A multicentre, randomised, double-blind, controlled, phase IIIb study to assess the efficacy and safety of Rivaroxaban 10mg od versus Enoxaparin 4000 IU for VTE PROphylaxis in NOn Major Orthopaedic Surgery. The PRONOMOS study

Published: 14-04-2016
Last updated: 17-04-2024

The primary objective is to demonstrate the non-inferiority of rivaroxaban 10 mg versus enoxaparin 4000 IU relevant to the occurrence of major VTEs up until the end of the treatment (for example, cast or splint removal). The power of the study...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46019

Source
ToetsingOnline

Brief title
PRONOMOS

Condition

- Other condition

Synonym
flebitis, venous thromboembolism

Health condition

preventie diepe veneuze trombose

Research involving
Human

Sponsors and support

Primary sponsor: Centre Hospitalier Universitaire de Saint-Etienne
Source(s) of monetary or material Support: Centre Hospitalier Universitaire Saint-Etienne

Intervention

Keyword: heparine, prevention, VTE

Outcome measures

Primary outcome

The primary efficacy endpoint, major venous thromboembolic events (VTE), is a composite endpoint which includes proximal (asymptomatic and symptomatic) deep vein thromboses (DVT), symptomatic events (distal and proximal DVTs, pulmonary embolisms) and VTE-related deaths up until the end of the treatment period.

Secondary outcome

1- Major bleeding. Major bleeding is defined as a haemorrhagic event meeting at least on of the following criteria:

- Fatal bleeding;

- Critical bleeding (intracranial, intraocular, intraspinal, pericardial, retroperitoneal);

- Clinically overt bleeding (at surgical or extrasurgical site) associated with a decrease in the haemoglobin level of more than 2 g/dL (20 g/l; 1.24 mmol/L) compared with the pre-randomisation level;

- Clinically overt bleeding (at surgical or extrasurgical site) leading to

transfusion of two or more units of whole blood or blood cell concentrates;

- Bleeding located at the surgical site and leading to re-operation or to any unusual medical intervention or procedure for relief (e.g. draining or puncture of a haematoma at the surgical site, transfer to an ICU or emergency department).

2- Clinically relevant non-major bleeding is defined as external bleeding which does not meet the criteria for major bleeding and corresponds to any bleeding necessitating a specific medical intervention or unplanned, unscheduled consultation or specific treatment cessation, or resulting in a deterioration of the subject's quality of life. A few examples are given below:

- Epistaxis that lasts more than five minutes or is recurrent or necessitates packing,
- Spontaneous macroscopic haematuria or haematuria lasting more than 24 hours after instrumentation,
- Gastrointestinal haemorrhage (melena or rectorrhagia),
- Haemoptysis,
- Subcutaneous haematoma > 100 cm^2.

3- Overt thrombocytopenia: platelet count <100 giga/L or * 50% drop in the platelet count as compared with the first post-operative count performed in local laboratories for all centres. During the study, platelet count will be monitored in accordance with country-specific recommendations and in cases of bleeding and recurrent VTE.

4- All cause mortality during treatment.

All suspected VTE, all deaths and all haemorrhagic episodes will be evaluated

blindly by an independent central adjudication committee (ICAC). The results

will form the basis of final analyses.

Study description

Background summary

Several national guidelines or expert recommendations published in some Western European countries do recommend thromboprophylaxis, at least in certain patients presenting with other VTE risk factors. In practice, the use of thromboprophylaxis in immobilised patients with isolated lower limb injuries varies greatly. Although no treatment has yet been approved for this indication, LMWH treatments are widely used in at-risk patients. There is however no consensus on the type, dose and duration of thromboprophylaxis. In addition, daily injections of LMWH, while effective, represent a heavy burden on the patients, particularly in cases of prolonged immobilisation. Rivaroxaban is a direct oral anticoagulant which develops a potent anti-Xa action. In major orthopaedic surgery, it has proven to be more effective and as innocuous as LMWH treatments (enoxaparin 4000 IU once-daily) in patients due to undergo total hip or knee arthroplasty (RECORD programme). Up until now, it has been approved in VTE prevention after total hip and knee arthroplasties. These indicated uses only represent 20 % of all orthopaedic surgical procedures. Patients in elective non major lower limb surgery and in traumatology are younger than those patients in prosthetic orthopaedic surgery. Therefore fewer VTEs and cardiovascular events are feared. These patients often receive thromboprophylaxis by injectable route for a total duration of about 6 weeks to 3 months. On the one hand, the risk of major bleeding is lower within this young population; and the other hand, convenience and cost should weigh in favour of rivaroxaban as no injections or platelet count monitoring are required.

Study objective

The primary objective is to demonstrate the non-inferiority of rivaroxaban 10 mg versus enoxaparin 4000 IU relevant to the occurrence of major VTEs up until the end of the treatment (for example, cast or splint removal). The power of the study should reveal the superiority of rivaroxaban 10 mg once-daily relevant to the occurrence of the primary endpoint. This superiority analysis will only be performed if the primary non-inferiority objective has been met.

The secondary objectives of the study are to evaluate the safety of rivaroxaban compared to enoxaparin in terms of:
1. Major bleeding
2. Non major, clinically relevant bleeding
3. Thrombocytopenia
4. All cause mortality during treatment.

Study design

Non-inferiority, multicentre, international, interventional, parallel arm, randomised, double blind study

Intervention

Group 1: once daily 1 rivaroxaban 10 mg tablet plus 1 injection placebo enoxaprarin 4000 IU per day
Group 2: 1 injection enoxaparine 4000 IU per day plus once daily 1 placebo rivaroxaban 10 mg tablet.

Study burden and risks

Small haematomas may appear at the site of Enoxaparin injection. They do not present any hazard and resorb on their own. Furthermore, as with any anticoagulant treatment, there is a risk of haemorrhage but it is low.

The burden of the is minimal bacause the treatment is in accordance to the daily practice regarding prevention of deep venous trombosis.

Contacts

Public
Centre Hospitalier Universitaire de Saint-Etienne

Direction Générale Pavillon 31
Saint-Etienne 42055
FR
Scientific
Centre Hospitalier Universitaire de Saint-Etienne

Direction Générale Pavillon 31
Saint-Etienne 42055
FR

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed and dated informed consent form,
2. Age * 18 years,
3. Hospitalised for non-major orthopaedic surgery of the lower limbs and requiringthromboprophylaxis according to the investigator*s judgement on VTE risk such Achilles* repair, knee (including unicompartmental knee prosthesis), tibial plateau, femur (non femoral head), tibial and ankle fractures and tibial osteotomy, tibial transposition, arthrodesis of leg articulation, ligament repair of the knee with a planned immobilisation or partial weight-bearing for more than 2 weeks, ligament repair of the ankle or any elective orthopaedic limb surgery requiring thromboprophylaxis.
4. An intended duration of treatment for at least 2 weeks.

Exclusion criteria

1. Major orthopaedic surgery of the lower limbs: Hip and Knee replacement, femoral neck and trochanteric fractures, spine surgery,
2. Polytrauma (each lesion being individually life-threatening) or any life-threatening lesions,
3. Low risk surgery without patient VTE risk: Forefoot surgery (i.e. Hallux Valgus), material removal,Meniscectomy, Knee arthroscopy (except for ligament repair), Meniscal suture, Diagnostic arthroscopy
4. Time between hospitalisation and surgery greater than 48 hours
5. More than one injection of LMWH since the end of surgery
6. More than two injections of LMWH before surgery
7. Women of childbearing potential not using a reliable contraceptive method throughout the study period (a list of reliable contraceptive methods is provided),
8. Women pregnant or breast-feeding during the study period,
9. Body weight less than 50 kg (to avoid bleeding over risk) or over 120 kg,
10. Concomitant treatment with VKA therapy or DOAs,

11. Concomitant treatment with clopidogrel, prasugrel and ticagrelor,
12. Concomitant use of strong inhibitors of both CYP3A4 and P-gp, i.e. all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole
13. Platelet count < 100 Giga/L,
14. Documented history of acquired or inherited bleeding disorder (e.g., von Willebrand's disease),
15. Severe renal failure with calculated creatinine clearance (Cockcroft Formula) < 30 mL/min,
16. Severe hepatic insufficiency with prothrombin time < 60% or liver impairment associated with coagulation disorders,
17. History of heparin induced thrombocytopenia,
18. Any other current significant medical condition that might interfere with treatment evaluation according to the investigator*s judgement,
19. Known hypersensitivity or other severe reaction to any component of the investigational medicinal product(s),
20. Participation in another clinical study involving an investigational medicinal product within 30 days prior to inclusion or concomitantly with this study,
21. Active bleeding or contraindication to anticoagulant therapy
22. Chronic alcoholic intoxication (cirrhotic patient),
23. Anticipated poor compliance of subject with study procedures

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-01-2018
Enrollment:	110

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Xarelto
Generic name:	rivaroxaban
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-04-2016
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	20-03-2017
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	12-09-2017
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	27-02-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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	EUCTR2015-000981-70-NL
ClinicalTrials.gov	NCT02401594
CCMO	NL55620.075.16