Clinical Case Studies in Venous Thromboembolism: Using Direct Oral Anticoagulants for Treatment and Secondary Prevention

Presented as a Live Webinar

Wednesday, April 12, 2017
12:00 PM – 1:00 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

Activity Overview

Clinical case studies will be used to illustrate the decision-making process regarding the acute treatment and secondary prevention of venous thromboembolism (VTE) based on recently updated guidelines and clinical trial data. Strategies for overcoming barriers to the appropriate use of direct oral anticoagulants and for ensuring long-term follow-up also will be discussed.

Learning Objectives

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

- Incorporate direct oral anticoagulants (DOACs) into existing venous thromboembolism (VTE) pathways, including strategies for ensuring appropriate long-term follow-up.
- Develop a plan for overcoming barriers to the appropriate use of DOACs for the acute treatment and secondary prevention 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 #: 0204-0000-17-428-L01-P
On-demand Activity ACPE #: 0204-0000-17-428-H01-P

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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.

List of Abbreviations

For a list of abbreviations used in this activity, please see page 37.

Webinar Information

Visit www.ashpadvantage.com/go/vteseries/webinar2 to find

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

Additional Educational Activities in this Initiative

- Upcoming live webinar in this educational initiative, "Contemporary Approaches for the Acute Treatment and Secondary Prevention of Venous Thromboembolism"
    - **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*)

Faculty

Alpesh Amin, M.D., MBA, FACC, MACP, SFHM
Thomas & Mary Cesario Chair of Medicine
Professor of Medicine, Business, Public Health, Nursing Science, and Biomedical Engineering
Executive Director, Hospitalist Program
Medical Director, Anticoagulation Services
University of California, Irvine
Irvine, California

Alpesh Amin, M.D., MBA, FACC, MACP, SFHM, is the Thomas & Mary Cesario Chair of the Department of Medicine at the University of California, Irvine (UCI). He is Professor of Medicine, Business, Public Health, Nursing Science, and Biomedical Engineering at UCI. He is also founder and executive director of the Hospitalist Program. At UCI, Dr. Amin has served as Vice Chair for Clinical Affairs and Quality, Chief of the Division of General Internal Medicine (GIM), Associate Program Director of the Internal Medicine Residency Program, and Medicine Clerkship Director. Dr. Amin obtained his Doctor of Medicine degree at Northwestern University Medical School in Chicago, and he completed his internship and residencies in internal medicine, including a chief residency, at UCI. He also earned a healthcare MBA degree at UCI. Dr. Amin is the first hospitalist to be named chief of a division of GIM, and then subsequently the first hospitalist to be named chair of a department of medicine nationally.

Throughout his career, Dr. Amin has been innovative in clinical, quality, and educational program development. He has advised the Hamad Medical Corporation (HMC) in Doha, Qatar on quality improvement efforts across eight hospitals under the national health ministry council. He has developed processes to improve patient care delivery looking at ways to reduce readmission and avoidable admissions, decrease length of stay and mortality, and improve customer service. Dr. Amin is an expert in implementation science and measuring outcomes to improve sustainable results. He has also applied information technology to improve the delivery of care through development of projects such as NHCPlus, eConsults, and Apps for Safe Anticoagulation Use.

During the course of his career, Dr. Amin has served as principal investigator, co-investigator, and faculty sponsor on clinical trials and research projects focusing on clinical topics, such as venous thromboembolism, pneumonia, and heart failure. His research interest is in health outcomes related to patient safety, quality improvement, and medical education. He is a member of Society of Hospital Medicine (SHM), American College of Physicians (ACP), Society of General Internal Medicine, Academic Chiefs and Leaders of General Internal Medicine (ACLGIM), Academic Alliance of Internal Medicine, and Association of Professors of Medicine. Within SHM, he has served as the Annual Meeting Course Director and on the Board of Directors. Dr. Amin has authored or co-authored over 170 peer-reviewed articles. He is the co-editor and co-author of Core Competencies for Hospital Medicine by SHM. Dr. Amin is also co-editor of the book, Contemporary Hospitalist Guide to Anticoagulation.

Dr. Amin has been honored by being named a Master of ACP, Senior Fellow of SHM, and Fellow of American College of Cardiology. He also has been awarded the ACP Special Recognition Award, ACP Top 10 Hospitalist Award, Orange County Physician of Excellence Award, and he was named one of “America’s Top Physicians” by the Consumers’ Research Council of America. In addition, he received the Alfred Soffer Award from ACCP, Venous Research Award for Quality Improvement and Implementation of Best Practices from the Venous Disease Coalition (VDC)/Vascular Disease Foundation (VDF), Exceptional Leadership Award from ACLGIM, CDC Healthcare-associated VTE Prevention Champion, and HMC Star of Excellence Award. He founded and directs the UCI Anticoagulation Clinic, which is recognized nationally as an AC Forum Center of Excellence.

Clinical Case Studies in Venous Thromboembolism: Using Direct Oral Anticoagulants for Treatment and Secondary Prevention

John Fanikos, R.Ph., MBA
Executive Director of Pharmacy Services
Brigham and Women's Hospital
Adjunct Professor of Clinical Pharmacy
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

John Fanikos, R.Ph., MBA, is Executive Director of Pharmacy Services at Brigham and Women's Hospital (BWH) in Boston, Massachusetts. He is responsible for the overall Pharmacy Department operations and its financial performance. Mr. Fanikos also serves as Adjunct Professor of Clinical Pharmacy at Massachusetts College of Pharmacy and Health Sciences. He earned his Bachelor of Science degree in Pharmacy at Massachusetts College of Pharmacy and his Master of Business Administration degree at Northeastern University. He completed an ASHP-accredited residency at BWH.

Mr. Fanikos has served in a number of different roles at BWH, including investigational drug pharmacist, inpatient and outpatient pharmacy supervisor, clinical preceptor, and pharmacy administrator. While fulfilling these roles, he has worked with patients on orthopedic, oncology, cardiology, and general medicine units. For the past 25 years, he has worked closely with the BWH Thromboembolism Research Group, and he has authored and co-authored many articles and textbook chapters on anticoagulant and antiplatelet medications. His research focus has been identifying and avoiding the problems and pitfalls of their use.

Mr. Fanikos is a member of the National Comprehensive Cancer Network (NCCN) panel that crafts guidelines for the treatment and prevention of thromboembolic disease. He serves as the treasurer and sits on the Board of Directors for the North American Thrombosis Forum (NATF), a nonprofit organization that provides a platform for those interested in thrombotic disorders to enhance disease education, awareness, advocacy, research, and prevention. He also serves on the Board of Directors for the Hospital Quality Foundation (HQF). Like NATF, HQF is a 503C charitable organization, and it is dedicated to improving the quality of healthcare by supporting the development and delivery of education related to medical practice.

Mr. Fanikos is Past President of the Massachusetts Society of Health-System Pharmacists. Both his father and brother are pharmacists, which makes him aware of many of the issues challenging the medical professions today.

Disclosures

In accordance with the Accreditation Council for Continuing Medical Education's Standards for Commercial Support and the Accreditation Council for Pharmacy Education's Standards for Commercial Support, ASHP requires that all individuals involved in the development of activity content disclose their relevant financial relationships. A person has a relevant financial relationship if the individual or his or her spouse/partner has a financial relationship (e.g. employee, consultant, research grant recipient, speakers bureau, or stockholder) in any amount occurring in the last 12 months with a commercial interest whose products or services may be discussed in the educational activity content over which the individual has control. The existence of these relationships is provided for the information of participants and should not be assumed to have an adverse impact on the content.

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- Alpesh Amin, M.D., MBA, FACC, MACP, SFHM, declares that he has served as a consultant for Boehringer Ingelheim Pharmaceuticals, Inc.; Portola Pharmaceuticals, Inc.; and Bristol-Myers Squibb and Pfizer Alliance (Faculty and Steering Committee)
- John Fanikos, R.Ph., MBA, declares that he has served on an advisory board for Portola Pharmaceuticals, Inc. and as a consultant for Boehringer Ingelheim Pharmaceuticals, Inc. (Faculty)
- Toby C. Trujillo, Pharm.D., BCPS-AQ Cardiology, FAHA, FCCP, declares that he has served as a consultant for Janssen Pharmaceuticals, Inc., and the 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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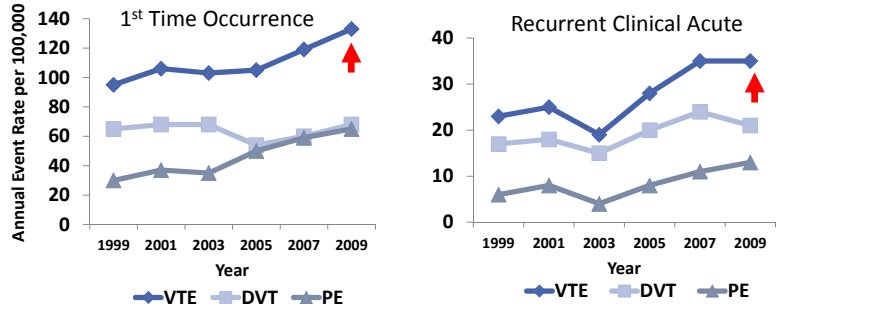
- Develop a plan for overcoming barriers to the appropriate use of DOACs for the acute treatment and secondary prevention of VTE.

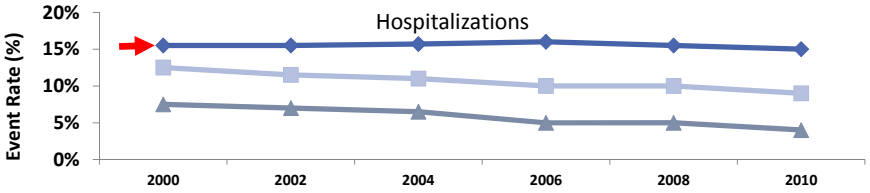
Outline

- VTE trends and VTE management
- VTE models and management plan
- VTE, patients, and DOAC selection
- VTE patient focus: preferences
- VTE follow-up and check lists
- Case presentations

U.S. Population-based VTE Trends

- 900,000 patients (1 to 2 per 1,000) afflicted with DVT or PE each year
- 60,000-100,000 Americans die of DVT or PE

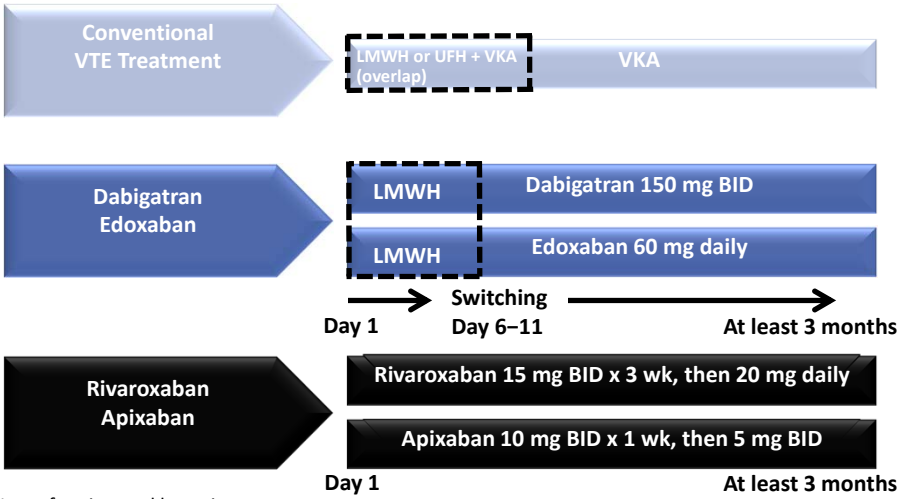




DVT = deep vein thrombosis
PE = pulmonary embolism

Huang W et al. *Am J Med.* 2014; 127: 829-39. Minges KE et al. *Am J Cardiol.* 2015; 116:1436-42. Beckman MG et al. *Am J Prev Med.* 2010; 38:S495-501.

Acute VTE Treatment Options



UFH = unfractionated heparin
LMWH = low-molecular-weight heparin or fondaparinux
VKA = vitamin K antagonists

Streiff MB et al. *J Thromb Thrombolysis*. 2016; 41:32-67.

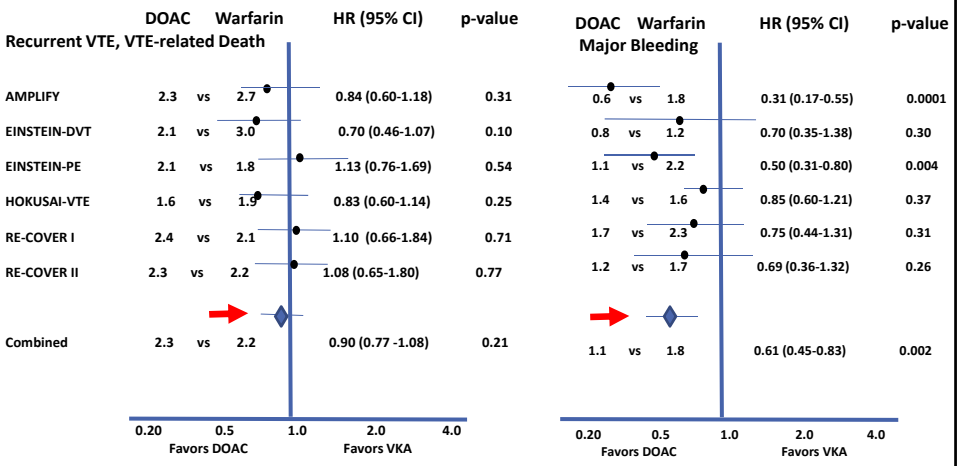
Phases of Treatment for VTE

Initiation (5-21 days)	Early Maintenance (3-6 months)	Extension (up to indefinite)
UFH, LMWH, fondaparinux Rivaroxaban 15 mg BID Apixaban 10 mg BID	Warfarin (INR 2.0-3.0) Rivaroxaban 20 mg daily Apixaban 5 mg BID Dabigatran 150 mg BID Edoxaban 60 mg daily	Warfarin (INR 2.0-3.0) Rivaroxaban 20 mg daily Apixaban 2.5 mg BID Dabigatran 150 mg BID --- Warfarin (INR 1.5-2.0) Aspirin 81 mg daily

Blondon M et al. *Circulation*. 2015; 132:1856-9.

Patients with VTE and DOACs: Outcomes

Meta-analysis (n=27,235)

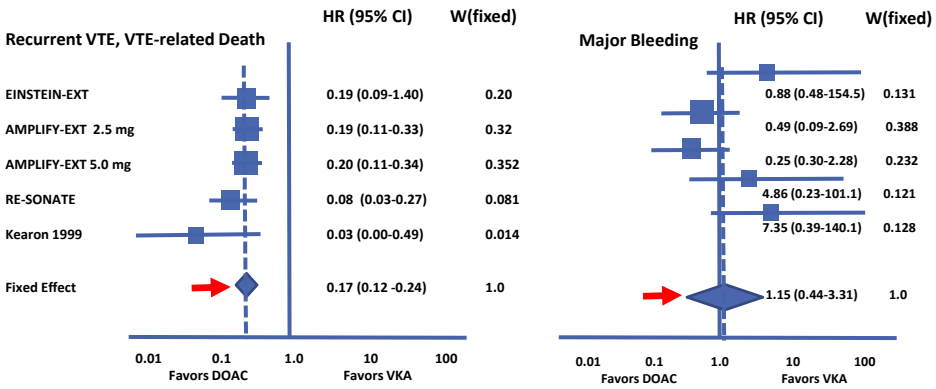


- 39% lower major bleeding
- 64% lower fatal bleeding
- 63% less intracranial hemorrhage vs. vitamin K antagonists

van Es N et al. *Blood*. 2014; 124:1968-75.

Extended VTE Treatment & DOACs: Outcomes

Meta-analysis (n=3,015)



- 83% relative risk reduction of recurrent VTE or VTE-related death (CI: 0.12-0.24, p<0.0001)
- No significant increase in the risk of major bleeding (CI: 0.40-3.31, p=0.38)

W = warfarin

Sindet-Pedersen C et al. *Thromb Res.* 2015; 136:732-8.

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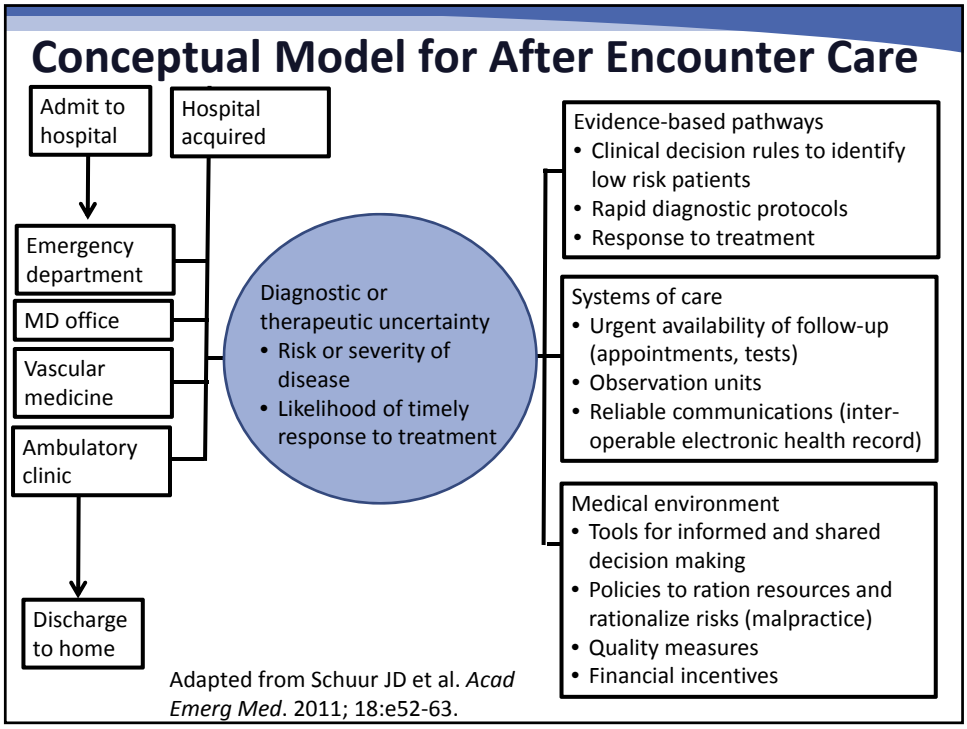
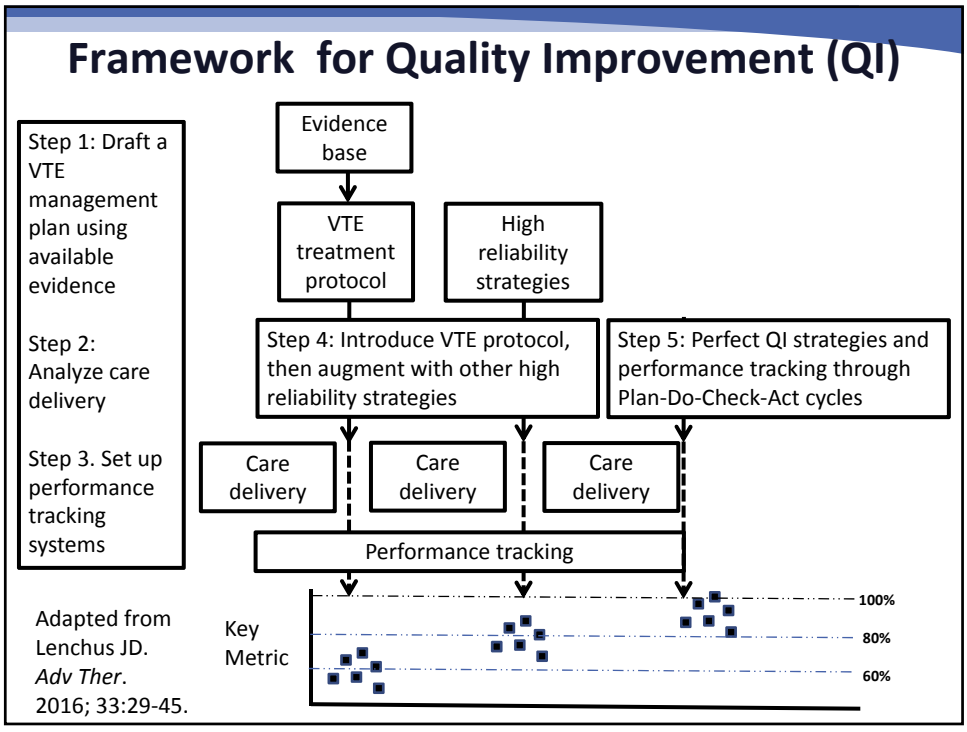
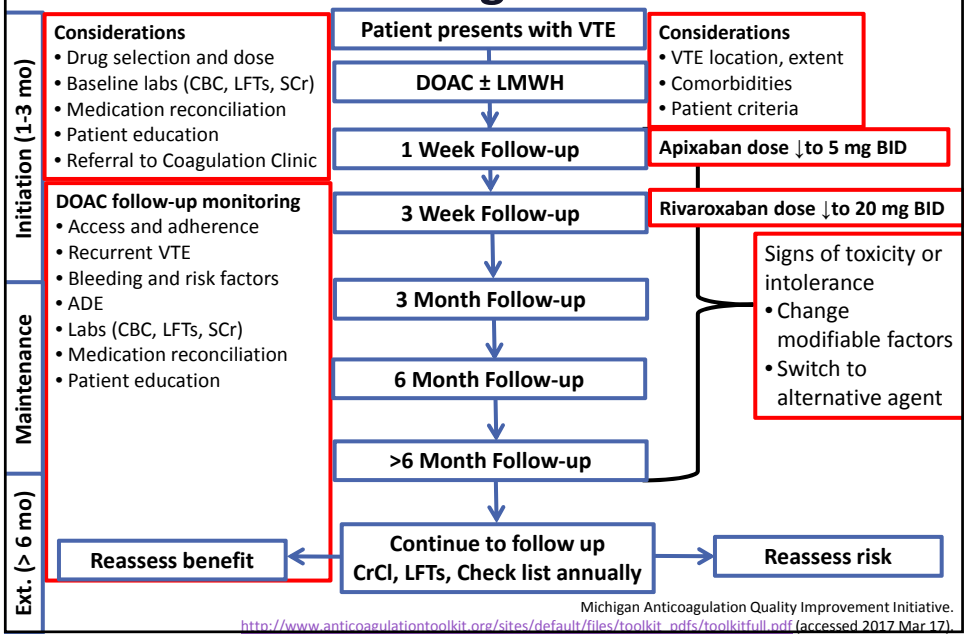




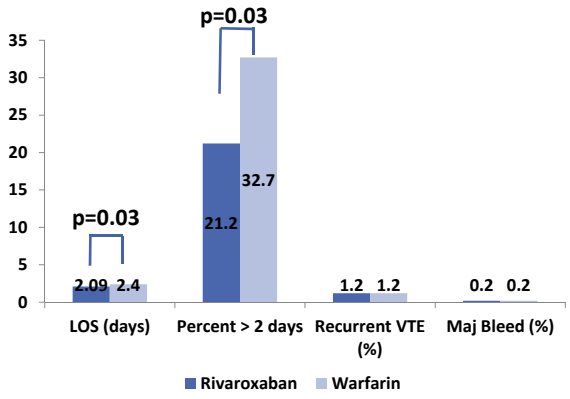
DOAC Management Plan



Michigan Anticoagulation Quality Improvement Initiative. http://www.anticoagulationtoolkit.org/sites/default/files/toolkit_pdfs/toolkitfull.pdf (accessed 2017 Mar 17).

VTE Patients Managed in Observation Status

- Comparison of PE patients managed through observation stays
- Rivaroxaban (n=401) vs. parenterally-bridged warfarin (n=401)
- U.S. claims data 2012-2015 identified PE patients
- Rivaroxaban use associated with
  - Shorter length of stay (-0.25 days)
  - Fewer encounters lasting >2 midnights (21.1% vs. 32.7%)
  - Lower total hospital costs (-$240) (p=0.03 for all)
  - No difference in recurrent VTE and major bleeding requiring readmission



Kohn CG et al. American Society of Hematology Meeting. San Diego, CA; 2016 Dec 3. https://ash.confex.com/ash/2016/webprogram/Paper88809.html (accessed 2017 Mar 22). Abstract 2337.

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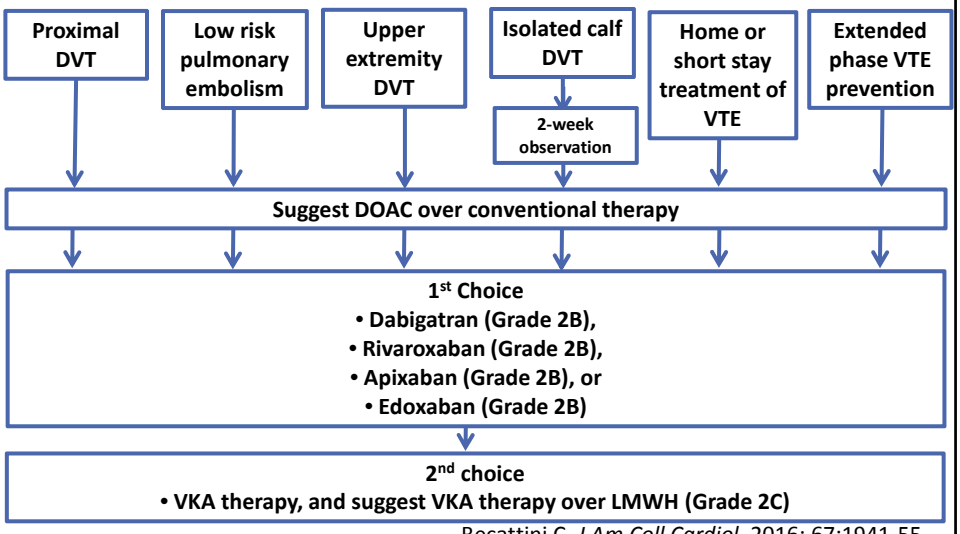
Initiation Phase: VTE Treatment



Becattini C. *J Am Coll Cardiol*. 2016; 67:1941-55.

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

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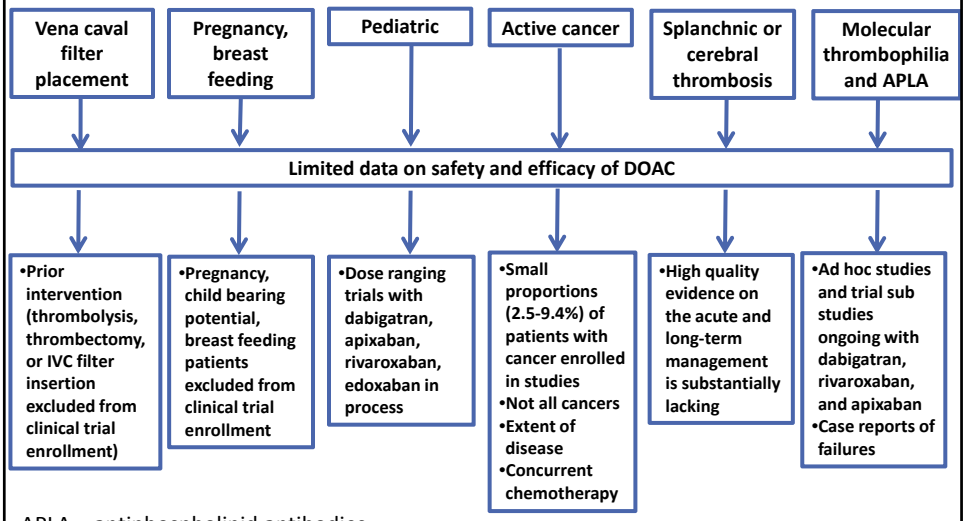
Initiation Phase: VTE Treatment



APLA = antiphospholipid antibodies

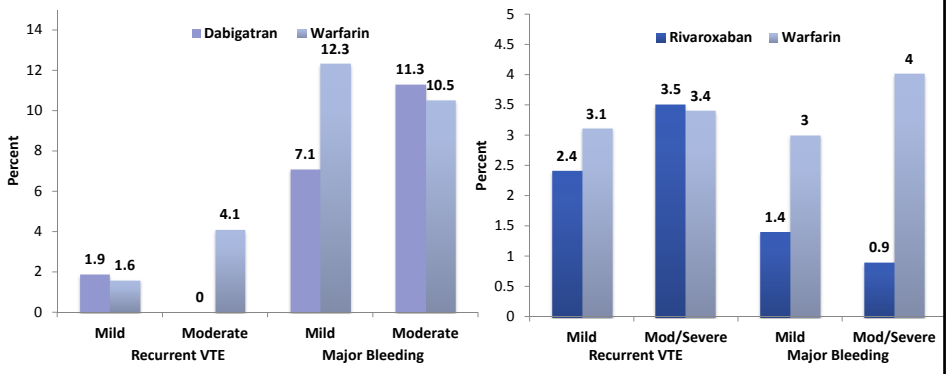
IVC = inferior vena caval filter

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

Becattini C et al. *J Am Coll Cardiol*. 2016; 67:1941-55.

Patients with VTE: Renal Dysfunction

- No effect observed on efficacy and safety
- Similar rates of recurrent VTE
- Trend in favor of rivaroxaban for major bleeding

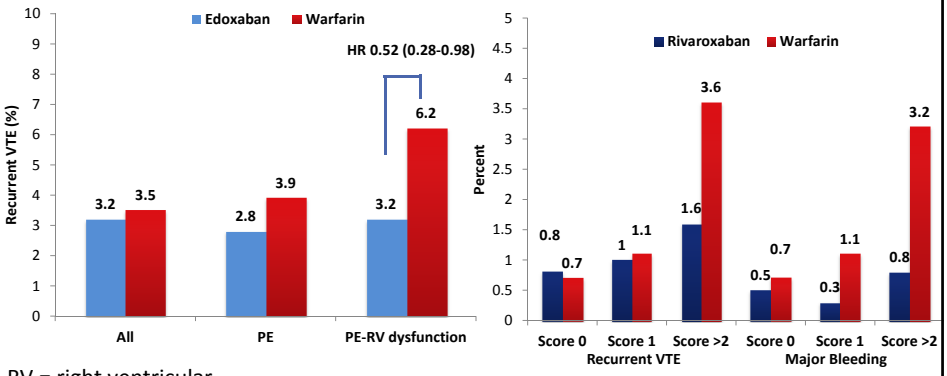


Schulman S et al. *Circulation*. 2014; 129:764-72.

Bauersachs M et al. *Thromb J*. 2014; 12:25.

Patients with VTE: Treatment of PE

- n=938 patients with RV dysfunction
- Edoxaban more effective than conventional treatment
- Post hoc analysis with simplified PESI score
- No treatment effect based on PESI score with rivaroxaban



RV = right ventricular
PESI = pulmonary embolism severity index

Hokusai-VTE Investigators. *N Engl J Med*. 2013; 369:1406-15.
Fermann GJ et al. *Acad Emerg Med*. 2015; 22:299-307.

Initiation Phase: Patient Criteria

Characteristic	Drug Choice	Comments
Renal disease (creatinine clearance <30 mL/min)	UFH, VKA	• DOACs and LMWH contraindicated with severe renal impairment • DOAC dosing is unique for each medication and level of renal function
Liver disease and coagulopathy	LMWH	• DOACs contraindicated if elevated baseline INR due to liver disease • VKA difficult to control and INR may not reflect antithrombotic effect
Taking medications known to interact with DOACs	LMWH	• Agents that increase or decrease drug exposure depending on the DOAC being used, including P-glycoprotein (Pgp) and strong CYP3A4 inducers and inhibitors (rifampin, ketoconazole, dronedarone, and itraconazole); eepends on the DOAC being used
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	• Coronary artery events appear to occur more often with dabigatran than with VKA • Has not been seen with the other DOACs, and they have demonstrated efficacy for coronary artery disease
Dyspepsia or history of gastrointestinal bleeding	VKA, apixaban	• Dabigatran can cause dyspepsia • Dabigatran, rivaroxaban, and edoxaban may be associated with more gastrointestinal bleeding than VKA
Extremes of weight (e.g. <50kg or >120kg) or BMI >40 kg/m^2	VKA	• Patients at extremes of weight represented a very small proportion of patients in DOAC VTE trials
Parenteral therapy to be avoided	Rivaroxaban, apixaban	• VKA, dabigatran, and edoxaban require initial parenteral therapy

Kearon C et al. *Chest*. 2016; 149:315-52. Burnett AE et al. *J Thromb Thrombolysis*. 2016; 41:206-32. Martin K. *J Thromb Haemost.* 2016; 14:1308-14.

Initiation Phase: Treatment Selection

Characteristic	RE-COVER I	RE-COVER II	EINSTEIN-DVT	EINSTEIN-PE	AMPLIFY	Hokusai-VTE
Patients receiving parenteral anticoagulation in DOAC group (%)	100	100	73	93	86	100
Median duration of parenteral anticoagulation in DOAC group (days)	9	9	1	1	1	7

Schulman S et al. *N Engl J Med*. 2009; 361:2342-52.
Schulman S et al. *Circulation*. 2014; 129:764-72.
Einstein Investigators et al. *N Engl J Med*. 2010; 363:2499-510.
Einstein-PE Investigators et al. *N Engl J Med*. 2012; 366:1287-97.
Agnelli G et al. *N Engl J Med*. 2013; 369:799-808.
Hokusai-VTE Investigators. *N Engl J Med*. 2013; 369:1406-15.

Initial Phase: Conversion from Parenteral Anticoagulants to DOACs

Drug	LMWH	Intravenous Unfractionated Heparin
Dabigatran	Stop LMWH, start dabigatran 0-2 hours before time of next scheduled administration of LMWH	Stop infusion and start dabigatran at the same time
Apixaban	Stop LMWH, start apixaban at time of next scheduled administration of LMWH	Stop infusion and start apixaban at the same time
Rivaroxaban	Stop LMWH, start rivaroxaban 0-2 hours before time of next scheduled evening administration of LMWH	Stop infusion and start rivaroxaban at the same time
Edoxaban	Stop LMWH , start edoxaban at time of next scheduled administration of LMWH	Stop the infusion and start edoxaban 4 hours later

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

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Initiation Phase: Patient Preferences

Characteristic	Drug Choice	Comments
Parenteral therapy to be avoided or patient unwilling or unable to self inject	Rivaroxaban, apixaban	• VKA, dabigatran, and edoxaban require initial parenteral therapy
Once daily oral therapy preferred	Rivaroxaban, edoxaban, VKA	• Consider concomitant medications for other conditions and opportunities to simplify daily schedule
Poor compliance	VKA	• INR monitoring can help to detect problems • Patients may be more compliant with a DOAC because it is less complex
Reversal agent needed	VKA, unfractionated heparin, dabigatran	• Discussion with patients on types of bleeding and prognosis and options with traditional therapies
Financial resources: cost, insurance coverage, licensing	VKA	• DOACs may require higher out-of-pocket expense • Insurance and co-payments vary among regions and with individual circumstances

Kearon C et al. *Chest*. 2016; 149:315-52.
Burnett AE et al. *J Thromb Thrombolysis*. 2016; 41:206-32.
Martin K. *J Thromb Haemost.* 2016; 14:1308-14.

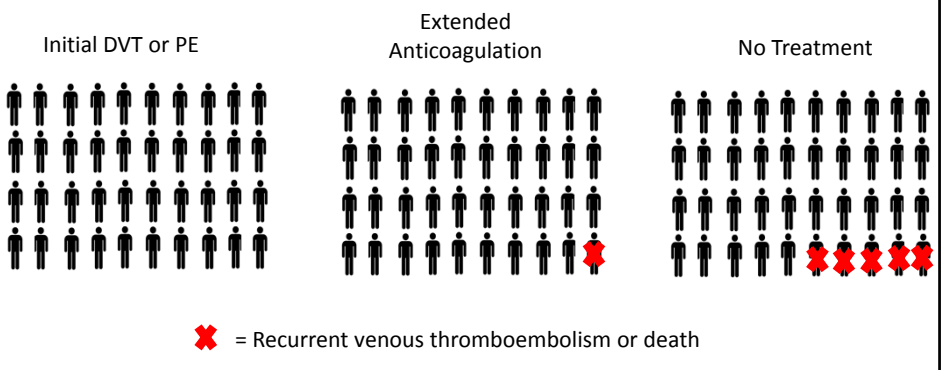
Models of Treatment Decision Making

Model	Basic Description	Difference from Shared Decision Making
Parent or proxy role	MD reviews medical situation and decides course of action	MD makes decisions based entirely on medical situation at hand. No involvement in patient values or preferences, only minimal patient participation to satisfy legal requirement for informed consent.
MD as best-agent decision maker	MD makes decision about treatment course but takes into consideration patient's values and preferences	There is no exchange of preference. MD makes final decision but seeks to understand and incorporate patient's values into decision-making process.
Shared decision making	**Open discussion integrating the medical issue and patient's preference and context to arrive at a course of action. Final decision is made by patient with MD collaboration.**	
Informed decision making	MD provides the patient with information on all available treatment options and leaves final decision completely to the patient without further input.	Patient acts as a consumer who chooses from the available options. MD does not state his or her preference and does not collaborate in the decision-making process

Seaburg L et al. *Circulation*. 2014; 129:704-10.

Shared Decision Making (cont)

- Tip 1: Present statistical information using absolute risk
- Tip 2: Highlight the incremental risks associated with treatment distinctly from baseline risks
- Tip 3: Use pictographs to communicate risk and benefit information



Barry MJ et al. *N Engl J Med*. 2012; 366:780-1.

Patient Assistance Programs

- Co-payment coupon card or voucher for patients
- Patients can obtain up to 12 30-day supplies (over 15 months)
- Patients with commercial insurance pay no more than $10-30 for each prescription, with a maximum benefit of $100 per month

The New York Times

"Drug Coupons: Helping a Few at the Expense of Everyone"

- Coupons for 23 drugs with a generic alternative resulted in extra $700 million to $2.7 billion in spending on drugs over five years

Drug	Co-pay	Discounted Co-pay	Retail Price	Insurer Cost
Lipitor	$360	$48	$2,004	$1,644
Crestor	$360	$216	$1,872	$1,512
Simvastatin	$120	$120	$336	$216

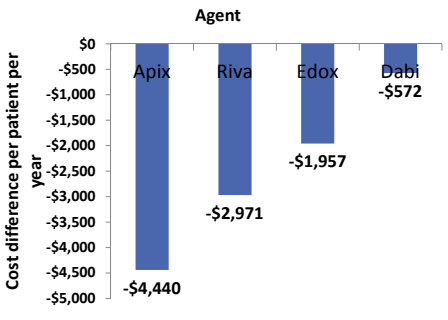
Patient Assistance Foundations and Funds

Sponsor	Website	Sponsor	Website
The Assistance Fund	www.theassistancefund.org	National Organization of Rare Disorders	www.rarediseases.org
Chronic Disease Fund	www.cdfund.org	Patient Access Network Foundation	www.panfoundation.org
Healthwell Foundation	www.healthwell.org	Patient Advocate Foundation	www.copays.org

Grande D. *JAMA*. 2012; 307:2375-6. Sanger-Katz M. *NY Times*. 2016 Oct 12. https://www.nytimes.com/2016/10/13/upshot/drug-coupons-helping-a-few-at-the-expense-of-everyone.html?_r=0 (accessed 2017 Mar 22). Dafny L. *N Engl J Med*. 2016; 375:2013-5.

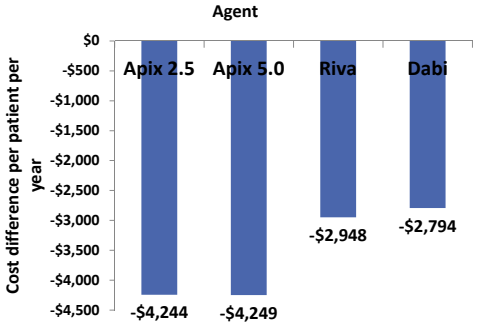
Real World Cost of VTE

Acute VTE Treatment



- Application of clinical trial event rates to U.S. population
- Estimates of annual cost vs. traditional treatment
- Savings generated from reductions in recurrent VTE and bleeding rates

Extended VTE Treatment



- Annual medical costs among claims database adjusted to 2013 costs
- Comparison of annual cost vs. traditional treatment
- Savings generated from reductions in recurrent VTE and bleeding rates

Amin A et al. *Clin Appl Thromb Hemost.* 2016; 22:5-11.
Amin A et al. *J Thromb Thrombolysis*. 2015; 40; 131-8.

Initiation Phase: Patient Education

DOAC Educational Points

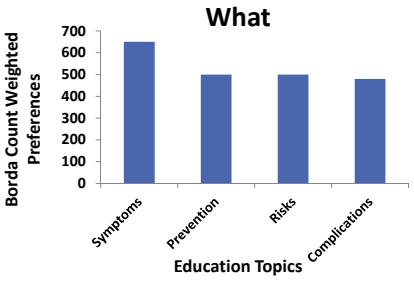
Anticoagulation basics	Indicate reason for initiating anticoagulation
	Review name of the anticoagulant drug (generic and trade) and how they work to reduce complications, onset, duration, and reversibility
	Duration of therapy
Risk benefit	Common signs and symptoms of bleeding, what to do when occurs
	Common signs and symptoms of blood clot, what to do when occurs
	Need for birth control for women of child-bearing age
Self care	Precautionary measures to reduce risk of trauma or bleeding (e.g., shaving, toothbrushing, acceptable physical activities)
Accessing healthcare	Which healthcare providers (e.g., physicians, dentists) to notify of use of anticoagulant therapy
	When to notify an anticoagulation provider (hospitalizations or dental, surgical, or invasive procedures scheduled)
	Carrying identification (e.g., identification card, medical bracelet, necklace)
Adherence	Potential drug interactions
	When to take an anticoagulant medication and what to do if dose is missed
Lab monitoring	Meaning and significance of the International Normalized Ratio
	Need for frequent INR testing, target INR values appropriate for treatment
	Narrow therapeutic index and emphasis on regular monitoring as a way to minimize bleeding and thrombosis risk
	Influence of dietary vitamin K use
Diet and lifestyle	Need to limit or avoid alcohol

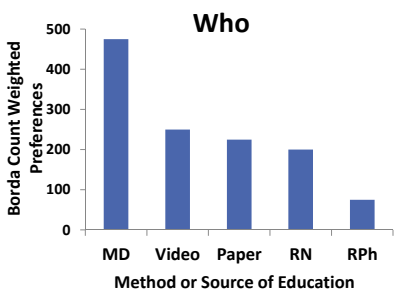
Warfarin Educational Points

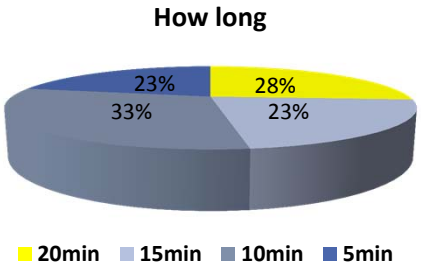
Garcia DA. *Ann Pharmacother*. 2008; 42:979-88.

Patient Preferences in VTE Education

- National sample of patients and family members
- Review of content and approaches to patient education related to VTE prevention and treatment in hospitalized patients







Popoola VO et al. *Plos One*. 2016; 11:e0152084.

Outline

- VTE trends and VTE management
- VTE models and management plan
- VTE, patients, and DOAC selection
- VTE patient focus: preferences
- VTE follow-up and check lists
- Case presentations

Maintenance Phase: Follow-up Monitoring Check List

Task	Interval	Comments
Assess compliance	Each visit	• Bring remaining medication: pill count and calculate average adherence • Re-educate on importance of strict intake schedule • Inform about compliance aids (e.g., special boxes, smartphone applications) • Dabigatran must remain in original packaging
Assess for recurrent thromboembolism	Each visit	• Systemic (peripheral, pulmonary) circulation
Assess for bleeding	Each visit	• If minor (nuisance) bleeding, are preventive measures possible? (e.g., PPI, saline nose spray); motivate patient to diligently continue anticoagulation • If bleeding with impact on quality-of-life or with significant risk, is prevention possible? (Consider changing anticoagulant)
Assess for other side effects	Each visit	• Assess for link to DOAC and decide whether to continue, temporarily stop, or change to different anticoagulant
Assess for new co-medications	Each visit	• Assess for P-gp inhibitors/inducers (if on dabigatran or edoxaban) or dual P-gp/CYP3A4 inhibitors (if on rivaroxaban or apixaban) • Assess for other medications that may increase risk of bleeding, such as anti-platelet agents
Assess labs	Yearly Q 6 mo Q 3 mo As needed	• Hgb, renal and liver function • Renal function if CrCl 30-60 mL/min* or if on dabigatran and >75 yr or fragile • Renal function if CrCl 15-30 mL/min* • If clinically indicated for conditions that may impact renal or hepatic function • Declining renal function may require DOAC dose adjustment

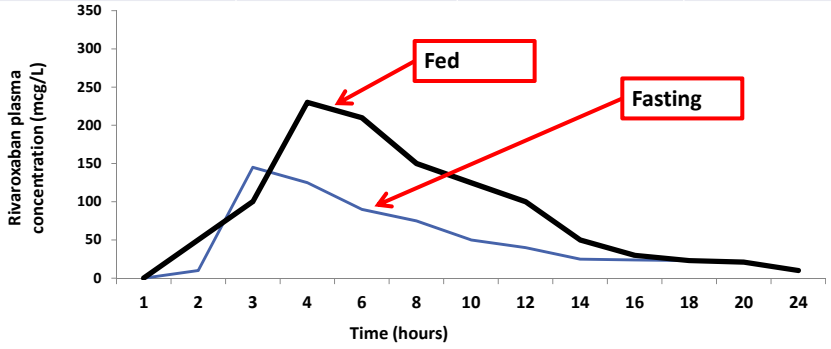
*Determined using Cockcroft-Gault formula and actual body weight

PPI = proton pump inhibitor

Heidbuchel H et al. *Eur Heart J*. 2016 Jun 9 [Epub ahead of print].

Rivaroxaban: Fasted vs. Fed States

Parameter	Fasted (range)	Fed (range)	Ratio Fed vs. Fasted (90% CI)
AUC (mcg x hr/L)-10 mg	1,234 (836-1,941)	1,219 (735-1,864)	0.98 (0.93-1.05)
Cmax 10 mg (mcg/L)	183.9 (94.5-288.2)	190.1 (105.4-332.2)	1.03 (0.94-1.14)
AUC (mcg x hr/L)-20 mg	1,477 (1,051-2,754)	2,048 (1,422-4,078)	1.39 (1.29-1.49)
Cmax 20 mg	159.9 (76.3-257.2)	282.4 (145.8-551.3)	1.76 (1.55-1.99)



Stampfuss J. *Int J Clin Pharmacol Therap.* 2013; 7:549-61.

Handling a Missed DOAC Dose

Dabigatran
- **Take ASAP same day**
- If next dose is <6 hr away, skip missed dose
- Dose should not be doubled to make up for missing dose

Rivaroxaban
- **Take ASAP same day**
- Continue on following day with QD regimen
- For patients receiving 15 mg BID, take dose immediately to ensure intake of 30 mg per day

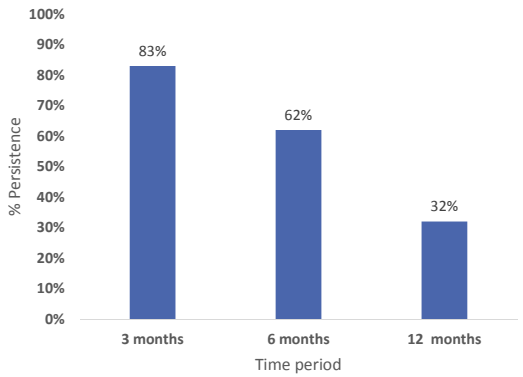
Apixaban
- **Take ASAP same day**
- Resume BID dosing
- Dose should not be doubled to make up for missed dose

Edoxaban
- **Take ASAP same day**
- Resume normal dosing next day
- Dose should not be doubled to make up for missing dose

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

Persistence with Anticoagulants in VTE

- 12 observational studies of VTE treatment
  - Included warfarin and DOACs
  - Persistence: "duration of time from initiation to discontinuation of therapy" in an individual patient
- All provided data for persistence
  - 3 months (n=71,969)
  - 6 months (n=58,940)
  - 12 months (n=68,235)
- Only two studies reported the risk of VTE recurrence based on nonpersistence – at 3 months and 12 months
- 17% patients being nonpersistent with anticoagulants in the crucial first 3 months and at high risk of VTE recurrence
- Persistence declined with increasing duration of treatment



Vora P et al. *Patient Prefer Adherence*. 2016; 10: 1657-65.

Maintenance Phase: Conversion from VKA to DOACs

Drug	Strategy
Dabigatran	Discontinue warfarin and begin dabigatran when INR is below 2.0 Start dabigatran at: 150 mg BID for CrCl >30mL/min*
Apixaban	Discontinue warfarin and begin apixaban when INR is below 2.0 Start apixaban at: 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE
Rivaroxaban	Discontinue warfarin and begin rivaroxaban when the INR is below 3.0 Start rivaroxaban at: 15 mg twice daily with food, for first 21 days After 21 days, transition to 20 mg once daily with food, for remaining treatment
Edoxaban	Discontinue warfarin and begin edoxaban when the INR is ≤ 2.5 Start edoxaban at: 60 mg once daily 30 mg once daily for patients with CrCL 15 to 50 mL/min* or body weight less than or equal to 60 kg or who use P-gp inhibitors

*CrCl determined using Cockcroft-Gault

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

Maintenance Phase: Conversion from DOACs to Other Anticoagulants

Drug	Parenteral Anticoagulants	Warfarin
Dabigatran	Discontinue dabigatran and start parenteral anticoagulant in 12 hours (CrCl ≥30 mL/min*) or 24 hours (CrCl <30 mL/min*)	• Start warfarin based on creatinine clearance: • For CrCl ≥50 mL/min,* start warfarin 3 days before discontinuing dabigatran. • For CrCl 30-50 mL/min,* start warfarin 2 days before discontinuing dabigatran. • For CrCl 15-30 mL/min,* start warfarin 1 day before discontinuing dabigatran. • For CrCl <15 mL/min,* no recommendations can be made. • Because dabigatran can increase INR, INR will better reflect warfarin's effect only after dabigatran has been stopped for at least 2 days
Apixaban	Discontinue apixaban and start parenteral anticoagulant at the next scheduled dose of apixaban	• Apixaban affects INR, so initial INR measurements during transition to warfarin may not be useful for determining appropriate dose of warfarin. • Discontinue apixaban and begin warfarin with a concomitant parenteral anticoagulant when next dose of apixaban would have been due, discontinuing the parenteral anticoagulant when INR reaches goal range.
Rivaroxaban	Discontinue rivaroxaban and start parenteral anticoagulant at next scheduled dose of rivaroxaban	• No clinical trial data available to guide converting patients from rivaroxaban to warfarin • Rivaroxaban affects INR, so INR measurements made during coadministration with warfarin may not be useful for determining appropriate dose of warfarin. • Discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin when next dose of rivaroxaban would have been taken
Edoxaban	Discontinue edoxaban and start parenteral anticoagulant at next scheduled dose of edoxaban	• If on edoxaban 60 mg/day, reduce to 30 mg/day and begin warfarin concomitantly • If on edoxaban 30 mg/day, reduce to 15 mg/day and begin warfarin concomitantly • During transition, INR should be done at least weekly just before daily dose of edoxaban (to minimize influence on INR) • Discontinue edoxaban once stable INR ≥ 2.0 is achieved

*CrCl determined using Cockcroft-Gault

Prescribing information.

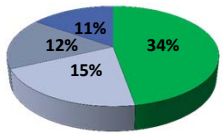
RIETE Predictive Score for bleeding

Condition	Point score
Recent major bleeding (<15 days before VTE)	2.0
Serum creatinine (>1.2 mg/dL)	1.5
Anemia (Hgb <13 g/dL in men or <12 g/dL in women)	1.5
Cancer	1
Clinically overt pulmonary embolism	1
Age > 75 years	1
Total	8 points

Point Score	Major Bleeding (%)	Risk
0	0.1	Low
1	1.4	
1.5-2	2.2	Moderate
2.5-3	4.4	
3.5-4	4.2	
4.5-5	4.9	High
5.5-6	11	
>6	20	

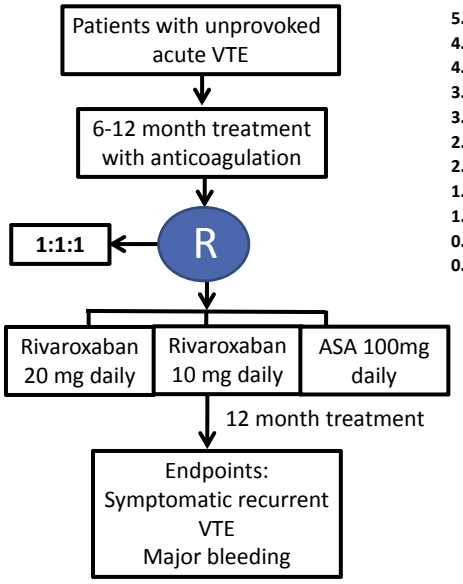
- Validation sample (n=6,752)
- First 3 months of treatment
- 1/3 of events were fatal
- High risk patients may warrant intervention

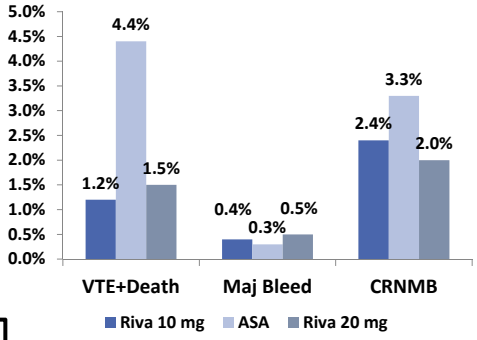
Bleeding Types



Ruíz-Giménez N et al. *Thromb Haemost*. 2008; 100:26-31.

EINSTEIN CHOICE



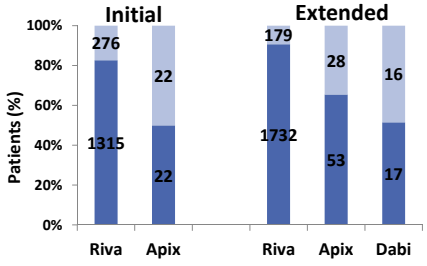


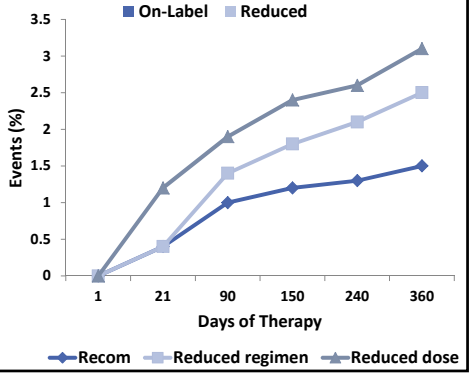
- Compared with aspirin, both rivaroxaban 10 mg and 20 mg reduced the relative risk of recurrent VTE by about 70% (approximately 3 percentage points)
- Rates of major and clinically relevant nonmajor bleeding were low and similar to those with aspirin

Weitz JI et al. *Thromb Haemost*. 2015; 114:645-50. Weitz JI et al. *N Engl J Med.* 2017; 376:1211-22.

Maintenance: Influence of DOAC Dosing

- Riete VTE Registry
- Initial therapy for VTE (n=1635)
  - 18% (n=298) prescribed a reduced dose or regimen
- Extended therapy for VTE (n=1725)
  - 13% (n=222) prescribed a reduced dose or regimen
- Those patients were more likely to be elderly, have cancer or renal insufficiency
- Overall, patients receiving DOACs at nonrecommended doses
  - Tenfold higher rate of VTE recurrence
  - Similar rate of major bleeding or death
- Higher rate of VTE recurrence was confirmed after adjusting for potentially confounding variables (age, body weight, recent bleeding, renal function, or active cancer)





Trujillo-Santos J et al. *Thromb Haemost.* 2017; 117:382-9.

Outline

- VTE trends and VTE management
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Clinical Case – JF: Low-risk, Healthy Patient with DVT

Presentation
- 62-year-old male
- 4 day history of right calf & thigh pain
- 1 week prior, traveled to China on business

Past Medical History
- Hyperlipidemia
- Benign prostatic hyperplasia

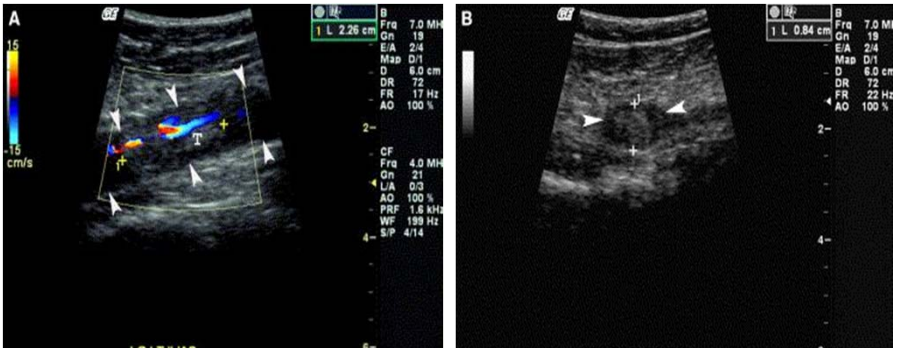
Current Medications
- Atorvastatin
- Tamsulosin

Physical Exam
- BP 110/88, P 80, R 14, POx 100%, T 98.6, 80 kg
- Right leg +2 edema, warm, tender to palpation, pulses +2

Labs
- Normal CBC, PT, PTT, Cr, UA
- Normal CXR, ECG

Tests
- Ultrasound revealed a right popliteal vein thrombosis

Compression Ultrasound with Color Flow Doppler



ED Diagnosis: DVT

Which of the following is an acceptable initial treatment choice for JF?

a. Dabigatran
b. Edoxaban
c. Rivaroxaban
d. Warfarin

JF is given an appropriate initial treatment. What of the following would be appropriate sub-acute treatment and secondary prevention of VTE in this case?

a. Apixaban 5 mg daily for 6 months
b. Dabigatran 150 mg once daily for at least 1 year
c. Rivaroxaban 20 mg daily for 3 months
d. Warfarin, INR range 2-3, indefinitely

JF has been taking an appropriate anticoagulant for 2 months. His DVT symptoms have resolved and he has no signs and symptoms of bleeding.
He calls the pharmacist at 11:30 AM.
He states he forgot to take his 8:00 AM dose.
What should JF do?

a. Take morning dose of anticoagulant now
b. Skip morning dose of anticoagulant and take next scheduled dose
c. Take morning dose of anticoagulant now and skip next scheduled dose
d. Stop oral anticoagulant and start subcutaneous LMWH as soon as possible

Clinical Case – FF: Resident in Assisted Living with PE

Presentation
- 85-year-old female
- Transferred from assisted living to ED with increasing SOB
- Fully ambulatory

Past Medical History
- Hyperlipidemia
- Hypertension
- DJD
- Hypothyroidism

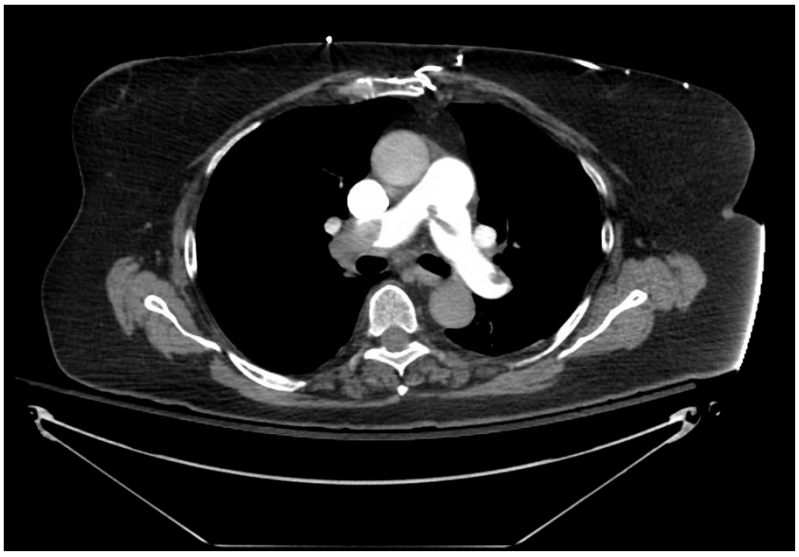
Current Medications
- Atorvastatin
- Amlodipine
- Hydrochlorothiazide
- Levothyroxine

Physical Exam
- BP 140/78, P 80, R 14, POx 94%, T 98.6, 50 kg
- Thin

Labs
- Normal CBC, PT, PTT, Cr 1.3, CrCl 46 mL/min, UA
- Normal CXR, ECG

Tests
- CTPA: Bilateral lower lobe single segmental defects
- Cardiac echo: No RV strain

Chest CT



What anticoagulant regimen is the best choice for FF's initial treatment?

a. Apixaban 10 mg twice daily
b. Dabigatran 150 mg twice daily
c. Edoxaban 30 mg once daily
d. Rivaroxaban 15 mg once daily

As part of FF's follow-up you are asked to contact her 72 hours after ED discharge. Which of the following would be the most important question to ask her at this time?

a. Have you installed a medical adherence app on your smart phone?
b. When did you last have your renal and hepatic function tested?
c. Have you been taking your medications correctly?
d. Have you noticed any change in the color of your stools?

Clinical Case – GF: DVT in History of Cancer

Presentation
- 78-year-old male
- 2 years status post radical prostatectomy
- Chief complaint during office visit to primary care physician is left calf discomfort

Past Medical History
- Hypertension

Current Medications
- Lisinopril

Physical Exam
- BP 120/78, P 80, R 12, POx 100%, T 98.6, 79 kg
- Left leg +2 edema, warm, tender to palpation, pulses +2

Labs
- Hgb 9.9, Hct 30
- Normal PT, PTT, Cr, UA
- Normal CXR, ECG

Tests
- Ultrasound revealed a left popliteal, posterior tibial, and peroneal vein thrombosis

GF prefers to be treated at home and with an oral regimen. What anticoagulant regimen is an acceptable choice for GF's initial treatment?

a. Unfractionated heparin as a bridge to warfarin
b. LMWH as a bridge to warfarin
c. Apixaban 10 mg twice daily
d. Edoxaban 60 mg daily
e. Rivaroxaban 20 mg once daily

GF has completed 3 months of treatment with no recurrent VTE or bleeding episodes. His work up for recurrent cancer was negative. Which of the following would you recommend?

a. Continue anticoagulation indefinitely
b. Continue anticoagulation for 3 months, then reassess
c. Stop the anticoagulation now

Clinical Case – EF: DVT and No Social Support

Presentation
- 55-year-old male presents to the ED
- Chief complaint is right calf and thigh swelling, pain, erythema

Past Medical History
- None available

Current Medications
- None

Physical Exam
- BP 130/85, P 82, R 14, POx 100%, T 98.8, 60 kg
- Right leg +1 edema, warm, tender to palpation, pulses +2

Labs
- D-dimer 1000 mg/mL, Hgb 10, Hct 29
- Normal PT, PTT, Cr, UA
- Normal CXR, ECG normal

Tests
- Ultrasound revealed a right femoral vein thrombosis

EF appears frail and much older than his stated age. The medical residents suggest the following dose adjustments. Which is the best choice?

a. Apixaban 10 mg twice daily
b. Dabigatran 75 mg twice daily
c. Edoxaban 30 mg once daily
d. Rivaroxaban 15 mg once daily

EF is given an appropriate first dose of a direct oral anticoagulant. Further inquiry reveals he has no local family or health insurance and resides in government-subsidized housing. The physician asks for direction. You suggest:

a. Find coupon card providing first 30 days of treatment free
b. Give him web addresses for foundations that will provide financial support
c. Convert EF to aspirin therapy
d. Convert EF to LMWH and warfarin therapy

Key Takeaways

- Key Takeaway #1
  - Create a management plan for acute VTE management and secondary prevention
- Key Takeaway #2
  - Develop a check list for critical steps in acute management and surveillance for optimal outcomes
- Key Takeaway #3
  - Be prepared to overcome barriers (educational, financial, persistence, etc) that may arise during therapy

Which of these practice changes will you consider making? Select all that apply.

a. Develop an anticoagulant management plan for VTE
b. Educate patients on the risk and benefits of anticoagulation therapy
c. Assess persistence with therapy, signs of bleeding, and thrombosis complications
d. Support those with financial barriers with viable solutions
e. Be prepared to convert patients from one anticoagulant to another

Selected Resources

- Agnelli G, Buller HR, Cohen A et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013; 369:799-808.
- Becattini C, Agnelli G. Treatment of venous thromboembolism with new anticoagulant agents. *J Am Coll Cardiol*. 2016; 67:1941-55.
- Burnett AE, Mahan CE, Vazquez SR et al. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis.* 2016; 41:206-32.
- EINSTEIN Investigators, Bauersachs R, Berkowitz SD et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010; 363:2499-510.
- EINSTEIN-PE Investigators, Büller HR, Prins MH et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012; 366:1287-97.

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- Hokusai-VTE Investigators, Büller HR, Decousus H et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013; 369:1406-15.
- Kearon C, Akl EA, Ornelas J et al. Antithrombotic therapy for VTE disease. CHEST Guideline and Expert Panel Report. *Chest*. 2016; 149:315-52.
- Schulman S, Kakkar AK, Goldhaber SZ et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014; 129:764-72.
- Schulman S, Kearon C, Kakkar AK et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009; 361:2342-52.

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

Self-assessment Questions

1. Which of the following best describes how a patient taking apixaban should be instructed to handle a missed dose?

    a. Take it as soon as possible that same day and resume normal dosing the next day. If dose is completely missed, do not double the next day's dose to make up for the missing dose.
    b. Take it as soon as possible that same day and resume normal dosing the next day. If dose is completely missed, double the next day's dose to make up for the missing dose.
    c. Take it as soon as possible that same day, except skip the missed dose if the next scheduled dose is less than 6 hours away. Do not double dose to make up for the missing dose.
    d. Take it as soon as possible that same day, except skip the missed dose if it is more than 6 hours past its scheduled time. Double the next day's dose to make up for the missing dose.

2. All of the following may be a barrier to effective treatment of venous thromboembolism (VTE) with direct oral anticoagulants EXCEPT

    a. Lack of established dosing for VTE in frail and elderly patients.
    b. Concern about documented increased risk of bleeding compared with warfarin.
    c. Lack of patient persistence with therapy over time.
    d. Cost of therapy and reimbursement issues.

Also see the polling questions within the activity.

Answers

1. a
2. b