Venous Thromboembolism: Using Evidence-based Guidelines for Selecting Acute and Extended Anticoagulant Therapy

Presented as a Live Webinar

Tuesday, April 4, 2017
1:00 PM – 2:00 PM ET

On-demand Activity
Live webinar recorded and archived to be watched at your convenience
Available after May 19, 2017

www.ashpadvantage.com/go/vteseries

This activity is sponsored and planned by the American Society of Health-System Pharmacists (ASHP).
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Activity Overview

This activity begins with an overview of the epidemiology, risk factors, and diagnosis of venous thromboembolism (VTE), followed by a review of the safety and efficacy of the direct oral anticoagulants for the acute treatment and secondary prevention of VTE. Current evidence-based guideline recommendations will also be discussed.

Learning Objectives

At the conclusion of this application-based educational activity, participants should be able to

- Discuss the epidemiology, risk factors, and diagnosis of venous thromboembolism (VTE).
- Compare the safety and efficacy of the direct oral anticoagulants (DOACs) with traditional therapies.
- Apply key recommendations in the updated guidelines for the management of VTE.

Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

This activity provides 1.0 hour (0.1 CEU – no partial credit) of continuing pharmacy education credit.

Live Activity ACPE #: 0204-0000-17-427-L01-P
On-demand Activity ACPE #: 0204-0000-17-427-H01-P

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Participants will process CE credit online at [http://elearning.ashp.org/my-activities](http://elearning.ashp.org/my-activities). For pharmacist participants, CPE credit will be reported directly to CPE Monitor. Per ACPE, CE credit must be claimed no later than 60 days from the date of the live activity or completion of a home-study activity.
List of Abbreviations

For a list of abbreviations used in this activity, please see page 34.

Webinar Information

Visit www.ashpadvantage.com/go/vteseries/webinar1 to find

- Webinar registration link
- Group viewing information and technical requirements
- CE webinar processing information

Additional Educational Activities in this Initiative

- Upcoming live webinars in this educational initiative, “Contemporary Approaches for the Acute Treatment and Secondary Prevention of Venous Thromboembolism”
    - Faculty Alpesh Amin, M.D., MBA, FACC, MACP, SFHM, and John Fanikos, R.Ph., MBA
    - Faculty Adam C. Cuker, M.D., M.S., and Paul P. Dobesh, Pharm.D., BCPS-AQ Cardiology, FCCP
- On-demand activities – Web-based activities for the 3-part webinar series available in May 2017 (1 hour CE each, please note that individuals who claim CE credit for a live webinar are ineligible to claim credit for the corresponding web-based activity)
Venous Thromboembolism: Using Evidence-based Guidelines for Selecting Acute and Extended Anticoagulant Therapy

Faculty

Toby C. Trujillo, Pharm.D., BCPS-AQ Cardiology, FAHA, FCCP, Initiative Chair
Associate Professor
University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences
Clinical Specialist - Anticoagulation/Cardiology
University of Colorado Hospital
Aurora, Colorado

Toby C. Trujillo, Pharm.D., BCPS-AQ Cardiology, FAHA, FCCP, is Associate Professor at the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences in Aurora. He also is a clinical specialist in anticoagulation and cardiology at University of Colorado Hospital.

Dr. Trujillo earned his Bachelor of Science degree in biochemistry from the University of California, Davis and his Doctor of Pharmacy degree from the University of California, San Francisco, where he also completed a residency in pharmacy practice. He then went on to do a fellowship in cardiovascular pharmacotherapy at The University of Arizona. Dr. Trujillo is a board-certified pharmacotherapy specialist with added qualifications in cardiology.

In his current role, Dr. Trujillo is involved in the stewardship of antithrombotic medications across the UC Health system, which includes serving as co-chair of the anticoagulation subcommittee of the P&T committee, as well as coordinating and staffing the Inpatient Anticoagulation Thrombosis Management Service. Dr. Trujillo has served in several capacities within multidisciplinary healthcare organizations, such as the American Heart Association, American College of Cardiology, and Society of Critical Care Medicine. He has also served on committees and in leadership positions within the American College of Clinical Pharmacy, currently as a member of the ACCP Board of Regents. Dr. Trujillo is often invited to speak on a national level, and he authored several articles and book chapters in the area of cardiovascular pharmacotherapy.
Venous Thromboembolism: Using Evidence-based Guidelines for Selecting Acute and Extended Anticoagulant Therapy

Rachel P. Rosovsky, M.D., M.P.H.
Assistant Physician
Department of Hematology/Oncology
Massachusetts General Hospital
Instructor in Medicine
Harvard Medical School
Boston, Massachusetts

Rachel P. Rosovsky, M.D., M.P.H., is an assistant physician in the Department of Hematology/Oncology at Massachusetts General Hospital (MGH) in Boston and an instructor in medicine at Harvard Medical School (HMS).

Dr. Rosovsky earned her undergraduate degree from the University of Pennsylvania, Doctor of Medicine degree from Harvard Medical School, and Master in Public Health degree from Harvard School of Public Health. She completed her residency at Brigham and Women’s Hospital and fellowship at the Dana Farber Cancer Institute, both in Boston. She is board certified in hematology and medical oncology. She is an expert and leader in the field of venous thromboembolism (VTE), and her clinical and research interest and expertise revolve around the evaluation and treatment of patients with this condition.

Dr. Rosovsky is on the Board of Directors of the National Pulmonary Embolism Response Team (PERT) Consortium, and she is Chair of the Consortium’s Education Committee. She recently helped establish a national educational series for PERT members to discuss the most up-to-date topics and controversies in the work up and treatment of VTE, as well as a monthly newsletter highlighting current evidence-based literature on VTE. Dr. Rosovsky also serves on the Executive Committee of the MGH PERT and is the creator and director of the MGH PERT multidisciplinary follow-up clinic, the goals of which are to improve the care of patients with pulmonary embolism as they transition from inpatient to outpatient setting, standardize follow-up protocols, increase patient satisfaction, and expand patient education.

Dr. Rosovsky is actively engaged in the education of medical students, residents, and fellows. In addition to bedside teaching and supervision during outpatient clinics and inpatient rotations, she lectures at continuing medical education courses locally, nationally and internationally. Dr. Rosovsky is also actively involved in research, investigating the risks, diagnosis, and treatment of VTE and other benign hematological conditions. Past research includes an analysis of endothelial stress products and coagulation markers in patients with multiple myeloma treated with lenalidomide and dexamethasone and a study of VTE risk in cancer patients with increased tissue factor particles who are treated with a low molecular weight heparin (LMWH). Currently, she is participating in an international study comparing a LMWH product with one of the new direct oral anticoagulants (DOACs) in cancer patients with acute VTE. She is also the co-principal investigator on a multicenter study investigating the safety and efficacy of treating low risk deep vein thrombosis and pulmonary embolism (PE) in an outpatient setting, and she is the national lead investigator for an evaluation of a DOAC for low risk PE patients. She is involved in creating a PERT registry and national database to assess current treatments and long-term outcomes in patients with VTE. Through lectures, research, and written works that include original articles, book chapters, and scholarly reviews, she seeks to improve the care of patients with VTE and advance the understanding and treatment of this medical condition.
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- Alpesh Amin, M.D., MBA, FACC, MACP, SFHM, declares that he is a consultant for Bristol-Myers Squibb and Pfizer Alliance. (Steering Committee)
- All other faculty and planners report no financial relationships relevant to this activity.
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Rachel P. Rosovsky, M.D., M.P.H.
Massachusetts General Hospital
Harvard Medical School

Toby C. Trujillo, Pharm.D., BCPS-AQ Cardiology, FAHA, FCCP
University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado Hospital

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• Discuss the epidemiology, risk factors, and diagnosis of venous thromboembolism (VTE)
• Compare the safety and efficacy of the direct oral anticoagulants (DOACs) with traditional therapies
• Apply key recommendations in the updated guidelines for the management of VTE

Agenda

Overview of VTE epidemiology
• Discussion of pathophysiology and risk factors
• Diagnosis of VTE
• Treatment of VTE
  – Become familiar with the direct oral anticoagulants (DOACs)
  – Review safety and efficacy
Venous Thromboembolism: The Third Leading Cause of Cardiovascular Death

- DVT: 2 million
- PE: 600,000
- Silent PE: 1 million
- Post-thrombotic syndrome: 800,000
- Deaths: 60,000
- Pulmonary hypertension: 30,000

Estimated Cost of VTE Care in United States - $1.5 billion/year


Prevalence of Pulmonary Embolism

- 560 patients from 11 hospitals in Italy, 1st episode syncope
- Pulmonary embolism was identified in nearly one of every six patients hospitalized for a first episode of syncope

Increasing Incidence in the U.S.


Annual Incidence of VTE by Age

Agenda

- Overview of VTE epidemiology

Discussion of pathophysiology and risk factors

- Diagnosis of VTE
- Treatment of VTE
  - Become familiar with the direct oral anticoagulants (DOACs)
  - Review safety and efficacy
Risk Factors: Virchow’s Triad

STASIS
Anesthesia
Hospitalization
Immobilization
CHF/MI
CVA
Shock
Pregnancy
Obesity

VENOUS INJURY
Surgery
Trauma
Central venous catheter
Prior DVT
Burns
Fracture

HYPERCOAGULABILITY
Inherited coagulopathy
Acquired coagulopathy
Pregnancy or parturition
Hormonal therapy
Malignancy

Red = risk factors that hospitalized patients may experience


Deep Vein Thrombosis

Courtesy of Dr. Robert Schainfeld
VTE Pathophysiology

- DVT thrombi form in venous valve pockets and other areas of stasis
- Clots that originate or propagate above the knee are at higher risk of embolizing
- DVT clots can dislodge and travel through venous vasculature and heart to the lungs = PE

Pathophysiology of Pulmonary Embolism

- Increased RV afterload → RV dilatation
- RV TV insufficiency → RV wall tension
- Neurohormonal activation
  - Myocardial inflammation
  - RV O2 demand
  - RV ischemia

- Low cardiac output → Decreased systemic BP
- RV coronary perfusion
  - RV oxygen delivery
- Cardiogenic shock → Death

Adapted from Konstantinides et al. *Eur Heart J.* 2014; 35:3033-69, 3069a-3069k.
Venous Thromboembolic Events: Magnitude of the Problem

Agenda

- Overview of VTE epidemiology
- Discussion of pathophysiology and risk factors

Diagnosis of VTE

- Treatment of VTE
  - Become familiar with the direct oral anticoagulants (DOACs)
  - Review safety and efficacy
Pulmonary Embolism: Diagnosis

- General
  - History, physical exam, clinical suspicion
- Labs
  - CBC, LFTs, CMP
  - D-dimer
  - Biomarkers (troponin and BNP)
- Imaging
  - ECG
  - Chest x-ray
  - Ultrasound
  - CT angiogram
  - V/Q scan
  - Echocardiogram
- Scoring systems (Wells, Geneva, PERC)

BNP = B-type natriuretic peptide
CMP = comprehensive metabolic panel
LFTs = liver function tests
PERC = Pulmonary Embolism Rule-out Criteria

Should all unprovoked venous thromboembolic events be screened extensively for malignancy?

a. Yes
b. No
Screening for Occult Malignancy in VTE

- Multicenter, open-label, randomized, controlled trial in Canada
- 845 patients randomly assigned to limited occult-cancer screening or limited occult-cancer screening PLUS abdominal pelvic CT
- Primary outcome: confirmed cancer missed by screening and detected at 1-year follow-up period
- Results: 33 (3.9%) had new diagnosis of occult malignancy
  - 14 of 431 patients (3.2%) in limited-screening group and 19 of 423 patients (4.5%) in limited-screening-PLUS-CT group (P=0.28)
  - 4 occult cancers (29%) were missed by limited screening strategy, whereas 5 (26%) were missed by strategy of limited screening PLUS CT (P=1.0)


Screening for Occult Malignancy in VTE

- Available data **do not** support an extensive search for occult malignancy
- However, it is important to perform complete Hx/PE/labs and investigate symptoms or signs that suggest an underlying malignancy and to ensure that age-appropriate cancer screening tests have been performed
Agenda

- Overview of VTE epidemiology
- Discussion of pathophysiology and risk factors
- Diagnosis of VTE

Treatment of VTE

- Become familiar with the direct oral anticoagulants (DOACs)
- Review safety and efficacy

Historical Perspective

1st documented description and treatment of DVT in Middle Ages

Recent Approvals Changed the Anticoagulation Landscape

- **6/8/1954** Warfarin approved
- **7/20/1969** Neil Armstrong sets foot on the moon
- **11/9/1989** Berlin Wall falls
- **8/29/2005** Hurricane Katrina
- **12/28/2012** Apixaban approved

UFH and OAC used for PE 14-21 days in hospital

Where We Have Been: 9th ed, American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommendation (initial treatment)</th>
<th>ACCP Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT/PE</td>
<td>LMWH (preferred, once daily) Intravenous UFH Fondaparinux (preferred) SC UFH</td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td>Oral VKA on day 1 or 2, minimum overlap 5 days, INR &gt; 2.0</td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td>LMWH preferred long term to new oral AC in patients not receiving VKA</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>Provoked (surgical or nonsurgical, proximal or distal): 3 months over a shorter or longer duration</td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td>Unprovoked, first episode: 3 months, consider long term therapy</td>
<td>1B, 2B</td>
</tr>
<tr>
<td></td>
<td>Unprovoked, second episode: long term preferred unless high bleeding risk</td>
<td>1B, 2B</td>
</tr>
</tbody>
</table>


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**Direct Oral Anticoagulants**

- Rivaroxaban (Xarelto)
- Dabigatran (Pradaxa)
- Apixaban (Eliquis)
- Edoxaban (Savaysa)

**Ideal Anticoagulant**

<table>
<thead>
<tr>
<th>Disadvantage of Warfarin</th>
<th>Ideal Anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow onset of action</td>
<td>Fast onset of action, allowing for acute treatment of VTE and use post-procedures</td>
</tr>
<tr>
<td>Need for injectable agent</td>
<td></td>
</tr>
<tr>
<td>Slow resolution of action</td>
<td>Fast resolution of action, allowing for use peri-procedurally</td>
</tr>
<tr>
<td>Routine blood monitoring</td>
<td>No routine blood monitoring</td>
</tr>
<tr>
<td>Many drug interactions</td>
<td>No drug interactions</td>
</tr>
<tr>
<td>Interactions with diet</td>
<td>No interactions with diet</td>
</tr>
<tr>
<td>Wide range of therapeutic doses</td>
<td>Narrow-range, fixed doses</td>
</tr>
<tr>
<td>Unpredictable dose-response</td>
<td>Predictable dose-response</td>
</tr>
<tr>
<td>Teratogenic</td>
<td>Safe in pregnancy</td>
</tr>
<tr>
<td>Slow reversibility via vitamin K</td>
<td>Immediate reversibility</td>
</tr>
</tbody>
</table>

*No interactions organ dysfunction*
DOACs: Pharmacokinetics and Pharmacodynamics

<table>
<thead>
<tr>
<th>Property</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Direct factor IIa inhibitor</td>
<td>Direct factor Xa inhibitor</td>
<td>Direct factor Xa inhibitor</td>
<td>Direct factor Xa inhibitor</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>6 – 7%</td>
<td>80%</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td>Tmax</td>
<td>1.5 hr</td>
<td>2 – 4 hr</td>
<td>2 – 3 hr</td>
<td>1 – 2 hr</td>
</tr>
<tr>
<td>Half-life</td>
<td>12 – 14 hr</td>
<td>9 – 13 hr</td>
<td>8 – 15 hr</td>
<td>8 – 11 hr</td>
</tr>
<tr>
<td>Hepatic metabolism</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>P-gp</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>P-gp</td>
</tr>
<tr>
<td>Protein binding</td>
<td>35%</td>
<td>90%</td>
<td>87%</td>
<td>55%</td>
</tr>
<tr>
<td>Dialyzable</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Measurement</td>
<td>ECT, TT, aPTT</td>
<td>Anti-Xa, PT</td>
<td>Anti-Xa, dPT</td>
<td>Anti-Xa, PT</td>
</tr>
<tr>
<td>Renal elimination</td>
<td>80%</td>
<td>35%</td>
<td>25%</td>
<td>40%</td>
</tr>
<tr>
<td>Renal dosing</td>
<td>Yes</td>
<td>Yes</td>
<td>No?</td>
<td>Yes</td>
</tr>
<tr>
<td>Antidote</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Evolving Anticoagulation Strategies

Overlapping
- LMWH/Warfarin bridge
- UFH/Warfarin bridge

Switching
- LMWH to dabigatran (RE-COVER)
- LMWH to edoxaban (HOKUSAI)

Oral monotherapy
- Rivaroxaban (3 week high dose) (EINSTEIN)
- Apixaban (1 week high dose) (AMPLIFY)

DOACs for Acute VTE Treatment: Trial Designs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-COVER II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-COVER III</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMPLIFY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study design
- Randomized, double-blind, non-inferiority, parallel group
- Randomized, open-label, event-driven, non-inferiority, parallel group
- Randomized, double-blind, non-inferiority, parallel group
- Randomized, double-blind, non-inferiority, parallel group

Intervention
- 150 mg BID
- 15 mg BID x 3 wk → 20 mg daily
- 10 mg BID x 7 days → 5 mg BID
- 60 mg or 30 mg daily

Comparator
- Warfarin
- Enoxaparin → VKA
- Warfarin
- Warfarin

Parenteral anticoagulation
- Mandatory, ≥5 day
- Optional, maximum 48 hr
- Optional, maximum 36 hr
- Mandatory, ≥5 day

Primary efficacy endpoint
- Recurrent symptomatic VTE or death related to VTE
- Recurrent symptomatic VTE
- Recurrent symptomatic VTE, death related to VTE
- Recurrent symptomatic VTE

Primary safety endpoint
- Major bleeding
- Major or CRNM bleeding
- Major bleeding
- Major or CRNM bleeding

Duration of treatment
- 3 mo
- 6 mo
- 12 mo

Head-to-head studies have not been conducted, therefore comparative safety and efficacy have not been established.

DOACs vs. Warfarin for Acute VTE Treatment: Overview of Trial Results

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy endpoint, %</strong></td>
<td>RE-COVER I</td>
<td>RE-COVER II</td>
<td>EINSTEIN- DVT</td>
<td>EINSTEIN- PE</td>
</tr>
<tr>
<td></td>
<td>2.4 vs. 2.1</td>
<td>2.3 vs. 2.2</td>
<td>2.1 vs. 3.0</td>
<td>2.1 vs. 1.8</td>
</tr>
<tr>
<td><strong>Major bleeding, %</strong></td>
<td>1.6 vs. 1.9</td>
<td>1.2 vs. 1.7</td>
<td>0.8 vs. 1.2</td>
<td>1.1 vs. 2.2</td>
</tr>
<tr>
<td><strong>CRNM bleeding, %</strong></td>
<td>4.0 vs. 6.9</td>
<td>3.8 vs. 6.2</td>
<td>7.3 vs. 7.0</td>
<td>9.5 vs. 9.8</td>
</tr>
<tr>
<td><strong>Major and CRNM bleeding, %</strong></td>
<td>5.6 vs. 8.8</td>
<td>5.0 vs. 7.9</td>
<td>8.1 vs. 8.1</td>
<td>10.3 vs. 11.4</td>
</tr>
</tbody>
</table>

Head-to-head studies have not been conducted, therefore comparative safety and efficacy have not been established.


Extended VTE Treatment / Secondary VTE Prevention
Risk Factors for VTE Recurrence

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR/HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unprovoked proximal DVT</td>
<td>2.3 (1.8-2.9)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.6 (1.1-2.4)</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.8 (1.4-5.7)</td>
</tr>
<tr>
<td>Positive D-dimer testing</td>
<td>2.6 (1.9-3.5)</td>
</tr>
<tr>
<td>Residual thrombosis</td>
<td>1.5 (1.1-2.0)</td>
</tr>
<tr>
<td>Hereditary thrombophilia</td>
<td>1.5 (1.1-1.9)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>2.5 (1.4-4.2)</td>
</tr>
<tr>
<td>Antiphospholipid antibody</td>
<td>2.4 (1.3-4.1)</td>
</tr>
<tr>
<td>Asian and Pacific Islander ethnicity</td>
<td>0.7 (0.5-0.9)</td>
</tr>
</tbody>
</table>

RR = relative risk
HR = hazard ratio
CI = confidence interval

Risk of Recurrent DVT/PE Persists Following Discontinuation of Anticoagulation

Patients with a first episode of clinically symptomatic proximal DVT and/or PE (N=1626)

Average of 6 months of anticoagulation treatment

Patients discontinued anticoagulation and were followed for recurrent DVT/PE

## DOACs for Long-Term Secondary VTE Prevention: Overview of Trial Results

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy endpoint, %</td>
<td>1.8 vs. 1.3</td>
<td>0.4 vs. 5.6</td>
<td>1.3 vs. 7.1</td>
<td>3.8 vs. 11.6</td>
</tr>
<tr>
<td>Major bleeding, %</td>
<td>0.9 vs. 1.8</td>
<td>0.3 vs. 0.0</td>
<td>0.7 vs. 0.0</td>
<td>0.2 vs. 0.5</td>
</tr>
<tr>
<td>CRNM bleeding, %</td>
<td>4.7 vs. 8.4</td>
<td>5.0 vs. 1.8</td>
<td>5.4 vs. 1.2</td>
<td>3.0 vs. 2.3</td>
</tr>
<tr>
<td>Major and CRNM bleeding, %</td>
<td>5.6 vs. 10.2</td>
<td>5.3 vs. 1.8</td>
<td>6.0 vs. 1.2</td>
<td>3.2 vs. 2.7</td>
</tr>
</tbody>
</table>

Head-to-head studies have not been conducted, therefore comparative safety and efficacy have not been established.

*Compared with warfarin. All others compared with placebo.  

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## Prescribing Information Highlights: Indications

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of DVT, PE in patients who have been treated with a parenteral anticoagulant for 5-10 days</td>
<td>Treatment of DVT, PE</td>
<td>Take tablets with food</td>
<td>Treatment of DVT, PE</td>
<td>Treatment of DVT, PE following 5-10 days of initial therapy with a parenteral anticoagulant</td>
</tr>
<tr>
<td><strong>Reduction in risk of recurrence</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Reduction in risk of recurrence of DVT, PE in patients who have been previously treated</td>
<td>Reduction in risk of recurrence of DVT, PE</td>
<td>Take tablets with food</td>
<td>Reduction in risk of recurrent DVT, PE following initial therapy</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

Pradaxa (dabigatran etexilate mesylate) prescribing information. 2015 Nov.  
Xarelto (rivaroxaban) prescribing information. 2016 Aug.  
Eliquis (apixaban) prescribing information. 2016 Jul.  
Savaysa (edoxaban) prescribing information. 2016 Sep.
### Prescribing Information Highlights: Dosing

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If CrCl &gt;30 mL/min: 150 mg orally, BID after 5-10 day parenteral anticoagulation</td>
<td>15 mg orally BID with food for first 21 days for initial treatment of acute DVT, PE</td>
<td>10 mg orally BID for 7 days, followed by 5 mg orally BID</td>
<td>• 60 mg daily  • 30 mg day if CrCl 15-50 mL/min, body weight ≤60 kg, or who use certain P-gp inhibitors</td>
</tr>
<tr>
<td><strong>Reduction in risk of recurrence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If CrCl &gt;30 mL/min: 50 mg orally, BID after previous treatment</td>
<td>After initial treatment period, 20 mg orally daily with food for remaining treatment, long-term reduction in risk of recurrence</td>
<td>2.5 mg orally BID</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

Pradaxa (dabigatran etexilate mesylate) prescribing information. 2015 Nov.  
Xarelto (rivaroxaban) prescribing information. 2016 Aug.  
Eliquis (apixaban) prescribing information. 2016 Jul.  
Savaysa (edoxaban) [prescribing information. 2016 Sep.  

### Duration of Anticoagulant Therapy for VTE

- Provoked VTEs: 3 months [Grade 1B]
- Unprovoked VTEs: ≥ 3 months [Grade 1B]
  - Evaluation of risk vs. benefit for extended therapy after the initial 3 months  
  - Extended duration past 3 months – specific recommendations not given (at least 12 months total)
- First unprovoked VTE  
  - Low-moderate bleeding risk: extended therapy [Grade 2B]  
  - High bleeding risk: 3 months [Grade 1B]
- Second unprovoked VTE  
  - Low bleeding risk: extended therapy [Grade 1B]  
  - Moderate bleeding risk: extended therapy [Grade 2B]  
  - High bleeding risk: 3 months [Grade 2B]
- VTE + active cancer  
  - Extended therapy for low-moderate [Grade 1B] and high [Grade 2B] bleeding risk

Are the Direct Oral Anticoagulants First Line?

“In the absence of direct comparisons between DOACs ... no preference for one DOAC over another DOAC.”


Direct Oral Anticoagulants: Are they the new standard of care?

• What makes a new standard of care?
  – Effective
  – Safe
  – Simple and reliable
  – Adaptable and scalable
  – Patient satisfaction
Direct Oral Anticoagulants – VTE Treatment: Are they the new standard of care?

- Are they effective?
- Are they safe?
- Are they simple and reliable?
  - Can be given in fixed doses
  - Do not require routine monitoring
  - Have fewer food or drug interactions compared with warfarin
  - Are more predictable than warfarin

Direct Oral Anticoagulants – VTE Treatment

- Patient satisfaction?
  - Rivaroxaban significantly higher treatment satisfaction (convenience, effectiveness, and global satisfaction) compared with vitamin K antagonists

Direct Oral Anticoagulants – VTE Treatment

- Effective, safe, simple and reliable, and patients are satisfied
  - All approved for the treatment of DVT and PE
  - Do not require coagulation monitoring


Direct Oral Anticoagulants

- Questions to ask before placing patient on direct oral anticoagulant
  - Candidate for these drugs
  - Comorbidities that preclude use
  - Adherence issues
  - Cost concerns
Cautions with Direct Oral Anticoagulants

• Approved reversal agent only for dabigatran (others under investigation)
• No monitoring for effect
  – Adherence
  – Drug interactions
  – Organ dysfunction
• Renal and hepatic failure
• Reimbursement issues
  – Cost (warfarin $5/mo vs. $250-350/mo)
• Postmarketing bleeding rates
• Clinician familiarity
• Lack of guidelines
  – Bleeding complications

Cautions with Direct Oral Anticoagulants

• Unclear role in extensive DVT or massive PE
  – Patients excluded because often required advanced therapies
• Cannot be used on patients with valvular disease
• Have not been evaluated in conjunction with thrombolytic therapy
• Lack of data in patients at extreme weights
• Due to lack of antidote for the majority of agents, may not be appropriate for patient at high initial bleeding risk
  – Major trauma or surgery
Direct Oral Anticoagulants: Perioperative and Procedure Management

- How long to withhold medication?
  - Half-life of the drug
  - Bleeding risk of the procedure
  - Bleeding and thrombotic risk of the patient
  - Current dose
  - Renal function

Review package insert!


Patient Case: Pleuritic Chest Pain

- 26-year-old female presents with right sided pleuritic chest pain
- PCP placed her on enoxaparin as bridge to warfarin
Patient Case: Pleuritic Chest Pain

• She came to me for 2nd opinion regarding choice of anticoagulation

• Things to consider before placing her on DOAC
  – Pregnancy, cancer, bleeding, adherence, kidney and liver functions, lupus anticoagulant

Patient Case: Acute Shortness of Breath

• 62-year-old female with history of only hypertension presents to local emergency department with acute shortness of breath

• No identifiable risks
Take-home Points

• DOACs have similar efficacy and mortality profiles as warfarin, may have better bleeding profile
  • First-line choice in many patients
• No head to head trials with DOACs -- which one to use depends on patient factors and preferences
• Important for clinicians to understand when and how to use them and their limitations
• Screening for occult malignancy in unprovoked VTE not indicated, but age-specific cancer screening is
• Increase awareness in your hospitals about VTE

Reflection Question to Consider During Q&A
Which of these practice changes will you consider making?

a. Educate patients about the risk factors for VTE.
b. Be more attuned to signs and symptoms of VTE to facilitate timely diagnosis.
d. Review VTE dosing recommendations for anticoagulants to ensure patients receive appropriate doses.
e. Recommend therapy with a direct oral anticoagulant for VTE, when appropriate.
Selected References and Guidelines


Selected References and Guidelines

### Abbreviations Used in Presentation

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCP</td>
<td>American College of Chest Physicians</td>
</tr>
<tr>
<td>BID</td>
<td>twice daily</td>
</tr>
<tr>
<td>CBC</td>
<td>complete blood count</td>
</tr>
<tr>
<td>CHF</td>
<td>congestive heart failure</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CMP</td>
<td>comprehensive metabolic panel</td>
</tr>
<tr>
<td>CP</td>
<td>chest pain</td>
</tr>
<tr>
<td>CrCl</td>
<td>creatinine clearance</td>
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<tr>
<td>CRNM</td>
<td>clinically relevant nonmajor</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>CVA</td>
<td>cardiovascular accident</td>
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<tr>
<td>DOAC</td>
<td>direct oral anticoagulant</td>
</tr>
<tr>
<td>DVT</td>
<td>deep vein thrombosis</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
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<td>ECT</td>
<td>ecarin clotting time</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<td>Hx</td>
<td>history</td>
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<td>LFTs</td>
<td>liver function tests</td>
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<td>LMWH</td>
<td>low molecular weight heparin</td>
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<tr>
<td>LV</td>
<td>left ventricle</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>MOA</td>
<td>mechanism of action</td>
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<td>O2</td>
<td>oxygen</td>
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<td>OAC</td>
<td>oral anticoagulant</td>
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<td>P-glycoprotein</td>
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<td>PCP</td>
<td>primary care physician</td>
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<td>PE</td>
<td>physical exam</td>
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<tr>
<td>PE</td>
<td>pulmonary embolism</td>
</tr>
<tr>
<td>PERC</td>
<td>Pulmonary Embolism Rule-out Criteria</td>
</tr>
<tr>
<td>PT</td>
<td>prothrombin time</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
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<tr>
<td>RV</td>
<td>right ventricle</td>
</tr>
<tr>
<td>SC</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>UFH</td>
<td>unfractionated heparin</td>
</tr>
<tr>
<td>V/Q</td>
<td>ventilation perfusion lung scan</td>
</tr>
<tr>
<td>VTE</td>
<td>venous thromboembolism</td>
</tr>
</tbody>
</table>
Self-assessment Questions

1. As shown in Virchow’s Triad categorizing risk for venous thromboembolism (VTE), all of the following are examples of venous injury EXCEPT
   a. Surgery.
   b. Trauma.
   c. Fracture.
   d. Pregnancy.

2. Compared with warfarin, which of the following is an advantage of the direct oral anticoagulants?
   a. Reversal agent(s) readily available.
   b. Routine measurement of coagulation not required.
   c. Decreased cost.
   d. Clinician familiarity.

3. Patient GP is a 56-year-old woman who has DVT of the leg. She does not have cancer. According to the 2016 Chest guidelines, which of the following best describes the recommended anticoagulant therapy for the first 3 months?
   a. Dalteparin, aspirin, warfarin, or enoxaparin.
   b. Fondaparinux, dabigatran, aspirin, or edoxaban.
   c. Dabigatran, rivaroxaban, apixaban, or edoxaban.
   d. Dabigatran, rivaroxaban, apixaban, or warfarin.

Answers

1. d
2. b
3. c