Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis: multinational prospective cohort management study

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ABSTRACT

OBJECTIVE
To prospectively validate the HERDOO2 rule (Hyperpigmentation, Edema, or Redness in either leg; D-dimer level ≥250 µg/L; Obesity with body mass index ≥30; or Older age, ≥65 years), which states that women with none or one of the criteria can safely discontinue anticoagulants after short term treatment.

DESIGN
Prospective cohort management study.

SETTING
44 secondary or tertiary care centres in seven countries.

PARTICIPANTS
Of 3155 consecutive eligible participants with a first unprovoked venous thromboembolism (VTE, proximal leg deep vein thrombosis or pulmonary embolism) who completed 5-12 months of short term anticoagulant treatment, 370 declined to participate, leaving 2785 enrolled participants. 2.3% were lost to follow-up.

INTERVENTIONS
Women with none or one of the HERDOO2 criteria were classified as at low risk of recurrent VTE and discontinued anticoagulants (intervention arm), whereas anticoagulant management for high risk women (≥2 HERDOO2 criteria) and men was left to the discretion of the clinicians and patients (observation arm).

MAIN OUTCOME MEASURE
Recurrent symptomatic VTE (independently and blindly adjudicated) over one year of follow-up.

RESULTS
Of 1213 women, 631 (51.3%) were classified as low risk and 591 discontinued oral anticoagulant treatment. In the primary analysis, 17 low risk women who discontinued anticoagulants developed recurrent VTE during 564 patient years of follow-up (3.0% per patient year, 95% confidence interval 1.8% to 4.8%). In 323 high risk women and men who discontinued anticoagulants, 25 had VTE during 309 patient years of follow-up (8.1%, 5.2% to 11.9%), whereas in 1802 high risk women and men who continued anticoagulants 28 had recurrent VTE during 1758 patient years of follow-up (1.6%, 1.1% to 2.3%).

CONCLUSIONS
Women with a first unprovoked VTE event and none or one of the HERDOO2 criteria have a low risk of recurrent VTE and can safely discontinue anticoagulants after completing short term treatment.

TRIAL REGISTRATION
clinicaltrials.gov NCT00967304.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Current practice guidelines suggest that all patients with unprovoked venous thromboembolism (VTE) should continue anticoagulants long term unless they have a high risk of bleeding

Most patients with unprovoked VTE will not, however, develop recurrent VTE

To date, no single predictor or combination of predictors (clinical decision rule) has been developed and validated to identify a group of patients with unprovoked VTE at sufficiently low risk of recurrent VTE to safely discontinue anticoagulants

WHAT THIS STUDY ADDS

In the primary analysis, 17 women identified as having a low risk of recurrent VTE using the HERDOO2 rule who discontinued anticoagulants developed recurrent VTE during 564 patient years of follow-up (3.0% per patient year, 95% confidence interval 1.8% to 4.8%)

Using the HERDOO2 clinical decision rule allows clinicians to identify a large group of low risk group of women with unprovoked VTE who can safely discontinue anticoagulants

Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis and pulmonary embolism, is a common, potentially fatal yet treatable condition. After short term oral anticoagulant treatment, the risk of recurrent VTE after discontinuing anticoagulants is variable, depending on the presence or absence of provoking factors at the time of the initial event. Some patient subgroups with major provoking factors (eg, post-surgical VTE) have a low risk of recurrent VTE (1% at one year)[1] and anticoagulants can be safely discontinued after short term treatment.[2] However, more than 50% of patients with VTE do not have a major provoking factor.[3] In these patients with unprovoked VTE, the risk of recurrent VTE is substantially higher; up to 10% in the first year after stopping short term treatment, 5% in the subsequent year,[4] and 30% at eight years.[5] Recurrent VTE is fatal in 3.6% of cases.[6]

Oral anticoagulant treatment is effective at reducing the risk of recurrent VTE during treatment; oral anticoagulant treatment reduces the risk of recurrent VTE by 80-90%.[7] Longer term oral anticoagulant treatment likely only delays recurrent VTE compared with short term treatment.[8-10] The highest bleeding risks are observed during initial oral treatment. Patients who do not bleed during this time, termed "anticoagulant experienced" patients, are at lower risk of major bleeding

with ongoing treatment (1.3% per year).[7] Major bleeding is fatal in 11.3% of affected patients.[6]

Guidelines recommend long term anticoagulant treatment in patients with unprovoked VTE with non-high bleeding risks, but this is based on weak evidence (grade 2B)[11] owing to closely balanced competing risks and burdens of recurrent VTE and major bleeding. Hence, the clinical question of who should continue taking anticoagulants indefinitely and who can safely discontinue them after short term treatment for unprovoked VTE remains a high research priority.[9 10] To answer this important question, the long term risks and burdens of recurrent VTE must be balanced against the long term risks and burdens of oral anticoagulant treatment, especially major bleeding. The International Society on Thrombosis and Haemostasis suggests that it is safe to discontinue anticoagulants if the risk of recurrent VTE is less than 5% at one year after discontinuing treatment.[12] To date, no clinical decision rules [13-15] designed to achieve these standards have been prospectively validated.

We previously derived a clinical decision rule to identify patients at low risk of recurrent VTE who could discontinue anticoagulants.[15] The clinical decision rule, HERDOO2, identifies women with one or fewer of the four following criteria as being at low risk of recurrent VTE: Hyperpigmentation, Edema, or Redness in either leg; D-dimer level ≥250 µg/L during treatment with anticoagulants; Obesity with body mass index ≥30; and Older age, ≥65 years (fig 1).[15] No subgroup of men could be identified as low risk for recurrent VTE. Before adopting a clinical decision rule in clinical practice it should be prospectively validated in multiple clinical settings.[17] As such, we validated the HERDOO2 clinical decision rule in a multinational prospective cohort management study.

Methods

Study design

We conducted a prospective multinational cohort management study of patients with a first unprovoked VTE event who were included after 5-12 months of anticoagulant treatment. Women were classified as low risk if they had none or one of the four HERDOO2 criteria (fig 1). Women who met two or more criteria and all men were classified as high risk. Per protocol, low risk patients were to discontinue anticoagulants (intervention arm), whereas anticoagulant management in high risk patients was left to the discretion of the clinicians and patients (observation arm). Participants were then followed for one year for recurrent VTE and major bleeding. All patients provided written informed consent before participation.

Study participants and setting

Consecutive unselected patients at 44 secondary and tertiary care centres in seven countries (see supplementary appendix) were asked to participate if they had a first episode of major, symptomatic, objectively proved unprovoked VTE 5-12 months before enrolment (referred to as the index VTE). Index VTE was defined as unprovoked, in line with other studies,[18-20] in the absence of the following major VTE provoking factors: leg fracture or lower extremity plaster cast, immobilisation for more than three days, major surgery in the three months before the index VTE event, and no diagnosis of a malignancy in the past five years (with the exception of localised skin malignancy). Patients with malignancy arising after diagnosis of index VTE but before enrolment were not eligible for inclusion. Patients with previous episodes of provoked VTE were eligible. Index VTE associated with minor or weak risk factors such as travel, exogenous oestrogen, minor immobilisation, or minor surgery was considered unprovoked as it is unclear if the risk of recurrence in "weakly provoked" VTE is low enough to discontinue anticoagulants.[12] Objective confirmation of index major VTE comprised either deep vein thrombosis demonstrated with a non-compressible segment in the popliteal vein or more proximal leg veins on compression venous ultrasonography and/or pulmonary embolism demonstrated on a high probability perfusion scan[21] or a segmental or more proximal pulmonary artery filling defect on computed tomography (CT) pulmonary angiography. Index VTE had to have been managed for 5-12 months with an appropriate anticoagulant treatment, including initial treatment with either unfractionated heparin, low molecular weight heparin, rivaroxaban, or apixaban,

HER: any Hyperpigmentation, Edema, or Redness in either leg (ie, mild, moderate, or severe).
Assign 1 point for HER (ie, see visual guide below)   1 point
VIDAS D-dimer ≥250 µg/L   1 point
Obesity (body mass index ≥30)   1 point
Older age (≥65 years)   1 point

                                                                    TOTAL=

                                                                    Low risk: 0 or 1 point
                                                                    High risk: ≥2 points

Visual guide:
Note: Signs may be less apparent in patients with brown or black skin

Hyperpigmentation

None | Faint, speckled brownish discolouration around ankle | Obvious brownish discolouration around ankle and lower shin | Patches of dark, confluent, brownish discolouration around ankle and lower shin

Edema

No loss of bony landmarks; no pitting with pressure over ankle or shin | Minimal loss of bony landmarks; shallow pitting with pressure over ankle or shin | Noticeable swelling and loss of bony landmarks; moderate pitting with pressure over ankle or shin | Severe swelling and loss of bony landmarks; deep pitting with pressure over ankle or shin

Redness

Normal colour of leg | Faint redness of foot or lower leg | Moderate redness of foot or lower leg | Pronounced redness or purplish colour of foot and lower leg

Fig 1 | HERDOO2 score to identify women with unprovoked venous thrombosis (VTE) at low risk of recurrent venous thrombosis. Visual guide adapted from Kahn et al[16]

followed by 5-12 months of oral anticoagulant treatment with vitamin K antagonists (target international normalised ratio 2-3), dabigatran, rivaroxaban, apixaban, or edoxaban.

Patients were excluded if they were unable or unwilling to provide informed consent; were aged less than 18 years; had already discontinued oral anticoagulant treatment; required ongoing anticoagulation (eg, mechanical heart valves, atrial fibrillation, inferior vena cava filter, or had known high risk thrombophilia before enrolment. High risk thrombophilia included deficiency of protein S, protein C, or antithrombin, persistently positive antiphospholipid antibodies, or two or more known other thrombophilic defects (eg, homozygous for factor V Leiden mutation or prothrombin gene mutation, or compound heterozygous for factor V Leiden and prothrombin gene mutation)); were geographically inaccessible for follow-up; had planned to use exogenous oestrogen (patch, ring, oral contraceptive, or hormone replacement therapy) if anticoagulant treatment was discontinued; or had pregnancy associated index VTE (antepartum or postpartum (within 12 weeks of delivery)).

Standardised baseline patient assessment
The baseline assessment took place 5-12 months after the index VTE event, while patients were still receiving oral anticoagulant treatment. We documented demographic data, causes, and diagnostic or therapeutic management of the index VTE event. In women, body mass index was calculated and both legs were examined for hyperpigmentation, oedema, or redness. D-Dimer samples were drawn during anticoagulant treatment at the baseline assessment (at any time if the patient was using vitamin K antagonists or at the time of peak anticoagulant effect for the other oral anticoagulants (dabigatran 4-8 hours, apixaban 2-6 hours, rivaroxaban 2-6 hours, and edoxaban 2-6 hours)). Within one hour of collection, plasma samples were double centrifuged at 2500×g for 20 minutes and D-dimer testing was performed immediately. If testing was not available locally, samples were immediately frozen at −70ºC and transported on dry ice. D-dimer was measured using VIDAS D-dimer reagent on the VIDAS Instrument (bioMérieux, Marcy L'Etoile, France).

We then applied the HERDOO2 clinical decision rule. Per protocol, low risk women were to discontinue oral anticoagulant treatment, whereas continuation of anticoagulation in men and high risk women was left to the discretion of the clinicians and patients.

We also obtained baseline results for bilateral leg compression ultrasonography and either a ventilation-perfusion scan or perfusion only scan or CT pulmonary angiography. Baseline imaging was conducted to assist in the diagnosis of subsequent suspected recurrent VTE in patients who discontinued anticoagulants.

Follow-up and outcome assessment
Patients were contacted by telephone or seen in person at six months (two weeks either way). High risk patients were also telephoned or seen in person at one year (two

weeks either way), whereas all low risk patients were seen in person at one year (two weeks either way). A structured interview for suspected VTE or bleeding was conducted at these visits. We also recorded the use of oral anticoagulant treatment. In addition to these visits, patients were instructed to contact study staff if they developed symptoms of recurrent VTE or bleeding at any time during follow-up. Participants were withdrawn and censored at the time they withdrew consent and did not permit the collection of further follow-up data, were lost to follow-up, or died.

Outcomes
The primary outcome was adjudicated symptomatic major VTE (new popliteal vein or more proximal deep vein thrombosis and/or new pulmonary embolism in at least a segmental or more proximal pulmonary artery). Secondary outcomes included major bleeding and mortality.

Two physicians independently adjudicated all available information about patients who died or were suspected of having an outcome (adjudicators were not from the same institution as the study participant). Adjudicators were blinded to the result of the clinical decision rule assessment and to the presence or absence of anticoagulant treatment. The criteria used for the diagnosis of recurrent deep vein thrombosis and pulmonary embolism were as previously published[15] but in brief required documentation of new proximal deep vein thrombosis and/or segmental pulmonary embolism compared with baseline imaging (or index VTE imaging if baseline imaging was not available).[22] Deaths were adjudicated and categorised as due to pulmonary embolism (certain, highly probable, possible, or unlikely), bleeding, or other. Major bleeds were defined as clinically overt bleeding associated with death or a decrease in haemoglobin concentration of more than 20 g/L or transfusion of two or more units of whole blood or red blood cells or bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome).[23]

Statistical analysis
We sought a sample size sufficient to ensure that the risk of recurrent major VTE in low risk patients was at most 3% at one year (ie, upper bound of the confidence interval of the estimate of recurrent VTE at one year was <3%). To achieve this standard, at 80% power, with an anticipated rate of recurrent VTE of 1.8% at one year in low risk patients, we estimated we would require 828 low risk patients who discontinued anticoagulants (including a 9% inflation for censored patients). After beginning enrolment in our study, the International Society on Thrombosis and Haemostasis suggested that a recurrent VTE risk threshold of less than 5% at one year with an upper bound of the 95% confidence interval at 8% would be required to prove that patients with VTE could safely discontinue anticoagulants.[12] In light of this more liberal threshold, the steering committee approved a revised sample size of 600 low risk patients

who discontinued anticoagulants to more than adequately power the study to meet these recommended requirements.

In our a priori defined primary analysis, we determined the incidence of recurrent "major VTE" per patient year of follow-up in classifiable low risk patients who discontinued anticoagulants, and the exact binomial 95% confidence interval around this rate. In a priori planned analyses of secondary outcomes, we explored the rate of major bleeding, death due to pulmonary embolism, and total mortality. In a priori planned subgroup analyses, we also explored the risk of recurrent major VTE and major bleeding in classifiable high risk patients who continued anticoagulants and in high risk patients who discontinued anticoagulants. Only complete case analysis was conducted (ie, only classifiable patients were analysed). All analyses were conducted with SAS V 9.3 software (SAS institute, Cary, NC).

Patient involvement
Patient partners were not involved in the design or conduct of this study that began in 2008. Patient partners in the CanVECTOR network (www.canvector.ca) will be involved in dissemination/knowledge translation activities.

Results
Between November 2008 and February 2015, we approached 3155 eligible participants, of whom 370 declined to participate, leaving 2785 enrolled participants in 44 centres in seven countries (fig 2). Of these, 2779 were classifiable with the HERDOO2 clinical decision rule and six were not (D-dimer result

unavailable). Thirty two patients had no follow-up, leaving 2747 analysed patients with a mean age of 54.4 (SD 16.7 years), 44.3% were female, and 83.7% were white (table 1). In addition to the 32 patients with no follow-up, 31 patients had incomplete follow-up (63/2779 (2.3% lost to follow-up)). Index first unprovoked VTEs were isolated deep vein thrombosis (40.5%), isolated pulmonary embolism (38.9%), and deep vein thrombosis and pulmonary embolism (20.6%). Of 1213 women, 622 (51.3%) were classified as low risk with the clinical decision rule and, of these, 591 discontinued anticoagulants and 31 continued treatment. Of 2125 high risk patients (1534 men and 591 high risk women), 1802 (84.8%) continued anticoagulants and 323 (15.2%) discontinued treatment (fig 2).

Primary endpoint
Seventy participants had recurrent major VTE, with one death from pulmonary embolism (case fatality rate 1.4%, 95% confidence interval 0.3% to 7.7%). Of the 591 low risk women who discontinued anticoagulants, 17 developed recurrent major VTE during 564 patient years of follow-up (3.0% recurrent VTE per patient year, 95% confidence interval 1.8% to 4.8%) (table 2). A low risk patient, in retrospect, noted to have persistent unexplained thrombocytosis from the time of index VTE, was subsequently confirmed to have JAK-2 positive essential thrombocytosis at the time of VTE recurrence without anticoagulant treatment.

One additional low risk woman developed cerebral vein thrombosis during one year follow-up without anticoagulant treatment (not in a priori defined primary outcome). In a post hoc sensitivity analysis, including
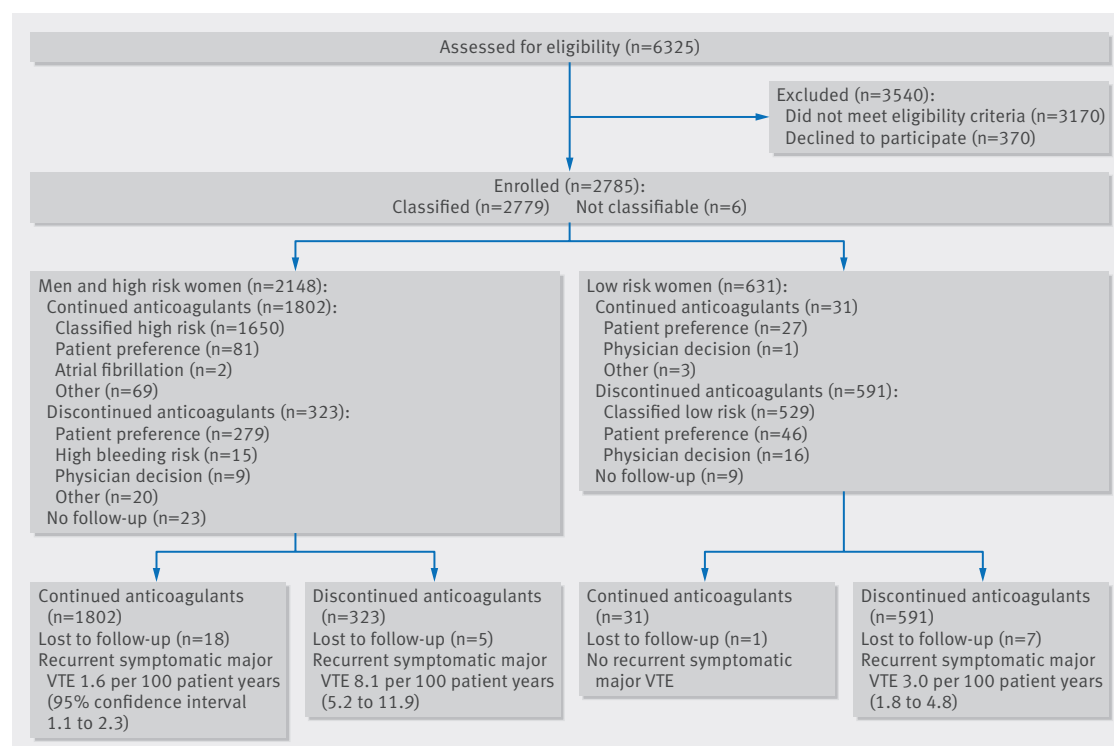

Fig 2 | Participant flow. VTE=venous thromboembolism

Table 1 | Baseline characteristics of study participants and subgroups. Values are numbers affected/Total No in sample (percentage) unless stated otherwise

Characteristics	Whole population (n=2747)	Men (n=1534)	High risk women (n=591)	Low risk women (n=622)
Mean (SD) age (years)	54.4 (16.7)	55.5 (14.4)	65.5 (15.6)	41.3 (14.2)
Mean (SD) body mass index	29.1 (6.8)	28.5 (5.7)	32.5 (8.1)	27.6 (6.9)
White ethnicity (n=2287)	2287/2734 (83.7)	1217/1527 (79.7)	543/589 (92.2)	527/618 (85.3)
Type of index VTE:				
Isolated DVT (n=1113)	1113/2747 (40.5)	716/1534 (46.7)	218/591 (36.9)	179/622 (28.8)
Isolated PE (n=1068)	1068/2747 (38.9)	483/1534 (31.5)	242/591 (40.6)	343/622 (55.1)
DVT and PE (n=566)	566/2747 (20.6)	335/1534 (21.9)	131/591 (22.2)	100/622 (16.1)
Known thrombophilia:				
Factor V Leiden (n=204)	204/2747 (7.4)	108/1534 (7.0)	33/591 (5.6)	63/622 (10.3)
Prothrombin gene variant (n=75)	75/2747 (2.7)	31/1534 (2.0)	18/591 (3.1)	26/622 (4.2)
Exogenous oestrogen (n=397)	397/2747 (14.4)	0	74/591 (12.5)	323/622 (51.9)
HERDOO2 criteria				
Hyperpigmentation, oedema, or redness of either leg at 5-12 months (n=295):	-*	-*	259/591 (43.8)	36/622 (5.8)
North America	-*	-*	188/365 (51.5)	23/342 (6.7)
Europe	-*	-*	68/205 (33.2)	9/229 (3.9)
India	-*	-*	3/20 (15.0)	4/48 (8.3)
Australia	-*	-*	0/1 (0)	0/3 (0)
D-dimer ≥250 µg/L (n=1325):	1325/2708 48.9)	721/1507 (47.8)	496/588 (84.4)	108/613 (17.6)
North America	669/1514 (44.2)	333/813 (41.0)	297/363 (81.8)	39/338 (11.5)
Europe	398/886 (44.9)	182/458 (39.7)	179/204 (87.8)	37/224 (16.5)
India	257/300 (85.7)	205/232 (88.4)	20/20 (100)	32/48 (66.7)
Australia	1/8 (12.5)	1/4 (25.0)	0/1 (0)	0/3 (0)
Older age, ≥65 years (n=837):	837/2747 (30.5)	447/1534 (29.1)	367/591 (62.1)	23/622 (3.7)
North America	446/1532 (29.1)	242/825 (29.3)	194/365 (53.2)	10/342 (2.9)
Europe	344/907 (37.9)	166/473 (35.1)	165/205 (80.5)	13/229 (5.7)
India	45/300 (15.0)	38/232 (16.4)	7/20 (35)	0/48 (0)
Australia	2/8 (25.0)	1/4 (25.0)	1/1 (100)	0/3 (0)
Obesity (body mass index ≥30) (n=1021):	1021/2747 (37.2)	500/1534 (32.6)	370/591 (62.6)	151/622 (24.3)
North America	721/1532 (47.1)	364/825 (44.1)	251/365 (68.8)	106/342 (31.0)
Europe	272/907 (30.0)	122/473 (25.8)	106/205 (51.7)	44/229 (19.2)
India	26/300 (8.7)	13/232 (5.6)	12/20 (60.0)	1/48 (2.1)
Australia	2/8 (25.0)	1/4 (25.0)	1/1 (100)	0/3 (0)
Anticoagulant at baseline or enrolment visit:				
Vitamin K antagonists (n=2050)	2050/2747 (74.6)	1140/1534 (74.3)	431/591 (72.9)	479/622 (77.0)
Rivaroxaban (n=476)	476/2747 (17.3)	279/1534 (18.2)	104/591 (17.6)	93/622 (15.0)
Other (n=221)	221/2747 (8.1)	115/1534 (7.5)	56/591 (9.5)	50/622 (8.0)
Anticoagulants after baseline or enrolment visit:				
Continued (n=1833)	1833/2747 (66.7)	1312/1534 (85.5)	490/591 (82.9)	31/622 (5.0)
Discontinued (n=914)	914/2747 (33.3)	222/1534 (14.5)	101/591 (17.1)	591/622 (95)

VTE=venous thromboembolism; DVT=deep vein thrombosis; PE=pulmonary embolism.
*Hyperpigmentation, oedema, or redness in either leg not collected in men.

Table 2 | Primary and secondary outcome analysis by risk category and whether anticoagulants were continued or discontinued in events (%) per 100 patient years (95% confidence intervals)

| Groups | Low risk women* who discontinued oral anticoagulants (n=591) | Men and high risk women* | | High risk* women who discontinued oral anticoagulants (n=101) |
		Discontinued oral anticoagulants (n=323)	Continued oral anticoagulants (n=1802)	
Primary outcome:				
Risk of recurrent major† VTE	3.0 (1.8 to 4.8)	8.1 (5.2 to 11.9)	1.6 (1.1 to 2.3)	7.4 (3.0 to 15.2)
Secondary outcomes:				
Risk of major‡ bleed	0.2 (0 to 1.0)	0.6 (0 to 2.3)	1.2 (0.8 to 1.8)	2.1 (0.3 to 7.6)
Recurrent PE death	0	0	0.1 (0 to 0.3)	0
Non-PE death	0.2 (0 to 1.0)	0.1.0 (0.2 to 2.8)	0.4 (0.2 to 0.8)	2.1 (0.3 to 7.6)

VTE=venous thromboembolism; PE=pulmonary embolism.
Not shown are results in low risk women who continued anticoagulants (n=31), patients with no follow-up (n=32), or not classifiable owing to missing D-dimer result (n=6).
*HERDOO2 criteria: hyperpigmentation, oedema, or redness in either leg at 5-12 months at baseline or enrolment visit, VIDAS D-dimer ≥250 µg/L during anticoagulant treatment, obesity with body mass index ≥30, or older age, ≥65 years. Low risk=0 or 1 of the criteria present; high risk=≥2 or the criteria present.
†Proximal deep vein thrombosis and segmental or greater PE.
‡According to definition by International Society on Thrombosis and Haemostasis.[23]

cerebral vein thrombosis in a modified primary outcome, the risk of recurrent VTE in low risk women would have been 3.2% (95% confidence interval 2.0% to 5.0%). In a second post hoc "worst case scenario" sensitivity analysis, assuming all low risk patients who discontinued anticoagulants who were lost to follow-up (n=16) developed recurrent VTE and including cerebral vein thrombosis in a modified primary outcome, the risk of recurrent VTE in low risk women would have been 5.7% (4.1% to 7.8%).

In 323 high risk patients who discontinued anticoagulants, 25 recurrent VTE events occurred during 309 patient years of follow-up (8.1% recurrent VTE per patient year, 95% confidence interval 5.2% to 11.9%). The risk of recurrent major VTE in high risk women who discontinued anticoagulants (7.4% 3.0% to 15.3%) was comparable with men who discontinued anticoagulants (8.4%, 5.0% to 13.2%). Twenty eight high risk patients who continued anticoagulants had recurrent VTE during 1758 patient years of follow-up (1.6% recurrent VTE per patient year, 95% confidence interval 1.1% to 2.3%) (see table 2).

Bleeding events
Twenty two major bleeds occurred during 1788 person years of follow-up in patients who continued anticoagulants (1.2% major bleeds per patient year, 95% confidence interval 0.8% to 1.9%) compared with three major bleeds during 874 years of follow-up in patients who discontinued anticoagulants (0.3% major bleeds per patient year, 0.1% to 1.0%). Two major bleeds resulted in death (major bleed case fatality rate was 8.0%, 95% confidence interval 2.2% to 25.0%).

Subgroup analyses
Of 429 low risk women of premenopausal age (<50 years) who discontinued anticoagulants, the risk of recurrent VTE was low regardless of whether their index VTE was associated with oestrogen (n=291) (1.4% per patient year, 95% confidence interval 0.4% to 3.7%) or not associated with oestrogen (n=138) (3.1% per patient year, 0.8% to 7.9%) (table 3). In contrast, the risk of

recurrent VTE was 5.7% per patient year (95% confidence interval 2.6% to 10.9%) in low risk women of postmenopausal age (≥50 years) who discontinued anticoagulants (n=162).

In additional subgroup analyses, there were no differences in the rate of recurrent VTE over one year follow-up in low risk women who discontinued anticoagulants according to 1) country or region of enrolment, 2) type of index VTE (isolated deep vein thrombosis, isolated

Table 3 | Subgroup analysis with primary outcome in risk group by continued or discontinued anticoagulants in events (%) per 100 patient years (95% confidence intervals)

Groups	Low risk women* who discontinued oral anticoagulants (n=591)
Age <50 (n=429):	2.0 (0.8 to 3.9)
Oestrogen (n=291)	1.4 (0.4 to 3.7)
No oestrogen (n=138)	3.1 (0.8 to 7.9)
Age ≥50 (n=162):	5.7 (2.6 to 10.9)
Oestrogen (n=24)	0
No oestrogen (n=138)	6.8 (3.1 to 12.8)
Type of index VTE:	
Isolated DVT (n=177)	3.0 (1.0 to 7.0)
Isolated PE (n=323)	3.9 (2.0 to 6.8)
DVT and PE (n=91)	0
Country or region:	
North America (n=334)	3.7 (1.9 to 6.6)
Europe (n=207)	2.5 (0.1 to 5.9)
India (n=47)	0
Australia (n=3)	0
Anticoagulant at baseline or enrolment visit:	
Vitamin K antagonist (n=459)	2.9 (1.6 to 5.0)
All non-vitamin K antagonists (n=132)	3.2 (0.9 to 8.3)
Known "weak" thrombophilia:	
Factor V Leiden (n=59)	3.5 (0.4 to 12.6)
Prothrombin gene variant (n=26)	3.9 (0.1 to 21.6)

VTE=venous thromboembolism; CVT=deep vein thrombosis; PE=pulmonary embolism.
*HERDOO2 criteria: hyperpigmentation, oedema, or redness in either leg at 5-12 months at baseline or enrolment visit, VIDAS D-dimer ≥250 µg/L during anticoagulant treatment, obesity with body mass index ≥30, or older age, ≥65 years. Low risk=0 or 1 of the criteria present.

pulmonary embolism, deep vein thrombosis and pulmonary embolism), or 3) type of anticoagulant treatment at the time of baseline visit (table 3).

Discussion

We prospectively validated a clinical decision rule to identify low risk patients who can safely discontinue anticoagulants after completing 5-12 months of treatment for a first unprovoked VTE. Women with none or one of the HERDOO2 criteria had a low risk of recurrent VTE and can safely discontinue anticoagulants after completing short term treatment. This is an important finding because using our rule over half of women with unprovoked VTE can safely discontinue anticoagulants and be spared the burdens, costs, and risks of indefinite anticoagulation.

The question of duration of anticoagulation for the prevention of recurrent VTE after a first unprovoked event is controversial.[24] Updated consensus guidelines suggest anticoagulants should be continued indefinitely in patients with unprovoked VTE with a non-high bleeding risk.[11 25] We have shown that half of women with unprovoked VTE, regardless of bleeding risk, can safely discontinue anticoagulants. The International Society on Thrombosis and Haemostasis suggests that it is appropriate to stop anticoagulants in subgroups with a point estimate of recurrent VTE at one year below 5% if the upper bound of the 95% confidence interval is less than 8%.[12] In our study, we have shown that the one year recurrent VTE point estimate and the upper bound of the 95% confidence interval in low risk women with one or none of the HERDOO2 criteria are both less than 5%.

Several individual predictors that seem to stratify the risk of recurrent VTE in patients with unprovoked index VTE have been identified, including sex, plasma D-dimer levels measured 1-2 months after discontinuation of oral anticoagulant treatment,[26] and residual venous obstruction using venous ultrasonography.[27 28] None of these individual predictors appears to adequately identify a subgroup of patients with unprovoked VTE with a sufficiently low risk of recurrence to safely discontinue anticoagulants. Other multivariable clinical decision rules have been developed but have not been prospectively validated, including the Vienna prediction model[13] and the DASH score.[14]

Whether men and high risk women require indefinite anticoagulation remains controversial and was not the primary focus of our study. However, future research to identify additional low risk subgroups who may be able to also discontinue anticoagulants, will be important given that a large proportion of "high risk" patients will not develop recurrent VTE during non-use of oral anticoagulants. For example, in our long term follow-up study of the derivation group for our clinical decision rule, the risk of VTE in men and high risk women during eight years' follow-up was less than 40% (ie, >60% did not recur in the long term).[5]

Strengths and limitations of this study

Strengths of this study include the homogenous patient population (we only included symptomatic major VTE and excluded distal deep vein thrombosis and subsegmental pulmonary embolism) treated uniformly with short duration anticoagulant treatment (5-12 months). We applied our clinical decision rule prospectively in patients in whom the clinical decision is uncertain (patients with weakly provoked and unprovoked VTE) and at the time point that clinicians generally use to assist patients in making this decision about long term treatment. The large sample size of the study permitted precise estimates of recurrence in low risk patients. Most low risk patients stopped anticoagulants (95%) as planned, suggesting the rule was acceptable to clinicians and patients. Our rule, consisting of a limited number of simple elements previously shown to have high interobserver reliability,[29] was applied by a wide variety of clinicians in a wide variety of settings in multiple countries, and performed well. We had minimal loss to follow-up (2.3%). All of our outcomes were symptomatic, objectively documented, and independently adjudicated compared with baseline imaging without knowledge of clinical decision rule classification or oral anticoagulant treatment. We included patients whose VTE was treated with vitamin K antagonists and direct oral anticoagulants, providing reassurance that our rule can be used with all contemporary treatment management strategies. We are optimistic that low risk women (none or one of the HERDOO2 criteria) will continue to be low risk in longer term follow-up as we showed in our derivation study.[5] It is likely that low risk women will have a low risk of recurrent VTE over longer term follow-up because patients with unprovoked VTE have a lower risk of recurrent VTE in the years that follow the first year without anticoagulants.[5] None the less, longer term follow-up of low risk women (none or one of the HERDOO2 criteria) should be the object of future research. Finally, study characteristics, participant characteristics, and outcomes were comparable between our derivation study population and validation study population (table 4).

Our work also has limitations. Firstly, in our derivation study we chose to explore all known potential predictors of recurrent VTE and we used complete case analysis rather than imputation of missing data in model building. We also chose to dichotomise our potential predictors at optimal cut points, minimise the final number of predictors, and use a simple scoring system to make the rule easy to use and more likely to be adopted in practice. However, by modeling with a dataset that contained a low event per predictor variable ratio, not imputing missing data, dichotomising variables at optimal cut points, and not using the exact or representative predictor variable weightings, we potentially derived a less powerful model and one that risked being over-fit. However, by validating our simple model in the current study we have shown that the HERDOO2 rule was not over-fit. Secondly, patients with known "high risk" thrombophilia were excluded hence our findings may not apply to these patients. Thirdly, we used a single

Table 4 | Comparison of study characteristics, participant characteristics, HERDOO2 predictor variable distribution, and primary outcome event rates in HERDOO2 derivation study and current HERDOO2 validation study. Values are numbers affected/Total numbers in sample (percentage) unless stated otherwise

Variables	Derivation study (n=646)	Validation study (n=2747)
Study characteristics		
Study design	Prospective cohort	Prospective cohort
Timeline	2001-06	2008-15
Setting	12 tertiary centres in four countries	44 secondary and tertiary centres in seven countries
Inclusion criteria	First objectively proved; unprovoked* major VTE† treated with anticoagulants for 5-7 months	First objectively proved; unprovoked* major VTE† treated with anticoagulants for 5-12 months
Exclusion criteria	Recurrent VTE during treatment; discontinued anticoagulants; require ongoing anticoagulants; known "high risk" thrombophilia	Recurrent VTE during treatment; discontinued anticoagulants; require ongoing anticoagulants; known "high risk" thrombophilia; plan on using exogenous oestrogen after stopping anticoagulants; pregnancy associated index VTE event
Primary outcome	Blind independent adjudicated recurrent major VTE† compared with baseline imaging	Blind independent adjudicated recurrent major VTE† compared with baseline imaging
Anticoagulation treatment after enrolment	Stopped in all participants	Low risk women (0 or 1 HERDOO2 criteria): anticoagulants stopped per protocol High risk women and men (≥2 HERDOO2 criteria): anticoagulant decision left to clinicians and patients (ie, observation only) (84.8% continued anticoagulants)
Mean follow-up (months)	18.0	11.6
Participant characteristics		
Men	332/646 (51.4)	1534/2747 (55.8)
Mean age (years)	52.5	54.4
White	597/646 (92.4)	2287/2734 (83.7)
Women with oestrogen associated index VTE	73/322 (22.6)	397/1213 (32.7)
Index VTE type:		
Isolated DVT	339/646 (52.5)	1113/2747 (40.5)
Isolated PE	194/646 (30.0)	1068/2747 (38.9)
DVT and PE	113/646 (17.5)	566/2747 (20.6)
HERDOO2 predictors in female participants at baseline examination:		
Hyperpigmentation, oedema, or redness in either leg	96/260 (36.9)	295/1213 (24.3)
D-dimer ≥250 µg/L during anticoagulant use	121/304 (39.8)	604/1201 (50.3)
Older age, ≥65 years	87/314 (27.7)	390/1213 (32.2)
Obesity with BMI ≥30	114/313 (36.4)	521/1213 (43.0)
HERDOO2 criteria present:		
0 or 1	164/314 (52.2)	622/1213 (51.3)
≥2	150/314 (47.8)	591/1213 (48.7)
Primary outcome event rates (recurrent major VTE (%) per 100 patient years (95% CI) (No affected)):		
All	9.3 (7.7 to 11.3)	2.6 (2.1 to 3.3)
Men:		
Discontinue anticoagulants	13.7 (10.8 to 17.0) (n=332)	8.4 (5.0 to 13.2) (n=222)
Continue anticoagulants	- (n=0)	1.2 (0.7 to 2.0) (n=1312)
High risk women (≥2 HERDOO2 criteria):		
Discontinue anticoagulants	14.1 (10.9 to 17.3) (n=150)	7.4 (3.0 to 15.3) (n=101)
Continue anticoagulants	- (n=0)	2.5 (1.3 to 4.4) (n=490)
Low risk women (0 or 1 of the HERDOO2 criteria):		
Discontinue anticoagulants	1.6 (0.3 to 4.6) (n=164)	3.0 (1.8 to 4.8) (n=591)
Continue anticoagulants	- (n=0)	0.0 (0.0 to 12.3) (n=31)

VTE=venous thromboembolism; DVT=deep vein thrombosis; PE=pulmonary embolism; BMI=body mass index.
*Absence of leg fracture or leg cast or major surgery in past three months, and no malignancy in past five years.
†Proximal DVT and/or segmental or greater PE.

D-dimer reagent and instrument (VIDAS D-dimer, bioMérieux, Marcy L'Etoile, France) at half of the usual cut point for D-Dimer testing that is used in diagnostic management. It is uncertain if other D-dimer assays can be used in our clinical decision rule. Fourthly, some subgroups require further elaboration. In women of premenopausal age (<50 years) with none or one of the HERDOO2 criteria who discontinued anticoagulants, the risk of recurrent VTE was low (<5% at one year) regardless of whether or not these women were using exogenous oestrogen at the time of their index VTE event (table 3). These results are consistent with previous studies, which suggest that women with oestrogen associated VTE have a comparable risk of recurrent VTE to age matched women with non-oestrogen associated VTE, suggesting that oestrogen is not an important independent predictor of recurrent VTE in otherwise unprovoked VTE.[30 31] Furthermore, we have previously shown that women with oestrogen associated VTE with a low HERDOO2 score had an eightfold lower risk of recurrent VTE than women with oestrogen associated VTE

and a high HERDOO2 score, highlighting the value of using HERDOO2 for risk stratification in women with oestrogen associated VTE.[30] In contrast, in the subgroup of women of postmenopausal age (≥50 years) with none or one of the HERDOO2 criteria who discontinued anticoagulants, the risk of recurrent VTE was higher than expected (point estimate 5.7%). As such, further validation of HERDOO2 is required in the subset of postmenopausal women. Finally, we had a limited number of non-white participants and as such our clinical decision rule should be further validated in other populations.

Conclusion

Women with none or one of the four HERDOO2 criteria: hyperpigmentation, oedema, or redness in either leg, D-dimer level ≥250 µg/L while using anticoagulants, obesity with body mass index ≥30, or older age, ≥65 years) have a low risk of recurrent VTE and can safely discontinue anticoagulants after completing short term anticoagulants after a first unprovoked VTE event. Further research is required to firmly establish the safety of using HERDOO2 to identify low risk non-white women and women aged more than 50 years.

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Supplementary information: Details of the REVERSE II Study Investigators