Lecture Themes

• VTE pathogenesis, etiology, and risk factors
• Investigation of suspected DVT/VTE
• VTE prophylaxis in medical patients
• Diagnosis of existing DVT in medical patients
• VTE treatment
• Role of NOACs in management of VTE
• Anticoagulation and bleeding
• More aggressive treatments for VTE

VTE Pathogenesis, Etiology, and Risk Factors

Pathogenesis of DVT and VTE

Distribution of DVT

• Deep veins of the calf
  – If isolated in calf, symptoms are uncommon
  – One-quarter to one-third extend to proximal veins if untreated
• Proximal lower extremity veins
  – Popliteal, common femoral, superficial femoral, iliac, pelvic
  – More likely to embolize to lungs
• Upper extremity veins
  – Rarer, less data available on diagnosis and treatment

VTE Epidemiology in the United States

- There are an estimated 900,000 discrete cases of VTE each year.
- There are 350,000 – 600,000 new VTE cases annually.
  - Two-thirds DVT, one-third PE.
  - More than 40% of DVT cases develop post-thrombotic syndrome.
- 3rd most common life-threatening CV disease.
  - Behind only MI and cerebrovascular accidents.
- Estimates of more than 100,000 deaths related to DVT/PE annually.
- Leading preventable cause of in-hospital death.

1. Available at: www.cdc.gov/ncbddd/dvt/data.html.

VTE and PE

Presentation and Consequences

- Leg swelling, discomfort (DVT)
- Dyspnea, chest pain, hemoptysis, hypoxemia (PE)
- Extended hospital length of stay
- Fatal PE (right ventricular failure)
- Treatment requires ≥3 months of anticoagulation
- Consequences of VTE/PE
  - Post-thrombotic syndrome
  - Chronic thromboembolic pulmonary hypertension (~4%)

Risk Factors for VTE: Virchow’s Triad

- **Venous Stasis**
  - Age >40
  - Immobility
  - CHF
  - Stroke
  - Paralysis, spinal cord injury
  - Hyponatremia, polythemia
  - Severe COPD
  - Anesthesia
  - Obesity
  - Varicose veins

- **Activation of coagulation**
  - Cancer
  - High estrogen states
  - Nephritic syndrome
  - Smoking
  - Pregnancy
  - Thrombophilia
  - Genetic disorders
  - Factor V Leiden
  - Antiphospholipid syndrome

- **Endothelial Damage**
  - Surgery
  - Prior VTE
  - Central invasive lines
  - Trauma
  - Sepsis

Risk Factors for VTE

- Growing incidence: increasing healthcare costs
- Surgeon General’s / NHLBI Workshop May 2006:
  - Opened new funding opportunities
  - National Quality Forum / The Joint Commission workshops 2006-08:
    - Focused jointly on VTE, proper anticoagulant use
  - Surgeon General’s report September 2008:
    - “Call to Action,” “Critical Research Priority.”
- VTE prevention is now a quality indicator, pay-for-performance criterion.


Changing Epidemiology of VTE

- Increasing age
  - Population is aging; fastest growing US demo is >75 years old
- Obesity
  - Incidence never higher
- Cancer:
  - Increasingly common; patients live longer after diagnosis
- Heart failure
  - Better medical and device therapy prolongs life
  - Other chronic illnesses / debilities associated with longer lifespan.

Investigation of Suspected DVT and PE

Differential Diagnosis of DVT
Conditions to be Ruled Out

- Cellulitis
- Baker's cyst
- Gout
- RA and other arthritides
- Pregnancy
- Venous obstruction without active DVT
- Lymphangitis
- Lymphatic obstruction
- Erythema nodosum
- Nonthrombotic effects of trauma
- Congestive heart failure
- Contact dermatitis

Presentation of DVT Varies by Setting
The DVT-Free Registry

<table>
<thead>
<tr>
<th>VTE Sign/Symptom</th>
<th>Presented as Outpatient (n = 2,725)</th>
<th>Presented as Inpatient (n = 2,726)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>41 (2%)</td>
<td>289 (11%)</td>
</tr>
<tr>
<td>Limb edema</td>
<td>2,241 (82%)</td>
<td>1,610 (59%)</td>
</tr>
<tr>
<td>Limb discomfort</td>
<td>1,902 (70%)</td>
<td>1,000 (37%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>450 (17%)</td>
<td>224 (8%)</td>
</tr>
<tr>
<td>Difficulty walking</td>
<td>359 (13%)</td>
<td>174 (6%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>363 (13%)</td>
<td>649 (24%)</td>
</tr>
</tbody>
</table>

Risk Factors for VTE and Bleeding in Medical Patients

Risk Factors for VTE in Hospitalized Medical Patients (PADUA: high risk is ≥ 4 points)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>3</td>
<td>Active peptic ulcer</td>
<td>4.15 (2.21-7.77)</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>3</td>
<td>Bleeding 3 mos</td>
<td>3.66 (2.21-5.99)</td>
</tr>
<tr>
<td>Reduced mobility</td>
<td>3</td>
<td>Platelets ≤50K</td>
<td>3.37 (1.84-6.47)</td>
</tr>
<tr>
<td>Known thrombophilic condition</td>
<td>3</td>
<td>Age 285 (vs &lt; 40)</td>
<td>2.86 (1.43-6.15)</td>
</tr>
<tr>
<td>Age ≥70</td>
<td>1</td>
<td>Hepatic (INR ≤1.5)</td>
<td>2.14 (1.19-3.93)</td>
</tr>
<tr>
<td>Renal (GFR &lt;30)</td>
<td>1</td>
<td>Renal (GFR &lt;30)</td>
<td>2.14 (1.44-3.19)</td>
</tr>
<tr>
<td>Heart and/or resp failure</td>
<td>1</td>
<td>ICU/CCU admission</td>
<td>2.19 (1.42-3.39)</td>
</tr>
<tr>
<td>AMI or ischemic CVA</td>
<td>1</td>
<td>Central venous cath</td>
<td>1.85 (1.18-2.86)</td>
</tr>
<tr>
<td>Acute infection or rheum disorder</td>
<td>1</td>
<td>Rheum disorder</td>
<td>1.78 (1.59-2.99)</td>
</tr>
<tr>
<td>BMI ≥30</td>
<td>1</td>
<td>Current cancer</td>
<td>1.75 (1.29-2.34)</td>
</tr>
</tbody>
</table>

VTE Prophylaxis in Medical Patients

- Emergency Physician / Hospitalist Opportunities
  - Early risk stratification
  - Thrombosis and bleeding risk
  - Serial re-assessments (including at time of discharge)
  - Early initiation of appropriate prophylaxis
  - Assurance of seamless transitions of care
  - Recognize if prophylaxis still being used at post-discharge ED visit
  - Address re-admission penalty issues
National Recommendations

• American College of Chest Physicians (ACCP)\(^1\): "We recommend that every hospital develop a formal strategy that addresses the prevention of thromboembolic complications"

• National Quality Forum (NQF)\(^2\): Evaluate each patient upon admission, and periodically thereafter, for the risk of DVT/PE. Utilize clinically appropriate methods to prevent DVT/VTE (Safe Practice 17)

• Joint Commission on Accreditation of Healthcare Organizations (JCAHO)\(^3\): Contraindications to DVT prophylaxis must be documented

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VTE Prophylaxis (Medical Patients)

2012 ACCP Guidelines

• For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with low-molecular-weight heparin [LMWH], low-dose unfractionated heparin (LDUH) bid, LDUH bid, or fondaparinux (Grade 1B)

• For acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding, we recommend against anticoagulant thromboprophylaxis (Grade 1B)

• For acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding, we suggest the optimal use of mechanical thromboprophylaxis with graduated compression stockings (GCS) (Grade 2C) or intermittent pneumatic compression (IPC) (Grade 2C) rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis (Grade 2B)

• In acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (Grade 2B)

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Investigation of Potential DVT

• DVT must be confirmed by objective tests for risk stratification and determination of pretest probability

**Radiology**
- Venography
- Duplex doppler
- CT venography
- MRI
- I\(^{125}\) fibrinogen uptake

**Laboratory**
- D-dimer
- Clotting factor assays

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VTE: Compression Doppler Ultrasound

("Doppler" or "Duplex Scan")

Diagnosis of Existing DVT in Medical Patients

Admissions into the Emergency Department

Diagnostic and Treatment Algorithm for Suspected DVT

Low Probability
- D-dimer
- Follow-up
- Duplex or echo / fond, outpatient testing
- Follow-up
- Treat

Intermediate Probability
- Duplex
- Venogram/SUS
- Treat

High Probability
- Duplex
- Venogram
- Treat

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3. Available at: www.jcaho.org/pms/core+measures/2adicu3dvt.pdf.
VTE Treatment

Traditional Initial Management of DVT in the ED
Ninth ACCP Consensus: 2012

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1C</td>
<td>Initial treatment with LMWH, UFH, or fondaparinux for at least 5 days and until the INR is ≥2.0 for 24 hours.</td>
</tr>
<tr>
<td>1A</td>
<td>Initiation of VKA together with LMWH, UFH, or fondaparinux on the first treatment day rather than delayed initiation of VKA.</td>
</tr>
<tr>
<td>1B</td>
<td>In patients with acute DVT of the leg and whose home circumstances are adequate, we recommend initial treatment at home over treatment in hospital.</td>
</tr>
<tr>
<td>2C</td>
<td>In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT). Patients who are most likely to benefit from CDT (extensive acute proximal [e.g., iliofemoral] DVT, symptoms for &lt;14 days, good functional status, life expectancy ≥1 year), who attach a high value to prevention of post-thrombotic 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.</td>
</tr>
</tbody>
</table>

Duration of Treatment for VTE

<table>
<thead>
<tr>
<th>VTE Condition</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provoked (transient, reversed risk)</td>
<td>3 months</td>
</tr>
<tr>
<td>Unprovoked</td>
<td>Indefinite*</td>
</tr>
<tr>
<td>Continuing Risk</td>
<td>Indefinite*</td>
</tr>
<tr>
<td>Unresolved cancer</td>
<td></td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td></td>
</tr>
</tbody>
</table>

* Need to make periodic assessment regarding:
  1. New patient risk factors for bleeding, thrombosis
  2. New knowledge
  3. Patient preference

Traditional Typical Outpatient DVT Regimen

- Enoxaparin 1 mg/kg SQ or fondaparinux 7.5 mg SQ in ED
- Patient and family teaching (perhaps in observation unit)
- Dispense enoxaparin or fondaparinux (5d supply) and warfarin (28x2.5 mg tabs)
- Enoxaparin 1 mg/kg SQ BID or fondaparinux 7.5 mg
- Warfarin titrated dose 2.5-10 q PM
- Daily INR for 5 days

Role of NOACs in Management of VTE
New Oral Agents

![Diagram showing the common pathway of thrombin and Xa blockers: Apixaban, Edoxaban, Rivaroxaban.]

New Paradigm Shift in the Management of VTE

- Some NOACs do not require bridging
- Fast onset of action
- Oral administration
- No need for routine INR monitoring
- Limited drug-drug and drug-food interactions

Changing the Paradigm – Outpatient

- Some new oral anticoagulants may offer VTE treatment without bridging to warfarin
- Could greatly facilitate VTE management by emergency physicians and hospitalists
- NOACs currently approved by FDA for VTE treatment:
  - Apixaban
  - Dabigatran
  - Edoxaban
  - Rivaroxaban

Treatment of DVT/PE: 3 Options

1. LMWH Injections, Once a Day
   - Warfarin (INR 2.0-3.0)

2. 5-7 Days of Treatment
   - Low Molecular Weight Heparin injections once a day
   - Direct oral anticoagulant (rivaroxaban, apixaban suitable as monotherapy; edoxaban, dabigatran require lead-in therapy)

NOAC Acute Treatment: Study Regimens

<table>
<thead>
<tr>
<th>Trial</th>
<th>Initial Heparin/Fondaparinux</th>
<th>Duration, months</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>No</td>
<td>6</td>
<td>BID</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>No</td>
<td>6</td>
<td>BID</td>
</tr>
<tr>
<td>RE-COVER</td>
<td>Yes</td>
<td>6</td>
<td>BID</td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>Yes</td>
<td>6</td>
<td>BID</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Yes</td>
<td>3–12</td>
<td>QD</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>No</td>
<td>3, 6, or 12</td>
<td>QD</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>No</td>
<td>3, 6, or 12</td>
<td>QD</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>No</td>
<td>3, 6, or 12</td>
<td>QD</td>
</tr>
</tbody>
</table>

Acute VTE Treatment Trials

<table>
<thead>
<tr>
<th>Drug, dosing</th>
<th>RE-COVER1,2</th>
<th>EINSTEIN3,4</th>
<th>AMPLIFY5</th>
<th>HOKUSAI6</th>
</tr>
</thead>
<tbody>
<tr>
<td>m</td>
<td>5132</td>
<td>8282</td>
<td>5400</td>
<td>8240</td>
</tr>
<tr>
<td>Design</td>
<td>2x blind</td>
<td>PROBE</td>
<td>2x blind</td>
<td>2x blind</td>
</tr>
<tr>
<td>Indication</td>
<td>VTE</td>
<td>DVT or PE</td>
<td>VTE</td>
<td>VTE</td>
</tr>
<tr>
<td>Heparin bridge</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Duration, months</td>
<td>6</td>
<td>3, 6, 12</td>
<td>6</td>
<td>3, 6, 12</td>
</tr>
</tbody>
</table>

Efficacy of NOACs in Acute Venous Thromboembolism: Recurrent VTE

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>NOAC %</th>
<th>Warfarin %</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER1</td>
<td>Dabigatran</td>
<td>2.4</td>
<td>2.1</td>
<td>1.10 (0.65-1.84)</td>
</tr>
<tr>
<td>Einstein-DVT2</td>
<td>Rivaroxaban</td>
<td>2.1</td>
<td>3.0</td>
<td>0.68 (0.45-1.48)</td>
</tr>
<tr>
<td>Einstein-PE3</td>
<td>Rivaroxaban</td>
<td>2.1</td>
<td>1.8</td>
<td>1.12 (0.75-1.68)</td>
</tr>
<tr>
<td>AMPLIFY4</td>
<td>Apixaban</td>
<td>2.3</td>
<td>2.7</td>
<td>0.84 (0.60-1.18)</td>
</tr>
<tr>
<td>HOKUSAI-VTE5</td>
<td>Edoxaban</td>
<td>3.2</td>
<td>3.5</td>
<td>0.89 (0.70-1.13)</td>
</tr>
</tbody>
</table>


Safety of NOACs in Acute Venous Thromboembolism: Major Bleeding

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>NOAC %</th>
<th>Warfarin %</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER1</td>
<td>Dabigatran</td>
<td>1.6</td>
<td>1.9</td>
<td>0.82 (0.45-1.48)</td>
</tr>
<tr>
<td>EINSTEIN-DVT2</td>
<td>Rivaroxaban</td>
<td>0.8</td>
<td>1.2</td>
<td>0.65 (0.33-1.30)</td>
</tr>
<tr>
<td>EINSTEIN-PE3</td>
<td>Rivaroxaban</td>
<td>1.1</td>
<td>2.2</td>
<td>0.48 (0.31-0.79)</td>
</tr>
<tr>
<td>EINSTEIN (pooled)</td>
<td>Rivaroxaban</td>
<td>1.0</td>
<td>1.7</td>
<td>0.54 (0.37-0.79)</td>
</tr>
<tr>
<td>AMPLIFY5</td>
<td>Apixaban</td>
<td>0.6</td>
<td>1.8</td>
<td>0.31 (0.17-0.55)</td>
</tr>
<tr>
<td>HOKUSAI-VTE6</td>
<td>Edoxaban</td>
<td>1.4</td>
<td>1.6</td>
<td>0.84 (0.59-1.21)</td>
</tr>
</tbody>
</table>


NOAC Acute Treatment: Meta-analysis of Efficacy/Safety

NOACs decrease the risk for recurrent VTE and major bleeding compared with VKAs

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pooled Abs Risk Difference, % (95% CI)</th>
<th>NNT With NOAC to Prevent 1 Event (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>-0.24 (-0.60–0.11)</td>
<td>417 (167 to -909)</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>0.01 (-0.06–0.08)</td>
<td>10,000 (1667 to -1250)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>-0.19 (-0.07–0.02)</td>
<td>10,000 (213 to -585)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>-0.60 (-1.33 to 0.12)</td>
<td>148 (64–476)</td>
</tr>
<tr>
<td>Non-fatal bleeding, critical site</td>
<td>-0.38 (-0.65 to 0.18)</td>
<td>239 (153-1066)</td>
</tr>
<tr>
<td>CRNM bleeding</td>
<td>-1.77 (-3.40 to -0.15)</td>
<td>1111 (588–2239)</td>
</tr>
<tr>
<td>Non-fatal ICH</td>
<td>0.14 (-0.03–0.30)</td>
<td>914 (232 to 3333)</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>-0.16 (-0.42–0.11)</td>
<td>1111 (588–2239)</td>
</tr>
<tr>
<td>Non-fatal ICH</td>
<td>0.14 (-0.31–0.03)</td>
<td>1111 (588–2239)</td>
</tr>
</tbody>
</table>

NOACs Compared With LMWH and Warfarin

Efficacy
- All 4 NOACs are noninferior to LMWH/VKA for efficacy, regardless of weight, PE vs DVT, chronic kidney disease, and cancer
- Edoxaban: prespecified submassive PE subgroup showed superiority

Safety of NOACs combined (meta-analysis; n=27,023)
- 38% less major bleeding
- 64% less fatal bleeding
- 63% less ICH than LMWH/VKA

Relative Comparison of NOACs

VTE recurrence and rates of major or clinically relevant non-major bleeding in VTE studies that compared NOACs with either LMWH and VKAs or VKAs

Take-home Message: Which NOAC?

Expert Opinions – Based on Clinical Characteristics and Affordability

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NOACs</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received initial parenteral anticoagulation</td>
<td>Apixaban, dabigatran, edoxaban, rivaroxaban</td>
<td>Allowance of 48–72 h of initial treatment before randomization</td>
</tr>
<tr>
<td>Chronic NSAID use</td>
<td>Apixaban</td>
<td>Concomitant use allowed in trial</td>
</tr>
<tr>
<td>Adherence challenges</td>
<td>Apixaban, rivaroxaban</td>
<td>Once-daily dosing</td>
</tr>
<tr>
<td>Propensity for bleeding</td>
<td>Apixaban, rivaroxaban</td>
<td>Clinical reductions in major bleeding</td>
</tr>
<tr>
<td>Multiple concomitant medications with potential drug interactions</td>
<td>Apixaban, edoxaban</td>
<td>Allow for dose reduction</td>
</tr>
<tr>
<td>Affordability</td>
<td>None; use aspirin or patient preference</td>
<td>NOACs have similar costs</td>
</tr>
</tbody>
</table>

NSAID = non-steroidal anti-inflammatory drug

For venous thromboembolism (VTE) and no cancer, as long-term anticoagulant therapy, we suggest dabigatran (Grade 2B), rivaroxaban (Grade 2B), apixaban (Grade 2B) or edoxaban (Grade 2B) over vitamin K antagonist (VKA) therapy, and suggest VKA therapy over LMWH (Grade 2C).

For VTE and cancer, we suggest low molecular weight heparin (LMWH) over VKA (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C) or edoxaban (Grade 2C).

We have not changed recommendations for who should stop anticoagulation at 3 months or receive extended therapy.

For VTE treated with anticoagulants, we recommend against an inferior vena cava filter (IVC) filter (Grade 1B).

For deep vein thrombosis (DVT), we suggest not using compression stockings routinely to prevent PTS (Grade 2B).

For subsegmental pulmonary embolism (PE) and no proximal DVT, we suggest clinical surveillance over anticoagulation with a low risk of recurrent VTE (Grade 2C), and anticoagulation over clinical surveillance with a high risk (Grade 2C).

We suggest thrombolytic therapy for PE with hypotension (Grade 2B), and systemic therapy over catheter directed thrombolysis (Grade 2C).

For recurrent VTE on a non-LMWH anticoagulant, we suggest LMWH (Grade 2C), and for recurrent VTE on LMWH we suggest increasing the LMWH dose (Grade 2C).


### Antithrombotic Therapy for VTE Disease

#### 2016 AACP CHEST Guideline

- For venous thromboembolism (VTE) and no cancer, as long-term anticoagulant therapy, we suggest dabigatran (Grade 2B), rivaroxaban (Grade 2B), apixaban (Grade 2B) or edoxaban (Grade 2B) over vitamin K antagonist (VKA) therapy, and suggest VKA therapy over LMWH (Grade 2C).
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- We have not changed recommendations for who should stop anticoagulation at 3 months or receive extended therapy.
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- We suggest thrombolytic therapy for PE with hypotension (Grade 2B), and systemic therapy over catheter directed thrombolysis (Grade 2C).
- For recurrent VTE on a non-LMWH anticoagulant, we suggest LMWH (Grade 2C), and for recurrent VTE on LMWH we suggest increasing the LMWH dose (Grade 2C).


### Take-home Message: Which NOAC?

**Expert Opinions – Based on Comorbidity Issues**

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>NOAC</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal dysfunction CrCl ≤25 to ≥30 mL/min</td>
<td>Apixaban</td>
<td>Trial exclusion criteria</td>
</tr>
<tr>
<td>PE with elevated biomarkers</td>
<td>Edoxaban</td>
<td>Subpopulations in trial with high-risk features</td>
</tr>
<tr>
<td>Prior MI</td>
<td>Apixaban, Edoxaban, Rivaroxaban</td>
<td>MI events associated with dabigatran</td>
</tr>
<tr>
<td>Cancer and thrombophilia</td>
<td>None</td>
<td>Limited data</td>
</tr>
<tr>
<td>Low body weight (&lt;60 kg)</td>
<td>Edoxaban</td>
<td>Trial dosing adjustment</td>
</tr>
</tbody>
</table>

MI = myocardial infarction


### Take-home Message: Options for Acute VTE Treatment

- All four NOACs are non-inferior to LMWH and warfarin for efficacy
- All four NOACs have less bleeding risk than LMWH and warfarin

### Managing Bleeding with NOACs

1. **Review**
   - Stop anticoagulation and antiplatelet therapy
   - Review time of last dose of anticoagulant
   - Review medications including aspirin, P2Y12 inhibitors, NSAIDs, P-gp inhibitors, CYP3A4 inhibitors
   - Assess for comorbid conditions, check for evidence of cardiac decompensation
   - Order baseline laboratory parameters including CBC with platelets, renal function tests, PT, aPTT
   - Maintain organ perfusion
   - Volume resuscitation
   - Pressors
   - Identify source of bleeding
   - Evaluate for transfusion

2. **Remove**
   - Gastric lavage for recent ingestion
   - Oral charcoal
   - Dialysis (dabigatran)

3. **Repair**
   - Assess need for surgery

4. **Reverse**
   - Vitamin K antagonists
     - Vitamin K
     - Contraindicated for poor hemodynamic condition
     - 4-factor prothrombin complex concentrate (FFP) for thrombocytopenia or if patient received anticoagulants
   - Direct acting oral anticoagulants
     - Consider FFP for poor hemodynamic condition
     - 4-factor prothrombin complex concentrate
     - Platelet transfusion (for thrombocytopenia or if patient received anticoagulants)

### Characteristics of Therapies for Warfarin Reversal

<table>
<thead>
<tr>
<th>Product</th>
<th>Time to Effect</th>
<th>Duration of Effect</th>
<th>Evidence for reversal efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral vitamin K</td>
<td>24 h</td>
<td>Days</td>
<td>++++</td>
</tr>
<tr>
<td>Intravenous vitamin K</td>
<td>8-12 h</td>
<td>Days</td>
<td>++++</td>
</tr>
<tr>
<td>Fresh frozen plasma (FFP)</td>
<td>Immediate</td>
<td>12-24 h</td>
<td>+++</td>
</tr>
<tr>
<td>Prothrombin concentrate complexes (PCC)</td>
<td>Immediate</td>
<td>12-24 h</td>
<td>++</td>
</tr>
<tr>
<td>Recombinant factor VIIa</td>
<td>Immediate</td>
<td>2-6 h</td>
<td>+</td>
</tr>
</tbody>
</table>

ACCP Guidelines for Reversing VKA Associated Bleeding

The Role of Vitamin K Reversal Differs for Managing an Elevated INR vs a Major Bleed

**ACCP Guidelines**

- INR >4.5: 20% INR but no evidence of bleeding
- Warfarin-associated major bleeding
  - Use 4-factor PCC to restore hemostasis
  - Administer slow intravenous injection of 5-10 mg vitamin K

**Goal:** Reduce the risk of bleeding due to high INR

**Goal:** Sustain the intervention to control bleeding

Kahn SR. *Chest.* 2012;141:e195S-e226S.

4-Factor PCC for Warfarin Reversal

**ACCP Guidelines Recommend 4-Factor PCCs for Warfarin Reversal in Patients With Major Bleeds**

- Warfarin-associated major bleeding
  - Use 4-factor PCC to restore hemostasis
  - Administer slow intravenous injection of 5-10 mg vitamin K
  - 4-factor PCC demonstrated hemostatic efficiency comparable with plasma with less volume and rapid infusion

**Proportion of Subjects With Effective Hemostasis Assessed Over 24 Hours**

- **FPC v/W K (p=100)**
- **Plasma-WH K (p=100)**
- 99.4% vs 1.1% (4.8, 18.8)

Kahn SR. *Chest.* 2012;141:e195S-e226S.

New and Emerging Antidotes

**Idarucizumab (BI 655075)**
- Target: Direct-acting oral anticoagulant (DOAC)
- Structure: Humanized antibody fragment to dabigatran
- FDA approved: October 2015

**Andexanet alpha (PRT064445)**
- Target: FXa inhibitors
- Structure: FXa lacking catalytic & binding activity

**Aripazine (PER977; Ciraparantag)**
- Target: Universal – all NOACs, heparin, LMWH
- Structure: Synthetic small molecule (D-arginine)

ACCP Guidelines for Outpatient Treatment: Patients With DVT/PE

**Acute DVT**

- Current guidelines recommend initial treatment at home over treatment in-hospital (Grade 1B)

**Low Risk PE**

- Current guidelines recommend early discharge over standard discharge (Grade 2B)

These recommendations are contingent on adequate home circumstances, including:

- Well-maintained living conditions
- Strong support network
- Phone access
- Patient feeling well enough for home treatment
- Ability to be promptly re-hospitalized

More Aggressive DVT Treatment

- More contemporary endovascular treatments have improved upon basic catheter-directed thrombolysis using:
  - Lytic drugs with greater fibrin specificity and lower allergenicity
  - Intrathrombus delivery of lytic agent
  - Catheter manipulations, aspiration catheters, maceration catheters
  - Venous angioplasty, venous stents
  - Catheter-Directed Thrombolysis in Acute Iliofemoral Vein Thrombosis Trial
  - Better patency at 6 months with endovascular management vs anticoagulant alone (ARR 69.2%, 95% CI 0.7-46.7%)


Isolated Pharmacomechanical Thrombolysis

**How It Works**

- Catheter guided over guidewire
- Thrombus isolated, targeted delivery of thrombolytic drug
- Single-setting treatment in 83% of cases

Used by permission.

More Aggressive DVT Treatment

- Newest endovascular techniques utilize local mechanical thrombus fragmentation, with or without aspiration
  - By sequestering clot before "enhanced" CDT, risk of both bleeding and PE are reduced
- AngioJet thrombectomy system
- Trellis thrombectomy device

Summary

- Diagnosis of DVT is often made in the ED
- Early identification and aggressive treatment can avoid not just prolonged pain and swelling and not just PE, but also long-term PTS
- There are multiple pharmacologic options for treating DVT in multiple settings
- ED/hospitalist referral for evaluation for endovascular therapy is appropriate in selected cases, especially with proximal DVT

Thank you for joining us today!

Please remember to complete the EVALUATION on the iPad.

Your participation will help shape future CME activities.
January 2011 ACEP Guidelines

Scope of Application
This guideline is intended for physicians working in hospital-based emergency departments or emergency department-based observation centers.

Inclusion Criteria
This guideline is intended for adult patients presenting to the emergency department with suspected pulmonary embolism.

Exclusion Criteria
This guideline is not intended to address the care of patients with pulmonary embolism in the presence of cardiac arrest or pregnancy, patients with absence of symptoms suggestive of pulmonary embolism, or pediatric patients.

Critical Questions

1. Do objective criteria provide improved risk stratification over gestalt clinical assessment in the evaluation of patients with possible pulmonary embolism?
   Level A recommendations None specified.
   Level B recommendations Either objective criteria or gestalt clinical assessment can be used to risk stratify patients with suspected pulmonary embolism. There is insufficient evidence to support the preferential use of one method over another.
   Level C recommendations None specified.

2. What is the utility of the Pulmonary Embolism Rule-out Criteria (PERC) in the evaluation of patients with suspected pulmonary embolism?
   Level A recommendations None specified.
   Level B recommendations In patients with a low pretest probability for suspected pulmonary embolism, consider using the PERC to exclude the diagnosis based on historical and physical examination data alone.
   Level C recommendations None specified.

3. What is the role of quantitative D-dimer testing in the exclusion of pulmonary embolism?
   Level A recommendations In patients with a low pretest probability for pulmonary embolism, a negative quantitative D-dimer assay* result can be used to exclude pulmonary embolism.
   Level B recommendations None specified.
   Level C recommendations In patients with an intermediate pretest probability for pulmonary embolism, a negative quantitative D-dimer assay* result may be used to exclude pulmonary embolism.

4. What is the role of the computed tomography (CT) pulmonary angiogram of the chest as the sole diagnostic test in the exclusion of pulmonary embolism?
   Level A recommendations None specified.
   Level B recommendations For patients with a low or pulmonary embolism unlikely (Wells score ≤ 4) pretest probability for pulmonary embolism who require additional diagnostic testing (eg, positive D-dimer result, or highly sensitive D-dimer test not available), a negative, multidetector CT pulmonary angiogram alone can be used to exclude pulmonary embolism.
   Level C recommendations
   1. For patients with an intermediate pretest probability for pulmonary embolism and a negative CT pulmonary angiogram result in whom a clinical concern for pulmonary embolism still exists and CT venogram has not already been performed, consider additional diagnostic testing (eg, D-dimer,* lower extremity imaging, ventilation-perfusion (VQ) scanning, traditional pulmonary arteriography) prior to exclusion of venous thromboembolism disease.
   2. For patients with a high pretest probability for pulmonary embolism and a negative CT angiogram result, and CT venogram has not already been performed, perform additional diagnostic testing (eg, D-dimer,* lower extremity imaging, VQ scanning, traditional pulmonary arteriography) prior to exclusion of venous thromboembolism disease.

*High sensitivity (eg, turbidimetric, ELISA).

Additional diagnostic testing

A negative, highly sensitive, quantitative D-dimer result in combination with a negative multidetector CT pulmonary angiogram result theoretically provides a posttest probability of venous thromboembolism disease less than 1%.
5. What is the role of venous imaging in the evaluation of patients with suspected pulmonary embolism?

**Level A recommendations** None specified.

**Level B recommendations** When a decision is made to perform venous ultrasound as the initial imaging modality, a positive finding in a patient with symptoms consistent with pulmonary embolism can be considered evidence for diagnosis of venous thromboembolism disease and may preclude the need for additional diagnostic imaging in the emergency department.

*Examples of situations in which a venous ultrasound may be considered as initial imaging may include patients with obvious signs of deep venous thrombosis for whom venous ultrasound is readily available, patients with relative contraindications for computed tomography (CT) scan (eg, borderline renal insufficiency, CT contrast agent allergy), and pregnant patients.*

**Level C recommendations**

1. For patients with an intermediate pretest probability for pulmonary embolism and a negative CT angiogram result, for whom a clinical concern for pulmonary embolism still exists and CT venogram has not already been performed, consider lower extremity venous ultrasound as an additional test to exclude venous thromboembolism disease (see question 4).

2. In patients with a high pretest probability for pulmonary embolism and a negative CT angiogram result, and CT venogram has not already been performed, perform additional testing to exclude venous thromboembolism disease (see question 4). As one of these additional tests, consider lower extremity venous ultrasound to exclude venous thromboembolism disease (see question 4).

6. What are the indications for thrombolytic therapy in patients with pulmonary embolism?

**Level A recommendations** None specified.

**Level B recommendations** Administer thrombolytic therapy in hemodynamically unstable patients with confirmed pulmonary embolism for whom the benefits of treatment outweigh the risks of life-threatening bleeding complications.*

*In centers with the capability for surgical or mechanical thrombectomy, procedural intervention may be used as an alternative therapy.

**Level C recommendations**

1. Consider thrombolytic therapy in hemodynamically unstable patients with a high clinical suspicion for pulmonary embolism for whom the diagnosis of pulmonary embolism cannot be confirmed in a timely manner.

2. At this time, there is insufficient evidence to make any recommendations regarding use of thrombolytics in any subgroup of hemodynamically stable patients. Thrombolytics have been demonstrated to result in faster improvements in right ventricular function and pulmonary perfusion, but these benefits have not translated to improvements in mortality.

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**Antithrombotic Therapy for VTE Disease** [2016 CHEST Guideline](https://www.chestjournal.org/article/S0009-9240(16)30955-7)

- Updated guidelines from the American College of Chest Physicians (ACCP) include the following:
  - For venous thromboembolism (VTE) and no cancer, as long-term anticoagulant therapy, we suggest dabigatran (Grade 2B), rivaroxaban (Grade 2B), apixaban (Grade 2B) or edoxaban (Grade 2B) over vitamin K antagonist (VKA) therapy, and suggest VKA therapy over LMWH (Grade 2C).
  - For VTE and cancer, we suggest low molecular weight heparin (LMWH) over VKA (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C) or edoxaban (Grade 2C).
  - We have not changed recommendations for who should stop anticoagulation at 3 months or receive extended therapy.
  - For VTE treated with anticoagulants, we recommend against an inferior vena cava filter (IVC) filter (Grade 1B).
  - For deep vein thrombosis (DVT), we suggest not using compression stockings routinely to prevent PTS (Grade 2B).
  - For subsegmental pulmonary embolism (PE) and no proximal DVT, we suggest clinical surveillance over anticoagulation with a low risk of recurrent VTE (Grade 2C), and anticoagulation over clinical surveillance with a high risk (Grade 2C).
  - We suggest thrombolytic therapy for PE with hypotension (Grade 2B), and systemic therapy over catheter directed thrombolysis (Grade 2C).
  - For recurrent VTE on a non-LMWH anticoagulant, we suggest LMWH (Grade 2C), and for recurrent VTE on LMWH we suggest increasing the LMWH dose (Grade 2C).