The Changing Face of Anticoagulant Therapy: Improving the Management of Patients at Risk for Venous Thromboembolism

Presented as a Midday Symposium at the 44th ASHP Midyear Clinical Meeting and Exhibition

Tuesday, December 8, 2009
Las Vegas, Nevada
Please be advised that this activity is being audio recorded for archival purposes and, in some cases, for repurposing of the content for enduring materials.
AGENDA

11:30 am – 11:35 am  Welcome and introduction  
Stuart T. Haines, Pharm.D., BCPS, FCCP, FASHP, FAPhA

11:35 am – 11:50 am  VTE Prophylaxis – Best Practices in 2009  
Stuart T. Haines, Pharm.D., BCPS, FCCP, FASHP, FAPhA

11:50 am - 12:10 pm  Questions, Dilemmas and Conundrums – Managing Patients with Unique Needs  
William E. Dager, Pharm.D., BCPS, FCSHP, FCCP, FCCM

12:10 pm – 12:30 pm  New Agents and Technologies for VTE Prophylaxis  
Toby C. Trujillo, Pharm.D., BCPS

12:30 pm – 1:10 pm  Panel Discussion – Audience Participation: Management and clinical challenges in improving the use of anticoagulant therapy for VTE prevention in health systems  
All Faculty

1:10 pm – 1:30 pm  Questions and Answers

FACULTY

Stuart T. Haines, Pharm.D., BCPS, FCCP, FASHP, FAPhA, Chair and Moderator  
Professor and Pharmacotherapy Specialist  
University of Maryland School of Pharmacy, Baltimore, Maryland  
Clinical Specialist  
West Palm Beach VA Medical Center, West Palm Beach, Florida

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UC Davis Medical Center  
Clinical Professor of Pharmacy  
University of California, San Francisco, and Touro School of Pharmacy  
Clinical Professor of Medicine  
University of California, Davis  
Sacramento, California

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Associate Professor  
School of Pharmacy, University of Colorado Denver  
Clinical Specialist – Cardiology/Anticoagulation  
University of Colorado Hospital  
Aurora, Colorado
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The faculty and planners report the following relationships:

**Stuart T. Haines, Pharm.D., FCCP, FASHP, FAPhA, Chair and Moderator**

Dr. Haines declares that he has been a stockholder (< $10,000) in Merck and that his spouse has served as a consultant for Procter & Gamble.

**William E. Dager, Pharm.D., BCPS, FCSHP, FCCP, FCCM**

Dr. Dager declares that he has no relationships pertinent to this activity.

**Toby C. Trujillo, Pharm.D., BCPS**

Dr. Trujillo declares that he has served as a consultant for Ortho-McNeil.

**Kristi N. Hofer, Pharm.D.**

Dr. Hofer declares that she has no relationships pertinent to this activity.
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**ACTIVITY OVERVIEW**

Anticoagulant therapy plays a critical role in managing patients at risk for venous thromboembolism (VTE), which is a substantial cause of morbidity and mortality in surgical patients in the United States despite the availability of evidence-based guidelines for thromboprophylaxis. The shortcomings of currently available anticoagulants and potential for patient harm have led to quality improvement initiatives to improve the use of these agents and research to develop agents with improved efficacy and safety profiles.

In this educational activity, the current state of VTE prophylaxis will be discussed, including the incidence, risk factors, clinical consequences, and impact on use of health care resources. Evidence-based guidelines regarding the primary prevention of VTE in high-risk patient populations will be reviewed. Changes in health-system pharmacy practice intended to improve the safety and effectiveness of anticoagulants and reduce the risk of VTE in surgical patients (e.g., the Surgical Care Improvement Project [SCIP], The Joint Commission National Patient Safety Goal 03.05.01 for reducing patient harm from anticoagulants) also will be addressed. Emerging anticoagulant agents and technologies for VTE prophylaxis will be described. Translating the findings from clinical trials into clinical practice and pearls for preventing VTE in complex clinical scenarios will be explored. The audience will be invited to participate in a panel discussion about formulary management considerations, quality improvement initiatives, and controversies related to anticoagulant use in health systems.

**ACTIVITY OBJECTIVES**

After participating in this knowledge-based educational activity, participants should be able to

- Describe the scope of the problem of venous thromboembolism (VTE), including incidence, risk factors, clinical consequences, and impact on use of health care resources.
- Outline current evidence-based guidelines for primary prevention of VTE.
- Identify a quality improvement initiative for improving the use of anticoagulants in patients at risk for VTE.
- Compare and contrast the efficacy and safety of emerging anticoagulant agents and technologies for VTE prophylaxis.
- Identify unique patient characteristics that necessitate adjusting the traditional approach to VTE prophylaxis.
- Describe a management dilemma pertaining to the use of anticoagulants for VTE prophylaxis faced by health-system pharmacists and a potential solution to the dilemma.
- State the key issues that need to be considered when contemplating the addition of a new anticoagulant agent to the health-system formulary.
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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 program provides 2.0 hours (0.2 CEUs) of continuing pharmacy education credit (ACPE activity #204-000-09-437-L01P).

Attendees must complete a Continuing Pharmacy Education Request online and may immediately print their official statements of continuing pharmacy education credit at the ASHP Learning Center at http://ce.ashp.org following the activity.

Complete instructions for receiving your statement of continuing pharmacy education online are on the next page. Be sure to record the five-digit session code announced during the activity.

Your educational opportunities related to preventing venous thromboembolism extend beyond today’s symposium…

A live webinar on January 21, 2010, where the faculty will explore issues raised based on questions posed by participants in today’s symposium (1 hour of CPE).

Informational podcast interviews with the faculty focusing on their experience in the prevention of venous thromboembolism and considerations regarding new anticoagulant agents.

E-Newsletters featuring participants’ ideas for incorporating information from this symposium into their practice, as well as updates on emerging information related to anticoagulation and preventing venous thromboembolism.

Web-based activity (2 hours of CPE, but please note that individuals who claim CPE credit for the live symposium are ineligible to claim credit for the Web-based activity).

Go to www.ashpadvantage.com/vte for more information and to sign up to receive email updates about this educational series.
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4. Click on the **click here link** to view sessions associated with the day of the activity. This activity was held on Tuesday, December 8, 2009.

5. Enter the session code, which was announced during the activity, and select the number of hours equal to your participation in the activity. Pharmacists should only claim credit for the amount of time they participate in an activity.

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7. Confirm your participation and click **submit**. Your transcript page will appear.

8. Click on **view/print statement of credit** next to the meeting name to print your CPE statement.

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<th>Date of Activity</th>
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Stuart T. Haines, Pharm.D., FCCP, FASHP, FAPhA, is Professor in the Department of Pharmacy Practice and Science at the University of Maryland School of Pharmacy in Baltimore, Maryland. Dr. Haines also serves as Clinical Pharmacy Specialist in the Diabetes Management Clinic at the West Palm Beach VA Medical Center in West Palm Beach, Florida. He is a Past-President of the American College of Clinical Pharmacy (ACCP), having served on the ACCP Board of Regents from 2002-2008. He is currently a member of the American Society of Health-System Pharmacists (ASHP) Commission on Credentialing (COC) – the body that sets standards and accredits pharmacy residency and technician training programs in the United States. He has served on numerous editorial boards including Pharmacotherapy, The Annals of Pharmacotherapy, Current Medical Research and Opinion, American Journal of Health-System Pharmacy (AJHP), the Journal of the American Pharmacists Association (JAPhA), as well as the Pharmacist’s Letter.

Dr. Haines earned his Bachelor of Science in pharmacy from the Massachusetts College of Pharmacy and Allied Health Sciences and his Doctor of Pharmacy degree from the University of Texas at Austin. He completed a pharmacy practice residency at the Brigham and Women's Hospital in Boston, as well as an ambulatory care residency at the University of Texas Health Science Center in San Antonio. He is a board-certified pharmacotherapy specialist (BCPS), and he is also board-certified in advanced diabetes management (BC-ADM). Dr. Haines is a fellow in the American College of Clinical Pharmacy (FCCP), the American Society of Health-System Pharmacists (FASHP), and the American Pharmacists Association (FAPhA). In 2006, Dr. Haines was elected a Distinguished Practitioner in the National Academies of Practice.

Dr. Haines’ scholarly interests include medication use behavior, diabetes management, women's health, cardiovascular disease prevention, and the evaluation of instructional methods.
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VTE Prophylaxis
Best Practices in 2009

Stuart T. Haines, Pharm.D., BCPS
Professor and Pharmacotherapy Specialist
University of Maryland School of Pharmacy
West Palm Beach VA Medical Center

Virchow’s Triad

Hereditary deficiencies, genetic mutations, acquired diseases, malignancy
Circulatory Stasis
Endothelial injury
Hypercoagulable State


Which of the following patients is at highest risk of developing deep vein thrombosis (DVT) in the next 30 days?

A. 28-year-old woman taking estrogen-containing oral contraceptive pills
B. 47-year-old man who is a participant on the "Biggest Loser" television program
C. 61-year-old woman hospitalized for heart failure exacerbation
D. 83-year-old man who has hip fracture repair surgery after being hit by a bus
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Who's at Risk VTE?

- Major surgery (esp. hip, knee, abdomen)
- Major trauma
- Malignancy (esp. metastatic)
- Major medical illness (CHF, MI, Sepsis)
- Prolonged immobility (> 4 days)
- Previous DVT / PE
- Increasing age (> 40 yrs)


Who’s at Risk VTE?

- Major surgery (esp. hip, knee, abdomen)
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Who’s at Risk for VTE?

- Thrombophilia/hypercoagulable states
  - Antithrombin III deficiency
  - Protein C or S deficiency
  - Activated protein C resistance/Factor V Leiden
  - Prothrombin (20210) gene mutation
  - Antiphospholipid antibodies
- Estrogen/raloxifene/tamoxifen use
- Pregnancy/post-partum
- Obesity

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From Theory to Performance Mandates
The Quality of Care Continuum

**MANDATORY**

6. Pay for Performance

**THEORY**

5. Practice and Outcomes Reporting

**PRACTICE**

4. Hospital/Physician Quality Measures

**VOLUNTARY**

3. Consensus Standards

2. Evidence-based Guidelines

1. Clinical Studies

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Clinical Practice Guidelines

- AHRQ Preventing Hospital Acquired VTE – A Guide to Effective Quality Improvement (August 2008)

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Clinical practice guidelines are useful BUT they:

A. aren't based solely on the evidence.
B. may not apply to your patient or population.
C. usually are out-of-date by the time they are published.
D. are full of opinions, may not apply, and are usually out-of-date.
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AHRO Top Ten Safety Practices According to Strength of Evidence

1. Appropriate VTE prophylaxis in patients at risk
2. Perioperative beta-blockade
3. Maximum sterile barriers for CVC insertion
4. Perioperative antibiotics to reduce post-surgical infections
5. Patients restating/recalling what they have been told during informed consent
6. Continuous aspiration of subglottic secretions to prevent ventilator-associated pneumonia
7. Pressure-relieving bedding to prevent pressure ulcers
8. Real-time ultrasonography to insert central venous catheters
9. Self-management of warfarin
10. Nutritional support in post-op and critically-ill patients

Quality Drivers for the Prevention of Venous Thromboembolism

- The Joint Commission - Prevention and Care of Venous Thromboembolism
- Surgical Care Improvement Project (SCIP)
- The Joint Commission - National Patient Safety Goals (NPSGs)

Joint Commission/National Quality Forum National Hospital Quality Measures

<table>
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<tr>
<th>VTE Core Performance Measures (October 1, 2009)</th>
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<tr>
<td>Risk Assessment and Prophylaxis</td>
</tr>
<tr>
<td>1. Documentation of VTE prophylaxis given or why no prophylaxis was given within 24 hours of hospital admission</td>
</tr>
<tr>
<td>2. Documentation of VTE prophylaxis given or why no prophylaxis was given within 24 hours of admission or transfer to ICU</td>
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<tr>
<td>VTE Outcomes</td>
</tr>
<tr>
<td>6. Incidence of potentially preventable hospital-acquired VTE</td>
</tr>
<tr>
<td>Stroke Core Performance Measures (October 1, 2009)</td>
</tr>
<tr>
<td>Prophylaxis</td>
</tr>
<tr>
<td>1. Documentation of VTE prophylaxis within 24 hours of hospital admission</td>
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- GOAL: reduce surgical complications by 25% by 2010
- Coalition of major public health groups/hospitals
  - Sponsored by CMS & CDC in collaboration with AMA, American College of Surgeons, American Hospital Association, VHA, Premier, and many others
- Participation in SCIP involves
  - Collecting and submitting data
  - Attending monthly conference calls to share best practices and implementation strategies
  - Making system changes based on quality improvement data

Surgical Care Improvement Project
VTE Prevention

PROCESS Measures

SCIP VTE-1
Ordered appropriate VTE prophylaxis anytime from hospital arrival to 24 hours after anesthesia end time.

SCIP VTE-2
Received appropriate VTE prophylaxis within 24 hours prior to anesthesia start time to 24 hours after anesthesia end time

Surgical Care Improvement Project
Proposed Measures for VTE

OUTCOME Measures (proposed)

SCIP VTE-3
Intra- or post-operative pulmonary embolism (PE) diagnosed during index hospitalization and within 30 days of surgery.

SCIP VTE-4
Intra- or post-operative DVT diagnosed during index hospitalization and within 30 days of surgery.
CMS “Never Events”

October 1, 2008: Medicare no longer pays for 8 selected secondary diagnoses (conditions that developed as a result of hospitalization)
- DVT or PE following knee or hip replacement

Joint Commission
National Patient Safety Goals

Requirement: ↓ Harm from Anticoagulant Therapy (NPSG.03.05.01)
Rationale:
• High risk of harm
• Management challenges
• Common cause of adverse drug events
• Poor standardization
Implementation:
✓ January 1, 2009: Full implementation

Which of the following NPSGs related to anticoagulants would have the greatest impact on patient outcomes:

A. Use unit dose and prefilled syringes only
B. Obtain a baseline INR before starting warfarin
C. Educate prescribers, staff, patients, and family
D. Measure and evaluate and anticoagulation practices
The Evolving Culture of Medicine

- 20th-century Characteristics
  - Autonomy
  - Solo practice
  - Continuous learning
  - Infallibility
  - Individual knowledge

- 21st-century Characteristics
  - Teamwork
  - Group practice
  - Continuous improvement
  - Interprofessional problem solving
  - Change


How Do We Close the Gap?
Essential Elements

- Institutional support and interprofessional teams
- Standardized order sets
- Algorithms/protocols/policies
  - Drug dosing (indications, preferred agents, duration)
  - Drug monitoring
  - Managing adverse events
  - Transitions in care and discharge planning
- Comprehensive educational program

Strategies to Improve Prophylaxis Rates

- Education
  - In-service programs, newsletters
- VTE risk assessment form
- Admission order set
- Informatics
  - Electronic alerts, computerized physician order entry (CPOE) prompts, links to guidelines
- Performance feedback

Conclusions

• Historically, implementing evidence-based care has been slow.

• Quality improvement organizations and government reimbursement policies now require prompt & extensive changes.

• Antithrombotic therapy is an opportunity for increased pharmacist involvement to improve quality.

• Multiple strategies will be required to achieve meaningful/measurable changes in quality.
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William E. Dager, Pharm.D., FCSHP, FCCP, FCCM, is a board-certified pharmacotherapy specialist who currently holds three academic positions. He is Clinical Professor of Pharmacy at the University of California, San Francisco (UCSF) School of Pharmacy and Clinical Professor of Medicine at the University of California, Davis (UC Davis) School of Medicine. He also serves as Clinical Professor at the Touro School of Pharmacy in Vallejo, California. As a clinical specialist at UC Davis Medical Center, he is responsible for managing challenging cases in anticoagulation, pharmacokinetics, and critical care. Dr. Dager also is clinically active with the cardiology service and serves as the director of the postgraduate year two (PGY2) residency in cardiology at UC Davis.

Dr. Dager earned his Doctor of Pharmacy degree at UCSF and completed a residency at the UC Davis Medical Center in Sacramento. In addition, he completed the University of Pittsburgh Nephrology Pharmaceutical Care Preceptorship. He is a fellow of the California Society of Hospital Pharmacists, American College of Clinical Pharmacy (ACCP), and Society of Critical Care Medicine (SCCM).

Dr. Dager's research interests focus on anticoagulation, critical care medicine, cardiovascular disease, and pharmacokinetics and pharmacodynamics. He has authored numerous articles, book chapters, and scientific reviews, and he has made numerous presentations at national and international educational conferences. He serves as a reviewer and editorial board member for several medical journals, and he currently is chair of the Editorial Advisory Board Panel on Anticoagulation for The Annals of Pharmacotherapy. Dr. Dager also is a site coordinator for the American Society of Health-System Pharmacists (ASHP) Research and Education Foundation Antithrombotic Pharmacotherapy Traineeship.

Dr. Dager has received multiple teaching and professional awards, including the 2008 ACCP Best Practice Award. He is a member of numerous professional organizations, including ACCP, ASHP, Sacramento Valley Society of Health-System Pharmacists, Anticoagulation Forum, International Society of Thrombosis and Haemostasis, and SCCM. He also currently serves as an instructor and regional affiliate faculty member in advanced cardiac life support for the American Heart Association.
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Questions, Dilemmas, and Conundrums—Managing Patients with Unique Needs

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Clinical Professor of Medicine
UC Davis School of Medicine

Why is Venous Thromboembolism (VTE) Prophylaxis Underused?
• Clinicians unaware of level of VTE risk
• Not a “single-specialty” disease
• Heterogeneous patient population
• Perceived difficulties in risk assessment
• Few studies of prophylaxis
  – Poorly-defined patient populations
  – Varied methods of deep vein thrombosis (DVT) diagnosis
  – Varied outcome definitions

American College of Chest Physicians (ACCP) 2008 VTE Prophylaxis Recommendations

Surgery
• General
  – Risk low, moderate, high
  – Multiple risk factors
  – Bleeding risk high
• Vascular
• Gynecologic
• Urologic
• Laparoscopic
• Bariatric
• Thoracic
• Coronary artery bypass

Orthopedic
• Total knee replacement (TKR) / total hip replacement (THR)
• Knee arthroscopy
• Hip fracture
• Spinal cord injury

Medical
• Acute illness
• Cancer
• Critical care
• Long-distance travel

Trauma
BURNS

Low-dose unfractionated heparin (UFH)
Low molecular weight heparin (LMWH)
Fondaparinux
Vitamin K antagonists (VKA)
Graduated compression stockings
Intermittent pneumatic devices

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Who should receive prophylaxis?
VTE risk score determines who gets prophylaxis
Not validated
- Advanced age
- History of VTE
- Malignancy
- Congestive heart failure
- Respiratory disease/chronic obstructive pulmonary disease
- Obesity (BMI >30 kg/m²)
- Immobility/length of stay > 2 days
- Surgery/trauma
- Stroke
- Acute medical illness
- Inflammatory bowel disease (Crohn’s disease/ulcerative colitis)
- Hypercoagulable states

BMI = body mass index

Who should receive prophylaxis?
Opt out: Everyone is invited except...
- Imminent invasive procedure
- Warfarin with INR >1.4 or on therapeutic anticoagulation
- Recent intraocular or intracranial surgery
- Thrombocytopenia
- Spinal tap or epidural anesthesia within 12 hr
- Other (specify in comments)
- Active bleeding
- Active or chronic severe liver disease
- Comfort care
- Healthy, fully ambulatory, <40 yr
- History of HIT/hypersensitivity to UFH, LMWH

HIT = heparin-induced thrombocytopenia
INR = international normalized ratio

How should prophylaxis be started?
- Was pre-op dose used?
- Was mechanical prophylaxis started?
- Busy PACU and patient to be transferred to floor
- Epidural catheter vs. peripheral nerve block
- Timing of dose post-op
  - Within 24 hours
- Combination therapy
  - Avoid UFH alone in orthopedics
- High bleeding risk
  - First 2-3 days
  - Knee > hip

PACU = post-anesthesia care unit
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Can you go the distance?

• Population dependent
  – Surgery prophylaxis (GI, orthopedic, trauma, etc.)
  – Medical patients
• ↑ Duration → ↓ VTE

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<th></th>
<th>THR</th>
<th>TKR</th>
<th>Hip Fx</th>
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<tbody>
<tr>
<td>DVT*</td>
<td>18-36%</td>
<td>5-22%</td>
<td>23-30%</td>
</tr>
</tbody>
</table>
| PE         | 0.9-28% | 1.5-10% | 3-11%

*Proximal DVT


Total knee replacement surgery

Total hip replacement surgery
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VTE is present but rarely accounted for

<table>
<thead>
<tr>
<th>Fondaparinux vs. Enoxaparin</th>
<th>Tx 9 days, Venography day 11</th>
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<tbody>
<tr>
<td><strong>Fondaparinux</strong></td>
<td><strong>Enoxaparin</strong></td>
</tr>
<tr>
<td>Fatal PE</td>
<td>0.1%</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>0.6%</td>
</tr>
<tr>
<td>Venography VTE</td>
<td>6.8%</td>
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</tbody>
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Warfarin Considerations

- INR target: ≤ 2 (AAOS) vs. 2 to 3 (ACCP)
  - ACCP: THR/TKR (grade 1A), hip fracture (grade 1B)
  - If the INR >1.8, are we treating existing sub-clinical thrombosis?
  - Pelvic fracture: ↑ Sensitivity in first week
- AAOS: duration 2-6 weeks
  - Start night before or night after THR or TKR surgery
- Rose AJ et al.
  - Is 1.7 to 3.3 an acceptable INR range?

American Academy of Orthopaedic Surgeons (AAOS) clinical guideline on pulmonary embolism in patients undergoing total hip or knee arthroplasty. URL in ref list.

Warfarin Considerations

- Initial dose
  - Withhold if epidural catheter present?
  - What if the plan is to remove the epidural in 8 hours?
- Wait 10-12 hours for first INR
- Monitoring pearls
  - Hemovac
  - Given and taken
  - Timing of education

American Academy of Orthopaedic Surgeons (AAOS) clinical guideline on pulmonary embolism in patients undergoing total hip or knee arthroplasty. URL in ref list.
**Aspirin for VTE Prophylaxis**

- **AAOS**
  - Patients at risk for PE (with high bleeding concerns)
  - 325 mg twice daily for 6 weeks
  - Start day of surgery
- **ACCP**: recommendation against (grade 1A)
- **PEP trial** – TKR/THR

American Academy of Orthopaedic Surgeons (AAOS) clinical guideline on pulmonary embolism in patients undergoing total hip or knee arthroplasty. URL in ref list.*

**LMWH for VTE Prophylaxis**

- **Starting dose and time**
  - AAOS/ACCP: start 12-24 hr post-op
  - Every 12 hr vs. every 24 hr (post-op and at discharge options)
  - Renal impairment
    - Enoxaparin: ½ dose for CrCl <30 mL/min: chronic kidney disease stages 4 and 5 (?)
      - 40 mg → 4-hr antifactor Xa 0.38 U/mL in hemodialysis
    - Dalteparin: no need to change dosing for CrCl >20 mL/min
- **Prolonged prophylaxis** – is 4-6 weeks part of the plan?
- **Insurance coverage**


**VTE Prophylaxis in Obesity**

Retrospective, multicenter, orthopedic surgery (n=817)

- Enoxaparin 40 mg/day subcutaneously, starting 12 hr before surgery
- Post-op day 7-10 bilateral venography VTE = 18.7%
- No relationship between weight or body surface area and thrombosis
- Strong relationship: BMI and thrombosis (*p*=0.0002)
  - BMI >32 kg/m² – 31.8% thrombosis
  - BMI <32 kg/m² – 16.7% thrombosis (*p*<0.001)
- No relationship between bleeding and BMI

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Should LMWH prophylactic doses be 20-25% higher? (Delay in meeting ambulation goals)

Scholten et al. n=481 bariatric surgery patients
- First 92 patients: Enoxaparin 30 mg subcut. q 12 hr
- Second 389 patients: Enoxaparin 40 mg subcut. q 12 hr

<table>
<thead>
<tr>
<th></th>
<th>30 mg q 12 hr</th>
<th>40 mg q 12 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>51.7</td>
<td>50.3</td>
</tr>
<tr>
<td>History of DVT (%)</td>
<td>3.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Procedure time (min)</td>
<td>213</td>
<td>175</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>5.67</td>
<td>3.31</td>
</tr>
<tr>
<td>DVT (%)</td>
<td>5.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Hemorrhage (no.)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>


Fondaparinux for VTE Prophylaxis
- 2.5 mg/day subcutaneously (hip fracture: grade 1A)
- Is this treatment as well?
  - Turpie et al. venography: decrease in “asymptomatic” VTE
  - Phase II PENTUA study (ACS): 2.5-12 mg/day no difference
  - Phase II Rembrandt (VTE treatment): 5-10 mg/day no difference
- Option in obesity?
- Bleeding concerns
  - Timing of dose: start 6-8 hr post-op


LMWH in the Critical Care Setting
- AT deficiency, fluid overload
- Enoxaparin 40 mg subcut. (n= 89)

% patients in target antifactor Xa range
- 4 hr 57%
- 12 hr 39%
- 24 hr 13%

<table>
<thead>
<tr>
<th></th>
<th>ICU</th>
<th>Ward</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{p}$ (L)</td>
<td>10.6</td>
<td>4.17</td>
</tr>
<tr>
<td>$Cl$ (L/hr)</td>
<td>0.64</td>
<td>1.01</td>
</tr>
<tr>
<td>No correlation with renal function</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Changing Face of Anticoagulant Therapy:
Improving the Management of Patients at Risk for Venous Thromboembolism

VTE Prophylaxis and HIT
• HIT is rare, but of some concern if patient receives > 6 days of heparin or is re-exposed within 3-4 months
• Risk for HIT from VTE prophylaxis
  – Orthopedic surgery and UFH?
  – UFH vs. LMWH vs. fondaparinux
    • Dose/duration as risk factors
  – Delayed onset (→ acute onset HIT)
• History of HIT (>100 days, antibody negative)
• Lepirudin: subcutaneous ($$)
• Rivaroxaban

Where is HIT found?
(a peek at my place)
A consecutive series of 180 patients with a suspicion of HIT high enough to initiate a direct thrombin inhibitor

Surveillance Ultrasound (US)
• How will subclinical thrombosis impact outcomes?
• Schmidt et al. THR/TKR: Pre-hospital DC US vs. sham US
  – US + DVT = 2.5% → therapeutic anticoagulation
  – No reduction in symptomatic VTE between cohorts
• ACCP 2008: recommendation against routine screening US (grade 1A)
• How will positive asymptomatic ultrasounds impact bench markers?

The Changing Face of Anticoagulant Therapy: Improving the Management of Patients at Risk for Venous Thromboembolism
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The Changing Face of Anticoagulant Therapy: Improving the Management of Patients at Risk for Venous Thromboembolism

Toby C. Trujillo, Pharm.D., BCPS
Associate Professor
University of Colorado Denver School of Pharmacy
Clinical Specialist – Cardiology/Anticoagulation
Director of Inpatient Anticoagulation – Thrombosis Management Service
University of Colorado Hospital
Aurora, Colorado

Toby C. Trujillo, Pharm.D., BCPS, is Associate Professor of Clinical Pharmacy at the University of Colorado Denver School of Pharmacy in Aurora, Colorado. He also serves as a Clinical Specialist in cardiovascular pharmacotherapy and anticoagulation at the 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. Dr. Trujillo completed a fellowship in cardiovascular pharmacotherapy at The University of Arizona, and he is a board certified pharmacotherapy specialist with added qualifications in cardiology.

Dr. Trujillo's current responsibilities at the University of Colorado Hospital include providing clinical pharmacy services to cardiology, as well as directing the inpatient anticoagulation – thrombosis management service. He also serves as co-chair of the anticoagulation subcommittee of the pharmacy and therapeutics committee. Dr. Trujillo currently serves as a preceptor to both pharmacy students and residents. He provides lectures at the School of Pharmacy on ischemic heart disease, antithrombotic therapy, and other cardiology and critical care topics.

Dr. Trujillo was recently appointed to the Clinical Pharmacology Committee, which resides under the Council on Clinical Cardiology within the American Heart Association. Dr. Trujillo has also served on a number of committees within the American College of Clinical Pharmacy, served as a speaker on numerous occasions on a national level, and authored several papers/book chapters in the area of cardiovascular pharmacotherapy. In addition to being a member of ASHP, Dr. Trujillo helped develop current standards for PGY2 cardiology residency training programs.
The Changing Face of Anticoagulant Therapy: Improving the Management of Patients at Risk for Venous Thromboembolism

New Agents and Technologies for VTE Prophylaxis

Toby C. Trujillo, Pharm.D., BCPS (AQ Cardiology)
Associate Professor
University of Colorado Denver – School of Pharmacy
Clinical Specialist – Cardiology/Anticoagulation
Director: Inpatient Anticoagulation – Thrombosis Management Service
University of Colorado Hospital

Advances in Non-Pharmacologic VTE Prophylaxis

- Epidural vs. general anesthesia
- New technologies

ANTICOAGULANT EVOLUTION

<table>
<thead>
<tr>
<th>Class</th>
<th>1930s</th>
<th>1940s</th>
<th>1980s</th>
<th>1990s</th>
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<tbody>
<tr>
<td>Target</td>
<td>Parenteral</td>
<td>Parenteral</td>
<td>Indirect</td>
<td>Direct</td>
</tr>
<tr>
<td>Route</td>
<td>Parenteral administration</td>
<td>Parenteral administration</td>
<td>Parenteral</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Parenteral</td>
<td>Parenteral</td>
<td>Parenteral</td>
<td>Parenteral</td>
</tr>
<tr>
<td></td>
<td>Parenteral</td>
<td>Parenteral</td>
<td>Parenteral</td>
<td>Parenteral</td>
</tr>
</tbody>
</table>

VKA = vitamin K antagonist; LMWH = low-molecular-weight heparin; ATIII = antithrombin III; FXa; FIIa; others

The Changing Face of Anticoagulant Therapy: Improving the Management of Patients at Risk for Venous Thromboembolism

Current Anticoagulant Options

<table>
<thead>
<tr>
<th>Intrinsic system (surface contact)</th>
<th>Extrinsic system (tissue damage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XIa</td>
<td>TF/VIIa</td>
</tr>
<tr>
<td>Thrombin activity (Prothrombin)</td>
<td>(Thrombin)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Fibrin Clot</td>
</tr>
</tbody>
</table>

Initiation

Amplification/propagation

- Vitamin K antagonists
- Direct thrombin inhibitors
- Indirect Factor Xa inhibitors

Thrombin activity


Limitations of Current Anticoagulant Options

- LMWH
  - Injections
  - Risk of thrombocytopenia
  - Enoxaparin: dosing adjustment in renal impairment
  - Dalteparin: no dosing data in renal impairment
  - Fondaparinux
    - Injections
    - Contraindicated if CrCl <30 mL/min
- Warfarin
  - Dietary considerations
  - Need for INR monitoring
  - Potential drug interactions
  - Non-adherence
  - Direct thrombin inhibitors
    - Injections
    - Expense
    - Organ function
    - Dosing

Targets For New Anticoagulants

<table>
<thead>
<tr>
<th>ORAL</th>
<th>PARENTERAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>rivaroxaban</td>
<td>dabigatran</td>
</tr>
<tr>
<td>apixaban</td>
<td>odiparcil</td>
</tr>
<tr>
<td>LYS17717</td>
<td>pegmusirudin</td>
</tr>
<tr>
<td>YM100</td>
<td>flovagatran</td>
</tr>
<tr>
<td>DU-176b</td>
<td>pegmusirudin</td>
</tr>
<tr>
<td>PRT-054021</td>
<td>Fibrinogen</td>
</tr>
</tbody>
</table>

Comparison of Investigational Oral Agents

<table>
<thead>
<tr>
<th></th>
<th>DABIGATRAN</th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Boehringer-Ingelheim</td>
<td>Bayer via Ortho McNeil</td>
<td>Pfizer with BMS</td>
</tr>
<tr>
<td>Brand Name</td>
<td>Pradaxa (Europe)</td>
<td>Pradax (Canada)</td>
<td>Xarelto n/a</td>
</tr>
<tr>
<td>Approval Status</td>
<td>Approved in Europe/Canada 2008</td>
<td>Approved in Europe/Canada 2008 3/09: FDA advisory panel approval 5/09: additional information requested</td>
<td>Will not submit to FDA in 2009 as previously expected</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Direct IIa inhibitor</td>
<td>Direct Xa inhibitor</td>
<td>Direct Xa inhibitor</td>
</tr>
</tbody>
</table>

Pharmacokinetic Comparison

<table>
<thead>
<tr>
<th>Property</th>
<th>Anamostat</th>
<th>Apixaban</th>
<th>Dabigatran Exurate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Thrombin</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bioavailability, %</td>
<td>&gt;90</td>
<td>&gt;90</td>
<td>6</td>
</tr>
<tr>
<td>Time to peak drug level, h</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>9</td>
<td>9-14</td>
<td>14-17</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>Once-daily</td>
<td>Twice-daily</td>
<td>Once or twice-daily</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Patent CYP1A2 and P-glycoprotein inhibitors</td>
<td>Patent CYP1A2 and P-glycoprotein inhibitors</td>
<td>Patent pump inhibitors</td>
</tr>
<tr>
<td>Heroin resistance, %</td>
<td>66</td>
<td>75</td>
<td>80</td>
</tr>
<tr>
<td>Safe in pregnancy</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Subjects</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>


Dabigatran Clinical Program

- **RE-MODEL** – VTE prevention in total knee replacement (TKR)
- **RE-NOVATE** – VTE prevention in total hip replacement (THR)
- **RE-MOBILIZE** – VTE prevention in TKR
- **RE-SOLVE** – VTE treatment
- **RE-COVER** – VTE treatment
- **RE-MEDY** – VTE treatment
- **RE-PLY** – Thrombosis prevention in atrial fibrillation
- **RE-DEEM** – Treatment of ACS with antiplatelet therapy
The Changing Face of Anticoagulant Therapy: Improving the Management of Patients at Risk for Venous Thromboembolism

### Dabigatran vs. Enoxaparin in Orthopedic Surgery

<table>
<thead>
<tr>
<th></th>
<th>RE-MOBILIZE(^1) (n=1896)</th>
<th>RE-MODEL(^2) (n=2076)</th>
<th>RE-NOVATE(^3) (n=3494)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient population</strong></td>
<td>TKR</td>
<td>TKR</td>
<td>THR</td>
</tr>
<tr>
<td><strong>Dabigatran dosage</strong></td>
<td>150 or 220 mg once daily</td>
<td>150 or 220 mg once daily</td>
<td>150 or 220 mg once daily</td>
</tr>
<tr>
<td><strong>Time of 1st dabigatran dose</strong></td>
<td>6-12 hr post-op</td>
<td>1-4 hr post-op</td>
<td>1-4 hr post-op</td>
</tr>
<tr>
<td><strong>Enoxaparin dosage</strong></td>
<td>30 mg twice daily(^*)</td>
<td>40 mg once daily(^1)</td>
<td>40 mg once daily(^2)</td>
</tr>
<tr>
<td><strong>Treatment duration</strong></td>
<td>12-15 days</td>
<td>6-10 days</td>
<td>28-35 days</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Total VTE, all-cause mortality</td>
<td>Total VTE, all-cause mortality</td>
<td>Total VTE, all-cause mortality</td>
</tr>
<tr>
<td><strong>Non-inferiority margin</strong></td>
<td>9.2%</td>
<td>9.2%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

\(^3\) Eriksson BI et al. Lancet. 2007; 370:949-56.

---

**RE-NOVATE:** *Dabigatran Etexilate vs. LMWH in THR*

*Dabigatran is non-inferior to enoxaparin*

![Graph showing non-inferiority margin for RE-NOVATE](image)

Dabigatran started with \(\frac{1}{2}\) dose 1-4 hr after surgery vs. Enoxaparin started 12-24 hr after surgery.  
Venogram at day 28-35.  

---

**RE-MOBILIZE:** *Dabigatran Etexilate vs. LMWH in TKR*

*Dabigatran is INFERIOR to enoxaparin*

![Graph showing inferiority margin for RE-MOBILIZE](image)

Dabigatran started with \(\frac{1}{2}\) dose 6-12 hr after surgery vs. Enoxaparin started 12-24 hr after surgery.  
Venogram on day 13-15.  
The Changing Face of Anticoagulant Therapy:
Improving the Management of Patients at Risk for Venous Thromboembolism

### Bleeding - Dabigatran

<table>
<thead>
<tr>
<th></th>
<th>RE-MOBILIZE</th>
<th>RE-MODEL</th>
<th>RE-NOVATE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabig 150 mg</td>
<td>0.6%</td>
<td>1.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Dabig 220 mg</td>
<td>0.6%</td>
<td>1.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1.4%</td>
<td>1.3%</td>
<td>1.6%</td>
</tr>
<tr>
<td><strong>Clinically Relevant Non-Major Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabig 150 mg</td>
<td>2.5%</td>
<td>6.8%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Dabig 220 mg</td>
<td>2.7%</td>
<td>5.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>2.4%</td>
<td>5.3%</td>
<td>3.5%</td>
</tr>
<tr>
<td><strong>Minor Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabig 150 mg</td>
<td>NR</td>
<td>8.4%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Dabig 220 mg</td>
<td>NR</td>
<td>8.8%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>NR</td>
<td>9.9%</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

*No differences vs. enoxaparin for any category of bleeding*

### Apixaban Clinical Program

- AMPLIFY – DVT/PE treatment
- AMPLIFY-EXT – Extended prevention of VTE after initial therapy
- ADVANCE 1, 2, and 3 – VTE prophylaxis in orthopedic surgery
- ADOPT – VTE prophylaxis in medically-ill patients
- ARISTOTLE – Stroke prophylaxis in atrial fibrillation
- AVERROES – Stroke prophylaxis in patients with atrial fibrillation and contraindications or intolerance to warfarin therapy
- APPRAISE 1 and 2 – Treatment of ACS with antplatelet therapy

### ADVANCE 1: Apixaban vs. Enoxaparin in TKA

“Apixaban is NOT non-inferior to enoxaparin”

Apixaban 2.5 mg twice daily starting 12-24 hr post-op vs. Enoxaparin 30 mg twice daily starting 12-24 hr post-op
Venogram at 10-14 days

The Changing Face of Anticoagulant Therapy: Improving the Management of Patients at Risk for Venous Thromboembolism

### Bleeding - Apixaban

**ADVANCE 1**

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Enoxaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>0.7%</td>
<td>1.4%</td>
</tr>
<tr>
<td><strong>Major or Clinically Relevant Bleeding</strong></td>
<td>2.9%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

Lower rate of bleeding for apixaban vs. enoxaparin


### Rivaroxaban Clinical Program

- **RECORD 1, 2, 3, & 4** – VTE prevention in orthopedic surgery
- **MAGELLAN** – VTE prevention in medically ill patients
- **EINSTEIN DVT** – Treatment of DVT
- **EINSTEIN DVT Extended** – Extended treatment duration of DVT
- **EINSTEIN PE** – Treatment of PE
- **ROCKET-AF** – Thrombosis prevention in atrial fibrillation
- **ATLAS ACS-2 TIMI-51** – Treatment of ACS with antiplatelet therapy

### Rivaroxaban in Orthopedic Surgery

<table>
<thead>
<tr>
<th></th>
<th>Hip Trials</th>
<th>Knee Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban dosing</td>
<td>10 mg qd</td>
<td>10 mg qd</td>
</tr>
<tr>
<td>Comparator dosing</td>
<td>Enoxaparin 40 mg</td>
<td>Enoxaparin 40 mg</td>
</tr>
<tr>
<td>Enoxaparin 35 days</td>
<td>Riva: 35 days</td>
<td>Riva: 35 days</td>
</tr>
<tr>
<td>Enoxaparin 14 days</td>
<td>Enoxaparin 30 mg bid</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>40 ± 4 days</td>
<td>36 ± 4 days</td>
</tr>
<tr>
<td>Target or ongoing enrollment</td>
<td>4541</td>
<td>2509</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Total VTE or death</td>
<td>Total VTE or death</td>
</tr>
</tbody>
</table>

The Changing Face of Anticoagulant Therapy:
Improving the Management of Patients at Risk for Venous Thromboembolism

**RECORD 1: Rivaroxaban vs. Enoxaparin in THR**
“Rivaroxaban is superior to enoxaparin”

- Rivaroxaban 10 mg once daily x 35 ± 4 days, starting 6-8 hr after surgery
- Enoxaparin 40 mg once daily x 35 ± 4 days, starting 12 hr before surgery


**RECORD 4: Rivaroxaban vs. Enoxaparin in TKR**
“Rivaroxaban is superior to enoxaparin”

- Rivaroxaban 10 mg once daily starting 6-8 hr after surgery vs.
- Enoxaparin 30 mg twice daily starting 12-24 hr after surgery

Venogram at 10-14 days


### Bleeding - Rivaroxaban

<table>
<thead>
<tr>
<th></th>
<th>RECORD 1</th>
<th>RECORD 2</th>
<th>RECORD 3</th>
<th>RECORD 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>0.3%</td>
<td>0.1%</td>
<td>0.6%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Clinically Relevant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Major Bleeding</td>
<td>2.9%</td>
<td>3.3%</td>
<td>2.7%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>2.4%</td>
<td>2.7%</td>
<td>2.3%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Non-Major Bleeding</td>
<td>5.8%</td>
<td>6.5%</td>
<td>4.3%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>5.8%</td>
<td>5.5%</td>
<td>4.4%</td>
<td>9.2%</td>
</tr>
</tbody>
</table>

No differences vs. enoxaparin for any category of bleeding

The Changing Face of Anticoagulant Therapy: Improving the Management of Patients at Risk for Venous Thromboembolism

New Antithrombotic Agents

Ideal Characteristics

• Broad therapeutic window
  • Low inter- and intra-patient variability
  • Stable and predictable dose-response relationship
  • No need for routine laboratory monitoring

• Rapid onset of action

• Oral route of administration
  • No need for parenteral-to-oral switch or available as parenteral and oral dosage forms
    • Use as single agent for acute and chronic indications and in both hospital and home settings

• No drug or dietary interactions

• Safe, with few or no adverse drug reactions (off target toxicities)

• Easily reversible with or without an antidote

• Reasonable cost?

Conclusions
The Changing Face of Anticoagulant Therapy: Improving the Management of Patients at Risk for Venous Thromboembolism

Panel Discussion – Audience Participation

Management and Clinical Challenges in Improving the Use of Anticoagulant Therapy for VTE Prevention in Health Systems

Clinical Challenge
Mr. Vegas (48 years old) is admitted for bariatric surgery. He weighs 430 lb (195 kg). He has a history of DVT (2006) treated with warfarin for 3 months. Which of the following is the best option for VTE prevention?

A. UFH 7500 units subcutaneously q 8 hr
B. Enoxaparin 40 mg subcutaneously q 12 hr
C. Fondaparinux 5 mg subcutaneously q 24 hr
D. Warfarin (previous dose) orally once daily to achieve INR 2-3

Discussion Notes:

Clinical Challenge
Mrs. Carson (63 years old) is admitted for abdominal surgery for colon cancer. She weighs 156 lb (70 kg). An epidural was placed for pain control, but the surgeon would like to remove it today (post-op day 1). When is an appropriate time to remove the catheter in relation to dalteparin given 5000 units daily?

A. ≤ 30 minutes after the most recent dose
B. At least 4 hr after the previous dose AND 12 hr before the next dose
C. At least 12 hr after the previous dose AND 6 hr before the next dose
D. At least 48 hr after the last dose

Discussion Notes:
The Changing Face of Anticoagulant Therapy:
Improving the Management of Patients at Risk for Venous Thromboembolism

Clinical Challenge
Mr. Genoa (58 years old) is admitted for CHF exacerbation. During a previous admission (1 month ago) he was given UFH 5000 units q 8 hr for VTE prophylaxis. His platelet count dropped from 260,000/μL to 130,000/μL at the time of discharge. No diagnostic tests for heparin-induced thrombocytopenia (HIT) were performed. What’s the best choice for VTE prophylaxis now?

A. UFH 5000 units subcutaneously q 8 hr
B. Enoxaparin 40 mg subcutaneously q 24 hr
C. Fondaparinux 2.5 mg subcutaneously q 24 hr
D. Warfarin orally once daily (INR 2-3)

Discussion Notes:

Clinical Challenge (Redux)
Mr. Genoa (58 yrs old) is admitted for CHF exacerbation. During a previous admission (1 month ago), he was given UFH 5000 units q 8 hr for VTE prophylaxis. His platelet count dropped from 260,000/μL to 130,000/μL at the time of discharge. No diagnostic tests for HIT were performed. What is the best choice for VTE prophylaxis now?

A. Apixaban 2.5 mg orally BID
B. Rivaroxaban 10 mg orally once daily
C. Dabigatran 150 mg orally BID
D. Fondaparinux 2.5 mg subcutaneously q 24 hr

Discussion Notes:
Management Challenge
Dr. Bonanza (orthopedic surgeon) prefers to use warfarin following hip and knee replacement surgery. Mrs. Jones had knee replacement surgery this morning. Epidural anesthesia was used, and the catheter will be removed tomorrow. Which of the following would be the best approach to VTE prophylaxis in this case?

A. UFH 5000 units subcutaneously q 12 hr, then warfarin after catheter removal
B. UFH 5000 units subcutaneously q 8 hr, then warfarin after catheter removal
C. Warfarin now
D. Rivaroxaban now, then warfarin after catheter removal

Discussion Notes:

Clinical Challenge
Mrs. Minden (73 years old) had hip replacement surgery 4 days ago. Fondaparinux 2.5 mg subcutaneously once daily was started 8 hr after surgery for VTE prophylaxis. She is being discharged to a rehabilitation facility today. For how long should fondaparinux be continued?

A. It should be stopped today
B. 10 more days
C. 21 more days
D. The patient should be transitioned to warfarin, and fondaparinux should be stopped when the INR >1.5

Discussion Notes:
Management Challenge
Virginia City Hospital is evaluating several new anticoagulant drugs (apixaban, dabigatran, idraparinux, and rivaroxaban) for potential addition to the formulary. Which of the following is most important for the P&T committee to consider during its deliberations?

A. Cost of each new agent  
B. Ease of use of new agents compared with older agents  
C. Effectiveness of new agents compared with older agents  
D. Safety of new agents compared with older agents

Discussion Notes:

Management Challenge
Dr. Henderson (cardiologist) has requested that dabigatran be added to the formulary for stroke prevention. Dr. Reno (orthopedic surgeon) has requested that apixaban be added to the formulary for DVT prevention. Which of the following is the best recommendation to the P&T committee?

A. Add dabigatran for both indications  
B. Add apixaban for both indications  
C. Add both agents for their respective indications  
D. Restrict use of both agents to cases of therapeutic failure of less expensive agents

Discussion Notes:
The Changing Face of Anticoagulant Therapy: Improving the Management of Patients at Risk for Venous Thromboembolism

Management Challenge
Dr. Mesquite (Chief of Orthopedic Surgery) has resisted using LMWH products and fondaparinux following hip and knee replacement surgery because “they’re just too risky,” preferring warfarin instead. Compared with warfarin, which of the following features of rivaroxaban would likely be the most appealing to Dr. Mesquite?

A. Fewer drug-drug interactions  
B. More rapid onset of anticoagulant effect  
C. Ease of administration - patient adherence  
D. Reduced need for laboratory monitoring

Discussion Notes:

Conclusions
- The results of clinical trials and clinical practice guideline recommendations won’t always apply to your patients or practice.

- New anticoagulant agents have some potential advantages over traditional agents, but we still have much to learn about their efficacy, safety, cost, and ease of use in various patient populations.
The Changing Face of Anticoagulant Therapy:
Improving the Management of Patients at Risk for Venous Thromboembolism

SELECTED REFERENCES


The Changing Face of Anticoagulant Therapy: Improving the Management of Patients at Risk for Venous Thromboembolism


SELF-ASSessment QUESTIONS

1. Venous thromboembolism (VTE) following knee or hip replacement surgery is a secondary diagnosis (condition that develops as a result of hospitalization) for which reimbursement is no longer provided by the Centers for Medicare & Medicaid Services.
   a. True.
   b. False.

2. A 2% reduction in surgical complications nationwide by 2010 is a goal of the Surgical Care Improvement Project.
   a. True.
   b. False.

3. The period after total hip or knee replacement surgery during which the risk for VTE is elevated lasts for:
   a. 5 days.
   b. 10 days.
   c. 15 days.
   d. 30 days.

4. The Joint Commission VTE core measure specifically states that each patient should have a VTE risk assessment performed at the time of admission to the hospital.
   a. True.
   b. False.

5. The incidence of asymptomatic VTE detected by venography after major orthopedic surgery is notably higher than the incidence of symptomatic VTE.
   a. True.
   b. False.

6. A target international normalized ratio of 2 to 3 during warfarin therapy for VTE prophylaxis after hip arthroplasty is recommended by:
   c. Both AAOS and ACCP.
   d. Neither AAOS nor ACCP.

7. Surveillance ultrasounds after major orthopedic surgery are not routinely recommended by ACCP because their use has not been shown to decrease the incidence of symptomatic VTE.
   a. True.
   b. False.
8. Which of the following correlates most strongly with the incidence of VTE in orthopedic surgery patients receiving enoxaparin as prophylaxis?
   a. Body mass index >32 kg/m$^2$.
   b. Body weight >90 kg.
   c. Body surface area >1.9 m$^2$.
   d. Waist circumference >40 inches.

9. Which of the following is an oral direct thrombin inhibitor?
   a. Apixaban.
   b. Dabigatran.
   c. Idraparinux.
   d. Rivaroxaban.

10. Which of the following statements about the pharmacokinetics of new anticoagulant agents is correct?
    a. Apixaban has a long half-life of 24 hours.
    b. Rivaroxaban has a short half-life of 2-3 hours.
    c. 80% of the parent compound for dabigatran is excreted renally.
    d. 15% of the parent compound for rivaroxaban is excreted renally.

11. Which of the following statements about the metabolism of and potential for interactions between other drugs and new anticoagulant agents is correct?
    a. Apixaban is extensively metabolized by and could interact with inhibitors of cytochrome P450 2D6 enzymes.
    b. Dabigatran is extensively metabolized by and could interact with inhibitors of cytochrome P450 2C9 enzymes.
    c. Dabigatran is extensively metabolized by and could interact with inhibitors of cytochrome P450 3A4 enzymes.
    d. Rivaroxaban is extensively metabolized by and could interact with inhibitors of cytochrome P450 3A4 enzymes.

12. Which of the following statements about the efficacy results of clinical trials comparing new anticoagulants with enoxaparin for VTE prophylaxis in orthopedic surgery patients is correct?
    a. Apixaban was superior to enoxaparin for preventing VTE in the ADVANCE 1 trial.
    b. Dabigatran was non-inferior to enoxaparin for preventing VTE in the RE-MOBILIZE trial.
    c. Enoxaparin was non-inferior to rivaroxaban for preventing VTE in the RECORD 1 trial.
    d. Rivaroxaban was superior to enoxaparin for preventing VTE in the RECORD 4 trial.
13. Which of the following statements about the rate of major or clinically relevant bleeding in clinical trials comparing new anticoagulants with enoxaparin for VTE prophylaxis in orthopedic surgery patients is correct?
   a. The rate was similar with apixaban and enoxaparin in the ADVANCE 1 trial.
   b. The rate was lower with dabigatran than enoxaparin in the RE-MOBILIZE trial.
   c. The rate was lower with enoxaparin than dabigatran in the RE-MODEL trial.
   d. The rate was similar with rivaroxaban and enoxaparin in the RECORD trials.

Answers
1. a
2. b
3. d
4. b
5. a
6. b
7. a
8. a
9. b
10. c
11. d
12. d
13. d