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Review

Current management of venous thromboembolism in Japan: Current epidemiology and advances in anticoagulant therapy

Mashio Nakamura (MD, PhD, FJCC)[a,b,*], Norikazu Yamada (MD, PhD)[a], Masaaki Ito (MD, PhD)[a]

[a] Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, Tsu, Japan
[b] Center for Pulmonary Embolism and Venous Thrombosis, Murase Hospital, Suzuka, Japan

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ABSTRACT

Venous thromboembolism (VTE), manifesting as either deep vein thrombosis or pulmonary embolism, is common worldwide including in Japan. The number of patients clinically diagnosed with VTE is increasing with the majority of cases occurring out-of-hospital and of milder severity. Cancer is the largest risk factor for VTE and VTE in cancer patients confers an increased 1-year mortality rate. However, the majority of VTE cases are considered "idiopathic" or "unprovoked." The limited efficacies of unfractionated heparin and warfarin have stimulated the development of new anticoagulant therapies. Recently, parenteral and oral administration of the Xa inhibitors fondaparinux and edoxaban, respectively, was approved in Japan. These agents have the potential to provide safer and more efficacious treatment options for VTE. Although further randomized studies are required to validate the utility of these agents, they are expected to substantially improve quality of life in VTE patients. This review summarizes the current status of VTE management in Japan focusing on current epidemiology and recent advances in anticoagulant therapy.

Contents

Introduction

Venous thromboembolism (VTE), manifesting as either deep vein thrombosis (DVT) or pulmonary embolism (PE), is common and results in long-term morbidity and mortality affecting >1–2 per 1000 individuals each year in the USA and Europe [1–3]. Patients with VTE have a high and persistent risk of recurrence, including nonfatal and fatal PE. The cumulative incidence of recurrent VTE is estimated to be at least 10% at 1 year and 30% at 5 years following withdrawal of anticoagulant therapy [4]. Several clinical guidelines for VTE have been published in the USA and Europe including the "2014 ESC (European Society of Cardiology) Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism" [5], "Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (2012)"

* Corresponding author at: Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, 2-174, Edobashi, Tsu 514-8507, Japan. Tel.: +81 59 231 5015; fax: +81 59 231 5201.
E-mail address: mashio@clin.medic.mie-u.ac.jp (M. Nakamura).

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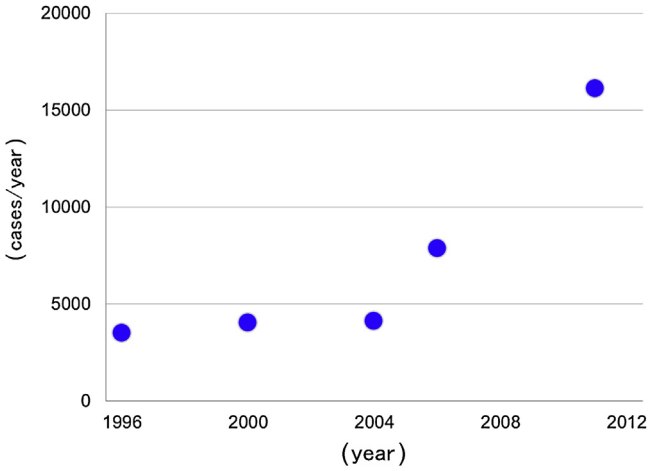

Fig. 1. Changes in the number of clinically diagnosed cases of pulmonary embolism in Japan over time.
Information compiled from Refs. [14–18].

[6], and "Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association (2012)" [7].

Concurrently, because of increased prevalence of venous thromboembolic risk factors through continued westernization of Japanese life and an aging society, the medical and social impacts of VTE have recently received increased attention. The first Japanese guidelines for the treatment of VTE were published in 2004 and revised in 2009 [8]. However, several recommendations were not supported by clinical evidence from Japanese patients, and data regarding real-world practice and guideline compliance are lacking.

Anticoagulant therapy is the cornerstone of VTE treatment. Standard anticoagulation treatment in Japan involves the use of unfractionated heparin (UFH), overlapped and followed by warfarin. Because of the need for frequent monitoring to assess bleeding risk, the efficacy of UFH and warfarin is often questioned, despite limited data on VTE treatment in Japanese patients. New parenteral and oral anticoagulant therapies overcome some limitations of standard therapy, including the need for injection and regular dose adjustments resulting from laboratory monitoring [9–13]. Recently, fondaparinux and edoxaban have been approved as alternative therapeutic options to UFH and warfarin in Japan and are expected to improve the prognosis of VTE.

The objective of this review is to discuss current VTE epidemiology and advances in anticoagulant therapy in Japan to provide a perspective on the clinical management of VTE.

Incidence of venous thromboembolism in Japan

Fig. 1 shows the number of clinically diagnosed PE cases in Japan measured by questionnaire surveys [14–18]. The number of patients with PE has increased 4.6-fold in the past 15 years with the annual incidence estimated to be 126 per 1,000,000 people in Japan in 2011. In contrast, as shown in Fig. 2, survey results from the Japanese Society of Anesthesiologists demonstrate that the incidence of postoperative PE significantly decreased from 2004 when Japanese VTE prophylaxis guidelines were published [19]. The proportions of PE occurring in hospital were 51% and 30% in 2000–2003 and 2011, respectively (Fig. 3A) [18,20]. Submassive and nonmassive severity types of PE were the most frequently diagnosed in 2000–2003 and 2011, respectively (Fig. 3B) [18,20]. In addition, an isolated calf vein thrombosis was recently found to be the most common diagnosed form of DVT (Fig. 3C) [18]. These results indicate that the number of VTE diagnoses occurring out-of-hospital and milder severities of VTE appear to be rapidly increasing in Japan. This change may be because of improved diagnostic accuracy resulting from rising awareness among medical staff, increased recognition of VTE, and advances in imaging modalities.

Risk factors for venous thromboembolism in Japan

Multiple risk factors, including genetic and acquired, or environmental, risk factors, are involved in the development of VTE. The Japan VTE Treatment Registry (JAVA) study is a nationwide, observational, multicenter, Japanese cohort study of consecutive patients with objectively-confirmed symptomatic PE,

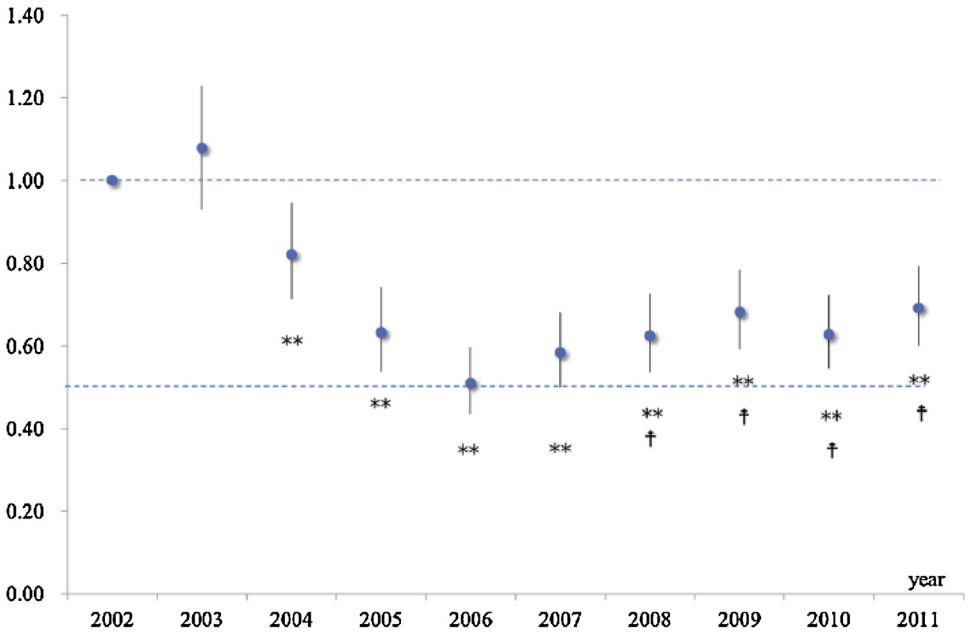

Fig. 2. Relative risk of perioperative symptomatic pulmonary embolism based on the 2002 incidence in Japan. Error bars represent 95% confidential intervals. $^{**}p < 0.01$ vs. 2002, $^{\dagger}p < 0.01$ vs. 2006.
From Kuroiwa et al. [19] with permission.