# *Cost-effectiveness of tailoring anticoagulant therapy by a VTE recurrence prediction model in patients with venous thrombo-embolism as compared to care-as-usual: the VISTA study.*

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OBJECTIVESThe objective is to quantify the cost-effectiveness and efficacy of formally applying the guideline evaluating the risk-benefit ratio of the duration of anticoagulant therapy (VKA treatment) by a previously developed VTE recurrence...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Pulmonary vascular disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON41715

**Source**
ToetsingOnline

**Brief title**
The VISTA study

### Condition

- Pulmonary vascular disorders
- Embolism and thrombosis

**Synonym**
Deep Venous Thrombosis, Pulmonary Embolism

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Utrecht
**Source(s) of monetary or material Support:** ZONMW projectnummer 171002214,Bayer,unrestricted educational grant van Bayer Shering Pharma te Mijdrecht.

## Intervention

**Keyword:** D-dimer, Deep Venous Thrombosis, Pulmonary Embolism, treatment duration

## Outcome measures

### Primary outcome

Main study parameter/endpoint

The primary outcome is the occurrence (incidence) of recurrent VTE during 24 months of follow-up after the initial 6 months of VKA treatment. Recurrent VTE is defined as proximal DVT and/or fatal or non-fatal PE as confirmed by compression ultrasonography for DVT and by (spiral CT) angiography and/or ventilation-perfusion lung scanning for PE. To prevent bias, interpretation of the compression ultrasonography as well as ventilation-perfusion lung scanning and/or (spiral CT) angiography will be blinded to allocated treatment strategy.

### Secondary outcome

Secondary study parameters/endpoints:

Safety and secondary outcomes are the occurrence of major bleedings, quality of life and cost-effectiveness. A major bleeding is defined by retroperitoneal or intracranial bleeding, a bleeding with lowering of haemoglobin levels of at least 2.0 g/dl, or a bleeding for which transfusion is needed of at least 2 units blood or surgical intervention or invasive procedures to stop the

bleeding. An independent and blinded adjudication committee will adjudicate each suspected thrombo-embolic recurrent event and death, as well as each potential bleeding event. A cost-effectiveness analysis will be performed from the societal perspective. With a Markov type decision model, costs and health effects as a consequence of difference of treatment are balanced against *care as usual*. Differences in costs result from different duration of treatment with VKA, from additional D-dimer tests, from treatment of recurrence of VTE and bleeding complications, and from productivity losses associated with recurrent events and bleeding complications. The time horizon used for the economic evaluation will be equal to the study period, i.e. a follow-up period of 24 months after an initial 6 months of VKA treatment. Quality of Life will be assessed at baseline, moment of intervention and during the follow-up period of 24 months, using both generic questionnaires (SF-36; EQ5D) and questions on health care consumption.

# Study description

**Background summary**

INTRODUCTION AND RATIONALE
Treatment of venous thrombo-embolism (VTE) * this is deep vein thrombosis (DVT) and pulmonary embolism (PE) * with vitamin K antagonists (VKA) is highly effective in reducing morbidity and mortality.[1,2] It reduces mortality caused by PE from 30 to 8%.[3,4] The initial treatment of VTE consists of at least 5 days of heparin (unfractionated or low-molecular-weight) overlapped with 3-6 months VKA (acenocoumarol, phenprocoumon or warfarin). Long-term treatment after initial therapy reduces the risk of recurrent VTE by over 90%.[5,7] However, after VKA discontinuation there is considerable risk of VTE recurrence, about 9% after one year.[2,5] VTE recurrence has a case-fatality rate of 5%.[6] VTE recurrence is highest immediately after VKA therapy discontinuation, and stabilizes in the subsequent 9 months.[7] Long term

treatment with VKA reduces the risk of VTE recurrence to 1% a year, but at a cost of 2% increasing risk of major bleedings.[8] Given the challenge to obtain (substantial) reduction in recurrent VTE risk versus increased risk of bleedings, there is much discussion about the optimal duration of VKA treatment in patients with VTE.[8,9] National and international guidelines on this topic suggest different strategies. The guideline from the 8th ACCP advices indefinite anticoagulant therapy for patients with a first unprovoked proximal DVT or PE and a low risk of bleeding.[9] The Dutch CBO consensus recommends for the same patients 6 months VKA therapy and indefinite when recurrence occurs.[5] However, there is limited evidence to ground these strategies. Caregivers and patients wrestle continuously with this question resulting in much uncertainty and widely varying durations of VKA therapy in daily practice.[10,11]

Observational studies show in patients with a first episode of unprovoked VTE, that a positive D-dimer test after VKA treatment indicates increased VTE recurrence risk [12-21,23]. This finding suggests that D-dimer testing can be used to determine in whom VKA prolongation seems beneficial. Hence, D-dimer guided VKA treatment strategy could minimize VTE recurrence (in whom longer VKA treatment is needed) and bleeding risk (in whom VKA treatment can be stopped). More recently, Eichinger and colleagues developed a prediction model that accurately predicts the risk of VTE recurrence in patients with a first episode of unprovoked VTE [22]. This prediction model was obtained by analysing several widely accepted factors related to VTE recurrence (Age, sex, location of VTE, BMI, factor V Leiden mutation, D-dimer levels and thrombin levels) in a cohort consisting of 929 VTE patients with a recurrence rate of 18.9% during a follow-up period of 43 months after VKA withdrawal. Only male sex, localisation (proximal DVT or PE) and elevated D-dimer levers were significantly associated with recurrence risk using a Cox proportional hazards model. Therefore, these factors were incorporated into the prediction model. The definition of a high recurrence risk if the risk exceeds 5% in 1 year, or 20% in 5 years, is based on widely accepted experts* consensus [24].

If for example * based on this model * the predicted VTE recurrence after stopping VKA treatment rate is high, patients may benefit from prolonged VKA treatment to prevent morbidity or even mortality that is associated with these VTE recurrences. If on the other hand the predicted VTE recurrence rate is low, patients can safely stop VKA treatment as possible VKA treatment complications * including (major) bleedings * no longer outweigh the benefits of long-term VKA treatment in these patients.

Such a *VTE recurrence prediction strategy* could increase the cost-effectiveness of VKA therapy in patients with VTE. Moreover, it gives physicians a more objective tool to tailor optimal duration of VKA therapy. This strategy of formal risk assessment has never been compared to care-as-usual in a randomized clinical trial (RCT). Only one small RCT exists on a D-dimer guided duration of VKA treatment. This RCT randomized VTE patients with high D-dimer levels at 3 months, to either stopping (control group) or continuing (index group) VKA treatment.[16] Patients with elevated D-dimer level at 3 months of treatment indeed benefit from prolonged VKA therapy: VTE

recurrence over on average 18 months was 15.0% in the control group (with no bleedings) versus 2.9% (with 1% bleedings) in the index group. As it was the first study in this area, it only included a small group of patients with unprovoked VTE. Moreover, it only randomized patients with an elevated D-dimer level. Hence, it remains unclear whether an even more accurate prediction model that also includes other patient characteristics and D-dimer testing has an improved overall effectiveness compared to care-as-usual with duration of VKA treatment to the physicians* discretion, let alone whether it is cost-effective. Prompted by the promising results of this small trial, the less straightforward clinical guidelines resulting in the large uncertainty of physicians when to stop VKA treatment, the resulting practice variation, we propose this study of evaluating the existing guideline with a formal risk assessment.

## Study objective

OBJECTIVES
The objective is to quantify the cost-effectiveness and efficacy of formally applying the guideline evaluating the risk-benefit ratio of the duration of anticoagulant therapy (VKA treatment) by a previously developed VTE recurrence prediction model (including type of VTE, gender and D-Dimer testing [22]) in patients with a (first) episode of unprovoked VTE as compared to care-as-usual where the duration of VKA treatment is conform current guidelines and physicians* discretion.
The tailoring of the (dis)continuation of VKA treatment will be done after 6 months of initial VKA treatment. The effectiveness will be expressed by comparing the cumulative incidences in recurrent VTE and bleeding complications over 24 months of follow-up.

## Study design

STUDY DESIGN
This is a pragmatic randomised multi-center trial in patients with a documented (first) episode of unprovoked DVT or PE. After presentation, informed consent is obtained. 5 months after the initial VTE event, patients are randomised to the index group (prediction model guided treatment of VKA, see flowchart below) or to the control group (care-as-usual, see flowchart below). The blocked randomisation will be performed within strata for centre and for type of VTE (DVT or PE).
Patients randomized to the index group that have a high risk of VTE recurrence after an initial 6 months of VKA treatment continue VKA treatment during the entire follow-up period of 24 months. A priori, we define a high risk of recurrence as > 5% in the first year or > 20% in the first five years (based on the prediction model [22] and experts* consensus [24]).
Patients randomized to the index group that (according to the prediction model) have a low risk of VTE recurrence after stopping VKA treatment (i.e. < 5% in

the first year or < 20% in the first five years) stop long-term VKA treatment after a standard initial treatment period of 6 months. After these 6 months, patients are followed-up for 24 months.
Treating physicians however can overrule this treatment decision if the risk of (major) bleeding during long-term VKA treatment is considered too high. This (usually) will be the case in patients with either one or more of the following characteristics: history of non reversible bleeding during VKA treatment, history of persistently poor anticoagulant control, chronic renal or hepatic failure, history of non cardio-embolic stroke, patient older than 75 years when diagnosed with VTE or if an informed patient wants to stop VKA treatment. Treating physicians are allowed to stop VKA treatment in these patients, even if VTE recurrence risk is high or continue treatment although the risk on recurrent VTE is low. As this is a pragmatic study aimed at improving clinical practice, such patients remain in the study and subsequently enter the follow-up period (after initial treatment of 6 months with VKA conform guidelines).
Patients randomized to the control group receive care-as-usual, according to current guidelines: usually 6 months of VKA treatment in all patients with a first episode of unprovoked VTE, sometimes longer. The decision whether or not to prescribe long-term VKA treatment is maily based on physicians* discretion. For comparison reasons, a D-dimer test will be performed after 6 months of initial VKA therapy and one month after discontinuation of VKA. To be able to confirm a recurrent VTE during follow up, a reference compression ultrasound will be performed after 6 months of treatment in both intervention arms.All patients, both controls and index, are followed-up for 24 months.

**Intervention**

Patients randomized to the index group, undergo a prediction model guided long-term treatment (see flow chart and study design). After six months of initial VKA therapy, a prediction model is applied on the day the patient is instructed to stop VKA treatment (day t=0). If the prediction model demonstrates a low risk of VTE recurrence (< 5% in the first year or < 20% at five years) at both visits (i.e. day t=0 and t=28 days), treatment stays ended. As soon as the result of the prediction model demonstrates a high risk of VTE recurrence, VKA treatment is continued or resumed for another 24 months. Treating physicians are allowed to overrule this treatment decision if patients have a high risk of bleeding during VKA treatment based on one of the following characteristics: history of non reversible bleeding during VKA treatment, history of persistently poor anticoagulant control, chronic renal or hepatic failure, history of non cardio-embolic stroke, patient older than 75 years when diagnosed with VTE, an active peptic ulcer or if an informed patient wants to stop VKA treatment.
As the D-dimer result (day 0) can be negative influenced by the VKA treatment, we choose to perform a second risk assessment in all * low risk* patients, 28 days after VKA discontinuation. As soon as one risk assessment yields an increased recurrence risk* including at day 0 (after stopping) * treatment is

immediately resumed for the follow-up period of 24 months, to rebalance the risk of recurrent VTE.
Although a very recent meta-analysis [23] proved that the timing of D-dimer testing after stopping VKA treatment does not affect the ability to distinguish patients with a higher or lower risk for recurrent VTE, we are certainly aware of the risk of recurring VTE during this period when VKA therapy is suspended. The only previous trial on this issue * as we discussed above [16] * performed a D-dimer assay only once at day 28, to determine the (dis)continuation of VKA treatment. Therefore, we will perform the first D-dimer assay at the moment of VKA withdrawal too.
After six months of VKA treatment, all patients will undergo a routine compression ultrasound (CUS). The investigators are not aware of the results of this CUS; only in case of suspected recurrence this 6-months-CUS will be used to be able to confirm the diagnosis recurrent DVT. Recanalization of the veines is assessed, resulting either in complete or non-complete recanalization.

### Study burden and risks

Study procedures:
At baseline (intake visit during VKA use), several patient characteristics will be asked to all patients (including gender, age, type of VTE event, co-morbid diseases and medication use, and known risk factors for VTE recurrence) Randomisation will be performed 5 months after the initial VTE event.
After 6 months of initial therapy, the intervention phase of the study will start. Patients randomized to the index group may undergo a maximum of 2 risk assessments, for which a maximum of 2 venapunctures for D-dimer testing will be required. For comparison reasons, patients randomized to the control group also undergo 2 venapunctures for D-dimer testing. The first blood sample will be drawn after 6 months of initial treatment (T=0); the second sample will be taken 28 days after discontinuation of VKA treatment. This test outcome has no consequences for the treatment duration; the physician is unaware of the outcome of this test as the investigators order the test. Only in case of suspected recurrence of VTE, the extent of recanalisation will be performed. At time of intake and intervention, as well as during all follow-up contacts, all patients will be asked to fill out *Quality of Life* questionnaires (using the SF36 and EuroQol questionnaires) & questions on health care use for the cost-effectiveness analyses. Furthermore the investigators will approach all patients at 3, 12 and 24 months during the follow-up phase of the study. Patients will be asked for the occurrence of recurrent VTE events.

## 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

The study population consists of consecutive patients with an unprovoked (idiopathic) VTE of the lower extremities or lungs who are referred to the Thrombosis Services for treatment with vitamin K antagonists. All patients have to be 18 years of age or older when inclusion takes place.

## Exclusion criteria

Patients with an initial indication for longer treatment with VKA (1 year or longer) * such as patients with recurrent VTE within 10 years, other indications like Atrial Fibrillation or Prosthetic heart valve. Ongoing malignancy (last treatment < 6months prior to VTE event). Only short term indication of VKA use (3 months) , conform current guidelines. This is surgery with general or spinal anaesthesia or lower limb fracture with casting within 3 months prior to diagnosis. VTE patients who are pregnant/ within first 6 weeks after labour. Physician states reason not to continue VKA therapy after 6 months of treatment (eg. bleeding risk). Participation in another trial.
Not willing or not able to give consent.

# Study design

## Design

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| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |

**Primary purpose:** Prevention

## Recruitment

NL

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 31-08-2011 |
| Enrollment: | 968 |
| Type: | Actual |

# Ethics review

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| Approved WMO Date: | 06-07-2011 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 13-02-2012 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 12-11-2013 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 26-11-2013 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |

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| Approved WMO Date: | 27-03-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 13-08-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 12-03-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 06-11-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |

# 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 |
|---|---|
| CCMO | NL34463.041.10 |
| Other | NTR TC=2680 |