NOACs 2013: Evolving Anticoagulation Options

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Objectives

Clinical overview the new oral anticoagulants and their management issues

Rivaroxaban
Dabigatran
Apixaban
Disclosure

• **Potential for conflict(s) of interest:**

  – Dr. Erik Yeo has received payment/funding/research support from organizations whose product(s) are being discussed in this talk. These organizations and the drugs involved are listed below.

<table>
<thead>
<tr>
<th>Organization</th>
<th>Drug Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boehringer</td>
<td>Dabigatran (Pradaxa)</td>
</tr>
<tr>
<td>Bayer</td>
<td>Rivaroxaban (Xarelto)</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Apixaban (Eliquis)</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Dalteparin (Fragmin)</td>
</tr>
<tr>
<td>Leo Pharma</td>
<td>Tinzaparin (Innohep)</td>
</tr>
</tbody>
</table>
Can We Improve Upon Current Therapy?

“What makes an Ideal Anticoagulant and are we there yet”

<table>
<thead>
<tr>
<th></th>
<th>LMWH</th>
<th>NOACs</th>
<th>VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple dosing formulation / route</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>PO or IV or SC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good Pharmacology Properties</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Rapid onset,</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Good bioavailability</td>
<td>Y</td>
<td>Y/N</td>
<td>N</td>
</tr>
<tr>
<td>Clinically useful half life</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>no drug-drug or drug-food interactions</td>
<td>Y</td>
<td>Y/N</td>
<td>N</td>
</tr>
<tr>
<td>Simple dosing frequency</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>OD &gt; BID &gt; intermittent &gt; continuous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring not required</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Minimal side effects</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Better safety compared to VKA</td>
<td>N</td>
<td>Y/N</td>
<td>-</td>
</tr>
<tr>
<td>Easily and rapidly reversible</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Reasonable cost</td>
<td>N</td>
<td>Y/N</td>
<td>Y</td>
</tr>
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</table>
Warfarin is Highly Effective for the Prevention of Stroke in AF or Recurrent VTE

**Stroke Prevention in Atrial Fibrillation**

**Standard Care:** Warfarin (INR 2.0-3.0)

- **64% RRR**
- **38% RRR**
- **40% RRR**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin vs. Placebo</td>
<td>1</td>
</tr>
<tr>
<td>Warfarin vs. ASA</td>
<td>1</td>
</tr>
<tr>
<td>Warfarin vs. ASA + Clopidogrel</td>
<td>2</td>
</tr>
</tbody>
</table>

**Treatment of Venous Thromboembolism (VTE)**

**Standard Care:** Warfarin (INR 2.0-3.0), initial parenteral anticoagulation until INR >2

**Chance of recurrent VTE in first 3 months**

- **47%**
  - If proximal DVT inadequately treated

- **<2%**
  - If adequate anticoagulant response is achieved
Using Warfarin Remains Challenging

- Only 55% of AF patients without contraindications receive warfarin\(^1\)

- Mean TTR is low in patients receiving warfarin

**Anticoagulant Choice**

A. UFH/LMWH

B. Warfarin

C. Rivaroxaban (Xarelto)

D. Dabigatran (Pradaxa)

E. Apixaban (Eliquis)

F. Fondaparinux*

G. Argatroban*

H. Hirudin/Bivalrudin*
# New Oral Anticoagulants (NOACs*)

<table>
<thead>
<tr>
<th>Site</th>
<th>Coagulation pathway</th>
<th>Approaches to Drug Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>TF/VIIa</td>
<td>Thrombin Inhibitors: dabigatran*</td>
</tr>
<tr>
<td>Propagation of Thrombin generation</td>
<td>X, IX, IXa, VIIIa</td>
<td>Factor Xa Inhibitors: rivaroxiban*, apixaban*</td>
</tr>
<tr>
<td>Thrombin activity</td>
<td>IIa</td>
<td>Thrombin Inhibitors: dabigatran*</td>
</tr>
</tbody>
</table>

- **Heparin**: Red circle
- **LMWH**: Green circle
- **VKA**: Yellow dot

*New Oral Anticoagulants (NOACs*)
Unfractionated Heparin

- Inpatient management only
- Indications: high risk bleeders or renal dysfunction
- Binds to antithrombin
- Accelerates inactivate thrombin (IIa) + factor Xa via antithrombin
- T1/2 : 60 min
- Measureable (anti-Xa activity), aPTT 1.5-2 x normal
- Bioavailability
  - Highly variable due to protein binding
- Bleeding complication
  - The risk of bleeding associated with IV unfractionated heparin (UFH) in patients with acute venous thromboembolism is < 3% in recent trials.
  - Bleeding risk increase with increasing heparin dosages and age (> 70 years)
- HIT 3-5% (some hospitals restrict use)
- Has become expensive (was cheap)
- Reversible (protamine)
Low Molecular Weight Heparins

- Enoxaparin (Lovenox), dalteparin (Fragmin), and tinzaparin (Innohep)
- Approved for inpatient and outpatient treatment of VTE.
- No monitoring required
  - >90% bio-available
  - Minimal protein binding
  - Levels are predictable when weight base dosing
- No heparin-induced thrombocytopenia (approx 1:1000)
- Renal clearance (CrCl: > 30 mL/min)
- Most cleared in 24 hours
  - Peak at 5-8 hours
  - Allows for OD or BID dosing
  - Measureable (anti-Xa level)
- Associated with less major bleeding compared with UFH in acute VTE
- Expensive
- Non-reversible (protamine only reverses IIa activity)
Rivaroxaban (Xarelto)  
oral direct Factor Xa inhibitor

- Synthetic oral, small molecule (MW 435)
- Binds all intravascular factor Xa
- Predictable pharmacology
  - Rapid onset (30 min)
  - Peak effect 2-4 hrs
  - Half-life ~ 5-9 hrs (young), 11-13 hrs (elderly)
  - High bioavailability (66-100%)
- Must be taken with food
- Low risk of drug–drug interactions
- No requirement for monitoring
- Renal clearance (35%)
- OD dosing
- EBM Indications
  - VTE prophylaxis,
  - non-valvular AF
  - VTE treatment
- Not reversible, possibly reversible PCC
- Ontario LU code for AF and VTE

Perzborn et al. 2005; Kubitza et al. 2005; 2006; 2007; Roehrig et al, 2005
Oral pro-drug, converted to dabigatran (MW 460),
Binds free and surface bound thrombin (IIa)
Predictable and consistent pharmacology
- Rapid onset of action (0.5 hr)
- Peak effect 1-3 hrs
- Half-life ~ 12-17 hr,
  ~ 80% renal excretion
- Low Bioavailability 7% (do not chew)
Absorption requires acidic gastric milieu (tartric acid)
Low potential for drug-drug interactions,
No drug-food interactions
No requirement for routine coagulation monitoring
Renal clearance (do not use CrCl<50mL/min)
BID dosing
Indications (like Rivaroxaban and Apixaban)
- VTE prophylaxis
- VTE Rx,
- non-valvular AF
Drug not reversible
Important side effects (gastric)
Ontario LU code AF

Apixaban: (Eliquis)
oral direct Factor Xa inhibitor

- Small synthetic oral molecule (MW 459)
- Binds both free and surface bound Xa active enzymatic site
- Predictable pharmacology
  - Rapid onset 30'  
  - peak 3-4 hrs  
  - Half-life ~ 8-15 hrs,
- Good bioavailability (50%)
- Hepatic clearance (75%) renal clearance (25%)
- Metabolized in liver via CYP3A4 and CYP independent mechanisms
- Low risk of drug–drug interactions
- No food interaction issues
- No requirement for monitoring
- BID dosing
- Indication
  - VTE prophylaxis  
  - Non-valvular AF  
  - VTE treatment
- No antidote, not reversible
- Lower bleeding risk

Perzborn et al. 2005; Kubitza et al. 2005; 2006; 2007; Roehrig et al, 2005
## Novel Oral Anticoagulants – Pharmacological Properties

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Dabigatran&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Factor Xa</td>
<td>Factor IIa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>OD</td>
<td>BID</td>
<td>BID</td>
</tr>
<tr>
<td><strong>Bioavailability, %</strong></td>
<td>80-100%*</td>
<td>6.5%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>5-13h</td>
<td>12-14 h</td>
<td>8-15 h</td>
</tr>
<tr>
<td><strong>Renal clearance</strong> (unchanged bioavailable drug)</td>
<td>~33%</td>
<td>85%</td>
<td>27%†</td>
</tr>
<tr>
<td><strong>Cmax</strong></td>
<td>2-4 h</td>
<td>1-2 h</td>
<td>3-4 h</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Strong inhibitors of both CYP3A4 and P-gp</td>
<td>P-gp inhibitors</td>
<td>Strong inhibitors of both CYP3A4 and P-gp</td>
</tr>
</tbody>
</table>

NOACs in Non-Valvular AF
## Atrial Fibrillation Trials vs. Warfarin

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td>RELY</td>
<td>ROCKET</td>
<td>ARISTOTLE</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Blinded dabigatran, open label W, PROBE noninferiority</td>
<td>DB, noninferiority</td>
<td>DB, noninferiority</td>
</tr>
<tr>
<td><strong>AF criteria</strong></td>
<td>AF x 1</td>
<td>AF x 2</td>
<td>AF or Afl x 2</td>
</tr>
<tr>
<td></td>
<td>&lt; 6 months</td>
<td>≥1 in &lt; 30 days</td>
<td>&lt; 12 months</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>110mg BID,</td>
<td>20mg Daily</td>
<td>5 mg BID</td>
</tr>
<tr>
<td></td>
<td>150mg BID</td>
<td>(15mg for CrCl 30-49)</td>
<td>2.5mg BID if ≥ 2 of: age ≥80, wt≤60, SrCr≥133</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>18 113</td>
<td>14 266</td>
<td>18 206</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>71</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td><strong>CHADS&lt;sub&gt;2&lt;/sub&gt;</strong></td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>% VKA naive</strong></td>
<td>50 %</td>
<td>38 %</td>
<td>43 %</td>
</tr>
<tr>
<td><strong>TTR</strong></td>
<td>64%</td>
<td>55%</td>
<td>62%</td>
</tr>
</tbody>
</table>

*NEJM 2009;361:1139; NEJM 2011;365;883; NEJM 2011;365;981*
RE-LY: Dabigatran in Non-valvular Atrial Fibrillation
(Time to first stroke / SSE)

- enrolment 15,000 patients
- Dabigatran 110 and 150 mg bid compared with warfarin (std of care)
- Treatment duration up to 3 years
- Superior and non-inferior for risk (Bleed)
- Non-inferior and superior for efficacy (Stroke)

DOI 10.1056/NEJMoa0905561
Rocket-AF: Rivaroxiban in Non-valvular Atrial AF
(Time to first stroke / SSE)

Rivaroxaban 188 patients, 1.7% per year
Warfarin 241 patients, 2.2% per year
HR 0.79 (95% CI, 0.66–0.96); P (superiority)=0.011

21% RRR
Aristotle: Apixaban in Non-valvular Atrial AF
(Time to first stroke / SSE)

A Primary Outcome: Stroke or Systemic Embolism

No. at Risk
Apixaban   9120  8726  8440  6051  3464  1754
Warfarin   9081  8620  8301  5972  3405  1768

Hazard ratio, 0.79 (95% CI, 0.66–0.95)
P = 0.01

HR 0.79 (95% CI, 0.66–0.95); P (superiority) = 0.011
21% RRR

Apixaban 212 patients, 1.27% per year
Warfarin 265 patients, 1.60% per year
Table 1. Comparison of clinical trials of the direct thrombin inhibitors and factor Xa inhibitors for anticoagulation in patients with atrial fibrillation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RE-LY⁴</th>
<th>ROCKET AF⁵</th>
<th>ARISTOTLE⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment groups</td>
<td>Dabigatran 150 mg BID; dabigatran 110 mg BID</td>
<td>Rivaroxaban 20 mg/d (15 mg/d for CrCl 30–49 mL/min)</td>
<td>Apixaban 5 mg BID</td>
</tr>
<tr>
<td>Control group</td>
<td>Dose-adjusted warfarin (INR = 2.0–3.0); TTR = 64%</td>
<td>Dose-adjusted warfarin (INR = 2.0–3.0); TTR = 55%</td>
<td>Dose-adjusted warfarin (INR = 2.0–3.0); TTR = 62%</td>
</tr>
<tr>
<td>Study design</td>
<td>Randomized, open-label</td>
<td>Randomized, double-blind, double-dummy</td>
<td>Randomized, double-blind, double-dummy</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
</tr>
<tr>
<td><strong>Patients' characteristics at baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>AF and ≥1 risk factor*</td>
<td>AF and ≥2 risk factors*</td>
<td>AF and ≥1 risk factor*</td>
</tr>
<tr>
<td>Mean CHADS₂ score†</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>71.5</td>
<td>73.0</td>
<td>70.0</td>
</tr>
<tr>
<td>Aspirin treatment, %</td>
<td>39.8</td>
<td>36.5</td>
<td>30.9</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke and systemic embolism</td>
<td>Dabigatran 150 mg: 1.11% (P &lt; 0.001* and P &lt; 0.001†); dabigatran 110 mg: 1.53% (P &lt; 0.001* and P = 0.34†); warfarin: 1.69%; Rivaroxaban: 2.1% (P &lt; 0.001* and P = 0.12†); warfarin: 2.4%; Apixaban: 1.27% (P &lt; 0.001* and P = 0.01†); warfarin: 1.60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>Dabigatran 150 mg: 3.64% (P = 0.051); dabigatran 110 mg: 3.75% (P = 0.13); warfarin: 4.13%; Rivaroxaban: 4.5% (P = 0.15); warfarin: 4.9%; Apixaban: 3.52% (P = 0.047); warfarin: 3.94%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Dabigatran 150 mg: 3.11% (P = 0.31); dabigatran 110 mg: 2.71% (P = 0.003); warfarin: 3.36%; Rivaroxaban: 3.6% (P = 0.58); warfarin: 3.4%; Apixaban: 2.13% (P &lt; 0.001); warfarin: 3.09%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>Dabigatran 150 mg: 0.30% (P &lt; 0.001); dabigatran 110 mg: 0.23% (P &lt; 0.001); warfarin: 0.74%; Rivaroxaban: 0.5% (P = 0.02); warfarin: 0.7%; Apixaban: 0.33% (P &lt; 0.001); warfarin: 0.80%</td>
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</tbody>
</table>

AF = atrial fibrillation; ARISTOTLE = Apixaban for Reduction in Stroke and Other Thrombotic Events in Atrial Fibrillation; CHADS = Congestive heart failure, hypertension, age, diabetes, prior stroke; CrCl = creatinine clearance; INR = international normalized ratio; RE-LY = Randomized Evaluation of Long-Term Anticoagulation in Therapy; ROCKET AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; TTR = time in therapeutic range.

*Risk factors: age ≥75 y; history of stroke, transient ischemic attack, or systemic embolism; symptomatic heart failure and/or left-ventricular ejection fraction <40%; diabetes mellitus; and/or need for antihypertensive treatment.

†Scale: 0 = 1.9% annual risk for stroke (95% CI, 1.2–3.0); 1 = 2.8% annual risk for stroke (95% CI, 2.0–3.8); 2 = 4.0% annual risk for stroke (95% CI, 3.1–5.1); 3 = 5.9% annual risk for stroke (95% CI, 4.6–7.3); 4 = 8.5% annual risk for stroke (95% CI, 6.3–11.1); 5 = 12.5% annual risk for stroke (95% CI, 8.2–17.5); and 6 = 18.2% annual risk for stroke (95% CI, 10.5–27.4).

*Primary outcome for noninferiority.

†Primary outcome for superiority.
Comparable Primary Efficacy and Safety

Figure 2  Comparable Primary Efficacy Endpoints of Stroke or Systemic Embolism

Figure 3  Comparable Primary Safety Endpoints of Major Bleeding

JACC 2012; 59(16):1413-25
NOACs in Venous Thrombosis
Recover I and II
(Dabigatran in acute VTE)

- Non-inferiority study
- enrolment 4,000 patients each study
- LMWH/Dabigatran 220 mg BID vs LMWH/warfarin (Std of care)
- Treatment duration up to 6 mths

Results
- Non-inferior efficacy (recurrent VTE) 30 events (2.4%) vs 27 events (2.1%)
- non-inferior for risk (Bleed) 20 events (1.6%) vs 24 events (1.9%)
**Einstein and Einstein PE**
(Rivaroxaban in acute VTE Treatment)

- Non-inferior study
- enrolment 3449 patients each study
- LMWH/rivaroxaban 15 mg BID x 3wk then 20 mg OD vs LMWH/warfarin (Std of care)
- Treatment duration of 3, 6 and 12 mths
- Additional extension of placebo vs drug

**Results**
- Non-inferior efficacy (recurrent VTE)
  36 events (2.1%) vs 51 events (3.0%)
- Non-inferior for risk (Bleed)
  36 events (8.1%) vs 51 events (8.1%)

---

Figure 2. Kaplan–Meier Cumulative Event Rates for the Primary Efficacy Outcome in the Two Studies.
VKA denotes vitamin K antagonist.
AMPLIFY (Apixaban in VTE Treatment)

Non-inferiority
N = 5395 Pts
Apixaban vs LMWH+OAC

Recurrent VTE (2.3% vs 2.7%) 0.84 (0.60-1.18)
Major bleeding (0.6% vs 1.8%) 0.31 (0.17-0.55)
All clinically relevant bleed (4.3% vs 9.7%) 0.44 (0.36-0.55)
VTE, VTE-related death, or major bleeding 0.62 (0.47-0.83)

Rates of other adverse events were similar in the two groups.

Apixaban was non-inferior to conventional therapy (P<0.001)
AMPLIFY and AMPLIFY-Ext
(Apixaban in VTE Treatment)

- Non-inferior study
- enrolment 2486 patients each study
- Std of care VTE treatment then apixaban (2.5/5 mg BID) or placebo
- Treatment duration of 12 mths

Results
- Superior efficacy (recurrent VTE) placebo 8.8% vs 1.7% for 2.5 and 5 mg
- Superior for risk (major bleed) placebo 0.5% vs 0.2% and 0.1% for 2.5 and 5 mg
- Superior for death: placebo 1.7% vs 0.8% and 0.5% for 2.5 and 5 mg
NOACs: Issues and Considerations
Dosing and Storage Considerations

**Rivaroxaban**

- 15 & 20mg
  - One tablet should be taken once daily with food\(^1\)
  - *No change in PK parameters when crushed and administered in applesauce or via NG tube\(^2\)
  - Store between 15 - 30°C\(^1\)

**Dabigatran**

- 110 & 150mg
  - One capsule should be taken twice daily with food, or on an empty stomach with water\(^3\)
  - Capsule should be taken whole and not chewed, broken, or opened\(^3\)
    - Bioavailability may increase 75% (1.8 fold) when the pellets are taken without the capsule shell
  - Store between 15 - 30°C in original package to protect from moisture\(^3\)
  - For bottles, use within 4 months of opening

**Apixaban**

- 2.5 & 5mg
  - One tablet should be taken twice daily with or without food\(^4\)
  - Store between 15 - 30°C\(^4\)

---

*note that crushed tablet data does not appear in Canadian PM
New Oral Anticoagulants: Total Drug Exposure (AUC) with Declining Renal Function

- **Rivaroxaban** (33% cleared renally*)
- **Dabigatran** (85% cleared renally)
- **Apixaban** (27% cleared renally†)

* active drug
† Factoring in the absolute bioavailability of apixaban, ~50% of the systemically available dose is eliminated in urine

---

Monitoring NOACs: Effect on Coagulation Testing

Anti-Xa
- Rivaroxaban, Apixaban, LMWH (similar effects on testing)
- Prolong aPTT>>PT>thrombin time

Anti-thrombin
- TT >> aPTT >PT
Drug-Drug Effects

P-Glycoprotein Interaction
Plasma concentration of the novel agents is affected by interaction with the efflux transporter P-glycoprotein (P-gp). Dabigatran etexilate (prodrug), rivaroxaban, and apixaban all act as a substrate for P-gp. Absorbed dabigatran etexilate, as an example, is ‘pumped’ back into the intestinal tract. P-gp inducers, inhibitors, and competitors all must be carefully considered in the context of the novel anticoagulants.

P-gp inducer (reduce drug concentrations)
rifampicin, carbamazepine and St. John’s wort contraindicated with all NOACs

P-gp inhibitors (increase drug concentrations)
ketoconazole, verapamil, amiodarone, dronedarone, quinidine, and clarithromycin contraindicated with all NOACs

P-gp competitor
atorvastatin: may increase dabigatran concentration; no effect on rivaroxaban
diltiazem: may increase apixaban and rivaroxaban; no effect on dabigatran.

Table 5 Effect on NOAC plasma levels (‘area under the curve, AUC’) from drug–drug interactions and clinical factors, and recommendations towards NOAC dosing

<table>
<thead>
<tr>
<th>Via</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban*</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>P-gp competition and CYP3A4 inhibition</td>
<td>+18%</td>
<td>No data yet</td>
<td>No effect</td>
</tr>
<tr>
<td>Digoxin</td>
<td>P-gp competition</td>
<td>No effect</td>
<td>No data yet</td>
<td>No effect</td>
</tr>
<tr>
<td>Verapamil</td>
<td>P-gp competition (and weak CYP3A4 inhibition)</td>
<td>+12–180% (reduce dose and take simultaneously)</td>
<td>No data yet</td>
<td>+53% (SR) (reduce dose by 50%)</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>P-gp competition and weak CYP3A4 inhibition</td>
<td>No effect</td>
<td>+40%</td>
<td>No data yet</td>
</tr>
<tr>
<td>Quinidine</td>
<td>P-gp competition</td>
<td>+50%</td>
<td>No data yet</td>
<td>+80% (reduce dose by 50%)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>P-gp competition</td>
<td>+12–60%</td>
<td>No data yet</td>
<td>No effect</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>P-gp and CYP3A4 inhibitor</td>
<td>+70–100% (US: 2 × 75 mg)</td>
<td>No data yet</td>
<td>+85% (reduce dose by 50%)</td>
</tr>
<tr>
<td>Ketoconazole; itraconazole; voriconazole; posaconazole</td>
<td>P-gp and BCRP competition; CYP3A4 inhibition</td>
<td>+140–150% (US: 2 × 75 mg)</td>
<td>+100%</td>
<td>No data yet</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Moderate CYP3A4 inhibition</td>
<td>No data yet</td>
<td>No data yet</td>
<td>+42% (if systemically administered)</td>
</tr>
<tr>
<td>Cyclosporin; tacrolimus</td>
<td>P-gp competition</td>
<td>No data yet</td>
<td>No data yet</td>
<td>+10%</td>
</tr>
<tr>
<td>Clarithromycin; erythromycin</td>
<td>P-gp competition and CYP3A4 inhibition</td>
<td>+15–20%</td>
<td>No data yet</td>
<td>No data yet</td>
</tr>
<tr>
<td>HIV protease inhibitors (e.g. ritonavir)</td>
<td>P-gp and BCRP competition or inducer; CYP3A4 inhibition</td>
<td>No data yet</td>
<td>Strong increase</td>
<td>No data yet</td>
</tr>
<tr>
<td>Rifampicin; St. ohn’s wort; carbamazepine; phenytoin; phenobarbital inducers</td>
<td>P-gp/ BCRP and CYP3A4/CYP2J2</td>
<td>−66%</td>
<td>−34%</td>
<td>−35%</td>
</tr>
<tr>
<td>Antacids (H2R, PPI, Al-Mg-hydroxide)</td>
<td>GI absorption</td>
<td>−12–30%</td>
<td>No data yet</td>
<td>No effect</td>
</tr>
</tbody>
</table>

Other factors

- Age ≥ 80 years: Increased plasma level
- Age ≥ 75 years: Increased plasma level
- Weight < 60 kg: Increased plasma level
- Renal function: Increased plasma level

Other increased bleeding risk

Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥ 3

Red, contraindicated
Orange: reduce dose
Yellow: consider dose reduction

Online: http://www.escardio.org/
### Switching Patients Between Warfarin and NOAC

#### Warfarin → NOAC

- Discontinue warfarin
- Check INR
- Initiate NOAC when the INR ≤ 2.0
  - Or
  - Initiate NOAC in 3 days
  - Or
  - Give 4 mg VK PO and start NOAC next day

#### Rivaroxaban → Warfarin

- NOAC should be continued concurrently with the VKA until the INR is ≥ 2.0
- First 2 days of the conversion period:
  - VKA can be given in the usual starting doses without INR testing
- Thereafter, INR should be tested just prior to the next dose of NOAC.
- Discontinue NOAC once the INR is >2.0
Discontinuation Before Elective Invasive or Surgical Procedures

Time to discontinue medication prior to procedure

**Rivaroxaban T1/2-9 hr**
- Determine patients risk of bleeding
  - Standard risk
    - 1 day
    - 2-4 days
    - ≥15%
  - High risk of bleeding or major surgery
    - At least 1 day
    - 0%

**Dabigatran T1/2-13 hr**
- Determine patients risk of bleeding
  - Standard risk
    - Estimate CrCl
      - 30-49 mL/min
        - 2-3 days
        - 15%
      - 50-79 mL/min
        - 1-2 days
        - <5%
      - ≥ 80 mL/min
        - 1 day
        - 12%
  - High risk of bleeding or major surgery
    - Estimate CrCl
      - 30-49 mL/min
        - 4 days
      - 50-79 mL/min
        - 2-3 days
      - ≥ 80 mL/min
        - 2 days

**Apixaban T1/2-11 hr**
- Determine patients risk of bleeding
  - Standard risk
    - 1 day
    - 2 days
    - ≥12%
  - High risk of bleeding or major surgery
    - At least 1.5 day
    - <5%

Xarelto® PM, 2013, 2012; Eliquis® PM November, 2012; Pradaxa ® PM November, 2012

Recommended

May be considered
Rivaroxaban and Apixaban Management of Bleeding

Minor

- Delay next dose or discontinue treatment (as appropriate)
- Appropriate symptomatic treatment
e.g. mechanical compression, surgical hemostasis, fluid replacement and hemodynamic support, blood products (PRBC or FFP) or platelets

Major

- Consider administration of one of the following procoagulants*:
  - Activated prothrombin complex concentrate (APCC)
  - Prothrombin complex concentrate (PCC)
  - Recombinant Factor-VIIa (rFVIIa)

*there is currently only very limited experience with the use of these products in individuals receiving rivaroxaban.
Dabigatran: Management of Bleeding

Patient with bleeding on dabigatran therapy

Mild bleeding:
- Delay next dose or discontinue treatment as appropriate

Moderate-Severe bleeding:
- Symptomatic treatment
- Mechanical compression
- Surgical intervention
- Fluid replacement and hemodynamic support
- Blood product transfusion
- Oral charcoal application* (if dabigatran etexilate ingestion <2 hours before)
- Hemodialysis

Life-threatening bleeding:
- Consideration of rFVIIa or PCC*
- Charcoal filtration*

*Recommendation based only on limited non-clinical data, there is no experience in volunteers or patients
New Orals: Clinical Summary

Over-arching Issues
- Rapid onset, easily managed and manipulated half lives, good bioavailability (except dabigatran)
- Twice daily dosing is problematic (Dabi and Apix)
- Well tolerated (dabigatran acidic milieu and poor bioavailability)
- Some drug related issues
- Renal clearance issues with dabigatran and rivaroxaban
- All new orals are non-reversible if bleed, for anti-Xa PCC have activity, dabigatran is dialyzable

VTE Prophylaxis
- New orals very effective, as good or better than best LMWH with similar bleeding risk
- Dosing: Dabigatran (220/150mg OD) and Rivaroxaban (10mg OD) vs Apixaban (2.5mg BID)
- Excellent opportunity for simplified and more extensive use in outpatients

Atrial Fibrillation
- New orals very effective, well studied (possibly superior to OAC: dabigatran, apixaban)
- Good or better than best VKA with similar or lower bleeding risk
- Dosing: Rivaroxaban 15/20 mg OD vs Dabigatran 110/150mg BID and Apixaban (2.5/5mg BID)
- Excellent opportunity for improved AC utilization in the 30% of indicated patients not treated with warfarin
- Trials not comparable: recommend drug selection based on other factors: dosing, cost, adverse effect profile, renal issues, bleeding risk control etc

VTE Treatment
- New orals effective, well studied (prophylaxis, non-valv AF, VTE)
- Non-inferior than best VKA with similar bleeding risk
- Dosing: Rivaroxaban 15 mg BID x 3wks then 20mg OD, Dabigatran 110/150mg BID and Apixaban (2.5/5mg BID)
- Dabigatran requires LMWH X 5 days for VTE
Case 1

83 yr old male, unwell with chronic AF, CHADsVasc 4 (HT, CHF, no CVA/TIA), on OAC 15 years (target INR 2-3), erratic INRs, GI bleed 4 yrs ago and spontaneous bleed in thigh 6 mths ago-resolved off of AC, GFR 30 ml/min

Choose AC best option
1) Dabigatran 110 PO BID
2) Rivaroxaban 15 mg PO OD
3) Apixaban 2.5 mg PO BID
4) Warfarin target INR 2-2.5
5) ASA 81
Case 2

79 yr old female, controlled, active metastatic breast cancer on letrozole (AI), develops left leg DVT and minimally symptomatic DVT, normal renal function

Choose best treatment option for first 6 mths
1) LMWH x 5-7 dys the warfarin (INR 2-3)
2) Dabigatran 220 mg PO BID or 110 PO BID
3) Rivaroxaban 15 mg PO BID x 3 weeks then 20 mg PO OD
4) Apixaban 10 mg PO BID x 7 dys then 5 mg PO BID
5) Weight based LMWH alone
Case 3

79 yr old male, unwell, chronic AF, prior stroke, CHADsVasc 6 (HT, CHF, CVA/TIA), on rivaroxaban 15 PO OD, needs a prostate Bx, GFR 40 ml/min

Choose recommendation for AC management for Bx
1) Stop rivaroxaban 3-5 days prior to Bx, restart 2 days after procedure
2) Stop rivaroxaban 2 days prior to Bx, restart D+1 10 mg then 15mg
3) Stop rivaroxaban 1 days prior to Bx, restart D+1 10 mg then 15 mg
4) Stop rivaroxaban 2 days prior to Bx, restart 2 days after (15 mg)
5) Stop rivaroxaban 3-5 days prior to Bx, restart 3 days after procedure (15 mg)