Master Class: DOAC Drug Interactions
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Disclosures

- Financial Disclosures: none

- Off-label/investigational uses discussed: none
Drug Interactions

- Elimination
- Metabolism
- Absorption
- DOAC Drug Level
- Clotting Factor Inhibition
- Bleeding/Thrombosis
DOAC Pharmacokinetics: Renal Elimination

- All DOACs undergo some degree of renal elimination

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Renal Elimination Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>80% Renal</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>36% Renal</td>
</tr>
<tr>
<td>Apixaban</td>
<td>27% Renal</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>50% Renal</td>
</tr>
</tbody>
</table>
DOAC Pharmacokinetics: Hepatic Metabolism

• Dabigatran and Edoxaban do not undergo significant hepatic metabolism

Hepatic CYP450 metabolism

Rivaroxaban

Apixaban

CYP3A4/5

18%

25%

↓ DOAC in blood

↑ Thrombosis risk

CYP3A4 inducer

↑ DOAC in blood

↑ Bleeding risk

CYP3A4 inhibitor

# Modifiers of CYP3A4

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong</strong></td>
<td><strong>Strong</strong></td>
</tr>
<tr>
<td>• ↓ AUC (\geq 80%)</td>
<td>• ↑ AUC (\geq 5\text{-fold (400%)})</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td>• ↓ AUC 50-79%</td>
<td>• ↑ AUC 2-4.9\text{-fold (101-399%)}</td>
</tr>
<tr>
<td><strong>Weak</strong></td>
<td>** Weak**</td>
</tr>
<tr>
<td>• ↓ AUC &lt;50%</td>
<td>• ↑ AUC 1.25-2\text{-fold (25-100%)}</td>
</tr>
</tbody>
</table>

[http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#table5-2](http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#table5-2)
DOAC Pharmacokinetics: Bioavailability

All DOACs are substrates for p-glycoprotein (p-gp)

- P-gp inducer: ↑ DOAC in blood, ↓ Thrombosis risk
- P-gp inhibitor: ↑ DOAC in blood, ↑ Bleeding risk

Modifiers of p-gp

• Not classified by magnitude of effect on substrates
• BUT...to be classified as a p-gp inhibitor, drug must ↑ AUC ≥ 1.25-fold (25%)
• No specifics given for p-gp inducers
DOACs and p-gp/CYP3A4 Inducers: PK Studies with **Rifampin**

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Study Details</th>
<th>AUC Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>n=22 healthy volunteers</td>
<td>↓ dabigatran AUC by 67%</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>Manufacturer study (n not specified)</td>
<td>↓ rivaroxaban AUC by 50%</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>n=20 healthy volunteers</td>
<td>↓ apixaban AUC by 54%</td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td>n=32 healthy volunteers</td>
<td>↓ edoxaban AUC by 34%</td>
</tr>
</tbody>
</table>


# DOACs and p-gp/CYP3A4 Inducers: Case Reports

## Dabigatran

<table>
<thead>
<tr>
<th>Case</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 y/o male with AF</td>
<td>had undetectable dabigatran trough level while taking dabigatran 150 mg BID and phenytoin</td>
</tr>
<tr>
<td>70 y/o male with AF</td>
<td>who developed a left atrial thrombus while taking dabigatran 150 mg BID and phenytoin</td>
</tr>
</tbody>
</table>

## Rivaroxaban

<table>
<thead>
<tr>
<th>Case</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>67 y/o female with AF</td>
<td>died from extensive PE while taking rivaroxaban 20 mg once daily and rifampin</td>
</tr>
<tr>
<td>60 y/o male</td>
<td>experienced DVT/PE on POD #4 after TKA while taking rivaroxaban 10 mg daily and nevirapine</td>
</tr>
<tr>
<td>68 y/o male with AF</td>
<td>experienced LA thrombus while taking rivaroxaban 20 mg daily and oxcarbazepine</td>
</tr>
<tr>
<td>53 y/o male</td>
<td>experienced PE after TKA while taking rivaroxaban 10 mg daily and carbamazepine</td>
</tr>
<tr>
<td>55 y/o male</td>
<td>experienced recurrent DVT while taking rivaroxaban 20 mg daily and carbamazepine</td>
</tr>
</tbody>
</table>

DOACs and p-gp/CYP3A4 Inducers: A Case Experience

66 y/o male with history of unprovoked recurrent DVT/PE, most recent 2004

- switched from warfarin to apixaban 2.5 mg BID due to poor TTR Dec 2015.
- June 2016 started carbamazepine for trigeminal neuralgia. DDI identified on report 1 week after CBZ initiated.
- Discontinued apixaban, re-initiated warfarin (no bridging).
- 2 days later pt experienced leg pain and was diagnosed with superficial LE thrombosis (INR=1.6).
DOACs and p-gp/CYP3A4 Inducers: Clinical Trial Experience and Labeling Guidelines

• None of the DOAC clinical trials allowed inducer use

• All 4 DOACs: “Avoid concomitant use”
DOACs and p-gp/CYP3A4 Inducers: Summary

• PK studies of healthy volunteers show inducers can reduce DOAC AUC 34-67% (weak-moderate inducer effect).
• Multiple case reports of thrombotic events caused by inducer interactions exist for dabigatran and rivaroxaban.
• Manufacturer labeling guidelines recommend against using p-gp CYP inducers with DOACs due to concern for reduced efficacy.

TAKE HOME POINT #1:

DOAC interactions with p-gp/CYP3A4 inducers appear to be clinically significant.

Avoid use of DOACs with p-gp/CYP3A4 inducers.
Difficult Real-World Questions

• What about drugs that are only CYP3A4 inducers and have no p-gp involvement?
  – Primidone, oxcarbazepine, nevirapine

• What if patient requires anticoagulation AND a p-gp/CYP3A4 inducer and cannot take warfarin?
  – Consider LMWH or fondaparinux
  – Can you increase the DOAC dose to overcome the DDI?
  – DOAC laboratory monitoring?
Comments?
DOACs and p-gp/STRONG
CYP3A4 Inhibitors: PK Studies with **Ketoconazole**

- **Dabigatran**
  - Manufacturer study (n not specified)
  - ↑ dabigatran AUC by 138%

- **Rivaroxaban**
  - n=20 healthy volunteers
  - ↑ rivaroxaban AUC by 158%

- **Apixaban**
  - n=18 healthy volunteers
  - ↑ apixaban AUC by 99%

- **Edoxaban**
  - n=37 healthy volunteers
  - ↑ edoxaban AUC by 87%

- **Strong**
  - ↑ AUC ≥ 5-fold (400%)

- **Moderate**
  - ↑ AUC ≥ 2.49-fold (101-399%)

- **Weak**
  - ↑ AUC < 1.25-2-fold (25-100%)

All DOACs p-gp
Riva: 18% CYP3A4
Apix: 25% CYP3A4

Weakened—moderate
### DOACs and p-gp/MODERATE CYP3A4 Inhibitors: PK Studies

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Inhibitors</th>
<th>N</th>
<th>Increase in AUC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>Verapamil</td>
<td>11</td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>16</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td>Diltiazem</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>Erythromycin</td>
<td>16</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td>Diltiazem</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td>33</td>
<td>85%</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>Erythromycin</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td>Erythromycin</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- Strong: \( \uparrow \text{AUC} \geq 5\)-fold (400%)
- Moderate: \( \uparrow \text{AUC} \geq 2-4.9\)-fold (101-399%)
- Weak: \( \uparrow \text{AUC} \leq 1.25-2\)-fold (25-100%)

**References:**
DOACs and p-gp/CYP3A4 Inhibitors: Published Case Reports?
DOACs and p-gp/CYP3A4 Inhibitors: Additive Effects

Rivaroxaban + Erythromycin at Varying Levels of Renal Function

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Effect of Erythromycin on Rivaroxaban Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (CrCl ≥ 80 mL/min)</td>
<td>↑ riva AUC by 39% (n=8)</td>
</tr>
<tr>
<td>Mild impairment (CrCl 50-79 mL/min)</td>
<td>↑ riva AUC by 76% (n=8)</td>
</tr>
<tr>
<td>Moderate impairment (CrCl 30-40 mL/min)</td>
<td>↑ riva AUC by 99% (n=8)</td>
</tr>
</tbody>
</table>

Other “Additive” Effects:
- Advanced age
- Low body weight
- Antiplatelets/NSAIDs

Antiplatelets/NSAIDs

• DOAC + Antiplatelet
  – DOAC + SAPT
  – DOAC + DAPT
    • Low-dose riva + DAPT → lower bleeding than warfarin + DAPT (AF patients)
    • But what about standard dose riva + DAPT?????

• DOAC + NSAID

DOACs and p-gp/CYP3A4 Inhibitors: Should we dose-reduce DOACs?

I tell you this as a cautionary tale: beware of getting what you want. It's bound to disappoint you.

— Jodi Picoult —

AZ QUOTES
DOACs and p-gp/CYP3A4 Inhibitors: Clinical Trial Experience with Dose Reduction

**ENGAGE AF-TIMI 48:**
warfarin vs
HD edoxaban vs LD edoxaban

- Edoxaban was dose-reduced by 50% in patients with at least one of the following criteria:
  - CrCl 30-50 mL/min
  - Body weight ≤ 60 kg
  - Taking p-gp inhibitors verapamil, quinidine, or dronedarone

<table>
<thead>
<tr>
<th>Exploratory Secondary Analysis: Patients taking a p-gp inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Stroke/SE (%)/year</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Warfarin (n=215)</td>
</tr>
<tr>
<td>HD edoxaban (n=227)</td>
</tr>
<tr>
<td>LD edoxaban (n=228)</td>
</tr>
</tbody>
</table>

DOACs and p-gp/CYP3A4 Inhibitors: Labeling Guidelines

**Dabigatran**
- **AF**: ↓ dabi to 75 mg BID in CrCl 30-50 mL/min + dronedarone or ketoconazole
- **VTE**: avoid use in patients with CrCl <50 mL/min taking p-gp inhibitors

**Rivaroxaban**
- Avoid with p-gp/STRONG CYP3A4 inhibitors
- Weigh risk/benefit when using in patients with CrCl 15-80 mL/min and p-gp/MODERATE CYP3A4 inhibitors

**Apixaban**
- ↓ apixa dose by 50% in patients taking p-gp/STRONG CYP3A4 inhibitors (no lower than apixa 2.5 mg BID)

**Edoxaban**
- **AF**: no dose adjustment recommendations
- **VTE**: ↓ edoxa to 30 mg once daily in patients taking p-gp inhibitors
DOACs and p-gp/CYP3A4 Inhibitors: Summary

• PK studies of healthy volunteers show STRONG inhibitors can increase DOAC AUC 87-138% (weak-moderate inhibitor effect) and MODERATE inhibitors can increase DOAC AUC 54-85% (weak inhibitor effect).

• No published case reports of bleeding events caused by inhibitor interactions alone.

• Consider additive effects of inhibitor when considering clinical significance of a DDI.

• Dabigatran, apixaban, and edoxaban have specific dose reduction guidance.

**TAKE HOME POINT #2:**

DOAC interactions with p-gp and/or moderate CYP3A4 inhibitors are likely only clinically significant when combined with other factors to affect DOAC plasma concentrations or bleeding risk:

- Advanced age
- Impaired renal function
- Low body weight
- Multiple inhibitors
- Antiplatelet use

If making an off-label dose reduction, make sure you have a leg to stand on in the face of possible reduced anti-thrombotic efficacy!
Difficult Real-World Questions

• If both inducers and inhibitors show only a weak-moderate effect on AUC, why does it seem that inducer interactions are clinically significant and moderate inhibitor interactions are not?

• Is the effect of multiple weak-moderate inhibitors additive?
DOACs and p-gp/CYP3A4 Inhibitors: My Case Experience

84 y/o female (wt=50 kg) with history of AF (CHA₂DS₂VASc=4), HTN, multiple myeloma in remission, chronic kidney disease

- Started on dabigatran 150 mg BID in 2012 when AF diagnosed
- 6 months later, switched to rivaroxaban 15 mg once daily due to GI upset with dabigatran
- Switched from rivaroxaban to apixaban 2.5 mg BID in 2014 due to declining renal function (CrCl ~30 mL/min), addition of dronedarone, and ability for dose adjustment
- In May 2016, ranolazine added for AF management (CrCl ~23 mL/min)
- Patient adamantly refused warfarin
- Apixaban anti-Xa assay June 2016...therapeutic
- No adverse events
Difficult Real-World Questions

- If both inducers and inhibitors show only a weak-moderate effect on AUC, why does it seem that inducer interactions are clinically significant and moderate inhibitor interactions are not?

- Is the effect of multiple weak-moderate inhibitors additive?

- Does an inducer cancel out an inhibitor?
  - 79 y/o male (wt=81 kg) with history of AF
    - $\text{CHA}_{2}\text{DS}_{2}\text{VASc}=3$ for age and HTN, no prior stroke
    - He is taking **dronedarone [p-gp+moderate CYP3A4 inhibitor]** for rhythm control
    - He is taking **primidone [CYP3A4 inducer, no p-gp effects]** for benign essential tremor
    - CrCl $\sim 60$ mL/min
    - started apixaban 5 mg BID in 2013
    - No adverse events

- DOAC laboratory monitoring?
COMPLAINTS
COMMENTS
COMPLIMENTS
Supplementary Material
### Doac Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td>• P-gp</td>
<td>• P-gp</td>
</tr>
<tr>
<td></td>
<td>• No CYP</td>
<td>• 18% CYP3A4/5, 2J2 (14%), hydrolysis (14%)</td>
</tr>
<tr>
<td></td>
<td>• 80% Renal</td>
<td>• 36% Renal</td>
</tr>
<tr>
<td><strong>Hepatic CYP450 metabolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• P-gp</td>
<td>• P-gp</td>
</tr>
<tr>
<td></td>
<td>• 25% CYP3A4/5 Minor: CYP1A2, 2C8, 2C9, 2C19, 2J2</td>
<td>• CYP3A4/5 “minimal”</td>
</tr>
<tr>
<td></td>
<td>• 27% Renal</td>
<td>• 50% Renal</td>
</tr>
<tr>
<td><strong>Renal elimination</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
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Measuring Drug Exposure: Area Under the Curve (AUC)

\[
AUC = \frac{\text{dose administered}}{\text{drug clearance}}
\n\]

DOAC DDIs-Inducers

P-gp/CYP3A4 Inducers (examples)
• Barbiturates (e.g., phenobarbital)
• Carbamazepine
• Dexamethasone
• Phenytoin
• Rifampin
• St. John’s Wort

CYP3A4 only Inducers (examples)
• Bosentan
• Efavirenz
• Enzalutamide
• Etravirine
• Nafcillin
• Nevirapine
• Oxcarbazepine
• Primidone

DOAC DDIs-Inhibitors

P-gp/CYP3A4 STRONG Inhibitors (examples)

- Clarithromycin
- Cobicistat
- Conivaptan
- Indinavir
- Itraconazole
- Ketoconazole
- Posaconazole
- Ritonavir
- Saquinavir
- Teleprevir
- Telithromycin
- Voriconazole

DOAC DDIs-p-gp Inhibitors

- Amiodarone (no dose adj for dabigatran)
- Azithromycin
- Bepridil
- Boceprevir
- Carvedilol
- Clarithromycin (no dose adj for dabigatran)
- Cobicistat
- Conivaptan
- Cyclosporine
- Diltiazem
- Dronedarone
- Duloxetine
- Fenofibrate
- Grapefruit
- Imatinib
- Indinavir
- Itraconazole
- Ketoconazole
- Lapatinib
- Ledipasvir
- Lovastatin
- Mefloquine
- Mifepristone
- Nelfinavir
- Nicardipine
- Posaconazole
- Propafenone
- Quinidine (no dose adj for dabigatran)
- Ranolazine
- Ritonavir
- Saquinavir
- Tacrolimus
- Tamoxifen
- Telaprevir
- Telithromycin
- Ticagrelor (no dose adj for dabigatran)
- Valspdar
- Verapamil (no dose adj for dabigatran)
DOAC DDI Resources

• FDA website: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers
  https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#table2-2

• Top Drug Interactions 2017: A Guide to Patient Management (Hansten and Horn)

• University of Washington Anticoagulation Service website:
  https://depts.washington.edu/anticoag/home/

• Pharmacists Letter (subscription required)

• Check primary literature for case reports

Anticoagulation FORUM