Home Treatment of Patients with Low-Risk Pulmonary Embolism with the Oral Factor Xa Inhibitor Rivaroxaban: Prospective Management Trial (HoT-PE)

Published: 14-12-2016
Last updated: 15-04-2024

Objective of the study: Primary objective: to determine whether early discharge and out-of-hospital treatment of patients with low-risk acute PE (as defined by the inclusion and exclusion criteria) with the new oral factor Xa inhibitor rivaroxaban…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Pulmonary vascular disorders
Study type	Observational invasive

Summary

ID

NL-OMON45455

Source
ToetsingOnline

Brief title
HoT-PE

Condition

- Pulmonary vascular disorders

Synonym
Low risk acute pulmonary embolism

Research involving
Human

Sponsors and support

Primary sponsor: University Medical Centre Johannes Gutenberg-University Mainz

Source(s) of monetary or material Support: Ministerie van OC&W,Bayer

Intervention

Keyword: muti-center, pulmonary embolism (PE), single-arm

Outcome measures

Primary outcome

The primary efficacy outcome is symptomatic recurrent venous thromboembolism (VTE) or death related to pulmonary embolism within 3 months after enrolment.

Secondary outcome

1) All-cause mortality within 7 days;

2) All-cause mortality within 3 weeks;

3) All-cause mortality within 3 months;

4) Overall duration of hospital stay (index event and repeated hospitalizations due to PE [index or recurrent event] or to a bleeding event) within 3 months;

5) Rehospitalization due to PE (index or recurrent event) or to a bleeding event within 3 months;

6) Generic and disease-specific quality of life at baseline, 1 week, 3 weeks, and 3 months;

7) Treatment satisfaction using the Anti-Clot Treatment Scale (ACTS) at 3 weeks and 3 months;

8) Utilization of medical resources at 1 week, 3 weeks, and 3 months (based on data from patients recruited at German study sites);

9) All-cause mortality at one year.

Safety outcomes:

1) Major bleeding, based on the ISTH definition, within 7 days, 3 weeks, and 3 months;

2) Clinically relevant bleeding, defined as a composite of major or clinically relevant non- major bleeding, within 7 days, 3 weeks, and 3 months;

3) Serious adverse events (SAE) within 7 days, 3 weeks, and 3 months

A Serious Adverse Event is defined as an event that at any dose (including overdose):

Results in death;

Is life-threatening;

Requires subject hospitalization or prolongation of existing hospitalization;

Results in persistent or significant disability/incapacity;

Is a congenital anomaly/birth defect;

Is an important medical event.

Study description

Background summary

In all home-treatment single-armed (management) and randomized trials performed thus far, conventional regimens of anticoagulation using subcutaneous low molecular-weight heparin followed by oral anticoagulants (vitamin K antagonists) were used; the bleeding risks and logistical problems associated with the latter drugs have repeatedly been emphasized (19-22).
The EINSTEIN-PE study (23) tested the new oral factor Xa inhibitor rivaroxaban in 4,832 patients at 263 sites in 38 countries. Recurrent symptomatic (or lethal) venous thromboembolism occurred in 2.1% of patients receiving rivaroxaban compared with 1.8% of those on standard enoxaparin/warfarin therapy. Rivaroxaban was thus non-inferior to standard therapy (P=0.003). Importantly, major bleeding was observed in only 1.1% of patients taking rivaroxaban compared with 2.2% of those on enoxaparin/warfarin (P=0.003). In

particular, intracranial bleeding occurred in one rivaroxaban patient compared with 10 patients receiving standard therapy. Based on the results of the EINSTEIN trial, rivaroxaban was approved for use as oral monotherapy for acute PE in Europe and North America in 2012.
New oral anticoagulants may provide a safe, user-friendly, and cost effective alternative to standard regimens; in particular, they offer the potential to radically change the management of acute PE at the low-risk end of the severity spectrum and facilitate home treatment for a large number of patients eligible for early discharge. Proof (or rejection) of this important concept is the aim of the present trial.

Study objective

Objective of the study:
Primary objective: to determine whether early discharge and out-of-hospital treatment of patients with low-risk acute PE (as defined by the inclusion and exclusion criteria) with the new oral factor Xa inhibitor rivaroxaban is feasible, effective, and safe.

Secondary objectives:
- determine whether early discharge and out-of-hospital treatment of low-risk acute PE with the new oral factor Xa inhibitor rivaroxaban can result in good quality of life and patient satisfaction; and
- To obtain valid health economic variables as the basis for a description of health care resource utilization compared to standard in-hospital care. This includes validation of a disease-specific quality of life questionnaire, validation of existing Markov models, and comparison to published data on in-hospital care patients.

Study design

Study design: HoT-PE is a prospective, multicenter, single-arm phase 4 management (cohort) study.
In patients clinically suspected of having acute PE, the diagnostic workup will be completed within 24 hours of admission. Treatment with an approved parenteral anticoagulant (unfractionated heparin administered intravenously, or low-molecular-weight heparin (LMWH), fondaparinux (administered subcutaneously), or rivaroxaban (administered orally) may be started before screening and enrolment. Anticoagulant treatment should be started upon clinical suspicion of PE and no later than 3 hours after confirmation of PE. Patients who fulfill all the inclusion criteria and meet none of the exclusion criteria will be enrolled in the study after providing written informed consent. The first dose of the study drug (rivaroxaban) will be given in-hospital, 2 hours or less before the time that the next (second) subcutaneous dosage of LMWH would have been due, or at the time of discontinuation of intravenous unfractionated heparin.

Additional baseline tests such as echocardiography and compression ultrasonography of the leg veins will be performed before discharge. These tests are recommended but not compulsory.
Patients will be discharged from the hospital within 48 hours of presentation.
A 24-hour emergency number will be provided by the study site.
Rivaroxaban will be taken for a total of at least 3 months. After that period, continuation of
anticoagulation and the anticoagulant drug to be used will be at the discretion of the patient*s
physician.
Follow-up will be performed at 8 days, 3 weeks, 3 months, and one year.

Study burden and risks

HoT-PE is a phase 4 clinical trial; rivaroxaban has been shown to be effective and safe for the treatment of acute PE and has been approved for use in this indication. This means that no additional harm can be expected for patients with acute PE who will be treated with the (already approved) rivaroxaban regimen. Of note, the current indication, by the European Medicines Agency, for rivaroxaban in acute PE does not explicitly mention (i.e. neither recommends nor excludes) immediate/early discharge and out-of-hospital treatment of the disease, but the evidence to support this strategy is very weak at present, since the vast majority (90%) of patients included in the EINSTEIN-PE trial were hospitalized during the initial phase (23).

If the hypothesis of HoT-PE is confirmed, early discharge (within 24 to 48 hours) and home treatment will become an attractive option for a large proportion of patients with acute PE. Based on the existing data, these may be as many as 50% of all patients with the disease (26). Considering the fact that venous thromboembolism is the third most frequent acute cardiovascular syndrome (after acute coronary syndrome and stroke) with an annual incidence rate of 23-69 cases per 100,000 population (27), the absolute number of patients to benefit from such a major change in paradigm will be very large. Home treatment, if confirmed to be effective and safe, could not only result in increased patient satisfaction and improved quality of life (these parameters will be assessed using standardized, validated questionnaires in the present trial), but it could also prove to be a cost effective approach by reducing hospitalization costs (a systematic pharmaco-economic analysis will be performed based on patient data collected at the German study sites). The potential socioeconomic implications of such a change are considerable and may include changes in the hospital reimbursement system which currently assumes (based on old data with injectable agents for the initial anticoagulation period along with the lack of a risk stratification concept and robust home treatment trials) that patients with acute PE need to be hospitalized for several days.

In addition, proposed clinical, imaging and laboratory criteria for identifying

low-risk PE will be validated for the first time in a large therapeutic trial. Thus, HoT-PE will be the largest-ever trial to translate a risk stratification model into clinical management of acute PE.

If, on the other hand, the hypothesis of HoT-PE is rejected and home treatment is found to be either ineffective or unsafe, then hospitalization will remain the gold standard for the initial treatment of the disease for the years to come.

The investigator will be informed about any relevant or new finding including AEs relating to treatment with the investigational medicinal product.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Age *18 years;
2) Ability of subject to understand character and individual consequences of clinical trial;
3) Signed and dated informed consent of the subject available before the start of any specific trial procedures;
4) Women of childbearing potential have to practice a medically accepted contraception (non-hormonal intrauterine device, two independent barriers, female or male surgical sterilization, or two years postmeno-pausal) during the trial, and a negative pregnancy test (serum or urine) should be available before inclusion in the trial;
5) Objectively confirmed diagnosis of acute PE by multidetector computed tomographic (CT) pulmonary angiography, pulmonary angiography, or V/Q lung scan according to established diagnostic criteria, with or without symptomatic deep vein thrombosis;
6) Absence of right ventricular (RV) enlargement or dysfunction, and of free floating thrombi in the right atrium or right ventricle on echocardiography or computed tomography.
On echocardiography, RV enlargement/dysfunction is absent when both criteria listed below are met:
- Right/left ventricular end-diastolic diameter ratio < 0.9 (apical or subcostal 4-chamber view)
- No paradoxical motion of the interventricular septum
On CT angiography, RV enlargement/dysfunction is absent when the following criterion is met:
- Right/left short-axis diameter ratio < 0.9 (transverse plane)

Exclusion criteria

-Hemodynamic instability at presentation, indicated by at least one of the following: (i) systolic blood pressure (SBP) < 100 mm Hg, or heart rate >100 beats per minute, or SBP drop by > 40 mm Hg, for > 15 min; (ii) need for catecholamines to maintain adequate organ perfusion and a systolic blood pressure of >100 mm Hg; (iii) need for cardiopulmonary resuscitation;
-Right ventricular (RV) enlargement or dysfunction, or free floating thrombi in the right atrium or right ventricle, detected by echocardiography or computed tomography;
-Treatment with low-molecular-weight heparin, fondaparinux, or unfractionated heparin for more than 48 hours, or more than a single dose of a vitamin K antagonist prior to inclusion in the study;
-Treatment with rivaroxaban, dabigatran, apixaban, edoxaban or any other new generation antithrombotics on admission;
-Use of a fibrinolytic agent, surgical thrombectomy, interventional (transcatheter) thrombus aspiration or lysis, or use of a cava filter to treat the index episode of PE;
- Need for supplemental oxygen administration to maintain oxygen saturation >90%;
-Pain requiring parenteral administration of analgesic agents;
-Other medical conditions/comorbidities requiring hospitalization;
- Acute PE diagnosed in a patient already hospitalized for another condition;

- Pregnancy or lactation;
- Active bleeding or known significant bleeding risk;
-Severe renal insufficiency (estimated GFR <15 ml/min/1.73m2) or end-stage renal disease;
-Severe hepatic failure;
-Known allergy or intolerance to rivaroxaban;
-Concomitant administration of strong inhibitors of P-gp and CYP3A4 such as azole antimycotic agents or HIV protease inhibitors;
-Need for long-term treatment vitamin K antagonists, or for antiplatelet agents except acetylsalicylic acid at a dosage <100 mg/day;
-Non-compliance or inability to adhere to treatment or to the follow-up visits; or lack of a family environment or support system for home treatment;
-Life expectancy less than 3 months.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-07-2017
Enrollment:	143
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:	14-12-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-01-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-05-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-10-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2013-001657-28-NL
CCMO	NL58418.101.16