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

Rachel P. Rosovsky, MD, MPH
October 19, 2017
Disclosures

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• Research Support: Janssen, BMS
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
1 in 4 people worldwide die of conditions caused by thrombosis. It is a leading cause of global death and disability.
Venous Thromboembolism: The Third Leading Cause of Cardiovascular Death

- **DVT**
  - 2 Million
  - Post-thrombotic Syndrome
    - 800,000
  - PE
    - 600,000
    - Deaths
      - 60,000
  - Silent PE
    - 1 Million
    - Pulmonary Hypertension
      - 30,000

Estimated Cost of VTE Care $1.5 Billion/year

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.
Age-, sex-adjusted VTE incidence did not change significantly over the 30-year period.

Incidence is increasing

Virchow’s Triad 2015

**STASIS**
- Anesthesia
- 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

Why worry about Pulmonary Embolus?

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

Increased RV afterload

RV dilatation

TV insufficiency

RV wall tension

Neurohormonal activation

Myocardial inflammation

RV O₂ demand

RV ischaemia

Cardiogenic shock

Death

BP = blood pressure; CO = cardiac output; LV = left ventricular; RV = right ventricular; TV = tricuspid valve.
Most Patients with PE do Well, but some do not

Abrahams van-Doorn P. and Hartmann IJC. Imaging Insights. 2011; 2: 705-715
Dalen JE. Chest. 2002; 122: 1801-17
PE Mortality (ICOPER)


*62.5% from recurrent PE
Pulmonary Embolism: Treatment Options
Therapeutic Alternatives in Acute Venous Thromboembolism

**Anticoagulation**
- Unfractionated Heparin
  - Continuous Intravenous
  - Full-Dose Subcutaneous
- Low-Molecular-Weight Heparin
- Direct Thrombin Inhibitors
- Synthetic Pentasaccharide Xa Antagonist
- Warfarin
- New oral Factor Xa inhibitors

**Thrombolytic Therapy**
- Systemic
- Catheter Directed
- Pharmacomechanical Catheter-Directed Thrombolysis (PCDT)

**Mechanical**
- Thromboaspiration
- Surgical Thrombectomy

**Adjunctive Therapy**
- Vena Caval Filter
- Extracorporeal support
Historical Perspective

- Raoul: 1st documented description and treatment of DVT in Middle Ages.
- Pain & swelling in calf which progressed to leg ulcers

Direct Oral Anticoagulants

- **Direct Thrombin Inhibitor**
  - Pradaxa: Dabigatran

- **Factor Xa inhibitors**
  - Xarelto: Rivaroxaban
  - Eliquis: Apixaban
  - Savaysa: Edoxaban
Direct Oral Anticoagulants

- Factor Xa Inhibitor
- DTI
- Thrombin
- Fibrinogen
- Fibrin

Reagents:
- XII
- XIa
- IXa
- Ca++
- PL
- HMWK
- PreK
- VIIa
- VII
- TF
- Ca++
- PL
Direct oral anticoagulants: Are they the new standard of care?

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

Are they effective?

Table 2. Efficacy Outcome of Recurrent VTE with Use of Non-Vitamin K Antagonist Oral Anticoagulants in Comparison With Vitamin K Antagonists in the Treatment of Acute VTE

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>n/N (%)</th>
<th>RR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>59/2691 (2.3)</td>
<td>0.84 (0.60–1.18)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>60/2553 (2.4)</td>
<td>1.09 (0.76–1.57)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>130/4118 (3.2)</td>
<td>0.89 (0.70–1.13)</td>
</tr>
<tr>
<td>Rivaroxaban†</td>
<td>86/4150 (2.1)</td>
<td>0.90 (0.68–1.20)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; RR, relative risk; and VTE, venous thromboembolism.

*RR was recalculated from the hazard ratio for optimal comparison (dabigatran [from RE-COVER II pooled analysis], edoxaban, and rivaroxaban [combined data from EINSTEIN-DVT and EINSTEIN-PE study]).

†Efficacy outcome for EINSTEIN studies was recurrent VTE, and not combined recurrent VTE or VTE-related death.

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

Dabigatran

Rivaroxaban

Apixaban

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

Are they safe?

Table 3. Safety Outcomes of Bleeding With Use of Non–Vitamin K Antagonist Oral Anticoagulants in Comparison With Vitamin K Antagonists in the Treatment of Acute Venous Thromboembolism

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Major Bleeding or Clinically Relevant Nonmajor Bleeding</th>
<th>Major Bleeding</th>
<th>ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence, n/N (%)</td>
<td>RR* (95% CI)</td>
<td>Incidence, n/N (%)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>115/2691 (4.3)</td>
<td>0.44 (0.36–0.55)</td>
<td>15/2691 (0.6)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>136/2553 (5.3)</td>
<td>0.63 (0.51–0.77)</td>
<td>37/2553 (1.4)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>349/4118 (8.5)</td>
<td>0.81 (0.71–0.94)</td>
<td>56/4118 (1.4)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>388/4150 (9.3)</td>
<td>0.94 (0.82–1.07)</td>
<td>40/4150 (1.0)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ICH, intracranial hemorrhage; and RR, relative risk.

*RR recalculated from the hazard ratio for optimal comparison (dabigatran [from RE-COVER II pooled analysis], edoxaban, and rivaroxaban [combined data from EINSTEIN-DVT and EINSTEIN-PE study]). ICH includes both fatal and nonfatal ICH with RR calculated from each study.

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

Dabigatran

Rivaroxaban

Apixaban

Edoxaban
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.
Direct Oral Anticoagulants

• *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
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.

LMWH = low molecular weight heparin
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

LMWH=low molecular weight heparin
Case 1: 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

LMWH = low molecular weight heparin
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) only given after initial parenteral anticoagulation therapy administered for median of 9 days (range 5-10).

- **Monitoring**: no need because of predictable PK
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

These drugs may also interact with warfarin but you can monitor that with INR
Case: The Case of Helpful Grandfather

- Babysitting sick grandson.
- Developed diarrhea shortly after.
- As a result, became dehydrated, lightheaded and fell, hitting his head.
- ER.
- CT head shows a small subdural bleed.
- Last dose was 24 hours ago.
Case 1: The Case of Helpful Grandfather

What would you do now?

1. Vitamin K
2. FFP (fresh frozen plasma)
3. Prothrombin Complex Concentrates (PCC)
4. FEIBA
5. rFVIIa
6. Charcoal
7. Hemodialysis
8. Antifibrinolytics
9. Hold drug
10. Idarucizumab

FEIBA = Factor VIII inhibitor bypassing fraction
rFVIIa = recombinant factor VIIa
Dabigatran

- **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.
  - Hemodialysis *
Antidote for Dabigatran: **Idarucizumab (Praxbind)**

- Monoclonal antibody against fragment on dabigatran
- Safety and effectiveness studied in trials
- FDA approved

Pollack et al. NEJM; 2015; 373:511-20.
Case: The Case of Helpful Grandfather

- Did fine with holding drug.
- Restarted a week later without any incident.
Case: The Case of Pleuritic Chest Pain

- 26 F - right sided pleuritic CP.
  - Thought pulled muscle --- woke up with sudden onset SOB.
- ER: Ddimer elevated; CTA → bilateral PE. LMWH, d/c Rivaroxaban.
- Met back with PCP who was unfamiliar with Rivaroxaban and placed on LMWH bridge to coumadin.
- On coumadin, INRs difficult to regulate, ranging from 1.2-4.8.
Case: “The Case of Pleuritic Chest Pain”

What do you do next?

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
Case: The Case of Pleuritic Chest Pain

• She came to me for 2\textsuperscript{nd} opinion regarding choice of anticoagulation.

• Things to consider
  • pregnancy, cancer, bleeding, compliance, kidney and liver functions, lupus anticoagulant
Case: The Case of Pleuritic Chest Pain

- Changed her to rivaroxaban.
Rivaroxaban

• **Stats**
  • Oral direct factor Xa inhibitor
  • Rapid onset: 2.5-4 hours
  • T1/2 life: 11-13 hours
  • Excretion: renal.
  • Dosing:
    • For VTE
      • 15 mg/bid x 3 weeks and then 20 mg/day.

VTE = venous thromboembolism
Rivaroxaban

- **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
Case: The Case of Chronic Thromboembolic Disease

- 45 yo man - DVT, PE, s/p IVC filter, severe symptomatic pulmonary HTN 2/2 chronic pulmonary thromboembolic disease.
- Elective pulmonary thromboembolectomy.
Rivaroxaban

- **Hemorrhage:**
  - Stop the drug.
  - Over 90% protein bound - cannot be dialyzed
  - Charcoal hemofiltration has been suggested.
  - Life-threatening bleeding:
    - PCC have been studied but very limited patient experience
  - Antidote
    - bioengineered recombinant variant of factor Xa, currently in clinical trials.

PCC: Prothrombin Complex Concentrates
Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., and Mark A. Crowther, M.D.

• Healthy volunteers
• Anti-Xa activity was reduced
• Phase III
Case: The Case of Importance of Follow Up.

- 48 M h/o idiopathic Guillain-Barré Syndrome 3 years prior, not treated and slowly resolved except residual numbness in lower extremities presented to OSH with acute SOB.
- CTA showed bilateral PE and RV/LV ratio >1. Given one dose lovenox and sent to MGH.
Case: The Case of Importance of Follow Up.

- At MGH:
  - Vitals: 87% on RA, initially required 15 L NC oxygen, HR 150, RR 28, BP 140/79. Breath every few words.
  - ECHO: RV dilated, hypokinetic, septal flattening, RVSP 54.
- Given his hypoxia, tachypnea, hypokinesis, decision was to proceed with CDT thrombectomy and lysis.
- Felt better next day and discharged on Apixaban.

RV: right ventricle
CDT: catheter directed thrombolysis
Apixaban

- **Stats**
  - Oral direct factor Xa inhibitor
  - Rapid onset: 3-4 hours
  - T1/2 life: 8-15 hours
  - Excretion: 25% renal and feces
  - Dosing:
    - **For treatment of VTE:**
      - 10 mg bid for 7 days followed by 5 mg bid.
Case: The Case of Importance of Follow Up.

- In hospital, HCT 26.8.
- Came to follow up clinic one month later.
- No problems with apixaban. Never felt better.
- HCT still 26.8.
- Work up revealed:
  - IgG 5328, IgA 22, IgM 6,
  - serum free kappa/lamda = 601/1.5 = 400 ratio
  - M spike: 4.31 IgG Kappa
- Just underwent bone marrow transplant.
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 cancer:
  - 14 of 431 patients (3.2%) in limited-screening group and 19 of 423 patients (4.5%) in limited-screening-PLUS-CT group (P=0.28).
  - 4 (29%) cancers were missed by limited screening strategy, whereas 5 (26%) cancers were missed by limited screening PLUS CT (P=1.0).

Carrier. NEJM. 373:8; 697. 2015.
Screening for Occult Malignancy in VTE

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

- Importance of the physical exam
- 54 F with idiopathic PE
  - sent home on LMWH as bridge to Edoxaban
  - physical exam
Edoxaban

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

**Dosing:**
- 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.

CrCL = creatinine clearance
Edoxaban

**Limitations**
- Need for heparin lead-in BUT -- encouraged investigators to enroll more patients with severe PE.

**Potential Advantage**
- Approximately 1/3 patients had right ventricular dysfunction.
- Reduction in recurrences in edoxaban group.
  - Rate of recurrent VTE in this subgroup was 3.3% in edoxaban group and 6.2% in warfarin group (HR, 0.52; 95% CI, 0.28 to 0.98).

VTE= venous thromboembolism
### Key differences between DOACs dosing in treatment of acute VTE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dosing</th>
<th>Transition Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>15 mg twice daily for 21 days</td>
<td>20 mg once daily</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>10 mg twice daily for 7 days</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td>Parenteral agent with UFH or LMWH for 5-10 days</td>
<td>60 mg once daily (30 mg once daily if CrCl 15-50 cc/min or weight &lt; 60 kg or on P-gp inhibitors)</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>Parenteral agent with UFH or LMWH for 5-10 days</td>
<td>150 mg twice daily</td>
</tr>
</tbody>
</table>

**Legend**
- **Red**: need for higher dose initially
- **Purple**: need for parenteral agent initially
- **Green**: once daily dosing
- **Blue**: twice daily dosing

UFH = unfractionated heparin; LWMH = low molecular weight heparin

Rosovsky, Merli. TVIR. 2017. *In press*
## Characteristics of the new agents

<table>
<thead>
<tr>
<th>Drug target</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours to Cmax</td>
<td>2-4 h</td>
<td>3-4 h</td>
<td>1-2 h</td>
<td>1-2 h</td>
</tr>
<tr>
<td>Half life</td>
<td>5-9 h (age 20-45)</td>
<td>12 h</td>
<td>10-14 h</td>
<td>12-17 h</td>
</tr>
<tr>
<td></td>
<td>11-13 h (age ≥65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elimination</td>
<td>36% renal</td>
<td>27% renal</td>
<td>50% renal</td>
<td>80% renal</td>
</tr>
<tr>
<td>Dosing</td>
<td>15 mg bid for 21 days followed by 20 mg daily</td>
<td>10 mg bid for 7 days followed by 5 mg bid</td>
<td>60 mg daily if CrCL &gt;50 mL/min. 30 mg daily if CrCL &lt;15 mL/min, ≤ 60 kg.</td>
<td>150 mg bid if CrCL &gt;30 mL/min</td>
</tr>
<tr>
<td>Requires initial parenteral anticoagulant for 5-10 days</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>P-glycoprotein CYP3A4</td>
<td>P-glycoprotein CYP3A4</td>
<td>P-glycoprotein</td>
<td>P-glycoprotein</td>
</tr>
<tr>
<td>Reversal agent</td>
<td>Adnexanet (in clinical trials)</td>
<td>Adnexanet (in clinical trials)</td>
<td>Adnexanet (in clinical trials)</td>
<td>Idarucizumab</td>
</tr>
<tr>
<td>Special considerations</td>
<td>Must be taken with food. Avoid if CrCL &lt;30 mL/min or Child-Pugh class B and C.</td>
<td>Avoid if CrCL &lt;15 mL/min or Child-Pugh class B and C.</td>
<td>Avoid if CrCL &lt;15 mL/min or Child-Pugh class B and C.</td>
<td>Avoid if CrCL &lt;30 mL/min or Child-Pugh class B and C. Avoid if dyspepsia and upper GI symptoms.</td>
</tr>
</tbody>
</table>

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**
  - Vitamin K antagonist or apixaban
- **Pregnancy**
  - LMWH
- **Poor compliance**
  - Arguments for INR vs DOACs
Cautions with Direct Oral Anticoagulants

- Approved reversal agent only for dabigatran (under trials)
- No monitoring for effect
- 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
Cautions with Direct Oral Anticoagulants

• Unclear role in extensive DVT or massive PE
  – Patients excluded because often required advanced therapies.

• Have not been evaluated in conjunction with thrombolytic therapy.

• Lack of data on patients at extreme weights.

• Due to lack of antidote*, agents may not be appropriate for patient at high initial bleeding risk.
  – major trauma or surgery

* Except for dabigatran

DVT = deep vein thrombosis
PE = pulmonary embolism
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
- Duration of anticoagulation
Switching to/from direct oral anticoagulant: Review package insert

### Table 15 Switching to DOACs

<table>
<thead>
<tr>
<th>Warfarin to DOAC</th>
<th>DOAC to warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warfarin to DOAC</strong></td>
<td><strong>DOAC to warfarin</strong></td>
</tr>
<tr>
<td>Dabigatran&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Start warfarin and overlap with dabigatran;</td>
</tr>
<tr>
<td>CrCl ≥ 50 mL/min, overlap 3 days</td>
<td>CrCl 30–50 mL/min, overlap 2 days</td>
</tr>
<tr>
<td>CrCl 15–30 mL/min, overlap 1 day</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Stop DOAC; start warfarin and LMWH at time of</td>
</tr>
<tr>
<td>next scheduled DOAC dose and bridge until INR ≥ 2.0</td>
<td></td>
</tr>
<tr>
<td>Apixaban&lt;sup&gt;a&lt;/sup&gt;</td>
<td>For 60 mg dose, reduce dose to 30 mg and start</td>
</tr>
<tr>
<td>warfarin concomitantly</td>
<td>For 30 mg dose reduce dose to 15 mg and start</td>
</tr>
<tr>
<td>warfarin concomitantly</td>
<td>Stop edoxaban when INR ≥ 2.0</td>
</tr>
<tr>
<td>Edoxaban&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(iv) UFH to DOAC</td>
</tr>
<tr>
<td>Dabigatran&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Start DOAC immediately after stopping iv UFH</td>
</tr>
<tr>
<td>Rivaroxaban&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Apixaban&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Edoxaban&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Start edoxaban 4 h after stopping iv UFH</td>
</tr>
</tbody>
</table>

As a general rule, we suggest that as INR drops below 2.5, a DOAC can be started.
As a general rule, we suggest that each DOAC can be started within 30 min after stopping (iv) UFH.

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<sup>a</sup> Recommendations adapted from company’s package insert

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

Jan Beyer-Westendorf, Franziska Michalski, Luise Tittl, Susann Hauswald-Dörschel, Sandra Marten

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

Initial Questions

Is the patient actively bleeding?
Where is the location and what is the severity of the bleed?
Can local hemostatic measures be applied or is a surgical invention or procedure required?
What DOAC is the patient taking and when was the last dose?
Does the patient have renal failure or liver disease which may affect metabolism or clearance of DOAC?
Is the patient on an antiplatelet or alternative medication that may further increase risk of bleeding?
Does the patient have comorbidities that may increase the risk of bleeding?
Is the patient hemodynamically stable?

Initial Testing

Complete Blood Count
Comprehensive Metabolic Panel to assess kidney and liver function
Coagulation tests: PT, PTT, INR
dTT (if on dabigatran) or anti-factor Xa (if on apixaban, rivaroxaban edoxaban)

Intervention: based on severity of bleed

Minor
- Local hemostatic measures
- Consider discontinuation of DOAC
- Surgical or procedural intervention if necessary

Moderate
- Local hemostatic measures
- Monitor closely
- Discontinue DOAC
- Surgical or procedural intervention if necessary
- Blood transfusion support if necessary

Severe
- Place in ICU and monitor closely
- Hemodynamic support if necessary
- Blood transfusion support if necessary
- Discontinue DOAC
- Activated charcoal if last dose <6 hours

Consider additional medications/interventions if life threatening bleed
- Idarucizumab if on dabigatran
- Hemodialysis if on dabigatran
- Adnexanet if on apixaban, rivaroxaban, or edoxaban and if available (only on trial currently)
- 3 or 4 factor PCC if on apixaban, rivaroxaban, or edoxaban (although limited data available and may be prothrombotic)
- Antifibrinolytic therapies if appropriate
- DDAVP in patients with impaired platelet function

* In some circumstances, may need to employ severe bleeding strategies
** Blood transfusion support: RBC, platelets, FFP, cryoprecipitate
† Adapted from Burnett et al. 2017
RBC = Red Blood Cells; FFP = Fresh Frozen Plasma
DDAVP = desmopressin; ICU = Intensive Care Unit

Rosovsky, Merli. TVIR. 2017. In press
Direct oral anticoagulants: Peri-operative questions

- Peri-operative/procedure management? How long to hold medication?
  - What drug patient taking
  - \( \frac{1}{2} \) life of the drug
  - Bleeding risk of procedure
  - Bleeding and thrombotic risk of patient
  - Current dose
  - Renal function
How long to hold novel oral agents for procedures:

Look at package inserts


<table>
<thead>
<tr>
<th>Renal function</th>
<th>Cessation</th>
<th>Estimated half-life (hours)</th>
<th>Low bleeding risk surgery (allow 2–3 t1/2 between last dose and surgery)</th>
<th>High bleeding risk surgery (allow 4–5 t1/2 between last dose and surgery)</th>
<th>Resumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &gt; 80</td>
<td>t1/2 ~ 14</td>
<td></td>
<td>Hold time: 28–42 h</td>
<td>Hold time: 56–70 h</td>
<td>1 day after procedure (~24 h post-op)</td>
</tr>
<tr>
<td>CrCl &gt; 50–79</td>
<td>t1/2 ~ 17</td>
<td></td>
<td>Hold time: 34–51 h</td>
<td>Hold time: 68–85 h</td>
<td>2–3 days after procedure (~48–72 h post-op)</td>
</tr>
<tr>
<td>CrCl 30–49</td>
<td>t1/2 ~ 19</td>
<td></td>
<td>Hold time: 38–57 h</td>
<td>Hold time: 76–95 h</td>
<td></td>
</tr>
<tr>
<td>CrCl 15–29</td>
<td>t1/2 ~ 28</td>
<td></td>
<td>Hold time: 56–84 h</td>
<td>Hold time: 112–140 h</td>
<td></td>
</tr>
<tr>
<td>CrCl &lt; 15</td>
<td>Unknown</td>
<td></td>
<td>Hold until resolved (e.g. if acute kidney injury) or consider transition to warfarin or UFH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Peri-procedural Guidelines

2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation

Duration of Anticoagulation
## Risk of recurrent VTE

<table>
<thead>
<tr>
<th>Type of VTE</th>
<th>1 year risk</th>
<th>5 year risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provoked by surgery</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Provoked by non surgical reversible risk</td>
<td>5%</td>
<td>15%</td>
</tr>
<tr>
<td>Unprovoked VTE</td>
<td>10%</td>
<td>30%</td>
</tr>
<tr>
<td>Cancer associated</td>
<td>15%</td>
<td>*</td>
</tr>
</tbody>
</table>

- Not predicted due to high mortality rate from cancer
- VTE = venous thromboembolism

Kearon et al. CHEST. 2012.
Who warrants long term anticoagulation?

- Depends on:
  - patient-specific bleeding risks
  - patient-specific thrombotic risks
  - patient values and preferences
Who warrants long term anticoagulation?

- Most likely to benefit
  - Idiopathic VTE
  - Active cancer
  - Antiphospholipid syndrome
  - Recurrent VTE
  - “high risk” thrombophilia

- Possible benefit
  - Provoked VTE with persistent risk factors
  - Unprovoked isolated distal DVT with persistent risk factors
  - Unprovoked incidental PE

VTE = venous thromboembolism
Clinical features associated with recurrent risk

- Several clinical features associated with recurrence; however, not completely defined on how to weigh each one.
  - proximal location of DVT or PE
  - obesity
  - male sex
  - several thrombophilic defects
  - D-dimer
  - residual vein thrombosis
  - IVC filter
2482 patients who completed 6-12 months of anticoagulation (equipoise) randomized to Apixaban 5 mg (treatment dose) or 2.5 mg (prophylactic dose) or placebo.

Apixaban reduced the risk of recurrent VTE without increasing the rate of major bleeding

Agnelli et al. NEJM. 2013.
3396 VTE patients, completed 6-12 months AC, equipoise, randomized to rivaroxaban 20 mg (rx dose), 10 mg (ppx dose) or aspirin.

Rivaroxaban reduced the risk of recurrent VTE compared to aspirin without increasing rate of major bleeding

AC = anticoagulation

Weitz et al. NEJM. 3017.
How do I apply these results to my patients?
One possible algorithm ...

1: Male would stop even if recurrence risk 16% in first year
   Female would stop even if recurrence risk 10% in first year

2: Male would stay on if recurrence risk 8% in first year
   Female would stay on even if recurrence risk 5% in first year

Kearon et al. Blood. 2014
Can you use the direct oral anticoagulants in cancer patients?

Studies included 5-10% cancer patients.

Ongoing clinical trials
Association Between Cancer and Thrombosis

• 1865: Armand Trousseau
• Migrans thrombophlebitis as forewarning of occult cancer.
Epidemiology: Cancer and Thrombosis

- Thrombosis is a common complication of cancer.
- Estimated incidence is 15% (4-30%).
Survival: Cancer and Thrombosis

Danish Cancer Registry (668 VTE 5371 without)

1-yr survival

- Cancer at time of VTE (668) 12%
- Cancer without VTE (5371) 36%

Survival, % of patients

Years after Diagnosis

VTE= venous thromboembolism

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.
- Current recommended therapy: LMWH

VTE = venous thromboembolism
LMWH = low molecular weight heparin
Cancer and VTE: CLOT Trial

Risk reduction = 52%

$P = 0.0017$

OAC

17%

Dalteparin

9%

Days post-randomization

Probability of recurrent VTE (%)

OAC = oral anticoagulant

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

LMWH= low molecular weight heparin
PE= pulmonary embolism
DT= deep vein thrombosis

Other Important Topics

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

• Clinically stable, good cardiopulmonary reserve.
• No contraindications (bleeding, severe renal or liver disease, or severe thrombocytopenia)
• Compliant with treatment
• Patient well enough and has support.
• No evidence of right heart strain

Outpatient Treatment Recommendations

Lab Testing
Please send if not already done:
- D-dimer
- Hypercoaguable Panel
- Beta-2 Glycoprotein
- Antiphospholipid Panel
- Prothrombin Gene Mutation
(4 blue top and 1 red top tube)

Known Pregnancy? Active Cancer? Liver Cirrhosis? Antiphospholipid Ab?

Yes

Enoxaparin
1 mg/kg Sq BID
(if <150 kg)

No

Rivaroxaban
15 mg PO BID
(with food)
* see note below

Antiphospholipid Ab Liver Cirrhosis

Warfarin 5 mg PO QHS

Pregnant or Active Cancer

Follow Up with Anticoagulation Management Services (2-3 days)

Clinic Follow Up (1 week)

* Please also see Clinic Follow Up Guidelines for details.
** Patients with CrCl 30-50 may require earlier follow up in clinic for repeat labs

Kabrhel, Rosovsky et al. Hospital Practice. 2017
Outpatient treatment of DVT/PE

Timely follow up is the most important component
Other Important Topics

Novel approaches to treatment of severe pulmonary embolism
Importance of expeditiously treating Pulmonary Embolism

- Fatal within 1 hour after the onset of symptoms in 10% of cases
- Untreated PE mortality rate ~30%
Pulmonary Embolism Response Team (PERT)
Multidisciplinary Collaboration

PERT

Emergency Medicine
Hematology/Oncology
Cardiology
Echocardiography
Research
Quality & Safety
Nursing
Cardiac and Thoracic Imaging
Cardiac Surgery
Pulmonary/Critical Care
Vascular Medicine and Intervention
Expeditious input and clinical judgment from multiple specialties to optimize therapy
Case of “Can I travel to Colorado?”

Patient involvement
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 Channick, MD; Michael R. Jaff, DO; Ido Weinberg, MD; Thoralf Sundt, MD; David M. Dudzinski, MD, JD; Josanna Rodriguez-Lopez, MD; Blair A. Parry, CCRC, BA; Savannah Harshbarger, BS; Yuchiao Chang, PhD; and Kenneth Rosenfield, MD
As soon as PERT launched
- Immediate response

PERT Data: Mortality

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

Expanding PERT Nationally and Internationally…
National PERT™ Consortium

• Launched May 2015
  – 5 committees
    • Governance: established 501c3
    • Education
    • Communication
    • Clinical practice and protocols
    • Research
    • Development
Other Important Topics

October 13
World Thrombosis Day

Educate patients and providers
Closing Reflections

- **DOACs**: exciting addition to treatment options for VTE. *1st line*
  - Similar efficacy as warfarin, better bleeding
  - Important for clinicians to understand when/how to use them and their limitations.
- Novel agents may be attractive alternative in cancer patients; their efficacy and safety is currently under investigation.
- Screening for occult malignancy in idiopathic VTE is not indicated but age specific cancer screening is.
- Increase VTE awareness
- Consider treating low risk VTE as outpatient
- 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
PERT = Pulmonary Embolism Response Team
Thank you
Reference


• Kabrhel C, Rosovsky R, Channick R et al. *A Multidisciplinary Pulmonary Embolism Response Team (PERT) - Initial 30-Month Experience with a Novel Approach to Delivery of Care to Patients with Sub-Massive and Massive PE.* Chest. 2016; Mar 19.
