ICYMI: New updates to antiretroviral drug interactions with direct oral anticoagulants

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Antiretroviral therapy (ART), especially HIV protease inhibitors and pharmacokinetic enhancers (i.e. ritonavir and cobicistat), can have significant drug-drug interactions with anticoagulant drugs. Health care providers should carefully consider potential drug-drug interactions before initiating or changing ART or treating comorbid conditions such as stroke or venous thromboembolism (VTE). The DHHS adult HIV guidelines were recently updated on October 25, 2018. In case you missed it (ICYMI), in the previous 2016 version of the guidelines, most direct oral anticoagulants (DOACs) were recommended to be avoided with many ARTs and the only recommended anticoagulant for use with HIV protease inhibitors was warfarin. However, in the most recent 2018 guideline update, the DHHS now recommends that certain DOACs can be safely combined with ART. ICYMI, a summary of the old 2016 and new 2018 DHHS HIV guideline recommendations on drug interactions between ART and DOACs is reviewed in Table 1. Dosing guidance and comparisons of all currently available DOACs is displayed in Table 2.

Since 2010, the United States Food and Drug Administration has approved several DOACs. Unlike warfarin that requires blood monitoring, the DOACs do not, making their use more convenient. DOACs include both rapid and short acting agents with good overall safety profiles and relatively low bleeding risks. Available medications in this class include apixaban (Eliquis\(^{®}\)), rivaroxaban (Xarelto\(^{®}\)), dabigatran (Pradaxa\(^{®}\)), edoxaban (Savaysa\(^{®}\)), and betrixaban (BevyXXa\(^{®}\)).

DOACs are a good choice for VTE prevention and treatment and stroke prevention in appropriately selected patients. These agents have shown to be highly effective, require less monitoring, and may reduce the risk of brain bleed (vs. warfarin). Although DOACs do not require routine laboratory monitoring and are not affected by dietary considerations, they tend to be more expensive than warfarin and are shorter acting, making it important for patients to remain adherent.
### Table 1. Difference in DHHS Guideline Recommendations Regarding Drug Interactions between Protease Inhibitors/Boosted Integrase Strand Transfer Inhibitor and Anticoagulants from the 2016 Guidelines vs the Updated 2018 Guidelines

<table>
<thead>
<tr>
<th>Anticoagulant Drug</th>
<th>ART</th>
<th>Effect on Concomitant Drug Concentrations</th>
<th>2016 Dosing Recommendations and Clinical Comments</th>
<th>2018 Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>PI/c, PI/r</td>
<td>↑ apixaban expected</td>
<td>Avoid concomitant use</td>
<td>Coadministration is not recommended in patients who require apixaban 2.5 mg twice daily. In patients who require apixaban 5 mg or 10 mg twice daily, reduce apixaban dose by 50%.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betrixaban (BevyxXa®)</td>
<td>ATV/c, ATV/r, LPV/r</td>
<td>↑ betrixaban expected</td>
<td>N/A Betrixaban was FDA approved July 2017</td>
<td>Administer an initial single dose of betrixaban 80 mg followed by betrixaban 40 mg once daily.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DRV/c, DRV/r</td>
<td>←→ betrixaban expected</td>
<td>No dosage adjustment necessary</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>ATV/c, ATV/r, LPV/r</td>
<td>↑ dabigatan expected With COBI 150 mg alone: Dabigatran AUC ↑110% to 127%</td>
<td>No dosage adjustment if CrCl &gt; 50 mL/min. Avoid coadministration if CrCl &lt; 50 mL/min.</td>
<td>Dabigatran dosing recommendation depends on indication and renal function. Refer to dabigatran dosing instructions for concomitant use with P-gp inhibitors in dabigatran prescribing information.</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DRV/c, DRV/r</td>
<td>←→ dabigatan expected</td>
<td>No dosage adjustment necessary</td>
<td>No dosage adjustment necessary</td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>ATV/c, ATV/r, LPV/r</td>
<td>↑ edoxaban expected</td>
<td>Avoid concomitant use</td>
<td>Stroke Prevention in nonvalvular atrial fibrillation indication: • No dose adjustment necessary Deep venous thrombosis and pulmonary embolism indication: • Administer edoxaban 30 mg once daily</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DRV/c, DRV/r</td>
<td>←→ edoxaban expected</td>
<td>No dosage adjustment necessary</td>
<td>No dosage adjustment necessary</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>PI/c, PI/r</td>
<td>↑ rivaroxaban</td>
<td>Avoid concomitant use</td>
<td>Coadministration is not recommended</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>PI/c</td>
<td>No data</td>
<td>No data</td>
<td>Monitor INR closely when stopping or starting PI/c and adjust warfarin dose accordingly. If switching between RTV and COBI, the effect of COBI on warfarin is not expected to be equivalent to RTV’s effect on warfarin.</td>
</tr>
<tr>
<td></td>
<td>PI/r</td>
<td>↓ warfarin possible</td>
<td>Monitor INR closely when stopping or starting PI/r and adjust warfarin accordingly</td>
<td>Monitor INR and adjust warfarin accordingly</td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td>↑↓ warfarin possible</td>
<td>Monitor INR and adjust warfarin accordingly</td>
<td>Monitor INR and adjust warfarin accordingly</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>Non-valvular Atrial Fibrillation - Stroke Prophylaxis</td>
<td>VTE Treatment</td>
<td>VTE Prophylaxis</td>
<td>Clinical Comments from DOAC Prescribing Information</td>
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</tbody>
</table>
| Apixaban (Eliquis®) | 5 mg BID; reduce dose to 2.5 mg BID if 2 or more of the following: - ≥80 yrs old - ≤ 60 kg - SCR ≥ 1.5 mg/dL | 10 mg BID for one week, then 5 mg BID | 2.5 mg BID | Strong dual CYP3A4 and P-glycoprotein inhibitors (eg, ketoconazole, itraconazole, ritonavir) 
Recommended apixaban doses >2.5 mg twice daily: Reduce apixaban dose by 50% 
Recommended apixaban dose of 2.5 mg twice daily: Avoid concomitant use. 
Strong dual CYP3A4 and P-glycoprotein inducers (eg, rifampin, carbamazepine, phenytoin, St John’s wort): Avoid concomitant use. |
| Betrixaban (BevyxXa®) | Not an FDA approved indication | Not an FDA approved indication | 160 mg as a single dose on day 1, followed by 80 mg once daily, CrCl 15-30 mL/min: 80 mg as a single dose, then 40 mg daily | Reduce betrixaban dose (initial and maintenance) by 50% for patients receiving or starting P-glycoprotein inhibitors (eg, amiodarone, azithromycin, clarithromycin, ketoconazole, verapamil). If patient also has severe renal impairment, avoid use of betrixaban. |
| Dabigatran (Pradaxa®) | 150 mg BID | Parenteral anticoagulation for 5-10 days; then dabigatran 150 mg BID | 110 mg for the first day, then 220 mg daily | Non-valvular AFib 
Any P-gp inducer (eg rifampin): avoid concurrent use 
Any P-gp inhibitor (eg amiodarone, clarithromycin, dronedarone, ketoconazole, verapamil and others) with CrCl <30 ml/min: Avoid concurrent use 
CrCl 15-30 mL/min: 75 mg BID (renal dose adjustment was not extensively studied) 
CrCl< 15 mL/min: use is not recommended |
|                      | | | | VTE Treatment/Prophylaxis 
Any P-gp inducer (eg rifampin): avoid concurrent use 
Any P-gp inhibitor (eg amiodarone, clarithromycin, dronedarone, ketoconazole, verapamil and others) with CrCl <50 ml/min: Avoid concurrent use |
| **Edoxaban**  
(Savaysa®) | 60 mg daily | Parenteral anticoagulation for 5-10 days; then  
Pt wt > 60 kg: 60 mg daily  
Pt wt <60 kg: 30 mg daily | Not and FDA approved indication | Non-valular AFib  
P-gp inhibitors: No dose adjustment necessary  
P-gp inducers: Avoid concurrent use  
CrCl>95 mL/min: efficacy is decreased, use not recommended  
CrCl 15-50 mL/min: 30 mg daily  
CrCl< 15 mL/min: use is not recommended  
VTE Treatment  
P-gp inhibitors (eg verapamil, quinidine, azithromycin, clarithromycin): 30 mg daily  
P-gp inducers (eg rifampin): Avoid concurrent use  
CrCl 15-50 mL/min: 30 mg daily  
CrCl< 15 mL/min: use is not recommended |
| **Rivaroxaban**  
(Xarelto®) | 20 mg once daily with evening meal  
CrCl 15-50 mL/min: 15 mg daily | 15 mg BID with food for 3 weeks; then 20 mg once daily with food  
CrCl< 30 mL/min: Avoid use | 10 mg once daily with or without food  
CrCl< 30 mL/min: Avoid use | Strong dual CYP3A4 and P-glycoprotein inhibitors (eg, ketoconazole, itraconazole, ritonavir): Avoid concomitant use  
Strong dual CYP3A4 and P-glycoprotein inducers (eg, rifampin, carbamazepine, phenytoin, St John’s wort): Avoid concomitant use. |

References:

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Section accessed [Nov. 15, 2018] [L-6-7, Table 19a]
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8. Pradaxa (dabigatran) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; March 2018.