Lessons from the trials

Hokusai-VTE: Edoxaban for the treatment of venous thromboembolism

Karim Said*

Aswan Heart Centre, Aswan, Egypt
*Email: kareemsaid@gmail.com

ABSTRACT

Venous thromboembolism is associated with a high morbidity and, if left untreated, may progress to fatal outcome. The standard treatment of venous thromboembolism consists of heparin followed by long-term treatment with a vitamin K antagonist. However, the use of vitamin K antagonist has several inherent problems and practical challenges. These challenges have prompted the search for new oral anticoagulant drugs including direct factor Xa inhibitors (e.g., rivaroxaban, apixaban and edoxaban) and thrombin inhibitors (e.g., dabigatran). To date, results for dabigatran, rivaroxaban, apixaban, for the treatment of VTE have been published. Recently, results of the 4th new oral anticoagulant agent, edoxaban, have been published in the Hokusai-VTE study. This review discusses the Hokusai-VTE study with special emphasis on its salient features (compared to other new oral anticoagulant studies) in addition to an overview on some key lessons learnt.

BACKGROUND

Venous thromboembolism (VTE), which includes deep-vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease after myocardial infarction and stroke.[1] It is estimated that 30% of people with VTE die within one month of diagnosis.[2] In addition, patients with a first episode of VTE are at high risk of recurrence: 20% after 3 years, 30% after 5 years, and 40% after 10 years.[3]

The standard treatment of VTE consists of heparin followed by long-term treatment with a vitamin K antagonist such as warfarin. Nevertheless, use of warfarin has several limitations including a delayed onset and offset of action; a narrow therapeutic index that requires close INR monitoring; an unpredictable and variable pharmacological response; bleeding complications (about 3% per year[4]); and food and drug interactions requiring frequent dosage adjustment.[5] These challenges have prompted the development of new oral anticoagulants (NOAC); these include direct factor Xa inhibitors (e.g., rivaroxaban, apixaban and edoxaban) and thrombin inhibitors (e.g., dabigatran). Through the more predictable pharmacokinetic profile and the wide therapeutic index, these NOAC are administered orally at fixed doses, with limited food and drug interactions and no need for dose adjustment or laboratory monitoring.[6] The role of the NOAC for treatment of acute VTE has been investigated in several randomised controlled trials,[7−10] which were typically designed and powered to show non-inferiority to vitamin K antagonists in terms of recurrence of acute VTE and risk of bleeding.

Edoxaban is a selective reversible direct inhibitor of activated factor X with a rapid onset of action and with a half-life of 9 to 11 hours that allows for once daily dosing.[6] This shorter half-life - compared with warfarin's half-life of 20 to 60 hours- may improve the drug overall safety profile but, conversely, will also result in less protection if doses are missed. Approximately one third of the drug is eliminated via renal excretion.[11] Compared to rivaroxaban and apixaban, edoxaban has a lower protein binding capacity of 40−59%.[12]

THE HOKUSAI-VTE STUDY

Hokusai-VTE study was a randomized, double-blind, non-inferiority study that was conducted to evaluate efficacy and safety of edoxaban for the treatment of VTE compared with warfarin.[13] The study is named after the famous Japanese artist and painter Katsushika Hokusai.

A total of 8292 patients with VTE were enrolled at 439 centers in 37 countries (4921 patients presented with DVT and 3319 with PE). All patients received initial therapy with open-label enoxaparin or unfractionated heparin for at least 5 days followed by double-blind edoxaban ($n = 4118$) or warfarin ($n = 4122$) for at least three months and up to a maximum of 12 months. Edoxaban was given at a dose of 60 mg once daily, or 30 mg once daily in the case of patients with (1) moderate renal impairment (creatinine clearance of 30 to 50 ml/minute); (2) low body weight (below 60 kg); or (3) in patients receiving concomitant treatment with potent P-glycoprotein inhibitors (eg, verapamil, and certain macrolide antibiotics or azole antifungals). The primary efficacy outcome was recurrent symptomatic VTE (the composite of DVT, non-fatal PE, and fatal PE). The principal safety outcome was clinically relevant bleeding (the composite of major or clinically relevant nonmajor bleeding) occurring during treatment or within 3 days after interrupting or stopping study drug.

Main results of Hokusai-VTE study can be summarized as follow: first, edoxaban was noninferior to warfarin with respect to the primary efficacy outcome of recurrent symptomatic VTE (3.2% in edoxaban group vs. 3.5% in the warfarin group; hazard ratio (HR), 0.89; 95% confidence interval (CI): 0.70 to 1.13; $p < 0.001$ for noninferiority). Second, edoxaban demonstrated superiority compared to warfarin in term of primary efficacy outcome of clinically relevant major or non-major bleeding (8.5% vs. 10.3%, respectively. HR, 0.81; 95% CI, 0.71 to 0.94; $p = 0.004$ for superiority). Both treatment groups were similar in term of major bleeding ($p = 0.35$ for superiority) but edoxaban group was superior in term of clinically relevant non-major bleeding ($p < 0.001$ for superiority). Third, the efficacy and safety of edoxaban were consistent across a broad range of subgroups, including age ≥ 75 years, a body weight of more than 100 kg; renal impairment; presenting diagnosis of PE versus DVT; and standard 60 mg vs reduced 30 mg dose. Fourth, the relative efficacy of edoxaban was not limited to patients receiving medication, but it was evident even among those who stopped treatment before 12 months. Fifth, among the 938 patients with PE and right ventricular dysfunction (defined as NT pro-BNP ≥ 500 pg/mL), edoxaban provided a 48% relative lower risk of recurrent VTE compared to warfarin (3.3% vs. 6.2%, respectively − HR, 0.52; 95% CI, 0.28 to 0.98).

The design of Hokusai-VTE study has several salient features. First, the study enrolled a broad range of VTE manifestations, ranging from limited proximal DVT to severe PE. In particular, the study had more extensive VTE disease compared with other NOAC studies (42% of DVT patients had involvement of common femoral or iliac vein and 46% of PE patients had involvement of multiple lobes with 25% or more of the entire pulmonary vasculature). Second, the study was designed to reflect clinical practice using flexible treatment duration of 3 to 12 months. The minimum of 3 month duration is consistent with American College of Chest Physicians Guidelines.[14] After these 3 months, physicians were allowed to adjust the duration of treatment according to their clinical judgment or in keeping with evolving evidence. Third, efficacy of edoxaban was evaluated at 12 months of follow- up, regardless of the duration of treatment (a study design that is different from that of other NOAC studies). This design allowed for a better understanding of the outcomes in clinical practice. Fourth, in contrast to other direct inhibitor of activated factor X studies that utilized single drug approach[8−10] both in the acute and extended phase of VTE, the Hokusai-VTE study used edoxaban after acute heparin therapy for 5 days. According to the authors, this design resembles the usual practice worldwide given the widespread acceptance and confidence in acute heparin therapy (especially in patients with extensive PE). Fifth, because of concerns that NOAC may confer a higher risk of bleeding among patients with renal impairment, the dose of the study drug was halved in patients with moderate renal impairment. Hokusai-VTE is the only trial of all NOAC trials to test dose reduction for patients with impaired kidney function or low body weight.

WHAT HAVE WE LEARNED?

- Results of Hokusai-VTE study parallel those of other NOAC for the treatment of VTE (AMPLIFY study for apixaban[10], EINSTEIN-DVT[8] and EINSTEIN-PE[9] studies for rivaroxaban and RECOVER study for dabigatran[7]). On the whole, NOAC were noninferior for efficacy and, to different degrees, superior for some bleeding endpoints compared with vitamin K antagonist. Direct head to head comparison of these agents with one another, and with warfarin, is needed to determine which NOAC confers the greatest protection from recurrent VTE with the lowest rate of bleeding complications.
- The important finding that edoxaban can reduce the risk of recurrent VTE among patients with PE and right ventricular dysfunction warrants specific consideration. Typically, these high risk patients (35% of total study population) are under-represented in similar trials. The observation that edoxaban nearly halved the rate of recurrent VTE in patients with PE and right ventricular dysfunction raises the question of whether edoxaban could be the preferred anticoagulant agent (or even to replace fibrinolysis when used) for a sector of patients with submassive PE.
- Results of this study could provide a rationale for continuing anticoagulant therapy for 12 months for patients with VTE. Based upon current guidelines,[14] patients with provoked VTE caused by reversible risk factors can generally stop anticoagulation after 3 months of treatment while patients with unprovoked VTE (for which the risk of VTE recurrence is as high as 40% at 5 years[3]), it may be appropriate to consider a longer course of therapy. The fact that 40% of patients in the Hokusai-VTE were treated for 12 months gave a chance to test the efficacy and safety of extended treatment of VTE after initial anticoagulation therapy. The Hokusai-VTE study confirmed the persistent risk of recurrent VTE after initial treatment and lends further support to extending the duration of anticoagulant therapy, particularly given the low rates of major bleeding with edoxaban.
- The ability to tailor the edoxaban dose (30 mg) in patients with low body weight or moderate renal impairment is a unique feature of this trial among other NOAC trials. Importantly, low-dose edoxaban performed as well as standard-dose edoxaban with respect to efficacy and safety in these high risk patients for bleeding complications (approximately 18 % of the overall patient population in this study).
- Based upon trial design, edoxaban was preceded by an initial heparin lead-in with a median duration of heparin therapy after randomization of 7 days. This heparin lead-in phase may represent a limitation for edoxaban use knowing that both rivaroxaban (in EINSTEIN trials[8,9]) and apixaban (in AMPLIFY trial[10]) demonstrated favorable results without the heparin lead-in to oral anticoagulation.

- It is unfortunate that the use of a fibrinolytic agent to treat an episode of PE was an exclusion criterion in Hokusai-VTE study (the same for other NOAC studies for the treatment of PE). It is estimated that 5% of patients with PE will be categorized as experiencing a massive PE,[15] being eligible for fibrinolysis. Indeed, no evidence currently exists on concomitant use of NOAC with fibrinolysis. This issue should be further addressed in future studies.

- Numbers of intracranial bleeding were notably low in edoxaban versus warfarin groups (6 vs. 18 patients). The same was observed for retroperitoneal bleeding (0 vs. 4 patients). Hence, not only the *rate* of bleeding with edoxaban is lower but also the *type* of bleeding is different. This observation is consistent with other NOAC when compared to warfarin.

- Among the overall study population, the rate of recurrent VTE during the study period was the same (3.3%) among patients presenting with DVT or PE. However, because VTE is a collective term for DVT and PE, not all recurrent VTE should be considered to have the same outcome. For example it has been reported that the risk of 1 month mortality from VTE is much greater after presenting with PE than DVT.[16] In addition, recurrent VTE episodes are 3 times more likely to be PE after an initial PE than after DVT.[17]

- Edoxaban (as other NOAC) should be used with caution in cancer patients with VTE as only a minority of these patients (about 9%) was included in the study. Despite the small sample size, the results favored edoxaban over warfarin with lower rates of recurrent VTE and a trend toward a lower safety profile in cancer patients receiving edoxaban. Notably, the noninferiority of edoxaban over warfarin in cancer patient does not necessarily equate to non-inferiority over LWMH (which is the preferred VTE treatment in cancer patients[14]).

- Translating the efficacy and safety that have been shown in this trial to real-world practice is often a challenge and should be taken cautiously. For instance, patients in this study were young (mean age is approximately 56 years with only 13% of patients above the age of 75 years) with approximately 93% of patients had a creatinine clearance of 50 ml/minute or more. This is not usually the case in the real-world practice where the majority of patients are old, with complex comorbidities, and are at higher bleeding risk. Furthermore, patients in clinical trials are more likely to be adherent to treatment. This is important with NOAC since if patients miss doses, anticoagulion is rapidly reversed, and they are at increased risk for recurrent VTE.

- Among patients receiving warfarin in the Hokusai-VTE study, the time in the therapeutic range was 63.5%, which is a higher percentage of time in the therapeutic range than the 40-50% seen in registries of clinical practice.[18,19] Hence, it is possible that event rates reported in the warfarin arm of the trial overestimate the potential performance in real world clinical practice. Accordingly, in real-world settings, edoxaban could produce better patient outcomes

- Finally, to optimize the use of edoxaban in clinical practice, the following issues should be considered: (1) Patient selection should be based upon careful revision of inclusion and exclusion criteria of the trial. Importantly edoxaban should not be given to patients with: creatinine clearance < 30 ml/min; significant liver disease or alanine transaminase ≥ 2 times the upper limit of normal; antiplatelet therapy (including aspirin in a dosage > 100 mg per day); or uncontrolled hypertension.(2). Dose selection: a dose of 60 mg once daily, or 30 mg once daily for low body weight (60 Kg) and moderate renal impairment (creatinine clearance of 30 to 50 ml/minute), (3). Drug interaction: specifically with systemic use of the strong P-glycoprotein inhibitors (eg, erythromycin, azithromycin, clarithromycin, ketoconazole or itraconazole) (4). Bleeding risk assessment; and (5). Patient compliance should be assured (in order not to miss a dose with consequent rapid reversibility of anticoagulation)

REFERENCES

[1] Anderson FA Jr, Wheeler HB. Physician practices in the management of venous thromboembolism: a community-wide survey. *J Vasc Surg*. 1992;16:707–771.

[2] Heit JA. Venous thromboembolism epidemiology: implications for prevention and management. *Semin Thromb Hemost*. 2002; (s2):3–14.

[3] Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, Iotti M, Tormene D, Simioni P, Pagnan A. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica*. 2007;92:199–205.

[4] Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American college of chest physicians evidence-based clinical practice guidelines (8th Edition). *Chest*. 2008;133:257S–298S.

[5] Hull RD, Raskob GE, Hirsh J, Jay RM, Leclerc JR, Geerts WH, Rosenbloom D, Sackett DL, Anderson C, Harrison L, Gent M. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal-vein thrombosis. *N Engl J Med.* 1986;315(18):1109–1114.

[6] Franchini M, Mannucci M. New anticoagulants for treatment of venous thromboembolism. *Eur J Intern Med.* 2012;23:692–695.

[7] Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ, RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med.* 2009;361:2342–2352.

[8] EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J.* 2010;363:2499–2510.

[9] EINSTEIN-PE Investigators, Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A, Berkowitz SD, Bounameaux H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med.* 2012;366:1287–1297.

[10] Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI, AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369:799–808.

[11] Camm AJ, Bounameaux H. Edoxaban. A new oral direct factor Xa inhibitor. *Drugs.* 2011;71:1503–1526.

[12] Gonsalves WI, Pruthi RK, Patnaik MM. The new oral anticoagulants in clinical practice. *Mayo Clin Proc.* 2013;88(5):495–511.

[13] Hokusai-VTE Investigators, Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med.* 2013;369:1406–1415.

[14] Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ, American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive Summary: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 suppl):7S–47S.

[15] Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the international cooperative pulmonary embolism registry (ICOPER). *Lancet.* 1999;353:1386–1389.

[16] Murin S, Romano PS, White RH. Comparison of outcomes after hospitalization for deep venous thrombosis or pulmonary embolism. *Thromb Haemost.* 2002;88:407–414.

[17] Kearon C. Natural history of venous thromboembolism. *Circulation.* 2003;107:I22–I30.

[18] Deitelzweig SB, Lin J, Kreilick C, Hussein M, Battleman D. Warfarin therapy in patients with venous thromboembolism: patterns of use and predictors of clinical outcomes. *Adv Ther.* 2010;27:623–633.

[19] Willey VJ, Bullano MF, Hauch O, Reynolds M, Wygant G, Hoffman L, Mayzell G, Spyropoulos AC. Management patterns and outcomes of patients with venous thromboembolism in the usual community practice setting. *Clin Ther.* 2004;26:1149–1159.