Direct Oral Anticoagulants in the Management of Venous Thromboembolism—Evidence From Major Clinical Trials

Erik W. Holy[a] and Jürg H. Beer[b,c]

For decades the antithrombotic management of venous thromboembolism (VTE) was limited to parenteral heparin formulations and oral vitamin K antagonists. Even though both classes of anti-coagulants are effective, they have several limitations, including a narrow therapeutic window and the need to monitor anticoagulant activity. Direct oral anticoagulants (DOACs) that specifically target factor IIa or Xa have emerged. Recent data suggest that they are at least as effective and as safe as conventional therapy and have practical advantages, such as fixed dose regimen and no need for laboratory monitoring. Hence, they represent a major step forward in the acute treatment and long-term prevention of VTE. In this review, we outline the use of DOACs in the management of VTE and provide an overview of recently published major trials.
Semin Hematol 51:131–138. © 2014 Elsevier Inc. All rights reserved.

I n clinical practice venous thromboembolisms (VTEs) such as deep vein thrombosis (DVT) and pulmonary embolism (PE) are common disorders associated with significant morbidity and mortality. Because of the large diversity of disease- and patient-specific risk factors, the management of VTE in the acute and long-term setting may pose a challenge to the treating physicians. The annual incidence of VTE is approximately 1–2 cases per 1,000 persons per year in the general population and is four- to sevenfold higher in patients with cancer.[1] The occurrence of VTE significantly increases the in-hospital mortality rate.[1,2] With recurrence rates of up to 10% per year, VTE is often regarded as a chronic disease.[3] For several decades, acute treatment and long-term man-agement of VTE has been limited to the use of low-molecular-weight heparin (LMWH) or unfractioned heparin (UFH) and vitamin K antagonists (VKAs). Although the clinical effectiveness of dose-adjusted VKA therapy for the prevention and treatment of thromboem-bolic disease is undisputed, VKAs face a number of limitations, including a narrow therapeutic window and varying pharmacokinetics due to frequent drug–drug and drug–food interactions. Recently, new direct oral anticoagulants (DOACs) have emerged that specifically target factor IIa (thrombin) or factor Xa in contrast to VKAs (Figure 1). In particular, the specificity and stable pharmacokinetics of these new agents obviate routine monitoring of anticoagulant activity. More importantly, recent large clinical trials have demonstrated at least a comparable efficacy of DOACs in terms of VTE recur-rence rates with an overall improved safety profile with regard to bleeding complications, compared with VKAs (Table 1 and Figure 2).

In this review, we recapitulate the results of recent clinical trials for the use of DOACs in the acute and long-term management of VTE.

OVERVIEW OF MAJOR CLINICAL TRIALS

Dabigatran

Acute and Long-Term Treatment

The efficacy and safety of the direct thrombin inhibitor dabigatran has been compared with warfarin for the treatment of acute VTE in two large double-blind and double-dummy, randomized, phase III clinical trials: RE-COVER and RE-COVER II.[4,5] In both trials, patients were randomized to receive fixed-dose dabigatran, 150 mg, twice daily, or dose-adjusted warfarin (interna-tional normalized ratio [INR] 2–3) for 6 months after an initial heparin treatment for a median of 9 days. The main difference between the two trials is that the follow-up study included a larger patient cohort and that the population in RE-COVER II was considered to be at a higher risk of recurrent VTE according to the site investigator's evaluation. The primary endpoint was non-inferiority in the 6-month incidence of recurrent VTE and VTE-related deaths. The results of both trials RE-COVER

[a]University Heart Center, University Hospital Zurich, Zurich, Switzer-land.
[b]Department of Internal Medicine, Cantonal Hospital of Baden, Baden, Switzerland.
[c]Laboratory for Platelet Research, Center of Molecular Cardiology, University of Zurich, Zurich, Switzerland.
Conflicts of interest:
Address correspondence to Erik W. Holy, MD, PhD, University Heart Center, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland. E-mail: erik.w.holy@gmail.com
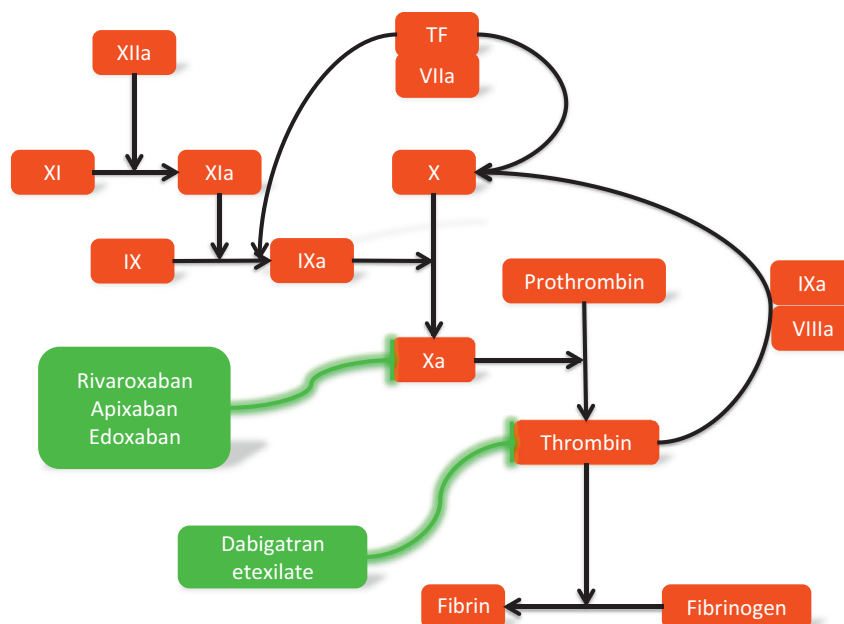
Figure 1. DOACs and their therapeutic targets in the coagulation cascade.

and RE-COVER II demonstrated that dabigatran had similar efficacy as warfarin (hazard ratio [HR] 1.10; 95% confidence interval [CI], 0.65–1.84; and HR 1.08; 95% CI, 0.64–1.80, respectively) for the prevention of recurrent VTE. In RE-COVER the rate of major bleeding was similar in the two groups (1.6% for dabigatran and 1.9% for warfarin, HR 0.82; 95% CI, 0.45–1.48). Although the incidence of major bleeding was similar in both groups, the overall rate of bleeding was higher in the warfarin cohort than in the dabigatran cohort (16.1% of patients for dabigatran and 21.9% for warfarin, HR 0.71; 95% CI, 0.59–0.85). RE-COVER II confirmed those results. In both trials, no significant difference in the frequency of adverse events, including death or myocardial infarction, was observed between both groups, with the exception of dyspepsia, which occurred more often in patients treated with dabigatran.

The two studies showed that a fixed dose of dabigatran is as effective as warfarin, with a safety profile that is similar to that of warfarin when given for the long-term treatment of VTE.

Extended Treatment

In the two parallel trials, RE-MEDY and RE-SONATE, the efficacy and safety of dabigatran were examined in the secondary prevention of VTE ("extended" VTE therapy).[6] The design of these trials was driven by the uncertainty over the optimal duration of anticoagulation treatment in patients with idiopathic or unprovoked VTE. Patients enrolled in these two studies of extended VTE therapy were deemed to have at least a moderate risk of VTE recurrence. In RE-MEDY almost 3,000 patients were randomly assigned to receive either dabigatran (150 mg twice daily) or warfarin for an

additional period of 6–36 months after an initial 3-month treatment course with anticoagulation. The primary efficacy outcome was a composite endpoint of recurrence of PE, DVT, and VTE-related death over a 6- to 36-month follow-up period. The HR for the composite primary endpoint for dabigatran compared with warfarin was 1.44 (95% CI, 0.78–2.64; $P = .01$ for non-inferiority). Of note, fewer major or clinically relevant bleeding events occurred in the dabigatran arm than in the warfarin arm (HR 0.54; 95% CI, 0.41–0.71; $P < .001$). It is important to mention that in the RE-MEDY trial a significant increase in the incidence of acute coronary syndromes (ACS) was noted with dabigatran compared with warfarin (0.9% v 0.2%; $P = .02$; corresponding to a number needed to harm [NNH][*] of 143 for the defined follow-up period). A similarly significant increase in the rate of ACS was initially also reported in the original analysis of the RE-LY trial, which investigated the efficacy and safety of dabigatran in the prevention of VTE in patients with non-valvular atrial fibrillation (NNH for ACS events = 244 over a follow-up period of 2 years).[7] This difference in the rate of ACS events was also described in a meta-analysis, in which an increased risk of ACS was reported with dabigatran compared with warfarin.[8] Nonetheless, further long-term follow-up and post hoc analyses are required to determine a relationship between the use of dabigatran and the observed incidence of ACS events.

[*]The number needed to harm (NNH) of a therapeutic intervention defines the number of patients that need to undergo a treatment over a time period before a specific adverse event of the treatment occurs in one patient. As a consequence a higher NNH indicates a lower likelihood of encountering the defined adverse event.