Anticoagulation for Venous Thromboembolism in the 21st Century: Practical Considerations

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Disclosures

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I do not plan to discuss use of off-label or unapproved use of product(s) or device(s).

I am not receiving commercial support for this program.
Topics for Today

- The venous thromboembolism problem
- Treatment/prevention with anticoagulants
  - The old way
  - The new way
    - Advantages and pitfalls
    - How to use and how to choose
- Approach to managing anticoagulant-associated bleeding
VTE in the United States

- Up to 1 - 2 million new cases per year in US
- At least 10 - 17% of PE are fatal

<table>
<thead>
<tr>
<th>Condition</th>
<th>Annual Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>530,000</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>~100,000</td>
</tr>
<tr>
<td>Highway fatalities</td>
<td>42,000</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>41,000</td>
</tr>
<tr>
<td>AIDS</td>
<td>15,000</td>
</tr>
</tbody>
</table>

- Men > Women
- African-American > Caucasian
- Incidence doubles with every 10 year increase in age
Age-Specific Incidence of First VTE (per year)

Adapted from Engbers et al., JTH 2010
Age-Specific Incidence of First VTE (per year)

Race/Ethnicity/Age and VTE Incidence

The Surgeon General’s Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism

2008

U.S. Department of Health and Human Services
**Treatment of Acute VTE**

**ACUTE TREATMENT**

Heparin, LMWH 5-10 days*

**LONG TERM SECONDARY PROPHYLAXIS**

Warfarin 3 months to indefinitely (INR target 2.5, range 2.0-3.0)

5 days is the minimum acceptable duration of heparin treatment

Use of warfarin requires long-term laboratory monitoring
## Why Look for New Anticoagulants?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Limitation</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Slow onset of action</td>
<td>Overlap with parenteral agent</td>
</tr>
<tr>
<td></td>
<td>Temporary prothrombotic state</td>
<td>Overlap with parenteral agent, thrombosis</td>
</tr>
<tr>
<td></td>
<td>Genetic variation in metabolism</td>
<td>Variable dose requirements</td>
</tr>
<tr>
<td></td>
<td>Numerous food &amp; drug interactions</td>
<td>Frequent lab monitoring, dose adjustments</td>
</tr>
<tr>
<td></td>
<td>Narrow therapeutic index</td>
<td>Frequent lab monitoring, dose adjustments</td>
</tr>
<tr>
<td>LMWH</td>
<td>Injectable</td>
<td>Ouch</td>
</tr>
<tr>
<td></td>
<td>Not ideal for long-term use</td>
<td>Ouch, osteoporosis</td>
</tr>
<tr>
<td></td>
<td>Serious adverse effects</td>
<td>HIT</td>
</tr>
<tr>
<td></td>
<td>Resource intensive</td>
<td>Requires lots of pigs</td>
</tr>
</tbody>
</table>
Case #1

46 yo executive with presents with a right leg popliteal DVT 3 days after arthroscopic knee surgery. She is treated with enoxaparin as a bridge to warfarin (target INR 2.5, range 2.0 to 3.0). After three weeks she remains on twice daily enoxaparin + warfarin with the following INRs:

1.2
1.4
1.6
1.6
1.8
1.7
1.5
1.8
1.9

How do you judge her anticoagulation management to date?
A New Era in Anticoagulants

NOACs → TSOACs → **DOACs**

Unfractionated Heparin

Low Molecular Weight Heparin

New Oral Xa Inhibitors
- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban

New Oral IIa Inhibitors
- Ximelagatran
- Dabigatran etexilate

Fibrin Clot
### Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Pradaxa</td>
<td>Xarelto</td>
<td>Eliquis</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Thrombin (IIa)</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Time to max effect</strong></td>
<td>2 hrs</td>
<td>2 - 4 hrs</td>
<td>3 hrs</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>12 – 14 hrs</td>
<td>7 – 13 hrs</td>
<td>8 – 13 hrs</td>
</tr>
<tr>
<td><strong>Route of elimination</strong></td>
<td>80% Renal</td>
<td>~33% Renal</td>
<td>~27% Renal</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>bid</td>
<td>qd, bid</td>
<td>bid</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>Yes</td>
<td>No*</td>
<td>No*</td>
</tr>
<tr>
<td><strong>Dialyzable</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>US FDA Approval Status</strong></td>
<td>Atrial fibrillation Acute VTE tx (after LMWH)</td>
<td>Atrial fibrillation VTE proph ortho surg Acute VTE tx</td>
<td>Atrial fibrillation VTE proph ortho surg Acute VTE tx</td>
</tr>
</tbody>
</table>
# Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Edoxaban</th>
<th>Betrixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade Name</td>
<td>Savaysa</td>
<td></td>
</tr>
<tr>
<td>Target</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td>Time to max effect</td>
<td>1 – 2 hrs</td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td>10 – 14 hrs</td>
<td></td>
</tr>
<tr>
<td>Route of elimination</td>
<td>~35% Renal</td>
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<td>No*</td>
<td>No*</td>
</tr>
<tr>
<td>Dialyzable</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>US FDA Approval Status</td>
<td>Atrial fibrillation Acute VTE tx (after LMWH)</td>
<td>Being studied for hospital → home VTE prevention</td>
</tr>
</tbody>
</table>
Lab Tests for Direct Anticoagulants

- No tests monitor efficacy
- Dabigatran (target = IIa)
  - Thrombin time most sensitive
  - aPTT > PT
- Rivaroxaban, edoxaban (target = Xa)
  - No effect on thrombin time
  - PT > aPTT
  - Anti-Xa level
- Apixaban
  - Little effect on routine coagulation times
- Use to assess presence of drug
- Tests in development to measure blood levels
Advantages/Disadvantages of TS Oral Anticoagulants

**Advantages**
- Oral
- Rapid onset of action
- Fixed dose, no monitoring
- Limited food/drug interactions
- Short half lives
- No need for bridging
- Convenient
- Potential for greater use
- Better and safer than warfarin
- Cost effective

**Disadvantages**
- No monitoring
  - No dose titration
  - No way to measure compliance
- Short half-lives
  - Poor compliance affects efficacy
- No antidote
- No dose adjustment for renal/hepatic insufficiency
- High drug cost
- Lack of familiarity with drugs
Trials of DOACs in Acute VTE Treatment
Recurrent VTE or VTE-Related Death

AMPLIFY Trial
Apixaban v Enox + warfarin

Meta Analysis of VTE Trials (N = 26,872): Recurrent VTE or VTE Death

van Es et al., Blood 2014;124:1968-75.
Trials of DOACs in Acute VTE Treatment
Major Bleeding

AMPLIFY Trial
Apixaban v Enox+warfarin

Meta Analysis of VTE Trials (N = 26,872): Major Bleeding

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Case #1

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She is treated with enoxaparin as a bridge to warfarin (target INR 2.5, range 2.0 to 3.0).
After two weeks she remains on twice daily enoxaparin + warfarin with the following INRs:
1.2
1.4
1.6
1.6
1.8
1.7
1.5
1.8
1.9

Switch to rivaroxaban,
(15 mg twice daily x 3 weeks)
20 mg once daily to complete 3 month course
Switching Anticoagulants

- **LMWH to DOAC**
  - Substitute DOAC for next LMWH dose

- **Warfarin to DOAC**
  - Stop warfarin
  - Initiate DOAC when INR <2.3

- **DOAC to LMWH**
  - Substitute LMWH for next DOAC dose

- **DOAC to warfarin**
  - This can be tricky…
Case #2

66 yo previously healthy man presents is brought to the ER by his wife with shortness of breath and pleuritic chest pain of about 2 days duration after return from a vacation in Australia. His CTPA is shown:

A duplex study shows a left popliteal DVT. He’s admitted and treated with IV heparin with a plan to switch to enoxaparin then bridge to warfarin.

Good plan?
Results of DOAC VTE Trials: Disease Distribution

<table>
<thead>
<tr>
<th></th>
<th>DVT</th>
<th>PE +/- DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 15,357; 57%)</td>
<td>(n = 11,589; 43%)</td>
</tr>
<tr>
<td>DOAC (n = 13,512)</td>
<td>7687</td>
<td>5792</td>
</tr>
<tr>
<td>VKA (n = 13,511)</td>
<td>7675</td>
<td>5797</td>
</tr>
</tbody>
</table>

van Es et al., Blood 2014;124:1968-75.
EINSTEIN-PE: Rivaroxaban for Acute PE Treatment

Acute, symptomatic, objectively verified PE with or without DVT

- Rivaroxaban 15 mg twice daily x 3 weeks then 20 mg once daily x 3-12 months
  N=2420

- Enoxaparin, 1 mg/kg q 12 h as a bridge to dose-adjusted VKA, INR 2-3 x 3-12 months
  N= 2413

- Randomized, open label, non-inferiority trial
- Primary efficacy outcome: Time to 1st symptomatic VTE by 1 year.
- Primary safety outcome: Clinically relevant bleeding

EINSTEIN-PE: Rivaroxaban for Acute PE Treatment

RECURRENT VTE

EFFICACY

BLEEDING

SAFETY

Case #2

66 yo previously healthy man presents is brought to the ER by his wife with shortness of breath and pleuritic chest pain of about 2 days duration after return From a vacation in Australia. His CTPA is shown:

A duplex study shows a left popliteal DVT. He’s admitted and treated with IV heparin with a plan to switch to enoxparin then bridge to warfarin.

Rivaroxaban 15 mg twice daily x 3 weeks → 20 mg once daily
### Which Agent to Choose

<table>
<thead>
<tr>
<th>Situation</th>
<th>Drug(s)</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive DVT, PE</td>
<td>Heparin, LMWH</td>
<td>Excluded from DOAC trials</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>LMWH</td>
<td>Warfarin, DOACs cross placenta</td>
</tr>
<tr>
<td>Cancer</td>
<td>LMWH</td>
<td>Superior to warfarin, ?DOACs</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>Warfarin*</td>
<td>Excluded from DOAC trials</td>
</tr>
<tr>
<td>CrCL &lt;30 mL/min</td>
<td>Warfarin*</td>
<td>Excluded from DOAC trials</td>
</tr>
<tr>
<td>CrCL 30 – 50 mL/min</td>
<td>Riva, Apix, Ed</td>
<td>Less renal excretion than dabigatran</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Riva, Apix, Ed</td>
<td>Dabi associated with GI sx in 10%</td>
</tr>
<tr>
<td>Recent GI bleed</td>
<td>Apix, Warfarin</td>
<td>Dabi, Riva, Ed associated with more GIB</td>
</tr>
<tr>
<td>Poor bid compliance</td>
<td>Warfarin, Riva, Ed</td>
<td>Apix, Dabi are twice daily</td>
</tr>
<tr>
<td>Lab issues</td>
<td>DOAC</td>
<td>No monitoring</td>
</tr>
<tr>
<td>$$ issues</td>
<td>Warfarin</td>
<td>Warfarin &lt; DOAC &lt; LMWH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Effect on OAC Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole &amp; other Azoles</td>
<td>Increase</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Increase</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Increase</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Increase</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Decrease</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole &amp; other Azoles</td>
<td>Increase</td>
</tr>
<tr>
<td>Clarithromycin, Erythromycin</td>
<td>Increase</td>
</tr>
<tr>
<td>Ritonavir, Lopinivir, Indinivir</td>
<td>Increase</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

**Dabigatran, Edoxaban:**
P-gp inhibitors _INCREASE_ drug exposure
P-gp inducers _DECREASE_ drug exposure
CYP3A4 interaction not important

**Rivaroxaban, Apixaban:**
P-gp inhibitors _INCREASE_ drug exposure
P-gp inducers _DECREASE_ drug exposure
CYP3A4 inhibitors _INCREASE_ drug exposure
CYP3A4 inducers _DECREASE_ drug exposure
Case #3

81 yo golfer with a history of recurrent VTE is on long term warfarin therapy, target INR 2.5 (range, 2.0 to 3.0). He has taken warfarin for ~22 years, he’s followed at the VA anticoagulation clinic with monthly INRs and his INR is typically 2.2 – 2.6. He has diabetes, hypertension, renal insufficiency (est GFR ~40) and is obese (BMI ~36 kg/m2).

He sees a television ad with Arnold Palmer advertising Xarelto and he asks his doctor if Xarelto is right for him.

Is it?
Who was overtly excluded from EINSTEIN trials?

- Creatinine clearance < 30 mL/min
- Liver dysfunction
  - Acute or chronic hepatitis
  - ALT > 3X ULN
- Hypertension
  - SBP > 180 mm Hg
  - DBP > 110 mm Hg
- IVC filter or thrombolysis
- Endocarditis
- Increased bleeding risk incl GI
- Pregnant or childbearing age w/o contraception
- Concurrent use of CYP3A4 inducer or inhibitor
Who else was excluded?

- Americans (~7%)
- Very old people
  - ~65% under age 65
  - ~13% over age 75
- Obese
  - ~14% were >100 kg
- Underweight
  - ~2% <50 kg
- Modest renal dysfunction
  - ~7% with CrCl 30 – 50 mL/min
- Cancer patients (~5%)
- Previous VTE (~20%)
Patient selection for DOAC

- Pay proper attention to
  - Liver & kidney function
  - Concurrent medications
  - Co-morbid conditions
  - Bleeding history

- Consider dose adjustments in select situations

- For now, avoid in
  - Antiphospholipid syndrome
  - Cancer
    - LMWH preferred up front
    - OK later on

- Use with care in morbidly obese**
  - BMI >40 kg/m2
  - Weight >120 kg

- Try to avoid fixing that which is not broken
Case #4

50 yo male presents with an unprovoked left iliofemoral DVT and bilateral PE and is treated with apixaban, 10 mg twice daily for 7 days followed by 5 mg twice daily according to the drug labeling. He is now referred for an opinion on anticoagulant duration after 6 months of treatment. He’s doing well and has completely recovered from the VTE event but is nervous to continue with apixaban for fear of bleeding, especially since there is no “antidote” for the drug in case of emergency.

What to do?
AMPLIFY-EXT: Apix v Placebo for Extended VTE Rx

Acute, symptomatic, objectively verified DVT and/or PE, completed 6 – 12 months of initial therapy

- Apixaban, 5 mg twice daily x 12 months
  - N = 813
- Apixaban, 2.5 mg twice daily x 12 months
  - N = 840
- Placebo, twice daily x 12 months
  - N = 829

• **Primary efficacy outcome:** Recurrent VTE or death from any cause
• **Primary safety outcome:** Major bleeding

AMPLIFY-EXT: Apix v Placebo for Extended VTE Rx
Efficacy & Safety Results

Efficacy:
VTE or Death

Safety:
Major Bleeding

# Extended VTE Rx with DOACs & VKA vs Placebo

Efficacy Results in Unprovoked VTE

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 Vitamin K antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kearon 1999</td>
<td>1</td>
<td>79</td>
<td>83</td>
<td>0.05 [0.01, 0.38] 1999</td>
</tr>
<tr>
<td>Couturaud 2015</td>
<td>3</td>
<td>184</td>
<td>25</td>
<td>0.11 [0.03, 0.36] 2015</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>263</td>
<td>270</td>
<td>42</td>
<td>0.09 [0.03, 0.25]</td>
</tr>
<tr>
<td>Total events</td>
<td>4</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.56 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **1.1.2 NOAC** | | | | |
| Bauersachs 2010  | 8                   | 602           | 42     | 0.18 [0.08, 0.38] 2010            |
| Agnelli 2013     | 28                  | 1653          | 73     | 0.18 [0.11, 0.28] 2013            |
| Schulman 2013    | 3                   | 681           | 35     | 0.08 [0.02, 0.26] 2013            |
| Subtotal (95% CI)| 2936                | 2085          | 45.7%  | 0.16 [0.11, 0.24]                |
| Total events     | 39                  | 150           |        |                                   |
| Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 2 (P = 0.43); I² = 0% |
| Test for overall effect: Z = 9.67 (P < 0.00001) |

| Total (95% CI)   | 3815                | 2963          | 100.0% | 0.21 [0.11, 0.42]                |
| Total events     | 108                 | 289           |        |                                   |
| Heterogeneity: Tau² = 0.61; Chi² = 36.83, df = 6 (P < 0.000001); I² = 84% |
| Test for overall effect: Z = 4.48 (P < 0.000001) |
| Test for subgroup differences: Chi² = 33.33, df = 2 (P < 0.000001), I² = 94.0% |

Case #4

50 yo male presents with an unprovoked left iliofemoral DVT and bilateral PE and is treated with apixaban, 10 mg twice daily for 7 days followed by 5 mg twice daily according to the drug labeling. He is now referred for an opinion on anticoagulant duration after 6 months of treatment. He’s doing well and has completely recovered from the VTE event but is nervous to continue with apixaban for fear of bleeding, especially since there is no “antidote” for the drug in case of emergency.

Apixaban, 2.5 mg twice daily
A 56 yo woman is anticoagulated with dabigatran, 150 mg twice daily after her second idiopathic DVT, which occurred approximately 2 years ago. The plan is for long-term anticoagulation for secondary thromboprophylaxis and she is doing well.

She will be undergoing an elective cholecystectomy in the near future, her NP calls to ask how to bridge her anticoagulation.

You recommend?
## Perioperative DOAC Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Bleeding Risk (2 – 3 drug half lives)</th>
<th>High Bleeding risk (4 – 5 drug half lives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &gt;50 ml/min</td>
<td>2 days</td>
<td>3 days</td>
</tr>
<tr>
<td>CrCl 30 – 50 ml/min</td>
<td>3 days</td>
<td>4 – 5 days</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &gt;50 ml/min</td>
<td>2 days</td>
<td>3 days</td>
</tr>
<tr>
<td>CrCl 30 – 50 ml/min</td>
<td>2 days</td>
<td>3 days</td>
</tr>
<tr>
<td>CrCl 15 – 30 ml/min</td>
<td>3 days</td>
<td>4 days</td>
</tr>
<tr>
<td>Apixaban</td>
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<td></td>
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<tr>
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<tr>
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<td>4 days</td>
</tr>
<tr>
<td>Edoxaban</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>3 days</td>
</tr>
<tr>
<td>CrCl 30 – 50 ml/min</td>
<td>3 days</td>
<td>4 days</td>
</tr>
</tbody>
</table>
Restart DOAC Post-Operatively

- Consider bleeding vs thrombosis risk
  - Low bleeding risk 12 – 24 hours post-op
  - High bleeding risk 48 – 72 hours post-op
- Consider starting with low dose
- LMWH prophylaxis if unable to take pills initially
- “Bridging” unnecessary
A 56 yo woman is anticoagulated with dabigatran, 150 mg twice daily after her second idiopathic DVT, which occurred approximately 2 years ago. The plan is for long-term anticoagulation for secondary thromboprophylaxis and she is doing well.

She will be undergoing an elective cholecystectomy in the near future, her NP calls to ask how to bridge her anticoagulation.

Dabigatran held for two days, restarted 24 hours after surgery
A 48 yo man on long term anticoagulation for a near-fatal idiopathic PE several years ago hates warfarin. Specifically he is inconvenienced by the laboratory monitoring and the food interactions that make his INR a nightmare to regulate. He had a major GI bleed when his INR was 11. His internist offered a choice between LMWH (enox injections, twice daily) or rivaroxaban, 20 mg po once daily. His wife preferred LMWH and he chose rivaroxaban. Two months later he is admitted with massive hematuria that developed while passing a kidney stone.

Question: Now what?
How do we reverse rivaroxaban without an antidote?
Does he need an IVC filter?
Real World Bleeding – The Dresden NOAC Registry
1776 patients followed

<table>
<thead>
<tr>
<th>Number (%)</th>
<th>Bleeding Events (1082 events in 762 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minor</td>
</tr>
<tr>
<td>Total in category</td>
<td>637 (59%)</td>
</tr>
<tr>
<td>Conservative Rx</td>
<td>637 (100%)</td>
</tr>
<tr>
<td>Surgery or intervention</td>
<td>0</td>
</tr>
<tr>
<td>RBC</td>
<td>0</td>
</tr>
<tr>
<td>FFP +/- PCC</td>
<td>0</td>
</tr>
</tbody>
</table>

Major Point: <<1% required “reversal” of anticoagulation
1 death from ICH

All cause mortality in patients hospitalized with OAC bleeding

<table>
<thead>
<tr>
<th></th>
<th>30 day</th>
<th>90 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban:</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>VKA:</td>
<td>7%</td>
<td>14%</td>
</tr>
</tbody>
</table>

General Principles of Management of Anticoagulant Bleeding

HASHTI

- Hold further doses of anticoagulant
- Consider Antidote if available
- Supportive care (volume resuscitation, inotropes if needed)
- Local or surgical Hemostatic measures
- Transfusion support if needed
- Investigate for a bleeding source

Management of Bleeding in Patients on Anticoagulants without Antidotes

Risk stratification

Minor bleeding
- Local hemostatic measures
- Consider anticoagulant withdrawal (balance thrombotic and bleeding risks)

Moderate bleeding
- General measures
  - Anticoagulant withdrawal
  - Mechanical compression
  - Monitor hemodynamic status
  - Volume replacement
  - Definitive interventions
- Blood product transfusion
  - RBC transfusion for anemia
  - Plasma for coagulopathy (e.g., DIC, dilutional)
  - Consider platelets for patients on antiplatelet agents

Severe/life-threatening bleeding
- General measures and blood product transfusion as per moderate bleeding
  - Intensive care setting
  - Hemodynamic support
  - Consider:
    - 4-factor PCC (50 U/kg)*
    - Activated PCC (80 U/kg)**
- Adjunctive therapies
  - Oral charcoal for dabigatran ingestion within 2 hours
  - Hemodialysis for dabigatran removal
  - Desmopressin
  - Antifibrinolytic agents

Siegal et al., Blood 2014;123:1152-1158.
A 48 yo man on long term anticoagulation for a near-fatal idiopathic PE several years ago hates warfarin. Specifically he is inconvenienced by the laboratory monitoring and the food interactions that make his INR a nightmare to regulate. He had a major GI bleed when his INR was 11. His internist offered a choice between LMWH (enox injections, twice daily) or rivaroxaban, 20 mg po once daily. His wife preferred LMWH and he chose rivaroxaban. Two months later he is admitted with massive hematuria that developed while passing a kidney stone.

Solution:

Hold rivaroxaban
Supportive care
21st Century Treatment of VTE: Practical Considerations

- Patient selection direct oral anticoagulants
  - Correct dosing for indication
  - Ability to find, obtain and pay for the drug
  - Follow up is no less important than monitored drug
    - Admit unstable or marginal patients
    - Within a week for acute VTE

- There is still a role for heparin/warfarin
  - But decreasing…