TREATING ACUTE DVT WITH DOACs
ADVANCES AND CHALLENGES

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Disclosure

Speaker name:

Armando Mansilha

I have the following potential conflicts of interest to report:

☑ Consulting
☐ Employment in industry
☐ Stockholder of a healthcare company
☐ Owner of a healthcare company

- Alfa Wassermann
- Bard
- Bayer
- BMS
- Boehringer
- Boston Scientific
- Leo
- Medtronic
- Pfizer
- Pierre Fabre
- Sanofi
- Servier
Principles of VTE treatment

PREVENT short-term and long-term sequelae

PREVENT clot extension, including PE

PREVENT
• Post-thrombotic syndrome
• Chronic thromboembolic pulmonary hypertension

PREVENTION of recurrence
Stages of VTE treatment

Active treatment
- Initial phase: 5-7 days
- Oral anticoagulant

Extended treatment
- Long-term phase: 3-6 months
- Oral anticoagulant
- 3 months - indefinite
- Oral anticoagulant

Agnelli et al. Hematology 2013; 471-47,
Kearon C, and Akl E A Blood 2014;123:1794-1801
Wisconsin Alumni Research Foundation-arin
+ 50 years of experience

- Unpredictable Response
- Routine Monitoring
- Frequent dose adjustments
- Narrow therapeutic window (INR 2-3)
- Slow onset and off-set of action
- Multiple drug interactions
- Multiple diet interactions
- Warfarin resistance

Oral Anticoagulation and Bleeding Risk

**Risk of Bleeding in Oral Anticoagulation Patients**

- Any hemorrhage: 3-6% per year
- Major hemorrhage: 1% per year (requiring admission or transfusion)
- Fatal hemorrhage: 0.3% per year

*ie 1 in 300 patients on warfarin dies from bleeding every year*

**Rate of bleeding according to INR – ISCOAT study**

- All bleeding
- Major bleeding

INR

1 - 2.9
3 - 4.4
4.5 - 6.9
≥7

Events per 100 patients years

100
50
0

Palareti G et al, Lancet 1996
VTE requires acute and extended treatment for prevention of recurrence

<table>
<thead>
<tr>
<th>Initial management</th>
<th>Secondary prophylaxis (3–6 months)</th>
<th>Extended prophylaxis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral AC* ≥5 days¹</td>
<td>Warfarin</td>
<td>Apixaban 10 mg BID 7 days⁵</td>
</tr>
<tr>
<td>Parenteral AC* ≥5 days¹</td>
<td>Dabigatran 150 mg BID¹²</td>
<td>Apixaban 5 mg BID 6 months</td>
</tr>
<tr>
<td>Parenteral AC* ≥5 days¹</td>
<td>Edoxaban 60 mg OD¹³</td>
<td>Apixaban 2.5 mg BID</td>
</tr>
<tr>
<td>Rivaroxaban 15 mg BID 21 days⁴</td>
<td>Rivaroxaban 20 mg OD</td>
<td></td>
</tr>
<tr>
<td>Apixaban 10 mg BID</td>
<td>Apixaban 5 mg BID</td>
<td></td>
</tr>
</tbody>
</table>

*LMWH, Fondaparinux or UFH; †Dabigatran 110 mg BID for aged ≥80 years, concomitant verapamil, or based on individual assessment of thromboembolic/bleeding risk; ‡Edoxaban 30 mg OD for CrCl 15–50 mL/min, weight ≤60 kg, certain concomitant P-gp inhibitors

Acute treatment of DVT/PE: DOACs non-inferior to warfarin for prevention of recurrent DVT/PE in their Phase III trials

<table>
<thead>
<tr>
<th>Study</th>
<th>DOAC</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER™ / RE-COVER™ II*</td>
<td>2.4%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Dabigatran¹</td>
<td>HR: 1.09 (95% CI: 0.76–1.57)</td>
<td>HR: 0.89 (95% CI: 0.66–1.19)</td>
</tr>
<tr>
<td>EINSTEIN-DVT/ EINSTEIN-PE*</td>
<td>2.1%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Rivaroxaban²</td>
<td>HR: 0.84 (95% CI: 0.60–1.18)</td>
<td>HR: 0.82 (95% CI: 0.60–1.14)</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>2.3%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Apixaban³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hokusai-VTE†</td>
<td>1.6%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Edoxaban⁴</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Direct comparisons cannot be made as no head to head data is available

*Pooled data; oral drug treatment period only; †On treatment
Acute treatment of DVT/PE: DOACs associated with less major bleeding versus warfarin in their Phase III trials*

Direct comparisons cannot be made as no head to head data is available

*Statistically significant reductions for dabigatran, rivaroxaban, and apixaban vs warfarin, numerical reduction for edoxaban vs warfarin; †Pooled data; oral drug treatment period only; ‡Pooled analysis; §On treatment

VTE requires acute and extended treatment for prevention of recurrence

**Initial management**
- **Parenteral AC** ≥5 days
- **Parenteral AC** ≥5 days
- **Parenteral AC** ≥5 days
- **Rivaroxaban 15 mg BID**
- **Apixaban 10 mg BID**

**Secondary prophylaxis (3–6 months)**
- Warfarin
- Dabigatran 150 mg BID
- Edoxaban 60 mg OD
- Rivaroxaban 20 mg OD
- Apixaban 5 mg BID

**Extended prophylaxis (years)**
- Rivaroxaban 20 mg OD
- Apixaban 5 mg BID
- Apixaban 2.5 mg BID

*LMWH, fondaparinux or UFH; †Dabigatran 110 mg BID for aged ≥80 years, concomitant verapamil, or based on individual assessment of thromboembolic/bleeding risk; ‡Edoxaban 30 mg OD for CrCl 15–50 mL/min, weight ≤60 kg, certain concomitant P-gp inhibitors

Duration of therapy should be individualized after careful assessment of treatment benefit against risk of bleeding

**Short duration** (at least 3 months):
- Proximal DVT associated with transient risk factors (e.g. recent surgery, trauma, immobilization)
- Distal DVT

**Extended treatment**: Unprovoked DVT or DVT associated with permanent risk factors

Risk of Recurrence

Provoking factor for VTE
- Major reversible risk factor
  - Surgery - very low risk
  - Non-surgical risk factors (trauma, immobilization, pregnancy, estrogens) - low risk
- Persistent or progressive risk factor (cancer) – high risk

Unprovoked VTE
- Several parameters can be evaluated - moderately high risk

Previous VTE
- A second episode of VTE has a 50% higher risk of recurrence compared with the first one

P. de Jong et al. BJH, 2012;158:433-441
Risk of Recurrence – unprovoked VTE

- **Sex** - Men have higher risk than women (HR – 1.9)
- **Site of VTE** - Proximal DVT versus distal DVT – higher risk (HR – 2.08)
- **D-Dimer** (1 month after stopping anticoagulation)
  
  When positive the risk is higher (HR – 2.27)
- **Antiphospholipid syndrome**
  
  Persistent LA or high titers of ACAS or B₂GP₁ – higher risk
- **Hereditary thrombophilias**
  
  AT deficiency or multiple thrombophilias – higher risk
- **Post-thrombotic syndrome**
  
  PTS  Recurrence (ipsilateral DVT)

P. de Jong et al. BJH, 2012;158:433-441
Risk of Bleeding

Patients characteristics
- Older age (>75 ys)
- Previous bleeding
- Cancer
- Hypertension
- Diabetes
- Cerebrovascular disease
- Renal insufficiency
- Liver disease

Antithrombotics
- Poor INR control
- Antiplatelet agents
- NSAIDs

Recent surgery
Frequent falls

P. de Jong et al. BJH, 2012;158:433-441
Primary Efficacy Outcome
Recurrent symptomatic VTE and VTE-related deaths

- RE-SONATE: 0.4%
- EINSTEIN-EXT: 1.3%
- AMPLIFY-EXT: 1.7%

80–92% reduction in events

Safety outcome
Major or CRNM bleedings

Conclusions

- DOACs are non-inferior to warfarin for active VTE treatment - prevention of recurrent or fatal VTE and present a favourable safety profile - significant reductions in major or clinically-relevant non major bleedings with NOACs vs warfarin.

- DOACs can be used for extended treatment with high efficacy and low bleeding risk.

- Easier management

Not approved for:

- VTE associated with cancer
- VTE associated with high-risk thrombophilia (AFS)

Contra-indications:

- Pregnant women
- Patients with severe renal impairment or severe liver disease
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