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Review Article

# Cancer-associated thrombosis: investigating the role of new oral anticoagulants

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ABSTRACT

Venous thromboembolism (VTE) is a common complication of cancer and has a significant impact on morbidity and mortality in patients with malignancies. Low molecular weight heparins (LMWHs) currently represent the drug of choice for both initial and long-term treatment of cancer-associated thrombosis. In recent years, however, a new class of novel oral anticoagulants (NOACs) inhibiting directly thrombin or activated factor X have been proposed as an alternative therapeutic option on the basis the results of subgroup analyses of phase III randomized controlled trials, including few cases of patients with cancer. After analysis of the available literature data, we conclude that although potentially interesting, future research specifically conducted in cancer patients is needed to clarify the role of these newer anticoagulant agents in prevention and treatment of cancer-related VTE.


**Contents**



## Introduction

Cancer and venous thromboembolism (VTE), defined as deep vein thrombosis (DVT), pulmonary embolism (PE) or both, are closely associated [1]. Patients with malignancy have a four- to six-fold higher relative risk of VTE than age and sex matched controls [2,3], and VTE is reported in up to 20 percent of patients with malignancies [4]. On the other hand, according to the International Registry of Patients with Venous Thromboembolism (RIETE), cancer was present in 20 percent of patients with VTE [5]. Furthermore, VTE is an independent prognostic factor for mortality and the second leading cause of death among patients with cancer [6]. Recurrence of VTE is also a major concern in cancer patients. A prospective analysis of more than 800 patients with VTE revealed that the 12-month cumulative incidence of recurrent VTE was three-fold higher in cancer patients than in those without [7]. Previous studies have also clearly demonstrated that the development of symptomatic thrombosis and VTE recurrence in patients with cancer are both associated with a significantly reduced survival [8,9]. Therefore, the treatment and prevention of VTE in cancer patients represents a major challenge for physicians in daily practice. The low molecular weight heparins (LMWHs), thanks to their high safety and efficacy profile, are actually recommended as the treatment of choice for acute and long-term management of cancer-associated VTE [10–14]. In recent years, however, a generation of novel oral anticoagulants (NOACs) has been introduced and evaluated in clinical trials. These pharmacologic agents were found to be at least as safe and effective as traditional anticoagulant therapies (i.e., LMWHs and vitamin-K antagonists [VKA]) for treatment of acute VTE and for secondary VTE prophylaxis [15,16]. Two types of NOACs are currently available: the factor Xa inhibitors apixaban, edoxaban and rivaroxaban, and the thrombin inhibitor dabigatran (see Fig. 1 and Table 1 for their

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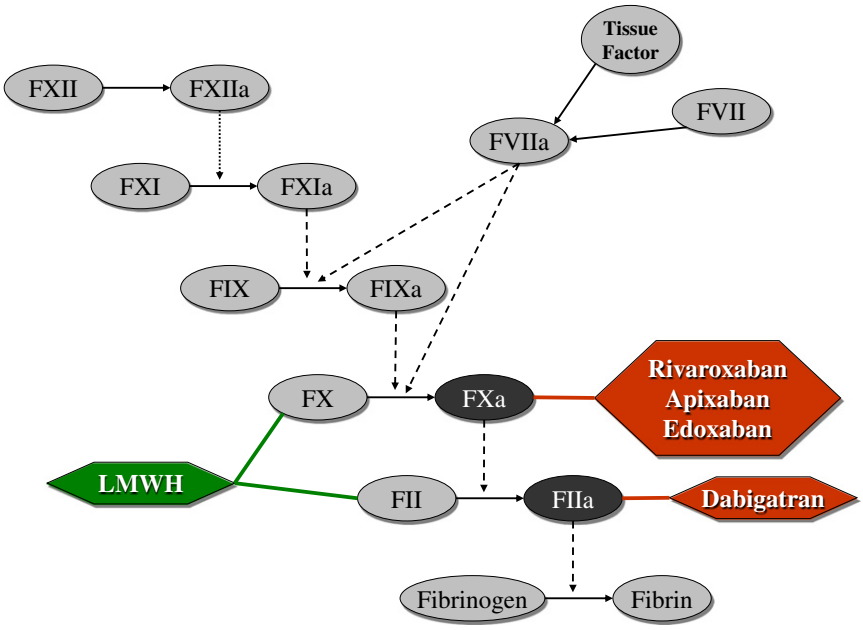


**Fig. 1.** Mechanisms of action of new oral anticoagulants. *F, factor; LMWH, low molecular weight heparin.*

mechanisms of action and their leading characteristics) [17,18]. To date, dabigatran, rivaroxaban and apixaban have been licensed by the US Food and Drug Administration (FDA) and European Medicines Agency for prophylaxis and treatment of patients with VTE, whereas edoxaban has only been licensed in Japan for this indication. This review will focus on the potential of these novel direct, target-specific oral anticoagulant agents in the setting of cancer-associated VTE.

## Search Methods

We reviewed the medical literature for published clinical trials evaluating the efficacy and safety of NOACs in patients with cancer. The MEDLINE electronic database was searched without temporal limits using an English language restriction. The Medical Subject Heading and key words used were the following: “new oral anticoagulants”, “novel oral anticoagulants”, “direct oral anticoagulants”, “target specific oral anticoagulants”, “non-vitamin K antagonist oral anticoagulants”, “dabigratan”, “rivaroxaban”, “apixaban”, “edoxaban”, “venous thromboembolism”, “pulmonary embolism”, “deep vein thrombosis”, “primary prophylaxis”, “secondary prophylaxis”, “cancer”, “malignancy”, “tumor”, “therapy”, “bleeding”, “survival“ “death”. We also screened reference list of most relevant reviews for further eligible studies not captured in our initial literature search. Search terms were also applied to abstracts from the latest international oncology and hematology congresses on hemostasis and thrombosis.

## Clinical Data on NOAC Use in Cancer Patients

The use of the NOACs in patients with cancer is potentially attractive as they have favourable pharmacokinetics, do not require subcutaneous injections or anticoagulation monitoring and have few significant drug interactions (Table 1). Unfortunately, beside a randomized trial with apixaban [19], no other studies have specifically addressed the role of NOACs in cancer-associated VTE and all available data come from subgroup analyses of small number of cancer patients recruited in the large phase III randomized acute VTE trials. These data are analysed separately for each NOAC in the following paragraphs, and summarized in Table 2. Notably, none of these studies compared the new agents to LMWH alone, which is actually the standard of care in this clinical setting.

**Dabigatran Etexilate**, the only oral direct thrombin inhibitor currently available, is a prodrug rapidly converted to the active form dabigatran once absorbed from the gastrointestinal tract. It is primarily excreted by the kidneys with a half-life of 12-17 hours (Table 1), that can be increased up to 34 hours in individuals with severe renal impairment [20]. The RE-COVER and RE-COVER II studies were both phase III

**Table 1**
Main characteristics of NOACs.

| Characteristics | Direct thrombin inhibitor | Factor Xa inhibitors | | |
|---|---|---|---|---|
| | Dabigratan | Apixaban | Edoxaban | Rivaroxaban |
| Bioavailability (%) | 3-7 | 50 | 62 | 80 |
| Time to peak concentration (hours) | 1-3 | 1-3 | 1-3 | 2-4 |
| Half-life (hours) | 12-17 | 8-15 | 8-10 | 7-13 |
| Renal clearance (%) | 80 | 25 | 35 | 66 |
| Dosing regimen | 110-150 mg twice daily | 2.5-5 mg twice daily | 15-30 mg once daily | 10-30 mg once daily |
| Metabolism | P-glycoprotein | P-glycoprotein, CYP3A4 | P-glycoprotein, CYP3A4 | P-glycoprotein, CYP3A4 |
| Licensed indications | Nonvalvular AF (NA, EU)<br>VTE treatment (US)<br>VTE prevention after major orthopedic surgery (CA, EU) | Nonvalvular AF (NA, EU)<br>VTE treatment (US)<br>VTE prevention after major orthopedic surgery (CA, EU) | Nonvalvular AF (US)<br>VTE treatment (US)<br>VTE prevention after major orthopedic surgery (Japan) | Nonvalvular AF (NA, EU)<br>VTE treatment (NA, EU)<br>VTE prevention after major orthopedic surgery (NA, EU) |

Abbreviations: AF, atrial fibrillation; NA, North America; EU, Europe; CA, Canada; US, United States.