Anticoagulation Therapy in 2019: Exploring Beyond Warfarin

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To enter the Q&A and polling questions for this activity, go to ascp.com/qa and click on the title of this activity, as seen below.
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Cardiology, FASCP

- Professor-Midwestern University in Glendale, AZ
- Ambulatory Care Pharmacist-Cardiac Solutions

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Disclosure – Dr. Pogge and Dr. Sibicky

We have no actual or potential conflicts of interest to disclose.

Learning Objectives

At the conclusion of this knowledge-based activity, the participant will be able to:

- **Compare and contrast indications for direct oral anticoagulants, emphasizing recent indication expansions**
- Discuss the use of direct oral anticoagulants in elderly individuals taking into account co-morbid disease states
- Describe current strategies to prevent and treat bleeding in patients on direct oral anticoagulants
- Identify anticoagulation resources that can be utilized in current practice
Audience Polling

What is your favorite direct oral anticoagulant to recommend for elderly patients (≥ 65 years of age)?

A. Dabigatran
B. Rivaroxaban
C. Apixaban
D. Edoxaban

The History of Direct Oral Anticoagulants (DOACs)

Abbreviations:
AF = atrial fibrillation
FDA = food and drug administration
VTE = venous thromboembolism
PAD = peripheral artery disease
CAD = coronary artery disease
Red agents are reversal agents

Drug approvals and databases. 2019. Available at:
https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases
### Summary of DOACs Based on Indication

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Apixaban (Eliquis®)</th>
<th>Edoxaban (Savaysa®)</th>
<th>Betrixaban (Bevyxxa®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose in atrial fibrillation</strong></td>
<td>150 mg twice a day with or without food</td>
<td>20 mg once daily with a large meal (food ↑ bioavailability)</td>
<td>5 mg twice daily with or without food</td>
<td>60 mg once daily with or without food</td>
<td>Not FDA-approved</td>
</tr>
<tr>
<td><strong>Dose adjustments in atrial fibrillation</strong></td>
<td>CrCl 15-30 mL/min*: 75 mg twice daily</td>
<td>CrCl 15-50 mL/min*: 15 mg once daily with food</td>
<td>Dose reduction of 2.5 mg twice daily if 2 or more of the following: Age ≥ 80 yrs, Wt ≤ 60 kg, SCr ≥ 1.5 mg/dL</td>
<td>Not recommended if CrCl &gt; 95 mL/min; CrCl 15 to 50 mL/min*: 30 mg once daily</td>
<td>Not FDA-approved (For VTE prophylaxis: CrCl 15 to 30 mL/min: 80 mg X 1, then 40 mg daily)</td>
</tr>
<tr>
<td><strong>Dose in VTE treatment</strong></td>
<td>150 mg twice daily after 5-10 days of parenteral anticoagulant</td>
<td>15 mg every 12 hours for 21 days then 20 mg daily</td>
<td>10 mg twice daily for 7 days then 5 mg twice daily</td>
<td>60 mg once daily after 5-10 days of parenteral anticoagulant Wt ≤ 60 kg: 30 mg once daily</td>
<td>Not FDA-approved</td>
</tr>
<tr>
<td><strong>Dose in VTE prophylaxis</strong></td>
<td>150 mg twice daily</td>
<td>10 mg daily</td>
<td>2.5 mg twice daily</td>
<td>Not FDA approved</td>
<td>160 mg X 1; then 80 mg daily (see above)</td>
</tr>
<tr>
<td><strong>Dose in CAD/PAD</strong></td>
<td>Not FDA approved</td>
<td>2.5 mg twice daily</td>
<td>Not FDA approved</td>
<td>Not FDA approved</td>
<td>Not FDA-approved</td>
</tr>
</tbody>
</table>

* Patients with a CrCl < 30 ml/min were excluded from clinical trials

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### How are we going to keep all these doses straight?!?!?!
Assessing Stroke Risk in Atrial Fibrillation

**Table 1: CHA₂DS₂-VASc Condition Points**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure or LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension; (diagnosis regardless of BP)</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke or TIA or thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (Defined as prior MI, PAD, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex Category (female gender)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 2: Risk Factors, CHA₂DS₂-VASc Score, Recommended Treatment**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>CHA₂DS₂-VASc Score</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF plus 2 or more non gender risk factor</td>
<td>≥ 2 in men</td>
<td>Anticoagulation strongly recommended</td>
</tr>
<tr>
<td></td>
<td>≥ 3 in women</td>
<td></td>
</tr>
<tr>
<td>AF plus 1 or more non gender risk factor</td>
<td>1 in men</td>
<td>Anticoagulation is preferred</td>
</tr>
<tr>
<td></td>
<td>2 in women</td>
<td>ASA monotherapy or no antithrombotic therapy may be considered</td>
</tr>
<tr>
<td>AF plus 0 non gender risk factors</td>
<td>0 in men</td>
<td>No antithrombotic therapy preferred</td>
</tr>
<tr>
<td></td>
<td>1 in women</td>
<td></td>
</tr>
</tbody>
</table>

↑ Score = ↑ Risk

**What is NEW with DOACs?**

- Expanded indications
  - Low dose DOACs for extended VTE treatment
  - Chronic stable coronary artery disease/periarterial artery disease (CAD/PAD)

- Special populations
  - Cancer
  - Renal dysfunction
DOACs in Extended VTE Treatment

• Extended VTE treatment = ~3 months to indefinite
• Patient population of interest is unprovoked FIRST VTE
  • CHEST 2016 guidelines recommend long term anticoagulation in those with low-moderate risk of bleeding
  • Older adults may have a high risk of bleeding which would favor no extended anticoagulation therapy
• Traditionally, anticoagulation is continued at the treatment dose

—

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparator 1</th>
<th>Comparator 2</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EINSTEIN-CHOICE</td>
<td>Rivaroxaban 10 mg daily*</td>
<td>Aspirin 100 mg daily</td>
<td>Lower rates of recurrent nonfatal or fatal VTE with no difference in bleeding rates</td>
</tr>
<tr>
<td>AMPLIFY-EXT</td>
<td>Apixaban 2.5 mg twice daily*</td>
<td>Placebo</td>
<td></td>
</tr>
</tbody>
</table>

*Application: Rivaroxaban 10 mg daily and apixaban 2.5 mg twice daily are FDA approved for extended VTE treatment after at least 6 months of therapeutic anticoagulation

• Limitations
  • Recurrent VTE and bleeding rates were low
  • Average age ~56-59 years

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Rivaroxaban in Chronic CAD/PAD

- Rivaroxaban + aspirin is approved to reduce the risk of major cardiovascular events in chronic CAD/PAD based on results of the COMPASS trial
- Rivaroxaban 2.5 mg twice daily + aspirin 100 mg daily vs aspirin 100 mg daily for 23 months
  - Lower rate of the primary outcome of CV death, stroke, or nonfatal myocardial infarction in the rivaroxaban group: NNT = 76
  - Lower rate of all cause mortality: NNT = 143
  - Bleeding was higher in the rivaroxaban group: NNH = 83
    - Mainly gastrointestinal bleeding

What about our geriatric patients who are at a higher risk of bleeding??

### Rivaroxaban in CAD/PAD: Geriatric Subgroup

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of patients</th>
<th>NNT</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 years</td>
<td>4334</td>
<td>48</td>
<td>500</td>
</tr>
<tr>
<td>&gt; 65 years</td>
<td>13,944</td>
<td>91</td>
<td>63</td>
</tr>
</tbody>
</table>

Application: Of those > 65 years, 91 patients would need to be treated for 23 months with rivaroxaban + ASA instead of ASA alone to prevent 1 CV death, stroke, or nonfatal MI while only 63 patients would need to be treated for 23 months for 1 patient to experience a bleeding event

Risk >>> Benefit
DOACs in Cancer-associated Thrombosis (CAT)

<table>
<thead>
<tr>
<th>CAT Prophylaxis in High Risk Patients (Khorana score ≥ 2)</th>
<th>CAT Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up: 6 months</td>
<td>All agents were given at the current FDA-approved VTE treatment dose</td>
</tr>
<tr>
<td>CASSINI: Rivaroxaban 10 mg daily vs. placebo</td>
<td>Average follow-up: 6 months</td>
</tr>
<tr>
<td>Results: No difference in VTE rates and similar major bleeding rates</td>
<td>Select-D: Rivaroxaban vs dalteparin</td>
</tr>
<tr>
<td></td>
<td>Results: ↓ rate of VTE, similar major bleeding rates, ↑ rates of non-major bleeding</td>
</tr>
<tr>
<td>ADAM VTE: Apixaban vs dalteparin</td>
<td>Results: ↓ rate of VTE and similar major bleeding rates</td>
</tr>
<tr>
<td>AVERT: Apixaban 2.5 mg twice daily vs. placebo</td>
<td>HOKUSAI CANCER: Edoxaban vs dalteparin</td>
</tr>
<tr>
<td>Results: ↓ rate of VTE and similar major bleeding rates</td>
<td>Results: No difference in VTE rates, ↑ major bleeding with edoxaban, similar rates of non-major bleeding</td>
</tr>
</tbody>
</table>

Bottom Line: Rivaroxaban, apixaban, or LMWH may be considered for VTE prophylaxis in high risk patients. LMWH is the standard of care for CAT. Edoxaban, rivaroxaban, and apixaban may be considered as alternatives; they may increase bleeding risk, particularly in GI cancers.


DOACs in Renal Dysfunction

- Patients with atrial fibrillation and renal dysfunction are at a increased risk of systemic embolic events and bleeding relative to those without chronic kidney disease
  - Stroke risk increases 7% with every 10 mL/min/1.73 m² decrease in eGFR

- Cockcroft-Gault was used to estimate creatinine clearance in all phase III clinical trials of DOAC
  - Utilized ACTUAL body weight

End Stage Renal Disease on Hemodialysis (HD)

- Initially pharmacokinetic data showed apixaban may be a safe alternative to warfarin
- Most recently, a retrospective cohort study came to the following conclusions (for patients with atrial fibrillation):
  - Apixaban 5 mg twice daily as compared to warfarin was associated with a lower incidence of stroke/SE, major bleeding, and death
  - Apixaban 2.5 mg twice daily as compared to warfarin was associated with a lower incidence of major bleeding but no difference in the rates of stroke/SE or death

**Bottom line:** Apixaban 2.5 mg twice daily should only be used in HD patients with atrial fibrillation if they are ≥ 80 years or weigh ≤ 60 kg

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**Poll:** Which of the following agents would be best to recommend for cancer associated thromboprophylaxis?

Poll: To access the polling questions, go to this link: ascp.com/qa and select the “Anticoagulation Therapy in 2019: Exploring Beyond Warfarin” activity, as seen below.
Self-Assessment Question

Which of the following agents would be best to recommend for cancer associated thromboprophylaxis?

A. Rivaroxaban 15 mg twice daily for 21 days then 20 mg once daily
B. Edoxaban 60 mg daily
C. Dabigatran 150 mg twice daily
D. **Apixaban 2.5 mg twice daily**

Learning Objectives

At the conclusion of this knowledge-based activity, the participant will be able to:

- Compare and contrast indications for direct oral anticoagulants, emphasizing recent indication expansions
- **Discuss the use of direct oral anticoagulants in elderly individuals taking into account co-morbid disease states**
- Describe current strategies to prevent and treat bleeding in patients on direct oral anticoagulants
- Identify anticoagulation resources that can be utilized in current practice
DOACs in the Elderly

• Elderly individuals are often underrepresented in clinical trials
• Bleeding risk is higher in elderly adults
• American Geriatrics Society/Beers Criteria 2019
  • Dabigatran and rivaroxaban are listed in the 2019 AGS/Beers Criteria to be used cautiously in those 75 years of age and older
  • Dabigatran has a lack of safety data in those with CrCl < 30 mL/min

DOACs for AF in the Elderly

• Among adults ≥ 75 years of age, randomized controlled trials have demonstrated that DOACs have a lower frequency of stroke/systemic embolism and a noninferior risk of major bleeding when compared to warfarin
  • Improved efficacy
  • Equivalent safety
• A recent retrospective observational study confirmed these findings in adults ≥ 80 years and observed that each agent may differ in their major bleeding rates
DOAC vs Warfarin in AF

Key Points
- All DOAC offer improved efficacy
- Apixaban was superior in all categories
- Major bleeding was similar with dabigatran
- Major bleeding was ↑ with rivaroxaban

DOACs for VTE in the Elderly

Results from VTE randomized controlled trial have shown that DOACs as compared to warfarin in those ≥ 75 years provide at least equal efficacy (possibly improved) as well as ↓ rates of major bleeding.
Inappropriate Dosing in the Elderly

- Overdosing and underdosing are common in elderly patients
- Underdosing has been seen more commonly in older adults (studies have shown up to 30%)
  - Underdosing may be more common with apixaban
  - Remember: only reduce the dose if patients have atrial fibrillation and meet 2 of the 3 criteria (age ≥ 80 years, weight ≤ 60 kg, SCr ≥ 1.5 mg/dL)
- For dabigatran and rivaroxaban, dose reduction should only be done if CrCl < 30 mL/min (dabigatran) or 15-50 mL/min (rivaroxaban)

DOAC Counseling Points

- Dabigatran is a prodrug given in an acidic core
  - Increased risk of GI upset
  - Must store in original container – NOT in pill boxes
  - Swallow whole, do not crush
- Rivaroxaban should be given with the largest meal of the day
  - This may NOT be the evening meal for all of our patients
  - Real world data suggests rivaroxaban is associated with a higher rate of GI bleeding
- Apixaban and rivaroxaban may be crushed for administration
Poll: In atrial fibrillation patients who are ≥ 75 years of age, DOACs are more effective than warfarin at preventing strokes/systemic embolism

**Poll:** To access the polling questions, go to this link: ascp.com/qa and select the “Anticoagulation Therapy in 2019: Exploring Beyond Warfarin” activity, as seen below.

Self-Assessment Question

In atrial fibrillation patients who are ≥ 75 years of age, DOACs are more effective than warfarin at preventing strokes/systemic embolism

A. **True**
B. False
Learning Objectives

At the conclusion of this knowledge-based activity, the participant will be able to:

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- Identify anticoagulation resources that can be utilized in current practice

Bleeding and Risk Factors

<table>
<thead>
<tr>
<th>NON-MODIFIABLE RISK FACTORS</th>
<th>MODIFIABLE RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age (linear increase over age 60)</td>
<td>• Alcohol use</td>
</tr>
<tr>
<td>• Sex (male, OR = 1.5)</td>
<td>• Anemia</td>
</tr>
<tr>
<td>• Race (African decent, OR = 4)</td>
<td>• Chronic steroid or NSAID therapy</td>
</tr>
<tr>
<td>• Renal or hepatic insufficiency (eGFR &lt; 30, OR = 2),</td>
<td>• Low body weight</td>
</tr>
<tr>
<td>• History of prior bleed</td>
<td>• Uncontrolled comorbidities (e.g., peptic ulcer disease, diabetes)</td>
</tr>
</tbody>
</table>

OR = odds ratio; eGFR = estimate glomerular filtration rate, NSAID = nonsteroidal anti-inflammatory drug
### HAS-BLED Bleeding Risk Score

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal function (on dialysis, transplant, SCr &gt; 2.6)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal liver function (cirrhosis, bilirubin &gt; 2X ULN, AST/ALT/ALP &gt; 3X ULN)</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs (unstable/high INRs, &lt; 60% time in therapeutic range)</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (&gt; 65 years old)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs (aspirin or NSAIDs) --OR-- alcohol use</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

**Maximum Score = 9**

<table>
<thead>
<tr>
<th>HAS-BLED Score</th>
<th>Bleeds per 100 patient years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>4</td>
<td>8.7</td>
</tr>
<tr>
<td>5-9</td>
<td>No data</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- Scr = serum creatinine, ULN = upper limit of normal, AST = aspartate aminotransferase, ALT = alanine aminotransferase, ALP = alkaline phosphatase, INR = international normalized ratio, NSAIDs = non-steroidal anti-inflammatory drugs

---

**ATRIA**

- 3 points each: anemia, severe renal disease (eGFR < 30 or HD)
- 2 points: age ≥ 75
- 1 point each: any prior hemorrhage, diagnosed hypertension

**Rate of Bleeding (Points)**

<table>
<thead>
<tr>
<th>Rate of Bleeding (Points)</th>
<th>Event Rate per 100 Patient Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0-3)</td>
<td>0.76</td>
</tr>
<tr>
<td>Intermediate (4)</td>
<td>2.62</td>
</tr>
<tr>
<td>High (5-10)</td>
<td>5.76</td>
</tr>
</tbody>
</table>

**ORBIT**

- 1 point: age ≥ 75, insufficient kidney function (eGFR < 60), treatment with an antiplatelet
- 2 points each: reduced Hgb or Hct or history of anemia, bleeding history

**Rate of Bleeding (Points)**

<table>
<thead>
<tr>
<th>Rate of Bleeding (Points)</th>
<th>Event Rate per 100 Patient Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0-2)</td>
<td>2.4</td>
</tr>
<tr>
<td>Intermediate (3)</td>
<td>4.7</td>
</tr>
<tr>
<td>High (4-7)</td>
<td>8.1</td>
</tr>
</tbody>
</table>
HEMORR2HAGES

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic or renal disease</td>
<td>1</td>
</tr>
<tr>
<td>Ethanol use disorder</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Older age (&gt; 75 years)</td>
<td>1</td>
</tr>
<tr>
<td>Reduced platelet count/function (includes aspirin therapy)</td>
<td>1</td>
</tr>
<tr>
<td>Re-bleeding risk (history of prior bleed)</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
</tr>
<tr>
<td>Genetic factors</td>
<td>1</td>
</tr>
<tr>
<td>Excessive fall risk</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>Risk of Major Bleed per 100 patient Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>5.3</td>
</tr>
<tr>
<td>3</td>
<td>8.4</td>
</tr>
<tr>
<td>4</td>
<td>10.4</td>
</tr>
<tr>
<td>≥ 5</td>
<td>12.3</td>
</tr>
</tbody>
</table>

Risk Reduction Strategies and Checklist

<table>
<thead>
<tr>
<th>Interval</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence</td>
<td>Each visit</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>Each visit</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Each visit</td>
</tr>
<tr>
<td>Side effects</td>
<td>Each visit</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Each visit</td>
</tr>
<tr>
<td>Blood sampling</td>
<td>6-months/yearly</td>
</tr>
<tr>
<td></td>
<td>X-monthly</td>
</tr>
<tr>
<td>Manage modifiable risk factors for bleeding</td>
<td>Each visit</td>
</tr>
<tr>
<td>Reassess if anticoagulant is appropriate</td>
<td>Each visit</td>
</tr>
</tbody>
</table>
Bleeding Severity and Assessment

<table>
<thead>
<tr>
<th>Amount or severity of bleed?</th>
<th>Last dose of medication?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location?</td>
<td>Intentional or unintentional overdose?</td>
</tr>
<tr>
<td>Actively bleeding?</td>
<td>History of renal or hepatic dysfunction?</td>
</tr>
<tr>
<td>Medications? (including anticoagulant, antiplatelets)</td>
<td>Comorbidities? (e.g., thrombocytopenia)</td>
</tr>
</tbody>
</table>

- Life-threatening or imminently fatal bleeding (e.g., massive GI bleed, intracranial, retroperitoneal)
- Minor bleeding (e.g., slow GI bleed, soft-tissue bleeding, epistaxis)

Consider DOAC Properties

<table>
<thead>
<tr>
<th></th>
<th>Half-life (Normal Renal/Hepatic Function)</th>
<th>Five Half-lives</th>
<th>Renal/Hepatic Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>12-17 hours</td>
<td>2.5-3.5 days</td>
<td>80-85% renal</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>5-9 hours</td>
<td>1-2 days</td>
<td>35% renal; accumulation possible in severe hepatic impairment</td>
</tr>
<tr>
<td>Apixaban</td>
<td>8-15 hours</td>
<td>1.5-3 days</td>
<td>25% renal; accumulation possible in severe hepatic impairment</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>6-11 hours</td>
<td>1.5-2 days</td>
<td>35% renal; accumulation possible in severe hepatic impairment</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>19-27 hours</td>
<td>4-5.5 days</td>
<td>11% renal; not recommended in hepatic impairment</td>
</tr>
</tbody>
</table>

Strategies for Minor Bleeding

- Observation
- Local measures (e.g., pressure)
- Anticoagulant discontinuation or interruption
- Potential antifibrinolytic agents (e.g., tranexamic acid, epsilon-aminocaproic acid)
  - Data is limited on use for DOAC-associated bleeding
  - Utility if other agents cannot be used due to bleeding risk or comorbidities
  - Usually available in an acute care setting, low cost, low risk of thrombosis

Available Strategies for Major Bleeding with DOACs

- Antidotes:
  - Idarucizumab for dabigatran
  - Andexanet alfa for factor Xa inhibitors
- Prothrombin complex concentrate (PCC)
- Antifibrinolytics
- Oral activated charcoal (if last dose ingested in previous 3 hours)
- There is a lack of data for use of fresh frozen plasma (FFP), desmopressin (DDAVP), or recombinant activated factor VII (rFVIIa)
Idarucizumab: Mechanism of Action

Idarucizumab: Dosing

- **Dose:**
  - 5 grams total: 2 x 2.5 gram IV infuse over 5-10 minutes no more than 15 minutes apart
  - If aPTT elevated or clinically relevant bleeding persists, can give additional 5 g dose
- **Adverse effects:** injection site reaction, headache, constipation, nausea
- **Cost:** ~$4,452 (2 x 2.5 g/50 mL vials)
Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD)

• Included patients who were older, median age 78 years (range 48-93)
• Separated into two groups: A (uncontrolled bleeding), B (undergoing surgical procedure)
• 100% reversal of anticoagulation based on ecarin clotting time and dilute thrombin time
• Thrombotic events occurred in 6.3% in Group A and 7.4% in Group B
• Mortality rate was 18.8% in Group A and 18.9% in Group B

Andexanet Alfa: Mechanism of Action
## Andexanent Alfa: Dosing

<table>
<thead>
<tr>
<th>Factor Xa inhibitor</th>
<th>Factor Xa inhibitor last dose</th>
<th>Timing of Last Dose of Factor Xa inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>≤ 5 mg</td>
<td>Low dose</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 mg or unknown</td>
<td>High dose</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>≤ 10 mg</td>
<td>Low dose</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 mg or unknown</td>
<td>High dose</td>
</tr>
</tbody>
</table>

### Cost
- Low dose:
  - Apixaban: 100 mg ($3,300), 200 mg ($6,600)
  - Rivaroxaban: 100 mg ($3,300), 200 mg ($6,600)
- High dose:
  - Apixaban: 100 mg ($3,300), 200 mg ($6,600)
  - Rivaroxaban: 100 mg ($3,300), 200 mg ($6,600)

### Andexanet Alfa – A Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors (ANNEXA)

#### ANNEXA A and ANNEXA R
- Dose-ranging trials in healthy, older volunteers (median age 57.9 years)
- Anti-factor Xa activity reduced > 90% for both apixaban and rivaroxaban
- No adverse events, thrombosis, or immune response noted

#### ANNEXA 4
- Multi-center, prospective, open-label, single group trial
- Patients with acute bleeding (mean age 77 years)
- Anti-factor Xa activity reduced and 79% of patients achieved excellent or good hemostasis
- Safety population (n=67): mortality 15%, thrombosis 18% (30% occurred within 3 days)
PCCs for Major Bleeding

Activated prothrombin complex concentrate (aPCC)
- 4-factor (II, VII, IX, X – factor eight inhibitor bypassing activity, FEIBA®)
- Factor VII is mostly activated
- Can be used for dabigatran reversal if idarucizumab unavailable
- Can be used for factor Xa reversal as alternative

Unactivated prothrombin complex concentrate (PCC)
- 3-factor (II, IX, X – Profilnine®)
- 4-factor (II, VII, IX, X inactive forms – Kcentra®)
- 4F-PCC preferred for factor Xa inhibitor reversal if andexanet unavailable
- Limited data comparing to andexanet
- Can be used for dabigatran reversal if idarucizumab unavailable

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Poll: Which of the following antidotes is preferred for reversing the effects of dabigatran?

Poll: To access the polling questions, go to this link: ascp.com/qa and select the “Anticoagulation Therapy in 2019: Exploring Beyond Warfarin” activity, as seen below.
Self-Assessment Question

Which of the following antidotes is preferred for reversing the effects of dabigatran?

A. Andexanet alfa
B. Unactivated 4-factor PCC (Kcentra®)
C. Fresh frozen plasma (FPP)
D. Idarucizumab

Learning Objectives

At the conclusion of this knowledge-based activity, the participant will be able to:

- Compare and contrast indications for direct oral anticoagulants, emphasizing recent indication expansions
- Discuss the use of direct oral anticoagulants in elderly individuals taking into account co-morbid disease states
- Describe current strategies to prevent and treat bleeding in patients on direct oral anticoagulants
- Identify anticoagulation resources that can be utilized in current practice
American College of Cardiology

Clinical Toolkits
Atrial fibrillation

Expert Consensus Decision Pathways
Bleed Management in Anticoagulation
http://www.onlinejacc.org/content/early/2017/11/10/jacc.2017.09.1085-ga-2.4
6614759.1124719807.1566231834.1429624554.1562025473

Infographics
DOAC Dosing for Atrial Fibrillation (AFib)

Mobile Applications
AnticoagEvaluator
ManageAnticoag
https://www.acc.org/tools-and-practice-support/mobile-resources

ACC: Atrial Fibrillation Clinical Toolkit

ACC has pulled together a toolkit to help you treat your patients with atrial fibrillation (AFib) based on the most recent evidence and best practices. Developed by experts and field-tested, the AFib Toolkit is a valuable and free reference or point-of-care resource you can use on your own time.

Diagnosis & Risk Assessment
Assess and document your patients’ symptoms, functional status, thromboembolic risk, and bleeding risk at every visit
SAF Scale | CHA2DS2-VASc | HAS-BLED | Combo Calculator

Treatment & Management
Recommended appropriate antithrombotic therapy and choose safe and effective AFib medications
Sinus Rhythm Therapy Flow Chart | Rate-Rhythm Dosing Table | Anticoag Dosing Table

Patient Education
Educate patients on their treatment strategy and the indications, risks, and benefits of prescribed medications
AFib Condition Center | Cardioversion Fact Sheet | Anticoagulant Fact Sheet
ACC: Bleed Management in Anticoagulation
Expert Consensus Decision Pathway


ACC: DOAC Dosing for Atrial Fibrillation Infographic

To download the infographic and see citations visit ACC.org/Infographics
**ACC: Mobile Applications**

**AnticoagEvaluator**
- CHA₂DS₂-VASc calculator
- HAS-BLED assessment
- Cockroft-Gault calculator

**ManageAnticoag**
- Periprocedural management of anticoagulation including interruption and bridging
- Addressing and acute bleed
- How to reinitiate anticoagulation

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Journal findings: JACC Podcast, The European Heart Journal Podcast
Reviews and News: This Week in Cardiology, Medscape Cardiology Podcast

**Videos**
Feedspot Top 25 Cardiology YouTube Channels
(https://blog.feedspot.com/cardiology_youtube_channels/)
Practice Guide from the ESC

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

https://www.escardio.org/Guidelines/Recommended-Reading/Heart-Rhythm/Novel-Oral-Anticoagulants-for-Atrial-Fibrillation

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When playing as a slideshow, this slide will display live content

Social Q&A
To access Q&A, go to this link: ascp.cnf.io and select the “Anticoagulation Therapy in 2019: Exploring Beyond Warfarin” activity, as seen below.
Anticoagulation Therapy in 2019: Exploring Beyond Warfarin

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