Anticoagulation Considerations in Patients with Chronic Kidney Disease

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Objectives

» Describe the differences in pharmacology between the traditional and new oral anticoagulants (NOAC).
» Explain the pharmacokinetic differences and drug interaction potential among the anticoagulants.
» Compare the indications and monitoring parameters for use of anticoagulants in patients with CKD.
» Describe management strategies for anticoagulation therapies with special considerations for persons with CKD.
Challenges with Current Oral Antithrombotic Therapy

» Increased risk of:
  – Major and minor bleeding (supratherapeutic INR)
  – Embolism (subtherapeutic INR)

» Need for routine anticoagulation monitoring

» Dosing variability

» Need for continuous patient education

» Drug/drug and food/drug interactions

» Slow onset/offset of action
Epidemiology of AF

» Most common arrhythmia in U.S.
  – Projected to affect 2.7-6.1 million in 2010

» Affects men more than women

» Incidence and prevalence increase with age
  – 70% of patients with AF between 65-85 yr

» Lifetime risk of AF in men and women ≥40 yr ~ 25%

Patients with ESRD on HD have higher prevalence of AF compared with the general population
   – Ranging from 7 – 27%

Prevalence of AF in non-dialysis dependent CKD is similar to the dialysis population
   – 18-21%

An independent inverse relationship exists between AF and GFR.

Soliman EZ, et al. CRIC. Am Heart J. 2010;159(6):1102-1107
Stroke in AF

» Incidence of all-cause stroke in patients with AF is 5%

» AF is an independent risk factor for stroke (↑ risk of stroke by 4-5-fold)
  ~15-20% of all strokes in the U.S. are caused by AF

» Risk for stroke ↑ with age

» Stroke risk persists even in asymptomatic AF

» ↑ risk of mortality

Stroke Risk Stratification in AF

» CHADS$_2$ score

- Congestive heart failure = 1 point
- Hypertension = 1 point
- Age $\geq$ 75 years = 1 point
- Diabetes = 1 point
- Stroke/TIA = 2 points

TIA = transient ischemic attack

### CHADS$_2$ Score and Risk:
Adjusted Stroke Rate per 100 patient-years

<table>
<thead>
<tr>
<th>Score</th>
<th># of patients</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>1.9 (1.2 – 3)</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>2.8 (2 – 3.8)</td>
</tr>
<tr>
<td>2</td>
<td>523</td>
<td>4.0 (3.1 – 5.1)</td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>5.9 (4.6 – 7.3)</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>8.5 (6.3 – 11.1)</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>12.5 (8.2 – 17.5)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>18.2 (10.5 – 27.4)</td>
</tr>
</tbody>
</table>

Gage BF et al. *JAMA*. 2001;285:2864-70
# CHA2DS2-VASc Score for Estimating Stroke Risk in AF

<table>
<thead>
<tr>
<th>Factor</th>
<th>Points</th>
<th>Score</th>
<th>TE Rate at 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C: CHF/LV dysfunction</strong></td>
<td>1 point</td>
<td>0 points:</td>
<td>0% LOW</td>
</tr>
<tr>
<td><strong>H: HTN</strong></td>
<td>1 point</td>
<td>1 point:</td>
<td>0.6% INTER</td>
</tr>
<tr>
<td><strong>A: Age ≥75 years</strong></td>
<td>2 points</td>
<td>2 points:</td>
<td>1.6% HIGH</td>
</tr>
<tr>
<td><strong>D: Diabetes</strong></td>
<td>1 point</td>
<td>3 points:</td>
<td>3.9%</td>
</tr>
<tr>
<td><strong>S: Stroke/TIA</strong></td>
<td>2 points</td>
<td>4 points:</td>
<td>1.9%</td>
</tr>
<tr>
<td><strong>V: Vascular disease†</strong></td>
<td>1 point</td>
<td>5 points:</td>
<td>3.2%</td>
</tr>
<tr>
<td><strong>A: Age 65-74 years</strong></td>
<td>1 point</td>
<td>6 points:</td>
<td>3.6%</td>
</tr>
<tr>
<td><strong>S: Sex (female)</strong></td>
<td>1 point</td>
<td>7 points:</td>
<td>8.0%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>8 points:</td>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 points:</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

† Prior MI, PAD, or aortic plaque

HAS-BLED Score for Estimating Bleeding Risk in AF

n = 3,665 patients taking warfarin from SPORTIF cohort

<table>
<thead>
<tr>
<th>Events</th>
<th>Score</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H: HTN</strong></td>
<td>1 point</td>
<td>0 points: 0.9%</td>
</tr>
<tr>
<td><strong>A: Abnormal renal/liver function</strong></td>
<td>1 point each</td>
<td>1 point: 3.4%</td>
</tr>
<tr>
<td><strong>S: Stroke</strong></td>
<td>1 point</td>
<td>2 points: 4.1%</td>
</tr>
<tr>
<td><strong>B: Bleeding history/predisposition</strong></td>
<td>1 point</td>
<td>3 points: 5.8%</td>
</tr>
<tr>
<td><strong>L: Labile INR (TTR &lt;60%)</strong></td>
<td>1 point</td>
<td>4 points: 8.9%</td>
</tr>
<tr>
<td><strong>E: Elderly (&gt;65 yr)</strong></td>
<td>1 point</td>
<td>5 points: 9.1%</td>
</tr>
<tr>
<td><strong>D: Drugs†/alcohol</strong></td>
<td>1 point each</td>
<td>TOTAL</td>
</tr>
</tbody>
</table>

† Antiplatelets, NSAIDS, or steroids

ESRD and Bleeding

» HAS-BLED defined decreased kidney function as the presence of long-term dialysis therapy, kidney transplantation, or SCr ≥2.26 mg/dL.

» ESRD is associated with increased bleeding risk, including intracerebral hemorrhage and gastrointestinal bleeding

» SCr > 1.5 mg/dl has been associated with increased rates of major bleeding

## Stroke Prevention in Atrial Fibrillation

### Guideline Recommendations

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; score</th>
<th>ACCP (Grade of rec)</th>
<th>ACCF/AHA/HRS (Class of rec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No therapy (2B)</td>
<td>Aspirin (I)</td>
</tr>
<tr>
<td>1</td>
<td>OAC (1B)</td>
<td>OAC or aspirin (IIa)</td>
</tr>
<tr>
<td></td>
<td>Dabi &gt; warfarin*</td>
<td>Dabi alt to warfarin†</td>
</tr>
<tr>
<td>≥ 2</td>
<td>OAC (1A)</td>
<td>OAC (I)</td>
</tr>
<tr>
<td></td>
<td>Dabi &gt; warfarin*</td>
<td>Dabi alt to warfarin†</td>
</tr>
</tbody>
</table>

* 2B: Except in patients with CrCl < 30 ml/min, mitral stenosis, stable CAD, recent ACS, or s/p intracoronary stent
† Except in patients with prosthetic heart valves, hemodynamically significant valvular heart disease, CrCl < 15 ml/min, or advanced liver disease

Rivaroxaban & apixaban not approved at time of guideline publication; not included

Etiology of Thromboembolism

Venous Stasis
- Immobilization
- Age > 40
- Obesity
- CHF
- AMI
- General anesthesia
- Varicose veins

Vascular Injury
- Trauma
- Surgery
- CV or PA catheter
- History TE
- Cardiac pacemaker

Hypercoagulable State
- Malignancy
- High dose estrogen
- Pregnancy
- Polycythemia vera
- Activated protein C
- Protein C/S deficiency
- ATIII deficiency
- Hyperhomocysteinemia

Endothelial Injury
- Antiphospholipid Syndrome
- Plasminogen AI excess
- Heparin cofactor II deficiency
- Nephrotic Syndrome
Etiology of Thromboembolism

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- Immobilization
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- Plasminogen AI excess
- Heparin cofactor II deficiency
- Nephrotic Syndrome

All 3 components are enhanced in CKD
RIETE Registry

» Prospective, multicenter observational registry of consecutive pts with acute VTE

» Retrospective analysis of 10,526 pts

<table>
<thead>
<tr>
<th>CrCL ml/min</th>
<th>N (%)</th>
<th>Fatal PE; OR (95% CI)</th>
<th>Fatal Bleeding; OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>9234 (88)</td>
<td>1.0%; reference</td>
<td>0.2%; reference</td>
</tr>
<tr>
<td>30-60</td>
<td>704 (6.7)</td>
<td>2.6%; 2.7 (1.6 – 4.4) ‡</td>
<td>0.3%; 1.5 (0.4 – 6.7) ‡</td>
</tr>
<tr>
<td>&lt;30</td>
<td>588 (5.6)</td>
<td>6.6%; 7.2 (4.9 – 11)‡</td>
<td>1.2%; 6.5 (2.7 – 16)‡</td>
</tr>
</tbody>
</table>

‡ P<0.001 for comparison between CrCL < 30 or 30 – 60 and pts with CrCL > 60

Antithrombotic Drugs

Intrinsic

- XII
- XI
- IX
- VIII
- VII
- AT

UFH
LMWH

Extrinsic

- Tissue Factor
- Pentasaccharide Xa Inhibitors

Factor Xa Inhibitors

Warfarin
Direct Thrombin Inhibitors

Common

- Fibrinogen
- Fibrin Clot
## Comparison of Drugs and Regimens

<table>
<thead>
<tr>
<th>Antithrombotic Drugs</th>
<th>New</th>
<th>Old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant effect</td>
<td>Targeted/Specific</td>
<td>Complex</td>
</tr>
<tr>
<td>Kinetics</td>
<td>Reproducible</td>
<td>Variable</td>
</tr>
<tr>
<td>SC/PO availability</td>
<td>Reproducible</td>
<td>Variable</td>
</tr>
<tr>
<td>PK/PD</td>
<td>Predictable</td>
<td>Variable</td>
</tr>
<tr>
<td>Dose</td>
<td>Fixed</td>
<td>Variable</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>Few or none</td>
<td>Frequent</td>
</tr>
<tr>
<td>Treatment Regimens</td>
<td>Simple</td>
<td>Complex</td>
</tr>
</tbody>
</table>
## Anticoagulant Targets

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Targets</th>
<th>Generic names</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K antagonists</td>
<td>II, VII, IX, X, Prot C &amp; S</td>
<td>Warfarin, anisindione, dicumarol</td>
<td>Oral</td>
</tr>
<tr>
<td>Heparin</td>
<td>Xa and IIa equally predom, then VIIa, IXa, Xla</td>
<td>Heparin</td>
<td>Injectable (IV, SC)</td>
</tr>
<tr>
<td>LMWH</td>
<td>Xa more than IIa</td>
<td>Enoxaparin, dalteparin, tinzaparin</td>
<td>Injectable (SC)</td>
</tr>
<tr>
<td>Factor Xa inhibitors</td>
<td>Indirect: Xa by binding to AT</td>
<td>Fondaparinux &amp; investigational agents: idraparinux &amp; idrabiotaparin</td>
<td>Injectable (SC)</td>
</tr>
<tr>
<td></td>
<td>Direct: Xa (do not bind to AT)</td>
<td>Rivaroxaban, Apixaban</td>
<td>Oral</td>
</tr>
<tr>
<td>Direct Thrombin inhibitors</td>
<td>IIa</td>
<td>Argatroban, lepirudin, bivalirudin, Dabigatran</td>
<td>Injectable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral</td>
</tr>
</tbody>
</table>
Warfarin Pharmacodynamics: Vitamin K Recycling

Hypoactive clotting factors

Vitamin KH₂

Vitamin K₁

Active clotting factors

Vitamin K 2,3 epoxide

Vitamin K epoxide reductase

7-OH-Warfarin

S-WARFARIN

CYP2C9
INR = \left( \frac{\text{Patient's PT in Seconds}}{\text{Mean Normal PT in Seconds}} \right)^{\text{ISI}}

INR = \text{International Normalized Ratio}
ISI = \text{International Sensitivity Index}
Intensity of Anticoagulation (INR)

Clinical Events

Thromboembolic → Therapeutic Window → Hemorrhagic

Intensity of Anticoagulation (INR)
Comparative Mechanism of Action: Fondaparinux and the Heparins

**UNFRACTIONATED HEPARIN**

1. AT
2. AT → Xa
3. AT → Thrombin

**LMWH**

1. AT
2. AT → Xa
3. AT → Thrombin

**FONDAPARINUX**

1. AT
2. AT → Xa
3. AT → Thrombin
## Comparative Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Molecular weight in daltons</th>
<th>Anti-Xa: Anti-IIa</th>
<th>T 1/2</th>
<th>Protein bind</th>
<th>Elimin</th>
<th>Dose Depend clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>12,000 – 15,000 (3000 - 30,000)</td>
<td>1:1</td>
<td>30 -150 min.</td>
<td>++++</td>
<td>1. Saturable binding processes 2. Renal</td>
<td>yes</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>4,500 (3000-8000)</td>
<td>2.7:1</td>
<td>4.5 hrs</td>
<td>+</td>
<td>Renal</td>
<td>No</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>5000 (2000-9000)</td>
<td>2:1</td>
<td>3-5 hrs</td>
<td>+</td>
<td>Renal</td>
<td>No</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>4,500 (3,000–6,000)</td>
<td>1.9:1</td>
<td>3-4 hrs</td>
<td>+</td>
<td>Renal</td>
<td>No</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>1728</td>
<td>&gt;100:1</td>
<td>17 hrs</td>
<td>none</td>
<td>Renal</td>
<td>no</td>
</tr>
</tbody>
</table>
Pharmacokinetic Advantages of LMWH over Unfractionated Heparin

» Less binding to plasma proteins and to proteins released from activated platelets and endothelial cells
» More predictable anticoagulant response
» Better bioavailability at low doses
» Dose independent clearance mechanism
» Longer half-life
LMWH Clearance

» Mainly through kidney, since short heparin chains are less able to bind to liver macrophages

» LMWHs have predictable pharmacokinetics, but pts with renal impairment may have decreased LMWH clearance, LMWH accumulation, and bleeding complications
# LMWH and Fondaparinux Dosing

<table>
<thead>
<tr>
<th>LMWH</th>
<th>Indication</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>VTE prophylaxis</td>
<td>30 mg SC q12h or 40 mg SC daily</td>
</tr>
<tr>
<td></td>
<td>VTE treatment</td>
<td>1 mg/kg SC q12h or 1.5 mg/kg SC daily</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>VTE prophylaxis</td>
<td>2500 – 5000 IU SC daily</td>
</tr>
<tr>
<td></td>
<td>VTE treatment</td>
<td>200 IU/kg SC daily or 100 IU/kg SC q12h</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>VTE prophylaxis</td>
<td>50-75 IU/kg SC daily or 3500 IU SC daily</td>
</tr>
<tr>
<td></td>
<td>VTE treatment</td>
<td>175 IU/kg SC daily</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>VTE prophylaxis</td>
<td>2.5 mg daily</td>
</tr>
<tr>
<td></td>
<td>VTE treatment</td>
<td>≤50 kg: 5 mg SC daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50-100 kg: 7.5 mg SC daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;100 kg: 10 mg SC daily</td>
</tr>
</tbody>
</table>
Risk of LMWH accumulation and bleeding

» Based on
  – Degree of renal insufficiency
  – Doses of LMWH used
  – Number of doses
  – Type of LMWH

» Most studies evaluating LMWHs have excluded patients with renal insufficiency or have evaluated small numbers of these patients.
Pharmacokinetic differences among LMWH

- LMWHs with smaller chain lengths, such as enoxaparin, depend more on renal elimination than LMWH with longer chain lengths (tinzaparin and dalteparin)

Risk of Major Bleed with Enox in Pts with Severe Renal Insuff (CrCL <30 ml/min)

- All studies (n=12): OR 2.6 (1.3 – 5.0)
- No dose adjustment (n=7): OR 3.9 (1.8 – 8.5)
- Adjusted dose (n=4): OR 0.59 (0.09 – 3.78)

Reduced bleeding Risk

Increased Bleeding Risk

Reduced dose of enoxaparin in this group avoids excess major bleeding.

# LMWH and Fondaparinux Package Insert Dosage Recommendations for Renal Impairment

<table>
<thead>
<tr>
<th>LMWH</th>
<th>PI Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>CrCL &lt; 30 mL/min: use with caution</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>CrCL &lt; 30 mL/min: Prophylaxis – 30mg SC daily</td>
</tr>
<tr>
<td></td>
<td>Treatment – 1mg/kg SC daily</td>
</tr>
<tr>
<td></td>
<td>STEMI: 30 mg IV bolus, then 1 mg/kg daily</td>
</tr>
<tr>
<td></td>
<td>Elderly: no bolus, 0.75 mg/kg q12 hr</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>CrCL &lt; 30 mL/min: use with caution</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>CrCL &lt; 30 ml/min: use is contraindicated</td>
</tr>
</tbody>
</table>
ACCP 2012 Guidelines

7.1 Therapeutic Dose of LMWH in Patients With Decreased Renal Function: For patients receiving therapeutic LMWH who have severe renal insufficiency (calculated CrCL < 30 mL/min), suggest a reduction of the dose rather than using standard doses (Grade 2C).

ACCP 2012 Guidelines

» Appropriate dose of LMWH in pts with severe CKD (CrCL< 30 ml/min) is uncertain

» Clearance of the anti-Xa effect of LMWH correlates with CrCL (enoxaparin, dalteparin)
  – Exception: Tinzaparin not shown to correlate with CrCL

» If severe renal insuff and therapeutic AC required, suggest UFH over LMWH

» If LMWH is used in pts with severe renal insuff for therapeutic AC, suggest monitor anti-Xa.

Primary Prophylaxis for Venous Access Related to Hemodialysis

- 2.45. For patients undergoing hemodialysis via an AV fistula, suggest routine use of VKAs or LMWH as fistula thromboprophylaxis as compared with no therapy (Grade 2C).

- 2.46. For patients undergoing hemodialysis via central venous access, suggest routine use of VKAs or LMWH for thromboprophylaxis as compared with no therapy (Grade 2C).
Use of LMWH in dialysis

» Limited clinical data exists on LMWH in HD pts

» From the enoxaparin package insert:
  “Hemodialysis: In a single study, elimination rate appeared similar but AUC was two-fold higher than controls, after a single 0.25 or 0.5 mg/kg dose.”

» Reduced dosing strategies have been used with varying degrees of success
Enoxaparin in HD pts

- Retrospective cohort compared HD pts: 82 enoxaparin vs. 82 IV UFH pts
- Mean dose of enox was 0.7 ± 0.2 mg/kg/day (range 0.4 – 1)
- No significant difference in major bleeding (6.1% vs. 11%) or VTE (0% vs. 2.4%)
- Hospital LOS shorter in enox group: 20 ±53.8 vs. 28.9 ±44.5 days, p=0.02
- Conclusions: therapeutic dosing of enoxaparin in reduced doses 0.4 – 1 mg/kg/day, was as safe as IV UFH in stable pts on HD.

# Anticoagulants: Clinical Profiles

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>UFH</th>
<th>LMWH</th>
<th>Direct thrombin inhibitors</th>
<th>Factor Xa inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding outside target</td>
<td>Multiple targets</td>
<td>Multiple targets</td>
<td>Relatively low</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Monitoring for efficacy</td>
<td>INR</td>
<td>aPTT</td>
<td>Anti-Factor Xa</td>
<td>Not required</td>
<td>Not required</td>
</tr>
<tr>
<td>Monitoring for safety</td>
<td>INR, CBC, LFTs</td>
<td>Platelet count</td>
<td>Anti-Factor Xa, Platelet count, SCr</td>
<td>CBC, SCr</td>
<td>CBC, SCr</td>
</tr>
<tr>
<td>Variability of response</td>
<td>Yes</td>
<td>Yes</td>
<td>Relatively low</td>
<td>Relatively low</td>
<td>None</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>No</td>
<td>2%-5%</td>
<td>1%-2%</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Pharmacokinetics of the NOAC
Absorption

» Dabigatran
   – Integrity of capsule must be preserved during administration (e.g., do not crush/open)
     ○ Bioavailability increases by 75% without intact capsule

» Rivaroxaban
   – Bioavailability increases by 23 – 39% with food
     ○ Recommended to be taken with evening meal for the 15 mg and 20 mg dose

» Apixaban
   – Can be taken without regard to meals
Dabigatran: Ensuring Appropriate Use
Capsule Stability

» Dabigatran exetilate requires an acid environment for absorption
» Capsules contain multiple drug pellets
» Each pellet has a tartaric acid core (coated with drug) that creates an acidic microenvironment to improve dissolution and absorption independent of gastric pH

DO NOT CRUSH, CHEW OR BREAK CAPSULES

Dabigatran: Ensuring Appropriate Use

Capsule Stability

- Once bottle is opened, contents must be used within 4 months
  - Cap on bottle contains dessicant to reduce moisture and avoid degradation
- Blister packs should be used in inpatient setting
# Pharmacokinetics of NOAC

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tmax</strong></td>
<td>1.25-3 hours</td>
<td>2-4 hours</td>
<td>3-4 hours</td>
</tr>
<tr>
<td><strong>T ½ (hrs)</strong></td>
<td>12-17</td>
<td>5-9</td>
<td>8-15</td>
</tr>
<tr>
<td></td>
<td>14-17 elderly</td>
<td>11-13 in elderly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-18 mod CKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Conjugation (no CYP involvement)</td>
<td>Oxidation (via CYP3A4 and CYP2J2) and hydrolysis</td>
<td>Oxidation (via CYP3A4) and conjugation</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Renal: 80%</td>
<td>Renal: 66% (36% as unchanged drug)</td>
<td>Renal: 27% as unchanged drug</td>
</tr>
<tr>
<td><strong>Dialyzability</strong></td>
<td>Yes</td>
<td>Not expected</td>
<td>Minimal</td>
</tr>
<tr>
<td><strong>Liver dysfunction</strong></td>
<td>No issues</td>
<td>Avoid in mod or severe liver dysfxn</td>
<td>Avoid in severe liver dysfxn</td>
</tr>
<tr>
<td><strong>Reversibility</strong></td>
<td>No antidote</td>
<td>No antidote</td>
<td>No antidote</td>
</tr>
</tbody>
</table>
# Effect of Renal Function on Half-life

<table>
<thead>
<tr>
<th>Half-life (Hr)</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCL&gt;80 ml/min</td>
<td>14</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>CrCL 50 – 79 ml/min</td>
<td>17</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>CrCL 30-49 ml/min</td>
<td>19</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>CrCL &lt; 30 ml/min</td>
<td>28</td>
<td>10</td>
<td>17</td>
</tr>
</tbody>
</table>

# NOAC dosing for Renal Dysfunction

## Atrial Fibrillation

<table>
<thead>
<tr>
<th>NOAC</th>
<th>CrCl &gt;30 mL/min: 150 mg BID</th>
<th>CrCl 15-30 mL/min: 75 mg BID or avoid if on P-gp inhibitor</th>
<th>CrCl &lt;15 mL/min: contraindicated</th>
<th>CrCL 30 – 50 ml/min: Consider reduced dose of 75 mg BID if on dronadarone or ketoconazole</th>
<th>VTE Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CrCL &gt; 30 ml/min: LMWH or UFH x 5-10 days then dabigatran 150 mg BID</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>CrCl &gt;50 mL/min: 20 mg daily</td>
<td>CrCl 15-50 mL/min: 15 mg daily</td>
<td>CrCl &lt;15 mL/min: contraindicated</td>
<td>15 mg BID x 21 days then 20 mg daily for CrCL &gt; 30 ml/min</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>Most patients: 5 mg BID</td>
<td>Any 2: SCr ≥1.5 + Age ≥ 80 or weight ≤60: 2.5 mg BID</td>
<td></td>
<td>10 mg BID x 7 days then 5 mg BID</td>
<td></td>
</tr>
</tbody>
</table>

---

Apixaban in ESRD

» Recommended dose for AF in dialysis is 5mg BID.
  – Reduce dose to 2.5 mg BID if age ≥80 or weight ≤60 kg

» Pts on dialysis were not studied in clinical trials. Dosing based on PK and PD data (anti-Factor Xa activity)

Use with caution
Drug Interactions of NOAC
Pharmacodynamic drug interactions with NOACs, LMWH, fondaparinux, warfarin

- Increased risk of bleeding with concomitant administration of
  - Antiplatelet agents
  - ASA
  - NSAIDs & COX-2 inhibitors
  - Heparins & LMWH
  - Other anticoagulants

- Avoid unless benefits outweigh risks
P-glycoprotein drug interactions
<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Dabigatran| **p-GP inhibitors:**
|           | CrCl 30-50 mL/min: ↓ dose to 75 mg BID with ketoconazole or dronedarone
|           | CrCl 15-30 mL/min: AVOID concomitant use
|           | **p-GP inducers:** AVOID concomitant use with rifampin                                                                                     |
| Rivaroxaban| **p-GP inhibitors and strong CYP3A4 inhibitors:**
|           | Avoid concomitant use (e.g., ketoconazole, itraconazole, ritonavir, conivaptan)                                                              |
|           | **p-GP inducers and strong CYP3A4 inducers:**
|           | Avoid concomitant use (e.g., carbamazepine, phenytoin, rifampin, St. John’s wort)                                                          |
| Apixaban  | **p-GP inhibitors and strong CYP3A4 inhibitors:**
|           | Reduce dose to 2.5 mg BID. If already taking 2.5 mg BID, avoid concomitant use (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) |
|           | **p-GP inducers and strong CYP3A4 inducers:**
|           | Avoid concomitant use (e.g., carbamazepine, phenytoin, rifampin, St. John’s wort)                                                          |

Product Information, Pradaxa®; Product Information, Xarelto®; Product Information, Eliquis®.
Examples of DIs with Warfarin

Perspective
Over-the-Counter Products (OTC)
Prescription Products (RX)
Herbal Products
Drug Interactions
Pharmacokinetic Mechanisms

» Reduced absorption/bioavailability: cholestyramine

» Alterations in protein binding: phenytoin

» Alterations in metabolism
  – enzyme induction: rifampin, barbiturates, carbamazepine
  – enzyme inhibition: fluconazole, cimetidine, ciprofloxacin, erythromycin, etc.

» Stereoselective alteration in metabolism (R or S enantiomer)
  – S is 5 times more potent
  – Metronidazole (S), TMP-Sulfa (S), omeprazole (R), cimetidine (R)
  – amiodarone (R & S)

» Alteration in plasma clearance/excretion
  – thyroid hormones
Drug Interactions: Patient Considerations

» Consider how drug works/metabolism/protein binding

» Intensified monitoring
  – initiation of concomitant drug therapy
  – discontinuation of concomitant drug therapy

» Careful drug history
  – Prescription
  – PRN
  – OTC and herbals
Switching on and Off Anticoagulants
NOAC Switching Between Agents

» Parenteral to NOAC
  – UFH: when infusion d/c
  – LMWH: when next LMWH dose due

» Warfarin to NOAC
  – Dabigatran
    • Start when INR < 2.0
  – Rivaroxaban
    • Start when INR < 3.0
  – Apixaban
    • Start when INR < 2.0

» NOAC to parenteral
  – Dabigatran
    • CrCl ≥ 50 ml/min: wait 1 – 2 days
    • CrCl < 50 ml/min: wait 3 – 5 days
  – Rivaroxaban & Apixaban
    • Start when next rivaroxaban dose due (e.g., 24 hours)

» NOAC to warfarin
  – Dabigatran
    • CrCl ≥ 50 ml/min: wait 3 days
    • CrCl 31 – 50 ml/min: wait 2 days
    • CrCl 15 – 30 ml/min: wait 1 day
  – Rivaroxaban
    • Bridge with parenteral therapy
  – Apixaban
    • Bridge with parenteral therapy
# Pre-operative Management for invasive procedures

<table>
<thead>
<tr>
<th>Drug</th>
<th>Last dose prior to surgery</th>
<th>Low bleeding risk surgery</th>
<th>High bleeding risk surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCL &gt; 50 ml/min</td>
<td>1 day (24 hr)</td>
<td>2 days</td>
<td></td>
</tr>
<tr>
<td>CrCL 30 – 50 ml/min</td>
<td>2 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCL &lt;30 ml/min</td>
<td>4 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rivaroxaban or apixaban</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCL &gt; 50 ml/min</td>
<td>1 day (24 hr)</td>
<td>2 days</td>
<td></td>
</tr>
<tr>
<td>CrCL 30 – 50 ml/min</td>
<td>1-2 days</td>
<td>3-4 days</td>
<td></td>
</tr>
<tr>
<td>CrCL &lt; 30 ml/min</td>
<td>2 days</td>
<td></td>
<td>4 days</td>
</tr>
</tbody>
</table>

Nutescu EA. Am J Health-Syst Pharm 2013;70:1914-29
Post-operative management

» Timing of first dose after surgery:
  – Minor surgery: 24-48 hrs
  – Major surgery: 48 – 72 hr
  – Need adequate hemostasis

» If UFH or LMWH used as bridging for pts at high risk for embolism: NOAC resumed when UFH infusion d/c’d or when next scheduled dose of LMWH due

Management of NOAC Major Bleeding

» Initial Assessment:
  – Hemodynamic stability
  – Source of bleeding
  – Time since last dose
  – Renal function
  – Baseline coagulation testing

» General measures:
  – Stop anticoagulant
  – Mechanical compression of site
  – Monitor hemodynamic status
  – Volume replacement
  – Definitive interventions
  – Oral Activated charcoal for dabi ingestion (within 2h)
  – RBC transfusion for anemia
  – FFP for coagulopathy (e.g. dilutional)
  – Platelet transfusion for pts on anti-plt tx

» Severe/life-threatening bleeding
  – ICU
  – Hemodynamic support

» Consider:
  – 4-factor PCC (50 U/kg) for riva/apix
  – APCC (80 U/kg) for dabi

» Adjunctive therapies:
  – Hemodialysis for dabi
  – Desmopressin
  – Antifibrinolytic agents

» Antidotes in the pipeline
  – Idarucizumab
  – Andexanet alfa
## Concentrated Blood Factor Products

<table>
<thead>
<tr>
<th>Brand Names</th>
<th>rFactor VIIa</th>
<th>3-factor PCC</th>
<th>4-factor PCC</th>
<th>Activated PCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novo-Seven®</td>
<td>Bebulin® Profilnine®</td>
<td>Octaplex® Beriplex® KCentra®</td>
<td>FEIBA®</td>
<td></td>
</tr>
<tr>
<td>U.S. Availability</td>
<td>YES</td>
<td>YES</td>
<td>Approved 2013</td>
<td>YES</td>
</tr>
<tr>
<td>Factors Provided</td>
<td>VII</td>
<td>II, IX, X</td>
<td>II, VII, IX, X</td>
<td>II, VII, IX, X</td>
</tr>
<tr>
<td>Activated?</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

PCC = prothrombin complex concentrate

If Assessing Drug Presence

» Dabigatran
  - Normal thrombin time: No drug present
  - Elevated aPTT: Drug present
  - Normal aPTT: Cannot rule out drug effect

» Rivaroxaban and Apixaban
  - Elevated PT or UFH/LMWH/drug-specific anti-Xa:
    o Drug present
  - Normal PT or UFH/LMWH anti-Xa:
    o Cannot rule out drug effect
    o Note: PT more sensitive to rivaroxaban than apixaban
  - Elevated drug-specific anti-Xa: Drug present
Conclusions: Anticoagulant Choices in Renal Impairment (CrCL < 30 ml/min)

» Drugs with no significant renal clearance:
   – IV UFH
   – Warfarin
   – Argatroban
   – Apixaban: base on PK data only

» Drugs with significant dependence on renal clearance
   – LMWH: Consider dose reduction &/or anti-Xa monitoring
   – Fondaparinux
   – Rivaroxaban
   – Dabigatran
Conclusions

» Patients with renal insufficiency have an increased risk for bleeding and thrombosis compared to the general population
» Few clinical trials exist for patients with severe renal impairment
» Reduced dosing is recommended for some of the anticoagulants based on renal function
» Lack of clinical data, reversibility, and ability to easily monitor the anticoagulant effect of the NOACs limits their use in severe renal impairment
SELF ASSESSMENT QUESTIONS
Self Assessment Question

» Which anticoagulant uses INR to monitor the anticoagulant effects?

» a. Dabigatran (direct thrombin inhibitor)
» b. Rivaroxaban (direct Factor Xa inhibitor)
» c. Enoxaparin (LMWH)
» d. Warfarin
Self Assessment Question

Which anticoagulants are cleared primarily renally?

A. Warfarin
B. Dabigatran
C. Fondaparinux
D. Unfractionated heparin
E. Apixaban
F. Rivaroxaban
Self Assessment Question

Which is the largest drug by molecular weight and chain length?

A. Fondaparinux
B. Heparin
C. Dalteparin
D. All of the products are of equal weight and chain length
Self Assessment Question

Which drug is not metabolized by CYP450?

A. Warfarin
B. Dabigatran
C. Rivaroxaban
D. Apixaban
Self Assessment Question

» For which drug does a patient need to maintain a consistent vitamin K intake?

» A. Dabigatran

» B. Warfarin

» C. Enoxaparin

» D. Rivaroxaban