Risk, predictors, impact and outcome of anticoagulation-associated abnormal menstrual bleeding in female patients with VTE * the TEAM-VTE study

Published: 20-07-2018
Last updated: 10-01-2025

The primary objective of the TEAM-VTE study is to assess and specify the rate of new-onset abnormal menstrual bleeding in female in their fertile age, anticoagulated for an incident case of venous thromboembolism (VTE).The secondary objectives of...

Ethical review	Approved WMO
Status	Completed
Health condition type	Embolism and thrombosis
Study type	Observational invasive

Summary

ID

NL-OMON55518

Source
ToetsingOnline

Brief title
VTE-TEAM

Condition

- Embolism and thrombosis

Synonym
venous thromboembolism, venous thrombosis

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

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

Intervention

Keyword: Anticoagulation, Mentrual bleeding, Venous thromboembolism

Outcome measures

Primary outcome

The primary endpoints of the TEAM-VTE study is the incidence of new-onset abnormal menstrual bleeding. Abnormal menstrual bleeding is binary defined as 1) self-reported *increased menstrual volume* (regardless of regularity, incidence, or duration) according to the FIGO classification or 2) a PBAC score >100.

Secondary outcome

The secondary endpoints of the TEAM-VTE study include:

1) Rate of clinical relevant non-major and major (menstrual) bleeding according to the ISTH criteria;

2) Change in rate of abnormal menstrual bleeding after diagnosis of VTE compared to last 3 months before initiation of anticoagulants, and during the follow-up period.

3) Impact of new-onset abnormal menstrual bleeding on QoL as assessed with the MBQ and PEmb-QoL;

4) Predictors of new-onset abnormal menstrual bleeding;

5) Changes in contraceptive measures during the study: details, incidence, causes and effect on primary endpoint and recurrent VTE;

6) Changes in anticoagulation therapy: details, incidence, causes and effect on primary endpoint and recurrent VTE;

7) Presence of underlying gynaecological or other morbidities as explanation

for abnormal menstrual bleeding.

Study description

Background summary

The risk of abnormal menstrual bleeding in women with childbearing potential treated with anticoagulant drugs is increased, although solid studies to quantify the prevalence of abnormal menstrual bleeding or the treatment thereof are lacking to date. This issue is mostly relevant for patients with venous thromboembolism (VTE), i.e. deep vein thrombosis (DVT) or acute pulmonary embolism (PE), because other diseases that necessitates active anticoagulant treatment are rare in female patients in the age category 18 to 50 years. In general, abnormal menstrual bleeding is associated with negative perceptions and limited social and professional activities as well with a significant poorer quality of life compared with patients with normal menstrual bleeding. Several specific aspects are especially relevant for the occurrence of abnormal menstrual bleeding in anticoagulated female VTE patients, i.e. choice of anticoagulation therapy, use of hormonal contraception (HC) and treatment of abnormal menstrual bleeding. While on one hand Direct oral anticoagulant (DOACs) have been associated with a lower overall bleeding risk - in particular significantly lower fatal and intracranial bleeding - compared to the conventional treatment of VTE being vitamin k antagonists (VKA), the risk of abnormal uterine bleeding in women treated with factor Xa inhibitors has been reported to be higher than with VKAs.The underlying mechanism for the difference in these bleeding patterns is yet unknown. With DOACs being recommended as the treatment of first choice for VTE, more and more female patients with childbearing potential may suffer from even higher risks of abnormal menstrual bleeding. Because most data on this subject originates from post-hoc analysis, there is currently no sound scientific evidence for providing recommendations with regard to the optimal anticoagulant regimen in VTE patients of childbearing age.
The use of HC is common among women of childbearing age and associated with a higher risk of VTE. Patients with hormone-associated VTE receive anticoagulant treatment for at least three months and are instructed to discontinue HC, as the risk of VTE recurrence is low after discontinuation of hormonal therapy.The optimal timing of HC withdrawal is however uncertain since HC may be conceived as risk factor for recurrent VTE during anticoagulant treatment, although this is not supported by available evidence. Notably, hormonal treatment with HC is often required to reduce the severity of abnormal menstrual bleeding.5 Studies focussing on treatment of abnormal menstrual bleeding in anticoagulated patients are scarce and of poor quality with low

patients numbers and often retrospective data acquisition. Available data confirms the aggravating effect of anticoagulant treatment on the menstrual bleeding pattern and the potential protective effect of a progestin-releasing intra uterine devices. Studies evaluating other interventions such as tranexamic acid are lacking, although this treatment is being applied in clinical practice.

Study objective

The primary objective of the TEAM-VTE study is to assess and specify the rate of new-onset abnormal menstrual bleeding in female in their fertile age, anticoagulated for an incident case of venous thromboembolism (VTE).

The secondary objectives of the TEAM-VTE study are:
1. To assess the predictors of new-onset abnormal menstrual bleeding in anticoagulated female VTE patients in their fertile age;
2. To assess the impact of new-onset abnormal menstrual bleeding in anticoagulated female VTE patients in their fertile age on quality of life;
3. To assess the results of routine counselling and clinical work-up of anticoagulated female VTE patients in their fertile age with new-onset abnormal menstrual bleeding;
4. To assess the reasons for and consequences of modifications in contraceptive measures and anticoagulant treatment in female VTE patients in their fertile age;
5. To assess the association of use of oral contraceptives and new-onset abnormal menstrual bleeding, other bleeding and recurrent VTE in female VTE patients in their fertile age

Study design

This study is an international, multicenter, academically sponsored, observational study, that focusses on fertile female patients with proven symptomatic deep vein thrombosis of the legs (DVT) or acute pulmonary embolism (PE). The incidence and severity of abnormal menstrual bleeding will be assessed for each menstrual period and correlated to quality of life. Causes of abnormal menstrual bleeding other than active anticoagulant treatment will be assessed. Treatment of abnormal menstrual bleeding (all within routine clinical care) will be evaluated for efficacy and safety.

Study burden and risks

This is an observational study; patients do not have direct benefits of participating in this study other than helping in increasing our knowledge of the subject under study. The burden of the study is limited and includes completing a menstrual score chart every menstrual cycle and a quality of life questionnaire at the end of the study. Two lay persons/patient representatives

have been involved in the study design and have indicated that the burden is low. Patients are not expected to experience harm from study participation.

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) Ability of subject to understand the character and individual consequences of this clinical study;
2) Signed and dated informed consent of the subject available before the start of any specific study procedures;
3) Age *18 years and * 50 years;
4) Confirmed symptomatic first or recurrent VTE;
a. DVT: incompressibility of proximal or distal veins of the affected leg by compression ultrasonography or venous filling defect on multi-detector computed

tomography venography. The diagnosis of ipsilateral recurrent DVT is defined as a CUS that shows incompressibility of a different venous segment than at the reference CUS examination, or in case of a pronounced increase in vein diameter (*4 mm) of a previous non-compressible venous segment, or by an abnormal signal of Magnetic resonance direct thrombus imaging (MRDTI);
b. PE: both first and recurrent PE are diagnosed in case of at least one filling defect in the pulmonary artery tree on multi-detector computed tomography pulmonary angiography (CTPA) up to the subsegmental level, or high probability result of ventilation perfusion scintigraphy;
5) Childbearing potential, i.e. with active menstrual cycle with or without hormonal regulation of any kind initiated for reasons of either contraception or for treatment of abnormal menstrual bleeding;
6) Inclusion before the first day of next menstrual cycle after VTE diagnosis or within 1 month after the VTE diagnosis, whichever comes first.

Exclusion criteria

1) Woman between the ages of 18 and 50 who were subjected to hysterectomy or chemically induced menopause;
2) Woman between the ages of 18 and 50 with premature menopause (established before study inclusion);
3) Planned treatment with parenteral anticoagulation (and no switch to oral drugs);
4) Medical or psychological condition that would not permit completion of the study or signing of informed consent, including life expectancy less than 6 months, or unwillingness to sign informed consent;
5) Non-compliance or inability to adhere to the follow-up visits;
6) Pregnancy or post-partum (first three months) associated VTE;
7) Active in vitro fertilization (IVF) treatment or planned IVF treatment during the study period.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-12-2018
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	20-07-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	22-05-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	01-03-2021
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

ID: 24079
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL64567.058.17
Other	Volgt

Study results

Date completed:	31-10-2021
Results posted:	31-10-2022
Actual enrolment:	24

First publication
20-10-2022