Drug/Drug and Drug/Food Interactions with Target-Specific Oral Anticoagulants

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Thrombosis Service

Nothing to disclose
Effects of Drug/Food Interactions

↑/↓ TSOAC exposure

Pharmacodynamic effects??

Adverse clinical outcomes??
Drug Absorption: Food

Dabigatran
Take with or without food
High-fat meal delays time to $C_{\text{max}}$ from 1 hour to 3 hours

Rivaroxaban
10-mg dose: Take with or without food
15-mg and 20-mg doses: Take WITH food (enhances bioavailability)

Apixaban
Take with or without food

Drug Absorption: Gastric pH

Dabigatran

Rivaroxaban
Absorption independent of gastric pH
No change in drug exposure when given with antacids, ranitidine, omeprazole

Apixaban
Absorption independent of gastric pH
No interaction identified when co-administered with famotidine

Dabigatran Etexilate

“renders the extent of absorption of dabigatran etexilate independent of variations in gastric pH”

“The concomitant use of proton pump inhibitors nor H2 antagonists did not appreciably change the trough concentration of dabigatran.”

“Overall drug exposure (Cmax and AUC) is reduced by 20-25% if dabigatran-treated patients are given proton pump inhibitors although this is not considered clinically relevant.”

Drug-Drug Interactions: P-glycoprotein

Gut → Bloodstream

P-gp inducer

P-gp inhibitor

Gut → Bloodstream

Gut → Bloodstream
# Dabigatran Drug-Drug Interactions: P-glycoprotein

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<thead>
<tr>
<th>Strong P-glycoprotein Inhibitors</th>
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<td>Carbamazepine</td>
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<td>Dexamethasone</td>
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<td>Phenytoin</td>
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<td>Rifampin</td>
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U.S. Food and Drug Administration, Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers.

Hansten PD, Horn JR. The Top 100 Drug Interactions 2012 Edition.

Dabigatran etexilate
Prescribing Information

• The concomitant use of dabigatran with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided.

• The use of P-gp inhibitors (verapamil, amiodarone, quinidine, and clarithromycin) does not require a dose adjustment of dabigatran. These results should not be extrapolated to other P-gp inhibitors.

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<td>Indinavir</td>
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<td>Itraconazole</td>
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<td>Ketoconazole</td>
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<td>Lapatinib</td>
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<td>Lovastatin</td>
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<td>Mefloquine</td>
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<tr>
<td>Mifepristone</td>
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<tr>
<td>Nelfinavir</td>
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<tr>
<td>Nicardipine</td>
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<tr>
<td>Posaconazole</td>
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<tr>
<td>Propafenone</td>
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Drug Interactions: Rivaroxaban and Apixaban

**Rivaroxaban**

“Avoid concomitant use of rivaroxaban with combined P-gp and strong CYP 3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, and conivaptan).”

“Avoid concomitant use of rivaroxaban with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St John’s wort).”

**Apixaban**

“The dose of apixaban should be decreased to 2.5 mg twice daily when it is co-administered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin).”

“Avoid concomitant use of apixaban with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St John’s wort) because such drugs will decrease exposure to apixaban.”

# Drug-Drug Interactions: CYP3A4

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<tr>
<th>CYP3A4 Inhibitors</th>
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<tbody>
<tr>
<td>amiodarone</td>
<td>cyclosporine</td>
</tr>
<tr>
<td>amprenavir</td>
<td>dalfopristin</td>
</tr>
<tr>
<td>aprepitant</td>
<td>danazol</td>
</tr>
<tr>
<td>atazanavir</td>
<td>darunavir</td>
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<tr>
<td>basiliiximab</td>
<td>dasatinib</td>
</tr>
<tr>
<td>boceprevir</td>
<td>delavirdine</td>
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<td>chloramphenicol</td>
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<tr>
<td>clarithromycin</td>
<td>erythromycin</td>
</tr>
<tr>
<td>conivaptan</td>
<td>ethinyl estradiol</td>
</tr>
<tr>
<td>crizotinib</td>
<td>fluconazole</td>
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U.S. Food and Drug Administration, Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers. 
Hansten PD, Horn JR. The Top 100 Drug Interactions 2012 Edition.
**Drug-Drug Interactions:**

**P-glycoprotein AND CYP3A4**

<table>
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<tr>
<td>amiodarone</td>
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<td></td>
<td>phenytoin</td>
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<tr>
<td></td>
<td>rifampin</td>
</tr>
<tr>
<td></td>
<td>St John's wort</td>
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Rivaroxaban Metabolism

Rivaroxaban → CYP3A4 → Inactive Metabolites ≈ 51%

Rivaroxaban → Unchanged Drug ≈ 49%

Apixaban Metabolism

Apixaban

CYP3A4

Inactive Metabolites ≈ 25%

Unchanged Drug ≈ 75%

Drug-Drug Interactions: Renal Clearance

- **Dabigatran**
  - Non-renal: ≈ 20%
  - Renal: ≈ 80%

- **Rivaroxaban**
  - Non-renal: ≈ 28%
  - Renal: ≈ 66%

- **Apixaban**
  - Non-renal: ≈ 75%
  - Renal: ≈ 25%

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P-gp

CYP3A4

Renal

↑/↓ TSOAC exposure

Pharmacodynamic effects??

Adverse clinical outcomes??
Dabigatran Etexilate

Dabigatran

P-gp

Renal

↑/↓ TSOAC exposure

Pharmacodynamic effects??

Adverse clinical outcomes??
Rivaroxaban

↑/↓ TSOAC exposure
Pharmacodynamic effects??
Adverse clinical outcomes??
Apixaban

- P-gp
- CYP3A4
- Renal

↑/↓ TSOAC exposure

Pharmacodynamic effects??

Adverse clinical outcomes??
Drug-Drug Interactions: Antiplatelet Agents

**TSOAC + Low-dose ASA** (eg, 81 mg daily)
- All major TSOAC clinical trials have allowed concomitant low-dose ASA
- ↑ bleeding rates when TSOACs combined with low-dose ASA

**TSOAC + dual antiplatelet therapy** (eg, ASA + clopidogrel)
- For all TSOACs: significant ↑ in major bleeding when used concomitantly with dual antiplatelet therapy
Drug-Drug Interactions: NSAIDS

**Dabigatran**
- NSAIDS allowed in all clinical trials
- Per manuf PI, no interactions with diclofenac
- Post-hoc pooled analysis of 3 TKA/THA trials showed no ↑ risk of bleeding with concomitant NSAIDs

**Rivaroxaban**
- Chronic NSAID treatment an EXCLUSION criterion in clinical trials
- General statement about potential increased bleeding risk with concomitant NSAIDs
- Pre-specified pooled analysis of RECORD 1-4 trials showed no ↑ risk of bleeding with concomitant NSAIDs

**Apixaban**
- NSAIDS allowed in all clinical trials
- Per manuf PI, no interaction and no dose adjustment required with concomitant naproxen use
- General statement about potential increased bleeding risk with concomitant NSAIDs

↑ GIB

Drug-Food Interactions: Grapefruit

- Strong P-gp AND intestinal CYP3A4 inhibitor
- No current US package labeling guidance for TSOACs
- Health Canada (rivaroxaban prescribing information): Grapefruit juice is a moderate CYP3A4 inhibitor. Therefore, an increase in rivaroxaban exposure following grapefruit juice consumption is not expected to be clinically relevant.”

Sneak Peak...Edoxaban

• Absorption unaffected by food—can be administered with or without food
• Half-life $\approx 10$ hours
• $\approx 35$-40% renal clearance
• P-gp substrate
• CYP$_3$A$_4$ substrate

New Paradigm of Drug Interaction Management

Warfarin

- Many reported drug interactions
- Much published literature and clinical expertise to guide management
- INR monitoring
- Warfarin dose adjustment

TSOACs

- Few reported drug interactions
- Little published literature or clinical expertise to guide management
- No established laboratory monitoring method
- TSOAC dose adjustment???
TSOAC Drug Interactions
Exist...How do we manage them?

• Prevention/Education to patients/providers
• How are interactions with non-anticoagulant drugs handled?
  – Dose reduction/increase of target drug
  – Change interacting drug to non-interacting drug
  – Consider duration of interacting drug: short-term vs long-term and level of risk/toxicity
• Importance of anticoagulation specialist/pharmacist involvement and follow-up!
• Specific management strategies...
### Clarithromycin/TSOAC Interaction

<table>
<thead>
<tr>
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<th>U.S. FDA</th>
<th>Health Canada</th>
<th>EMA</th>
</tr>
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<tr>
<td><strong>Dabigatran</strong></td>
<td>Do not use if CrCl &lt;30 mL/min</td>
<td>No dose adjustment is recommended; use with caution</td>
<td>“a clinically relevant interaction cannot be excluded...close monitoring should be exercised...notably in patients having mild to moderate renal impairment”</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>No precautions necessary unless renally impaired (do not use if CrCl &lt;50 mL/min)</td>
<td>“may increase the risk of bleeding particularly in patients with underlying disease conditions, and elderly. Caution is required.”</td>
<td>No clinically relevant interaction</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>Reduce apixaban dose to 2.5 mg BID, or avoid if already on apixaban 2.5 mg BID</td>
<td>Not specifically addressed</td>
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# Amiodarone/TSOAC Interaction

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<tr>
<td>Apixaban</td>
<td>Not specifically addressed</td>
<td>Similar effect to diltiazem; no dose adjustment required; use with caution</td>
<td>Considers amiodarone a less potent CYP3A4 inhibitor; no dose adjustment required</td>
</tr>
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</table>
Good Rule of Thumb

“If not otherwise specifically described, close clinical surveillance (looking for signs of bleeding or anemia), along with a sense of caution is required when dabigatran is co-administered with P-glycoprotein inhibitors, especially in the elderly, i.e., >75 years of age. Consideration should be given to avoiding use of strong P-gp inhibitors with dabigatran, unless deemed medically essential.”

TSOACS Drug-Drug and Drug-Food Interactions Summary

**Dabigatran**
- Concomitant P-gp inhibitors/inducers
- Renal function
- Elderly (age >75 years)
- Concomitant antiplatelet agents/NSAIDs

**Rivaroxaban**
- Take with food
- Concomitant strong P-gp inhibitors/inducers AND CYP3A4 inhibitors/inducers
- Renal function
- Elderly (age >75 years)
- Concomitant antiplatelet agents/NSAIDs

**Apixaban**
- Concomitant strong P-gp inhibitors/inducers AND CYP3A4 inhibitors/inducers
- Combination of older age, renal dysfunction, and low body weight
- Concomitant antiplatelet agents/NSAIDs
THANK YOU