Less is more?
Low-intensity anticoagulation for the extended treatment of VTE

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ATW Pharmacotherapy Rounds

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Epidemiology

- Estimated incidence: 1.22-1.43 per 1000 patient-years
- DVT: 0.78-1 per 1000 patient-years
- PE: 0.38-0.45 per 1000 patient-years
- Case fatality:
  - 30-day: 1.9-9.6%
  - 1-year: 7.8-19.5%
- DVT: Post-thrombotic syndrome 43%
- PE: Pulmonary hypertension 2.4%

Rates of recurrence

- Major transient risk factor (surgery)
  - 1-year recurrence: 1%
  - 5-year recurrence: 3%
- Non-surgical transient risk factor
  - 1-year recurrence: 5%
  - 5-year recurrence: 15%
- Unprovoked
  - 1-year recurrence: 10%
  - 5-year recurrence: 30%
- Cancer
  - 1-year recurrence: 15%

VTE treatment duration: CHEST 2016

- Provoked
  - 3 months
  - Extended
- Unprovoked
  - High bleeding risk
    - 3 months
  - Low bleeding risk
    - 3 months
    - Extended
- Cancer
  - Extended
  - Indefinite

Rate of recurrent VTE with long-term treatment vs. extended treatment

Kearon et al. 1999

- First unprovoked VTE
  - 3 months of anticoagulation: warfarin vs. placebo x24 months
  - Recurrent VTE at 10 months:
    - Warfarin: 1.3% /year
    - Placebo: 27.4% /year
  - Major bleeding:
    - Warfarin: 3.8% /year
    - Placebo: 0% /year

Objectives

- Examine the rationale behind the recommendations of CHEST 10th Edition of the Antithrombotic Guideline
- Compare risk versus benefit of the extended treatment of venous thromboembolism (VTE)
- Explore the efficacy of different modalities within low-intensity anticoagulation
- Select patient populations suitable for the extended treatment with low-intensity anticoagulation
Rate of recurrent VTE with long-term treatment vs. extended treatment

Agnelli et al. 2001
- First unprovoked DVT
- 3 months of anticoagulation -> warfarin x9 months vs. therapy discontinuation
- >24 months follow-up
- Recurrent VTE:
  - Warfarin: 15.7%
  - Placebo: 15.8%
- Major bleeding:
  - Warfarin: 3%
  - Placebo: 1.5%

Duration of anticoagulation: real life patterns

Treatment >12 months
- PE
- Body weight <75
- HF
- Anemia
- Cancer
- Transient risk factors

Clinical question:
Can low-intensity anticoagulation offer a higher net benefit in the extended treatment of VTE?
Low-intensity anticoagulation: PREVENT trial

- Unprovoked VTE
- Full dose warfarin x >3 months -> low-intensity warfarin (INR 1.5-1.9) vs. placebo
- Rate of recurrent VTE
  - Placebo: 7.2% /year
  - Low-intensity warfarin: 2.6% /year

Low-intensity warfarin is more effective than placebo

\[ P<0.01 \]

\[ N=508 \]

Low-intensity anticoagulation: ELATE trial

- Unprovoked VTE
- >3 months of conventional anticoagulation -> Low-intensity warfarin (INR 1.5-2.0) vs. conventional-intensity warfarin (INR 2-3)
- VTE recurrence
  - Low-intensity: 1.9% /year
  - Conventional-intensity: 0.7% /year
- Major bleeding
  - Low-intensity: 1.1% /year
  - Conventional-intensity: 0.8% /year

Low-intensity warfarin is less effective than conventional-intensity warfarin with no reduction in the rate of major bleeding

\[ N=738 \]

Low-intensity anticoagulation: INSPIRE analysis

- Combined analysis of WARFASA and ASPIRE trials
- First unprovoked VTE
- Initial treatment -> ASA 100 mg vs. placebo
- VTE recurrence
  - ASA: 7.5%/year
  - Placebo: 5.1%/year
- Major bleeding
  - ASA: 0.5%/year
  - Placebo: 0.4%/year

ASA is more effective than placebo with no difference in the rate of major bleeding

\[ N=1244 \]

CHEST 10th Edition of the Antithrombotic Guideline recommendations

- In patients with DVT of the leg or PE who receive extended therapy, we suggest that there is no need to change the choice of anticoagulant after the first 3 months (Grade 2C)
- In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE (Grade 2B)
- We note that whereas apixaban 5 mg bid is used for long-term treatment, apixaban 2.5 mg bid is used for extended therapy

\[ N=2482 \]
Inclusion criteria
• Symptomatic proximal DVT or PE
• Unprovoked, or
• Provoked with risk factors for recurrence

Exclusion criteria
• PLT <100,000/mm$^3$
• Hgb <9 g/dL
• Conditions with high risk of serious bleeding
• SCr >2.5 mg/dL
• CrCl <25 mL/min
• Hepatic disease
• Dual antiplatelet therapy
• ASA >165 mg/day
• Documented thrombophilia
• Cancer with indication for indefinite anticoagulation

Baseline characteristics
• Age – yr: ~57 ±15
• CrCl >50 mL/min: ~90%
• Index event PE: ~35%
• Unprovoked event: ~90%
• Risk factors for recurrence
  • Previous VTE: ~12%
  • Thrombophilia: ~4%
  • Immobilization: ~3%
  • Active cancer: 1.5%
In patients with first unprovoked VTE at low risk of bleeding extended treatment for 12 months with either reduced- or full-dose apixaban after initial 6-12 months of standard anticoagulation significantly reduces the rate of VTE recurrence as compared to placebo.

- Both doses offer comparable reduction

- Reduced-dose apixaban has not been shown to cause less major bleeding events than full-dose

- Rates of major bleeding were low with both doses

In patients with VTE in equipoise for continued anticoagulation, the risk of recurrent event was significantly lower with rivaroxaban at either a treatment dose (20 mg) or a prophylactic dose (10 mg) than with aspirin without a significant increase in bleeding rates.

FDA approval:
Reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE
10 mg once daily after at least 6 months of standard anticoagulant treatment.
EINSTEIN-CHOICE: Critique

- Methods:
  - Not designed to compare reduced to full dose of rivaroxaban
- Intervention
  - Extended treatment duration: 12 months
- Patient population
  - Equipoise is not defined
  - Low risk of bleeding and low risk of recurrence
  - Provoking factors are not specified
  - Unclear if provoking factors persisted beyond completion of initial treatment

Based on the results of EINSTEIN-CHOICE trial, what patient(s) would be candidate(s) for extended treatment with reduced-dose rivaroxaban?

A. 78-year old female with a history of 3 unprovoked DVTs (last ~10 years ago), anemia of CKD and chronic debility
B. 75-year old male with first PE in the setting of 10-day hospitalization and PMH of cirrhosis, GI bleed and DM
C. 47-year old male with distal DVT in the setting of multiple knee arthrocentesis for joint infection and PMH of obesity and DM
D. 25-year old with history of DVT acquired on a flight from Indonesia
E. 37-old male with PE and no PMH

EINSTEIN-CHOICE: Applicability

<table>
<thead>
<tr>
<th>Provoked</th>
<th>Unprovoked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>First incidence</td>
</tr>
<tr>
<td>Low/moderate risk of bleeding</td>
<td>High risk of bleeding</td>
</tr>
<tr>
<td>3 months Grade 1B</td>
<td>3 months Grade 1B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrent</th>
<th>Extended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk of bleeding</td>
<td>Moderate risk of bleeding</td>
</tr>
<tr>
<td>3 months Grade 2B</td>
<td>3 months Grade 2B</td>
</tr>
</tbody>
</table>

EINSTEIN-CHOICE: Conclusion

- In patients with VTE provoked by minor transient risk factors or first unprovoked VTE at low risk of bleeding extended treatment for 12 months with either reduced- or full-dose rivaroxaban after initial 6-12 months of standard anticoagulation results in significant reduction in the rate of VTE as compared to aspirin
  - Full and reduced doses offer comparable risk reduction
- Reduced-dose rivaroxaban has not been shown to cause less major bleeding than full-dose
  - Rates of major bleeding were low with both doses

Reduction of NOACs: meta-analysis

<table>
<thead>
<tr>
<th>Reduced-dose (%)</th>
<th>Full-dose (%)</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1967</td>
<td>N=1920</td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Major/CRNM bleeding</td>
<td>2.7</td>
<td>3.7</td>
</tr>
</tbody>
</table>

CRNM=clinically relevant non major bleeding
RR=risk ratio

Reduced-dose NOACs: meta-analysis

• Critique:
  - Heterogeneous patient population (provoked vs unprovoked VTE)
  - Composite of major and CRNM bleeding for safety outcome

• Conclusion:
  - Extended treatment of VTE with reduced- or full-dose apixaban/rivaroxaban in patients with first unprovoked or provoked by minor transient factors event who are at low risk of bleeding results in comparable risk of recurrent VTE at 12 months
  - There is no difference in the rate of major and CRNM bleeding between the two doses

Conclusion: reduced-dose apixaban/rivaroxaban

• More effective than placebo/ aspirin for the extended treatment of VTE in selected patients with first unprovoked VTE or VTE provoked by minor transient risk factors who are at a low risk of bleeding
  - At 12 months, efficacy is comparable to the efficacy of full-dose treatment, but is not associated with lower incidence of bleeding
  - Cannot be recommended over full-dose extended treatment of VTE

Findings of AMPLIFY-EXT or EINSTEIN-CHOICE do not apply to all the patients receiving extended therapy

Efficacy and safety of reduced-dose anticoagulation was demonstrated for the first 12 months of the extended treatment only

Recommendation: modalities for treatment of provoked VTE

Recommendation: modalities for treatment of first unprovoked VTE

Recommendation: modalities for treatment of recurrent unprovoked VTE

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Appendices

Appendix A. Duration of antithrombotic therapy for VTE disease
Appendix B. Guideline definitions
Appendix C. Predicting risk of VTE recurrence
Appendix D. Algorithm: low-dose anticoagulation for the extended treatment of VTE disease
Appendix E. Abbreviations
Appendix A. Duration of antithrombotic therapy for VTE disease, CHEST 10th Edition of the Antithrombotic Guideline

Appendix B. Definitions

**Duration of treatment**
Long-term therapy: minimum duration of anticoagulation, usually 3 months
Extended therapy: treatment for longer than 3 months, usually indefinitely

**Type of VTE**
**Provoked**
- Major transient risk factor during the 3 months before diagnosis of VTE
  - Surgery with general anesthesia for greater than 30 minutes
  - Confined to bed in hospital
  - Cesarean section
- Minor transient risk factors during the 2 months before the diagnosis of VTE
  - Surgery with general anesthesia for less than 30 minutes
  - Admission to a hospital for less than 30 days with an acute illness
  - Estrogen therapy
  - Pregnancy or puerperium
  - Confinement to bed out of hospital for at least 3 days with an acute illness
  - Leg injury associated with reduced mobility for at least 3 days
  - Flight >8 hours
- Persistent risk factor
  - Active cancer
  - Intrinsic risk factors: hereditary thrombophilias, male sex, older age, chronic inflammatory conditions*
- Unprovoked (idiopathic VTE): not meeting criteria for provoked by a transient risk factor or by cancer**

*Presence of non-environmental or intrinsic risk factors does not influence whether an episode of VTE is considered unprovoked or provoked
**Term unprovoked is preferred

**Bleeding risk**
Low risk of bleeding: no bleeding risk factors
Moderate risk of bleeding: one bleeding risk factor
High risk of bleeding: two or more bleeding risk factors
Appendix C. Predicting risk of VTE recurrence

The Vienna Prediction Model

Risk of recurrence in patients with first unprovoked VTE

**HER DOO2 score**

Women with first unprovoked VTE may be able to discontinue anticoagulation after 5-7 months of therapy if they have <2 of the following factors (annual risk of recurrence <1.6%):

- Post-thrombotic signs: hyperpigmentation, edema, redness of leg
- D-dimer level > 250 microgram/L
- Body mass index > 30 kg/m²
- Age > 65 years


DASH score

Consider long-term anticoagulation only in patients with unprovoked VTE if DASH score ≤1 (annualized recurrence rate 3.9%)

- Abnormal post-coagulation D-dimer: +2 points
- Age <50 years: +1
- Male sex: +1
- Hormone use at the time of VTE (women only): -2
Appendix D.

Any VTE
Completed long-term treatment

**Provoked**
- Surgery
  - Stop therapy
- Other
  - Low risk of bleeding
    - Consider extended therapy
    - Full-dose anticoagulation *PREFERRED*
  - High risk of bleeding
    - Stop therapy
    - Reduced-dose anticoagulation
      - Apixaban 2.5 mg bid or
      - Rivaroxaban 10 mg daily

**Unprovoked**
- First episode
  - Low risk of bleeding
    - Consider extended therapy
    - Full-dose anticoagulation *PREFERRED*
  - Moderate risk of bleeding
    - Stop therapy
    - Reduced-dose anticoagulation
      - Apixaban 2.5 mg bid or
      - Rivaroxaban 10 mg daily
  - High risk of bleeding
    - Aspirin *ONLY if anticoagulation is not feasible (e.g. patient refuses)*

- Recurrent episode
  - Low risk of bleeding
    - Consider extended therapy
    - Full-dose anticoagulation
  - Moderate risk of bleeding
    - Consider stopping therapy
    - Full-dose anticoagulation
Appendix E. Abbreviations

ASA – aspirin
CKD – chronic kidney disease
CrCl – creatinine clearance
CRNM – clinically relevant non-major bleeding
DM – diabetes mellitus
DVT – deep vein thrombosis
FDA – Food and Drug Administration
GIB – gastro-intestinal bleed
Hgb – hemoglobin
INR – international normalized ratio
NOAC – novel anticoagulant
NSAID – non-steroidal anti-inflammatory drug
PE – pulmonary embolism
Plt – platelets
PMH – past medical history
R – randomization
RR – risk ratio
SCr – serum creatinine
VTE – venous thromboembolism