Anticoagulant Therapy in Venous Thromboembolic Diseases

GEORGE J. RUBEIZ, MD
COMMUNITY HOSPITALS OF INDIANAPOLIS
Oral Anticoagulants in VTE

- Impact of VTE disease
- Complications of VTE
- Review Of Older Anticoagulantants
- Review of Newer Oral Anticoagulants (NOACS)
- CHEST Guidelines Highlights
Oral Anticoagulants in VTE

- Incidence 1-2/1000 in the general population
- Recurrence is one of the major complications
- With full anticoagulation, risk of recurrence in the first 6-12 months 2-3%
- Risk of recurrence: 5-10% within the first year after the discontinuation of anticoagulation
- Yearly risk of significant bleeding 1-2% on warfarin, lower with Newer Oral Anti-Coagulants
- Standard of therapy evolving.
Virchow’s Triad
Rudolf Virchow
1821–1902

Oral Anticoagulants in VTE

- Circulatory Stasis
- Endothelial Injury
- Hypercoagulable State

Fibrin
Platelet
Blood flow
RBC
Oral Anticoagulants in VTE

Lower Extremity Deep Venous Thrombus

Pulmonary Arterial Embolus

Perfusion defect
Oral Anticoagulants in VTE

Consequences of VTE

• Recurrent VTE
• Post-thrombotic syndrome (PTS)$^1$
  – Presence of leg symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and signs (pretibial edema, skin induration, hyperpigmentation, new venous ectasia, redness and pain during calf compression)
• Chronic thromboembolic pulmonary hypertension (CTPH)$^2$
  – Elevated systolic and mean PAP
  – Normal pulmonary-capillary wedge pressure
  – Angiographic abnormalities
• Mortality

Oral Anticoagulants in VTE Post-Thrombotic Syndrome

Telangiectases

Varicose veins

Hyper-Pigmentation

Ulceration

Bergan, et al. NEJM 2006;355:488
Consequences of Idiopathic VTE: High Incidence of Recurrence

Of 528 patients with first-episode, venography-confirmed DVT, 101 experienced ≥1 recurrent VTE.

Patients were treated with an initial course of standard heparin or LMWH (~10 days); oral anticoagulation was initiated during the first week and continued for at least 3 months.

Of 223 patients with first-time, acute PE, 32 experienced ≥1 recurrent VTE during follow up.

Patients were treated with adjusted-dose unfractionated heparin; oral anticoagulation was initiated during the first week and continued for at least 6 months.

Consequences of Idiopathic VTE: High Incidence of Post-thrombotic Syndrome

Of 528 patients with first-episode, venography-confirmed DVT, 119 developed PTS after at least 3 months of treatment with LMWH. Patients were treated with an initial course of standard heparin or LMWH (~10 days); oral anticoagulation was initiated during the first week and continued for at least 3 months.

Consequences of Idiopathic VTE: Chronic Thromboembolic Pulmonary Hypertension

Of 223 patients with first-time acute PE, 7 developed CTPH. CTPH did not develop in any of the 132 remaining patients with more than 2 year follow up. Patients were treated with adjusted-dose unfractionated heparin; oral anticoagulation was initiated during the first week later and continued for at least 6 months.

Oral Anticoagulants in VTE
Older Drugs- Heparin

- 1916: Heparin discovered by Jay McLean, MD
- 1937: Development of pharmacological anticoagulant: introduced for thrombosis treatment
- 1940’s: Clinical utility of UFH in DVT untapped until 1970s use of unfractionated heparin in DVT prophylaxis
- 1980’s (Early): Widespread use as anticoagulant- various indications
- 1980’s (late): Early reports of HIT

Oral Anticoagulants in VTE
Older Drugs- LMW Heparins

Unfractionated Heparin
(heterogeneous mixture extracted for gut mucosa)

LMW Heparin
(heterogeneous mixture)

CLEAVAGE PROCESS
Chemical or enzymatic

BEGETS
Oral Anticoagulants in VTE
Older Drugs - LMW Heparins

High MW and LMW Heparin Chains

- Anti-IIa and anti-Xa
- Sensitivity to PF4
- Non specific binding
- Less inhibition thrombin generation

- Anti-Xa
- Resistant to PF4
- Little non specific binding
- Inhibition thrombin generation

MW (daltons)

% 0 0.1 0.2 0.3 0.4 0.5 0.6 0.7

LMWH

Unfractionated heparin

MW (daltons) 0 5,000 10,000 15,000

18 saccharides

5,400
Oral Anticoagulants in VTE
Older Drugs: Warfarin

- 1930s: farmers noticing cattle hemorrhaging related to eating spoiled sweet clover silage
- 1939: bis-hydroxycoumarin (dicoumarol) identified
- 1948: marketed as potent rat killer
  - Named Warfarin (Wisconsin Alumni Research Foundation)
- 1951: Army recruit failed suicide attempt with dose of warfarin rodenticide
- Subsequent use as a potent anticoagulant for the past 65 years
Oral Anticoagulants in VTE
Older Drugs- Warfarin

• Advantage
  – Low cost
  – Familiarity
  – Effective (if done the “right” way)

• Disadvantage
  – Narrow therapeutic index: requires frequent blood draws for monitoring
  – Multiple drug and/or food interactions
  – Variability in dose response
  – Slow onset
Oral Anticoagulants in VTE
Newer Anticoagulants

- Factor IX
- Factor X
- Factor VII
- Factor II
- Factor IIa
- Fibrinogen
- Fibrin
- Anti-FXa drugs
  - Apixaban
  - Betrixaban
  - Edoxaban
  - Rivaroxaban
  - LY 517717
  - TAK 442
  - YM 150
- Anti-FIIa drugs
  - Dabigatran
  - Ximelagatran
  - AZD 0837
- VKA drugs
  - Tecarfarin
  - Warfarin
# Oral Anticoagulants in VTE

## Newer Anticoagulants

<table>
<thead>
<tr>
<th>Features</th>
<th>Warfarin</th>
<th>New Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable</td>
<td>Fixed</td>
</tr>
<tr>
<td>Dose/Effect relationship</td>
<td>Linear</td>
<td>Predictable</td>
</tr>
<tr>
<td>Indications</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Food effect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Antidote</td>
<td>Yes</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Drug Cost</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>
## Oral Anticoagulants in VTE
### Newer Anticoagulants - Comparison

<table>
<thead>
<tr>
<th>Features</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>IIa</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Molecular Weight</strong></td>
<td>628</td>
<td>436</td>
<td>460</td>
<td>548</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Bioavailability (%)</strong></td>
<td>6</td>
<td>80</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td><strong>Time to peak (h)</strong></td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Half-life (h)</strong></td>
<td>12-17</td>
<td>9-17</td>
<td>9-14</td>
<td>9-10</td>
</tr>
<tr>
<td><strong>Renal excretion (%)</strong></td>
<td>80</td>
<td>36 (unchgd)</td>
<td>65 (total)</td>
<td>25 (total)</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>Yes</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Product Information.
Ufer M. Thrombosis and Haemostasis. 2010;103:572-585
### Oral Anticoagulants in VTE

#### Newer Anticoagulants - Indications

<table>
<thead>
<tr>
<th>Features</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Ila</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Stroke Red NVAF</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>VTE treatment</strong></td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
</tr>
<tr>
<td><strong>Extended VTE</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Orthopedic</strong></td>
<td>Hip</td>
<td>Hip/Knee</td>
<td>Hip/Knee</td>
<td>No</td>
</tr>
<tr>
<td><strong>Medical prophylaxis</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>Yes</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

* After initial 5-10 days of parenteral therapy
## Oral Anticoagulants in VTE
### Factor XA Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>EINSTEIN DVT and PE* (N=8281)</th>
<th>AMPLIFY (N=5395)</th>
<th>RE-COVER I and II* (N=5107)</th>
<th>HOKUSAI (N=8240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT only, N (%)</td>
<td>3389 (40.9)</td>
<td>3532 (65.5)</td>
<td>3499 (68.5)</td>
<td>4921 (59.7)</td>
</tr>
<tr>
<td>PE only, N (%)</td>
<td>3597 (43.4)</td>
<td>1359 (25.2)</td>
<td>1136 (22.2)</td>
<td>2505 (30.4)</td>
</tr>
<tr>
<td>Unprovoked event, N (%)</td>
<td>5255 (63.5)</td>
<td>4845 (89.8)</td>
<td>1817 (35.6)</td>
<td>5410 (65.7)</td>
</tr>
<tr>
<td>Recent trauma/surgery, N (%)</td>
<td>1486 (17.9)</td>
<td>Excluded</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Cancer at baseline, N (%)</td>
<td>462 (5.6)</td>
<td>169 (3.1)</td>
<td>221 (4.3)</td>
<td>208 (2.5)</td>
</tr>
<tr>
<td>Elderly, N (%)</td>
<td>1283 (15.5)</td>
<td>749 (13.9)</td>
<td>529 (10.4)</td>
<td>1104 (13.4)</td>
</tr>
<tr>
<td>Previous VTE, N (%)</td>
<td>1610 (19.4)</td>
<td>872 (16.2)</td>
<td>1099 (21.5)</td>
<td>1520 (18.4)</td>
</tr>
</tbody>
</table>
Oral Anticoagulants in VTE
Factor XA Inhibitors

_F Xa may be a better target than thrombin_

- Has few functions outside coagulation (compared with thrombin)
- Has a wider therapeutic window than thrombin (separation of efficacy and bleeding), _in vitro_
- Thrombin inhibitors are associated with rebound thrombin generation; no evidence with Xa inhibitors
- Efficacy of heparin-based anticoagulants improves as anti-Xa selectivity increases: UFH < LMWH < fondaparinux
Oral Anticoagulants in VTE
Factor XA Inhibitors

EXTENDED ANTICOAGULATION

Factors That Determine Extended Anticoagulation
- Unprovoked DVT
- Active Cancer
- Location
- First, second or subsequent event

Guidelines Recommend Extended Anticoagulation if:
- First unprovoked proximal DVT and low/moderate risk of bleeding
- VTE and active cancer and low, moderate or high risk of bleeding
- A second unprovoked VTE and low or moderate risk of bleeding

Kearon C. et al. Chest 2012;141 (2 Supl);e419S-e494S
Oral Anticoagulants in VTE
Factor XA Inhibitors

EXTENDED ANTICOAGULATION

Vienna Prediction Model

Risk Factors predictive of higher recurrence rate in unprovoked VTE

- Male Sex
- Proximal DVT as opposed to distal
- PE as opposed to DVT
- Elevated D-dimer levels

Oral Anticoagulants in VTE

Potential Concerns of Novel Anticoagulants

• No or limited FDA-approved antidotes
• No methods assessing compliance
• No monitoring
• Reduced awareness of the therapy
• Cost
Oral Anticoagulants in VTE
Factor XA Inhibitors

- XIIa
- Xla
- IXa
- VIIa

Tissue factor

Rivaroxaban
Apixaban
Edoxaban
LMH

Factor II (prothrombin)

Fibrinogen → Fibrin clot

Dabigatran
DTI
LMH
1. In patients with proximal DVT or pulmonary embolism (PE), we recommend long-term (3 months) anticoagulant therapy over no such therapy (Grade 1B).
For patients with DVT of the leg or PE and no cancer who are not treated with dabigatran, rivaroxaban, apixaban, or edoxaban, we suggest VKA therapy over low-molecular weight heparin (LMWH) (Grade 2C).

2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).
Remarks: Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy.
3. In patients with DVT of the leg or PE and cancer (“cancer-associated thrombosis”), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C).

4. 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).

Remarks: It may be appropriate for the choice of anticoagulant to change in response to changes in the patient's circumstances or preferences during long-term or extended phases of treatment.
5. In patients with a proximal DVT of the leg or PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B), or (iii) extended therapy (no scheduled stop date) (Grade 1B).

6. In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B) and (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B), and recommend treatment for 3 months over extended therapy if there is a high risk of bleeding (Grade 1B). Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).
7. In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor, we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C), we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B), and we recommend treatment with anticoagulation for 3 months over extended therapy (no scheduled stop date) (Grade 1B).

Remarks: Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however, it is anticipated that not all patients who are diagnosed with isolated distal DVT will be prescribed anticoagulants.
8. In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B), and we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B).

Remarks: After 3 months of treatment, patients with unprovoked DVT of the leg or PE should be evaluated for the risk-benefit ratio of extended therapy. Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however, it is anticipated that not all patients who are diagnosed with isolated distal DVT will be prescribed anticoagulants.
9. In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).

Remarks: Patient sex and D-dimer level measured a month after stopping anticoagulant therapy may influence the decision to stop or extend anticoagulant therapy (see text). In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).
10. In patients with a second unprovoked VTE and who have a (i) low bleeding risk (see text), we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months (Grade 1B); (ii) moderate bleeding risk (see text), we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B); or (iii) high bleeding risk (see text), we suggest 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 2B).

Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).
Aspirin for Extended Treatment of VTE

12. 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).

Remarks: Because aspirin is expected to be much less effective at preventing recurrent VTE than anticoagulants, we do not consider aspirin a reasonable alternative to anticoagulant therapy in patients who want extended therapy. However, if a patient has decided to stop anticoagulants, prevention of recurrent VTE is one of the benefits of aspirin that needs to be balanced against aspirin's risk of bleeding and inconvenience. Use of aspirin should also be reevaluated when patients stop anticoagulant therapy because aspirin may have been stopped when anticoagulants were started.
13. In patients with acute isolated distal DVT of the leg and (i) without severe symptoms or risk factors for extension (see text), we suggest serial imaging of the deep veins for 2 weeks over anticoagulation (Grade 2C) or (ii) with severe symptoms or risk factors for extension (see text), we suggest anticoagulation over serial imaging of the deep veins (Grade 2C).

Remarks: Patients at high risk for bleeding are more likely to benefit from serial imaging. Patients who place a high value on avoiding the inconvenience of repeat imaging and a low value on the inconvenience of treatment and on the potential for bleeding are likely to choose initial anticoagulation over serial imaging.

14. In patients with acute isolated distal DVT of the leg who are managed with anticoagulation, we recommend using the same anticoagulation as for patients with acute proximal DVT (Grade 1B).
Catheter-Directed Thrombolysis for Acute DVT of the Leg

16. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over CDT (Grade 2C).

Remarks: Patients who are most likely to benefit from CDT, who attach a high value to prevention of postthrombotic syndrome (PTS), and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.

Compression Stocking to Prevent PTS

18. In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS (Grade 2B).

Remarks: This recommendation focuses on prevention of the chronic complication of PTS and not on the treatment of symptoms. For patients with acute or chronic symptoms, a trial of graduated compression stockings is often justified.
Whether to Anticoagulate Subsegmental PE

19. In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation (Grade 2C) or (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance (Grade 2C).

Remarks: Ultrasound imaging of the deep veins of both legs should be done to exclude proximal DVT. Clinical surveillance can be supplemented by serial US imaging of the proximal deep veins of both legs to detect evolving DVT (see text). Patients and physicians are more likely to opt for clinical surveillance over anticoagulation if there is good cardiopulmonary reserve or a high risk of bleeding.
Treatment of Acute PE Out of the Hospital

20. In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (eg, after the first 5 days of treatment) (Grade 2B).
Catheter-Based Thrombus Removal for the Initial Treatment of PE

24. Patients with acute PE and are treated with thrombolytic agent, we suggest systemic thrombolytic therapy using a peripheral vein over CDT (Grade 2C).

Remarks: Patients who have a higher risk of bleeding with systemic thrombolytic therapy and who have access to the expertise and resources required to do CDT are likely to choose CDT over thrombolytic therapy.

25. In patients with acute PE associated with hypotension and who have (i) a high bleeding risk, (ii) failed systemic thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise/resources are available, we suggest catheter-assisted thrombus removal over no such intervention (Grade 2C).

Remarks: Catheter-assisted thrombus removal refers to mechanical interventions, with or without catheter directed thrombolysis.
29. In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily (Grade 2C).

Remarks: Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and should prompt the following assessments: (1) reevaluation of whether there truly was a recurrent VTE; (2) evaluation of compliance with anticoagulant therapy; and (3) consideration of an underlying malignancy. A temporary switch to LMWH will usually be for at least 1 month.

30. In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), we suggest increasing the dose of LMWH by about one-quarter to one-third (Grade 2C).

Remarks: Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and should prompt the following assessments: (1) reevaluation of whether there truly was a recurrent VTE; (2) evaluation of compliance with anticoagulant therapy; and (3) consideration of an underlying malignancy.
Oral Anticoagulants in VTE
Newer Anticoagulants

- **Thrombin Inhibitors**
  1. **Dabigatran**: pro-drug, renal clearance - twice daily

- **Factor Xa Inhibitors**
  1. **Rivaroxaban**: renal/hepatic clearance - once daily
  2. **Apixaban**: hepatic >> renal clearance - twice daily
  3. **Edoxaban**: hepatic > renal clearance - once daily

*Adapted from Circulation 2010;121:1523-1532*