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Full Length Article

"HERDOO2" clinical decision rule to guide duration of anticoagulation in women with unprovoked venous thromboembolism. Can I use any D-Dimer?

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ABSTRACT

Background: The "HERDOO2 rule" is a prospectively validated clinical decision rule used to identify low-risk women who can safely discontinue anticoagulants after completing 5–12 months of anticoagulant treatment for unprovoked venous thromboembolism. The VIDAS® D-Dimer (DD) assay, a component of the rule, was used in the derivation and validation of the rule at half the usual diagnostic cut-point for exclusion of venous thrombosis. It is unknown if other commercial DD assays used at a corresponding cut-point will categorize patients at high concordance with the VIDAS® DD.

Objective: To determine if other available automated quantitative DD assays have high enough concordance with the VIDAS® DD assay to allow their use within the "HERDOO2" clinical decision rule.

Methods: Frozen plasma samples from a sub-set (n = 248) of female participants in the "HERDOO2" validation study were tested using five DD assays: VIDAS®, Innovance®, HemosIL®, Tina-quant® and Liatest®, with duplicate testing for 50 samples. First, using the mean DD for 50 samples with duplicate results, we determined the optimal cut-point values for each test that corresponded with a VIDAS® DD result of 250 μg/L using linear regression analysis. Next, kappa analysis was conducted on the DD results of the remaining 198 samples to determine concordance between each tested DD at the respective optimal cut-point and the VIDAS® DD at 250 μg/L. In a separate analysis we determined the concordance at half the usual venous thrombosis exclusion cut-point.

Results: Regression analysis of the DD results in 50 samples identified the optimal cut-point for each DD assay to match a VIDAS® DD cut-point of 250 μg/L: Innovance® 177 μg/L, Liatest® 233 μg/L, Tina-quant® 48 μg/L and HemosIL® 56 μg/L. Next, in 198 different samples, the concordance of VIDAS® DD (≥ 250 μg/L or < 250 μg/L) was explored at the optimal cut-point of the other DD assays. The concordance was poor for all DD assays: Innovance® (kappa 0.38 (95% CI, 0.26–0.51)), Liatest® (kappa 0.38 (95% CI, 0.25–0.50)), HemosIL® (kappa 0.36 (95% CI, 0.23–0.49)) and Tina-quant® (kappa 0.30 (95% CI, 0.16–0.43)). Similar poor concordance was identified using half of the diagnostic DD cut-point for each tested assay: Innovance® (kappa 0.44 (95% CI, 0.32–0.56)), Liatest® (kappa 0.38 (95% CI, 0.25–0.51)), HemosIL® (kappa 0.04 (95% CI, −0.01—0.08)) and Tina-quant® (kappa 0.04 (95% CI, −0.004–0.07)).

Conclusion: The "HERDOO2 rule" is the only prospectively validated clinical decision rule that can be used to identify low-risk women with unprovoked venous thrombosis who can safely discontinue anticoagulants. An important implementation issue is whether any commercial DD assay can be used in the HERDOO2 rule, and at what cut-point. Our analysis shows that the HemosIL®, Innovance®, Liatest® and Tina-quant® DD assays should not be used in the "HERDOO2" rule due to poor concordance with the VIDAS® DD assay and unacceptable misclassification of women at high and low risk of recurrent venous thrombosis.

1. Background

Venous thromboembolism (VTE) is a common, potentially fatal yet treatable condition. The duration of anticoagulation for a first unprovoked venous thromboembolism (VTE) is considered one of the most important unanswered questions in VTE management [1].

Current guidelines suggest indefinite anticoagulation in patients with a first unprovoked VTE without a high risk of bleeding [2].

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Box 1
HERDOO2 clinical decision rule to identify low-risk women with unprovoked venous thromboembolism who can discontinue anticoagulants after 5–12 months of anticoagulant therapy.

Men continue and HERDOO2
All men continue oral anticoagulants
Women with 2 or more of the following features should continue oral anticoagulants:

1) HER: any Hyperpigmentation, Edema, Redness of either lower extremity
2) VIDAS D- Dimer: ≥250 μg/L
3) Obesity: BMI ≥ 30 kg/m^2
4) Older age: ≥65 years

However, these are low grade recommendations and do not support individualized treatment decisions based on risk of VTE recurrence.

The HERDOO2 rule (see Box 1) has been derived [3] and validated [4] to identify low risk women who can safely discontinue anticoagulants after completing 5–12 months of anticoagulant therapy. Women with a HERDOO2 score of 0 or 1 have a 3% risk of recurrent VTE in the first year after discontinuing anticoagulants. A VIDAS® D-Dimer (bioMérieux, Marcy L'Etoile, France) is a component of the rule and was used in both the derivation and validation studies. Importantly, the VIDAS® D-Dimer (DD) cut-off level of 250 μg/L, used for the application of the HERDOO2 rule, is half of the level used for the exclusion of VTE in patients with a suspected diagnosis of VTE (500 μg/L). A crucial implementation issue when applying the rule in varied clinical settings is whether other commercial DD assays can be used in the HERDOO2 rule and at what cut-point. Clinicians, patients, policymakers, and regulatory authorities will need to be confident that other DD assays can lead to near identical HERDOO2 classification prior to permitting their use in making this decision about indefinite treatment.

The importance of accurate classification cannot be understated. A single DD measurement is used in the HERDOO2 rule to determine if a patient should receive indefinite anticoagulation or stop anticoagulation. False negatives may lead to inappropriate clinical decisions: stopping anticoagulants and exposing patients to a significant risk of recurrent VTE, which can be fatal. False positives may lead to unnecessary ongoing anticoagulation, exposing patients to a significant risk of major hemorrhage for an extended period, possibly lifelong.

The purpose of the study was to establish the appropriateness of using alternate DD assays when applying the HERDOO2 clinical decision rule. We sought to determine the concordance (kappa) of four commonly used, commercially available, automated quantitative DD assays compared to the VIDAS® D-Dimer Exclusion™ II, at an equivalent cut-point in samples from women with unprovoked VTE.

2. Methods

This D-Dimer concordance study was funded by bioMérieux, the makers of the VIDAS® DD assay. bioMérieux had no role in the design of this study or its execution, analyses, interpretation of the data, writing of the manuscript or decision to submit results. Our objectives were to 1) determine the cut-point for 4 commercially available quantitative DD assays that corresponds to a cut-point of 250 μg/L with the VIDAS® DD assay and then 2) compare the classification performance of four commercially available quantitative DD assays at the optimised cut-point to the VIDAS® D-Dimer Exclusion™ II assay at a cut-point of 250 μg/L.

In the REVERSE II study [4] we obtained consent from most enrolled patients to collect and store plasma samples for future research. Study participants were patients with unprovoked VTE and all samples were collected during oral anticoagulant treatment, 5–12 months after diagnosis. The samples were frozen and maintained at −80 °C. We retrieved samples from 248 randomly selected female participants who consented to future use of their samples. We limited this sub-study to women as in the HERDOO2 rule, DD results influence risk stratification only in women. Samples were shipped on dry ice. After thawing the samples, five commercially available DD tests (Table 1) were performed per their product inserts. The tests were conducted in three accredited clinical laboratories and one research laboratory in Ontario and Quebec, Canada, by trained laboratory personnel who were blinded to all clinical data, the results of any previous DD tests for the same participant, and the reference standard result. These laboratories were selected because they had the equipment for the DD assays and personnel that were experienced with the test.

To evaluate the reliability of the VIDAS® DD, we compared the results from the REVERSE II study where VIDAS® DD was measured at the individual study sites to the results of the central VIDAS® DD testing that was conducted for this study.

We determined the optimal cut-point for each individual DD assay that matches the VIDAS® DD cut-point of 250 μg/L by plotting separate

Table 1
D-Dimer assays and instrumentation.

D-Dimer assay	Instrument	Lower limit of detection
HemosIL® D-Dimer HS (Instrumentation Laboratory, Bedford Massachusetts, USA)	ACL-TOP 500 System (performed in London, Ontario, Canada)	203 μg/L
Innovance® D-Dimer (Siemens Healthcare Diagnostics, Erlangen, Germany)	CS-2100i System (performed in Ottawa, Ontario, Canada)	170 μg/L
Stago STA®-Liatest® D-Di (Diagnostica Stago, Asnières sur Seine, France)	Stago STA Satellite USB System (performed in Ottawa, Ontario, Canada)	270 μg/L
Tina-quant® D-Dimer Gen. 2 (Roche Diagnostics, Mannheim, Germany)	Roche/Hitachi cobas® c System (performed in Montreal, Quebec, Canada)	150 μg/L
VIDAS® D-Dimer Exclusion™ II (bioMérieux, Marcy-l'Etoile, France)	bioMérieux mini VIDAS® Analyzer (performed in Ottawa, Ontario, Canada)	50 μg/L