Clinical Pharmacogenetics Implementation Consortium guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update.

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Clinical Pharmacogenetics Implementation Consortium (CPIC)

Lee CR, Luzum JA, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update. Clin Pharmacol Ther. 2022 Nov;112(5):959-967. [43 references] PubMed

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Overview

Guideline Objective

To provide information that facilitates the interpretation of clinical *CYP2C19* genotype test results to guide clopidogrel prescribing

Note:

- Recommendations for use of other laboratory tests, such as platelet function monitoring, as well as cost-effectiveness analyses, are beyond the scope of this document.
- The guideline does not focus on demographic and other clinical variables, such as adherence to therapy, age, diabetes mellitus, obesity, smoking, and concomitant use of other drugs that may influence clopidogrel efficacy and clinical decision making.

Patient Population

Patients requiring antiplatelet therapy

Recommendations

Recommendation Statements

Antiplatelet Therapy Recommendations based on CYP2C19 Phenotype When Considering Clopidogrel for Cardiovascular Indications

CYP2C19 Phenotype[a]	Implications for Phenotypic Measures	Therapeutic Recommendation	Classification of Recommendation[b] - Acute Coronary Syndrome (ACS) and/or Percutaneous Coronary Intervention (PCI)[c]	Classification of Recommendation[b] - Non-ACS, Non-PCI Cardiovascular Indications[d]
CYP2C19 ultrarapid metabolizer	Increased clopidogrel active metabolite formation; lower on-treatment platelet reactivity; no association with higher bleeding risk	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	No recommendation
CYP2C19 rapid metabolizer	Normal or increased clopidogrel active metabolite formation; normal or lower on-treatment platelet reactivity; no association with higher bleeding risk	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	No recommendation

CYP2C19 normal metabolizer	Normal clopidogrel active metabolite formation; normal on-treatment platelet reactivity	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	Strong
CYP2C19 likely intermediate metabolizer	Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid standard dose clopidogrel (75 mg) if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong[e]	No recommendation[e]
CYP2C19 intermediate metabolizer	Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid standard dose (75 mg) clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong	No recommendation
CYP2C19 likely poor	Significantly reduced	Avoid clopidogrel if possible. Use	Strong[e]	Moderate[e]

metabolizer	clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	prasugrel or ticagrelor at standard dose if no contraindication		
CYP2C19 poor metabolizer	Significantly reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong	Moderate

a Refer to the CYP2C19 Allele Frequency Table for phenotype frequencies for major race/ethnic groups, and the CYP2C19 Diplotype-Phenotype Table for a complete list of possible diplotypes and phenotype assignments.

b See the "Recommendation Rating Scheme" field.

c ACS and/or PCI includes patients undergoing PCI for an ACS or non-ACS (elective) indication.

d Non-ACS, non-PCI cardiovascular indications include peripheral arterial disease and stable coronary artery disease following a recent myocardial infarction outside the setting of PCI.

e The strength of recommendation for "likely" phenotypes are the same as their respective confirmed phenotypes. "Likely" indicates the uncertainty in the phenotype assignment, but it is reasonable to apply the recommendation for the confirmed phenotype to the corresponding "likely" phenotype.

Antiplatelet Therapy Recommendations based on CYP2C19 Phenotype When Considering Clopidogrel for Neurovascular

Indications[a]

CYP2C19 Phenotype[b]	Implications for Phenotypic Measures	Therapeutic Recommendation	Classification of Recommendation[c]	Other Considerations
CYP2C19 ultrarapid metabolizer	Increased clopidogrel active metabolite formation; lower on-treatment platelet reactivity	No recommendation	No recommendation	
CYP2C19 rapid metabolizer	Normal or increased clopidogrel active metabolite formation; normal or lower ontreatment platelet reactivity	No recommendation	No recommendation	
CYP2C19 normal metabolizer	Normal clopidogrel active metabolite formation; normal on-treatment platelet reactivity	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	
CYP2C19 likely intermediate metabolizer	Reduced clopidogrel active metabolite formation;	Consider an alternative $P2Y_{12}$ inhibitor at standard dose if clinically	Moderate[d]	Alternative $P2Y_{12}$ inhibitors not impacted by CYP2C19 genetic

	increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	indicated and no contraindication		variants include ticagrelor and ticlopidine. Prasugrel is contraindicated in patients with a history of stroke or TIA[e]
CYP2C19 intermediate metabolizer	Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Consider an alternative $P2Y_{12}$ inhibitor at standard dose if clinically indicated and no contraindication	Moderate	Alternative $P2Y_{12}$ inhibitors not impacted by CYP2C19 genetic variants include ticagrelor and ticlopidine. Prasugrel is contraindicated in patients with a history of stroke or TIA[e]
CYP2C19 likely poor metabolizer	Significantly reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid clopidogrel if possible. Consider an alternative $P2Y_{12}$ inhibitor at standard dose if clinically indicated and no contraindication	Moderate[d]	Alternative $P2Y_{12}$ inhibitors not impacted by CYP2C19 genetic variants include ticagrelor and ticlopidine. Prasugrel is contraindicated in patients with a history of stroke or transient ischemic attack (TIA)[e]

CYP2C19 poor metabolizer	Significantly reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid clopidogrel if possible. Consider an alternative $P2Y_{12}$ inhibitor at standard dose if clinically indicated and no contraindication	Moderate	Alternative $P2Y_{12}$ inhibitors not impacted by CYP2C19 genetic variants include ticagrelor and ticlopidine. Prasugrel is contraindicated in patients with a history of stroke or TIA[e]

a Neurovascular disease includes acute ischemic stroke or transient ischemic attack, secondary prevention of stroke, or prevention of thromboembolic events following neurointerventional procedures, such as carotid artery stenting and stent-assisted coiling of intracranial aneurysms.

b Refer to the CYP2C19 Allele Frequency Table for phenotype frequencies for major race/ethnic groups, and the CYP2C19 Diplotype-Phenotype Table for a complete list of possible diplotypes and phenotype assignments.

c See the "Recommendation Rating Scheme" field.

d The strength of recommendation for "likely" phenotypes are the same as their respective confirmed phenotypes. "Likely" indicates the uncertainty in the phenotype assignment, but it is reasonable to apply the recommendation for the confirmed phenotype to the corresponding "likely" phenotype.

e Given limited outcomes data for genotype-guided anti-platelet therapy for neurovascular indications, selection of therapy should depend on individual patient treatment goals and risks for adverse events.

Evidence Rating Scheme

Levels of Evidence

CPIC assigns levels to the evidence linking genotype to phenotype. The literature-based evidence summarized in the *Supplement* (see the "Supporting Documents" field) is graded* on a scale of high, moderate and weak, defined as follows:

- **High**: Evidence includes consistent results from well-designed, well-conducted studies.
- **Moderate**: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence.
- **Weak**: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of

evidence, or lack of information.

* Valdes R, Payne DA, et al., editors. Laboratory medicine practice guidelines. Laboratory analysis and application of pharmacogenetics to clinical practice. Washington (DC): National Academy of Clinical Biochemistry; 2010.

Recommendation Rating Scheme

Strength of Recommendations

CPIC's therapeutic recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: in vivo pharmacokinetic and pharmacodynamic data, in vitro enzyme activity of tissues expressing wild-type or variant-containing protein, in vitro enzyme activity from tissues isolated from individuals of known genotypes, and in vivo pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of antiretroviral agents*:

- **Strong** recommendation for the statement: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
- **Moderate** recommendation for the statement: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.
- **Optional** recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
- **No recommendation**: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

* Adolescents PoAGfAa. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington (DC): Department of Health and Human Services; 2011. p. 1-166.

Related Content

Supporting Documents

- Supplement; 2022.
- Incorporation of Pharmacogenomics into Routine Clinical Practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process; 2014 Feb.

Implementation Tools

- *CYP2C19* Allele Definition Table.
- *CYP2C19* Allele Functionality Table.
- *CYP2C19* Frequency Table.
- *CYP2C19* Diplotype-Phenotype Table.
- *CYP2C19* Gene Resource Mapping.
- Drug Resource Mapping: Clopidogrel.
- Clinical Decision Support:
  - *CYP2C19* Consult Text and Implementation Workflow.
  - Clopidogrel Pre- and Post-Test Alerts and Flow Charts.

Patient Education

No patient education materials available.

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TRUST Scorecard

Composition of Guideline Development Group (GDG)

Multidisciplinary GDG Members	**Yes**
Methodologist Involvement	**Yes**
Incorporation of Patient and Public Perspective	★☆☆☆☆

Systematic Review of Evidence

Literature Search	★★★★☆
Study Selection	★★★☆☆
Evidence Synthesis	★★★☆☆

Foundations for Recommendations

Strength of Evidence Grade	★★★☆☆
Description of Benefits and Harms of Recommendations	★★★★★
Summary of Evidence Supporting Recommendations	★★★★☆
Strength of Recommendations Rating	★★★★★
Clear Articulation of Recommendations	★★★★☆

Funding Source — **Yes**

Disclosure and Management of Financial Conflicts of Interests — ★★★★☆

External Review — ★★★☆☆

Updating — ★★★★☆

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