ANTICOAGULANT DRUG INTERACTIONS

New Agents, New Concerns

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Director, Anticoagulation Services
UWMedicine Department of Pharmacy
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## CONFLICTS OF INTEREST

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant</td>
<td>none</td>
</tr>
<tr>
<td>Research support</td>
<td>none</td>
</tr>
<tr>
<td>Speaker’s bureau</td>
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<tr>
<td>Honoraria</td>
<td>Aspen Pharma/Australia (Oct 2015)</td>
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<tr>
<td></td>
<td>Roche Diagnostics/Australia (Oct 2015)</td>
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<tr>
<td>Ownership interest</td>
<td>none</td>
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<tr>
<td>Other</td>
<td>none</td>
</tr>
</tbody>
</table>
OBJECTIVES

Following this presentation, the participant should be able to:

1. assess the potential for interactions between DOACs and other medications

2. evaluate current evidence of DOAC drug interactions

3. identify patient management issues posed by the possibility of interactions between DOACs and other medications
CONCURRENT USE OF WARFARIN WITH POTENTIALLY INTERACTING DRUGS

Source: pharmacy claims data from a pharmacy benefits manager
N: 134,833 patients receiving warfarin during a 1-yr index period

- Any Interacting Medication: 81.6%
- Increased INR Response Anticipated: 64.8%
- Decreased INR Response Anticipated: 5.3%
- Increased Bleeding Risk Anticipated: 20.1%

WARFARIN DRUG INTERACTIONS
MECHANISMS THAT CAN ELEVATE INR

1. Increased catabolism of clotting factors  →  thyroid hormones
2. Decreased synthesis of clotting factors  →  MTT side chain cephalosporins
3. Impaired vitamin K production  →  broad spectrum antibiotics
4. Inhibition of warfarin metabolism  →  EXTENSIVE LIST
WARFARIN METABOLISM

S-warfarin
- 90% oxidation
- CYP-2C9 → 7-hydroxywarfarin
- CYP-2C9 → 6-hydroxywarfarin
- CYP-3A4 → 10-hydroxywarfarin
- CYP-3A4 → 4'-hydroxywarfarin
- 10% reduction
- SS-alcohol
- SR alcohol

R-warfarin
- 60% oxidation
- CYP-1A2 → 6-hydroxywarfarin
- CYP-1A2 → 7-hydroxywarfarin
- CYP-3A4 → 10-hydroxywarfarin
- CYP-3A4 → 4'-hydroxywarfarin
- CYP-2C19 → 8-hydroxywarfarin
- 40% reduction
- RS-alcohol
- RR-alcohol

Warfarin metabolism involving CYP enzymes: 2C9, 2C19, 3A4.
### WARFARIN INTERACTIONS INVOLVING CYP450 ENZYMES

<table>
<thead>
<tr>
<th>ENANTIOMER</th>
<th>METABOLIC PATHWAY</th>
<th>ENZYME INHIBITORS</th>
<th>ENZYME INDUCERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>S Warfarin</td>
<td>CYP2C9</td>
<td>amiodarone, fluconazole, metronidazole, TMP/SMX</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CYP3A4</td>
<td>erythromycin</td>
<td>carbamazepine, nafcillin, phenobarbital, rifampin, St John’s wort</td>
</tr>
<tr>
<td>R Warfarin</td>
<td>CYP1A2</td>
<td>cimetidine, ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CYP3A4</td>
<td>erythromycin</td>
<td>carbamazepine, nafcillin, phenobarbital, rifampin, St John’s wort</td>
</tr>
</tbody>
</table>
WARFARIN DRUG INTERACTIONS MECHANISMS THAT CAN REDUCE INR

1. Increased synthesis of clotting factors → vitamin K estrogens
2. Decreased catabolism of clotting factors → methimazole PTU
3. Decreased absorption of warfarin → colestipol cholestyramine
4. Induction of warfarin metabolism → EXTENSIVE LIST
DRUG INTERACTION VARIABILITY

- In patient susceptibility
- In magnitude of response
- In time of onset
- In duration of effect
WARFARIN DRUG INTERACTIONS WITH AZOLE ANTIFUNGAL AGENTS

Fluconazole (n=18)

Voriconazole (n=5)

Itraconazole (n=6)

WARFARIN DRUG INTERACTION VARIABLES

- CYP2C9 genotype
- VKORC1 phenotype
- COMORBID DISEASES
- OTHER DRUGS
- DIET
- AGE

clotting factor synthesis and degradation
absorption/ metabolism/ elimination of warfarin
absorption/ metabolism/ elimination of interacting drug

SUSCEPTIBILITY
MAGNITUDE
ONSET
DURATION
Interacting drugs are not absolutely contraindicated in patients taking warfarin.

When adding/discontinuing an interacting drug:

- increase frequency of INR monitoring
- adjust dosing of warfarin as needed
## DOACs – DIRECT ORAL ANTICOAGULANTS

<table>
<thead>
<tr>
<th></th>
<th>DABIGATRAN</th>
<th>APIXABAN</th>
<th>RIVAROXABAN</th>
<th>EDOXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct MOA</td>
<td>IIIa inhibitor</td>
<td>Xa inhibitor</td>
<td>Xa inhibitor</td>
<td>Xa inhibitor</td>
</tr>
<tr>
<td>Brand Name</td>
<td>Pradaxa</td>
<td>Eliquis</td>
<td>Xarelto</td>
<td>Savaysa</td>
</tr>
</tbody>
</table>

- Fixed dose
- More predictable & stable anticoagulant response
  - Rapid onset & offset
- Broader therapeutic window
- No monitoring
**DABIGATRAN PHARMACOKINETIC CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Prodrug</th>
<th>dabigatran etexilate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>mediated by P-gp</td>
</tr>
<tr>
<td>Bioconversion to Active drug</td>
<td>Converted to <em>dabigatran</em> via esterase-catalyzed hydrolysis</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>2 - 3 hours</td>
</tr>
<tr>
<td>$T_{\frac{1}{2}}$</td>
<td>12 - 17 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Conjugation (no involvement of CYP)</td>
</tr>
<tr>
<td>Renal Clearance</td>
<td>80%</td>
</tr>
</tbody>
</table>
P-GLYCOPROTEIN
DRUG TRANSPORT PROTEIN

- P = “permeability”
- Functions as an “efflux pump” to mediate absorption of drugs that are P-gp “substrates”
- Present in small intestine, as well as blood-brain barrier, liver, kidneys

MECHANISM OF P-GP DRUG INTERACTIONS

Effect of interacting drug on P-gp | Effect on absorption of substrate drug | Effect on serum concentrations of substrate drug | EXAMPLE
--- | --- | --- | ---
P-gp Inhibitor | increase | increase | VERAPAMIL
P-gp Inducer | decrease | decrease | RIFAMPICIN (RIFAMPIN)

### DABIGATRAN - VERAPAMIL INTERACTION (P-gp inhibitor)

<table>
<thead>
<tr>
<th>Part 1:</th>
<th>multiple dose verapamil in 20 volunteers (mean age 38.3 +/- 11.3 years; mean BMI 23.9 +/- 2.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. reference:</td>
<td>DE 150mg single dose (then 4 day washout)</td>
</tr>
<tr>
<td>B. reference:</td>
<td>V-IR 120mg bid x 3 days (days 1-3)</td>
</tr>
<tr>
<td>C. test:</td>
<td>V-IR 120mg bid x 4 days (days 4-7)  + DE 150mg on day 4, 1hr after V-IR</td>
</tr>
<tr>
<td>D. test:</td>
<td>V-IR 120mg bid x 1 day (day 8)  + DE 150mg on day 8, 2 hrs before V-IR</td>
</tr>
<tr>
<td>E. test:</td>
<td>V-IR 120mg tid x 1 day (day 9) then V-IR 120mg qid x 3 days (days 10-12)  + DE 150mg on day 12, 1 hr after V-IR</td>
</tr>
</tbody>
</table>

DE: dabigatran etexilate; V: verapamil; IR: immediate release

## DABIGATRAN - VERAPAMIL INTERACTION

<table>
<thead>
<tr>
<th>Part 2:</th>
<th>single dose verapamil in 20 volunteers (mean age 40.1 +/- 10.1 years; mean BMI 23.9 +/- 2.9)</th>
</tr>
</thead>
</table>

**F. reference:** DE 150mg single dose  
**G. reference:** V-IR 120mg single dose  
**H. test:** V-IR 120mg 1 hr before DE 150mg  
**I. test:** V-IR 120mg concomitantly with DE 150mg  
**J. test:** V-ER 240mg concomitantly with DE 150mg

DE: dabigatran etexilate; V: verapamil; IR: immediate release; ER: extended release
EFFECT OF VERAPAMIL ON TOTAL DABIGATRAN PLASMA CONCENTRATION (ng/ml)

DE: dabigatran etexilate
IR: immediate release
ER: extended release

EFFECT OF VERAPAMIL ON TOTAL DABIGATRAN EXPOSURE RATIO

VERAPAMIL – DAGIBATRAN INTERACTION

1. single-dose verapamil had more impact on dabigatran exposure than multiple-dose verapamil

2. immediate release verapamil had more impact on dabigatran than extended release verapamil

3. increasing the verapamil dose did not increase the effect on dabigatran exposure

4. glucuronidation, Cl and t½ of dabigatran did not change

5. absorption of dabigatran etexilate PRIOR to exposure to verapamil minimized the interaction

Consistent with other P-gp inhibitor interactions

### DRUG INTERACTION RECOMMENDATIONS FOR DABIGATRAN + VERAPAMIL

<table>
<thead>
<tr>
<th>FDA</th>
<th>HC</th>
<th>EMA</th>
<th>TGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF: Avoid concomitant use in pts with CrCl &lt; 30ml/min</td>
<td>Use with caution</td>
<td>Reduce dabigatran dose to 110mg bid</td>
<td>Use with caution</td>
</tr>
<tr>
<td>VTE: avoid concomitant use in pts with CrCl &lt; 50ml/min</td>
<td>Avoid simultaneous initiation</td>
<td></td>
<td>Simultaneous initiation of both drugs is contraindicated</td>
</tr>
<tr>
<td></td>
<td>Give dabigatran 2 hrs prior to verapamil</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:**
- FDA: US Food and Drug Administration
- HC: Health Canada
- EMA: European Medicines Agency
- TGA: Australian Therapeutic Goods Administration
OTHER P-gp INHIBITOR INTERACTIONS NOTED IN FDA BRIEFING MATERIALS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Admin Time (vs dabig)</th>
<th>Change in AUC</th>
<th>Change in CMax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>600mg</td>
<td>0</td>
<td>58% ↑</td>
<td>50% ↑</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500mg</td>
<td>1 hr prior</td>
<td>9% ↓</td>
<td>13% ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500mg bid</td>
<td>19% ↑</td>
<td>15% ↑</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>400mg</td>
<td>0</td>
<td>138% ↑</td>
<td>135% ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400mg qd</td>
<td>153% ↑</td>
<td>149% ↑</td>
</tr>
<tr>
<td>Quinidine</td>
<td>600mg</td>
<td>1 hr prior</td>
<td>86%</td>
<td>nd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1000mg</td>
<td>54% ↑</td>
<td>56% ↑</td>
</tr>
<tr>
<td>Dronedarone*</td>
<td>N/R</td>
<td>N/R</td>
<td>“73-99% increase in exposure”</td>
<td></td>
</tr>
</tbody>
</table>


* http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022512s007lbl.pdf
DABIGATRAN PLASMA CONCENTRATIONS IN RE-LY PROBABILITY OF ADVERSE EVENTS

Reilly PA et al. JACC 2014; 63:321-8
DABIGATRAN PLASMA CONCENTRATIONS IN RE-LY

<table>
<thead>
<tr>
<th></th>
<th>TROUGH</th>
<th>PEAK</th>
</tr>
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<tbody>
<tr>
<td>Max</td>
<td>809</td>
<td>1000</td>
</tr>
<tr>
<td>P90</td>
<td>215</td>
<td>383</td>
</tr>
<tr>
<td>Mean</td>
<td>91</td>
<td>175</td>
</tr>
<tr>
<td>P10</td>
<td>40</td>
<td>74</td>
</tr>
<tr>
<td>Min</td>
<td>1.04</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Reilly PA et al. JACC 2014; 63:321-8
1) Increased exposure is associated with higher bleeding risk

2) Increase exposure occurs with
   a) Advance age
   b) Reduced renal function
   c) Drug interactions

3) No data available regarding clinical outcomes resulting from drug interactions
DIFFERENTIAL RESPONSE TO DABIGATRAN/CLARITHROMYCIN INTERACTION

Dabigatran concentrations before and after exposure to clarithromycin, a P-gp inhibitor

Pharmacokinetic profiles of three volunteers. Fit of dabigatran plasma concentration with (solid line) and without (dashed line) clarithromycin. Grey circles represent data obtained without clarithromycin. White circles represent data obtained with clarithromycin.

DOAC DRUG INTERACTION VARIABLES

P-gp genotype
CYP3A4 genotype
UNDERLYING ILLNESS
RENAL FUNCTION
AGE

absorption/ metabolism/ elimination of DOAC
absorption/ metabolism/ elimination of interacting drug

SUSCEPTIBILITY
MAGNITUDE
ONSET
DURATION
RECOMMENDATIONS
DABIGATRAN AND P-GP INHIBITORS*

**EXAMPLES**

<table>
<thead>
<tr>
<th>Amiodarone</th>
<th>Diltiazem</th>
<th>Ketoconazole</th>
<th>Propafenone</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>Dronedarone</td>
<td>Lapatinib</td>
<td>Quinidine</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Erythromycin</td>
<td>Mefloquine</td>
<td>Ritonavir</td>
<td></td>
</tr>
<tr>
<td>Conivaptan</td>
<td>Indinavir</td>
<td>Nelfinavir</td>
<td>Saquinavir</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>intraconazole</td>
<td>Nicardipine</td>
<td>Tacrolimus</td>
<td></td>
</tr>
</tbody>
</table>

- Inhibitors of P-gp can increase dabigatran effect
- **Avoid combined use of P-gp inhibitors with dabigatran** in patients with renal impairment (Crcl <50 mL/minute) or age ≥80 years
- Licensed product information in most countries **contraindicates** use of dabigatran with the following individual P-gp inhibitors:
  - in all patients: cyclosporine, dronedarone, intraconazole, ketoconazole
- Licensed product information in most countries suggests dose reduction of dabigatran if combined with the following individual P-gp inhibitors: amiodarone, verapamil, quinidine

* recommendations from UpToDate 2015, developed with Hanston & Horn (identification of P-gp inhibitors) and FDA/HC/EMA (product labelling)
DABIGATRAN - RIFAMPICIN INTERACTION (P-gp inducer)

Part 1: multiple dose verapamil in 24 volunteers (age 22-44 years; mean BMI 25.1)

A. reference: DE 150mg single dose

B. test: R 600mg qday x 7 days (days 2-8) + DE 150mg on day 9

C. test: DE 150mg on day 16 (after 7 day R washout)

D. test: DE 150mg on day 23 (after 14 day R washout)

DE: dabigatran etexilate; R: rifampicin;

DABIGATRAN - RIFAMPICIN INTERACTION


**DE:** dabigatran etexilate; **R:** rifampicin;

AUC: 67% ↓
Cmax: 65.5% ↓
(Tmax, t ½, Cl: unaffected)

○ day 1 (dabig alone)
● day 9 (dabig + rifampicin)
■ day 16 (7 day washout)
□ (day 23 (14 day washout)}
RECOMMENDATIONS
DABIGATRAN AND P-GP INDUCERS

**EXAMPLES**
Barbiturates                        Phenytoin
Carbamazepine                       Rifampin
Dexamethasone,                       St Johns wort

• Inducers of P-gp can decrease dabigatran effect

• **Avoid combined use** of dabigatran with P-gp inducers

• Reduced concentrations of dabigatran may persist for ≥1 week after stopping a P-gp inducer

* recommendations from UpToDate 2015, developed with Hanston & Horn (identification of pGP inducers) and FDA/HC/EMA (product labelling)
P-GP MEDIATED ABSORPTION OF DOACs

Dabigatran
- Gut
- P-gp
- Esterase-mediated hydrolysis
- no CYP450
- Dabigatran
- t₁/₂ = 12-17 h
- Bio-availability 3-7%
- ~20%
- ~80%

Edoxaban
- Gut
- P-gp
- Edoxaban
- CYP3A4
- Bio-availability 52%
- t₁/₂ = 9-11 h
- ~50% (4% CYP3A4)

EDOXABAN DRUG INTERACTIONS WITH P-GP INHIBITORS

Design: crossover, 2-period, 2-treatment studies in health subjects

DABIGATRAN vs EDOXABAN
P-gp MEDIATED DRUG INTERACTIONS

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>7%</td>
<td>62%</td>
</tr>
<tr>
<td>P-gp involvement</td>
<td>Small intestine</td>
<td>Small intestine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kidney</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>↑ 12-58%</td>
<td>↑ 40%</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>↑ 73%</td>
<td>↑ 85%</td>
</tr>
<tr>
<td>Quinidine</td>
<td>↑ 53%</td>
<td>↑ 77%</td>
</tr>
<tr>
<td>Verapamil</td>
<td>↑ 23-54%</td>
<td>↑ 53%</td>
</tr>
</tbody>
</table>
EDOXABAN DRUG INTERACTION WITH P-GP INDUCER RIFAMPIN

Design: crossover, 2-period, 2-treatment studies in health subjects

Rifampin decreased edoxaban exposure through P-gp induction that reduced oral bioavailability

## EDOXABAN CLEARANCE


<table>
<thead>
<tr>
<th>Analyte</th>
<th>Dose Detected in Feces (Mean %)</th>
<th>Dose Detected in Urine (Mean %)</th>
<th>Total Recovery (% Dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Dose</td>
<td>62.2</td>
<td>35.4</td>
<td>97.6</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>49.1</td>
<td>23.8</td>
<td>72.8</td>
</tr>
<tr>
<td>M6</td>
<td>1.66</td>
<td>0.45</td>
<td>2.11</td>
</tr>
<tr>
<td>M8</td>
<td>0.34</td>
<td>BLQ</td>
<td>0.34</td>
</tr>
<tr>
<td>M1</td>
<td>BLQ</td>
<td>1.85</td>
<td>1.85</td>
</tr>
<tr>
<td>M4</td>
<td>1.93&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.56&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.49</td>
</tr>
<tr>
<td>Other minor unknown peaks</td>
<td>0.05</td>
<td>1.37</td>
<td>ND</td>
</tr>
</tbody>
</table>

Oxidation via CYP3A4
EDOXABAN DRUG INTERACTIONS WITH P-GP INDUCER RIFAMPIN

Design: crossover, 2-period, 2-treatment studies in health subjects

Rifampin increased exposure to the edoxaban M6 metabolite, formed via CYP3A4

Rifampin is a dual P-gp/CYP3A4 inducer

## COMPARATIVE METABOLISM OF DOACs

<table>
<thead>
<tr>
<th></th>
<th>DABIGATRAN</th>
<th>EDOXABAN</th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activation</strong></td>
<td>prodrug dabigatran etexilate is rapidly converted to active drug dabigatran via hydrolysis</td>
<td>None</td>
<td>None</td>
<td>none</td>
</tr>
<tr>
<td><strong>Absorption</strong></td>
<td>Mediated by P-gp</td>
<td>Mediated by P-gp</td>
<td>Mediated by P-gp</td>
<td>Mediated by P-gp</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Conjugation (no CYP involvement)</td>
<td>Hydrolysis (&lt;4% oxidation by CYP3A4)</td>
<td>~ 2/3 hepatic (oxidation via CYP3A4 [33%] and CYP2J2) and hydrolysis</td>
<td>~ 1/3 hepatic (oxidation via CYP3A4 [25%]) and conjugation</td>
</tr>
<tr>
<td><strong>Renal Elimination</strong></td>
<td>80%</td>
<td>50%</td>
<td>33%</td>
<td>25%</td>
</tr>
</tbody>
</table>
RIVAROXABAN DRUG INTERACTIONS WITH COMBINED P-gp/CYP3A4 INHIBITORS

<table>
<thead>
<tr>
<th>Drug</th>
<th>P-gp inhibition</th>
<th>CYP3A4 inhibition</th>
<th>AUC</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>ketoconazole 200mg qd</td>
<td>strong</td>
<td>strong</td>
<td>↑82%</td>
<td>↑53%</td>
</tr>
<tr>
<td>ketoconazole 400mg qd</td>
<td>strong</td>
<td>strong</td>
<td>↑158%</td>
<td>↑72%</td>
</tr>
<tr>
<td>ritonavir 600mg bid</td>
<td>strong</td>
<td>strong</td>
<td>↑153%</td>
<td>↑55%</td>
</tr>
<tr>
<td>clarithromycin 500mg bid</td>
<td>moderate</td>
<td>strong</td>
<td>↑54%</td>
<td>↑40%</td>
</tr>
<tr>
<td>Erythromycin 500mg tid</td>
<td>moderate</td>
<td>moderate</td>
<td>↑34%</td>
<td>↑48%</td>
</tr>
<tr>
<td>Fluconazole 400mg qd</td>
<td>none</td>
<td>moderate</td>
<td>↑42%</td>
<td>↑28%</td>
</tr>
</tbody>
</table>

Tacrolimus: P-gp inhibitor  
Cyclosporine: P-gp inhibitor and CYP3A4 inhibitor

<table>
<thead>
<tr>
<th></th>
<th>Tacrolimus</th>
<th>Cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Mean GFR</td>
<td>103 ml/min</td>
<td>65 ml/min</td>
</tr>
<tr>
<td>Rivaroxaban dose reduction</td>
<td>none</td>
<td>3 pts</td>
</tr>
<tr>
<td>Mean Rivaroxaban trough (ng/ml)</td>
<td>20.3 (+/- 14.4)</td>
<td>131.7 (+/- 119.5)</td>
</tr>
<tr>
<td>Bleeding complications</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Wannhoff A et al. *Transplantation* 2014; 98:e12-e13
# COMPARATIVE METABOLISM OF DOACs

<table>
<thead>
<tr>
<th></th>
<th>DABIGATRAN</th>
<th>EDOXABAN</th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activation</strong></td>
<td>prodrug dabigatran etexilate is rapidly converted to active drug dabigatran via hydrolysis</td>
<td>None</td>
<td>None</td>
<td>none</td>
</tr>
<tr>
<td><strong>Absorption</strong></td>
<td>Mediated by P-gp</td>
<td>Mediated by P-gp</td>
<td>Mediated by P-gp</td>
<td>Mediated by P-gp</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Conjugation (no CYP involvement)</td>
<td>Hydrolysis (&lt;4% oxidation by CYP3A4)</td>
<td>~ 2/3 hepatic (oxidation via CYP3A4 [33%] and CYP2J2) and hydrolysis</td>
<td>~ 1/3 hepatic (oxidation via CYP3A4 [25%]) and conjugation</td>
</tr>
<tr>
<td><strong>Renal Elimination</strong></td>
<td>80%</td>
<td>50%</td>
<td>33%</td>
<td>25%</td>
</tr>
</tbody>
</table>
APIXABAN INTERACTIONS WITH P-gp/CYP3A4 INHIBITORS

Ketoconazole: strong dual inhibitor of P-gp/CYP3A4

Diltiazem: moderate dual inhibitor of P-gp/CYP3A4

APIXABAN INTERACTIONS WITH P-gp/CYP3A4 INHIBITORS

Effect on Apixaban Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Ketoconazole</th>
<th>Diltiazem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>62%</td>
<td>31%</td>
</tr>
<tr>
<td>AUC</td>
<td>99%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Pulmonary embolism due to interaction between rivaroxaban and carbamazepine

Background
The introduction of the new oral anticoagulant drugs (NOACs) has recently been paid much attention. The main advantage of these drugs is that routine monitoring of the anticoagulant effects does not seem necessary.

Case description
A 53-year-old man who had just undergone partial knee arthroplasty went to the emergency department with shortness of breath and respiratory chest pain. The symptoms arose the day after thromboprophylaxis was switched from dalteparin 5000 IU QD to rivaroxaban 10 mg QD. The patient also used carbamazepine 600 mg BID for epilepsy. Based on a CT scan the patient was diagnosed with pulmonary embolisms. Use of carbamazepine, a CYP3A4 inducer, probably led to an increased clearance of rivaroxaban resulting in pulmonary embolisms.
**RECOMMENDATIONS**

**RIVAROXABAN/APIXABAN WITH P-gp and STRONG CYP3A4 INHIBITORS***

**EXAMPLES**

<table>
<thead>
<tr>
<th>clarithromycin</th>
<th>itraconazole</th>
<th>posaconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>conivapatan</td>
<td>ketoconazole</td>
<td>ritonavir</td>
</tr>
<tr>
<td>indinavir</td>
<td>lopinavir</td>
<td>saquinavir</td>
</tr>
<tr>
<td>itraconazole</td>
<td>nelfinavir</td>
<td>voriconazole</td>
</tr>
</tbody>
</table>

- P-gp and strong CYP3A4 inhibitors can increase rivaroxaban and apixaban effect
- **Avoid combined use of rivaroxaban or apixaban with P-gp and strong CYP3A4 inhibitors**

*recommendations from UpToDate 2015, developed with Hanston & Horn (identification of P-gp inhibitors) and FDA/HC/EMA (product labelling)*
RECOMMENDATIONS
RIVAROXABAN/APIXABAN WITH
P-gp and MODERATE CYP3A4 INHIBITORS*

**EXAMPLES**

<table>
<thead>
<tr>
<th>amiodarone</th>
<th>cyclosporine</th>
<th>erythromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>cimeditine</td>
<td>diltiazem</td>
<td>tamoxifen</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>dronedarone</td>
<td>verapamil</td>
</tr>
</tbody>
</table>

- P-gp and moderate CYP3A4 inhibitors can increase rivaroxaban and apixaban effect.
- **Avoid combined use of rivaroxaban with P-gp and moderate CYP3A4 inhibitors** in patients with renal impairment (CrCl ≤80 ml/min).
- **Avoid combined use of apixaban with P-gp and moderate CYP3A4 inhibitors** in patients with severe renal impairment (CrCl ≤ 30 ml/min), age ≥ 80 yrs, or low body weight (≤ 60kg).

* recommendations from UpToDate 2015, developed with Hanston & Horn (identification of P-gp inhibitors) and FDA/HC/EMA (product labelling)
RECOMMENDATIONS
RIVAROXABAN/APIXABAN WITH STRONG P-gp and/or CYP3A4 INDUCERS

EXAMPLES
barbiturates phenytoin
carbamazepine rifampin
dexamethasone St Johns wort

• Strong inducers of P-gp and/or CYP3A4 can decrease rivaroxaban/apixaban effect

• Avoid combined use of rivaroxaban or apixaban with strong inducers of P-gp and/or CYP3A4

• Reduced concentrations of rivaroxaban or apixaban may persist for ≥1 week after stopping a strong inducer of P-gp and/or CYP3A4

* recommendations from UpToDate 2015, developed with Hanston & Horn (identification of pGP inducers) and FDA/HC/EMA (product labelling)
DOAC DRUG INTERACTION UNKNOWNS

• Volunteers vs patients
• Drug interaction studies vs clinical exposure
• Single dose vs multiple doses of interacting drug
• Variability in response
• Serum concentrations vs clinical outcomes
Drug Interaction **Management** vs Drug Interaction **Avoidance**
SUMMARY

Following this presentation, the participant should be able to:

1. assess the **potential** for interactions between DOACs and other medications

2. evaluate **current evidence** of DOAC drug interactions

3. identify **patient management issues** posed by the possibility of interactions between DOACs and other medications