Anticoagulation Strategies for Venous Thromboembolism: Trends, Updates and the Role of Direct Oral Anticoagulants (DOACs)

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Agenda

- Become familiar with the direct oral anticoagulants (DOACs)
- Recent advances in venous thromboembolism (VTE)
  - Cancer and clotting
  - Outpatient treatment of VTE
  - Novel approaches to treating pulmonary embolism.

Pulmonary Embolism: Scope of the Problem

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

Estimated Cost of VTE Care $1.5 Billion/year

Conflicts of Interest

No disclosures
Incidence is increasing

![Graph showing increasing incidence over time.]


Why worry about Pulmonary Embolus?

- Fatal within 1 h after the onset of symptoms in 10% of cases
- Untreated PE mortality rate ~30%

Most Patients with PE do Well, but some do not

![Graph showing estimated prevalence and mortality.]

Abrahams van Doorn P and Hartmann IJC. Imaging Insights. 2011; 2: 705-715

Pathophysiology of Pulmonary Embolism

![Diagram illustrating pathophysiology of pulmonary embolism.]

Abrahams van Doorn P and Hartmann IJC. Imaging Insights. 2011; 2: 705-715
Eur Heart J. 2014 Nov 14;35(43):3033-69, 3069a-3069k

PE Mortality (ICOPER)

![Graph showing PE mortality rates.]


Virchow’s Triad 2015

**STASIS**
- Anaesthesia
- Hospitalization
- Immobilization
- CHF/MI
- CVA
- Shock
- Pregnancy
- Obesity

**VENOUS INJURY**
- Surgery
- Trauma
- Prior DVT
- Burns
- Fracture

**HYPERCOAGULABILITY**
- Inherited Coagulopathy
- Acquired Coagulopathy
- Pregnancy/Parturition
- Hormonal Therapy
- Malignancy

![Diagram illustrating Virchow’s Triad.]


Most Patients with PE do Well, but some do not

Abrahams van Doorn P and Hartmann IJC. Imaging Insights. 2011; 2: 705-715
Dake MD. Chest. 2002; 122: 1801-17

Historical Perspective

Time Line

Direct Oral Anticoagulants

- Xarelto: Rivaroxaban
- Pradaxa: Dabigatran
- Eliquis: Apixaban
- Savaysa: Edoxaban

Direct oral anticoagulants: Are they the new standard of care?

- What makes a new standard of care?
  - Effective
  - Safe
  - Simple and reliable
  - Adaptable and scalable
  - Patient satisfaction

Are they effective?

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Recurrent VTE or VTE-related death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>0.94 (0.86-1.03)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>0.99 (0.97-1.01)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>0.99 (0.97-1.01)</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>0.98 (0.96-1.00)</td>
</tr>
</tbody>
</table>

Bacchus et al. Arterioscler Thromb Vasc 2015;
Direct oral anticoagulants: Are they effective?

- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

Direct oral anticoagulants: Are they safe?

- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

Are they effective?

Direct Oral Anticoagulants

- Are they simple and reliable?
  - can be given in fixed doses
  - do not require routine monitoring
  - have fewer food or drug interactions
  - are more predictable than warfarin.

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

Direct Oral Anticoagulants Effective, safe, simple and reliable and patients are satisfied

All approved for the treatment of DVT and PE
None require monitoring
Direct Oral Anticoagulants

- Questions to ask before placing patient on direct oral anticoagulant
  - Candidate for these drugs
  - Comorbidities that preclude them
  - Compliance
  - Cost

Case: The Case of Helpful Grandfather

- 70 male developed PE while vacationing.
- LMWH as bridge to warfarin.
- His INRs difficult to control, range 1.5-5 despite dietary and medication compliance.

Case: The Case of Helpful Grandfather

What would you do now?
1. Keep on Warfarin
2. Change to Fondaparinux
3. Change to LMWH
4. Change to Dabigatran
5. Change to Rivaroxaban
6. Change to Apixaban
7. Change to Edoxaban

Dabigatran

- Stats
  - Oral direct thrombin inhibitor (DTI)
  - Rapid onset: 2 hours
  - T1/2 life: 12-17 hours
  - Clearance: renal
  - Dosing:
    - For VTE
      - 150 mg bid (creatinine clearance >30 mL/min)
  - Monitoring: no need because of predictable PK

Dabigatran

- Trials
  - RE-LY
    - Prevention of stroke/VTE in atrial fibrillation
  - RE-MODEL, RE-NOVATE, RE-MOBILIZE
    - Prevention of VTE after orthopedic procedures
  - RE-COVER, RE-MEDY and RE-SONATE
    - Treatment of VTE
- Approval
  - To prevent stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
  - To treat deep vein thrombosis and pulmonary embolism in patients who have been treated with a parenteral anticoagulant for 5-10 days.
  - To reduce the risk of recurrence of deep vein thrombosis and pulmonary embolism in patients who have been previously treated.

Dabigatran

- Limitations
  - For VTE treatment, first dose only given after initial parenteral anticoagulation therapy administered for median of 9 days (range 5-10).
  - FDA approval: only after parenteral anticoagulation and not as monotherapy.
Dabigatran: Concerns

- Unclear how to use in individuals with low body weight or those who are morbidly obese.
- Drug interactions: p-glycoprotein
  - Inhibit (increases drug effect):
    - ketoconazole, quinidine, amiodarone, verapamil
  - Induce (decreases drug effect):
    - rifampin, St. John’s wart

US FDA and the Europe are currently evaluating post-marketing reports.
- >250 serious bleeding events worldwide leading to death.
- Median age of bleeding events was 80 years.
- Questions safe dosing and monitoring in older patients with reduced renal function and other comorbidities.

Re-Align study:
- Mechanical heart valves: dabigatran vs warfarin
- Dabigatran was associated with increased rates of VTE and bleeding complications vs warfarin.

Case: The Case of Helpful Grandfather

Hemorrhage
- Stop drug.
  - Half life: 12-17 hours
  - If normal renal function, expect effects gone in 72-96 hours.
  - Obtain stat aPTT and PT-INR.
    - Normal suggests Dabigatran effect gone.
  - Treat supportively with RBC if need.

Antidote for Dabigatran: Idarucizumab (Praxbind)
- Monoclonal antibody against fragment on dabigatran

Case: "The Case of Pleuritic Chest Pain"

- 26 F - right sided pleuritic CP.
- ER: Ddimer elevated; CTA → bilateral PE. LMWH
- Discharged on Rivaroxaban.
Rivaroxaban

**Stats**
- Oral direct factor Xa inhibitor
- Rapid onset: 2.5-4 hours
- T1/2: 11-13 hours
- Excretion: renal.
- Dosing:
  - For post operative thromboprophylaxis in orthopedic surgery: 10 mg/day
  - For non valvular Aflb (to prevent strokes and systemic embolism): 20 mg/day
  - For VTE: 15 mg/bid x 3 weeks and then 20 mg/day.

**Trials**
- ROCKET
  - Prevention of stroke/VTE in atrial fibrillation
- RECORD 1-4
  - Prevention of VTE after orthopedic procedures
- EINSTEIN
  - Treatment of VTE
- MAGELLAN
  - Extended Duration

**Approval**
- VTE prevention after hip or knee arthroplasty
- VTE treatment and for stroke prevention in non valvular atrial fibrillation.
- VTE treatment and reduction in risk of recurrent VTE.

**Renal and hepatic issues:**
- Not recommended for creatinine clearance <30 mL/min.
- Contraindicated for significant hepatic impairment.
- Take with food.

**Drug Interactions**
- CYP-3A4 & P-glycoprotein

**Hemorrhage:**
- Drug discontinuation since short half-life.
- Over 90% protein bound - cannot be dialyzed
- Charcoal hemofiltration has been suggested.
- Life-threatening bleeding
- Antidote
  - bioengineered recombinant variant of factor Xa, currently in testing.

**Case: The Case of Chronic Thromboembolic Disease**

**Andexanet Alfa** for the Reversal of Factor Xa Inhibitor Activity

Siegel et al. NEJM; 373:2413-24.
Case: The Case of Importance of Follow Up.

- 48 M with idiopathic PE.
- CT: bilateral PE
- Treated with catheter directed therapy.
- Discharged on Apixaban.

Apixaban

- **Stats**
  - Oral direct factor Xa inhibitor
  - Rapid onset: 3-4 hours
  - T1/2 life: 8-15
  - Excretion: 25% renal and feces
  - 87% protein bound so no role for hemodialysis
  - Dosing:
    - For post operative thromboprophylaxis in orthopedic surgery:
      - 2.5 mg bid
    - For prevention of stroke in NVAF (Non Valvular Atrial Fibrillation):
      - 5 mg bid
    - Patients with 2 following factors: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, dose is 2.5 mg bid.
    - For treatment of VTE:
      - 10 mg bid for 7 days followed by 5 mg bid.
    - For reducing risk of recurrent VTE following initial therapy:
      - 2.5 mg bid

Apixaban Trials

- **Trials**
  - ARISTOTLE and AVERROES
  - ADVANCE 1, 2, and 3
  - AMPLIFY
  - Extended VTE treatment: ADOPT trial

Based on this case…

Do you need to screen all idiopathic clots for occult malignancy?

**Question #1**

Should all idiopathic venous thromboembolic events (VTE) be screened extensively for malignancy?

1. Yes
2. No

Screening for Occult Malignancy in VTE

- Multicenter, open-label, randomized, controlled trial in Canada.
- 845 patients randomly assigned to limited occult-cancer screening or limited occult-cancer screening PLUS abdominal pelvic CT.
- Primary outcome: confirmed cancer missed by screening and detected at 1-year follow-up period
- Results: 33 (3.9%) had new diagnosis of occult:
  - 14 of 431 patients (3.2%) in limited-screening group and 19 of 423 patients (4.5%) in limited-screening-PLUS-CT group (P=0.26).
  - 4 occult cancers (29%) were missed by limited screening strategy, whereas 5 (26%) were missed by strategy of limited screening PLUS CT (P=1.0).
Importance of the physical exam

Prevention of stroke/VTE in patients with idiopathic PE

For the treatment of deep vein thrombosis and pulmonary embolism (DVT and PE):

1. Oral direct factor Xa inhibitors (e.g., Edoxaban)
2. Oral direct thrombin inhibitors (e.g., Dabigatran)

Overview: Characteristics of the new agents

Edoxaban

- **Stats**
  - Oral direct factor Xa inhibitor
  - Rapid onset: 1-2 hours
  - T1/2 life: 10-14 hours
  - Excretion: renal.

- **Dosing**
  - For treatment of NVAF (Non Valvular Atrial Fibrillation):
    - 60 mg daily if CrCl > 95 mL/min.
    - 30 mg daily if CrCl 15 to 50 mL/min.
    - Do not use in patients with CrCl > 95 mL/min.
  - For treatment of DVT and PE: after initial parenteral agent
    - 60 mg once daily.
    - 30 mg daily if CrCl 15 to 50 mL/min or weight < 60 kg.

Potential Advantage

- **Trials**
  - ENGAGE AF
    - Prevention of stroke/VTE in atrial fibrillation
  - Hokusai VTE
    - Treatment of VTE

Approval

- To reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF).
- For the treatment of deep vein thrombosis and pulmonary embolism following 5 to 10 days of initial therapy with parenteral anticoagulant.

Available data do not support an extensive search for occult malignancy; however, it is important to perform complete Hx/PE/Labs and pursue symptoms or signs which suggest an underlying malignancy and to ensure that age-appropriate cancer screening tests have been performed.
Difference between new agents

• Bridging
  – Dabigatran and edoxaban require bridging
  – Rivaroxaban and apixaban do not require bridging

• Dosing
  – Rivaroxaban and apixaban start with higher dose initially
  – Rivaroxaban and edoxaban are once/day
  – Apixaban and dabigatran are twice/day

• Other issues
  – Take rivaroxaban with food

Other factors to consider with new agents

• Cancer
  – LMWH is still preferred agent

• Liver disease or coagulopathy
  – LMWH is the preferred agent

• Coronary artery disease
  – Avoid dabigatran

• Dyspepsia or history of GI bleed
  – VKA or apixaban

• Pregnancy
  – LMWH

• Poor compliance
  – Arguments for INR vs NOACs

Cautions with Direct Oral Anticoagulants

• Approved reversal agent only for dabigatran (under trials)
• No monitoring for effect
  – Adherence & Compliance
• Renal and hepatic failure
• Reimbursement issues
  – COST (warfarin $5/mo vs $250-350/mo)
• Post marketing bleeding rates
• Clinician familiarity
• Lack of guidelines
  – bleeding complications

Advantages with Direct Oral Anticoagulants

• Oral
• No need for monitoring
• No need for titration or dose adjustments
• Short onset
• Short half life
• Predictable absorption and metabolism
• Few drug-drug interactions
• Few dietary restrictions

Are the direct oral anticoagulants first line?

“In the absence of direct comparisons between NOACs ... no preference for one NOAC over another NOAC.”
Direct oral anticoagulants: Important questions

- How to switch from one agent to another
- Menstrual bleeding
- Peri-operative/procedure management: how long to hold medication
- How long to keep someone on anticoagulation

Direct oral anticoagulants: Menstrual bleeding

Management and outcomes of vaginal bleeding and heavy menstrual bleeding in women of reproductive age on direct oral anti-factor Xa inhibitor therapy: a case series

- Prospective study from Dresden Registry for DOACs.
- 72 vaginal bleeding events in 57 (31%) of 183 women of reproductive age, (59 cases of heavy menstrual bleed).
- Anatomical abnormalities associated with more intense bleeding and increased risk of recurrent bleeding.
- Recommend screening for anatomical abnormalities in this subgroup of patients.


Duration of Anticoagulation

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

Peri-procedural Guidelines

Other Important Topics

Can you use the direct oral anticoagulants in cancer patients?

Studies included 5-10% cancer patients. Ongoing clinical trials

Epidemiology: Cancer and Thrombosis

• Thrombosis is common complication of cancer.
• Estimated incidence is 15% (4-30%).

Cancer and Thrombosis

Association Between Cancer and Thrombosis

Epidemiology: Cancer and Thrombosis

Cancer patients vs non cancer patients:
• 2-3 times more likely to have recurrent VTE.
• 2-6 times more likely to have hemorrhagic complications from anticoagulant therapy.
• Decreased survival in cancer patients with VTE compared to patients without VTE
• Current recommended therapy: LMWH

VTE = venous thromboembolism
LMWH = low molecular weight heparin

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Cancer and VTE: CLOT Trial

Risk reduction = 52%
$P = 0.0017$

Prob($VTE\%)$ vs Days after randomization

OAC = oral anticoagulant

Cancer and VTE: CHARGE Trial

Hazard Ratio: 0.65 (90% CI, 0.41-1.03)

No difference: major bleed

Tinzaparin: less non major bleed

P< 0.07


Cancer and the new agents

• CHEST guidelines:
  – In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C) or edoxaban (Grade 2C).
  – Ongoing studies with DOACS in cancer

Other Important Topics

Do all patients with DVT or PE need to be admitted: Data behind outpatient treatment

• Clinically stable with good cardiopulmonary reserve.
• No contraindications such as recent bleeding, severe renal or liver disease, or severe thrombocytopenia (ie, <70,000/mm3).
• Expected to be compliant with treatment
• Patient feels well enough to be treated at home and has support.
• No presence of right ventricular dysfunction or increased cardiac biomarker levels.


Outpatient Treatment for VTE

*20. In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (eg, after the first 3 days of treatment) (Grade 2B).
Outpatient treatment of DVT/PE

Timely follow up is the most important component

Other Important Topics

Novel approaches to treatment of severe pulmonary embolism

Communication and Coordination of Services?

Multidisciplinary Collaboration

Pulmonary Embolism Response Team (PERT)

Mission
To advance the diagnosis, treatment and outcomes of patients with severe pulmonary embolism (PE)

Vision
To become the center of excellence in the science of pulmonary embolism care through multidisciplinary collaboration in clinical care, education and research

PERT Program Flow Map

Expeditious input and clinical judgment from multiple specialties to optimize therapy
**Pulmonary Embolism Response Team (PERT)**

**Case of “Can I travel to Colorado?”**

**Patient involvement**

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**PERT Team at MGH**

**A Multidisciplinary Pulmonary Embolism Response Team**

Initial 30-Month Experience With a Novel Approach to Delivery of Care to Patients With Submassive and Massive Pulmonary Embolism

Christopher Kabrhel, MD, MPH; Rachel Rosovsky, MD, MPH; Richard Chemick, MD; Michael A. Zeff, DO; Jais Hembro, MD; Shawn Sund, MD; David M. Doctors, MD, JD; Joanna Kudlacz-Copis, MD; Blair A. Henry, COHC, BV, Gawain Hamilton, BS, Susan Cheng, PhD; and Kenneth Rosenfeld, MD.

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**PERT Data: Activations**

- As soon as PERT launched
  - Immediate response
- Virtual consult
  - Average length = 25 mins.
  - Range = 5-15 physicians
  - Off hours/weekends = 53%

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**PERT Data: Mortality**

- Massive PE mortality 25%
- Lower than National average of 52%
- Does our approach improve outcomes?

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**Expanding PERT Nationally and Internationally…**

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**PERT National Consortium**

Launched May 2015
March was VTE Awareness Month
Educate patients and providers

Take Home Points

• DOACs have similar efficacy and mortality profiles as warfarin, many have better bleeding profile. THEY ARE NOW FIRST LINE.
• No head to head trials with DOACs -- which one to use depends on patient factors and preferences.
• Important for clinicians to understand when and how to use them and their limitations.
• Novel agents may be attractive alternative in cancer patients; efficacy and safety is currently under investigation.
• Screening for occult malignancy in idiopathic VTE is not indicated but age specific cancer screening is.
• Increase awareness about VTE.
• Treatment for life threatening pulmonary embolism may be best served via multidisciplinary approach. PERT National Consortium has been created and will study this approach.

VTE – venous thromboembolism

Thank you

Reference

• Kabrhel C, Rosovsky R, Channick R et al. A Multidisciplinary Pulmonary Embolism Response Team (PERT): A Model for Improved Outcomes with a Focus on Delivery of Care to Patients with Submassive and Massive PE. Chest 2015; Mar 19.