HERDOO2 Rule to Guide Treatment Duration for Unprovoked Venous Thrombosis: The REVERSE II Study

Venous Thromboembolism (VTE)

- Major VTE (proximal leg deep vein thrombosis (DVT) and pulmonary embolism (PE))
  - must be treated with a minimum of 3-6 months anticoagulation (short term)
- Stop or continue anticoagulants indefinitely?
  - Anticoagulants effective: 80-90% RRR
  - Anticoagulants cause major bleeding: ~1-2% per year in “anticoagulant experienced” patients
Stop anticoagulants (OAC) after short term therapy for VTE?

- **YES**, stop anticoagulants if risk of recurrent VTE off of anticoagulants is <5% at 1yr (ISTH)
  - Provoked (major transient risk factor) (e.g. major surgery)

- **UNCERTAIN**
  - Unprovoked (~50% of all VTE)
  - Provoked (minor transient risk factor) (e.g. minor trauma)

Kearon, JTH, 2016
Unprovoked VTE: Continue anticoagulants indefinitely?

ACCP (2016) and ESC (2014) consensus guidelines

• “Suggest anticoagulants should be continued indefinitely in unprovoked VTE patients with non-high bleeding risk” (GRADE 2B- Weak recommendation)
Unprovoked VTE Risk Stratification

• Identify *High risk* patients who should continue and *Low risk* patients who can discontinue

• Individual predictors alone not good enough
  – Gender
  – D-Dimer off of anticoagulants
  – Residual venous thrombosis

• Multivariate Clinical Decision Rule (CDR) may be the answer!
The REVERSE* I (RI) study
Prospective cohort to derive a CDR to guide duration

1st Unprovoked VTE (n=646)

STOP OAC

Anticoagulants

5 months  7 months  q 6 months

- Enrolled
- Baseline predictors (n=69):
  - History
  - Physical
  - Lab (including D-dimer)
  - VTE imaging

Adjudicated outcome
symptomatic major
- DVT
- PE

*REVERSE: REcurrent VEnous thromboenbolism Risk Stratification Evaluation

Rodger, CMAJ, 2008
“Men Continue and HERDOO2”

- **Men should continue** anticoagulants
  - 13.9% annual risk of recurrent VTE off of anticoagulants in derivation study

- **Women with ≥ 2 HERDOO points should continue** anticoagulants
  - 14.1% annual risk of recurrent VTE off of anticoagulants in derivation study

- **Women with ≤ 1 HERDOO point can discontinue** anticoagulants
  - 1.6% annual risk of recurrent VTE off of anticoagulants in derivation study

**HERDOO Predictors**
- Hyperpigmentation or Edema or Redness (HER) in either leg
- D-Dimer (Vidas)
  - ≥ 250 ug/L (not 500)
- Obesity, BMI ≥ 30
- Older age ≥ 65 years

Rodger, CMAJ, 2008
Clinical Decision Rules (CDR)
Unprovoked Major VTE (n=2785) in 44 centers

Adjudicated outcome ascertainment -

Major VTE - Major Bleeding

5 months

Unprovoked= Absence of…
- Fracture or cast
- Surgery with GA
- Immobilization ≥3 days
- Malignancy ≤ 5 years

Primary Outcome: Recurrent Major VTE In Low Risk ♀ who discontinue

STOP OAC

STOP OAC

Men Continue and HERDOO2

Low (0 or 1 HERDOO)

High

Exclusions
- No consent
- <18 yrs old
- Discontinued anticoagulants
- Needed ongoing anticoagulation (e.g. AF, known high risk thrombophilia)
- Unable to follow-up
- Planned ongoing exogenous estrogen
- Pregnancy-associated VTE
Participant Flow

Assessed for eligibility
- Not eligible (n=3170)
- Eligible (n=3155)

Enrolled (n=2785)
- No D-Dimer (n=6)

HERDOO2 Classification

Men and High Risk Women (n=2148)
- No follow-up (n=23)

Continued Anticoagulants (n=1802)
Lost to follow-up (n=18)

Discontinued Anticoagulants (n=323)
Lost to follow-up (n= 5)

Low Risk Women (n=631)
- No follow-up (n= 9)

Discontinued Anticoagulants (n=591)
Lost to follow-up (n=7)

Continued Anticoagulants (n=31)
Lost to follow-up (n=1)

12 month Follow-Up

Primary Outcome:
Recurrent Major VTE
## The Population

<table>
<thead>
<tr>
<th></th>
<th>Whole Population (n=2747)</th>
<th>Low-risk Women (n=622)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (SD)</strong></td>
<td>54.4 (16.7)</td>
<td>41.3 (14.2)</td>
</tr>
<tr>
<td><strong>Caucasian (n=2287)</strong></td>
<td>83.7%</td>
<td>85.3%</td>
</tr>
<tr>
<td><strong>Type of Index VTE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated DVT (n=1113)</td>
<td>40.5%</td>
<td>28.8%</td>
</tr>
<tr>
<td>Isolated PE (n=1068)</td>
<td>38.9%</td>
<td>55.1%</td>
</tr>
<tr>
<td>DVT and PE (n=566)</td>
<td>20.6%</td>
<td>16.1%</td>
</tr>
<tr>
<td>Exogenous Estrogen (n=397)</td>
<td>14.4%</td>
<td>51.9%</td>
</tr>
</tbody>
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Results

**HERDOO2 Classification**

**Men and High Risk Women (n=2148)**
- **Continued Anticoagulant (n=1802)**
  - Recurrent VTE: 1.6 per 100 patient years
  - 95% CI: 1.1-2.3

- **Discontinued Anticoagulants (n=323)**
  - Recurrent VTE: 8.1 per 100 patient years
  - 95% CI: 5.2-11.9

**Low Risk Women (n=631)**
- **Discontinued Anticoagulants (n=591)**
  - Recurrent VTE: 3.0 per 100 patient years
  - 95% CI: 1.8-4.8

- **Continued Anticoagulant (n=31)**
  - Recurrent VTE: None
Results

**HERDOO2 Classification**

- Men and High Risk Women (n=2148)
- 12 month Follow-Up
- Discontinued Anticoagulants (n=591)
- Recurrent VTE: 3.0 per 100 patient years
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Low Risk Women (n=631)

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Recurrent VTE: None
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Low Risk Women (n=631)

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  - 95% CI: 1.1-2.3
- Discontinued Anticoagulants (n=323)
  - Recurrent VTE: 8.1 per 100 patient years
  - 95% CI: 5.2-11.9
- Discontinued Anticoagulants (n=31)
  - Recurrent VTE: None

Hereditary Disorders of Blood Coagulation (HERDOO2)
Subgroups of Low Risk Women

<table>
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<tr>
<th>Sub-Group</th>
<th>Recurrent VTE per 100 pt yrs</th>
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<td><strong>Type of index VTE</strong></td>
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</tr>
<tr>
<td>• Isolated DVT (n=177)</td>
<td>3.0 (1.0-7.0)</td>
</tr>
<tr>
<td>• Isolated PE (n=323)</td>
<td>3.9 (2.0-6.8)</td>
</tr>
<tr>
<td>• DVT and PE (n=91)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Initial short term anticoagulant</strong></td>
<td></td>
</tr>
<tr>
<td>• Vitamin K antagonist (n=459)</td>
<td>2.9 (1.6-5.0)</td>
</tr>
<tr>
<td>• Rivaroxaban (n=84)</td>
<td>5.1 (1.4-13.3)</td>
</tr>
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### Subgroups of Low Risk Women: Pre/post Menopausal

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<th>Recurrent VTE per 100 pt yrs</th>
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</thead>
<tbody>
<tr>
<td>Age &lt; 50 (n=429)</td>
<td>2.0 (0.8-3.9)</td>
</tr>
<tr>
<td>• Estrogen (n=291)</td>
<td>1.4 (0.4-3.7)</td>
</tr>
<tr>
<td>• No Estrogen (n=138)</td>
<td>3.1 (0.8-7.9)</td>
</tr>
<tr>
<td>Age ≥ 50 (n=162)</td>
<td>5.7 (2.6-10.9)</td>
</tr>
</tbody>
</table>
Discussion

• Largest prospective cohort management study of unprovoked VTE patients

• Safe to discontinue anticoagulants in low risk ♀(0 or 1 HERDOO criteria)
  – Point estimate (3.0%) and upper bound of 95% CI(4.8%) both below 5% at 1 year threshold
  – ~50% of women with unprovoked VTE spared burdens, costs and risks of lifelong anticoagulation
Discussion

• **Strengths**
  – Large homogenous population with minimal loss to follow-up (2.2%)
  – Simple memorable CDR applied on anticoagulants at clinically relevant time-point

• **Only CDR that has been prospectively validated**
  – DASH and Vienna Prediction Model not been prospectively validated
Conclusion

Women with a first unprovoked VTE and 0 or 1 HERDOO2 criteria have a low risk of recurrent VTE

• can safely discontinue anticoagulants after completing short-term treatment

HERDOO2 Rule

Hyperpigmentation or Edema or Redness (HER) in either leg
D-Dimer (Vidas) – ≥ 250 ug/L (not 500)
Obesity, BMI ≥ 30
Older age ≥ 65 years
Thank you REVERSE II Investigators

**North America**
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**HERDOO2 Rule**
- Hyperpigmentation or Edema or Redness (HER)
  - in either leg
- D-Dimer (Vidas) $\geq 250 \text{ ug/L (not 500)}$
- Obesity, BMI $\geq 30$
- Older age $\geq 65$ years