

Apixaban versus Dalteparin for the Treatment of Acute Venous Thromboembolism in Patients with Cancer: The Caravaggio Study

Giancarlo Agnelli¹ Cecilia Becattini¹ Rupert Bauersachs^{2,3} Benjamin Brenner⁴ Mauro Campanini⁵
 Alexander Cohen⁶ Jean Marie Connors⁷ Andrea Fontanella⁸ Gualberto Gussoni⁹
 Menno V. Huisman¹⁰ Catherine Lambert¹¹ Guy Meyer^{12,13} Andres Muñoz¹⁴
 Joaquim Abreu de Sousa¹⁵ Adam Torbicki¹⁶ Melina Verso¹ Giorgio Vescovo¹⁷ for the Caravaggio
 Study Investigators

¹ Internal Vascular and Emergency Medicine – Stroke Unit, University of Perugia, Perugia, Italy

² Department of Vascular Medicine, Klinikum Darmstadt GmbH, Darmstadt, Germany

³ Centre for Thrombosis and Hemostasis, University Medical Center, Mainz, Germany

⁴ Institute of Hematology and BMT, Rambam Health Care Campus, Technion – Israel Institute of Technology, Haifa, Israel

⁵ Department of Medicine, Azienda Ospedaliero Universitaria “Maggiore della Carità,” Novara, Italy

⁶ Guy’s and St Thomas’ NHS Foundation Trust Hospital, King’s College London, London, United Kingdom

⁷ Hematology Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, United States

⁸ Department of Medicine, Buon Consiglio Fatebenefratelli Hospital, Naples, Italy

⁹ Fadoi Research Center, Milan, Italy

¹⁰ Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden University, Leiden, The Netherlands

Address for correspondence Giancarlo Agnelli, MD, Internal Vascular and Emergency Medicine and Stroke Unit, University of Perugia, Perugia, Italy (e-mail: giancarlo.agnelli@unipg.it).

¹¹ Division of Hematology, Thrombosis and Hemostasis Unit, Cliniques Universitaires Saint-Luc, Catholic University of Louvain, Brussels, Belgium

¹² Hôpital Européen Georges Pompidou, Assistance Publique Hôpitaux de Paris, Paris, France

¹³ Université Paris Descartes, Sorbonne Paris Cité, Paris France

¹⁴ Medical Oncology Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain

¹⁵ Surgical Oncology Department, Institut Português Oncologie, Porto FG, EPE, Porto, Portugal

¹⁶ Departments of Pulmonary Hypertension, Thromboembolic Disease and Cardiology, Medical Center for Postgraduate Education, Otwock, Poland

¹⁷ Internal Medicine, S. Antonio Hospital, Padua, Italy

Thromb Haemost 2018;118:1668–1678.

Abstract

International and national guidelines recommend low-molecular-weight heparin for the treatment of venous thromboembolism (VTE) in patients with cancer. The aim of the Caravaggio study is to assess whether oral apixaban is non-inferior to subcutaneous dalteparin for the treatment of acute proximal deep vein thrombosis and/or pulmonary embolism in patients with cancer. The study is an investigator-initiated, multi-national, prospective, randomized, open-label with blind end-point evaluation (PROBE), non-inferiority clinical trial (NCT03045406). Consecutive patients are randomized to receive oral apixaban or subcutaneous dalteparin for 6 months. Apixaban is given at a dose of 10 mg twice daily for the first 7 days and then 5 mg twice daily; dalteparin is given at a dose of 200 IU/kg for the first month and then 150 IU/kg once daily. The primary outcome of the study is objectively confirmed recurrent VTE as assessed by a central independent adjudication committee unaware of study treatment allocation. The primary safety outcome is major bleeding defined according to the guidelines of

Keywords

- ▶ venous thromboembolism
- ▶ cancer
- ▶ apixaban

received
 January 15, 2018
 accepted after revision
 July 5, 2018

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 Stuttgart · New York

DOI <https://doi.org/10.1055/s-0038-1668523>.
 ISSN 0340-6245.

the International Society of Thrombosis and Haemostasis. Assuming a 6-month incidence of the primary outcome of 7% with dalteparin and an upper limit of the two-sided 95% confidence interval of the hazard ratio below the pre-specified margin of 2.00, 1,168 patients will be randomized considering an up to 20% loss in total patient-years ($\beta = 80\%$; α one-sided = 0.025). The Caravaggio study has the potential, along with other recently performed or on-going studies, to make less cumbersome the management of VTE in patients with cancer by replacing parenteral with oral anticoagulation.

Introduction

Cancer and venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), are linked by a two-way association.¹ Indeed, approximately 15% of patients with cancer experience one or more episodes of VTE during the course of their disease,² while approximately 20% of patients with VTE have cancer at the time of the presentation of VTE.³ In addition, approximately 4% of patients with VTE are newly diagnosed with cancer at the time of the presentation of VTE or in the year thereafter.⁴ Patients with cancer and VTE have a high risk of recurrent VTE and bleeding complications during anticoagulant treatment compared with patients without cancer^{5,6} and this makes cancer patients a distinct population which requires specific clinical trials on the treatment of VTE.

For the treatment of VTE in patients with cancer, international guidelines recommend low-molecular-weight heparin (LMWH) for at least 3 to 6 months over LMWH followed by vitamin K antagonists (VKAs)^{7–11} (► **Table 1**). In the CLOT study, dalteparin was associated with a statistically significant 52% reduction in the risk of recurrent VTE over 6 months' treatment compared with LMWH followed by VKAs (conventional treatment) with a comparable rate of major bleeding and death.¹² In the CATCH trial, a non-statistically significant 35% risk reduction of recurrent VTE in favour of tinzaparin was observed compared with the conventional treatment without differences in the rates of major bleeding and death.¹³ A meta-analysis which included six studies in patients with cancer and VTE showed a statistically significant 44% risk reduction for recurrent VTE in favour of LMWH compared with the conventional treatment with a non-significant 7% increase in major bleeding.¹⁴ Although recommended by guidelines, treatment with LMWH in cancer-associated VTE has several limitations. These include the inconvenience of subcutaneous injections for at least 6 months in patients who are already receiving complex anti-cancer treatment and the risk for heparin-induced thrombocytopenia. Furthermore, treatment with LMWH is associated with the same risk for major bleeding as conventional treatment.

Direct oral anticoagulants (DOACs) were tested in six phase III studies on the treatment of acute VTE and were shown by meta-analyses to be at least as effective as and safer than the conventional treatment.^{15,16} Based on these results, DOACs are currently recommended as first line

treatment in the majority of patients with VTE.¹¹ Sub-group analyses in cancer patients included in the phase III trials on VTE treatment showed encouraging results both in terms of efficacy and safety.^{17–20} A meta-analysis on cancer patients included in the phase III trials showed similar efficacy and safety profiles of DOACs in comparison with VKAs for the treatment of acute VTE.²¹ However, DOACs are currently not recommended for the treatment of VTE in cancer patients mainly because the phase III clinical trials included only a limited number of these patients. Furthermore, patients with cancer for whom treatment with LMWH was deemed appropriate were excluded from these studies. The patients with cancer included in phase III clinical trials with DOACs also had lower rates of metastatic disease and lower mortality than those included in the CATCH and CLOT trials, with limited data regarding active cancer treatments which could have affected both efficacy and safety of DOACs.

Given the limitations of LMWH and the potential advantages of DOACs, several trials on the treatment of VTE in cancer patients have recently been published or are currently on-going. The recently published Hokusai VTE cancer in 1,050 patients with VTE and cancer showed an incidence of the composite of recurrent VTE and major bleeding of 12.8% in the edoxaban group and 13.5% in the dalteparin group (hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.70–1.36; $p = 0.006$ for non-inferiority).^{22,23} In this study, rates of recurrent VTE were of 7.9 and 11.3% in the edoxaban and dalteparin groups, respectively, and major bleeding rates were of 6.9 and 4.0%, respectively. Findings from the recently presented pilot study Select-D in 406 patients with VTE and cancer indicate an increase in bleeding with rivaroxaban.²⁴ The observed increase in bleeding in the DOAC arms of these studies underscores the need for further studies evaluating other DOACs or DOAC regimens in the treatment of cancer-associated VTE.

We report here the design of the Caravaggio study, a trial comparing the direct factor Xa inhibitor apixaban with the LMWH dalteparin for the treatment of acute VTE in patients with cancer (NCT03045406).

Aim of the Study

The aim of this study is to assess whether oral apixaban is non-inferior to subcutaneous LMWH dalteparin for the treatment of newly diagnosed proximal DVT and/or PE in patients with cancer.

Table 1 Recommendations from international guidelines on anticoagulant treatment of VTE in cancer patients

	Initial treatment	Long-term treatment	Optimal duration
ESMO, 2011 ⁷	Weight-adjusted LMWH or UFH If creatinine clearance is < 25–30 mL/min anti-Xa monitoring is proposed	LMWH or VKA	For at least 3–6 months For patient with metastatic disease, receiving neoadjuvant CHT, the optimal duration should be individually assessed. For cancer patients receiving chemotherapy in palliative setting, an indefinite treatment should be proposed
NCCN, 2011 ⁸	Weight-adjusted LMWH, UFH or fondaparinux	LMWH is preferred for the first 6 months as monotherapy; or VKA	Minimum time of 3–6 months for DVT and 6–12 months for PE Indefinite anticoagulation is proposed in patients with active cancer or persistent risk factors
ASCO, 2015 ⁹	LMWH is recommended for the initial 5–10 days	LMWH	For at least 6 months
ITAC, 2016 ¹⁰	First 10 days: LMWH are recommended (1B); UFH and fondaparinux can be also used (2B)	LMWHs are preferred over VKA (1A)	For a minimum of 3 months (1A). After 3–6 months, termination or continuation of anticoagulation should be based on individual assessment of the benefit-to-risk ratio
ACCP, 2016 ¹¹	LMWH are suggested over VKA (2B) or DOAC (2C)	LMWH are suggested over VKA(2B) or DOAC (2C)	For at least 3 months In patients with VTE and active cancer, and who do not have a high bleeding risk, extended anticoagulation (no scheduled stop date) is recommended. In patients with VTE and active cancer, and who have a high bleeding risk, extended anticoagulation (no scheduled stop date) is suggested

Abbreviations: CHT, chemotherapy; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

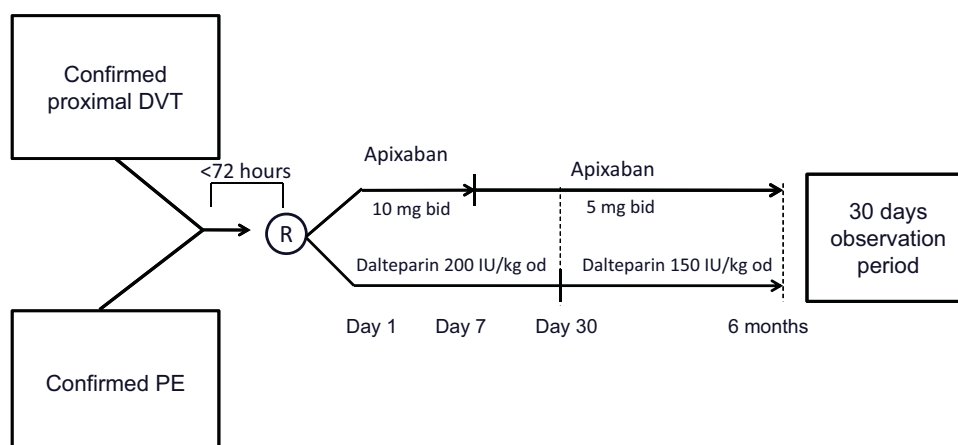
Study Design

The Caravaggio study is an investigator-initiated, multi-national, prospective, randomized, open-label with blind end-point evaluation (PROBE), non-inferiority clinical trial.

The study compares 6-month treatment with oral apixaban or subcutaneous dalteparin in consecutive cancer patients with newly diagnosed proximal DVT and/or PE (→ Fig. 1). The study has been planned to be conducted in 140 centres in 10 European countries and in the United States.

Randomized, open-label, PROBE, non-inferiority study

Treatment period: 6 months

**Fig. 1** Study design.

Rationale for the Prospective Randomized Open-Label Blind Evaluation design

The PROBE design was chosen for the Caravaggio study as double-blinding would have required daily subcutaneous injection of placebo in the apixaban recipients. Ethically, the use of daily injectable placebo and the related inconvenience for patients that already need complex treatment for cancer are difficult to justify. The assessment of the study outcomes made by a central independent adjudication committee unaware of study treatment allocation is a reasonable guarantee of the appropriateness as well as the consistency of the assessment of study outcome events in the two treatment groups.

Study Population and Eligibility

Consecutive adult cancer patients with a newly diagnosed symptomatic or incidental proximal lower-limb DVT or symptomatic or incidental PE or both DVT and PE are eligible for the study.

DVT is defined as proximal if located in the popliteal or a more proximal vein. For the purpose of this study, incidental DVT or PE are unsuspected events detected by imaging performed for cancer diagnosis or staging and not to confirm the clinical suspicion of VTE. To be included in the study, patients with incidental DVT need to have thrombosis located in the popliteal or a more proximal vein and incidental PE emboli involving a segmental or more proximal pulmonary artery. The criteria required for the diagnosis of DVT and PE are listed in ► **Supplementary Table S1** (available in the online version).

Patients with any type of confirmed cancer other than basal-cell or squamous cell carcinoma of the skin, primary brain tumour, known intra-cerebral metastases or acute leukaemia are eligible for the study.

For the purpose of this study, patients with active cancer are those with cancer diagnosed within the past 6 months, those receiving treatment for cancer at the time of inclusion or during 6 months prior to randomization, or those with recurrent locally advanced or metastatic disease. Patients with a history of cancer are defined as those with cancer diagnosed within 2 years before the study inclusion and not fulfilling the criteria for active cancer.

Exclusion criteria, classified into four categories including patient characteristics (age, Eastern Cooperative Oncology Group stage and life expectancy), issues related to anticoagulant treatment, issues related to bleeding risk and standard exclusion criteria for clinical trials with anticoagulant agents, are listed in ► **Table 2**.

Rationale for Inclusion of Patients with a History of Cancer

Sub-analyses of the Hokusai and AMPLIFY studies^{19,20} showed a similar risk of recurrence in patients with active cancer and those with history of cancer diagnosed within 2 years before inclusion in the study. In the AMPLIFY study, the rate of recurrence in the conventional treatment arm was 6.4 and 6.3% in patients with active cancer and history of cancer, respectively.¹⁹ Based on these observations, the

Caravaggio study will allow the randomization of patients diagnosed with history of cancer as defined by the study protocol.

Rationale for Inclusion of Cancer Patients with Incidental VTE

In patients with cancer, both DVT and PE may be detected in those undergoing imaging for purposes of cancer diagnosis, staging, re-staging or surveillance and not be clinically suspected at the time of detection. Patients with incidental VTE may not necessarily be asymptomatic, as they often report symptoms and signs that are due to VTE but are attributed to cancer disease or anti-cancer therapy. In cohort studies, the risks of recurrence, anticoagulation-related bleeding and death were reported to be similar in patients with incidental and symptomatic VTE events.^{25–27} Therefore, guidelines recommend treating the majority of patients with incidentally detected VTE with anticoagulation as would be done for patients with symptomatic VTE.^{7–11}

Including patients with incidental VTE as well as those with a history of cancer broadens the spectrum of randomized patients towards more closely approximating clinical practice and enhances the external validity of the Caravaggio study.

Study Treatments and Treatment Allocation

All patients included in the Caravaggio study receive anticoagulant treatment after the diagnosis of DVT and/or PE has been confirmed. Administration of therapeutic doses of LMWH, fondaparinux or unfractionated heparin is allowed for a maximum of 72 hours before study randomization.

After providing informed consent, patients are randomized on a 1:1 basis to receive monotherapy with either apixaban or dalteparin (► **Fig. 1**). The study treatments are given for 6 months.

Apixaban is given orally at a dose of 10 mg twice daily for the first 7 days (starting 12 hours after the last injection of LMWH, if given before randomization) and then 5 mg twice daily thereafter for the remainder of the 6-month treatment period. The regimen chosen for apixaban is the same as validated for the treatment of VTE in the AMPLIFY study.²⁸

Dalteparin is administered subcutaneously, at a dose of 200 IU/kg for the first month, after which the dose is reduced to 150 IU/kg once daily for the following 5 months. The maximum daily dose allowed for dalteparin is 18,000 IU. The regimen chosen for dalteparin is the same as validated in the CLOT study.¹² Since the study was extended to the United States, an amendment to the protocol was submitted to adjust the dose of dalteparin in patients with platelet count between 50 and $100 \times 10^9/L$ according to the label of the drug in this country.

No further dose adjustment of the study drugs is foreseen but these can be temporarily withheld in case of a platelet count lower than $50 \times 10^9/L$ or an any condition associated with an increased bleeding risk, including surgery, procedures or deterioration of renal function.

Randomization of eligible patients is centrally performed through an interactive web-based randomization system. Randomization is stratified by the type of VTE (symptomatic

Table 2 Eligibility criteria

Inclusion criteria	
A newly diagnosed, objectively confirmed symptomatic or unsuspected proximal lower-limb DVT or symptomatic PE or unsuspected PE in a segmental or more proximal pulmonary artery	
Any type of cancer (other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumour or intra-cerebral metastases and acute leukaemia) that meets at least one of the following: <ul style="list-style-type: none"> • Active cancer defined as diagnosis of cancer within 6 months before the study inclusion, or receiving treatment for cancer at the time of inclusion or any treatment for cancer during 6 months prior to randomization, or recurrent locally advanced or metastatic cancer • Cancer diagnosed within 2 years before the study inclusion (history of cancer) 	
Signed and dated informed consent	
Exclusion criteria	
Related to patient	Age < 18 years
	ECOG performance status III or IV
	Life expectancy of less than 6 months
Related to anticoagulant treatment	Administration of therapeutic doses of LMWH, fondaparinux or unfractionated heparin (UFH) for more than 72 hours before randomization
	Three or more doses of a vitamin K antagonist before randomization
	Thrombectomy, vena cava filter insertion or thrombolysis used to manage the index episode
	Indication for anticoagulant treatment for a disease other than the index VTE
	Concomitant use of strong inhibitors or inducers of both cytochrome P-450 3A4 and P-glycoprotein ^a
Related to bleeding risk	Concomitant thienopyridine therapy (clopidogrel, prasugrel or ticagrelor) or aspirin over 165 mg daily or dual anti-platelet therapy
	Active bleeding or a high risk of bleeding contraindicating anticoagulant treatment
	Recent (in the last 1 month prior to randomization) brain, spinal or ophthalmic surgery
	Haemoglobin level lower than 8 g/dL (5.0 mmol/L) or platelet count < 75 × 10 ⁹ /L or history of heparin induced thrombocytopenia
	Creatinine clearance < 30 mL/min based on the Cockcroft–Gault equation
	Acute hepatitis, chronic active hepatitis, liver cirrhosis or an alanine aminotransferase level three times or more and/or bilirubin level two times or more the upper limit of the normal range
	Uncontrolled hypertension (systolic BP > 180 mm Hg or diastolic BP > 100 mm Hg despite anti-hypertensive treatment)
Standard criteria	Bacterial endocarditis
	Hypersensitivity to the study drugs or to any of their excipients
	Patient's participation in other pharmacotherapeutic program with an experimental therapy that is known to affect the coagulation system
	Women of childbearing potential (WOCBP) who do not practice a medically accepted highly effective contraception during the trial and 1 month beyond
	Pregnancy, or breast feeding
	Any condition that as judged by the investigator would place the subject at increased risk of harm if he/she participated in the study

Abbreviations: BP, blood pressure; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; EHRA, European Heart Rhythm Association; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; VTE, venous thromboembolism.

^aFor details see EHRA guidelines.⁴⁷

vs. incidental) and the category of cancer (active cancer vs. history of cancer), allowing for a balanced proportion of patients with incidental VTE or history of cancer in the two treatment groups. The maximum proportion of patients entering the strata of incidental VTE or history of cancer is set at 20% of the overall study population for each of the strata as only a limited proportion of these patients were included in randomized clinical trials on VTE treatment in cancer patients.

Study Outcomes

The primary outcome of the study is objectively confirmed recurrent DVT or PE occurring during the study treatment

period, which includes proximal DVT of the lower limbs (symptomatic or incidental), symptomatic DVT of the upper limbs and PE (symptomatic, incidental or fatal).

All deaths are to be adjudicated concerning their causes by the central independent adjudication committee. PE is to be adjudicated as the cause of death based on objective diagnostic testing made before death or autopsy or when PE is the most probable cause of a sudden and unexplained death.

To adjudicate an incidental PE as an outcome event, there must be one or more new filling defects in segmental or more-proximal arteries on pulmonary computed tomography angiography, which is (are) evident on the adjudication study images and was (were) not present on the index or

interval study images. The criteria required for the diagnosis of recurrent VTE are listed in **►Supplementary Table S2** (available in the online version).

Several secondary efficacy outcomes are to be analysed including symptomatic recurrent VTE and quality of life. The secondary efficacy outcomes are shown in **►Supplementary Table S3** (available in the online version).

The principal safety outcome is major bleeding defined according to the guidelines of the International Society of Thrombosis and Haemostasis as acute clinically overt bleeding associated with one or more among the following: a decrease in haemoglobin of 2 g/dL or more, a transfusion of two or more units of packed red blood cells, bleeding that occurs in at least one of the following critical sites (intracranial, intra-spinal, intra-ocular, peri-cardial, intra-articular, intra-muscular with compartment syndrome or retro-peritoneal), bleeding that is fatal (defined as a bleeding event that the independent central committee adjudicate as the primary cause of death or contributing directly to death) and bleeding that necessitates surgical intervention. The list of the secondary safety outcomes is shown in **►Supplementary Table S4** (available in the online version).

A central independent adjudication committee whose members are unaware of treatment allocation will adjudicate all suspected study outcomes and all deaths occurring during the study period.

Surveillance and Follow-Up

The study requires the following scheduled visits: enrolment, 4 weeks, 3 months, 6 months and 7 months after randomization. Additional visits are performed if new symptoms and/or signs of VTE or major bleeding occur during the study period or anytime it is deemed necessary by the investigator. Clinical examination, laboratory and diagnostic imaging are performed if the patient develops symptoms or signs suggestive of recurrent VTE.

Sample Size of the Study

The study hypothesis is that apixaban is non-inferior to dalteparin with respect to the primary study outcome (recurrence of VTE) with a pre-specified non-inferiority margin of 2.00 for the upper limit of the two-sided 95% CI of the HR. Assuming an estimated 6-month incidence of the primary efficacy outcome of 7% with dalteparin, 934 patients will be required to have 80% power to show the non-inferiority of apixaban at a one-sided α level of 0.025. This sample is increased to 1,168 patients to account for up to 20% loss in total patient-years. This estimate is consistent with a drop-out rate of 40% assuming patients discontinue uniformly during the follow-up (mean discontinuation time equal to 3 months).

Expected VTE Recurrence Rate in the Comparison Treatment Arm (Dalteparin)

The reference values for the expected incidence of recurrent VTE with dalteparin are derived from the results of the CLOT and CATCH trials.^{12,13} Similarly to Caravaggio, these two

studies adopted a PROBE design, compared LMWH (dalteparin or tinzaparin, respectively) with warfarin and had study treatment duration of 6 months. The incidence of recurrent VTE was 8.0% with dalteparin in the CLOT study and 7.2% with tinzaparin in the CATCH trial. Furthermore, the recurrence rate in LMWH-treated patients was 7% in a meta-analysis on cancer patients enrolled in the phase III trials on the treatment of VTE.¹⁴ The 6-month VTE rate seen with dalteparin in the Hokusai VTE cancer study was 8.8%, confirming the relative stability over time of the risk of recurrent VTE in LMWH-treated cancer patients.²³ This recurrence rate was confirmed by a recently presented large health care insurance claims databases analysis from January 2011 to September 2016.²⁹ Therefore, the 7% recurrence rate assumed in the Caravaggio study for patients randomized to receive dalteparin is based on consistent evidence.

Expected Recurrence Rate with Apixaban

In a post hoc analysis of the AMPLIFY study, 169 patients had active cancer and 365 a history of cancer without active cancer at baseline.¹⁹ Among patients with active cancer, recurrent VTE occurred in 3.7 and 6.4% of patients who received apixaban or conventional treatment, respectively (relative risk, 0.56, 95% CI, 0.13–2.37). Among patients with a history of cancer, recurrent VTE occurred in 1.1 and 6.3% of evaluable patients in the apixaban and conventional treatment groups, respectively (relative risk, 0.17, 95% CI, 0.04–0.78). Based on these figures, that are supported by a network meta-analysis,³⁰ it is expected that the recurrent VTE rate in the apixaban-treated patients will not be significantly higher than the rate observed in the LMWH-treated patients.

Rationale for Non-Inferiority Margin (Delta) Choice

The objective of Caravaggio is to demonstrate that oral apixaban is non-inferior to the subcutaneous LMWH dalteparin for the treatment of VTE in patients with cancer. The results of this study could lead to a more tolerable treatment (both for the patients and caregivers) and, in some countries, less expensive therapy than the currently recommended LMWH. These objectives deal with unmet clinical needs in the setting of the VTE treatment in cancer patients. The choice of a relatively large delta for efficacy is accepted in exchange for the convenience and potential compliance benefits, provided that a putative superiority to placebo is not left in doubt (EMA/CPMP/EWP/2158/99 Document. Guideline on the choice of non-inferiority margin. July 27, 2005). The considerations related to convenience and compliance are particularly cogent in patients with cancer that require complex and difficult cancer treatment. The values and the limitations of the non-inferiority design in clinical trials have been recently reviewed.³¹ The non-inferiority design appears reasonable when evaluating new treatments that offer greater convenience for the patients while providing similar efficacy. Based on these assumptions, the upper limit of the two-sided 95% CIs of the HR below the pre-specified margin of 2.00 planned for our study is considered as acceptable from a clinical and methodological point of view. Moreover, the non-inferiority margins set for the

Caravaggio study are of the same order of magnitude to those used in pivotal trials on VTE therapy with DOACs.^{28,32–36} These studies were accepted by the European Medicines Agency and Food and Drug Administration (FDA) for the registration of DOACs for the indication ‘treatment of VTE’.

Statistical Analysis

The primary efficacy dataset will consist of all randomized subjects who received at least one dose of study drug (modified intention-to-treat [ITT] population). The safety dataset (as-treated) will consist of all treated subjects (randomized subjects who received at least one dose of study drug).

Secondary efficacy datasets will consist of all randomized subjects (ITT) and the per-protocol (PP) population as defined in the pre-defined statistical analysis plan. Briefly, the PP population will consist of all randomized patients who complete the study fully compliant with the protocol and without any major violation or deviation. Secondary efficacy analyses based on the ITT and PP populations will be considered as supportive.

The time to first event of the primary outcome during the 6-month study period will be analysed using a Cox’s proportional hazard model including the treatment group and stratification factors as covariates. The evaluation of the primary objective will be done by considering the time from randomization to the first recurrent VTE (primary study outcome) or to the occurrence of death unrelated to VTE (competing event) or to the last follow-up if neither a recurrent VTE or a competing event occur within the 6-month follow-up (censored time). The apixaban-to-comparator HR adjusted for the competing risk of death unrelated to VTE will be computed with associated two-sided 95% CI by resorting to the Fine and Gray regression model.³⁷ Superiority of apixaban in comparison to dalteparin will be tested as a secondary analysis of the primary end-point only after non-inferiority has been demonstrated for the experimental treatment group (apixaban) relative to the control group (dalteparin).

The rate of major bleeding (the primary safety outcome) and clinically relevant non-major bleeding in patients treated with apixaban or dalteparin will be compared by using the safety dataset.

Rationale for Using a Competing Risk Analysis

A significant proportion of patients with cancer included in clinical trials on the treatment of VTE ultimately die due to cancer progression during the study period. The 6-month mortality was 39 and 32% in CLOT and CATCH studies, respectively,^{12,13} and the 12-month mortality was approximately 45% in the Hokusai cancer study.²³ In the CLOT study, 90% of death in each group was due to the progression of cancer. Due to the high mortality rate in patients with cancer and VTE, the standard statistical method of Kaplan–Meier to evaluate time to recurrence is limited when death is considered a censored event. The Kaplan–Meier method handles death as censored observation, which conceptually implies that the subjects retain the probability of recurrence even after death. As the risk of VTE recurrent is zero in a dead patient, by ignoring the effect of death as a competitive risk, the method of Kaplan–

Meier over-estimates the cumulative incidence of VTE. A more appropriate statistical analysis accounts for both death and VTE as competitive risks.³⁸ The competitive risk analysis handles the competing events as actual events rather than censoring observations and recognizes that death terminates the ability to observe a VTE. Therefore, the probability of experiencing a recurrence is adjusted for a competing event (death) that occurred prior to the development of the VTE outcome. The Gray’s test is considered the more appropriate test to assess differences between two study groups when competing risks are present.

The issue of competing risks is well recognized in the oncology literature although it has been applied inconsistently to the analysis of clinical studies assessing anti-thrombotic treatments in cohorts with a high incidence of death such as cancer patients. Comparisons between treatment groups in the CATCH study accounted for deaths not due to fatal PE as a competing risk.¹³

All data summaries and listings will be performed using the SAS System version 9.4 under Windows 10 PRO operating system.

Study Organization

The study is performed in accordance with the provisions of the Declaration of Helsinki and local regulations. Protocol and amendments have to be approved by the Institutional Review Board or Ethic Committee at each study centre.

The promoter of Caravaggio is Federazione delle Associazioni dei Dirigenti Ospedalieri Italiani (FADOI) Foundation. The study is co-ordinated by the Clinical Research Unit of the University of Perugia in Italy, by the Research Department of FADOI Foundation and the Steering Committee of the study. Data are collected, maintained and will be analysed by Exom Group in Italy under the supervision of the Steering Committee members.

The study is supported by a grant in aid by Bristol-Myers Squibb and Pfizer. Apixaban will be supplied by Bristol-Myers Squibb and dalteparin by Pfizer. Bristol-Myers Squibb and Pfizer did not have any role in study design, and does not have any role in the study conduction, data collection and analysis.

Study Committees

The structure of the Caravaggio study includes a Steering Committee, a central independent adjudication committee and a Data and Safety Monitoring Board (DSMB).

Steering Committee

The Steering Committee of the study is composed by the National Coordinators of the participating countries and by members of the University of Perugia and FADOI. The study was designed by the Steering Committee members. The Steering Committee members have the final responsibility for the conduction of the study as well as the verification and analyses of all the study data. All the members of the Steering Committee have access to the study data, vouch for their accuracy and completeness; they will contribute to the

interpretation of the results, approve the final version of the manuscript verifying the fidelity of the article to the study protocol and make the decision to submit the manuscript for publication. The writing committee, composed by members of the Steering Committee, will write the manuscript and vouch for the accuracy and completeness of the reported data.

Adjudication Committee

A central independent adjudication committee, whose members are unaware of treatment allocation, adjudicates all suspected outcome events and the qualifying diagnosis, the anatomical extent of the initial DVT or PE. The Central Adjudication Committee is composed of medical specialists in oncology, radiology and vascular medicine.

Data and Safety Monitoring Board

An independent DSMB periodically reviews the study outcomes with all information available concerning treatment allocation. A DSMB charter was provided to the board members before the start of the study. The DSMB is composed of three expert clinicians with experience in the conduction and monitoring of clinical trials.

Study Monitoring

Monitoring procedures are followed to comply with Good Clinical Practice guidelines. The risk for the occurrence of quality and safety issues is regularly and centrally monitored through the use of a "Risk Based Monitoring and Management" platform. Study-specific risk indicators and related scores were defined and are closely and centrally monitored during the entire study period for each of following six risk categories: (1) site management quality, (2) data quality, (3) data timeliness, (4) source documents verification, (5) milestone delay and (6) subject safety. Caravaggio is a paperless study which utilizes integrated clinical data management and remote data capture solutions that include functionalities in key areas such as drug supply and randomization, data collection and serious

adverse event (SAE) reporting. An Oracle database enables management of all clinical trial data in a single system, improving accuracy, visibility and data integrity.

Adverse Event Reporting

This study follows a targeted approach to collection and reporting of adverse events (AEs) and SAEs. All AEs occurring after the subject signs the informed consent form and through month 6 or the end of treatment date, whichever occurs first, whether observed by the investigator or reported by the patient, are recorded on the AEs section of the electronic case report form.

AEs are described using the Medical Dictionary for Regulator Activities.

On-Going Studies Comparing DOACs with LMWH for the Treatment of Cancer-Associated VTE

Several trials aimed at improving the anticoagulant treatment in patients with cancer-associated VTE by comparing DOACs with LMWH are currently on-going (► **Table 3**).

CANVAS is a 940-patient study with the primary objective of evaluating whether DOACs are as effective as one of the FDA-approved injectable agents (dalteparin, enoxaparin or fondaparinux), given alone or transitioned to VKAs (NCT02744092).³⁹ Any of the four DOACs approved for the treatment of VTE (apixaban, dabigatran, edoxaban or rivaroxaban) could be used in the DOACs arm.

The CASTA DIVA investigators randomize 200 cancer patients with VTE to receive either rivaroxaban or dalteparin to assess the 3-month rate of recurrence and major bleeding (NCT02746185).⁴⁰

The main aim of the ADAM-VTE trial is to test the hypothesis that apixaban is associated with a significantly lower rate of major bleeding compared with dalteparin in the treatment of 300 patients with acute VTE and active malignancy.⁴¹

Table 3 On-going trials with DOACs versus LMWH on treatment of VTE in cancer patients

Trial (ref)	Sample size (N)	Study design	DOACs	Comparator	Primary outcome (s)	Treatment duration
CANVAS ³⁹	940	Randomized, open label	Any DOAC	LMWH or fondaparinux alone or with VKA	VTE recurrence	6 months
CARAVAGGIO	1,126	Randomized, open label, blinded end-point (PROBE), non-inferiority	Apixaban	Dalteparin	VTE recurrence Major bleeding	6 months
CASTA-DIVA ⁴⁰	200	Randomized, open label	Rivaroxaban	Dalteparin	VTE recurrence Major bleeding	3 months
ADAM VTE ⁴¹	300	Randomized, open label, superiority	Apixaban	Dalteparin	Major bleeding	6 months
CONKO ⁴²	450	Randomized, open label	Rivaroxaban	LMWH	Patient-reported treatment satisfaction	3 months

Abbreviations: DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

The CONKO study is a randomized, open-label study designed to evaluate the treatment satisfaction in 450 patients with VTE and cancer treated with rivaroxaban or dalteparin.⁴²

Anticipated Results and Implications for Clinical Practice

It is anticipated that the Caravaggio study will demonstrate that apixaban is non-inferior compared with dalteparin for the treatment of DVT and PE in patients with cancer. The Caravaggio study has the potential, along with other studies with similar objective and design, to improve the treatment of VTE in patients with cancer by making VTE management simpler and less cumbersome for patients who are already receiving complex anti-cancer treatment and management. An additional potential advantage associated with the oral administration of apixaban, as of other DOAC, could be the improvement of treatment adherence and persistence. Indeed, adherence to and persistence on guideline-recommended LMWH given for long-term VTE treatment in patients with cancer is quite low and much less than generally appreciated by clinicians. Most patients are discontinuing LMWH after 2 to 3 months and either continuing with VKA, which is less effective or definitively stopping anticoagulation, and thus, they are at increased risk of recurrent VTE.⁴³⁻⁴⁵

To increase the external validity of the study, we include in the study patients affected by the large majority of cancers. Although in patients with primary brain cancer or brain metastases anticoagulant treatment is not contraindicated, these patients are excluded from the study as there are not even preliminary data on the use of DOACs in these patients. The same applies to patients with acute leukaemia.

In the Hokusai VTE Cancer study, major bleeding was found to be increased in patients who entered the study with gastrointestinal cancer. Patients with gastrointestinal cancer (including the upper gastrointestinal tract) are not excluded from Caravaggio and are expected to account for approximately 20% of the entire study population. The type of gastrointestinal malignancy, location and stage of cancer disease in these patients will be formally and carefully scrutinized and compared with the Hokusai cancer population in a pre-specified analysis as reported in the Statistical Analysis plan. To ensure patient safety, the DSMB received a mandate to monitor bleeding (and its severity) in patients with gastrointestinal cancer. The apixaban regimen evaluated in Caravaggio is the same evaluated in the Amplify study. This is the only DOAC regimen which was not associated with an increase in gastrointestinal bleeding in the phase III trials of VTE treatment.¹⁶ The inclusion of patients with gastrointestinal cancer in Caravaggio has substantial clinical implications for clinical practice. Indeed, should the bleeding associated with apixaban in these patients be as excessive as that seen with edoxaban in the Hokusai VTE cancer (in comparison with the conventional treatment), this finding will definitively indicate that patients with gastrointestinal cancer should be denied DOACs for the treatment

of VTE. On the other hand, if an increase in bleeding in these patients is not seen, this observation will be of remarkable clinical importance and patients with gastrointestinal cancer will be able to safely take advantage of an oral treatment that does not require monitoring. This observation could also reinforce the need for specific studies on the effect of the different DOACs on the gastrointestinal system.

In the Caravaggio study, apixaban is given as a single drug approach, validated in the Amplify study, which involves a higher dose given for the first 7 days. This difference in DOAC regimens has remarkable implications. It is possible that, in cancer patients who have high risk of early recurrence, this approach may not be as effective as some period of LMWH treatment, either because the dose of apixaban is not high enough or the period of more intense dosing is not long enough. On the other hand, a more balanced regimen could reduce the risk of bleeding seen in Hokusai VTE cancer study. A time-course analysis of the thromboembolic and bleeding events similar to that made in the Amplify study could be helpful in understanding the time course of the thromboembolic and bleeding events.⁴⁶ In addition, the knowledge achieved from the Caravaggio study will provide evidence for improving the design of further studies and updating current practice guidelines.

What is known about this topic?

- Cancer patients with venous thromboembolism (VTE) are at increased risk of recurrence and bleeding during anticoagulant treatment.
- For the treatment of VTE in patients with cancer, international guidelines recommend low-molecular-weight heparin (LMWH) for at least 3 to 6 months over LMWH followed by vitamin K antagonists.
- Direct oral anticoagulants are an effective and safe treatment for VTE, but limited data are currently available with these agents in patients with concomitant cancer.

What does this paper add?

- This paper reports details on the design of the Caravaggio study.
- The Caravaggio study will assess whether oral apixaban is non-inferior to subcutaneous LMWH dalteparin for the treatment of newly diagnosed proximal DVT and/or PE in patients with cancer.
- The Caravaggio study has the potential to make the management of VTE less cumbersome in patients with cancer by replacing parenteral with oral anticoagulation.

Conflict of Interest

Giancarlo Agnelli reports personal fees from Bayer Healthcare, Bristol-Myers-Squibb, Daiichi Sankyo and Pfizer. Rupert Bauersachs has received funding from

Bayer, BMS, Boehringer Ingelheim, Daiichi-Sankyo and Pfizer for consulting work and speaker bureaus. Cecilia Becattini reports personal fee from Bayer HealthCare and Bristol-Myers-Squibb. Benjamin Brenner has received personal fees from Bayer Healthcare, Pfizer, Leo Pharma, Sanofi and Rovi Laboratories. Mauro Campanini reports no potential conflict of interest. Alexander Cohen has received consulting fees from AbbVie, ACI Clinical, Aspen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Boston Scientific, CSL Behring, Daiichi-Sankyo, GlaxoSmithKline, GLG, Guidepoint Global, Johnson and Johnson, Leo Pharma, Medscape, McKinsey, Navigant, ONO, Pfizer, Portola, Sanofi, Takeda, Temasek Capital and TRN; he reports advisory board membership with Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Johnson and Johnson, ONO, Pfizer, Portola and Sanofi; and payments for lectures including speakers bureau services, payments for preparation of reports and payment for development of educational presentations from Aspen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi, GlaxoSmithKline, Johnson and Johnson, Medscape, Pfizer and Portola. He is an advisor to the U.K. Government Health Select Committee, the all-party working group on thrombosis, the Department of Health and the NHS, on the prevention of VTE. He is also an advisor to Lifeblood: The Thrombosis Charity and is the founder of the European educational charity the Coalition to Prevent Venous Thromboembolism. Jean Connors reports personal fees from Boehringer Ingelheim, Bristol Meyer Squibb/Pfizer, Unum Therapeutics and Proteostasis. Gualberto Gussoni reports no potential conflict of interest. Andrea Fontanella reports no potential conflict of interest. Menno Huisman has received research grants from ZonMW, Boehringer Ingelheim, Pfizer-Bristol-Myers-Squibb and Bayer Health; and has provided lectures and consultations for Bayer Health Care, Pfizer- Bristol-Myers Squibb and Boehringer Ingelheim. Guy Meyer has served as uncompensated advisor for Bayer Healthcare, Leo Pharma, BMS-Pfizer, Daiichi Sankyo, as a speaker (uncompensated) for Leo Pharma, Sanofi Aventis, Boehringer-Ingelheim and Bayer and received research grants or support through its institution from Leo Pharma, Boehringer-Ingelheim, Sanofi Aventis and Bayer Healthcare. He received travel and accommodation support from Leo Pharma, Boehringer-Ingelheim, Bayer Healthcare, BMS-Pizer and Daiichi Sankyo. Andrés Muñoz reports personal fees from Sanofi, Leo Pharma, Bayer Healthcare and Rovi. Joachim Jabreu Sousa reports no potential conflict of interest. Adam Torbicki reports honoraria for consultancy and/or lectures from Actelion, AOP, Arena, Bayer, Pfizer, MSD and United Therapeutics. Melina Verso reports no potential conflict of interest. Giorgio Vescovo reports no potential conflict of interest.

References

- Agnelli G. Venous thromboembolism and cancer: a two-way clinical association. *Thromb Haemost* 1997;78(01):117–120
- Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. *Br J Cancer* 2010;102(Suppl 1):S2–S9
- Mahé I, Sterpu R, Bertoletti L, et al; RIETE Investigators. Long-term anticoagulant therapy of patients with venous thromboembolism. What are the practices? *PLoS One* 2015;10(06):e0128741
- Carrier M, Lazo-Langner A, Shivakumar S, et al; SOME Investigators. Screening for occult cancer in unprovoked venous thromboembolism. *N Engl J Med* 2015;373(08):697–704
- 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):3484–3488
- Chee CE, Ashrani AA, Marks RS, et al. Predictors of venous thromboembolism recurrence and bleeding among active cancer patients: a population-based cohort study. *Blood* 2014;123(25):3972–3978
- Mandalà M, Falanga A, Roila F; ESMO Guidelines Working Group. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol* 2011;22 (Suppl 6):vi85–vi92
- Streiff MB, Bockenstedt PL, Cataland SR, et al. Venous thromboembolic disease. *J Natl Compr Canc Netw* 2011;9(07):714–777
- Lyman GH, Bohlke K, Khorana AA, et al; American Society of Clinical Oncology. Venous thromboembolism prophylaxis and treatment in patients with cancer: American society of clinical oncology clinical practice guideline update 2014. *J Clin Oncol* 2015;33(06):654–656
- 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
- Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease. CHEST guidelines and expert panel report. *Chest* 2016; 149(02):315–352
- Lee AY, Levine MN, Baker RI, et al; Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003;349 (02):146–153
- Lee AYY, Kamphuisen PW, Meyer G, et al; CATCH Investigators. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA* 2015;314(07):677–686
- van Es N, Bleker SM, Wilts IT, Porreca E, Di Nisio M. Prevention and treatment of venous thromboembolism in patients with cancer: focus on drug therapy. *Drugs* 2016;76(03):331–341
- van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klokk FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost* 2014;12(03):320–328
- van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood* 2014;124(12):1968–1975
- 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(01): e37–e46
- Schulman S, Goldhaber SZ, Kearon C, et al. Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. *Thromb Haemost* 2015;114(01):150–157
- 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):2187–2191

- 20 Raskob GE, van Es N, Segers A, et al; Hokusai-VTE investigators. 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(08):e379–e387
- 21 Vedovati MC, Germini F, Agnelli G, Becattini C. Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. *Chest* 2015;147(02):475–483
- 22 van Es N, Di Nisio M, Bleker SM, et al. Edoxaban for treatment of venous thromboembolism in patients with cancer. Rationale and design of the Hokusai VTE-cancer study. *Thromb Haemost* 2015;114(06):1268–1276
- 23 Raskob GE, van Es N, Verhamme P, et al; Hokusai VTE Cancer Investigators. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med* 2018;378(07):615–624
- 24 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):2017–2023
- 25 den Exter PL, Hooijer J, Dekkers OM, Huisman MV. Risk of recurrent VTE and mortality in patients with cancer incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients. *J Clin Oncol* 2011;29:2405–2409
- 26 Agnelli G, Verso M, Mandalà M, et al. A prospective study on survival in cancer patients with and without VTE. *Intern Emerg Med* 2014;9:559–567
- 27 Van der Hulle T, den Exter PL, Planquette B, et al. Risk of recurrent VTE and major haemorrhage in cancer-associated incidental pulmonary embolism among treated and untreated patients: a pooled analysis of 926 patients. *J Thromb Haemost* 2016;14:105–113
- 28 Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369(09):799–808
- 29 Streiff MB, Milentijevic D, McCrae K, et al. Effectiveness and safety of anticoagulants for the treatment of venous thromboembolism in patients with cancer. *Am J Hematol* 2018;93(05):664–671
- 30 Posch F, Königsbrügge O, Zielinski C, Pabinger I, Ay C. Treatment of venous thromboembolism in patients with cancer: A network meta-analysis comparing efficacy and safety of anticoagulants. *Thromb Res* 2015;136(03):582–589
- 31 Mauri L, D'Agostino RB Sr. Challenges in the design and interpretation of noninferiority trials. *N Engl J Med* 2017;377(14):1357–1367
- 32 Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361(24):2342–2352
- 33 Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363(26):2499–2510
- 34 Büller HR, Prins MH, Lensin AW, et al; EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366(14):1287–1297
- 35 Büller HR, Décousus H, Grosso MA, et al; Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369(15):1406–1415
- 36 Schulman S, Kakkar AK, Goldhaber SZ, et al; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation* 2014;129(07):764–772
- 37 Fine JP, Gray RJ. A proportional hazards model for the sub-distribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509
- 38 Li G, Cook DJ, Levine MA, et al; PROTECT Investigators for the Canadian Critical Care Trials Group; Australian and New Zealand Intensive Care Society Clinical Trials Group. Australian and New Zealand Intensive Care Society Clinical Trials Group. Competing risk analysis for evaluation of dalteparin versus unfractionated heparin for venous thromboembolism in medical-surgical critically ill patients. *Medicine (Baltimore)* 2015;94(36):e1479
- 39 Direct Oral anticoagulants (DOACs) versus LMWH+/- warfarin for VTE in cancer (CANVAS). Available at: <https://clinicaltrials.gov/ct2/show/record/NCT02744092>. Accessed July 23, 2018
- 40 Cancer associated thrombosis, a pilot treatment study using rivaroxaban (CASTA-DIVA). Available at: <https://clinicaltrials.gov/ct2/show/NCT02746185>. Accessed July 23, 2018
- 41 McBane li R, Loprinzi CL, Ashrani A, et al. Apixaban and dalteparin in active malignancy associated venous thromboembolism. The ADAM VTE Trial. *Thromb Haemost* 2017;117(10):1952–1961
- 42 Rivaroxaban in the treatment of venous thromboembolism in cancer patients: a randomized phase III study (CONKO-011). Available at: <https://clinicaltrials.gov/ct2/show/NCT02583191>. Accessed July 23, 2018
- 43 Kahn SR, Springmann V, Schulman S, et al. Management and adherence to VTE treatment guidelines in a national prospective cohort study in the Canadian outpatient setting. *The Recovery Study. Thromb Haemost* 2012;108(03):493–498
- 44 Khorana AA, Yannicelli D, McCrae KR, et al. Evaluation of US prescription patterns: Are treatment guidelines for cancer-associated venous thromboembolism being followed? *Thromb Res* 2016;145:51–53
- 45 van der Wall SJ, Klok FA, den Exter PL, et al. Continuation of low-molecular-weight heparin treatment for cancer-related venous thromboembolism: a prospective cohort study in daily clinical practice. *J Thromb Haemost* 2017;15(01):74–79
- 46 Raskob GE, Gallus AS, Sanders P, et al. Early time courses of recurrent thromboembolism and bleeding during apixaban or enoxaparin/warfarin therapy. A sub-analysis of the AMPLIFY trial. *Thromb Haemost* 2016;115(04):809–816
- 47 Steffel J, Verhamme P, Potpara TS, et al; ESC Scientific Document Group. 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):1330–1393