Prothrombin Complex Concentrates as Reversal Agents for New Oral Anticoagulants

Lessons from Preclinical Studies with Beriplex

Gerhard Dickneite, PhD

KEYWORDS

- Beriplex • Prothrombin complex concentrate • New oral anticoagulants
- Anticoagulant reversal

KEY POINTS

- The preclinical study results obtained with Beriplex have demonstrated consistent reversal of new oral anticoagulant (NOAC)-associated bleeding and provide encouraging evidence for the use of this nonactivated 4-factor prothrombin complex concentrate for NOAC reversal.
- There is a need for clinical data, particularly in bleeding patients, to further validate this reversal strategy.
- The lack of correlation between coagulation parameters and hemostasis observed in some of the studies needs to be explored further to help guide clinician diagnostics.

INTRODUCTION

New oral anticoagulants (NOACs) represent an effective anticoagulation therapy option and have several advantages over warfarin and other vitamin K antagonists (VKAs), including a low potential for food and drug interactions, a relatively short half-life, and a rapid and reliable onset of action.[1–4] NOACs include the activated factor II (FIIa), or thrombin, inhibitor (dabigatran etexilate [Pradaxa, Prazaxa]) and FXa inhibitors (rivaroxaban [Xarelto], apixaban [Eliquis], and edoxaban [Lixiana]).[5,6] These agents specifically inhibit important elements in the coagulation cascade, unlike

Conflict of Interest Statements: Prof. Dr G. Dickneite is an employee of CSL Behring and owns CSL Behring stock.
Editorial assistance was provided by Alan Saltzman at Fishawack Communications Ltd, with a grant from CSL Behring, Marburg, Germany.
CSL Behring, Preclinical R&D, PO Box 1230, Marburg 35002, Germany
E-mail address: Gerhard.Dickneite@cslbehring.com

Clin Lab Med 34 (2014) 623–635
http://dx.doi.org/10.1016/j.cll.2014.06.001 **labmed.theclinics.com**
0272-2712/14/$ – see front matter

VKAs, which interfere with the synthesis of multiple vitamin K-dependent factors (VKDFs; eg, FII, FVII, FIX, and FX) (Fig. 1).

Clinical trials of NOACs have demonstrated their noninferiority or superiority over VKAs for the prevention of thrombotic events.[5] Nevertheless, NOAC therapy is still associated with a risk for bleeding complications.[5] Although this risk is apparently lower than that for VKAs,[5] it is still a significant issue, as bleeding in patients on anticoagulants has been associated with poorer outcomes.[7–11] This is further compounded by the fact that no validated strategy for NOAC reversal is yet available. Presently, the treatment of choice for VKA reversal is prothrombin complex concentrate (PCC), coadministered with vitamin K.[12] PCCs contain significant quantities of VKDFs II, IX, and X, with either low (3-factor [3F]-PCC) or therapeutic levels (4-factor [4F]-PCC) of FVII, and replace the VKDFs that are deficient as a result of VKA therapy.[13] The efficacy of PCCs for urgent VKA reversal was demonstrated in a recent phase IIIb clinical trial in which treatment with a nonactivated 4F-PCC (Beriplex) was shown to be at least as good as plasma for urgent VKA reversal in patients with acute major bleeding.[14] Further details on this trial and other studies that have evaluated the effectiveness of 4F-PCC for VKA reversal can be found elsewhere in this supplement.[15]

Currently, only preclinical and early clinical results have been published on NOAC reversal, including the use of VKA reversal agents, such as PCCs. Theoretically, PCCs could overcome the anticoagulant effects of FIIa and FXa inhibitors by enhancing thrombin generation.[16] However, because the reversal of the anticoagulant effect would be mechanistically different from that for VKAs, procedures for the use of PCCs in the reversal of NOAC-associated bleeding would need to be validated. Interestingly, in one recent report of reversal of dabigatran-associated intestinal bleeding, treatment with the 4F-PCC Octaplex resulted in control of hemorrhagic complications in 4 of the 5 patients included in the study.[17]

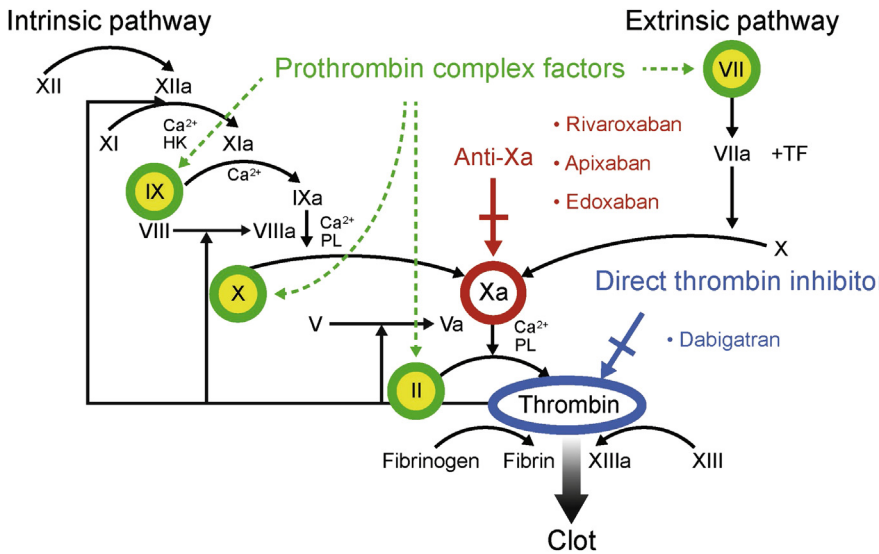

Fig. 1. Coagulation cascade and biological targets for NOACs and PCCs. HK, high molecular weight kininogen; PL, platelet membrane phospholipid; TF, tissue factor.