ANTICOAGULATION FOR VENOUS THROMBOEMBOLISM (VTE) IN SPECIAL POPULATIONS

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CONTENT

- Special populations:
  Extreme body weight, renal failure and pregnancy

- Review of guideline-recommendations for VTE in special populations
  - Dose adjustment of parenteral anticoagulation (heparin products)
  - Evidence for oral anticoagulants

- New evidence for areas of uncertainty
  - The use of new anticoagulation strategies
EXTREME BODY WEIGHT AND RISKS FOR VTE AND VTE-TREATMENT RELATED-COMPLICATIONS

- Obesity increases the risk of venous thromboembolic complications by 2.5 fold (US DHHS)
- Excess body weight increases also the risk of recurrent VTE (Austrian registry on recurrent VTE)
- In obese patients receiving parenteral anticoagulation with heparin products, the rates of hemorrhage appear to be higher.
- Clinical prediction algorithms for long term anticoagulant related-bleeding indicate that body weight influences the risk.
- Obese patients are under-represented in clinical trials.

The American journal of medicine. 2005 Sep 1;118(9):978-80

Archives of internal medicine. 2008 Aug 11;168(15):1678-83
American heart journal. 2003 Jul 1;145(1):33-41
<table>
<thead>
<tr>
<th>Guideline/ Society</th>
<th>Year of publication</th>
<th>Heparin/LMWH</th>
<th>DOAC</th>
</tr>
</thead>
</table>
| **ACCP**           | 2012                | VTE prophylaxis and treatment: Weak  
  ▪ Non-controlled cohort studies  
  ▪ Pharmacokinetics studies |  |
| **ASH**            | 2016                |  |
| **Journal of thrombosis and Thrombolysis** |  |
| **ISTH**           | 2016                | AF/VTE/arthroplasty prophylaxis: Moderate  
  ▪ Randomized control studies  
  ▪ Pharmacokinetics studies |  |
|                    |                     |  |
|                     |                     | ▪ Standard DOAC dosing for BMI ≤ 40 kg/m² and weight ≤ 120 kg |  |

- **Guideline Statements for the Use of Anticoagulants in Extreme Body Weight Patients**

- **ACCP: 2012**
  - VTE prophylaxis and treatment: Weak
    - Non-controlled cohort studies
    - Pharmacokinetics studies

- **ASH: 2016**
  - Dose adjustment by actual body weight
  - Dose capping should be avoided
  - LMWH + obesity: Twice daily regime for treatment dose
  - For body weight < 40 kg: UFH is preferred
  - No routine use of anti-Xa level

- **ISTH: 2016**
  - AF/VTE/arthroplasty prophylaxis: Moderate
    - Randomized control studies
    - Pharmacokinetics studies
  - Standard DOAC dosing for BMI ≤ 40 kg/m² and weight ≤ 120 kg

**Notes:**
- Chest. 2012;141(2 Suppl):e419S-7236S
- Blood advances. 2018 Nov 27;2(22):3257-91
Di Nisio et al. 2016: Subanalysis of EINSTEIN DVT/PE studies
- RCT open label comparing rivaroxaban versus LMWH/VKA for acute proximal lower extremity DVT/PE.
- BMI ≥ 30 (N=1630), BMI ≥ 35 (861)
- Comparison of recurrent thrombosis and bleeding outcomes by body weight and BMI group levels:
  - ≤ 50Kg versus 50-100 kg versus > 100kg
  - BMI: < 25 versus 25-29 versus 30-34
- The risk (HR) for recurrent VTE and clinical relevant bleeding was similar across groups at 21 days and at completion of study.

Beyer-Westendorf et al. 2018: The prospective Dresden DOAC registry
- Multicenter prospective registry enrolling consecutive patients started on DOAC with follow-up phone interviews. N=3432
- BMI categories as per WHO classification (< 18.5, 18.5-24.9, 25-29.9, 30-34.9, ≥35)
- BMI < 18.5 (0.5%), BMI 30-34.9 (21.3%), BMI 35-39.9 (7.2%), BMI ≥ 40 (2.9%)
- No indication that elevated BMI is associated with a lack of NOAC effectiveness (CV outcomes) or safety (major bleeding)
- BMI < 18.5: higher rates of CV outcomes and major bleeding.

Kushnir et al. 2019: Single center analysis of VTE/AF morbidly obese adult patients (BMI ≥ 40)
- Retrospective analysis, single center study. VTE (N=366), AF (N=429)
- BMI ≥ 50 (24%)
- Apixaban (N=150), Rivaroxaban (N=326), VKA (319)
- The recurrent VTE, stroke and major bleeding outcomes were not different across groups.
EXTREME BODY WEIGHT AND VTE MANAGEMENT: CONCLUSIONS

1. For those patients requiring parenteral anticoagulation with low molecular heparins, the dose should be adjusted according to the actual body weight.
2. Routine use of anti-Xa levels to adjust dosage of low molecular weight heparins is not recommended.
3. When selecting oral anticoagulants, risks and benefits as well as patient-preferences need to be discussed.
4. Direct oral anticoagulants have now available data to support their use in obese patients.
5. Data are still needed for the use of direct oral anticoagulants in underweight (BMI < 18.5) and extremely obese patients (BMI > 40)
Renal disease is related to an increased risk of VTE (2-8 fold).

Patients with severe renal failure (< 30mL/min) have 2-4 fold increment in the risk of major bleeding during anticoagulation treatment.

Renal failure + VTE: Increased risk of fatal outcomes
- Severe renal failure: 6.6% fatal PE
- 1.2% fatal bleeding

Severe renal failure is a consistent exclusion criteria in VTE clinical trials.
<table>
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<tbody>
<tr>
<td></td>
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<td>Quality of evidence</td>
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<td>Recommendation</td>
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<td>VTE prophylaxis/treatment: Weak</td>
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<tr>
<td></td>
<td></td>
<td>- Pharmacokinetics studies</td>
<td>- Randomized control studies</td>
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<tr>
<td></td>
<td></td>
<td>- Non-controlled cohort studies</td>
<td>- Pharmacokinetics studies</td>
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<tr>
<td></td>
<td></td>
<td>- Post hoc analysis</td>
<td></td>
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<tr>
<td>Guidance statement</td>
<td>2016</td>
<td>Weak evidence for use in CrCl impairment (&lt; 30 mL/min)</td>
<td></td>
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<tr>
<td>Journal of thrombosis and Thrombolysis</td>
<td></td>
<td>- Dose adjustment according to Cr Cl</td>
<td></td>
</tr>
<tr>
<td>ASH</td>
<td>2018</td>
<td>Cr Cl &lt; 30 mL/min: No anti-Xa activity monitoring Follow adjustments in product labeling</td>
<td>No specific recommendations on dose adjustment</td>
</tr>
</tbody>
</table>

- **ACCP Guidance statement**
  - *Journal of thrombosis and Thrombolysis* 2016
  - *Journal of thrombosis and thrombolysis* 2016 Jan 1;41(1):165-86
  - *Blood advances* 2018 Nov 27;2(22):3257-91
## Renal Disease and VTE Management: Dose Adjustment of Oral Anticoagulants

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>VKA (Warfarin)</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Venous thromboembolism (treatment)</strong></td>
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</tbody>
</table>
| **United States** | No dose adjustment | GFR > 30: 150 mg BID  
GFR 15–30: 75 mg BID  
ESRD: contraindicated | GFR ≥ 30: 15 mg BID for 21 d,  
then 20 mg QD  
GFR < 30: contraindicated | 10 mg BID for 7 d, then 5 mg BID  
No dose adjustment | GFR > 50: 60 mg QD  
GFR 15–50 OR weight ≤ 60 kg OR P-gp inhibitors: 30 mg QD |
| **Europe** | No dose adjustment | GFR > 50: 150 mg BID  
GFR 30–50: 110 mg BID if high bleeding risk  
GFR < 30: contraindicated | Same as United States | GFR > 15: same as US  
ESRD: contraindicated | GFR > 50: 60 mg QD  
GFR 15–50 OR weight ≤ 60 kg OR P-gp inhibitors: 30 mg QD  
ESRD: contraindicated |
Gollamudi et al. 2018: Safety of Apixaban in Patients with CKD Stage V and ESRD with VTE
- Case control study (N=9,000 patients) from 26 integrated US healthcare systems (1/6 US population)
- Cases: renal disease stage V or ESRD on apixaban for VTE (N=990)
- Controls: ESRD on VKA for VTE (N=8110)
- Primary endpoint: 30-day and 90-day bleeding rates (excluded history GIB, ICH, AF, trauma, cancer, cirrhosis)
- Pooled bleeding rates (GI and ICH) favored apixaban (absolute difference 18% and 19%)
- Use of VKA, antiplatelets; uncontrolled hypertension, AA ethnicity, age >65 were associated with risk of bleeding.

Reed et al. 2018: Safety and effectiveness of apixaban compared to warfarin in dialysis patients
- Retrospective study (N=164 patients), single center of ESRD patients on anticoagulation (VTE/AF/prophylaxis)
- Comparison of VKA versus apixaban for overall bleeding rate and recurrent thrombotic events.
- Lower bleeding rates with apixaban (16% difference for major bleeding): 0.31 event per person year.
- Similar recurrent thrombotic events.
1. For those patients requiring parenteral anticoagulation with low molecular heparins and estimated creatinine clearance < 30 mL/min, dose reduction is advised and anti-Xa level monitoring for dose adjustment may be needed.

2. Avoid the use of low molecular heparins in patients requiring hemodialysis.

3. The appropriate dose adjustment of direct oral anticoagulants is unknown for patients with severe renal dysfunction, including patients requiring hemodialysis.
PREGNANCY AND RISKS FOR VTE AND VTE-TREATMENT RELATED-COMPLICATIONS

- VTE during pregnancy occurs in ~ 1/1,000 deliveries.
- 40% of VTE occurs during the first trimester.
- VTE is the leading cause of maternal mortality.

- Most of the bleeding complications during VTE treatment develop after delivery.

- Due to placental transfer, many of the conventional anticoagulation options are contraindicated.

Increment in procoagulants: Fibrinogen, Factors VII, VIII, X, vWF, PAI-1

Increased venous stasis

American journal of obstetrics and gynecology. 2001 Jan 1;184(2):104-10

Thrombosis and haemostasis. 2007;97(02):186-90
<table>
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<th>DOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCP</td>
<td>2012</td>
<td>VTE prophylaxis: Weak-Moderate</td>
<td>VTE prophylaxis/Treatment: Weak</td>
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<tr>
<td>ANZJOG</td>
<td>2012</td>
<td>§ Observational studies (C-section)</td>
<td>§ Case report</td>
</tr>
<tr>
<td>SOGC</td>
<td>2014</td>
<td>§ Small prospective studies (C-section)</td>
<td>§ Pharmacovigilance repository</td>
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<tr>
<td>RCOG</td>
<td>2015</td>
<td>§ Randomized controlled studies (prior VTE)</td>
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<tr>
<td>ACOG</td>
<td>2018</td>
<td>VTE treatment: Moderate</td>
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<tr>
<td>ASH</td>
<td>2018</td>
<td>§ Randomized controlled studies</td>
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<tr>
<td>ESC</td>
<td>2018</td>
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<tr>
<td></td>
<td></td>
<td><strong>LMWH Prophylaxis +/- pneumatic compression devices</strong></td>
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<td></td>
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<td>Thrombophilia carrier without family history VTE: Postpartum</td>
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<tr>
<td></td>
<td></td>
<td>Prior history of VTE: Postpartum</td>
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<tr>
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<td></td>
<td>History of unprovoked: Antepartum-postpartum</td>
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<tr>
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<td></td>
<td>Family history VTE + homozygous FVL/ antithrombin III deficiency/compound thrombophilia: antepartum-postpartum</td>
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<tr>
<td></td>
<td></td>
<td>Prior history of VTE+thrombophilia: antepartum-postpartum</td>
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<tr>
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<td>C-section with &gt; 1 additional risk factors for VTE that will persist in the postpartum period</td>
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<td><strong>Treatment: LMWH (body weight adjusted): once or twice daily</strong></td>
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<td></td>
<td></td>
<td><strong>Duration: 3 months (including 6 weeks post-partum)</strong></td>
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<tr>
<td>ASH</td>
<td>2018</td>
<td>Not recommended during pregnancy/lactation</td>
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</tr>
<tr>
<td>ISTH</td>
<td>2016</td>
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</tr>
</tbody>
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References:
- Chest. 2012;141(2 Suppl):e419S-7236S
- ANZJOG. 2012;52:14–22
- J Obstet Gynaecol Can 36(6):527–53
- Blood advances. 2018 Nov 27;2(22):3257-91
- Journal of Thrombosis and Haemostasis. 2016, 14: 1673–1676
**ISTH 2016: The international ISTH registry**

**VigiBase: The World Health Organization**

- WHO global database of individual case safety reports of suspected adverse drug reactions.
- > 16 X 10^6 reports from 136 countries participation in the WHO International Drug Monitoring Program.
- 60 identified cases of exposure to DOAC during pregnancy and reported outcomes
  - 42 cases of abortion (43% had an alternative cause)
  - 8 cases of congenital abnormality (63% had an alternative cause)
  - 6 cases of fetal growth restriction (33% had an alternative cause)
<table>
<thead>
<tr>
<th>Variable</th>
<th>Reporting Odds Ratio</th>
<th>95% CI low</th>
<th>95% CI high</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban vs All drugs</td>
<td>0.85</td>
<td>0.44</td>
<td>1.63</td>
<td>Spontaneous abortion - cases without alternative causes</td>
</tr>
<tr>
<td>Rivaroxaban vs All drugs</td>
<td>2.18</td>
<td>1.44</td>
<td>3.29</td>
<td>Spontaneous abortion - all cases</td>
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<tr>
<td>Rivaroxaban vs Warfarin</td>
<td>0.86</td>
<td>0.37</td>
<td>1.99</td>
<td>Spontaneous abortion - cases without alternative causes</td>
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<td>Rivaroxaban vs Warfarin</td>
<td>0.79</td>
<td>0.47</td>
<td>1.32</td>
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<tr>
<td>Rivaroxaban vs All drugs</td>
<td>10.61</td>
<td>3.95</td>
<td>28.51</td>
<td>Intrauterine growth retardation - cases without alternative causes</td>
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<tr>
<td>Rivaroxaban vs All drugs</td>
<td>13.28</td>
<td>5.48</td>
<td>32.18</td>
<td>Intrauterine growth retardation - all cases</td>
</tr>
<tr>
<td>Rivaroxaban vs Warfarin</td>
<td>1.68</td>
<td>0.45</td>
<td>6.25</td>
<td>Intrauterine growth retardation - all cases</td>
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<tr>
<td>Apixaban vs All drugs</td>
<td>5.46</td>
<td>2.42</td>
<td>12.32</td>
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<tr>
<td>Apixaban vs Warfarin</td>
<td>1.97</td>
<td>0.82</td>
<td>4.72</td>
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<td>5.55</td>
<td>2.11</td>
<td>14.63</td>
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<tr>
<td>Apixaban vs All drugs</td>
<td>19.04</td>
<td>7.82</td>
<td>46.36</td>
<td>Induced abortion - all cases without alternative causes</td>
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<tr>
<td>Apixaban vs Warfarin</td>
<td>5.86</td>
<td>2.01</td>
<td>17.06</td>
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<tr>
<td>Apixaban vs Rivaroxaban</td>
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<td>2.27</td>
<td>18.35</td>
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<tr>
<td>Apixaban vs Rivaroxaban</td>
<td>2.50</td>
<td>1.01</td>
<td>6.23</td>
<td>Spontaneous abortion - all cases</td>
</tr>
</tbody>
</table>
1. Thrombotic risk stratification early on pregnancy is critical to provide adequate prophylaxis/treatment strategies for VTE.

2. Low molecular weight heparin(s) are the medication(s) of choice for prophylaxis and treatment of VTE.

3. Weight based dose regimes are preferred for treatment.

4. Due to maternofetal risks, oral anticoagulants are not recommended during pregnancy.