Apixaban for the treatment of venous thromboembolism in patients with cancer: a prospective randomized open blinded end-point (probe) study - the Caravaggio study

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

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Embolism and thrombosis
Study type	Interventional

Summary

ID

NL-OMON50094

Source
ToetsingOnline

Brief title
Caravaggio

Condition

- Embolism and thrombosis

Synonym
newly diagnosed proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE)

Research involving
Human

Sponsors and support

Primary sponsor: Fondazione FADOI Italian Federation of Hospital Internists
Source(s) of monetary or material Support: projectgebonden financiering FADOI (Italiaanse onderzoeksgroep universiteit van Peruglia)

Intervention

Keyword: Cancer, Deep vein thrombosis, Pulmonary embolism

Outcome measures

Primary outcome

Primary efficacy outcome: Objectively confirmed recurrent VTE occurring during

the study treatment period, that means the composite of:

Proximal DVT of the lower limbs (symptomatic or unsuspected)

DVT of the upper limb (symptomatic)

PE (symptomatic or unsuspected)

Primary safety outcome is major bleeding, defined (as per ISTH guidelines), as

acute clinically overt bleeding associated with one or

more of the following:

- decrease in hemoglobin of 2 g/dl (1.2 mmol/L) or more;

- transfusion of 2 or more units of packed red blood cells;.

- bleeding that occurs in at least one critical site

[intracranial,intra-spinal, intraocular (within the corpus of the eye; thus, a

conjunctival bleed is not an intraocular bleed), pericardial, intraarticular,

intramuscular with compartment syndrome, or retroperitoneal];

- bleeding that is fatal;

- bleeding that necessitates acute surgical intervention

Secondary outcome

Secondary efficacy outcomes:

The individual components of the primary efficacy outcome

Symptomatic recurrence of the VTE

All cause death

The composite of primary efficacy outcome plus major bleeding

The composite of primary efficacy outcome plus major bleeding plus all cause death

The composite of primary efficacy outcome plus all cause death

Any major cardiovascular event, fatal or non fatal (including acute Myocardial Infarction or ischemic stroke)

All venous thromboembolic events (including splanchnic vein thrombosis and cerebral vein thrombosis)

Quality of Life according to the Anti-Cot Treatment Scale (ACTS) (see appendix 2)

Secondary safety outcomes include:

· Clinically relevant non-major bleeding event defined as acute clinically overt bleeding that does not meet the criteria for major

and consists of:

- any bleeding compromising hemodynamics;

- spontaneous hematoma larger than 25 cm2, or 100 cm2 if there was a traumatic

cause;

- intramuscular hematoma documented by ultrasonography;

- epistaxis or gingival bleeding requiring tamponade or other medical intervention or bleeding from venipuncture for >5 minutes;

- hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after invasive procedures;

- hemoptysis, hematemesis or spontaneous rectal bleeding requiring endoscopy or other medical intervention;

- or any other bleeding considered to have clinical consequences for a patient such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug, or associated with pain or impairment of activities of daily life.

· Clinically relevant bleeding defined as the composite of major and clinically relevant non-major bleeding

· Permanent early discontinuation of study drug due to safety reasons.

Study description

Background summary

Venous thromboembolism (VTE) is a common clinical event in patients with cancer. The development of VTE is presumed to be due to the production of pro-coagulant molecules by cancer cells and to the pro-coagulant effective cancer cells spread into the circulation. It should be taken into account that

cancer surgery and chemotherapy are associated with a substantial increase in the risk of VTE (1). The risk for bleeding complications on anticoagulant therapy is also higher in cancer patients than in non-cancer patients such making crucial the balance between benefit and risk (1). The CLOT study, performed more than 15 years ago, showed that in patients with cancer associated VTE, anticoagulant treatment with the LMWH dalteparin was more effective and similarly safe compared to vitamin K antagonists (2). These results were confirmed in studies with a more limited number of patients (3). Thus, current guidelines recommend the use of :MWH, given subcutaneously, for the acute and long term treatment of VTE in cancer patients (4-5). In the recently published CATCH study in cancer patients, the LMWH tinzaparin was associated with a non-significant 35% risk reduction in recurrence of VTE compared to vitamin K antagonists (6).In the CTACH study, there were no differences in the incidence of major bleeding between the two treatment groups. Due to the high risk for recurrence, cancer patients who experience VTE are candidate to indefinite treatment duration or to prolong treatment until cancer is completely cured (4-5). The availability of an oral anticoagulant treatment, as effective and safe as LMWH would be a substantial advantage for patient with cancer who develop VTE. During the last years, new oral anticoagulants given at fixed doses without the need of laboratory monitoring and dose adjustments were shown to be as effective as and probably safer than vitamin K antagonists for the treatment of VTE (7). The results of phase III clinical trialled to their approval for the acute and long term treatment of VTE. Unfortunately, the clinical trials on the treatment of VTE with the new oral anticoagulants included only a limited number of patients with cancer. Thus, whether the results obtained in the general population of patients with VTE also attain to cancer patients remains undefined. Subgroup analysis on the efficacy and safety profile of the anti-Xa oral agent apixaban for the treatment of VTE in cancer patients have been recently reported (8-11). In these patient with all the limitations related to a subgroup analysis, apixaban appeared to be at least as effective as LMWH given with and followed by vitamin K antagonists (10). A recent meta-analysis in cancer patients showed a similar efficacy and safety profile of of new oral anticoagulants in comparison with LMWH given with and followed by vitamin K antagonists for the treatment of VTE (12).

Study objective

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

Study design

This is a multinational, prospective, randomized, open table, blinded end-point (PROBE) non-inferiority study comparing apixaban to the LMWH dalteparin in the

treatment of VTE in patients with cancer.

Intervention

Subcutaneous injections with the anticoagulant as well as blood sampling 4 times during the study.

Study burden and risks

The nature and extend of the burden and risks for participants in this study are:

In general, the subjects will need to take an anticoagulant with its risks. However, the subjects will have to take this for there current diagnosis (VTE_ anyway and therefore there is no additional burden for the subject in participating in this trial as far as anticoagulation other than the ones described already under E9.
There will be visits to the clinic for this trial and the estimated duration of those visits are approximately 4.5 hours for the entire participation, and this includes the screening visit 9which is 72 hours or less until enrollment), the enrollment visit, the 4 week and 3 months and 6 months visit and the end of study visit, as well as potentially any unscheduled visit. The subjects will undergo blood sampling for hematology and chemistry.
If the subject is randomized to the injectable anticoagulant, there will also be the daily subcutaneous injections of those.
Risks that are not expected are potential risk of allergy and potentially any unknown or unexpected reaction.

The potential benefit is that oral anticoagulant can may prescribed in future of this patients.

Contacts

Public
Fondazione FADOI Italian Federation of Hospital Internists

Via F. Grossi Gondi 49
Rome 00162
IT
Scientific
Fondazione FADOI Italian Federation of Hospital Internists

Via F. Grossi Gondi 49
Rome 00162

IT

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

A newly diagnosed, objectively confirmed symptomatic or unsuspected, proximal lower limb DVTor a symptomatic PE or an unsuspected PE in a segmental or more proximal pulmonary artery. and any type of cancer (other than basal cell or squamous cell carcinoma of the skin, primary brain tumors or intracerebral metastasis and acute leukemia that meets at least one of the following: 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).

Exclusion criteria

less than 18 years of age. ECOG performance status III or IV. Life expectancy of less than 6 months. Related to anti coagulant therapy: 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 anti coagulant 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. Related to bleeding risks: concomitant thienopyridine therapy (clopidogrel, pasugrel or ticagrelor) or aspirin over 165 mg daily oe dual antiplatlet therapy. Active bleeding or a high risk of bleeding contraindicating anticoagulant therapy. `recent (in the last 1 month prior to randomization) brain, spinal or

ophthalmic surgery. Hemoglobin level lower than 8 g/dl (5.0 mmil/Liter or platelet count less than 75 x 10 to the 9th/L or history of heparin induced thrombocytopenia. Creatinine clearance less than 30 ml/min based on the Cockcroft Gault equation. Acute hepatitis, chronic active hepatitis, liver cirrhosis, or an alanine aminotransferase level 3 times or more and/or bilirubin level 2 times or more of of the higher of the upper limit of the normal range. uncontrolled hypertension (systolic BP more than 180 mm HG or diastolic BP more than 100 mm Hg despite antihypertensive treatment. Standard criteria: Bacterial endocarditis, hypersensitivity to the study drugs or to any of their excipients, patients participating in other pharmacy therapeutic program with an experimental therapy that is know to effect the coagulation system, women of child bearing potential (WOCBP) who do not practice a medically accepted high effective contraception during the trial and one months beyond, pregnancy or breast feeding, any condition that is judged by the investigator that would place the subject at increased risk or harm if (s)he participated in the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-08-2017
Enrollment:	180
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Apixaban
Generic name:	Eliquis
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	09-02-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	12-07-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	24-10-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	01-12-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	18-06-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	06-12-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	28-01-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	27-02-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	24-12-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR003093-40 NL-NL
CCMO	NL60090.058.17