment option in patients presenting with DOAC-associated bleeding complications.

**Development of new specific reversal agents for DOACs**

Idarucizumab is a humanised antigen binding fragment (Fab) of a mouse antibody designed to specifically target dabigatran etexilate. In vitro, the anti-
body binds with high affinity to dabigatran etexilate and, in spite of structural homologies with thrombin, the antibody does not bind to known thrombin substrates. In mice (tail bleeding) and porcine (liver bleeding) studies the antibody reduced the blood loss and mortality. Recently, results were published and showed that the antibody in a dose of 1-8 gram given as bolus resulted in a dose dependent normalisation of the coagulation assays in dabigatran-treated volunteers. In 2014, a large international study was started (REVERSE-AD; ClinicalTrials.gov nr. NCT02104947). In this study, patients with dabigatran-associated bleeding complications will be treated with Idarucizumab to evaluate the effect in real-life bleeding patients. In the Netherlands this study already started in the Academic Medical Center, Onze Lieve Vrouwe Gasthuis and Maastricht Universitair Medisch Centrum. Other centers will be recruited in 2015.

Andexanet alpha is a modified recombinant factor Xa. This protein lacks the membrane binding gamma-carboxyglutaminacid (GLA) and catalytic-domain which makes it inactive but able to bind with high affinity to rivaroxaban and apixaban, resulting in competitive inhibition of the anticoagulant effect of factor Xa inhibitors. In rivaroxaban-treated rats and rivaroxaban-spiked human plasma, andexanet alpha normalised several coagulation assays. This compound is currently undergoing clinical evaluation in human volunteers (www.ClinicalTrials.gov; NCT01758432). In 2015 a study in patients with factor Xa inhibitor-associated bleeding will start. Interestingly, andexanet alpha may also reverse the anticoagulant effects of indirect factor Xa inhibitors (low-molecular-weight heparin and fondaparinux).

Finally, PER977 is the newest specific antidote. This synthetic protein has binding places for direct thrombin inhibitors, direct factor Xa inhibitors and indirect factor Xa inhibitors (heparin, low-molecular-weight heparin and fondaparinux). PER977 might become a universal antidote for anticoagulants. Recently, it was shown that PER977 is able to reverse the anticoagulant effect of edoxaban.

Conclusion
While DOACs lead to improvement and simplification of long-term anticoagulant therapy, bleeding will remain the most important complication. For most patients, the risk of bleeding is outweighed by the protective antithrombotic effect. Due to the large number of patients who use anticoagulants, physicians will frequently encounter anticoagulant-associated bleeding complications. Therefore, it is important that hospitals have protocols in place for the management of anticoagulant-associated bleeding complications. Several national and international guidelines can be used to prepare a local protocol. The lack of a specific reversal agent is a only a relative drawback of DOACs as compared to VKA, as supportive measures will suffice in the majority of major DOAC-associated bleeding complications. For severe,
life-threatening bleeding complications, non-specific prohaemostatic agents such as PCC are currently being recommended (Figure 8.1), although there is little experience with PCC for this indication. In the near future prospective registries will provide useful data on the effects of PCC in case of real-life bleeding complications and emergency interventions. The development of specific inhibitors for dabigatran etexilate and factor Xa inhibitors is promising and may simplify the reversal of DOACs and the management of severe bleeding complications.

Figure 8.1 | Potential management plan for patients presenting with DOAC-associated bleeding.

**Bleeding while treated with a DOAC**

- **Mild Bleeding**
  - Delay next dose or discontinue DOAC
  - Reconsider concomitant medication (antiplatelet agents)
  - Mechanical compression

- **Moderate to severe bleeding**
  - Surgical, endoscopic, or radiological intervention
  - Consider charcoal if <2 h after last drug intake
  - Supportive measures:
    - Fluid replacement
    - Thrombocyte suppletion if thrombocytes < 50x10⁹/L or concomitant use of antiplatelet drugs
    - If needed, replacement of red blood cells and/or fresh frozen plasma
    - Maintain adequate diuresis

- **Life-threatening bleeding**
  - Consider:
    - Four-factor PCC 25-50 IU/kg (repeat 1-2x if needed), or:
    - aPCC 100-200 IU/kg
    - rVIIa 90 μg/kg (only as last resort)

Abbreviations: DOAC, direct oral anticoagulant; PCC, Prothrombin Complex Concentrate (e.g. Cofact, Beriplex, Octaplex); aPCC, Activated Prothrombin Complex Concentrate (FEIBA); rVIIa, Recombinant activated factor VII (NovoSeven, NiaStase). Adapted from references.²⁶,²⁷
Reference list


