



REVIEW

Recent advances in the treatment and prevention of venous thromboembolism in cancer patients: role of the direct oral anticoagulants and their unique challenges [version 1; peer review: 2 approved]

Dominique Farge 1-3, Corinne Frere 4,5

¹Université de Paris, IRSL, Paris, France

²Assistance Publique Hôpitaux de Paris, Saint-Louis Hospital, Internal Medicine, Autoimmune and Vascular Disease Unit, Paris, France

³McGill University, Montral, QC, Canada

⁴Sorbonne Université, INSERM UMRS_1166, Institute of Cardiometabolism And Nutrition, Paris, France

⁵Assistance Publique Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Department of Haematology, Paris, France

v1 **First published:** 27 Jun 2019, 8(F1000 Faculty Rev):974 (<https://doi.org/10.12688/f1000research.18673.1>)
Latest published: 27 Jun 2019, 8(F1000 Faculty Rev):974 (<https://doi.org/10.12688/f1000research.18673.1>)

Abstract

Venous thromboembolism (VTE) is a common complication in patients with cancer and is associated with poor prognosis. Low-molecular-weight heparins (LMWHs) are the standard of care for the treatment of cancer-associated thrombosis. Primary VTE prophylaxis with LMWH is recommended after cancer surgery and in hospitalized patients with reduced mobility. However, owing to wide variations in VTE and bleeding risk, based on disease stage, anti-cancer treatments, and individual patient characteristics, routine primary prophylaxis is not recommended in ambulatory cancer patients undergoing chemotherapy. Efforts are under way to validate risk assessment models that will help identify those patients in whom the benefits of primary prophylaxis will outweigh the risks. In recent months, long-awaited dedicated clinical trials assessing the direct oral anticoagulants (DOACs) in patients with cancer have reported promising results. In comparison with the LMWHs, the DOACs were reported to be non-inferior to prevent VTE recurrence. However, there was an increased risk of bleeding, particularly in gastrointestinal cancers. Safe and optimal treatment with the DOACs in the patient with cancer will require vigilant patient selection based on patient characteristics, co-morbidities, and the potential for drug–drug interactions.

Keywords

venous thromboembolism, cancer, low molecular weight heparin, direct oral anticoagulant

Open Peer Review

Reviewer Status

	Invited Reviewers	
	1	2
version 1 published 27 Jun 2019		

F1000 Faculty Reviews are written by members of the prestigious **F1000 Faculty**. They are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

- Thein Hlaing Oo**, The University of Texas M.D. Anderson Cancer Center, Houston, USA
- Philippe Girard**, Institut Mutualiste Montsouris, Paris, France

Any comments on the article can be found at the end of the article.

Corresponding author: Dominique Farge (dominique.farge-bancel@aphp.fr)

Author roles: **Farge D:** Investigation, Methodology, Project Administration, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Frere C:** Investigation, Methodology, Project Administration, Validation, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2019 Farge D and Frere C. This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Farge D and Frere C. **Recent advances in the treatment and prevention of venous thromboembolism in cancer patients: role of the direct oral anticoagulants and their unique challenges [version 1; peer review: 2 approved]** F1000Research 2019, **8** (F1000 Faculty Rev):974 (<https://doi.org/10.12688/f1000research.18673.1>)

First published: 27 Jun 2019, **8**(F1000 Faculty Rev):974 (<https://doi.org/10.12688/f1000research.18673.1>)

Introduction

Data from large registries indicate that the risk of developing venous thromboembolism (VTE) is four- to seven-fold greater for cancer patients compared with non-cancer patients, and the incidence of cancer-associated thrombosis (CAT) is increasing worldwide¹⁻⁵. As many as half of CAT cases are incidentally detected⁶. Multiple factors contribute to the risk of CAT; these include cancer type and stage, surgery, medical anti-cancer therapies, central venous catheter use, treatments for co-morbidities, and individual patient characteristics, such as extremes in body weight, malnutrition, and advanced age⁷. Thromboembolism is the second leading cause of death after cancer progression in this patient population². CAT is a marker of poor prognosis; cancer patients who develop VTE are six times less likely to survive than cancer patients without VTE¹. Management of VTE with anticoagulant therapies in patients with cancer is challenging because these patients are more likely to experience VTE recurrence and major bleeding events on anticoagulants relative to non-cancer patients⁸, which may be explained by expression of fibrinolytic factors by malignant cells, disseminated intravascular coagulation and thrombocytopenia, vascular invasion, and certain anti-cancer therapies^{9,10}.

Low-molecular-weight heparins (LMWHs) have been recommended over vitamin K antagonists (VKAs) as the first-line treatment for CAT for over 15 years¹¹ on the basis of three positive (CANTHANOX¹², CLOT¹³, and LITE¹⁴) out of five (CANTHANOX¹², CLOT¹³, LITE¹⁴, ONCENOX¹⁵, and CATCH¹⁶) randomized controlled trials (RCTs) which demonstrated that LMWHs are more effective and at least as safe as VKAs. LMWHs are recommended for at least 3 to 6 months for the treatment of established VTE¹⁷⁻²². Primary VTE prophylaxis is recommended for cancer surgery and hospitalized patients with reduced mobility but is not recommended routinely in ambulatory cancer patients receiving systemic anti-cancer treatments.

Despite being the best anticoagulant option in patients with cancer, the use of a parenteral anticoagulant is sometimes a barrier to treatment and may result in low treatment compliance. In addition, the cost of LMWH treatment is prohibitive in certain health-care systems. In recent years, direct oral anticoagulants (DOACs) have become an alternative to LMWH for the treatment of CAT. Like LMWH, DOACs have a rapid onset of action with predictable pharmacodynamics, but they have the convenience of oral administration. Initial evidence supporting the use of DOACs in the treatment of CAT was provided by analyses of cancer patient subgroups (3–9%)²³⁻²⁹ included in the landmark DOAC trials, which were conducted in the general patient population³⁰⁻³⁵. In the past two years, dedicated head-to-head trials in the cancer patient population have been published with promising results³⁶⁻⁴⁰. Although DOACs offer certain advantages over parenteral anticoagulants, they present their own set of unique treatment challenges that require appropriate patient selection for their use. Here, we summarize the new evidence on DOAC anticoagulant therapy in cancer patients and still-unanswered questions and controversies in the field.

New evidence for the use of DOACs in patients with cancer

Treatment and secondary prophylaxis of established cancer-associated VTE

Results from three dedicated RCTs assessing the safety and efficacy of the DOACs in the treatment of CAT patients compared with LMWH have recently become available³⁶⁻³⁸.

The patients included in these trials reflect a more representative cross-section of the overall cancer patient population; more than half of participants had a metastatic disease (53.0–65.5%) and more than two thirds were receiving systemic anti-cancer therapy (70.0–74.0%). All studies excluded patients with an ECOG (Eastern Cooperative Oncology Group) score of more than 2. The rates of VTE recurrence and major bleeding in the LMWH groups across DOAC studies are consistent with the rates documented in the landmark trials which demonstrated the superiority of LMWH over VKA (CANTHANOX¹², CLOT¹³, and LITE¹⁴) to prevent VTE recurrence in cancer patients with no increase in bleeding.

The Hokusai-VTE³⁶ and SELECT-D³⁷ trials compared the safety and efficacy of DOAC and LMWH in the treatment of established CAT (Table 1). In Hokusai-VTE³⁶, 1050 cancer patients with symptomatic or incidentally diagnosed VTE were randomly assigned to either edoxaban (60 mg daily after at least 5 days of LMWH therapy) or dalteparin (200 IU/kg daily for 1 month followed by 150 IU/kg daily) for 6 to 12 months. Edoxaban was non-inferior to LMWH in the composite primary outcome measure of recurrent VTE or major bleeding within 12 months after randomization regardless of treatment duration (hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.70–1.36, $P = 0.006$ for non-inferiority, $P = 0.87$ for superiority). An analysis of the components of the primary outcome measure demonstrated that VTE recurrence rates were numerically lower with edoxaban, but that this difference was not statistically significant (7.9% [edoxaban] versus 11.3% [dalteparin], $P = 0.09$). Major bleeding was more common with edoxaban (6.9% versus 4.0%, $P = 0.04$), whereas rates of clinically relevant non-major bleeding and mortality were similar between groups. The higher rate of major bleeding in the edoxaban group was driven by gastrointestinal (GI) bleeding in patients with GI cancer. In Hokusai-VTE, patients were excluded if the need for several P-glycoprotein (P-gp) inhibitors, such as ritonavir, nelfinavir, indinavir, or saquinavir, was anticipated. Systemic use of other P-gp inhibitors, namely itraconazole, itraconazole, erythromycin, azithromycin, or clarithromycin, was not permitted at inclusion but was permitted if needed during the study with appropriate dose adjustments of edoxaban.

In the SELECT-D pilot trial³⁷, 406 cancer patients with symptomatic or incidental pulmonary embolism (PE) or symptomatic lower-extremity proximal deep vein thrombosis (DVT) were randomly assigned to rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily) or dalteparin (200 IU/kg daily for 1 month followed by 150 IU/kg daily). The 6-month cumulative rate of recurrent VTE after randomization

Table 1. Randomized clinical trials assessing the efficacy and safety of direct oral anticoagulants in the treatment of cancer-associated thrombosis.

Randomized clinical trials	Hokusai-VTE cancer ³⁶	SELECT-D ³⁷	ADAM-VTE ³⁸
Number of randomly assigned patients	1050	406	300
Trial design	Non-inferiority	Pilot	Superiority
DOAC	Edoxaban: Dalteparin for at least 5 days followed by edoxaban 60 mg once daily for 6 to 12 months	Rivaroxaban: 15 mg twice daily for 3 weeks followed by 20 mg once daily for 2 to 6 months	Apixaban: 10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months
Comparator	LMWH: Daltaparin 200 IU/kg once daily first 30 days followed by 150 IU/kg daily	LMWH: Daltaparin 200 IU/kg once daily first 30 days followed by 150 IU/kg daily	LMWH: Daltaparin 200 IU/kg once daily first 30 days followed by 150 IU/kg daily
Primary outcome measures	Composite measure of recurrent VTE or major bleeding within 12 months after randomization	VTE recurrence in the 6 months after randomization	Major bleeding including fatal bleeding
Primary outcome results	<ul style="list-style-type: none"> • Edoxaban: 12.8% • Dalteparin: 13.5% 	<ul style="list-style-type: none"> • Rivaroxaban: 4% • Dalteparin: 11% 	<ul style="list-style-type: none"> • Apixaban: 0% • Dalteparin: 2.1%
Major secondary outcomes	Recurrent VTE <ul style="list-style-type: none"> • Edoxaban: 7.9% • Dalteparin: 11.3% Major bleeding <ul style="list-style-type: none"> • Edoxaban: 6.9% • Dalteparin: 4.0% 	Major bleeding <ul style="list-style-type: none"> • Rivaroxaban: 13% • Dalteparin: 4% CRNMB <ul style="list-style-type: none"> • Rivaroxaban: 6% • Dalteparin: 4% 	Recurrent VTE (DVT, PE, fatal PE) <ul style="list-style-type: none"> • Apixaban: 3.4% • Dalteparin: 14.1% Major + fatal + CRNMB <ul style="list-style-type: none"> • Apixaban: 9.0% • Dalteparin: 9.0%

CRNMB, clinically relevant non-major bleeding; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; VTE, venous thromboembolism.

was significantly lower with rivaroxaban compared with dalteparin (HR 0.43, 95% CI 0.19–0.99). Cumulative clinically relevant non-major bleeding rates were higher with rivaroxaban (HR 3.76, 95% CI 1.63–8.69), but major bleeding rates were not statistically different between the groups (6% [rivaroxaban] versus 4% [dalteparin], HR 1.83, 95% CI 0.68–4.96). Of note, during the interim analysis, the data and safety monitoring study committee determined that although the overall bleeding events did not cross the safety boundary of excess in clinically relevant bleeding, the patients with esophageal or esophagogastric junction tumors had a trend toward major bleeding. Therefore, as a precaution, such types of patients were subsequently excluded from enrollment. Six-month survival did not differ between the two treatment arms. Major bleeding occurred more frequently with rivaroxaban than with dalteparin in patients with esophageal or gastroesophageal cancer (36% [rivaroxaban] versus 11% [dalteparin]). Most major bleeding events in the rivaroxaban group were GI. Most clinically relevant non-major bleeding events occurring with rivaroxaban were GI or genitourinary. Concomitant use of the following strong cytochrome P450 3A4 inhibitors or inducers was excluded: human immunodeficiency virus protease inhibitors or systemic ketoconazole and rifampicin, carbamazepine, or phenytoin. Concomitant use of P-gp inhibitors or inducers was excluded.

Results from the ADAM trial (ClinicalTrials.gov Identifier: NCT02585713)³⁸ were presented in December 2018 at the 60th American Society of Hematology annual meeting. Cancer

patients with established CAT, including upper-extremity and splanchnic vein thrombosis, were randomly assigned to either apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily) or dalteparin (200 IU/kg daily for 1 month followed by 150 IU/kg daily) for 6 months. The primary outcome measure of major bleeding rate was similar between the two treatment groups (0 [apixaban] versus 3/142 (2.1%) [dalteparin], $P = 0.9956$). The secondary outcome of VTE recurrence rate was lower with apixaban compared with LMWH (HR 0.26, 95% CI 0.09–0.80, $P = 0.0182$). Strong CYP3A4 inducers were excluded from the study.

Treatment satisfaction. Few studies have assessed the quality of life (QoL) of cancer patients with CAT treated by LMWH. The prospective TROPIQUE (n = 409 patients with cancer)⁴¹ and QUAVITEC (n = 400 patients with cancer)⁴² cohort studies reported that most patients were satisfied or very satisfied and reassured about treatment efficacy and experience with side effects under LMWH, which did not hinder QoL improvements in those who survived to 6-month follow-up. In Hokusai-VTE³⁶, treatment termination as a result of inconvenience of dosing was reported in 4% of patients on edoxaban and 14.9% of patients on dalteparin. In the ADAM trial, QoL surveys in the ADAM-VTE trial³⁸ revealed a better tolerance to apixaban compared with dalteparin. Premature discontinuation of anticoagulant treatment in the study occurred in significantly fewer patients receiving apixaban compared with dalteparin (15%; $P = 0.0012$).

In conclusion, anticoagulant therapy with the DOACs in the treatment of established CAT resulted in similar or better rates of recurrent VTE but was associated with a higher risk of bleeding, particularly in GI and genitourinary cancers. The underlying cause of the susceptibility of the GI tract to bleeding may be due to accumulation of active drug or chemotherapy toxicity⁴³. Overall, these first trials suggest a favorable risk-benefit ratio for DOACs in the treatment and secondary prevention of established CAT. However, their safe and optimal use will require appropriate patient selection and monitoring of several parameters, particularly since the theoretical risks of drug–drug interactions have not been investigated in patients with cancer.

Primary prophylaxis of cancer-associated VTE

About 5 to 10% of ambulatory cancer patients initiating chemotherapy will develop CAT, and up to 74% of CAT cases occur in the outpatient setting⁴⁴. The widely varying risk of VTE and bleeding across cancer types, stages, cancer treatments, and individual patients has resulted in study findings in this patient population that have been difficult to interpret. Two large RCTs compared LMWH with placebo in patients with different cancer types and found a significant reduction in the relative risk of VTE but with a small difference in the respective absolute risk^{45,46}. A recent systematic review and meta-analysis reported that primary prophylaxis with LMWH compared with no treatment in all cancers reduced the rate of VTE, while significantly

increasing the risk of major bleeding⁴⁷. However, the number needed to treat was 30, supporting previous conclusions that primary prophylaxis should not be used across patients with cancer⁴⁷. Studies in pancreatic cancer which is associated with considerably high VTE risks yielded better risk-benefit ratios^{48,49}.

Several ongoing efforts to stratify patients according to VTE risk are under way in order to identify the appropriate patients who stand to benefit from primary prophylaxis. The Khorana score⁵⁰, which is based on readily available clinical and laboratory parameters, was developed for ambulatory patients initiating chemotherapy and is the most widely studied risk assessment model. The model was validated in independent studies⁵¹, although recent publications questioned its reproducibility in certain patient populations⁵²⁻⁵⁴. Several modifications of the Khorana score have been proposed to improve its predictive strength and are currently being studied, including the extended Vienna Cancer and Thrombosis Study (CATS) score⁵¹ and the Protecht score⁵⁵, as well as a simplified clinical prediction model incorporating only tumor-site category and D-dimer⁵⁶. The recent DOAC trials assessing the safety and efficacy of DOACs for the primary prophylaxis VTE in ambulatory cancer patients initiating chemotherapy aimed to address this issue by stratifying patients according to VTE risk (Table 2)^{39,40}. The studies used the Khorana score⁵⁰, which continues to be the most widely accepted VTE risk assessment model in this cancer patient population.

Table 2. Randomized clinical trials assessing the efficacy and safety of direct oral anticoagulants in the prophylaxis of cancer-associated thrombosis.

Randomized clinical trials	CASSINI ³⁹	AVERT ⁴⁰
Number of randomly assigned patients	841	574
Trial design	Superiority	Superiority
DOAC	Rivaroxaban: 10 mg once daily	Apixaban: 2.5 mg twice daily
Comparator	Placebo	Placebo
Primary outcome measures	<ul style="list-style-type: none"> • Composite measure of DVT, PE, and VTE-related death • Major bleeding 	<ul style="list-style-type: none"> • Objectively documented VTE (proximal DVT and PE) over a 6-month follow-up period • Major bleeding
Primary outcome results	Composite on-treatment <ul style="list-style-type: none"> • Rivaroxaban: 2.6% • Placebo: 6.4% Composite – up to 6 months <ul style="list-style-type: none"> • Rivaroxaban: 6.0% • Placebo: 8.8% Major bleeding <ul style="list-style-type: none"> • Rivaroxaban: 2.0% • Placebo: 1.0% 	VTE <ul style="list-style-type: none"> • Apixaban: 4.2% • Placebo: 10.2% Major bleeding <ul style="list-style-type: none"> • Apixaban: 3.5% • Placebo: 1.8%
Major secondary outcomes	CRNMB <ul style="list-style-type: none"> • Rivaroxaban: 2.7% • Placebo: 2.0% 	CRNMB <ul style="list-style-type: none"> • Apixaban: 7.3% • Placebo: 5.5%

CRNMB, clinically relevant non-major bleeding; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

The CASSINI trial³⁹ assessed the safety and efficacy of rivaroxaban in ambulatory cancer patients initiating chemotherapy with intermediate to high risk of VTE (Khorana score of at least 2). Eight hundred forty-one patients were randomly assigned to either treatment with rivaroxaban (10 mg once daily) or placebo for up to 6 months. The primary outcome did not differ between the groups over the entire 6-month observation period (8.8% under placebo versus 6.0% under rivaroxaban; HR 0.66, 95% CI 0.40–1.09, $P = 0.10$). Patients who received rivaroxaban compared with those under placebo while on treatment had fewer primary outcome events, which was a composite measure of symptomatic or asymptomatic DVT or PE and VTE-related death (6.4% under placebo versus 2.6% under rivaroxaban, HR 0.40, 95% CI 0.20–0.80). There was no difference in major bleeding between the two groups (HR 1.96, 95% CI 0.59–6.49). Patients with primary or metastatic brain tumors were excluded from the study. The majority of enrolled patients had pancreatic (32.6%), gastric and gastroesophagus (20.9%), or lung (15.9%) cancer or lymphoma (7%).

The AVERT trial⁴⁰ compared primary prophylaxis with apixaban (2.5 mg twice daily) with placebo in 573 ambulatory cancer patients initiating chemotherapy for up to 6 months. The primary outcome was symptomatic and incidental VTE occurrence. Patients receiving apixaban had a lower risk of VTE occurrence compared with placebo (7.3% under placebo versus 1% under apixaban, HR 0.14, 95% CI 0.26–0.65, $P < 0.001$). The risk of major bleeding was increased on apixaban (HR 2.00, 95% CI 1.01–3.95, $P = 0.046$). The majority of enrolled patients had gynecologic (25.7%), pancreatic (13.5%), or lung (10%) cancer or lymphoma (25.2%).

When results from the two studies were combined, the absolute difference in the incidence of symptomatic VTE between the DOAC and the placebo groups was 2.5% in the primary intention-to-treat analysis, which corresponds to a number needed to treat of 40 patients⁵⁷. Together, these DOAC studies indicate that primary prophylaxis in cancer patients with a Khorana score of at least 2 results in significantly lower rates of VTE. However, the risk of major bleeding was increased with apixaban. In both studies, patients considered to have a high bleeding risk were excluded. There was a high rate of discontinuation, in both the treatment and placebo groups.

Unanswered questions and controversies

There are multiple disease-related factors, including drug absorption, distribution, metabolism, and elimination, that can affect anticoagulant pharmacokinetics in patients with cancer (reviewed in 58). The risks of over- or under-coagulating with DOACs, despite their predictable pharmacodynamics, as a result of renal or hepatic impairment, potential drug–drug interactions, and patient characteristics such as weight and age require vigilance (reviewed in 59,60). Finally, the optimal treatment duration of anticoagulation after 3 to 6 months for patients with CAT remains unanswered. Table 3 summarizes the characteristics of the available DOAC.

Special considerations in patients with cancer

Vomiting and diarrhea are side effects of cancer treatment and can limit absorption. Changes related to inflammation and collection of extra-vascular fluids can affect distribution of the DOAC. Similarly, changes in body composition, such as reduced lean body mass, a common occurrence in elderly patients with cancer, reduce the distribution volume and increase the risk of acute toxicity, particularly when combined with anti-cancer therapy^{61,62}. Decreased lean body mass can also result in an overestimation of renal function, which can put the patient at risk of over-anticoagulation⁵⁸. Thrombocytopenia, common in patients with cancer, is also a bleeding concern. Metabolism through the cytochrome P450 is altered in cancer, and there is large inter-individual variability in CYP3A activity in patients with cancer⁶³, further complicating attempts to predict the potential clinical impact of specific drug–drug interactions. Altered hepatic function and inflammatory responses have been proposed as an underlying mechanism for a decrease in drug metabolism through the CYP system in patients with cancer^{64,65}. Furthermore, these patients are typically on multiple medications, increasing the risk of drug–drug interactions. Thus, anticoagulant pharmacokinetics can be widely variable across patients with cancer, rendering prediction of the dose–response relationship difficult. Overall, patients with cancer tend to be elderly, receive multiple concomitant drug therapies, and are more likely to have some degree of hepatic or renal insufficiency.

Renal and hepatic impairment

About 60% of patients with cancer have decreased renal function⁶⁶ and this decline is sometimes sudden. Major or fatal bleeding can occur following a rapid decline in renal function in patients on anticoagulants. Renal and hepatic impairment will affect the plasma levels of the different DOACs on the basis of their respective mechanisms of elimination⁶⁷. Moderate hepatic impairment (Child–Pugh B) increases plasma levels of rivaroxaban only (127%). There are no data on severe hepatic impairment.

Thrombocytopenia

Thrombocytopenia can develop directly from tumor invasion of bone marrow, as a result of secondary immune-mediated responses, or following myeloablative chemotherapy⁶⁰. In patients with cancer and thrombocytopenia, the risk of bleeding is increased. Full doses of anticoagulant can be used for the treatment of established CAT if the platelet count is above 50 G/L and bleeding is not evident; for patients with a platelet count below 50 G/L, decisions about treatment and dose should be made on a case-by-case basis¹¹ and available data do not support one management strategy over another (LMWH or DOAC).

Drug–drug interactions

Drugs that significantly induce or inhibit CYP3A4, a member of the hepatic cytochrome P450 enzyme system, or ATP-binding cassette transporters, such as P-gp and breast cancer-resistant protein (BCRP), can change the plasma concentration of DOACs (reviewed in 59,67,68). Limited studies have

Table 3. Characteristics of direct oral anticoagulants used or being investigated in patients with cancer.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	LMWH
Target	FIIa	FXa	FXa	FXa	Indirect FXa/FIIa
Prodrug	Yes	No	No	No	No
Bioavailability	3–7%	10 mg dose: 100% 20 mg dose: 100% when taken together with food; 66% under fasting conditions Inter-individual variability: 30–40%	~50% Inter-individual variability: 30%	~62%	90–98% Subcutaneous
Renal excretion (percentage of administered dose)	5% (4% unchanged)	66% (33% unchanged)	27% (22% unchanged)	35% (24% unchanged)	High
Biliary-fecal excretion (percentage of administered dose)	95%	34%	56%	62%	Low
Metabolism	Glucuronidation	CYP3A4 (75%) > CYP2j2	CYP3A4 (50%)	Hydrolysis > CYP3A4 (27%)	Desulphation, Depolymerization (<10%)
Interaction with P-glycoprotein inducers/inhibitors	Yes	Yes	Yes	Yes	No

LMWH, low-molecular-weight heparin.

documented the effects of co-administration of DOACs and strong inhibitors and inducers of CYP3A4 and P-gp⁶⁷.

All DOACs undergo an efflux transport mainly via P-gp, mediating drug absorption and excretion. Altered P-gp function is one mechanism of chemotherapy resistance, in which its activity limits absorption of the chemotherapy agent into malignant cells^{69,70}. This pharmacodynamic profile suggests that inhibitors or inducers of P-gp can lead to over- or under-anticoagulation. However, this theoretical risk is difficult to predict given the wide inter-individual variability on P-gp activity⁷¹. Rivaroxaban and apixaban are both substrates of CYP3A4 and therefore susceptible to changes in plasma concentrations when given concomitantly with drugs that induce or inhibit CYP3A4⁶⁷. Rivaroxaban and apixaban are also substrates of BCRP.

For all of the DOACs, concomitant administration of rifampicin, a strong inducer of CYP3A4 and P-gp, produces clinically important decreases in DOAC plasma concentrations and increases the risk of thrombosis^{72–74}. The product monographs for all of the DOACs indicate that concomitant administration with the CYP3A4 and P-gp inducers rifampicin, carbamazepine, and phenytoin and also phenobarbital in the case of apixaban, edoxaban, and rivaroxaban should be carried out with caution or avoided^{75–78}.

DOAC drug–drug interaction with cancer therapies

DOAC absorption can be altered by cancer treatments such as surgery and radiotherapy⁵⁸. The concomitant administration of

DOACs with anti-cancer and adjunctive pharmacotherapies that are inhibitors or inducers of P-gp and CYP3A4 poses a theoretical risk of VTE or bleeding by pushing circulating DOAC levels outside the therapeutic range. Direct studies on interactions between DOAC and anti-cancer therapies are not available. Certain chemotherapies, hormone therapies, and targeted therapies, such as tyrosine kinase inhibitors, are potent CYP inducers or inhibitors. Some anti-cancer treatments can also induce or inhibit P-gp. Potential interactions have been compiled (reviewed in 58–60,79) and are summarized in Table 4.

Treatment duration for established CAT

Determining the optimal duration of anticoagulation in the treatment of established CAT remains an unresolved issue. RCTs that compared LMWH with VKA for the treatment of acute VTE in this setting followed the participants for only 3 to 6 months^{12–16}. Since the risk of recurrent VTE remains high as long as the cancer is active, extended duration of anticoagulant therapy is usually proposed despite the lack of evidence from RCTs as long as specific anti-cancer treatments, classically defined by the use of anti-cancer surgery, chemotherapy, radiotherapy, and growth factors, are being delivered¹¹. Data are still insufficient to evaluate the specific VTE risk associated with long-term immunotherapy.

Conclusions

New dedicated clinical trial evidence showing an efficacy of DOAC that is similar to or better than LMWH in the treatment and secondary prevention of CAT offers a new treatment option to patients with cancer. However, increased bleeding risks

Table 4. Anti-cancer treatments predicted to affect direct oral anticoagulant plasma levels through moderate to strong interaction with CYP3A4 or P-glycoprotein or both.

	CYP3A4	P-glycoprotein
Inducers	Antimitotic agents: paclitaxel, ifosfamide, mitotane Tyrosine kinase inhibitors: vemurafenib, dabrafenib, vemurafenib Hormone therapy: enzalutamide Immunomodulators: dexamethasone, prednisone	Antimitotic agents: vinblastine Anthracyclines/anthracenediones: doxorubicin Tyrosine kinase inhibitors: vandetanib, sunitinib Immunomodulators: dexamethasone
Inhibitors	Tyrosine kinase inhibitors: imatinib, crizotinib, idelalisib, lapatinib, nilotinib Hormone therapy: bicalutamide, abiraterone Immunomodulators: cyclosporine	Tyrosine kinase inhibitors: imatinib, crizotinib, nilotinib, lapatinib, Hormone therapy: abiraterone, tamoxifen, enzalutamide, Immunomodulators: tacrolimus, cyclosporine,
Substrates	Antimitotic agents: paclitaxel, docetaxel, vinblastine, vincristine, vinorelbine Topoisomerase inhibitors: etoposide, irinotecan Anthracyclines/anthracenediones: doxorubicin Alkylating agents: ifosfamide, busulfan Tyrosine kinase inhibitors: crizotinib, imatinib, dasatinib, nilotinib, erlotinib, gefitinib, lapatinib, sunitinib, vandetanib Monoclonal antibodies: brentuximab Hormone therapy: abiraterone, enzalutamide, tamoxifen, flutamide Immunomodulators: cyclosporine, dexamethasone, sirolimus, everolimus, temsirolimus, tacrolimus	Antimitotic agents: paclitaxel, vinblastine, vincristine, docetaxel Antimetabolites: methotrexate Topoisomerase inhibitors: irinotecan, etoposide Anthracyclines/anthracenediones: doxorubicin, daunorubicin, idarubicin Alkylating agents: bendamustine Intercalating agents: mitomycin C Tyrosine kinase inhibitors: imatinib, nilotinib, lapatinib, crizotinib, vemurafenib Immunomodulators: cyclosporine, sirolimus, everolimus, temsirolimus, tacrolimus, dexamethasone

Adapted from^{59-60,68,79}.


compared with LMWH, particularly in GI and genitourinary cancers, indicate a need for caution. Administering DOACs to cancer patients with CAT will necessitate individualized treatment decisions that consider patient characteristics, comorbidities, and the potential for drug–drug interactions. Primary prophylaxis in ambulatory cancer patients initiating chemotherapy remains an area of uncertainty. The incorporation of VTE risk assessment models into clinical trial designs to stratify patients according to VTE risk may help identify cancer patients likely to benefit from primary VTE prophylaxis. The two recent trials assessing the safety and efficacy of DOACs in the prevention of VTE included patients with a

Khorana score of at least 2 and reported a significant reduction in the rates of VTE, but the trial investigating apixaban reported increased bleeding risk. Future studies will continue to clarify which patients with cancer should receive primary thromboprophylaxis and the safety profiles of the different DOACs in this clinical setting.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

- Chew HK, Wun T, Harvey D, *et al.*: **Incidence of venous thromboembolism and its effect on survival among patients with common cancers.** *Arch Intern Med.* 2006; **166**(4): 458–64.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Khorana AA, Francis CW, Culakova E, *et al.*: **Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy.** *J Thromb Haemost.* 2007; **5**(3): 632–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Walker AJ, Card TR, West J, *et al.*: **Incidence of venous thromboembolism in patients with cancer - a cohort study using linked United Kingdom databases.** *Eur J Cancer.* 2013; **49**(6): 1404–13.
[PubMed Abstract](#) | [Publisher Full Text](#)
-  Cronin-Fenton DP, Søndergaard F, Pedersen LA, *et al.*: **Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006.** *Br J Cancer.* 2010;



- 103(7): 947–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
5. Heit JA, Spencer FA, White RH: **The epidemiology of venous thromboembolism.** *J Thromb Thrombolysis.* 2016; **41**(1): 3–14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 6. van Es N, Bleker SM, Di Nisio M: **Cancer-associated unsuspected pulmonary embolism.** *Thromb Res.* 2014; **133 Suppl 2**: S172–S178.
[PubMed Abstract](#) | [Publisher Full Text](#)
 7. Timp JF, Braekkan SK, Versteeg HH, *et al.*: **Epidemiology of cancer-associated venous thrombosis.** *Blood.* 2013; **122**(10): 1712–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
 8. Prandoni P, Lensing AW, Piccioli A, *et al.*: **Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis.** *Blood.* 2002; **100**(10): 3484–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 9. Kamphuisen PW, Beyer-Westendorf J: **Bleeding complications during anticoagulant treatment in patients with cancer.** *Thromb Res.* 2014; **133 Suppl 2**: S49–S55.
[PubMed Abstract](#) | [Publisher Full Text](#)
 10. Caine GJ, Stonelake PS, Lip GY, *et al.*: **The hypercoagulable state of malignancy: pathogenesis and current debate.** *Neoplasia.* 2002; **4**(6): 465–73.
[PubMed Abstract](#) | [Free Full Text](#)
 11. Farge D, Bounameaux H, Brenner B, *et al.*: **International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer.** *Lancet Oncol.* 2016; **17**(10): e452–e466.
[PubMed Abstract](#) | [Publisher Full Text](#)
 12. **F** Meyer G, Besse B, Doubre H, *et al.*: **Anti-tumour effect of low molecular weight heparin in localised lung cancer: a phase III clinical trial.** *Eur Respir J.* 2018; **52**(4): pii: 1801220.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 13. Lee AY, Levine MN, Baker RI, *et al.*: **Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer.** *N Engl J Med.* 2003; **349**(2): 146–53.
[PubMed Abstract](#) | [Publisher Full Text](#)
 14. Hull RD, Pineo GF, Brant RF, *et al.*: **Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer.** *Am J Med.* 2006; **119**(12): 1062–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
 15. **F** Deitcher SR, Kessler CM, Merli G, *et al.*: **Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period.** *Clin Appl Thromb Hemost.* 2006; **12**(4): 389–96.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 16. Lee AYY, Kamphuisen PW, Meyer G, *et al.*: **Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial.** *JAMA.* 2015; **314**(7): 677–86.
[PubMed Abstract](#) | [Publisher Full Text](#)
 17. Watson HG, Keeling DM, Laffan M, *et al.*: **Guideline on aspects of cancer-related venous thrombosis.** *Br J Haematol.* 2015; **170**(5): 640–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 18. Easaw JC, Shea-Budgell MA, Wu CM, *et al.*: **Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 1: prophylaxis.** *Curr Oncol.* 2015; **22**(2): 133–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 19. Easaw JC, Shea-Budgell MA, Wu CM, *et al.*: **Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 2: treatment.** *Curr Oncol.* 2015; **22**(2): 144–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 20. Lyman GH, Khorana AA, Kuderer NM, *et al.*: **Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update.** *J Clin Oncol.* 2013; **31**(17): 2189–204.
[PubMed Abstract](#) | [Publisher Full Text](#)
 21. **F** Lyman GH, Bohilke K, Khorana AA, *et al.*: **Venous thromboembolism prophylaxis and treatment in patients with cancer: American society of clinical oncology clinical practice guideline update 2014.** *J Clin Oncol.* 2015; **33**(6): 654–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 22. **F** Kearon C, Akl EA, Ornelas J, *et al.*: **Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report.** *Chest.* 2016; **149**(2): 315–52.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 23. Schulman S, Goldhaber SZ, Kearon C, *et al.*: **Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer.** *Thromb Haemost.* 2015; **114**(1): 150–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 24. Prins MH, Lensing AW, Brighton TA, *et al.*: **Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials.** *Lancet Haematol.* 2014; **1**(1): e37–e46.
[PubMed Abstract](#) | [Publisher Full Text](#)
 25. Agnelli G, Buller HR, Cohen A, *et al.*: **Oral apixaban for the treatment of venous thromboembolism in cancer patients: Results from the AMPLIFY trial.** *J Thromb Haemost.* 2015; **13**(12): 2187–91.
[PubMed Abstract](#) | [Publisher Full Text](#)
 26. **F** Raskob GE, van Es N, Segers A, *et al.*: **Edoxaban for venous thromboembolism in patients with cancer: results from a non-inferiority subgroup analysis of the Hokusai-VTE randomised, double-blind, double-dummy trial.** *Lancet Haematol.* 2016; **3**(8): e379–e387.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 27. Carrier M, Cameron C, Delluc A, *et al.*: **Efficacy and safety of anticoagulant therapy for the treatment of acute cancer-associated thrombosis: a systematic review and meta-analysis.** *Thromb Res.* 2014; **134**(6): 1214–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 28. van der Hulle T, den Exter PL, Kooiman J, *et al.*: **Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism.** *J Thromb Haemost.* 2014; **12**(7): 1116–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
 29. Vedovati MC, Germini F, Agnelli G, *et al.*: **Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis.** *Chest.* 2015; **147**(2): 475–83.
[PubMed Abstract](#) | [Publisher Full Text](#)
 30. **F** Schulman S, Kearon C, Kakkar AK, *et al.*: **Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism.** *N Engl J Med.* 2009; **361**(24): 2342–52.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 31. Schulman S, Kakkar AK, Goldhaber SZ, *et al.*: **Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis.** *Circulation.* 2014; **129**(7): 764–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
 32. **F** EINSTEIN–PE Investigators, Büller HR, Prins MH, *et al.*: **Oral rivaroxaban for the treatment of symptomatic pulmonary embolism.** *N Engl J Med.* 2012; **366**(14): 1287–97.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 33. **F** EINSTEIN Investigators, Bauersachs R, Berkowitz SD, *et al.*: **Oral rivaroxaban for symptomatic venous thromboembolism.** *N Engl J Med.* 2010; **363**(26): 2499–510.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 34. Hokusai-VTE Investigators, Büller HR, Décousus H, *et al.*: **Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism.** *N Engl J Med.* 2013; **369**(15): 1406–15.
[PubMed Abstract](#) | [Publisher Full Text](#)
 35. **F** Agnelli G, Buller HR, Cohen A, *et al.*: **Oral apixaban for the treatment of acute venous thromboembolism.** *N Engl J Med.* 2013; **369**(9): 799–808.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 36. **F** Raskob GE, van Es N, Verhamme P, *et al.*: **Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism.** *N Engl J Med.* 2018; **378**(7): 615–24.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 37. **F** Young AM, Marshall A, Thirlwall J, *et al.*: **Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D).** *J Clin Oncol.* 2018; **36**(20): 2017–23.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 38. McBane RD, Wysokinski WE, Le-Rademacher J, *et al.*: **Apixaban, Dalteparin, in Active Cancer Associated Venous Thromboembolism, the ADAM VTE Trial.** *Blood.* 2018; **132**(Suppl 1): 421.
[Reference Source](#)
 39. **F** Khorana AA, Soff GA, Kakkar AK, *et al.*: **Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer.** *N Engl J Med.* 2019; **380**(8): 720–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 40. **F** Carrier M, Abou-Nassar K, Mallick R, *et al.*: **Apixaban to Prevent Venous Thromboembolism in Patients with Cancer.** *N Engl J Med.* 2019; **380**(8): 711–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 41. Cajfinger F, Debourdeau P, Lamblin A, *et al.*: **Low-molecular-weight heparins for cancer-associated thrombosis: Adherence to clinical practice guidelines and patient perception in TROPIQUE, a 409-patient prospective observational study.** *Thromb Res.* 2016; **144**: 85–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
 42. Farge D, Cajfinger F, Falvo N, *et al.*: **Quality of life in cancer patients undergoing anticoagulant treatment with LMWH for venous thromboembolism: the QUAVITEC study on behalf of the Groupe Francophone Thrombose et Cancer (GFTC).** *Oncotarget.* 2018; **9**(43): 26990–26999.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 43. Vanassche T, Hirsh J, Eikelboom JW, *et al.*: **Organ-specific bleeding patterns of anticoagulant therapy: lessons from clinical trials.** *Thromb Haemost.* 2014; **112**(5): 918–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
 44. Spencer FA, Lessard D, Emery C, *et al.*: **Venous thromboembolism in the outpatient setting.** *Arch Intern Med.* 2007; **167**(14): 1471–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

45. Agnelli G, George DJ, Kakkar AK, *et al.*: **Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer.** *N Engl J Med.* 2012; 366(7): 601–9. [PubMed Abstract](#) | [Publisher Full Text](#)
46. Agnelli G, Gussoni G, Bianchini C, *et al.*: **Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study.** *Lancet Oncol.* 2009; 10(10): 943–9. [PubMed Abstract](#) | [Publisher Full Text](#)
47. **F** Di Nisio M, Porreca E, Candeloro M, *et al.*: **Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy.** *Cochrane Database Syst Rev.* 2016; 12: CD008500. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
48. Maraveyas A, Waters J, Roy R, *et al.*: **Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer.** *Eur J Cancer.* 2012; 48(9): 1283–92. [PubMed Abstract](#) | [Publisher Full Text](#)
49. Pelzer U, Opitz B, Deuschinoff G, *et al.*: **Efficacy of Prophylactic Low-Molecular Weight Heparin for Ambulatory Patients With Advanced Pancreatic Cancer: Outcomes From the CONKO-004 Trial.** *J Clin Oncol.* 2015; 33(18): 2028–34. [PubMed Abstract](#) | [Publisher Full Text](#)
50. Khorana AA, Kuderer NM, Culakova E, *et al.*: **Development and validation of a predictive model for chemotherapy-associated thrombosis.** *Blood.* 2008; 111(10): 4902–7. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
51. Ay C, Dunkler D, Marosi C, *et al.*: **Prediction of venous thromboembolism in cancer patients.** *Blood.* 2010; 116(24): 5377–82. [PubMed Abstract](#) | [Publisher Full Text](#)
52. **F** van Es N, Di Nisio M, Cesarman G, *et al.*: **Comparison of risk prediction scores for venous thromboembolism in cancer patients: A prospective cohort study.** *Haematologica.* 2017; 102(9): 1494–501. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
53. **F** Mansfield AS, Tafur AJ, Wang CE, *et al.*: **Predictors of active cancer thromboembolic outcomes: Validation of the Khorana score among patients with lung cancer.** *J Thromb Haemost.* 2016; 14(9): 1773–8. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
54. **F** Bezan A, Posch F, Ploner F, *et al.*: **Risk stratification for venous thromboembolism in patients with testicular germ cell tumors.** *PLoS One.* 2017; 12(4): e0176283. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
55. Verso M, Agnelli G, Barni S, *et al.*: **A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score.** *Intern Emerg Med.* 2012; 7(3): 291–2. [PubMed Abstract](#) | [Publisher Full Text](#)
56. **F** Pabinger I, van Es N, Heinze G, *et al.*: **A clinical prediction model for cancer-associated venous thromboembolism: A development and validation study in two independent prospective cohorts.** *Lancet Haematol.* 2018; 5(7): e289–e298. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
57. **F** Agnelli G: **Direct Oral Anticoagulants for Thromboprophylaxis in Ambulatory Patients with Cancer.** *N Engl J Med.* 2019; 380(8): 781–3. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
58. **F** Bellesoeur A, Thomas-Schoemann A, Allard M, *et al.*: **Pharmacokinetic variability of anticoagulants in patients with cancer-associated thrombosis: Clinical consequences.** *Crit Rev Oncol Hematol.* 2018; 129: 102–12. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
59. Short NJ, Connors JM: **New oral anticoagulants and the cancer patient.** *Oncologist.* 2014; 19(1): 82–93. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
60. **F** Mosarla RC, Vaduganathan M, Qamar A, *et al.*: **Anticoagulation Strategies in Patients With Cancer: JACC Review Topic of the Week.** *J Am Coll Cardiol.* 2019; 73(11): 1336–49. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
61. **F** Bigot F, Boudou-Rouquette P, Arrondeau J, *et al.*: **Erlotinib pharmacokinetics: a critical parameter influencing acute toxicity in elderly patients over 75 years-old.** *Invest New Drugs.* 2017; 35(2): 242–6. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
62. Huillard O, Mir O, Peyromaure M, *et al.*: **Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients.** *Br J Cancer.* 2013; 108(5): 1034–41. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
63. Baker SD, van Schaik RH, Rivory LP, *et al.*: **Factors affecting cytochrome P-450 3A activity in cancer patients.** *Clin Cancer Res.* 2004; 10(24): 8341–50. [PubMed Abstract](#) | [Publisher Full Text](#)
64. Shedlofsky SI, Israel BC, McClain CJ, *et al.*: **Endotoxin administration to humans inhibits hepatic cytochrome P450-mediated drug metabolism.** *J Clin Invest.* 1994; 94(6): 2209–14. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
65. Slaviero KA, Clarke SJ, Rivory LP: **Inflammatory response: an unrecognised source of variability in the pharmacokinetics and pharmacodynamics of cancer chemotherapy.** *Lancet Oncol.* 2003; 4(4): 224–32. [PubMed Abstract](#) | [Publisher Full Text](#)
66. Launay-Vacher V, Janus N, Deray G: **Renal insufficiency and cancer treatments.** *ESMO Open.* 2016; 1(4): e000091. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
67. **F** Bertoletti L, Ollier E, Duillard C, *et al.*: **Direct oral anticoagulants: Current indications and unmet needs in the treatment of venous thromboembolism.** *Pharmacol Res.* 2017; 118: 33–42. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
68. **F** Riess H, Prandoni P, Harder S, *et al.*: **Direct oral anticoagulants for the treatment of venous thromboembolism in cancer patients: Potential for drug-drug interactions.** *Crit Rev Oncol Hematol.* 2018; 132: 169–79. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
69. Chien AJ, Moasser MM: **Cellular mechanisms of resistance to anthracyclines and taxanes in cancer: intrinsic and acquired.** *Semin Oncol.* 2008; 35(2 Suppl 2): S1–S14; quiz S39. [PubMed Abstract](#) | [Publisher Full Text](#)
70. Wu CP, Hsieh CH, Wu YS: **The emergence of drug transporter-mediated multidrug resistance to cancer chemotherapy.** *Mol Pharm.* 2011; 8(6): 1996–2011. [PubMed Abstract](#) | [Publisher Full Text](#)
71. Fitzgerald JL, Howes LG: **Drug Interactions of Direct-Acting Oral Anticoagulants.** *Drug Saf.* 2016; 39(9): 841–5. [PubMed Abstract](#) | [Publisher Full Text](#)
72. Mendell J, Chen S, He L, *et al.*: **The effect of rifampin on the pharmacokinetics of edoxaban in healthy adults.** *Clin Drug Investig.* 2015; 35(7): 447–53. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
73. Vakkalagadda B, Frost C, Byon W, *et al.*: **Effect of Rifampin on the Pharmacokinetics of Apixaban, an Oral Direct Inhibitor of Factor Xa.** *Am J Cardiovasc Drugs.* 2016; 16(2): 119–27. [PubMed Abstract](#) | [Publisher Full Text](#)
74. Härtter S, Koenen-Bergmann M, Sharma A, *et al.*: **Decrease in the oral bioavailability of dabigatran etexilate after co-medication with rifampicin.** *Br J Clin Pharmacol.* 2012; 74(3): 490–500. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
75. Bayer: **Xarelto Product Monograph 2018.** [Reference Source](#)
76. Servier: **LIXIANA Product monograph 2017.** [Reference Source](#)
77. Pfizer: **ELIQUIS product monograph 2018.** [Reference Source](#)
78. Boehringer Ingelheim: **PRADAXA product monograph 2019.** [Reference Source](#)
79. **F** Steffel J, Verhamme P, Potpara TS, *et al.*: **The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation.** *Eur Heart J.* 2018; 39(16): 1330–93. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

Open Peer Review

Current Peer Review Status:  

Editorial Note on the Review Process

F1000 Faculty Reviews are written by members of the prestigious F1000 Faculty. They are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

- Philippe Girard**
Institut du Thorax Curie-Montsouris, Institut Mutualiste Montsouris, Paris, France
Competing Interests: No competing interests were disclosed.
- Thein Hlaing Oo**
Section of Thrombosis and Benign Hematology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research