D-DIMER FOR GUIDING DURATION OF ANTICOAGULATION IN UNPROVOKED VENOUS THROMBOEMBOLISM (VTE)

The HERDOO2 clinical decision rule

KEY POINTS

- Clinicians currently lack guidance on the optimal duration of oral anticoagulant therapy in patients with unprovoked VTE.
- Men with unprovoked VTE are at high risk of recurrence.
- A simple clinical decision rule (HERDOO2) based on D-dimer, clinical and demographic predictors aids in risk stratification of women with unprovoked VTE.
- Using the HERDOO2 rule clinicians can safely discontinue anticoagulants in half of women with unprovoked VTE who will be spared the burdens, costs and risks of indefinite anticoagulation.

Duration of oral anticoagulant therapy (OAT) in VTE

Decisions on the duration of OAT are guided by the risk of recurrent VTE after OAT discontinuation, the risk of major bleeding when on OAT as well as the case-fatality rates of both events which is 3-fold higher for major bleeding than for recurrent VTE [1].

The International Society on Thrombosis and Haemostasis (ISTH) recommends that it is justified to stop anticoagulants if the recurrence rate is no more than 5% at 1 year [2]. The risk of VTE recurrence after stopping OAT is not the same in all VTE patients and depends on its etiology; i.e. the presence or absence of precipitating (or provoking) risk factors [3].

Up to 50% of patients with a first VTE are classified as unprovoked because of lack of a provoking cause [1]. However, due to the intermediate recurrence risk in such patients the risk of fatal VTE after stopping therapy is about equal to the risk of fatal bleeding if therapy is continued.

Because of the balanced risks of fatal VTE and fatal bleeding in patients with unprovoked VTE, clinicians do not have clear guidance on whether to continue or discontinue anticoagulants [1].

VTE etiology and duration of OAT: balancing case-fatality rates of recurrence and bleeding.

VTE etiology [3]	Recurrent VTE in first year (without OAT)		Bleeding in first year (with OAT)		Recommended OAT duration [4]
	(%)	Fatal events per 1000 *	(%)	Fatal events per 1000 **	
Provoked, transient risk factor (e.g. surgery)	3	1.1	2	2.3	SHORT (3 months)
Unprovoked	6	2.2	2	2.3	Still controversial (Extended therapy if bleeding risk is low)
Provoked, persistent risk factor (e.g. cancer)	12	1.3	2	2.3	INDEFINITE (extended therapy)

Optimize duration of OAT in unprovoked VTE: the HERDOO2 clinical decision rule

The solution will be to focus on an individualized approach based on risk predictors to stratify unprovoked VTE patients with sufficiently low or high risk for recurrence to better justify the decision to discontinue or continue OAT [1].

The **REVERSE▲ I** study showed high recurrence risk (13.7%; 95% CI 10.8 - 17.0%) in 332 men with unprovoked VTE but could not find any predictors to identify a low risk subgroup [6].

Using a multivariate approach the study derived a simple clinical decision rule - **HERDOO2** - in 314 women with unprovoked VTE: 163 patients with 0 or 1 predictor were at low risk of VTE recurrence 1 year after stopping OAT (1.6%; 95% CI 0.3 - 4.6%) whereas the 151 patients with 2 or more predictors were at high risk (14.1%; 95% CI 10.9 - 17.3%).

Because the VTE recurrence rate in the low risk group (1.6%) was well below the safety limit of 5% recommended by the ISTH, the findings of the **REVERSE I derivation study** suggest that women with 0 or 1 points in the rule can safely stop OAT after short-term duration.

This was subsequently proven in the **REVERSE II validation study** in which 591 low risk patients discontinued anticoagulants after 5-12 months [7]. The VTE event rate after 1 year of follow-up was 3.0% (95% CI 1.8% to 4.8%) which is below the recommended safety limit of 5%.

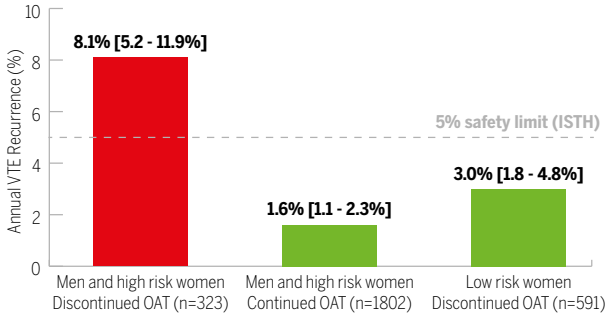
HERDOO2 clinical decision rule: risk of VTE recurrence in women with unprovoked VTE [6].

Predictor	Points
Hyperpigmentation, Edema or Redness in either leg (signs of PTS)	1
D-dimer ≥ 250 µg/L (VIDAS® D-Dimer Exclusion™ II)	1
Obesity (body mass index ≥ 30 kg/m²)	1
Older age (≥ 65 years)	1
Interpretation	**TOTAL**
Low risk – consider discontinuation of OAT	**0 or 1**
High risk – consider continuation of OAT	**≥ 2**

PTS: post-thrombotic syndrome
Predictors are assessed while the patient is still on oral anticoagulants

▲ REcurrent VEnous thromboembolism Risk Stratification Evaluation.

REVERSE II Study: safe discontinuation of OAT in low risk women [7].



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"With this rule we can confidently tell half of the women we see that they are at low risk of having another blood clot. This means they can stop taking blood thinners once their initial clot is treated, sparing them the cost, inconvenience and risks of taking life-long medication."

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