OUTPATIENT MANAGEMENT OF VENOUS THROMBOEMBOLISM

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DISCLOSURES

• None
OBJECTIVES

• Recognize indications of outpatient vs inpatient management of venous thromboembolism (VTE)

• Recognize pros and cons of Target Specific Oral Anticoagulants (TSOACs) over warfarin

• Recognize determinants of duration of anticoagulant therapy

• Assess areas of high-value care in outpatient management of VTE.
CONTENTS

• INTRODUCTION

• MANAGEMENT ISSUES
  – Inpatient vs outpatient initial management
  – Choice of anticoagulant
  – Temporary cessation of anticoagulation
  – Duration of anticoagulation

• HIGH VALUE CARE OPTIONS

• CONCLUSION
INTRODUCTION

• 1-2 cases of VTE per 1000 population annually.
• Case fatality rate: 5%-12%
• Tends to recur
  – Recurrence rate: 3%-10% per year
  – At 10 yrs: 40%
  – With anticoagulation:
    • Recurrence rate: 1% per year
    • Bleeding rate: 3% per year
ALGORITHM

Patients with signs or symptoms of VTE

Prediction rule

D-dimer level

Imaging

Treatment

Interim anticoagulation
What are the ISSUES?

- Inpatient vs outpatient management at diagnosis
- Warfarin vs TSOACs
- Fixed duration vs indefinite anticoagulation
Question 1

28 yo man, presents to ED with acute onset right calf pain and swelling. Exam is unremarkable except right calf swelling and tenderness. US shows right popliteal vein DVT.

You recommend:

A. Admit to medicine to start anticoagulation
B. CT chest to look for PE
C. Give the first dose of anticoagulation in ED, then outpatient treatment and close follow up
D. Discharge with serial outpatient ultrasounds

Correct answer is c
Contraindications to outpatient management

– Medical factors:
  • PE with hemodynamic or respiratory instability
  • Extensive ileofemoral thrombus
  • Active bleeding
  • Severe hypertension
  • Thrombocytopenia \( \leq 50,000 \)

– Social factors
  • Inability to understand or comply with recommendations
Question 2

Patient in question1, treatment options include:

A. UFH bolus and infusion and start warfarin when aPTT is therapeutic
B. LMWH and start warfarin after the 1st dose
C. Rivaroxaban
D. Dabigatran
E. Apixaban
F. B and C
G. B, C, D and E

Correct answer is G
WARFARIN vs TSOACS

CONVENTIONAL MANAGEMENT

UFH/LMWH
Fondaparinux
Thrombolysis
Embolectomy
Surgery

VKAs (INR 2.0-3.0)
LMWH
VKAs

Initial treatment
5-10 days

Long-term treatment
at least 3 months

Extended treatment
indefinite
Warfarin

- Initiate warfarin on D1 after starting LMWH.
- Consider starting with warfarin 10mg/d dose x 2 days followed by INR based dosing.
- Therapeutic goal: INR between 2-3.
- Monitoring frequency: q 1-2 weeks until therapeutic INR x 2; then q month. Consider q 12week monitoring if consistently stable INR.
- Use validated nomograms for dosing decisions.
- Systematic and coordinated approach.
- Discontinuation: Abrupt without any taper.
- Patient education
Warfarin

- Single slightly supra or subtherapeutic (≤ +/- 0.5) INR:
  - no dose change; recheck INR in 1-2 weeks.

- INR between 4-10 & no bleeding:
  - Hold dose x 2 days and restart at lower dose

- INR > 10 & no bleeding:
  - Vit K 2.5 - 5mg po, hold dose x 2-4 days and restart at lower dose

- Any INR & bleeding:
  - Hold coumadin, Vit K iv, FFPs or PCC depending on the site and severity of bleeding.
Warfarin: Peri-operative Management

- **Discontinue**: 5 days before surgery
- **Resume**: 12-24 hours after surgery depending on the procedure, associated risk of bleeding and achievement of adequate hemostasis.
- **Bridging therapy**:
  - Temporary use of heparin for a patient on long-term anticoagulation who is about to undergo a surgical procedure
  - *Balance the risk of thromboembolism with the risk of bleeding*
  - *Take patient’s personal goals into consideration*
Bridging Therapy

Risk level for thromboembolism

• **High:**
  – Recent (within 3 m) VTE
  – Severe thrombophilia

• **Intermediate:**
  – VTE within 3-12 m
  – Non-severe thrombophilia
  – Recurrent VTE
  – Active cancer

• **Low:**
  – VTE>12 m previous and no other risk factors

Risk of bleeding

• **High**
  – Major cardiac surgery
  – Carotid endarterectomy
  – Neurosurgery

• **Intermediate:**
  – All others

• **Low:**
  – Minor dental, dermatologic or eye procedures
Warfarin: **narrow therapeutic index**

- Requires monitoring
- Drug and food interactions
- Pharmacogenetics: Polymorphisms of CYP2C9 and Vit K epoxide reductase complex 1 (VKROC1)
- Percent of time in therapeutic range (TTR): 58%
- Warfarin is underused: <70% of patients with indication for use
Warfarin: Need For Alternative Anticoagulants

• Disadvantages:
  – Narrow therapeutic index
  – Delayed onset and offset of effect
  – Genetic variability
  – Drug interactions
  – Dietary interactions
  – Monitoring requirements
  – Dose adjustment requirements
## TSOACs
### Dabigatran, Rivaroxaban & Apixaban

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Direct factor IIa inhib.</td>
<td>Direct factor Xa inhib.</td>
<td>Direct factor Xa inhib.</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Bioavailability %</strong></td>
<td>3-7</td>
<td>80</td>
<td>66</td>
</tr>
<tr>
<td><strong>Protein Binding %</strong></td>
<td>35</td>
<td>&gt;90</td>
<td>87</td>
</tr>
<tr>
<td><strong>Route of elimination</strong></td>
<td>Urine ~80%, feces ~20%</td>
<td>Urine ~70%, feces ~30%</td>
<td>Urine ~25%, feces ~70%</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Twice/day</td>
<td>Once/day*</td>
<td>Twice/day</td>
</tr>
</tbody>
</table>

* Twice per day after acute VTE

Smythe et al. Pharmacotherapy 2013 pre published
TSOACs vs Warfarin: Pharmacology

• Advantages:
  – **Narrow** Wide therapeutic index
  – **Delayed** Rapid onset and offset of effect
  – **No** Genetic variability
  – **Minimal** Drug interactions
  – **No** Dietary interactions
  – **No** Monitoring requirements
  – **No** Dose adjustment requirements
TSOACs vs Warfarin: Pharmacology

• Disadvantages:
  – Renal elimination except apixaban
  – Monitoring
    • Compliance issues
  – No antidote
  – Limited experience
# TSOACs vs Warfarin: Clinical evidence

<table>
<thead>
<tr>
<th>Outcome Study</th>
<th>RR</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrent VTE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-Cover (dabigatran)</td>
<td>1.10</td>
<td>0.66</td>
<td>1.84</td>
<td>11.2</td>
</tr>
<tr>
<td>Einstein-DVT (rivaroxaban)</td>
<td>0.70</td>
<td>0.46</td>
<td>1.07</td>
<td>16.7</td>
</tr>
<tr>
<td>Einstein-PE (rivaroxaban)</td>
<td>1.13</td>
<td>0.76</td>
<td>1.69</td>
<td>18.4</td>
</tr>
<tr>
<td>Amplify (apixaban)</td>
<td>0.84</td>
<td>0.60</td>
<td>1.18</td>
<td>25.4</td>
</tr>
<tr>
<td>Hokusai (edoxaban)</td>
<td>0.83</td>
<td>0.60</td>
<td>1.14</td>
<td>28.3</td>
</tr>
<tr>
<td><strong>Subtotal (I² = 0%, P = 0.46)</strong></td>
<td>0.88</td>
<td>0.74</td>
<td>1.05</td>
<td>100</td>
</tr>
<tr>
<td><strong>Fatal PE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-Cover (dabigatran)</td>
<td>0.33</td>
<td>0.03</td>
<td>3.18</td>
<td>18.0</td>
</tr>
<tr>
<td>Einstein-DVT (rivaroxaban)</td>
<td>2.98</td>
<td>0.12</td>
<td>73.04</td>
<td>9.0</td>
</tr>
<tr>
<td>Einstein-PE (rivaroxaban)</td>
<td>2.00</td>
<td>0.18</td>
<td>21.99</td>
<td>16.0</td>
</tr>
<tr>
<td>Amplify (apixaban)</td>
<td>0.50</td>
<td>0.05</td>
<td>5.57</td>
<td>16.0</td>
</tr>
<tr>
<td>Hokusai (edoxaban)</td>
<td>1.33</td>
<td>0.30</td>
<td>5.96</td>
<td>41.1</td>
</tr>
<tr>
<td><strong>Subtotal (I² = 0%, P = 0.71)</strong></td>
<td>1.02</td>
<td>0.39</td>
<td>5.96</td>
<td>100</td>
</tr>
<tr>
<td><strong>Overall mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-Cover (dabigatran)</td>
<td>0.99</td>
<td>0.55</td>
<td>1.81</td>
<td>7.1</td>
</tr>
<tr>
<td>Einstein-DVT (rivaroxaban)</td>
<td>0.77</td>
<td>0.51</td>
<td>1.17</td>
<td>14.6</td>
</tr>
<tr>
<td>Einstein-PE (rivaroxaban)</td>
<td>1.16</td>
<td>0.80</td>
<td>1.68</td>
<td>18.3</td>
</tr>
<tr>
<td>Amplify (apixaban)</td>
<td>0.79</td>
<td>0.53</td>
<td>1.19</td>
<td>15.6</td>
</tr>
<tr>
<td>Hokusai (edoxaban)</td>
<td>1.05</td>
<td>0.82</td>
<td>1.33</td>
<td>44.4</td>
</tr>
<tr>
<td><strong>Subtotal (I² = 0%, P = 0.50)</strong></td>
<td>0.97</td>
<td>0.83</td>
<td>1.14</td>
<td>100</td>
</tr>
</tbody>
</table>

### TSOACs vs Warfarin: Clinical evidence

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NOACs n % Range</th>
<th>VKAs n % Range</th>
<th>Pooled absolute risk difference, % (95% CI)</th>
<th>NNT with NOACs to prevent one event (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>241/12 151</td>
<td>273/12 153</td>
<td>-0.24 (-0.60 to 0.11)</td>
<td>417 (167 to −909)</td>
</tr>
<tr>
<td>2.0</td>
<td>1.6–2.4</td>
<td>1.8–3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal PE</td>
<td>9/12 151</td>
<td>9/12 153</td>
<td>0.01 (-0.06 to 0.08)</td>
<td>10 000 (1667 to −1250)</td>
</tr>
<tr>
<td>0.07</td>
<td>0.04–0.10</td>
<td>0.0–0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td>290/12 197</td>
<td>298/12 193</td>
<td>-0.10 (-0.47 to 0.28)</td>
<td>1000 (213 to −357)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.5–3.2</td>
<td>1.7–3.1</td>
<td>-0.67 (-1.13 to −0.21)</td>
<td>149 (88–476)</td>
</tr>
<tr>
<td>1.1</td>
<td>0.6–1.6</td>
<td>1.2–2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal bleeding at a critical site</td>
<td>28/12 179</td>
<td>77/12 193</td>
<td>-0.38 (-0.65 to −0.10)</td>
<td>263 (153–1000)</td>
</tr>
<tr>
<td>0.23</td>
<td>0.08–0.32</td>
<td>0.18–1.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>806/12 179</td>
<td>1024/12 193</td>
<td>-1.77 (-3.40 to −0.15)</td>
<td>56 (29–667)</td>
</tr>
<tr>
<td>6.6</td>
<td>3.9–9.5</td>
<td>6.9–9.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal intracranial bleeding</td>
<td>11/12 179</td>
<td>31/12 193</td>
<td>-0.14 (-0.31 to 0.03)</td>
<td>714 (323 to −3333)</td>
</tr>
<tr>
<td>0.09</td>
<td>0.00–0.12</td>
<td>0.00–0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major gastrointestinal bleeding</td>
<td>28/8079</td>
<td>43/8071</td>
<td>-0.16 (-0.42 to 0.11)</td>
<td>625 (238–909)</td>
</tr>
<tr>
<td>0.35</td>
<td>0.17–0.71</td>
<td>0.53–0.23–0.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>7/12 179</td>
<td>21/12 193</td>
<td>-0.09 (-0.17 to 0.00)</td>
<td>1111 (588–0)</td>
</tr>
<tr>
<td>0.06</td>
<td>0.01–0.08</td>
<td>0.07–0.29</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Beyond Warfarin: A New Era

## Conventional Management

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>Long-term treatment</th>
<th>Extended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10 days</td>
<td>at least 3 months</td>
<td>indefinite</td>
</tr>
</tbody>
</table>

- **UFH/LMWH**
- **Fondaparinux**
- **Thrombolysis**
- **Embolectomy**
- **Surgery**

## Future Management

<table>
<thead>
<tr>
<th>LMWH/fondaparinux</th>
<th>Dabigatran 150 mg b.i.d.</th>
<th>Dabigatran 150 b.i.d.</th>
</tr>
</thead>
</table>

- **Rivaroxaban**
  - 15 mg b.i.d. (3 weeks)
  - 20 mg o.d.
  - 20 mg o.d.

- **Apixaban**
  - 10 mg b.i.d. (1 week)*
  - 5 mg b.i.d.*
  - 5 mg b.i.d.
Conversion: Warfarin and TSOACs

- **Warfarin to TSOACS:**
  - Start TSOACs at the time of next dose of warfarin and when INR is < 3 for rivaroxaban, and <2 for apixaban and dabigatran.

- **TSOACs to warfarin:**
  - Start LMWH and warfarin at the time of the next dose of rivaroxaban or apixaban.
  - Start warfarin 1-3 days before discontinuing dabigatran depending on creatinine clearance.
Question 3

Patient develops DVT 4 weeks post knee replacement surgery; you recommend anticoagulation for:

A. 1 month
B. 3 months
C. 12 months
D. Indefinitely

Correct answer is B
DURATION OF ANTICOAGULATION

• **First Provoked:** 3 months

• **Recurrent provoked:** 3 months with prophylaxis around high risk situations

• **Catheter associated:** 3 months or until catheter in place whichever is longer; remove catheter if non-functional and not necessary.

• **Distal DVT:**
  – serial imaging and symptom assessment >> anticoagulation if progression or severe symptoms
  – anticoagulation period depends on provoking factors

• **Recurrent unprovoked:** Indefinite
DURATION OF ANTICOAGULATION

First unprovoked:

- Evaluate risks and benefits of continued anticoagulation after 3 months, and then periodically for as long as anticoagulation is continued
  - Persistent risk factors for VTE like cancer, immobility, obesity, high risk thrombophilias
  - Risk factors for bleeding

- Use of prediction models
  - Age
  - Gender
  - D-dimer
Prediction model: DASH

Data from databases pooled:

• 1818 patients with 22.4 months of median follow-up
• Proximal DVT or PE
• No antecedent risk factor: surgery, trauma, active cancer, immobility, or pregnancy and the puerperium
• Included VTE associated with hormonal therapy and thrombophilia, except antiphospholipid syndrome and antithrombin deficiency

Tosetto et al. JTH 2012 prepub
Prediction model: DASH

• Abnormal D-dimer +2
• Age < 50 years +1
• Male sex +1
• Hormone-associated -2
# Prediction model: DASH

<table>
<thead>
<tr>
<th>DASH Score</th>
<th>Annualized Recurrence Rate (95% CI)</th>
<th>Cumulative Recurrence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-year</td>
<td>2-years</td>
</tr>
<tr>
<td>-2</td>
<td>1.8 (0.5-7.6)</td>
<td>2.4</td>
</tr>
<tr>
<td>-1</td>
<td>1.0 (0.4-2.6)</td>
<td>1.9</td>
</tr>
<tr>
<td>0</td>
<td>2.4 (1.4-4.2)</td>
<td>4.2</td>
</tr>
<tr>
<td>1</td>
<td>3.9 (2.9-5.3)</td>
<td>5.1</td>
</tr>
<tr>
<td>2</td>
<td>6.3 (5.0-8.1)</td>
<td>8.4</td>
</tr>
<tr>
<td>3</td>
<td>10.8 (8.7-13.4)</td>
<td>14.6</td>
</tr>
<tr>
<td>4</td>
<td>19.9 (13.9-28.2)</td>
<td>21.9</td>
</tr>
</tbody>
</table>

Tosetto et al. JTH 2012 Jun;10(6):1019-25
HIGH VALUE CARE

• CLINIC VISITS: FREQUENCY AND TYPE
• PREVENTION AND MANAGEMENT OF COMPLICATIONS
  – Vit K supplements
  – Pharmacogenetic testing
  – Compression Stockings
Question 4

Which of the following practices have not shown to improve time in therapeutic range (TTR) with warfarin use?

A. Vit K supplementation
B. Pharmacogenetic testing
C. Monitoring by a physician
D. Patient self-management
E. All of the above

Correct answer is E
CLINIC VISITS

• **Frequency:**
  – Patient compliance
  – Change in health status
  – Change in diet or medications
  – INR
  – Stable INR and warfarin dose for 3 months: consider frequency of upto 12 weeks

• **Type**
  – Anticoagulation clinic
  – Patient self-testing and self-management
VITAMIN K SUPPLEMENTS

• Observational study using food diaries showed most stable control over time in patients with highest tertile of Vit K intake

• Three RCTs of Vit K vs placebo:
  – Modest increase in TTR (3.54%)
  – No difference in major bleeding or thromboembolic events

Rombouts EK. J Thromb Haemost.2007; 5(10): 2043-2048
Sconce E. Blood. 2007; 109(6): 4219-2423
CHEST 2012;141(2)(Suppl):e152s-e184s
PHARMACOGENETIC TESTING

• 4 RCTs looking at pharmacogenetic testing based initial warfarin dosing vs empiric dosing
  – No difference in time to therapeutic range or time in therapeutic range
  – Cost-effective analysis: incremental ratios were as high as $200,000-$300,000 per QALY.

Caraco Y. Clin Pharmacol The. 2008;83(3):460-470
Anderson JL. Circulation 2007;116(22):2563-2570
Huang SW. Pharmacogenet Genomics. 2009; 19(3):226-234
CHEST 2012;141(2)(Suppl):e152s-e184s
COMPRESSION STOCKINGS

• Results of multiple RCTs: CS started within 2 weeks of DVT and continued for 2 years reduce the incidence of post-thrombotic syndrome (PTS) by 50%.

• May improve symptoms of established PTS
CONCLUSION

• Initial outpatient management of VTE may be appropriate in low-risk patients.

• Choice of anticoagulant should be based on the relative pros and cons of the available agents, and patients’ preference.

• Outpatient management of warfarin requires a systematic and coordinated approach, and good patient education.

• Duration of anticoagulation depends on the circumstances around the event, assessment of bleeding risk, use of prediction models and patients’ personal goals of therapy.
Question 1

28 yo man, presents to ED with acute onset right calf pain and swelling. Exam is unremarkable except right calf swelling and tenderness. US shows right popliteal vein DVT.
You recommend:

A. Admit to medicine to start anticoagulation
B. CT chest to look for PE
C. Give the first dose of anticoagulation in ED, then outpatient treatment and close follow up
D. Discharge with serial outpatient ultrasounds

Correct answer is c
Question 2

Patient in question 1, treatment options include:

A. UFH bolus and infusion and start warfarin when aPTT is therapeutic
B. LMWH and start warfarin after the 1st dose
C. Rivaroxaban
D. Dabigatran
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G. B, C, D and E

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Which of the following practices have not shown to improve time in therapeutic range (TTR) with warfarin use?

A. Vit K supplementation
B. Pharmacogenetic testing
C. Monitoring by a physician
D. Patient self-management
E. All of the above

Correct answer is E
THANK YOU

manila.gaddh@emory.edu