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Editorial

Therapeutic options for the treatment of venous thromboembolism in case of warfarin intolerance: Effects of novel oral anticoagulants

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Standard treatment for venous thromboembolism

Pulmonary embolism (PE) is a fatal complication of venous thromboembolism (VTE). Several clinical situations are recognized as risk factors for VTE including cancer, surgery, immobilization, pregnancy and postpartum, major trauma, use of oral contraceptives, and congenital or acquired coagulation disorders. In most cases, PE develops as a consequence of deep vein thrombosis (DVT), which is a common complication after surgery, in particular, total knee or hip arthroplasty (TKA, THA). Since PE often causes recurrent VTE and serious complications such as chronic thromboembolic pulmonary hypertension, anticoagulation therapy should be recommended to prevent fatal PE and to minimize the risk of developing recurrent VTE. Currently, standard treatment for PE involves the overlapping intravenous or subcutaneous administration of low-molecular weight heparin (LMWH), unfractionated heparin (UFH), or fondaparinux with oral vitamin K antagonists (VKAs), which means actually warfarin. In acute phase of PE, more aggressive treatment such as intravenous thrombolysis or transcatheter thromboembolectomy would be required if the patient's hemodynamics are unstable. Although the optimal duration of anticoagulation therapy in the treatment of VTE remains unclear, administration of LMWH, UFT, or fondaparinux for at least 5 days in the acute phase and the use of VKAs for 3 months or more in the chronic phase are recommended in the guidelines of the European Society of Cardiology (ESC) [1] and the American College of Chest Physicians (ACCP) [2].

Alternatives to warfarin in case of ineffectiveness or intolerance of warfarin

Warfarin, the sole available VKA in Japan, is widely used for the secondary prevention of VTE. As is well-known, warfarin has many clinical limitations such as multiple food and drug interactions, slow onset and slow offset of its action, and narrow therapeutic range to prevent thrombosis and minimize hemorrhagic complications. Therefore, monitoring of international ratio (INR) of prothrombin time is necessary to obtain the beneficial antithrombotic effect of warfarin. However, it is often difficult to maintain the levels of INR within the optimal therapeutic range, resulting in the ineffectiveness of warfarin. When unexpected clinical findings such as recurrent or repetitive VTE develop under warfarin therapy despite the levels of INR being within the optimal window, other possibilities should be ruled out, i.e. warfarin dose may simply be insufficient for the patient, heparin-induced thrombocytopenia is complicated by coadministration with heparin, or patients have any underlying coagulation disorder such as protein C or S deficiency and antiphospholipid antibody syndrome. Warfarin allergy, which can be diagnosed by a drug-induced lymphocyte stimulation test, can also become the reason for intolerance and the abandonment of warfarin treatment. In these cases, alternatives to warfarin should be considered. Although novel oral anticoagulants (NOACs), including thrombin inhibitor dabigatran, factor Xa inhibitors rivaroxaban and apixaban, are currently allowed for use only in patients with nonvalvular atrial fibrillation (NVAF) in Japan, the use of NOACs could be chosen as a therapeutic option for patients with VTE because NOACs have potential action for anticoagulation as well as conventional anticoagulants (Fig. 1). Indeed, some NOACs have been approved for VTE prophylaxis in Europe, Canada, the USA, and other countries. Only in Japan, another factor Xa inhibitor edoxaban has recently been approved for VTE prophylaxis after orthopedic surgery with TKA or THA [3], but it has not yet been approved for NVAF.

In the present case report [4], alternative use of rivaroxaban was effective for the treatment of acute DVT and PE in a patient with warfarin allergy. Since only rivaroxaban has the approval as a single oral treatment option for acute symptomatic DVT [5] and acute symptomatic PE [6] in western counties, the selection of rivaroxaban would be appropriate as a result. However, according to previous clinical trials, the efficacy and safety of dabigatran [7–11] and apixaban [12] are similar to those of rivaroxaban [5,6], even though the inhibitory sites in the coagulation cascade between factor Xa inhibitors and thrombin inhibitors are pharmacologically different (Fig. 1). Therefore, any NOAC as an alternative to warfarin can be considered in cases of ineffectiveness of or intolerance to warfarin.

In addition, recent case reports demonstrated that NOACs could also be substituted for ineffective warfarin in patients with NVAF,

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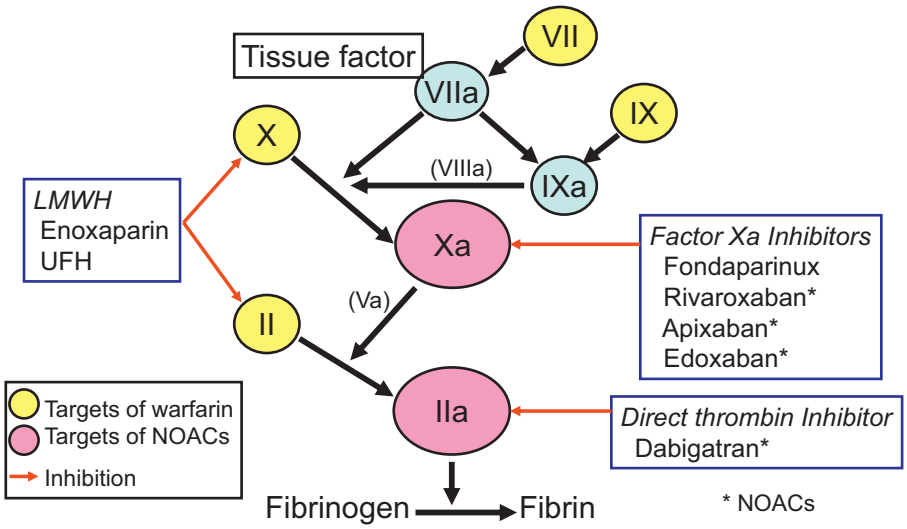

Fig. 1. The simplified coagulation cascade and inhibitory sites of anticoagulants.
LMWH, low-molecular weight heparin; UFH, unfractionated heparin; NOACs, novel oral anticoagulants.

resulting in the resolution of left atrial appendage thrombus with dabigatran [13] or rivaroxaban [14].

References

[1] Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galie N, Pruszczyk P, Bengel F, Brady AJ, Ferreira D, Janssens U, Klepetko W, Mayer E, Remy-Jardin M, Bassand JP. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J 2008;29:2276–315.

[2] Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e419S–94S.

[3] Fuji T, Fujita S, Tachibana S, Kawai Y. A dose-ranging study evaluating the oral factor Xa inhibitor edoxaban for the prevention of venous thromboembolism in patients undergoing total knee arthroplasty. J Thromb Haemost 2010;8:2458–68.

[4] Yamaguchi J, Makino K, Kusunose Y, Higa S, Takagi T, Suzuki K, Lee T. Dramatic response to low-dose rivaroxaban in an Asian patient with deep vein thrombosis and pulmonary embolism. J Cardiol Cases 2013, http://dx.doi.org/10.1016/j.jccase.2013.05.002.

[5] The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499–510.

[6] The EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287–97.

[7] Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Buller HR. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet 2007;370:949–56.

[8] Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Kalebo P, Christiansen AV, Hantel S, Hettiarachchi R, Schnee J, Buller HR. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost 2007;5:2178–85.

[9] Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber SZ. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013;368:709–18.

[10] Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342–52.

[11] Fuji T, Fuijita S, Ujihira T, Sato T. Dabigatran etexilate prevents venous thromboembolism after total knee arthroplasty in Japanese patients with a safety profile comparable to placebo. J Arthroplasty 2010;25:1267–74.

[12] Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699–708.

[13] Morita S, Ajiro Y, Uchida Y, Iwade K. Dabigatran for left atrial thrombus. Eur Heart J 2013, May, http://dx.doi.org/10.1093/eurheartj/eht148.

[14] Hammerstingl C, Potzsch B, Nickenig G. Resolution of giant left atrial appendage thrombus with rivaroxaban. Thromb Haemost 2013;109:583–4.

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