Overview of Azole Metabolism and Drug Interactions

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Fluc</th>
<th>Itra</th>
<th>Posa</th>
<th>Vor</th>
<th>Isavu</th>
</tr>
</thead>
<tbody>
<tr>
<td>2C19</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
<td>++*</td>
</tr>
<tr>
<td>2C9</td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>3A4</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Other</td>
<td>UGT+</td>
<td>P-gp+</td>
<td>UGT+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Fluc</th>
<th>Itra</th>
<th>Posa</th>
<th>Vor</th>
<th>Isavu</th>
</tr>
</thead>
<tbody>
<tr>
<td>2C19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>2C9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>3A4</td>
<td>+++</td>
<td>+</td>
<td></td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UGT1A4+</td>
</tr>
</tbody>
</table>

*CYP 2C19 polymorphisms: 15-20% Asians, 3-5% of Caucasians, Blacks are poor metabolizers

Note: see below for factors impacting extent of, onset/offset of interactions

Select substrates of shared CYP pathways

- **3A4 substrates:**
  - amiodarone, dronedarone, many statins (e.g. atorvastatin, lovastatin, simvastatin), methadone, suvorexant, guanfacine
  - tacrolimus, cyclosporine, sirolimus, everolimus, prednisolone (the active metabolite of prednisone)
  - rivaroxaban, apixaban, edoxaban (minor), warfarin (minor)
  - rifampin (weak) other pathways), rifabutin, letermovir (minor) maribavir,
  - venetoclax, midostaurin, ivosidenib, TKIs (gilteritinib, ibritinib, ponatinib, dasatinib)

- **3A4 inducer:** rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine

- **3A4 inhibitor:** ritonavir (strong), maribavir (weak), cyclosporine (weak)

- **2C9 substrate:** warfarin, phenytoin, phenobarbital

- **2C19 substrate:** warfarin, clopidogrel, phenobarbital (minor)

- **UGT substrate:** mycophenolate

- **UGT inducer:** rifampin, rifabutin

- **P-gp substrate:** digoxin, tacrolimus, cyclosporine, sirolimus, everolimus, rifampin, rivaroxaban, apixaban, edoxaban, dabigatran, letermovir

- **P-gp inhibitor:** amiodarone, ritonavir, maribavir

Timeline for enzyme induction & inhibition

- **Onset**
  - Inhibition occurs quickly (days).
    - e.g. Max CYP3A4 inhibition observed within 2 days with voriconazole use
    - Note: dose-dependent (e.g. fluconazole 100mg vs 800mg)
  - CYP induction can take up to 14 days since this is via increased synthesis or decreased breakdown of CYP isoenzymes.

- **Offset**
  - Can vary depending on various factors, e.g. age (elderly → slower offset), mechanism of CYP inhibition (reversible vs irreversible), half-life of drug, duration of drug use prior to and during interaction.
References:


