Diagnosis and Management of Hypercoagulability and the Direct Oral Anticoagulants: Interpreting the Data

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Disclosures

Janssen – rivaroxaban

BMS – apixaban

Boehringer Ingelheim – dabigatran, idarucizumab

Instrumentation Laboratory – coagulation diagnostics
Agenda

- **Risk Factors and Pathophysiology**
- Initial Rx and Prognosis of VTE
- Management of VTE/evaluation of acquired and inherited thrombophilias (cancer, APLS, hereditary thrombophilia)
- Duration of anticoagulation/Risk Stratification
- Direct oral anticoagulants (aka NOACs)
Risk Factors for VTE

Transient/Provoked/Secondary

- Surgery
- Trauma (major trauma or lower-extremity injury)
- Acute medical illness
- Immobilization
- Estrogen-containing contraceptives or hormone replacement therapy
- Pregnancy/puerperium
- Central venous catheters
- Prolonged air travel (operationally manage as idiopathic)

Persistent

- Obesity
- Chronic Medical Illnesses
  - Cancer and its therapy
  - Inflammatory bowel disease
  - Nephrotic syndrome
  - Myeloproliferative neoplasms/PNH
- Paralysis

Idiopathic/Unprovoked
VTE Risk Factor Model

Intrinsic Thrombosis Risk

- Anticoagulant deficiencies
  - Antithrombin 20-fold \( \uparrow \) RR
  - Protein S 10-fold \( \uparrow \)
  - Protein C 10-fold \( \uparrow \)
- Prothrombin 3-fold \( \uparrow \)
- Factor V Leiden 3-8 fold \( \uparrow \)

Acquired Risk Factors
- Age
- Previous VTE
- Cancer
- Obesity
- LA/\( \uparrow \) APLA levels

Triggering Factors
- Estrogens
- Pregnancy
- Surgery
- Immobilization

Prophylaxis

Thrombosis Threshold

VTE

from Folsom A
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Initial Treatment of DVT/PE

- Parenteral AC followed by VKA or DOAC (“2 drug approach”)
  - UFH (IV with PTT monitoring)/LMWH or Fondaparinux (SC without coagulation monitoring) overlapping with warfarin for at least 5 days until INR > 2 for 1-2 days
  - Start warfarin on day 1 to achieve INR of 2-3, treat for 3-6 months; clinical utility of pharmacogenomic testing for 2Cy9 and VKORC1 polymorphisms not established
  - Dabigatran or Edoxaban

- Oral factor Xa inhibition (“one drug approach”)
  - Start **rivaroxaban** on day 1 at 15 mg bid x 3 weeks followed by 20 mg daily
  - Start **apixaban** on day 1 at 10 mg bid x 1 week followed by 5 mg bid daily
  - No laboratory monitoring required
Now that DOACs are approved for VTE treatment, when should we use them? Wouldn’t use (or be cautious) in:

Never in pregnancy-associated VTE or post-partum (if breast feeding)

Massive PE (hemodynamically unstable) or DVT (phlegmasia cerulea dolens) where thrombolysis is a consideration

Very obese or frail patients (? weight >275 or <110 lb)

Renal dysfunction (creatinine clearance <30 mL/min) or major drug-drug interactions

Patients with altered GI anatomy (gastric bypass procedures)

Would be cautious in "difficult" or highly prothrombotic patients (recurrent VTE on established therapies such as warfarin or LMWH, APLS, active cancer, HIT, etc.)
Risk of recurrent VTE after discontinuing anticoagulation in a cohort of 1626 patients
Prandoni P et al, Haematologica 2007

10% per year
3% per year

Idiopathic
Secondary
Duration of anticoagulant treatment: Summary

3 months is equivalent to 6 months. Extending anticoagulation is highly effective in eliminating recurrences (>90% relative risk reduction), but only as long as treatment is continued albeit with an increased risk of bleeding.

Unprovoked DVT/PE is associated with a high recurrence risk after the discontinuation of anticoagulation, which is greatest during the first 2 years.

2016 ACCP Guidelines

- For VTE without cancer, we suggest DOACs instead of VKA for the first 3 months and beyond (2B)
- For VTE treated with anticoagulation, we recommend against an IVC filter (1B).
- In patients with recurrent VTE on oral anticoagulation, we suggest switching to LMWH at least temporarily (2C).
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• Direct oral anticoagulants (aka NOACs)
# Predictors of Recurrence in Patients with Idiopathic/Unprovoked VTE

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calf vs Proximal DVT</td>
<td>~0.5</td>
</tr>
<tr>
<td>≥ 1 Prior VTE</td>
<td>~1.5</td>
</tr>
<tr>
<td>Antiphospholipid Antibody Syndrome</td>
<td>~2.0</td>
</tr>
<tr>
<td>Hereditary Thrombophilia</td>
<td>~1.5</td>
</tr>
<tr>
<td>Males vs Females</td>
<td>~1.6</td>
</tr>
</tbody>
</table>

*Kearon C, et al. Chest 2012*
Antiphospholipid antibody Syndrome

APLS is associated with SLE, cancer, infections, drugs; often idiopathic
Antiphospholipid Antibody Syndrome (APLS)


- **Clinical criteria:**
  - Venous or arterial thrombosis
  - Recurrent fetal loss

- **Laboratory criteria:** persistently positive tests 12 wks apart
  - Lupus Anticoagulant (functional coagulation test)
  - ↑ Cardiolipin antibodies (IgG or IgM)
    (medium or high titer: >40 GPL/MPL or >99th percentile)
  - ↑ β₂-glycoprotein I antibodies (IgG or IgM) (>40 or >99th percentile)

1st unprovoked thrombotic event in APLS ⇒ high risk for recurrent thrombosis ⇒ long-term anticoagulation with a vitamin K antagonist (INR 2-3)
Venous Thromboembolism in Cancer

Common (~20% of all patients with VTE)

Increased risk of recurrent VTE on VKA
  Can occur with a therapeutic INR ("warfarin failure")

2016 ACCP Guidelines
  Chronic low molecular weight heparin suggested over warfarin (Grade 2B) or DOACs (Grade 2C)
  In patients with recurrent VTE on long term LMWH, we suggest increasing dose of LMWH by one quarter to one third (2C).

Observational studies of rivaroxaban and apixaban are showing favorable outcomes with respect to efficacy and safety.
Evaluation for occult malignancy in the patient presenting with unprovoked VTE

Available data do not support an extensive search for occult malignancy (i.e., CT scans); it is however important to pursue symptoms or signs which suggest an underlying malignancy and to ensure that age-appropriate screening tests have been performed.

Carrier M. New Eng J Med 2015
# Sites of Thrombosis

<table>
<thead>
<tr>
<th>ABNORMALITY</th>
<th>ARTERIAL</th>
<th>VENOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Prothrombin 20210A</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>AT Deficiency</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Protein C Deficiency</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Lupus Anticoagulant</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Prevalence of Defects in Caucasian Patients with Venous Thrombosis

Factor V Leiden (FVL) 12-40%

Prothrombin Gene Mutation (PGM) 6-18%

Deficiencies of AT, Protein C, Protein S 5-15%

Antiphospholipid Antibody Syndrome ~5%

Unknown 20-70%

Several new variants have been found by candidate and genome-wide screens – all common and weak (OR < 1.5) (Smith NL, JAMA 2007; Bezemer ID, JAMA 2008; Li Y, JTH 2009)

Genetic risk score based on 5 most strongly associated SNPs (FVL, PGM, ABO blood group, 1 SNP in fibrinogen γ gene and 1 in factor XI gene performed similarly to one based on 31 SNPs (de Haan, Blood 2012)
Hereditary Thrombophilia and Obstetric Complications

- Significantly increased risk for second and third trimester fetal loss (~3-fold ↑)
- No association with preeclampsia, IUGR
- Role of LMWH to prevent recurrent fetal loss
  - One positive trial in thrombophilic women
  - Multiple negative trials in women with recurrent losses before 20 weeks including thrombophilic women (TIPPS, Lancet 2014)
The “Hypercoagulable Workup”

- Genetic test for Factor V Leiden mutation
- Genetic test for Prothrombin G20210A mutation
- Functional assay of Antithrombin
- Functional assay of Protein C
- Functional assay of Protein S
  - Free Protein S Antigen (“best” diagnostic assay)
  - Total Protein S Antigen
- Tests for Antiphospholipid Antibody Syndrome
  - Lupus anticoagulant
  - Cardiolipin/β2-glycoprotein I antibodies
- No reason to measure homocysteine levels
- Never test for MTHFR polymorphisms (C677T, A1298C)
# Acquired Deficiencies in Antithrombin, Protein C, or Protein S

<table>
<thead>
<tr>
<th>ANTITHROMBIN</th>
<th>PROTEIN C</th>
<th>PROTEIN S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Pregnancy</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>Liver Disease</td>
<td>Liver Disease</td>
</tr>
<tr>
<td>DIC</td>
<td>DIC</td>
<td>DIC</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major surgery</td>
<td></td>
<td>Inflammation</td>
</tr>
<tr>
<td>Acute thrombosis</td>
<td>Acute thrombosis</td>
<td>Acute thrombosis</td>
</tr>
</tbody>
</table>

Treatment with:

- Heparin
- Warfarin
- Estrogens
- Warfarin
- Estrogens

Caveats:

1. Don’t draw these tests when patients present with VTE or are receiving anticoagulants.
2. Abnormal results drawn at presentation with VTE must be confirmed. Draw protein C and S after discontinuing warfarin for a minimum of 1 week.
Risk of Recurrent Venous Thrombosis in Patients with Inherited Thrombophilia

- Definite risk factors for 1st episodes of VTE
- “Paradoxically” heterozygosity for Factor V Leiden (FVL) or Prothrombin G20210A do not substantially increase recurrence risk.
- Antithrombin, Protein C, Protein S Deficiency
  - High in selected kindreds with strong clinical penetrance (retrospective studies)
  - Uncertainty regarding recurrence risk without a positive family history
What do the ACCP guidelines say about the presence of hereditary thrombophilia with respect to the duration of anticoagulation?

The presence of hereditary thrombophilia has not been used as a major factor to guide duration of anticoagulation for VTE in these guidelines because evidence from prospective studies suggests that these factors are not major determinants of the risk of recurrence.
Who Should Be Tested?

General population

- Any patient with VTE
- Any patient with spontaneous VTE
- Younger patient with VTE
- Younger patient with VTE + family history
- Nobody

Liberal

Conservative
Testing for Hereditary Defects in Patients with Thrombosis and No Family History

**PRO**
- Improve understanding of pathogenesis of VTE
- Identify and counsel affected family members

**CON**
- Infrequently identify patients in whom the identification of an abnormality should alter their management
- No evidence of “direct particular benefit to family members” (because of low absolute risk of an initial VTE)
- Potential for overaggressive management of propositus and asymptomatic affected relatives (if screening undertaken)
- Cost of testing/consultations
- Create undue anxiety
  (Negative insurance implications)
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- **Duration of anticoagulation/Risk Stratification**
- Direct oral anticoagulants (aka NOACs)
# ACCP Evidenced-Based Clinical Practice Guidelines

<table>
<thead>
<tr>
<th>Indication</th>
<th>Duration of Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal DVT/PE secondary to a transient risk factor</td>
<td>3 months</td>
</tr>
<tr>
<td>1st isolated, unprovoked distal DVT</td>
<td></td>
</tr>
<tr>
<td>Idiopathic proximal DVT or PE</td>
<td>3-6 months or indefinite</td>
</tr>
<tr>
<td>2nd Unprovoked DVT or PE</td>
<td>Long-term</td>
</tr>
</tbody>
</table>
Duration of anticoagulant treatment
What do the ACCP guidelines say?

- **2008** We recommend that patients with a first idiopathic VTE be evaluated for long-term treatment. If no contra-indication, we recommend long-term treatment *(Grade 1A).*
  - Values and preferences: This recommendation attaches a relatively high value to prevention of recurrent VTE and a lower value to the burden of long-term anticoagulant therapy.

- **2012** In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy *(Grade 2B).*
Extension of warfarin treatment beyond 3 to 6 months in 1\textsuperscript{st} unprovoked/idiopathic VTE

*Douketis JD et al. Ann Intern Med 2007;147:766-774*

In year 1 following cessation of anticoagulation, for 1000 patient-years

**Death by PE recurrence**
- 80 VTE recurrences
- Case-fatality rate 4-12%
- 3 to 10 deaths

**Death by major bleed**
- 20 to 60 bleeds
- Case-fatality rate 10%
- 2 to 6 deaths

\[ \text{NO MORTALITY BENEFIT FROM LONG-TERM ANTICOAGULATION WITH VITAMIN K-ANTAGONISTS (WARFARIN)} \]

⇒ A recurrent VTE rate of <5% per year has been considered "acceptable" (risk of anticoagulation > benefit)
Extended (or Chronic) Treatment - an Individualized Management Decision

- Consider
  - Recurrence risk: Unprovoked, Gender, D-dimer
  - Alternatives to warfarin: rivaroxaban, dabigatran, apixaban, aspirin
  - Patient preferences and values (includes lifestyle and occupation)
  - Bleeding risk: Patient characteristics, Stability of anticoagulation (if on warfarin)
Duration of anticoagulant treatment
Additional determinants of the risk of recurrence

Other elements that increase the risk of recurrence after stopping anticoagulant treatment include:

- Persistently elevated D-dimer levels off anticoagulants
- Male gender
- Residual thrombus on ultrasound (conflicting data difficult to standardize)

Clinical Prediction Models

- Vienna Prediction Model (gender, type of VTE, D-dimer on VKA)
- HERDOO (Hyperpigmentation, edema/leg redness, D-dimer, BMI, patient age)
- DASH (D-dimer post-VKA, age, gender, hormonal therapy)
D-dimer to guide prolongation of anticoagulant treatment? PROLONG I Study

First episode of unprovoked DVT or PE
N= 608

Initial minimum 3-month VKA treatment

D-dimer measured 1 month after VKA discontinuation

Abnormal
Randomize

Normal
Stop anticoagulants

Stop anticoagulants
Continue anticoagulants
# D-dimer for VTE: Risk Stratification

<table>
<thead>
<tr>
<th>Palareti 2006 (Simplify)</th>
<th>Negative (&lt;500 ng/mL)</th>
<th>Positive (&gt;500 ng/mL)</th>
<th>4.4% per year</th>
<th>10.9% per year</th>
<th>HR 2.49 (95% CI, 1.35-4.59)</th>
</tr>
</thead>
</table>

**D-Dimer < 500 ng/mL**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age &lt; 65</th>
<th>Age &gt; 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>0.4% per year</td>
<td>6.6% per year</td>
</tr>
<tr>
<td>Male</td>
<td>5.1% per year</td>
<td>8.1% per year</td>
</tr>
</tbody>
</table>

D-Dimer for VTE Risk Stratification


D-dimer to select patients with a first unprovoked VTE who have anticoagulants stopped at 3-7 months: a multicentre management study (D-Dimer Optimal Duration Study, DODS)

410 patients enrolled, mean age 51. 319 patients with negative D-dimer on VKA and 4 weeks later off VKA

<table>
<thead>
<tr>
<th></th>
<th>Recurrent VTE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire Cohort</td>
<td>6.6% per year</td>
<td>4.8-9.0</td>
</tr>
<tr>
<td>Men (n=180)</td>
<td>9.7% per year</td>
<td>6.7-13.7</td>
</tr>
<tr>
<td>Women (no estrogens=81)</td>
<td>5.4% per year</td>
<td>2.5-10.2</td>
</tr>
<tr>
<td>Women (estrogens=58)</td>
<td>0% per year</td>
<td>0.0-3.0</td>
</tr>
</tbody>
</table>
Other Considerations in Deciding on Long-Term Oral Anticoagulation

• Site of thrombosis
  • PE more likely to recur as PE, DVT as DVT

• Severity of Thrombosis
  • Massive PE
  • Ilio-femoral DVT
  • Severe post-phlebitic syndrome

• Age of patient
  • Prefer not to commit young patients to lifelong anticoagulation after a 1st event unless clearly very high risk for recurrence

• IVC filters (75% of retrievable filters never retrieved)
  • ↑ risk of recurrent DVT especially if VTE unprovoked if anticoagulation not continued
The Future: Will/should the superior safety profile of direct oral anticoagulants (DOACs) lead to the treatment of more patients with a 1st unprovoked VTE with extended therapy?

“Greater net clinical benefit with DOACs than VKAs”

DVT/PE recurrence
5 to 15% per year

Major bleeds
~0.5% per year
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Direct Oral Anticoagulants (DOACs)

Unfractionated Heparin

Low Molecular Weight Heparin

Direct Factor Xa Inhibitors
- Rivaroxaban
- Apixaban
- Edoxaban

Direct Thrombin (IIa) Inhibitors
- Dabigatran etexilate

Fibrin Clot
Advantages of **DOACs** vs. **Warfarin**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Warfarin</th>
<th>DOACs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable</td>
<td>Fixed</td>
</tr>
<tr>
<td>Food effect (vitamin K)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Offset</td>
<td>Long</td>
<td>Shorter</td>
</tr>
</tbody>
</table>

Eikelboom and Weitz. Circulation 2010
Direct Oral Anticoagulants have a Wide Therapeutic Window

Dose (concentration) of Anticoagulant
## Comparative Properties of Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran Etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td>6-7%</td>
<td>~80%</td>
<td>~66%</td>
<td>~60%</td>
</tr>
<tr>
<td><strong>T (max)</strong></td>
<td>2 h</td>
<td>2-4 h</td>
<td>3 h</td>
<td>1-2 h</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>12-14 h</td>
<td>7-13 h</td>
<td>8-13 h</td>
<td>9-11 h</td>
</tr>
<tr>
<td><strong>Protein Binding</strong></td>
<td>35%</td>
<td>90%</td>
<td>87%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Twice (or once) daily</td>
<td>Once (or twice) daily</td>
<td>Twice daily</td>
<td>Once daily</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>80% renal</td>
<td>67% renal (1/2 active) 33% fecal</td>
<td>25% renal 75% fecal</td>
<td>35% renal 65% fecal</td>
</tr>
<tr>
<td><strong>Potential Drug Interactions</strong></td>
<td>Potent P-gp inhibitors</td>
<td>Potent CYP 3A4 and P-gp inhibitors</td>
<td>Potent CYP 3A4 and P-gp inhibitors</td>
<td>Potent CYP 3A4 (&lt;4%) and P-gp inhibitors</td>
</tr>
</tbody>
</table>

Inhibitors: ketoconazole, ritonavir  
Inducers: rifampin, phenytoin, carbamazepine, St. John’s wort
# Direct Oral Anticoagulants: Approval Status in United States

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Replacement</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Knee Replacement</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Stroke Prevention in Atrial Fibrillation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Venous Thromboembolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Extended</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
</tbody>
</table>

DOACs should never be used in patients with prosthetic heart valves!
Summary: DOACs in Atrial Fibrillation

- At least as effective/safe as warfarin and can be given without laboratory monitoring
- Marked reduction in intracranial bleeding and decreased risk of fatal bleeding
- Slight increase in myocardial infarction rates with dabigatran
- Small increase in gastrointestinal bleeding with dabigatran and rivaroxaban

DOSE/SCHEDULE OF DOACs IN ATRIAL FIBRILLATION (US)

Dabigatran (twice daily)
- 150 mg BID in US
  - Dosing in renal impairment (CrCL15-29 mL/min) 75 mg BID

Rivaroxaban (once daily)
- Atrial fibrillation: 20 mg QD (with food) if CrCl ≥ 50 mL/min
  - Dosing in renal impairment (CrCl 15-49 mL/min) 15 mg QD

Apixaban (twice daily)
- 5 mg BID
  - 2.5 mg BID if any 2: age ≥ 80, wt ≤ 60 kg, Cr ≥ 1.5 mg/dL

Edoxaban (once daily)
- 60 mg QD if CrCl > 50 mL/min: should not be used if CrCl > 95 mL/min
  - Dosing in renal impairment (CrCl 15-50 mL/min) 30 mg QD
Assessing Presence or Levels of DOACs

<table>
<thead>
<tr>
<th>Drug Present (Qualitative test)</th>
<th>Oral Factor Xa Inhibitors</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (for rivaroxaban)</td>
<td>PT more sensitive than PTT</td>
<td>Thrombin time highly sensitive</td>
</tr>
<tr>
<td>PT more sensitive than PTT</td>
<td></td>
<td>PTT more sensitive than PT</td>
</tr>
<tr>
<td>Quantitative Assay</td>
<td>Chromogenic anti-factor Xa</td>
<td>Dilute thrombin time or Ecarin Clotting Time</td>
</tr>
</tbody>
</table>

Clinical applicability:

- PT/INR for rivaroxaban/edoxaban is variable depending on PT reagent. Apixaban has minimal effect in many PT assays, even at suprathervapeutic concentrations.

- Quantitative assays are not yet FDA-approved or widely available. Rapid, point-of-care assays would be required to make decisions in bleeding emergencies.
Comparison of Properties of Direct Oral Anticoagulants to Vitamin K Antagonists

<table>
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<th>Warfarin</th>
<th>DOACs</th>
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<tr>
<td>Effect of diet</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Specific Reversal Agent</td>
<td>Yes</td>
<td>Not yet for FXa Inhibitors</td>
</tr>
</tbody>
</table>
Idarucizumab: A specific reversal agent for the anticoagulant activity of dabigatran

- Humanized Fab fragment
  - Binds with high-affinity to dabigatran/metabolites
- Primarily renal excretion
- Terminal $t_{1/2}$ 10.3 hours
- No interaction with other drugs
- Reduces dabigatran-induced bleeding in animal models
- Leads to immediate, complete, and sustained reversal of dabigatran activity
Idarucizumab: Pivotal Study

- 90 patients with either serious bleeding (51) or need for urgent procedure (39)

- Most patients were elderly with atrial fibrillation (median age 76.5); 1/3 of serious bleeds were intracranial bleeding

- 5 grams administered (2 doses of 2.5 grams over 15 minutes)

- Efficacy assessed by dilute thrombin time and ecarin clotting time

Pollack et. al NEJM 2015
RESULTS: Primary endpoint in Group A: dTT and ECT
Reversal of dabigatran with idarucizumab

Dilute thrombin time

ECT (s)

Baseline
Between
vials
10–30
min
1h
2h
4h
12h
24h
Baseline
Between
vials
10–30
min
1h
2h
4h
12h
24h
Idarucizumab: Pivotal Study Findings

- Drug completely reversed anticoagulation within 30 min in >90% of patients within following start infusion
- Median time to bleeding cessation (i.e., when assessed to have stopped) was 11.4 hours
- “Normal hemostasis” as judged by surgeon/interventionalist (procedure group) achieved in 92% of patients
- Five thrombotic events and 18 deaths at 90 days (related to index event and comorbidities)
Andexanet - a decoy protein for factor Xa inhibitors

- 41 kD recombinant human Factor Xa molecule
  - Catalytic activity eliminated by substitution of active site serine by alanine
  - Gla domain removed to eliminate membrane binding and incorporation into prothrombinase complex
- Oral Factor Xa inhibitors as well as heparins/LMWH/fondaparinux (bound to AT) reversibly bind to active site of andexanet, inhibiting their ability to bind to Factor Xa
- Higher dose of andexanet required for rivaroxaban than for apixaban
- Half-life ($t_{1/2}$) ~1 hour – administered as an intravenous bolus followed immediately by a constant infusion over 2 hours
Antifactor Xa Activity Before and After Andexanet

- Anti-Xa levels reduced
- Apixaban: Andexanet vs. placebo (94% vs. 21% P<.001) bolus
- Rivaroxaban: Andexanet vs. placebo (92% vs 18% P<.001) bolus
- Apixaban: Andexanet vs. placebo (92% vs 33% P<.001) infusion
- Rivaroxaban: Andexanet vs. placebo (97% vs 45% P<.001) infusion

Non-neutralizing antibodies developed in 17% of patients 15-30 days after administration

NEJM 2015
Andexanet in Acute Major Bleeding

- Andexanet administered to 67 patients within 18 hours after the administration of a factor Xa inhibitor.
- Median patient age 77 with substantial cardiovascular disease.
- Intracranial bleeding 42%.
- Efficacy assessed by anti-factor Xa levels in 47 patients with baseline anti-factor level $\geq 75$ ng/mL.
- Follow-up: 30 days.

Connolly et al. NEJM 2016
Andexanet: Pivotal Study Findings

- Anti-factor Xa levels: Median decrease of 80% for rivaroxaban and 93% for apixaban from baseline following bolus, 39% and 30% at 4 hours
- Clinical hemostasis adjudicated as excellent or good in 37/47 (79%) 12 hours after andexanet infusion
- Thrombotic events in 12/67 (18%) and 10 deaths (15%) at 30 days (related to index event and comorbidities; ? role of andexanet binding to TFPI)
- Time from ED presentation to administration of andexanet bolus (mean 4.8 ± 1.8 hours)
Management of Major Bleeding in Patients on DOACs

Discontinue/hold anticoagulant

Supportive Care (IV fluids, packed RBCs)

Activated charcoal (if ingested in last 2 hours)

Localization/management of bleeding site (if possible)

If taking dabigatran, administer idarucizumab

- In life-threatening or uncontrolled bleeding
  - For emergency surgery/urgent procedures (if judged to have clinically significant plasma levels of dabigatran)

If taking an oral factor Xa inhibitor, consider administration of PCC until andexanet becomes available.
## Periprocedural Management of DOACs
### Timing of Interruption of DOACs Before Surgery/Invasive Procedures

<table>
<thead>
<tr>
<th>Calculated CrCl, mL/min</th>
<th>Half-life, h</th>
<th>Timing of Last Dose Before Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard Risk of Bleeding&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>13 (11-22)</td>
<td>24 h</td>
</tr>
<tr>
<td>&gt;50-≤80</td>
<td>15 (12-34)</td>
<td>24 h</td>
</tr>
<tr>
<td>&gt;30-≤50</td>
<td>18 (13-23)</td>
<td>2 d</td>
</tr>
<tr>
<td>≤30</td>
<td>27 (22-35)</td>
<td>4 d</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>12 (11-13)</td>
<td>24 h</td>
</tr>
<tr>
<td>≤30</td>
<td>Unknown</td>
<td>2 d</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td></td>
<td>24 h</td>
</tr>
</tbody>
</table>

<sup>A</sup> Examples: cardiac catheterization, ablation therapy, colonoscopy without removal of large polyps, uncomplicated laparoscopic procedures

<sup>N</sup> Examples: major cardiac/cancer/urologic/vascular surgery, insertion of pacemakers/defibrillators, neurosurgery, large hernia surgery
Adoption of Institutional Protocols/Clinical Pathways for DOACs to Achieve Optimal Outcomes: An Individualized Approach

Components: Patient Preference, Patient Selection, Drug Interactions, Compliance, Follow-up (e.g., DVT - ED to clinic), Monitoring (i.e., medication refills)

New oral anticoagulant ordered

Entered into database

Anticoag Pharmacy screening, inclusion + exclusion criteria, patient assessment

Appropriate

Drug dispensed

Not appropriate

Physician notified, alternative management

Adapted from Jonathan Halperin and Mary Cushman