Cytochrome P450 2C19 (CYP2C19) Pharmacogenomic Competency
A CYP2C19 ultrarapid metabolizer is prescribed omeprazole for GERD at the standard dose. Which of the following therapeutic recommendations is most appropriate based on the CYP2C19 phenotype and drug-specific risk?

a) Dispense omeprazole as prescribed
b) Recommend doubling the starting dose of omeprazole
c) Substitute omeprazole for another agent
Patients with which of the following CY2C19 phenotypes should avoid using clopidogrel?

a) Normal metabolizers
b) Poor metabolizers
c) Rapid metabolizers
d) Ultra-rapid metabolizers
Which allele is associated with increased CYP2C19 enzyme function?

a) *1
b) *3
c) *17
Objectives

• Upon completion of this competency, participants will be able to:
  • Recognize the different *CYP2C19* allele variants
  • Recognize the different CYP2C19 phenotypes
  • Assign the correct phenotype based upon the activity score
  • Make therapeutic recommendations for medications metabolized by CYP2C19 based on a patient’s predicted CYP2C19 phenotype
CYP2C19 is an enzyme that metabolizes many commonly prescribed medications

- Proton pump inhibitors, clopidogrel, voriconazole, etc.

Metabolism by CYP2C19 can either activate or inactivate a drug:

- **Clopidogrel**
  - Pro-drug, inactive
  - Metabolism by CYP2C19 results in Clopidogrel thiol H4, active

- **Voriconazole**
  - Active
  - Metabolism by CYP2C19 results in Voriconazole N-oxide, inactive

GOAL: Know the patient’s CYP2C19 phenotype prior to prescribing a medication that affected by CYP2C19 polymorphisms
CYP2C19 Allele Function
CYP2C19 Allele Variants

- CYP2C19 alleles are characterized into different functional groups:
  - Increased function
  - Normal function
  - Decreased function
  - No function
  - Uncertain function
# CYP2C19 Allele Functions

<table>
<thead>
<tr>
<th>Allele Function</th>
<th>Description</th>
<th>Examples Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased function</td>
<td>This allele encodes for the CYP2C19 enzyme that has increased metabolic activity compared to normal function</td>
<td>*17</td>
</tr>
<tr>
<td>Normal function</td>
<td>These allele encode for the CYP2C19 enzyme that has normal metabolic function</td>
<td>*1, *11, *13, *15</td>
</tr>
<tr>
<td>Decreased function</td>
<td>These alleles encode for the CYP2C19 enzyme with decreased metabolic function compared to normal function but higher than a no function</td>
<td>*9, *10, *16, *19</td>
</tr>
<tr>
<td>No function</td>
<td>These alleles encode for CYP2C19 enzyme that has little or no metabolic function</td>
<td>*2, *3, *4, *5, *6, *7, *8</td>
</tr>
<tr>
<td>Uncertain function</td>
<td>The metabolic function for CYP2C19 enzyme is uncertain</td>
<td>*12, *14, *23, *29</td>
</tr>
</tbody>
</table>

Assigning CYP2C19 Phenotype
CYP2C19 Phenotypes

- The assignment of CYP2C19 phenotype is based on the two alleles that the patient carries (also called genotype or diplotype)
- There are five CYP2C19 phenotypes

- Ultra-rapid metabolizer (UM)
- Rapid metabolizer (RM)
- Normal metabolizer (NM)
- Intermediate metabolizer (IM)
- Poor metabolizer (PM)

- In some instances, the CYP2C19 genotype result may be ambiguous and additional phenotype terminology is needed including:

  - Possible intermediate metabolizer
  - Possible poor metabolizer
  - Indeterminate

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid metabolizer (UM)</td>
<td>• Individual carrying two increased function alleles</td>
</tr>
<tr>
<td>Rapid metabolizer (RM)</td>
<td>• Individual carrying one normal function + one increased function allele</td>
</tr>
<tr>
<td>Normal metabolizer (NM)</td>
<td>• Individual carrying two normal function alleles</td>
</tr>
<tr>
<td>Intermediate metabolizer (IM)</td>
<td>• Individual carrying one normal function allele + no function allele</td>
</tr>
<tr>
<td></td>
<td>• Individual carrying one no function allele + increased function allele¹</td>
</tr>
<tr>
<td>Possible intermediate metabolizer</td>
<td>• Individual carrying one decreased function + increased function allele</td>
</tr>
<tr>
<td>Poor metabolizer (PM)</td>
<td>• Individual carrying two no function alleles</td>
</tr>
<tr>
<td>Possible poor metabolizer</td>
<td>• Individual carrying one decreased function + no function allele</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>• Individual carrying one or two uncertain function alleles</td>
</tr>
</tbody>
</table>
**CYP2C19 Allele Frequencies**

- **CYP2C19** allele frequencies are dependent on race
- *2* and *3* alleles are the most common variations

**2 allele**
- ~30% of Asians
- ~15% of Caucasians and African-Americans

**3 allele**
- ~8% of Asians
- <1% in Caucasians and African-Americans

- Prevalence of the CYP2C19 poor metabolizer phenotype:
  - Up to 25% of Asians
  - ~5% of Caucasians and African-Americans
CYP2C19 Phenotype Frequency in Europeans

- Ultrarapid metabolizer - very high activity
- Rapid metabolizer - increased activity
- Normal metabolizer - normal activity
- Intermediate metabolizer - decreased activity
- Poor metabolizer - low or no activity
- Indeterminate

- The exact percent of each phenotype group varies by ethnicity

• The exact percent of each phenotype group varies by ethnicity

- Ultrarapid metabolizer - very high activity
- Rapid metabolizer - increased activity
- Normal metabolizer - normal activity
- Intermediate metabolizer - decreased activity
- Poor metabolizer - low or no activity
- Indeterminate
Gene-Based Dosing Recommendations
Clopidogrel
Clopidogrel

Mechanism of action

- Antiplatelet which inhibits ADP-induced platelet aggregation

Indication

- Patients undergoing percutaneous coronary intervention (PCI) with stent placement
- Acute ischemic stroke or transient ischemic attack
- Secondary prevention of stroke or thromboembolic events
- Following neurointerventional procedures (e.g., intracranial aneurysm)
• Clopidogrel is a **pro-drug** that requires hepatic bioactivation.

• The activation of clopidogrel is a two-step process:
  - Clopidogrel is converted to 2-oxo-clopidogrel via CYP2C19, CYP1A2, and CYP2B6.
  - 2-oxo-clopidogrel is converted to the active thiol metabolite via CYP3A4/5, CYP2B6, CYP2C19, and CYP2C9.
CYP2C19 Polymorphisms Affect the Efficacy of Clopidogrel

- **CYP2C19 ultra-rapid and rapid metabolizers**
  - Increased clopidogrel bioactivation. No association with higher bleeding risk.
  - Initiate standard dose

- **CYP2C19 normal metabolizers**
  - Normal clopidogrel bioactivation.

- **CYP2C19 intermediate and poor metabolizers**
  - Reduced clopidogrel bioactivation. Increased risk for adverse cardiac and cerebrovascular events.
  - Avoid clopidogrel – contact Clinical Pharmacogenomics Program for alternatives

Voriconazole
Voriconazole

• Voriconazole, an azole antifungal, commonly used for prophylaxis and treatment of invasive fungal infections

• Voriconazole is predominately metabolized by CYP2C19 to inactive metabolite, voriconazole N-oxide

• Voriconazole clearance is also associated with patient age

Voriconazole CPIC Recommendations for Adults

- **CYP2C19 ultrarapid metabolizer**
  - Increased risk of subtherapeutic plasma trough concentrations and possible therapy failure
  - Consider an alternative agent*

- **CYP2C19 rapid metabolizer**
  - Prescribe recommended starting dose of voriconazole

- **CYP2C19 normal metabolizer**

- **CYP2C19 intermediate metabolizer**
  - Increased risk of supratherapeutic plasma trough concentrations and associated toxicity
  - Consider an alternative agent*

- **CYP2C19 poor metabolizer**

*If voriconazole is warranted, consider lowering the dose with careful TDM

Voriconazole CPIC Recommendations for Pediatrics

- **CYP2C19 ultrarapid metabolizer**
  - Increased risk of subtherapeutic plasma trough concentrations and possible therapy failure
  - Consider an alternative agent*

- **CYP2C19 rapid metabolizer**
  - Prescribe recommended starting dose of voriconazole

- **CYP2C19 normal metabolizer**

- **CYP2C19 intermediate metabolizer**
  - Increased risk of supratherapeutic plasma trough concentrations and associated toxicity
  - Consider an alternative agent*

- **CYP2C19 poor metabolizer**

*If voriconazole is warranted, consider lowering the dose with careful TDM

Proton Pump Inhibitors
Proton Pump Inhibitors (PPI)

Indications

- Peptic ulcer disease
- Gastroesophageal reflux disease (GERD)
- Erosive esophagitis
- GI prophylaxis
- *Helibacter pylori* infection
- Barrett’s esophagus
- Zollinger-Ellison syndrome
- Eosinophilic esophagitis
First-generation PPIs are primarily metabolized by CYP2C19 with minor contributions by CYP3A4.

- Omeprazole
- Pantoprazole
- Lansoprazole

CYP2C19

Hydroxy-(ome)-prazole

CYP3A4

Less active metabolites
Therapeutic Recommendations for *CYP2C19* and PPIs

<table>
<thead>
<tr>
<th>CYP2C19 Phenotype</th>
<th>Therapeutic Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid Metabolizer</td>
<td>Double the starting dose of the PPI (omeprazole, pantoprazole, lansoprazole)</td>
</tr>
<tr>
<td>Intermediate or Poor Metabolizer</td>
<td>No change in the initial starting dose of PPIs, but recommendations to reduce the dose by 50% if chronic therapy indicated (&gt; 12 weeks)</td>
</tr>
</tbody>
</table>

Amitriptyline
Amitriptyline Metabolism

- **CYP2C19** metabolizes amitriptyline to an active metabolite: nortriptyline.
- **CYP2D6** metabolizes amitriptyline and nortriptyline to less active hydroxy-metabolites.

Amitriptyline Metabolism

- **CYP2C19** metabolizes amitriptyline to an active metabolite: nortriptyline
- **CYP2D6** metabolizes amitriptyline and nortriptyline to less active hydroxy-metabolites

**Amitriptyline**

- CYP2D6 → 10-hydroxyamitriptyline (LESS ACTIVE)

**Nortriptyline**

- CYP2D6 → 10-hydroxynortriptyline (LESS ACTIVE)

• Because the tricyclic antidepressants have comparable pharmacokinetic properties, the dosing recommendations for amitriptyline may be applied to other tricyclic antidepressants including:
  • Clomipramine, imipramine, doxepin, and trimipramine
<table>
<thead>
<tr>
<th>CYP2C19 Phenotype</th>
<th>Therapeutic Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid metabolizer</td>
<td>Avoid tertiary amine tricyclic antidepressant* use – consider alternative drug not metabolized by CYP2C19</td>
</tr>
<tr>
<td>Normal metabolizer</td>
<td>Initiate therapy with recommended starting dose</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Initiate therapy with recommended starting dose</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Avoid tricyclic use – consider alternative drug not metabolized by CYP2C19</td>
</tr>
</tbody>
</table>

* Tertiary amine tricyclic antidepressants include: amitriptyline, clomipramine, imipramine, doxepin, and trimipramine

# Summary of Tricyclic Antidepressant Therapeutic Recommendations Based on CYP2C19 and CYP2D6 Phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>CYP2D6 ultra-rapid metabolizer</th>
<th>CYP2D6 normal metabolizer</th>
<th>CYP2D6 intermediate metabolizer</th>
<th>CYP2D6 poor metabolizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 ultra-rapid metabolizer</td>
<td>Avoid use</td>
<td>Consider alternative drug not metabolized by CYP2C19</td>
<td>Consider alternative drug not metabolized by CYP2C19</td>
<td>Avoid use</td>
</tr>
<tr>
<td>CYP2C19 rapid metabolizer</td>
<td>Avoid use</td>
<td>Consider alternative drug not metabolized by CYP2C19</td>
<td>Consider alternative drug not metabolized by CYP2C19</td>
<td>Avoid use</td>
</tr>
<tr>
<td>CYP2C19 normal metabolizer</td>
<td>Avoid use</td>
<td>Initiate therapy with recommended starting dose</td>
<td>Consider 25% reduction of recommended starting dose</td>
<td>Avoid use – if use is warranted, consider a 50% reduction of recommended starting dose</td>
</tr>
<tr>
<td>CYP2C19 intermediate metabolizer</td>
<td>Avoid use</td>
<td>Initiate therapy with recommended starting dose</td>
<td>Consider 25% reduction of recommended starting dose</td>
<td>Avoid use – if use is warranted, consider a 50% reduction of recommended starting dose</td>
</tr>
<tr>
<td>CYP2C19 poor metabolizer</td>
<td>Avoid use</td>
<td>Avoid use – if use is warranted, consider a 50% reduction of recommended starting dose</td>
<td>Avoid use</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

### Selective-Serotonin Inhibitors

<table>
<thead>
<tr>
<th>Medications</th>
<th>Mechanism of action</th>
<th>Indications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline</td>
<td>Inhibit the reuptake of serotonin → increase serotonin activity</td>
<td>Major depression disorder</td>
<td>Irritability, hyperactivity</td>
</tr>
<tr>
<td>Escitalopram</td>
<td></td>
<td>Generalized anxiety disorder</td>
<td>Agitation, shakiness or anxiousness</td>
</tr>
<tr>
<td>Citalopram</td>
<td></td>
<td>Obsessive-compulsive disorder</td>
<td>Gastrointestinal (N/V/D)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
<td>Panic disorder</td>
<td>Headache</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td></td>
<td>Posttraumatic stress disorder</td>
<td>Drowsiness</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td></td>
<td>Social anxiety disorder</td>
<td>Dizziness</td>
</tr>
</tbody>
</table>

#### Adverse Effects
- Irritability, hyperactivity
- Agitation, shakiness or anxiousness
- Gastrointestinal (N/V/D)
- Headache
- Drowsiness
- Dizziness
- Blurred vision
- Prolong QT interval
- Weight gain
- Decreased libido
Sertraline, citalopram, and escitalopram are primarily metabolized by CYP2C19 to less active metabolites.
50% dose reduction of standard maintenance dose of sertraline is recommended for CYP2C19 poor metabolizers
CYP2C19-guided recommendations for CYP2C19 ultrarapid, rapid, and poor metabolizers for es/citalopram

**Phenotypes**
- Ultra-rapid metabolizer
- Rapid metabolizer
- Normal metabolizer
- Intermediate metabolizer
- Poor metabolizer

**Safety/efficacy implications**
- Ultra-rapid metabolizer: Lower plasma concentrations will increase probability of therapeutic failure
- Rapid metabolizer: Consider alternative agent such as sertraline or initiate therapy with recommended starting dose.
- Normal metabolizer: Initiate therapy with recommended starting dose.
- Intermediate metabolizer: Consider alternative agent if no adequate response.
- Poor metabolizer: Consider alternative agent, or 50% reduction of standard maintenance dose and titrate up slowly.

**CPIC recommendations**
- Initiate therapy with recommended starting dose for normal and intermediate metabolizers.
- Consider alternative agent for rapid and poor metabolizers.

For More Information…

• For more information about *CYP2C19* and medications affected by *CYP2C19* polymorphisms, visit the CPIC guideline page at [https://cpicpgx.org/gene/cyp2c19/](https://cpicpgx.org/gene/cyp2c19/)

• For more information about the St. Jude implementation efforts for *CYP2C19* visit [www.stjude.org/CYP2C19](http://www.stjude.org/CYP2C19)
A CYP2C19 ultra-rapid metabolizer is prescribed omeprazole for GERD at the standard dose. Which of the following therapeutic recommendations is most appropriate based on the CYP2C19 phenotype and drug-specific risk?

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a) Dispense omeprazole as prescribed
b) Recommend doubling the starting dose of omeprazole
c) Substitute omeprazole for another agent

Correct Answer: B
Question #2

Patients with which of the following CY2C19 phenotypes should avoid using clopidogrel?

a) Normal metabolizers
b) Poor metabolizers
c) Ultra-rapid metabolizers
d) Rapid metabolizers
Patients with which of the following CY2C19 phenotypes should avoid using clopidogrel?

a) Normal metabolizers
b) Poor metabolizers
c) Ultra-rapid metabolizers
d) Rapid metabolizers

Correct Answer: B
Question #3

Which allele is associated with increased CYP2C19 enzyme function?

a) *1
b) *3
c) *17
Which allele is associated with increased CYP2C19 enzyme function?

a) *1
b) *3
c) *17

Correct Answer: C
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