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).

Supported by an educational grant from the Bristol-Myers Squibb and Pfizer Alliance

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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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The American Society of Health-System Pharmacists designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Participants will process CE credit online at 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.

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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"
    - **April 12, 2017:** Clinical Case Studies in Venous Thromboembolism: Using Direct Oral Anticoagulants for Treatment and Secondary Prevention (1 hour CE)
        - **F**aculty Alpesh Amin, M.D., MBA, FACC, MACP, SFHM, and John Fanikos, R.Ph., MBA
    - **May 10, 2017:** Clinical Case Studies in Venous Thromboembolism: Addressing Clinical Issues in Special Patient Populations (1 hour CE)
        - 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*)

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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.

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

Rachel P. Rosovsky, M.D., M.P.H.
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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)
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University of Colorado Hospital

Disclosures of Faculty and Planners

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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

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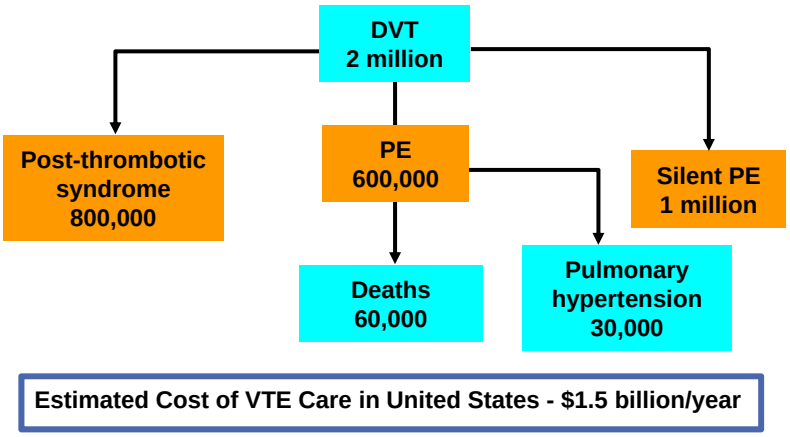
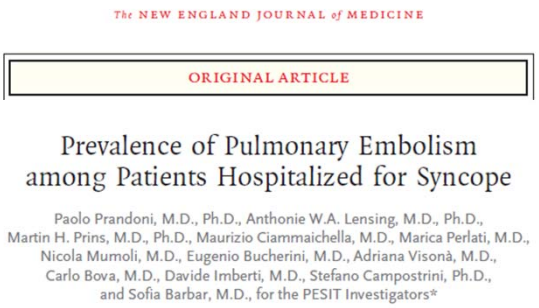
Venous Thromboembolism: The Third Leading Cause of Cardiovascular Death



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

Hirsh J, Hoak J. *American Heart Association*. 1996.
Heit J et al. *Blood*. 2005; 106: Abstract 910.
Anderson FA et al. *Am J Hematol*. 2007; 82:777-82.

Prevalence of Pulmonary Embolism


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevalence of Pulmonary Embolism among Patients Hospitalized for Syncope

Paolo Prandoni, M.D., Ph.D., Anthonie W.A. Lensing, M.D., Ph.D., Martin H. Prins, M.D., Ph.D., Maurizio Ciammaichella, M.D., Marica Perlati, M.D., Nicola Mumoli, M.D., Eugenio Bucherini, M.D., Adriana Visonà, M.D., Carlo Bova, M.D., Davide Imberti, M.D., Stefano Campostrini, Ph.D., and Sofia Barbar, M.D., for the PESIT Investigators*

- 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

Prandoni P et al. *N Engl J Med*. 2016; 375:1524-31.

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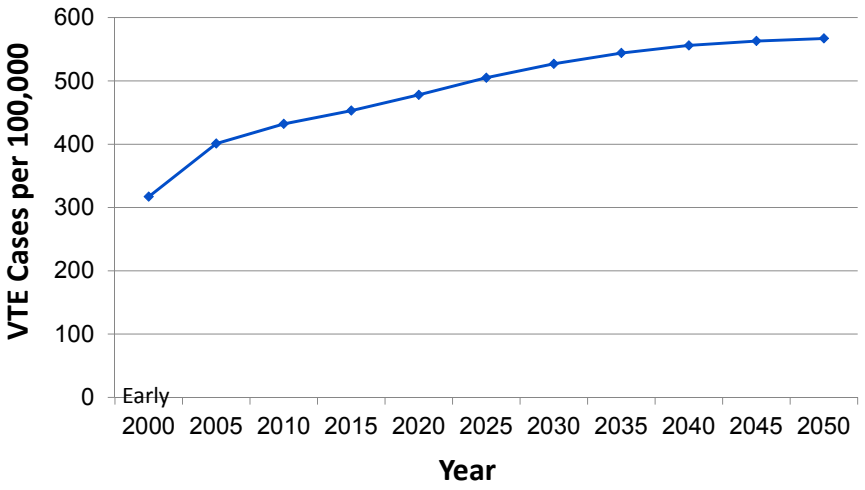
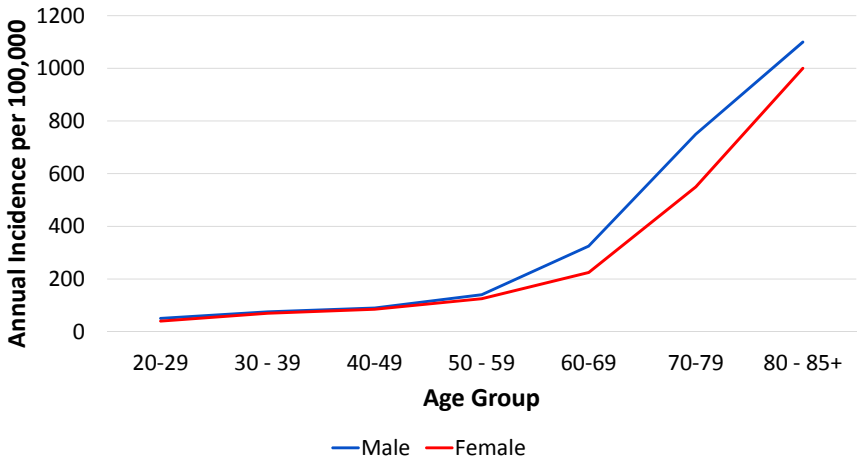
Increasing Incidence in the U.S.



Adapted from Deitelzweig SB et al. *Am J Hematol*. 2011; 86:217-20.

Annual Incidence of VTE by Age



Adapted from Heit JA et al. *J Thromb Thrombolysis*. 2016; 41:3-14.

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Risk Factors: Virchow's Triad

STASIS
Anesthesia
Hospitalization
Immobilization
CHF/MI
CVA
Shock
Pregnancy
Obesity

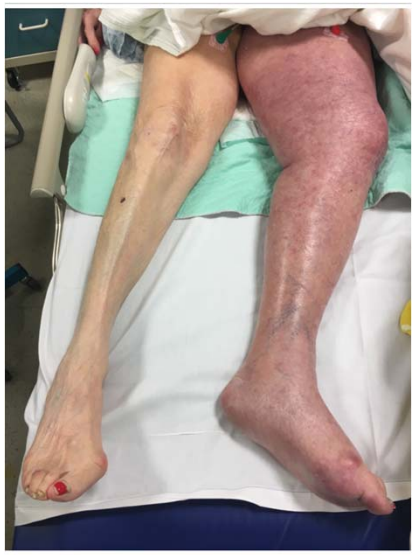
VENOUS INJURY
Surgery
Trauma
Central venous catheter
Prior DVT
Burns
Fracture

HYPERCOAGULABILITY
Inherited coagulopathy
Acquired coagulopathy
Pregnancy or parturition
Hormonal therapy
Malignancy

Red = risk factors that hospitalized patients may experience

Carman TL et al. *Cleve Clin J Med.* 1999; 66:113-23.

Deep Vein Thrombosis



Courtesy of Dr. Robert Schainfeld

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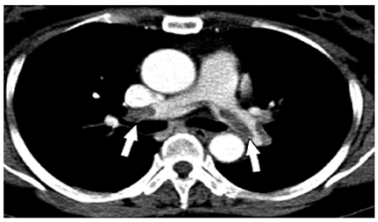
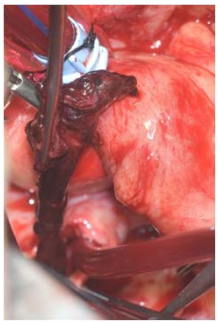
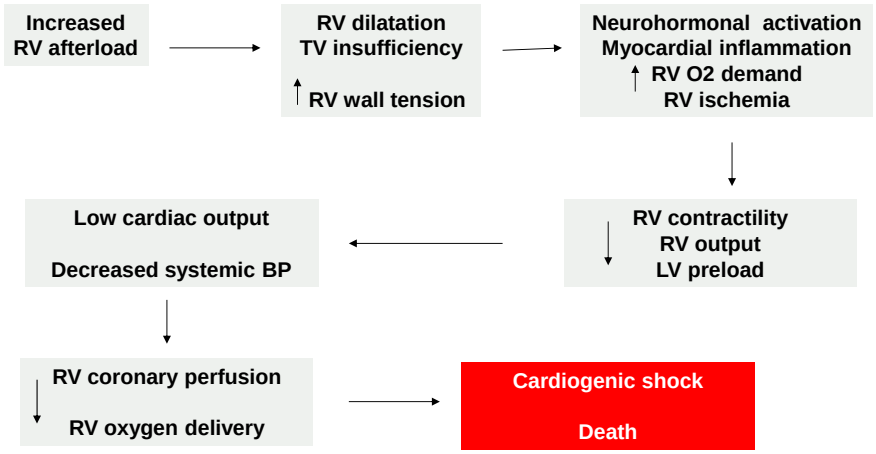
VTE Pathophysiology

- 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



Adapted from Konstantinides et al. *Eur Heart J*. 2014; 35:3033-69, 3069a-3069k.

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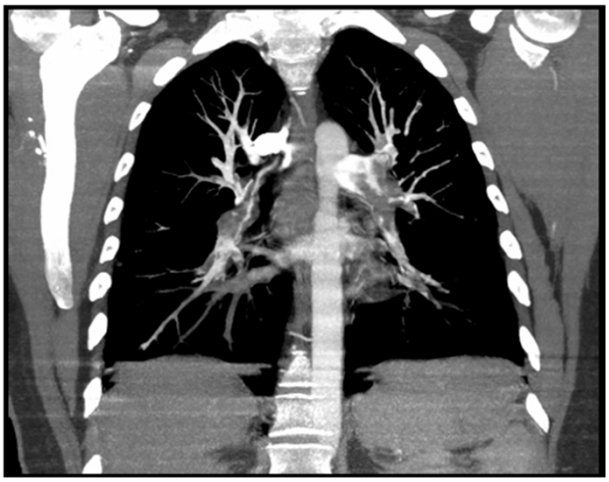
Venous Thromboembolic Events: Magnitude of the Problem



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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

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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)

Carrier M et al. *N Engl J Med*. 2015; 373:697-704.

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

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Historical Perspective

1st documented description and treatment of DVT in Middle Ages

de Saint Pathus G. La vie et les Miracles de Saint Louis. Paris: Bibliotheque National de France, 1330–50.

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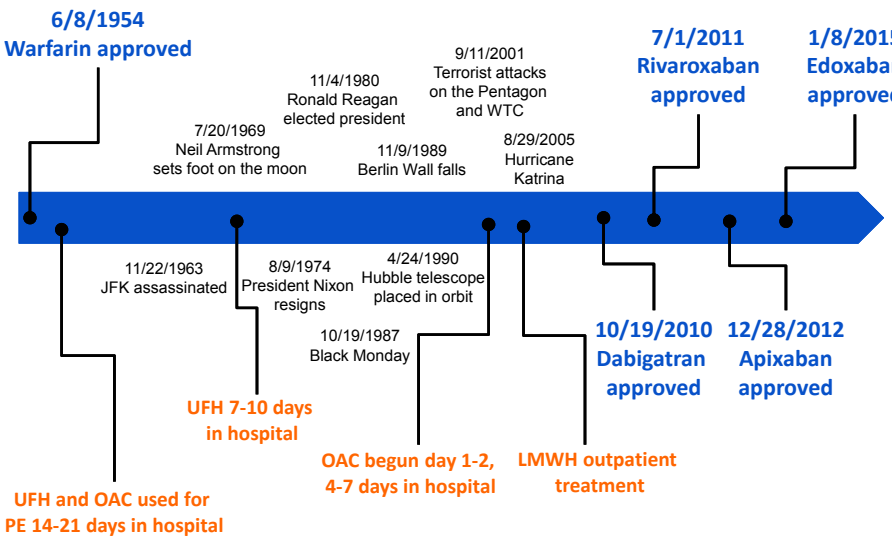
Recent Approvals Changed the Anticoagulation Landscape



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

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

Kearon C et al. *Chest.* 2012; 141(suppl 2):e419S–e494S.

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Direct Oral Anticoagulants

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

Ideal Anticoagulant

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

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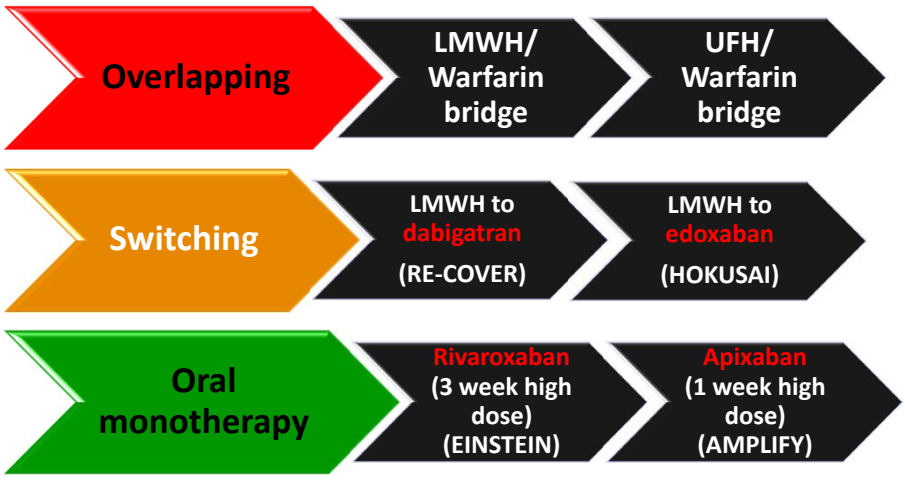
DOACs: Pharmacokinetics and Pharmacodynamics

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

Evolving Anticoagulation Strategies



Goldhaber SZ et al. *Lancet.* 2012; 379:1835-46.

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DOACs for Acute VTE Treatment: Trial Designs

	Dabigatran		Rivaroxaban		Apixaban	Edoxaban
	RE-COVER I[a]	RE-COVER II[a]	EINSTEIN-DVT[a]	EINSTEIN-PE[a]	AMPLIFY[a]	Hokusai-VTE[a]
Study design	Randomized, double-blind, non-inferiority, parallel group		Randomized, open-label, event-driven, non-inferiority, parallel group		Randomized, double-blind, parallel group	Randomized, double-blind, non-inferiority parallel group
Intervention	150 mg BID	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[b]
Comparator	Warfarin		Enoxaparin ⇒VKA		Enoxaparin ⇒ warfarin	Warfarin
Parenteral anti-coagulation[c]	Mandatory, ≥5 day		Optional, maximum 48 hr		Optional, maximum 36 hr	Mandatory, ≥5 day

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

[a]Patients excluded if CrCl <30 mL/min.
[b]In patients with CrCl of 30-50 mL/min, body weight ≤60 kg, or receiving strong P-gp inhibitors.
[c]UFH, LMWH, fondaparinux.

Dobesh PP et al. *Drugs*. 2014; 74:2015-32.

DOACs for Acute VTE Treatment: Trial Designs *(cont'd)*

	Dabigatran		Rivaroxaban		Apixaban	Edoxaban
	RE-COVER I	RE-COVER II	EINSTEIN-DVT	EINSTEIN-PE	AMPLIFY	Hokusai-VTE
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

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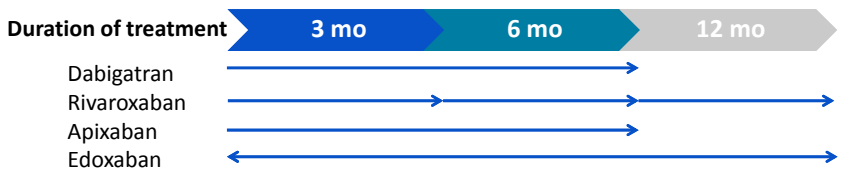

Dobesh PP et al. *Drugs*. 2014; 74:2015-32.

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

	Dabigatran		Rivaroxaban		Apixaban	Edoxaban
	RE-COVER I	RE-COVER II	EINSTEIN-DVT	EINSTEIN-PE	AMPLIFY	Hokusai-VTE
Primary efficacy endpoint, %	2.4 vs. 2.1	2.3 vs. 2.2	2.1 vs. 3.0	2.1 vs. 1.8	2.3 vs. 2.7	3.2 vs. 3.5
Major bleeding, %	1.6 vs. 1.9	1.2 vs. 1.7	0.8 vs. 1.2	1.1[a] vs. 2.2	0.6[a] vs. 1.8	1.4 vs. 1.6
CRNM bleeding, %	4.0 vs. 6.9	3.8 vs. 6.2	7.3 vs. 7.0	9.5 vs. 9.8	3.8[a] vs. 8.0	7.2[a] vs. 8.9
Major and CRNM bleeding, %	5.6[a] vs. 8.8	5.0[a] vs. 7.9	8.1 vs. 8.1	10.3 vs. 11.4	4.3[a] vs. 9.7	8.5[a] vs. 10.3

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

[a]Statistically significant reduction (red type).

Dobesh PP et al. *Drugs*. 2014; 74:2015-32.

Extended VTE Treatment / Secondary VTE Prevention

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Risk Factors for VTE Recurrence

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

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

Fahrni J et al. *Vasc Health Risk Manag*. 2015;11:451-9.

Risk of Recurrent DVT/PE Persists Following Discontinuation of Anticoagulation

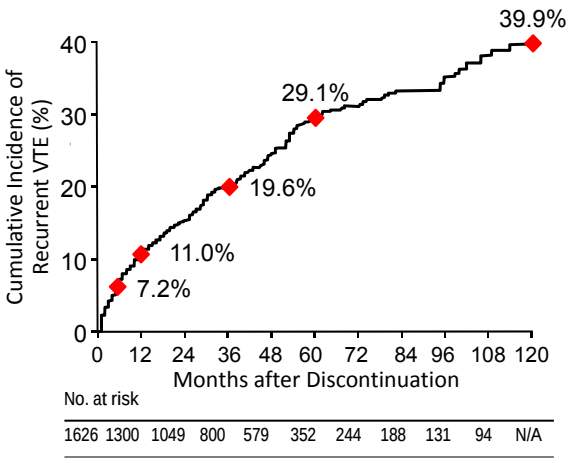
Patients with a first episode of clinically symptomatic proximal DVT and/or PE (N=1626)

↓

Average of 6 months of anticoagulation treatment

↓

Patients discontinued anticoagulation and were followed for recurrent DVT/PE



Adapted from Prandoni P et al. *Haematologica* 2007; 92:199-205.

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

	Dabigatran		Rivaroxaban	Apixaban	
	RE-MEDY 150 mg BID[a]	RE-SONATE 150 mg BID	EINSTEIN-Extension 20 mg daily	AMPLIFY-EXT 2.5 mg BID	AMPLIFY-EXT 5 mg BID
Primary efficacy endpoint, %	1.8 vs. 1.3	0.4 vs. 5.6	1.3 vs. 7.1	3.8 vs. 11.6	4.2 vs. 11.6
Major bleeding, %	0.9 vs. 1.8	0.3 vs. 0.0	0.7 vs. 0.0	0.2 vs. 0.5	0.1 vs. 0.5
CRNM bleeding, %	4.7 vs. 8.4	5.0 vs. 1.8	5.4 vs. 1.2	3.0 vs. 2.3	4.2 vs. 2.3
Major and CRNM bleeding, %	5.6 vs. 10.2	5.3 vs. 1.8	6.0 vs. 1.2	3.2 vs. 2.7	4.3 vs. 2.7

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

[a]Compared with warfarin. All others compared with placebo.

Dobesh PP et al. *Drugs*. 2014; 74:2015-32.

Prescribing Information Highlights: Indications

Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Initial treatment			
Treatment of DVT, PE in patients who have been treated with a parenteral anticoagulant for 5-10 days	Treatment of DVT, PE Take tablets with food	Treatment of DVT, PE	Treatment of DVT, PE following 5-10 days of initial therapy with a parenteral anticoagulant
Reduction in risk of recurrence			
Reduction in risk of recurrence of DVT, PE in patients who have been previously treated	Reduction in risk of recurrence of DVT, PE Take tablets with food	Reduction in risk of recurrent DVT, PE following initial therapy	Not indicated

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.

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Prescribing Information Highlights: Dosing

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

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

Kearon C et al. *Chest.* 2012; 141(suppl 2):e419S–e494S.
Kearon C et al. *Chest*. 2016; 149:315-52.

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Are the Direct Oral Anticoagulants First Line?

Antithrombotic Therapy for VTE Disease
CHEST Guideline and Expert Panel Report

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri Bounameaux, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy A. Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Woller, MD; and COL Lisa Moores, MD, FCCP

***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).

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

Kearon C et al. *Chest*. 2016; 149:315-52.

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

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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

Hohnloser SH et al. *Europace.* 2016; 18:184-90.

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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

Hohnloser SH et al. *Europace.* 2016; 18:184-90.

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

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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

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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!

Useful resource: Burnett AE et al. *J Thromb Thrombolysis*. 2016; 41:206-32.

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

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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

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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.
c. Review current guidelines for VTE treatment and secondary prevention.
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.

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- Kearon C, Akl EA, Ornelas J et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016; 149:315-52.

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Abbreviations Used in Presentation

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

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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

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