Cytochrome P450 2C19 (CYP2C19) Pharmacogenetic Competency

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
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Updated on 05/2018

Pre-test Question # 1

A patient has a reported pharmacogenetic test result of *CYP2C19 *1/*12*. What is the assigned phenotype?

a) Ultra-rapid metabolizer (UM)
b) Intermediate metabolizer (IM)
c) Poor metabolizer (PM)
d) Indeterminate

Pre-test Question # 2

A patient with a reported pharmacogenetic test result of *CYP2C19 *2A/*2A* who is receiving clopidogrel is at ____ risk of suffering from an adverse cardiovascular event (e.g. thrombosis) due to treatment failure.

a) Increased
b) Moderate
c) Decreased

Pre-test Question # 3

JH has an indication to start clopidogrel therapy. He has a reported pharmacogenetic test result of *CYP2C19 *2A/*3*. What is your recommendation to the physician regarding the use of clopidogrel?

a) Use clopidogrel at an increased dose
b) Use clopidogrel at a reduced dose
c) Use clopidogrel at a standard dose
d) Use an alternative antiplatelet agent

Pre-test Question # 4

Which of the following statements is most correct about a *CYP2C19 *17/*17* genotype?

a) Patients convert clopidogrel to an inactive metabolite to a greater extent than **1/*1* and therefore a decrease in clopidogrel dose is recommended
b) Patients convert clopidogrel to an active metabolite to a greater extent than **1/*1* but no change in clopidogrel dose is recommended
c) Patients convert clopidogrel to an active metabolite to a lesser extent than **1/*1* and therefore a decrease in clopidogrel dose is recommended
d) Patients convert clopidogrel to an active metabolite to a lesser extent than **1/*1* and therefore a change in therapy is recommended

Objectives

- Upon completion of this competency, participants will be able to:
  - Recognize the different *CYP2C19* allele variants
  - Describe the different CYP2C19 phenotypes
  - Assign the correct phenotype based upon the allele variants
  - Make therapeutic recommendations for patients based on their predicted CYP2C19 phenotype

Patient Case #1

- A 74-year-old patient with severe coronary artery disease started on clopidogrel following a percutaneous coronary intervention (PCI).
- After multiple episodes of in-stent restenosis, clopidogrel resistance was suspected.
- Platelet reactivity testing measured while on clopidogrel returned was high (suggestive of resistance).
- *CYP2C19* genotyping revealed that the patient has two no function alleles (**2/*2* genotype). The patient was classified as having a CYP2C19 poor metabolizer phenotype.
- Switched to prasugrel, reduction in platelet reactivity by 86% and no cardiovascular events since switching agents.

Rai M, et al. *Conn Med*. 2012;76(5):267-72.

Patient Case #2

- A 36 year-old patient with AML was started on voriconazole therapy at 4 mg/kg IV Q12hrs due to a positive *Aspergillus* antigen.
- After 1 day of therapy the patient complained of auditory hallucinations and laboratory tests were notable for elevated transaminases
- Pharmacogenomic testing revealed the patient is a CYP2C19 poor metabolizer (**2/*17* genotype)

LeMaitre F, et al. *Drug Metab Pharmacokinet.* 2013;28(5):439-41.

Patient Case #3

- A 12-year-old patient diagnosed with neuroblastoma develops signs and symptoms of gastroesophageal reflux disease (GERD) during therapy and is started on omeprazole therapy.
- He is a known CYP2C19 ultra-rapid metabolizer (**17/*17* genotype)

CYP2C19 Pharmacogenetics

CYP2C19

- CYP2C19 is an enzyme that metabolizes some commonly prescribed drugs
- Metabolism by CYP2C19 can either activate or inactivate a drug
  - Clopidogrel is a prodrug that is metabolized to an active form by CYP2C19
  - Amitriptyline is metabolized by CYP2C19 to a less active form

CYP2C19

- Genetic variations in the *CYP2C19* gene may lead to changes in metabolic activity of the CYP2C19 enzyme (increased or reduced function)

CYP2C19 Allele Variants

- *CYP2C19* alleles are categorized into different groups:
  - Normal function alleles
  - Decreased function alleles
  - No function alleles
  - Increased function alleles
  - Uncertain function alleles

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.
https://api.pharmgkb.org/v1/download/file/attachment/CYP2C19_frequency_table.xlsx

CYP2C19 Allele Variants

- *CYP2C19* normal function alleles:
  - These alleles encode for CYP2C19 enzymes with normal metabolic function
  - **1, *13, *15*

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.
https://api.pharmgkb.org/v1/download/file/attachment/CYP2C19_frequency_table.xlsx

CYP2C19 Allele Variants

- Certain *CYP2C19* alleles are characterized as decreased function alleles
  - These alleles will encode for a CYP2C19 enzyme that has little metabolic function
- Decreased function *CYP2C19* alleles include:
  - **9,*10*

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.
https://api.pharmgkb.org/v1/download/file/attachment/CYP2C19_frequency_table.xlsx

CYP2C19 Allele Variants

- Certain *CYP2C19* alleles are characterized as no function alleles
  - These alleles will encode for a CYP2C19 enzyme that has no metabolic function
- No function *CYP2C19* alleles include:
  - **2,*2A, *2B, *3, *4, *5, *6, *7, *8*

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.
https://api.pharmgkb.org/v1/download/file/attachment/CYP2C19_frequency_table.xlsx

CYP2C19 Allele Variants

- *CYP2C19* has an allele characterized by a increased expression of the enzyme
  - This results in increased CYP2C19 metabolic function compared to the normal function allele
- At this time, the only increased function *CYP2C19* allele is the **17* allele

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.
https://api.pharmgkb.org/v1/download/file/attachment/CYP2C19_frequency_table.xlsx

CYP2C19 Allele Variants

- For certain *CYP2C19* alleles, the function of the enzyme is uncertain and considered uncharacterized
- *CYP2C19* uncertain function alleles include:
  - **12, *14, *23*

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.
https://api.pharmgkb.org/v1/download/file/attachment/CYP2C19_frequency_table.xlsx

Assigning a CYP2C19 Phenotype

CYP2C19 Phenotypes

- The assignment of CYP2C19 phenotype is based on the function of 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)

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.

CYP2C19 Phenotypes

Phenotype	Definition
Ultra-rapid Metabolizer (UM)	• Two copies of an increased function allele.
Rapid metabolizer (RM)	• One normal function allele and one increased function allele.
Normal Metabolizer (NM)	• Two copies of a normal function allele.
Intermediate Metabolizer (IM)	• One copy of a no function allele and one copy of a normal function allele. • One copy of an increased function allele with one copy of a no function allele.[1]
Poor Metabolizer (PM)	• Two copies of a no function allele.
Indeterminate	• Two copies of an uncertain function allele. • One copy of an uncertain function allele with one copy of known function allele.

[1] As per the CYP2C19/Amitriptyline CPIC guideline update (2013): The currently available evidence indicates that the **17* increased function allele is unable to completely compensate for the **2* no function allele; however, these data have not been consistently replicated for the **2* or other no function alleles and is therefore a provisional classification.

CYP2C19 Phenotypes

- Ultra-rapid metabolizers (UM)
  - Have increased CYP2C19 enzyme activity compared to normal
  - Approximately 5% of the population
  - Diplotype example:
    - **17/*17*

CYP2C19 Phenotypes

- Rapid metabolizers
  - Have CYP2C19 enzyme activity slightly higher than normal but less than ultra-rapid metabolizers
  - One increased function allele and one normal function allele
  - Approximately 15% of the population
  - Diplotype example:
    - **1/*17*

CYP2C19 Phenotypes

- Normal metabolizers
  - Have normal CYP2C19 enzyme activity
  - Patient carrying two normal function alleles
  - Approximately 40% of the population
  - Diplotype examples:
    - **1/*1, *1/*15*

CYP2C19 Phenotypes

- Intermediate metabolizers
  - Have decreased CYP2C19 enzyme activity. The activity is in between normal and poor metabolizers
  - One normal function allele and one no function allele, or one no function allele and one increased function allele
  - Approximately 30% of the population
  - Diplotype examples:
    - **1/*2A, *2A/*17*

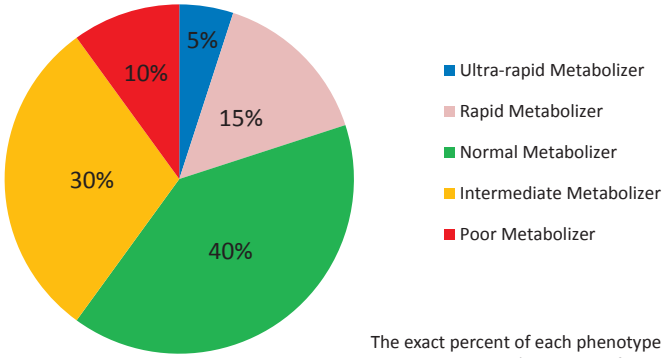
CYP2C19 Phenotypes

- Poor metabolizers (PM)
  - Have little or no CYP2C19 enzyme function
  - Patient carrying two no function alleles
  - 25% of Asians but only ~5% of Caucasians and African-Americans are poor metabolizers
  - Diplotype examples:
    - **2A/*2A*
    - **2A/*2B*

CYP2C19 Phenotypes

- Indeterminate
  - The expected phenotype cannot be determined based upon the *CYP2C19* genotype result
  - For example, a patient may have two copies of an indeterminate function allele or one copy of an indeterminate function allele and one copy of a known function allele
    - **1/*12*
    - **12/*14*

CYP2C19 Phenotypes



The exact percent of each phenotype group varies by ethnicity (up to 25% of Asian patients are CYP2C19 poor metabolizers)

CYP2C19 Phenotypes

- *CYP2C19* allele frequencies are dependent on ethnicity
- **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
    - Less than 1% in Caucasians and African-Americans
- Prevalence of poor metabolizer phenotype:
  - Up to 25% of Asians
  - ~5% of Caucasians and African-Americans

Gene-Based Dosing Recommendations

Clopidogrel

Clopidogrel

- Clopidogrel is an antiplatelet drug which inhibits ADP-mediated platelet activation and aggregation
- Clopidogrel is commonly used in patients undergoing percutaneous coronary intervention (PCI) with stent placement
- Other indications:
  - Acute coronary syndrome (ACS)
  - Stroke
  - Peripheral artery disease
- The 2013 CPIC guideline on clopidogrel and *CYP2C19* mainly focuses on ACS/PCI patients

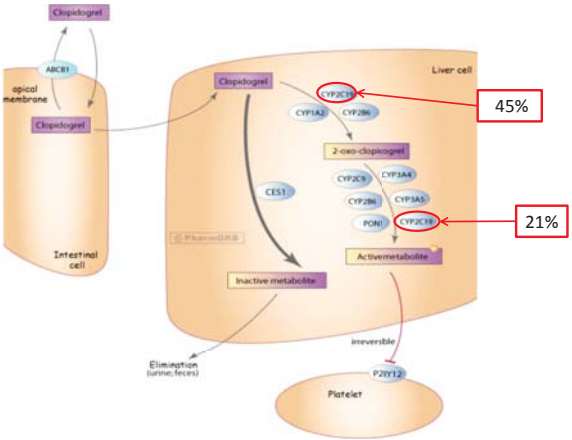
Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.

Clopidogrel

- Clopidogrel is a pro-drug that requires hepatic bioactivation
  - 85% of the drug is hydrolyzed by carboxylesterase 1, leaving only 15% to be converted to the active form
- The activation of clopidogrel is a two step process
  - Clopidogrel is converted to 2-oxoclopidogrel via CYP2C19 (45%), CYP1A2 (36%), and CYP2B6 (19%)
  - 2-oxoclopidogrel is converted to the active thiol metabolite via CYP3A4/5 (40%), CYP2B6 (33%), CYP2C19 (21%), and CYP2C9 (7%)
  - CYP2C19 contributes substantially to both oxidative steps required for active metabolite formation

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.
Kazui M, et al. *Drug Metab Dispos.* 2010;38(1):92-9.

Clopidogrel Metabolism



Sangkuhl K, et al. *Pharmacogenet Genomics.* 2010;20(7):463-5.

Clopidogrel

- Clopidogrel anti-platelet effect is closely related to CYP2C19 metabolism
  - <u>CYP2C19 ultra-rapid and rapid metabolizers</u>
    - Convert clopidogrel to the active thiol metabolite at a greater extent than normal
    - Possible increase in antiplatelet activity
    - No recommended clopidogrel dosage change
  - <u>CYP2C19 normal metabolizers</u>
    - Normal bio activation
    - No recommended clopidogrel dosage change

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.

Clopidogrel

- Clopidogrel anti-platelet effect is closely related to CYP2C19 metabolism
  - <u>CYP2C19 intermediate and poor metabolizers</u>
    - Poor bioactivation of clopidogrel to the active metabolite
    - Significantly reduced platelet inhibition leading to increased residual platelet aggregation
    - Significant increased risk for adverse cardiovascular events (e.g., thrombosis)
- CYP2C19 intermediate and poor metabolizers should NOT receive clopidogrel
  - Consider alternatives such as prasugrel or ticagrelor

Scott SA, et al. *Clin Pharmacol Ther.* 2013;94(3):317-23.

Amitriptyline

Amitriptyline

- Amitriptyline is a tricyclic antidepressant (TCA)
- Amitriptyline is commonly used for the treatment of depression and neuropathic pain
- Amitriptyline is metabolized by both CYP2C19 and CYP2D6, so both of the phenotype results must be considered when making dosing recommendations

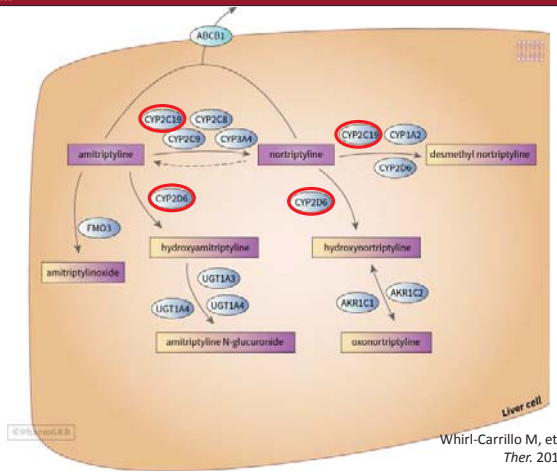
Hicks JK, et al. *Clin Pharmacol Ther.* 2016; doi: 10.1002/cpt.597

Amitriptyline

- The 2016 CPIC guideline on TCAs and *CYP2C19/CYP2D6* mainly focuses on recommendations when using for treatment of depression
  - At St. Jude, we recommend using the amitriptyline pharmacogenetic decision tree in the formulary to make dosing and therapy selection decisions for neuropathic pain
- Recommendations also apply to other tertiary amine TCAs
  - Doxepin
  - Clomipramine
  - Trimipramine
  - Imipramine

Hicks JK, et al. *Clin Pharmacol Ther.* 2016; doi: 10.1002/cpt.597

Amitriptyline Metabolism



Whirl-Carrillo M, et al. *Clin Pharmacol Ther.* 2012 Oct;92(4):414-7.

Amitriptyline

- **CYP2C19 ultra-rapid and rapid metabolizers**
  - Convert more amitriptyline to nortriptyline than normal
  - May reduce efficacy of therapy because of an altered amitriptyline:nortriptyline ratio
- **CYP2C19 normal metabolizers**
  - Normal conversion to nortriptyline, no dosing adjustment
- **CYP2C19 intermediate and poor metabolizers**
  - Convert less amitriptyline to nortriptyline than normal
  - May reduce the efficacy of therapy because of an altered amitriptyline:nortriptyline ratio

You should also consider the patient's CYP2D6 phenotype before making a clinical recommendation for amitriptyline

Hicks JK, et al. *Clin Pharmacol Ther.* 2016; doi: 10.1002/cpt.597

Amitriptyline

- A table providing recommendations for dosing of amitriptyline according to the *CYP2D6* and *CYP2C19* genotype test results can be found here (see Table 4)

Hicks JK, et al. *Clin Pharmacol Ther.* 2016; doi: 10.1002/cpt.597

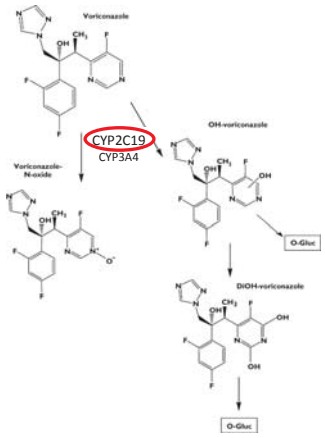
Voriconazole

Voriconazole

- Voriconazole is a triazole antifungal that is commonly used for prophylaxis and treatment of invasive fungal infections
- Voriconazole is predominately metabolized by CYP2C19 to inactive metabolites
- Voriconazole clearance is also associated with patient age

Moriyama B, et al. *Clin Pharmacol Ther.* 2016 Dec 16. doi: 10.1002/cpt.583.

Voriconazole Metabolism



Scholz I, et al. *Br J Clin Pharmacol*. 2009;68(6):906-15.

Voriconazole

- **CYP2C19 ultra-rapid metabolizers**
  - Increased metabolism of voriconazole to inactive metabolites
  - Increased risk of sub-therapeutic voriconazole plasma trough concentrations and possible therapy failure at normal doses
  - Choose an alternative agent that is not dependent on CYP2C19 metabolism such as isavuconazole, liposomal amphotericin B or posaconazole

Moriyama B, et al. *Clin Pharmacol Ther.* 2016 Dec 16. doi: 10.1002/cpt.583.

Voriconazole

- **CYP2C19 rapid metabolizers**
  - The probability of attaining therapeutic concentrations is modest with standard voriconazole dosing
  - **Adult** patients: choose an alternative agent that is not dependent on CYP2C19 metabolism such as isavuconazole, liposomal amphotericin B, or posaconazole
  - **Pediatric** patients (< 18 years old): No voriconazole dosing adjustments recommended

Moriyama B, et al. *Clin Pharmacol Ther.* 2016 Dec 16. doi: 10.1002/cpt.583.

Voriconazole

- **CYP2C19 normal and intermediate metabolizers**
  - Normal metabolism of voriconazole to inactive metabolites
  - No voriconazole dosing adjustments recommended
- **CYP2C19 poor metabolizers**
  - Significantly reduced metabolism of voriconazole to inactive metabolites
  - Increased risk of supra-therapeutic voriconazole plasma trough concentrations and associated toxicities at normal doses
  - Choose an alternative agent that is not dependent on CYP2C19 metabolism such as isavuconazole, liposomal amphotericin B, or posaconazole

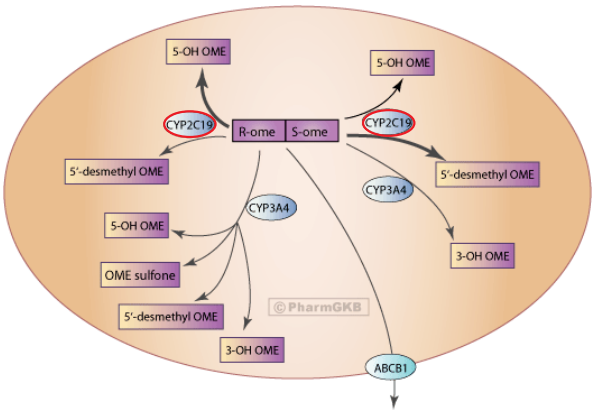
Moriyama B, et al. *Clin Pharmacol Ther.* 2016 Dec 16. doi: 10.1002/cpt.583.

Proton Pump Inhibitors:
Omeprazole, Lansoprazole, and Pantoprazole

Omeprazole

- Proton pump inhibitors (PPI) increase intragastric pH by inhibiting the H+/K+ ATPase enzyme system of parietal cells
- PPIs are commonly used in patients with gastroesophageal reflux disease (GERD) and gastric ulcers
- Other indications:
  - Duodenal ulcers
  - Zollinger-Ellison syndrome
  - Eradication of *Helicobacter pylori* infection

Omeprazole Metabolism



Whirl-Carrillo M, et al .*Clin Pharmacol Ther*. 2012;92(4):414-7.

PPIs: Omeprazole, Lansoprazole, Pantoprazole

- **CYP2C19 ultra-rapid metabolizers**
  - Faster than normal conversion of parent drug to inactive 5-hydroxy metabolites, agents may have reduced therapeutic efficacy because of decreased systemic serum concentrations
  - Consider doubling the starting dose omeprazole, lansoprazole and pantoprazole.
- **CYP2C19 normal and rapid metabolizers**
  - Normal PPI metabolism, no dosing adjustment
- **CYP2C19 intermediate and poor metabolizers**
  - Slower than normal conversion of parent drug to inactive metabolites
  - May improve therapeutic efficacy because of increased systemic serum concentrations

For More Information…

- For more information about CYP2C19 and clopidogrel dosing click here.
- For more information about CYP2D6, CYP2C19 and tricyclic antidepressant dosing click here.
- For more information about CYP2C19 and voriconazole dosing click here.
- For more information about CYP2C19 and proton pump inhibitor dosing click here.

For More Information…

- For more information about pharmacogenetics, visit the following websites:
  - CPIC®: https://cpicpgx.org/
  - PharmGKB: https://www.pharmgkb.org/
- For more pharmacogenetics service implementation resources visit the following website: www.stjude.org/pg4kds

Question # 1

A patient has a reported pharmacogenetic test result of *CYP2C19 *1/*12*. What is the assigned phenotype?

a) Ultra-rapid metabolizer (UM)
b) Intermediate metabolizer (IM)
c) Poor metabolizer (PM)
d) Indeterminate

Correct answer: d

Question # 2

A patient with a reported pharmacogenetic test result of *CYP2C19 *2A/*2A* who is receiving clopidogrel is at ____ risk of suffering from an adverse cardiovascular event (e.g. thrombosis) due to treatment failure.

a) Increased
b) Moderate
c) Decreased

Correct answer: a

Question # 3

JH has an indication to start clopidogrel therapy. He has a reported pharmacogenetic test result of *CYP2C19 *2A/*3*. What is your recommendation to the physician regarding the use of clopidogrel?

a) Use clopidogrel at an increased dose
b) Use clopidogrel at a reduced dose
c) Use clopidogrel at a standard dose
d) Use an alternative antiplatelet agent

Correct answer: d

Question # 4

Which of the following statements is most correct about a *CYP2C19 *17/*17* genotype?

a) Patients convert clopidogrel to an inactive metabolite to a greater extent than **1/*1* and therefore a decrease in clopidogrel dose is recommended
b) Patients convert clopidogrel to an active metabolite to a greater extent than **1/*1* but no change in clopidogrel dose is recommended
c) Patients convert clopidogrel to an active metabolite to a lesser extent than **1/*1* and therefore a decrease in clopidogrel dose is recommended
d) Patients convert clopidogrel to an active metabolite to a lesser extent than **1/*1* and therefore a change in therapy is recommended

Correct answer: b

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