Direct Oral Anticoagulants (DOACs)
Who Gets What?

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Disclosures

- No financial or commercial conflicts of interest

- No intended off-label recommendations
Major Reference
ACCP Consensus 2012


CHEST 2012; 141(2)(Suppl) February

Amended by more recent data and FDA approvals
Questions

• What are the differences between the newer oral anticoagulants (DOACs)?

• What are the indications for them?

• What is their role in AF, VTE, pregnancy, and perioperative care?

• What are the data with respect to number needed to treat, number needed to harm? What about irreversibility?
What are the differences between the DOACs?
Anticoagulant Mechanisms of Action

## New Oral Anticoagulants: Pharmacological Properties

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Dabigatran Etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>6.5%</td>
<td>66-80%</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>Better in acidic</td>
<td>Slightly delayed by food</td>
<td>Not affected by food</td>
</tr>
<tr>
<td></td>
<td>environment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(tartaric acid added)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sl delayed high-fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>1.25-3 h</td>
<td>0.5-4 h</td>
<td>0.5-3 h</td>
</tr>
<tr>
<td>Half-Life</td>
<td>7-17 h</td>
<td>3.2-11 h</td>
<td>8-15 h</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Converted to active</td>
<td>Metabolized by CYP3A4 (18%)</td>
<td>Metabolized by CYP3A4 and</td>
</tr>
<tr>
<td></td>
<td>drug</td>
<td>and CYP212 (14%)</td>
<td>CYP3A4 and 1A</td>
</tr>
<tr>
<td></td>
<td>by esterases in plasma or liver</td>
<td></td>
<td>1/2</td>
</tr>
<tr>
<td>Elimination</td>
<td>80% renal</td>
<td>66% renal</td>
<td>28% renal</td>
</tr>
</tbody>
</table>

Basic Features

• Oral administration
  • No clinically significant differences whether taken with or without food
    • More absorption without food for rivaroxaban at full doses
    • Tartaric acid moiety in dabigatran may create relatively more GI upset
  • Absorbed in the stomach and small intestine
    • Case reports document no apparent difference in bariatric surgery patients but limited data

• Fixed doses
  • No dietary or vitamin K concerns
  • Fewer medication interactions (vs. warfarin)
    • Rivaroxaban trials excluded more patients for other meds
## Dosing: Varies by Indication, Renal Function

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dabigatran Etezilate (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ortho surgery</td>
<td></td>
<td>10 mg/dy</td>
<td>2.5 mg/dy</td>
</tr>
<tr>
<td>↓ renal fctn (GFR)</td>
<td></td>
<td>Avoid if CrCl&lt;30</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>150 mg bid</td>
<td>20 mg/dy</td>
<td>5 mg bid</td>
</tr>
<tr>
<td>↓ renal fctn (GFR)</td>
<td>CrCl 15-30: 75 mg bid</td>
<td>CrCl 15-30:</td>
<td>15 mg/dy</td>
</tr>
<tr>
<td>Acute VTE</td>
<td>150 mg bid after 5-10 dys LMWH</td>
<td>15 mg bid x</td>
<td>10 mg bid x 7 dys</td>
</tr>
<tr>
<td>“Treatment” VTE</td>
<td></td>
<td>5 mg bid</td>
<td></td>
</tr>
<tr>
<td>Reduce risk of recurrence</td>
<td>150 mg bid</td>
<td>20 mg/day</td>
<td>2.5 mg bid</td>
</tr>
</tbody>
</table>
What are the indications for DOACs?
<table>
<thead>
<tr>
<th>Indication</th>
<th>Dabigatran Etexilate (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ortho surgery</td>
<td></td>
<td>10 mg/dy</td>
<td>2.5 mg/dy</td>
</tr>
<tr>
<td>↓ renal fcn (GFR)</td>
<td></td>
<td>Avoid if CrCl&lt;30</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>150 mg bid</td>
<td>20 mg/dy</td>
<td>5 mg bid</td>
</tr>
<tr>
<td>↓ renal fcn (GFR)</td>
<td>CrCl 15-30: 75 mg bid</td>
<td>CrCl 15-30: 15 mg/dy</td>
<td></td>
</tr>
<tr>
<td>Acute VTE</td>
<td>150 mg bid after 5-10 dys</td>
<td>15 mg bid</td>
<td>10 mg bid</td>
</tr>
<tr>
<td>“Treatment” VTE</td>
<td>15 mg bid 21 dys</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Reduce risk of recurrence</td>
<td>150 mg bid</td>
<td>20 mg/day</td>
<td>2.5 mg bid</td>
</tr>
</tbody>
</table>
DOACs: Not for Use in Some Populations (Yet)

- Pregnancy: animal studies and human placental models demonstrate new oral anticoagulants cross the placenta
  - Not advised in pregnancy

- Breast feeding: intact drug is found in breast milk in animal studies
  - Not advised for women who are breast-feeding

- Chronic kidney disease: apixaban an option

- Patients on interacting medication
  - Some HIV meds, seizure meds, some anti-arrhythmia meds
DOACs: Potential Medication Interactions

- Could have increased or decreased anticoag effect
- May be exacerbated with mild renal insufficiency

Table 2: Concomitant use with agents affecting cytochrome P450 3A4 and P-glycoprotein pathways.

<table>
<thead>
<tr>
<th>Effect on rivaroxaban plasma concentration</th>
<th>Strong inhibitors of both CYP3A4 and P-gp</th>
<th>Moderate to strong CYP3A4 and/or P-gp inhibitors</th>
<th>Strong inducers of CYP3A4</th>
<th>Substrates of CYP3A4 and/or P-gp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on rivaroxaban plasma concentration</td>
<td>Increase rivaroxaban plasma concentration</td>
<td>Increase plasma concentrations but the effect is not clinically relevant</td>
<td>Decrease rivaroxaban plasma concentration</td>
<td>No clinically relevant effect on rivaroxaban plasma concentration</td>
</tr>
</tbody>
</table>

**Drugs**

- HIV protease inhibitors
- Azole-antimycotics (Ketoconazole, Itraconazole, Voriconazole, Posaconazole)
- Fluconazole
- Erythromycin
- Clarithromycin
- Amiodarone
- Verapamil
- Rifaximin
- Phenobarbital
- Phenytoin
- Carbamazepine
- St John’s wort
- Digoxin
- Atorvastatin
- Midazolam

**Recommendation**

- Not recommended
- Permitted Use with caution in patients with renal impairment and increased risk of bleeding
- Permitted Use with caution
- Permitted

*Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided. CYP, cytochrome P450; P-gp, P-glycoprotein.
Cancer: DOACs Not Yet Indicated

- In patients with DVT or PE, and cancer, per ACCP:
  - LMWH over VKA

  CLOT study

  Lee, NEJM 349:146, 2003

- If not treated with LMWH, recommend VKA over rivaroxaban or dabigatran ("too few patients")

Kearon, Chest 141:e419S, 2012
What is the role of DOACs?

Atrial Fibrillation
ACCP 2012 Guidelines for A Fib

### CHADS\textsubscript{2} Score

One point each for:
- CHF
- Hypertension
- Age ≥75
- Diabetes mellitus
- Stroke/TIA history (2 pts)

<table>
<thead>
<tr>
<th>Score</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Nothing or ASA 75-325 mg</td>
</tr>
<tr>
<td>≥1</td>
<td>Oral anticoagulant (OAC) or ASA+clopidogrel (if not OAC candidate)</td>
</tr>
</tbody>
</table>

If OAC: favor dabigatran over warfarin

*Rivaroxaban or apixaban also?*

DOACs and Atrial Fibrillation
Pivotal Trial Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (n=18,113)</th>
<th>Rivaroxaban (n=14,264)</th>
<th>Apixaban (n=18,206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>71</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td>Renal fctn (CrCl, ml/min)</td>
<td>NR</td>
<td>Mean 67</td>
<td>16% 25-50</td>
</tr>
<tr>
<td>Mean CHADS2</td>
<td>2.1</td>
<td>3.47</td>
<td>2.3</td>
</tr>
<tr>
<td>ASA Use</td>
<td>39%</td>
<td>35%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Patients with valvular heart disease and artificial valves excluded

DOACs and A Fib
Primary Endpoint: Stroke, Systemtic Emb

**Table:**

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1.11</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2.1</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.27</td>
</tr>
</tbody>
</table>

* * p≤.01

DOACs and AF: Major Bleeding

Major Bleeding (%) - DOAC vs. Warfarin

- Dabigatran: 2.71%
- Rivaroxaban: 3.6%
- Apixaban: 2.18%

* p < .001

References:
DOACs and AF: Intracranial Bleed

ICH (%)

Dabigatran 0.3
Rivaroxaban 0.5
Apixaban 0.33

Warfarin

Dabigatran 0.74
Rivaroxaban 0.7
Apixaban 0.8

*p < .02

DOACs for A Fib: “Opt In”

- Generally an elderly population
- No valvular heart disease or artificial valves
- When to consider DOAC instead of warfarin:
  - Good renal function without co-morbidities likely to lead to unrecognized decreases in renal function
  - No interacting meds
    - If on meds with potential interaction, watch out for effects of reduced renal function, poorer clearance with age
  - Remembers their medication
    - Once-daily may be better than twice daily
- Limited concern for bleeding
- Variable INRs (but not from poor adherence)
What is the role of DOACs?

Venous Thromboembolism?
VTE Management

- LMWH + Warfarin

vs.

DOAC
Management of VTE: ACCP 2012

- **Acute Management:** active anticoagulation
  - Subcutaneous LMWH
  - Intravenous or subcutaneous UFH
  - Fondaparinux
  - *Rivaroxaban or apixaban*

- **Other Management Considerations**
  - Initiation of VKA (warfarin) on first day *(if not using rivaroxaban or apixaban)*
  - Continue LMWH/UFH until INR stable and $\geq 2.0$ for at least 24 hours
  - Treatment with LMWH/UFH for at least 5 days

ACCP 2012 Guidelines

In patients with DVT or PE, and no cancer, prefer:
- Vitamin K antagonist (VKA, e.g. warfarin) over LMWH
- If not treated with VKA, recommend LMWH over rivaroxaban or dabigatran

In patients with DVT or PE, and cancer, prefer:
- LMWH over VKA
- If not treated with LMWH, recommend VKA over rivaroxaban or dabigatran

Authors note single study for each new agent, few cancer patients (3-5%)

Kearon, Chest 141:e419S, 2012
## DOACs and VTE
### Pivotal Trial Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (n=2564)</th>
<th>Rivaroxaban DVT (n=3445)</th>
<th>Rivaroxaban PE (n=4817)</th>
<th>Apixaban (n=5395)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>55</td>
<td>55</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>Weight</td>
<td>Mean 85 kg (38-175)</td>
<td>14% &gt;100 kg</td>
<td>14% &gt;100 kg</td>
<td>19% &gt;100 kg</td>
</tr>
<tr>
<td>CrCl</td>
<td>30-50 ml/min</td>
<td>4.7%</td>
<td>6.8%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Hx prior clot</td>
<td>25%</td>
<td>19%</td>
<td>19%</td>
<td>16%</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>NR</td>
<td>7%</td>
<td>5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Isolated PE</td>
<td>21%</td>
<td>0.6%</td>
<td>75.2%</td>
<td>25.2%</td>
</tr>
<tr>
<td>Unprovoked</td>
<td>NR</td>
<td>62%</td>
<td>64%</td>
<td>90%</td>
</tr>
</tbody>
</table>

DOAC and VTE: Primary Endpoint Recurrent VTE

<table>
<thead>
<tr>
<th>Drug</th>
<th>DOAC (Recurrence)</th>
<th>Warfarin (Recurrence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>2.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Rivaroxaban DVT</td>
<td>2.1</td>
<td>3</td>
</tr>
<tr>
<td>Rivaroxaban PE</td>
<td>2.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Apixaban</td>
<td>2.3</td>
<td>2.7</td>
</tr>
</tbody>
</table>

DOACs and VTE
Major Bleeding

- **Dabigatran**: 1.6, 1.9
- **Rivaroxaban DVT**: 0.8, 1.2
- **Rivaroxaban PE**: 1.1, 2.2
- **Apixaban**: 0.6, 1.8


* * * p<.003
DOACs and VTE
“Clinically Relevant” or “All” Bleeding

<table>
<thead>
<tr>
<th>Drug</th>
<th>DOAC</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>5.6</td>
<td>8.8</td>
</tr>
<tr>
<td>Rivaroxaban DVT</td>
<td>8.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Rivaroxaban PE</td>
<td>10.3</td>
<td>11.4</td>
</tr>
<tr>
<td>Apixaban</td>
<td>4.3</td>
<td>9.8</td>
</tr>
</tbody>
</table>

*p<.003

DOACs for VTE: “Opt out”

- Often a younger, somewhat healthier population
- Non-inferior therapy, as safe or safer than current standard therapy
- Why NOT a DOAC?
  - As for a fib, consider renal function, interacting medications, concern about bleeding
  - Patient and provider comfortable uncomfortable without monitoring
    - Persistent or new symptoms, new clot – missed doses?
  - Concern about adherence
What is the role of DOACs?

Perioperative Management
THA, TKA or Hip Fracture Surgery

- Minimum 10-14 days, one of the following:
  - Heparin/LMWH, fondaparinux
  - Warfarin; for THA/TKA also apixaban, dabigatran, rivaroxaban
  - Aspirin (no dose specified)
  - IPC Device – at least 18 hours/day

- Use of LMWH + mechanical over ASA, warfarin (or new agents for THA/TKA)
  - Cite lack of longer-term safety data for new agents

- Both mechanical and pharmacologic while admitted

- Extended prophylaxis for 35 days
  - Use of new oral agents only if resistance to s.q.

DOACs and Ortho Prophylaxis
Pivotal Trial Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban TKA (n=2531)</th>
<th>Rivaroxaban THA (n=4541)</th>
<th>Apixaban TKA (n=3057)</th>
<th>Apixaban THA (n=5395)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>67</td>
<td>63</td>
<td>67</td>
<td>60</td>
</tr>
<tr>
<td>Mean Weight</td>
<td>80 kg (up to 150)</td>
<td>78 kg (up to 179)</td>
<td>78 kg</td>
<td>79 kg (up to 180)</td>
</tr>
<tr>
<td>Renal fctn (CrCl, ml/min)</td>
<td>Mean 105</td>
<td>7.5% 30-50</td>
<td>Mean 127</td>
<td>12% &lt; 60</td>
</tr>
</tbody>
</table>

DOAC started 12 hrs post-op
Enoxaparin (40 mg/day) started 12 hrs pre-op

**Rivaroxaban vs. Enoxaparin**

### TKA

- **VTE or Death**
  - Rivaroxaban: 18.9%
  - Enoxaparin: 9.6%
  - *p<0.01*

- **Clinical VTE**
  - Rivaroxaban: 2.6%
  - Enoxaparin: 1.0%
  - *p<0.01*

- **Any bleed**
  - Rivaroxaban: 4.9%
  - Enoxaparin: 4.8%

- **Major bleed**
  - Rivaroxaban: 0.6%
  - Enoxaparin: 0.5%

### THA

- **VTE or Death**
  - Rivaroxaban: 6.0%
  - Enoxaparin: 0.3%
  - *p<0.001*

- **Clinical VTE**
  - Rivaroxaban: 3.7%
  - Enoxaparin: 0.5%

- **Any bleed**
  - Rivaroxaban: 6.0%
  - Enoxaparin: 5.9%

- **Major bleed**
  - Rivaroxaban: 0.3%
  - Enoxaparin: 0.1%

**Most events venographic calf DVT**


Apixaban vs. Enoxaparin

### TKA

- **VTE or Death**: Apixaban 15, Enoxaparin 24
- **Clinical VTE**: Apixaban 1.1, Enoxaparin 2.17
- **Any bleed**: Apixaban 6.9, Enoxaparin 8.4
- **Major bleed**: Apixaban 0.6, Enoxaparin 0.9

*\( p < 0.01 \) (*)

### THA

- **VTE or Death**: Apixaban 1.4, Enoxaparin 11.7
- **Clinical VTE**: Apixaban 0.1, Enoxaparin 0.4
- **Any bleed**: Apixaban 11.7, Enoxaparin 12.6
- **Major bleed**: Apixaban 0.8, Enoxaparin 0.7

*\( p < 0.001 \) (*)

Most events venographic calf DVT; very few PE, none fatal


Lassen, *NEJM* 363:2487, 2010
Ortho Prophylaxis
Perspective and Controversy

- Clinical VTE
  - Low # of events
  - Few fatalities
- Clinical bleeding
  - More common
  - Few fatalities

Chan, *J Thromb Thrombolysis* online pub 11/2014
DOACs for Ortho Surgery: ??

- Hematologist’s view
  - Better protection, cheaper
  - Both LMWH and new agents are irreversible
  - Similar bleeding, although more surgical site bleeding with DOACs

- Depends on the orthopedist
  - If they’re OK with LMWH, then they should be OK with DOACs
  - If they use warfarin or ASA, bleeding will be higher with DOACs (but data suggest so will clotting…)}
DOACs as “Bridging Agents”

- NO data for use of DOACs instead of LMWH for bridging off and back onto warfarin
- Variable effect on INR
  - Difficult to assess effect of warfarin vs. DOAC in the post-op setting

What are the data with respect to NNT/NNH?

After all, they’re irreversible...
### DOACs and AF: Thromboembolism/Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>All cause stroke/embolism</th>
<th>Ischemic/unspecified stroke</th>
<th>Hemorrhagic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCKET AF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>( \chi^2 = 55.9, p = 0.104 )</td>
<td>( \chi^2 = 0.0, p = 0.522 )</td>
<td>( \chi^2 = 52.2, p = 0.124 )</td>
</tr>
</tbody>
</table>

DOACs and AF: Bleeding

NNT for DOACs vs. Warfarin

- Atrial Fibrillation
  - To avoid one hemorrhagic stroke, need to treat 153 (RR 0.43, 95% CI 0.34-0.55)
  - No difference in extracranial major bleeding
  - To save one life from any cause of death, need to treat 43 (RR 0.90, 95% CI 0.84-0.96)
  - No difference in MI
- No NNH calculable

DOACs for VTE: One Meta-analysis

Kakkos, Eur J Vasc Endovasc Surg 48:565, 2014

Symptomatic VTE

DVT
**DOACs for VTE: One Meta-analysis**


<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAs Events</th>
<th>NOAs Total</th>
<th>VKAs Events</th>
<th>VKAs Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER</td>
<td>1 1274</td>
<td>3 1265</td>
<td>30.1%</td>
<td>0.33 [0.03, 3.18] 2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>1 1731</td>
<td>0 1718</td>
<td>5.0%</td>
<td>2.80 [0.12, 73.04] 2010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>2 2419</td>
<td>1 2413</td>
<td>10.0%</td>
<td>2.00 [0.18, 21.99] 2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>1 2891</td>
<td>2 2704</td>
<td>19.9%</td>
<td>0.50 [0.05, 5.54] 2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td>4 4118</td>
<td>3 4122</td>
<td>30.0%</td>
<td>1.33 [0.30, 5.96] 2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>3 1279</td>
<td>0 1289</td>
<td>5.0%</td>
<td>7.05 [0.96, 53.64] 2014</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- **NOAs Events**: 13512
- **NOAs Total**: 13511
- **VKAs Weight**: 100.0%
- **Risk Ratio**: 1.39 [0.57, 2.96] 2014

**Total events**: 139

- **Heterogeneity**: Chi² = 3.64, df = 5 (P = 0.60); I² = 0%

**Test for overall effect**: Z = 0.62 (P = 0.53)

---

**Fatal PE**

---

**Non-fatal PE**

---
DOACs for VTE: One Meta-analysis

Kakkos, Eur J Vasc Endovasc Surg 48:565, 2014

- Major bleeding

- Clinically relevant non-major bleeding
DOACs for VTE: One Meta-analysis

Kakkos, Eur J Vasc Endovasc Surg 48:565, 2014

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAs Events</th>
<th>NOAs Total</th>
<th>VKAs Events</th>
<th>VKAs Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER</td>
<td>21</td>
<td>1274</td>
<td>21</td>
<td>1265</td>
<td>6.5%</td>
<td>0.99 [0.56, 1.81] 2009</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>38</td>
<td>1710</td>
<td>48</td>
<td>1711</td>
<td>15.2%</td>
<td>0.77 [0.51, 1.17] 2010</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>58</td>
<td>2412</td>
<td>60</td>
<td>2405</td>
<td>15.5%</td>
<td>1.16 [0.80, 1.68] 2012</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>41</td>
<td>2678</td>
<td>52</td>
<td>2889</td>
<td>18.1%</td>
<td>0.79 [0.53, 1.20] 2013</td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td>132</td>
<td>4118</td>
<td>126</td>
<td>4122</td>
<td>39.0%</td>
<td>1.05 [0.82, 1.33] 2013</td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>25</td>
<td>1280</td>
<td>25</td>
<td>1288</td>
<td>7.7%</td>
<td>1.01 [0.58, 1.84] 2014</td>
</tr>
</tbody>
</table>

Total (95% CI) 13478 13480 100.0% 0.98 [0.84, 1.14]

Total events 315 323

Heterogeneity: Ch² = 3.37, df = 5 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.75)

---

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAs Events</th>
<th>NOAs Total</th>
<th>VKAs Events</th>
<th>VKAs Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER</td>
<td>1</td>
<td>1274</td>
<td>1</td>
<td>1265</td>
<td>4.1%</td>
<td>0.99 [0.06, 15.86] 2009</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>2</td>
<td>1710</td>
<td>5</td>
<td>1711</td>
<td>20.4%</td>
<td>0.40 [0.08, 2.05] 2010</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>5</td>
<td>2412</td>
<td>4</td>
<td>2405</td>
<td>16.3%</td>
<td>1.25 [0.34, 4.64] 2012</td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td>2</td>
<td>4118</td>
<td>10</td>
<td>4122</td>
<td>40.8%</td>
<td>0.20 [0.04, 0.91] 2013</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>2</td>
<td>2678</td>
<td>3</td>
<td>2889</td>
<td>12.2%</td>
<td>0.67 [0.11, 4.01] 2013</td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>0</td>
<td>1280</td>
<td>1</td>
<td>1288</td>
<td>6.1%</td>
<td>0.34 [0.01, 0.63] 2014</td>
</tr>
</tbody>
</table>

Total (95% CI) 13478 13480 100.0% 0.51 [0.26, 1.01]

Total events 12 24

Heterogeneity: Ch² = 3.70, df = 5 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.94 (P = 0.05)

All-cause mortality

Fatal bleeding
DOACs for VTE: One Meta-analysis

Kakkos, Eur J Vasc Endovasc Surg 48:565, 2014

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAs Events</th>
<th>Total</th>
<th>VKAs Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER</td>
<td>50 1274</td>
<td></td>
<td>51 1265</td>
<td></td>
<td>9.8%</td>
<td>0.97 [0.68, 1.43] 2009</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>51 1731</td>
<td></td>
<td>73 1718</td>
<td></td>
<td>13.7%</td>
<td>0.69 [0.49, 0.99] 2010</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>83 2419</td>
<td></td>
<td>95 2413</td>
<td></td>
<td>18.0%</td>
<td>0.88 [0.65, 1.15] 2012</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>74 2576</td>
<td></td>
<td>120 2689</td>
<td></td>
<td>22.4%</td>
<td>0.62 [0.47, 0.82] 2013</td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td>120 4118</td>
<td></td>
<td>144 4122</td>
<td></td>
<td>27.0%</td>
<td>0.83 [0.66, 1.06] 2013</td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>45 1279</td>
<td></td>
<td>50 1289</td>
<td></td>
<td>9.3%</td>
<td>0.91 [0.81, 1.05] 2014</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>13497</td>
<td></td>
<td>13498</td>
<td></td>
<td>100.0%</td>
<td>0.79 [0.70, 0.90]</td>
</tr>
</tbody>
</table>

Total events: 423 NOAs, 534 VKAs
Heterogeneity: Chi² = 5.49, df = 5 (P = 0.38); I² = 9%
Test for overall effect: Z = 3.65 (P = 0.0003)

Net benefit
NNT for DOACs vs. Warfarin

- VTE treatment
  - To avoid one major bleed, need to treat 149-155 (RR 0.60-0.63)
  - To avoid one fatal bleed, need to treat 1111 (RR 0.36-0.51)
  - Absolute risk of dying from bleeding goes from 1.8/1000 to 0.9/1000
- No NNH calculable

_Eur JVasc Endovasc Surg_ 48:565, 2014;
Ortho Prophylaxis and Rivaroxaban NNT/NNH

Table 3 Kaplan–Meier event rates, rate difference, number needed to treat/number needed to harm, and net clinical benefit for total hip arthroplasty (RECORD1 and RECORD2) and total knee arthroplasty (RECORD3 and RECORD4) patients

<table>
<thead>
<tr>
<th>End point</th>
<th>Events per 10,000 patients</th>
<th>Rate difference (per 10,000 patients)</th>
<th>NNT or NNH</th>
<th>Net clinical benefit (sum of rate differences)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>Enoxaparin</td>
<td>(rivaroxaban – enoxaparin)</td>
<td>n</td>
</tr>
<tr>
<td>RECORD1\textsuperscript{11} and RECORD2\textsuperscript{12} (day 70) – total hip arthroplasty</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic VTE plus all-cause mortality</td>
<td>46</td>
<td>84</td>
<td>-38</td>
<td>-82 to 6</td>
</tr>
<tr>
<td>Nonfatal major bleeding</td>
<td>18</td>
<td>12</td>
<td>6</td>
<td>-15 to 26</td>
</tr>
<tr>
<td>RECORD3\textsuperscript{13} and RECORD4\textsuperscript{14} day 47) – total knee arthroplasty</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic VTE plus all-cause mortality</td>
<td>121</td>
<td>219</td>
<td>-98</td>
<td>-169 to -27</td>
</tr>
<tr>
<td>Nonfatal major bleeding</td>
<td>71</td>
<td>48</td>
<td>23</td>
<td>-19 to 64</td>
</tr>
</tbody>
</table>

NNT is 4-6x lower than NNH; comparator NOT placebo

Levitan Vasc Health Risk Manag 10:157, 2014
DOACs, Bleeding and Reversibility

- Bleeding is often fatal because the hole is too big or there are too many of them
  - no matter what drug is in the system

- No increase (actually, sometimes less) fatal bleeding in all studies for those on DOACs as compared to warfarin
  - Over 25,000 people exposed for up to two years and/or in a post-op setting
  - Large groups were 70-75 years old and 35% were also on ASA

Eerenberg, *Circulation* 124:1508, 2011
DOACs, Bleeding and Reversibility

- Primary focus: address the bleeding
- Efforts to address the drug
  - No benefit to FFP, vitamin K
  - Decrease quantity of drug
    - Activated charcoal if thought to still be in stomach
    - Dabigatran may be dialyzed
- Bypass the drug effect
  - Prothrombin complex (PCC), factor VIIa concentrates anecdotally used – no controlled trials
  - Recent study suggested aPCC may work best for anti-Xa (rivaroxaban, apixaban) but not anti-thrombin (dabigatran)

Eerenberg, *Circulation* 124:1508, 2011
4-Factor PCC: FDA Approved for Major Bleeding with Warfarin

- Kcentra (US) / Beriplex (Europe)
  - Approved for major bleeding with warfarin
  - Dosing guide per package insert:

<table>
<thead>
<tr>
<th>Table 1: Dosing Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-treatment INR</strong></td>
</tr>
<tr>
<td>2 – &lt; 4</td>
</tr>
<tr>
<td>4 – 6</td>
</tr>
<tr>
<td>&gt; 6</td>
</tr>
<tr>
<td><strong>Dose</strong> of Kcentra (units of Factor IX) / kg body weight</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>35</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td><strong>Maximum dose</strong> (units of Factor IX)</td>
</tr>
<tr>
<td>Not to exceed 2500</td>
</tr>
<tr>
<td>Not to exceed 3500</td>
</tr>
<tr>
<td>Not to exceed 5000</td>
</tr>
</tbody>
</table>

- Studies excluded patients with hx of arterial clot within last 3 months, APS, HIT, PC/PS/AT def
- No mortality benefit, ?increased risk of thrombosis

Questions – Some Answers

• What are the differences between the newer oral anticoagulants (DOACs)?
  Dosing/half-life, renal clearance, reversal strategy?

• What are the indications for them?
  A fib, VTE, ortho prophylaxis

• What is their role in AF, VTE, pregnancy, and perioperative care? (ortho proph, but not bridging)
  As safe/effective if used in the right person

• What are the data with respect to number needed to treat, number needed to harm?
  NNT <<< NNH; no clear impact of irreversibility
(Additional) Questions?