U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Services

CLINICIAN GUIDE

Utilizing Pharmacogenomic (PGx) Testing for Patients Undergoing Coronary Stenting

Using PGx testing to optimize outcomes

Post-percutaneous coronary intervention (PCI), dual-antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor and aspirin is the standard of care for secondary prevention of further major adverse cardiac events (MACE) and stent thrombosis.[1,2]

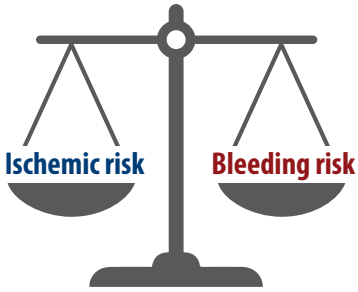

Table 1. $P2Y_{12}$ inhibitors and considerations for prescribing

	Clopidogrel[3]	Ticagrelor[4]	Prasugrel[5]
Platelet inhibition and subsequent bleed risk	⊕[1,6,7]	⊕⊕[1,7]	⊕⊕[1,6]
FDA boxed warnings	Diminished antiplatelet effect with poor *CYP2C19* function	Bleeding risk	Bleeding risk *(See Table 4 for age and weight considerations)*
FDA label contraindications	• Active bleeding • Hypersensitivity	• Active bleeding • History of ICH • Hypersensitivity	• Active bleeding • History of TIA or stroke • Hypersensitivity
Post-PCI FDA-approved indications	ACS, SIHD	ACS	ACS

FDA: Food and Drug Administration; ACS: acute coronary syndrome; SIHD: stable ischemic heart disease; ICH: intracranial hemorrhage; TIA: transient ischemic attack.
⊕ Risk of platelet inhibition and subsequent bleed risk is less for clopidogrel compared to ticagrelor or prasugrel;
⊕⊕ Risk of platelet inhibition and subsequent bleed risk is more for ticagrelor and prasurgrel when compared to clopidogrel.

Clopidogrel:

- Is the most widely prescribed $P2Y_{12}$ inhibitor due to lowest bleed risk, cost, and general patient tolerability.[1,8]
- Has variation in the degree of **platelet inhibition**, some of which is directly associated with genetic variations in metabolism by the cytochrome P450 ***CYP2C19* enzyme**.[8-10]
- Is a **prodrug** converted by *CYP2C19* to active metabolites that inhibit platelet aggregation. Patients who are intermediate or poor *CYP2C19* metabolizers have lower than expected concentrations of active metabolites. This results in **reduced platelet inhibition** and an **increased risk for future ischemic events**.

PGx testing identifies variation in *CYP2C19* function and is another tool to consider when optimizing DAPT in the post-PCI setting, in combination with other patient-specific factors.

There is a relative increased risk of adverse events for intermediate or poor *CYP2C19* metabolizers treated with clopidogrel post-PCI compared to normal or rapid metabolizers.[10]

Relative increased risk

57% MACE

181% Stent thrombosis

Meta-analysis of 9 studies totaling 9,685 patients[10]

Table 2. Studies have demonstrated improved outcomes with genotype-guided therapy[11]

	POPular Genetics[9]	TAILOR-PCI[12] & Ingraham et al[13]	Pereira et al[14]
Design	Open label, randomized controlled trial (RCT)	Multicenter, open label, prospective, RCT	Meta-analysis of 7 RCTs (including TAILOR-PCI)
Methods	Randomized to receive **prasugrel/ticagrelor** (n=1,246) **OR** *CYP2C19* genotype-guided **de-escalated therapy** (n=1,242) • Intermediate and poor metabolizers received prasugrel/ticagrelor • Normal metabolizers received clopidogrel	Randomized to receive **clopidogrel** (n=2,650) **OR** *CYP2C19* genotype-guided **escalated therapy** (n=2,652) • Intermediate and poor metabolizers received prasugrel/ticagrelor • Normal metabolizers received clopidogrel	Included trials where patients were randomized to **clopidogrel** or **prasugrel/ticagrelor** and reported the effect of *CYP2C19* metabolizer status on the incidence of MACE
Patient population	2,488 acute MI patients undergoing PCI	5,302 patients undergoing PCI for ACS (82%) or SIHD (18%)	15,949 patients (77% undergoing PCI; 98% with ACS)
Outcomes	**Non-inferiority** for death from any cause, MI, stent thrombosis, stroke, or major bleeding **22% reduction** in major and minor bleeding in genotype-guided group (p=0.04)	**PRIMARY COMPOSITE OUTCOME** in intermediate and poor metabolizers (n=1,849) **34% reduction** in composite MACE and stent thrombosis at 12 months (p=0.06);[§] no significant difference in cumulative incidence of major or minor bleeding **PRE-SPECIFIED, SECONDARY OUTCOME** using a time-to-event model[13] **39% reduction** in cumulative incidence of MACE over 12 months in genotype-guided group (p=0.011)	**30% risk reduction** for MACE with ticagrelor/prasugrel v. clopidogrel in *CYP2C19* intermediate or poor metabolizers but no effect in normal metabolizers *Statistically significant test of interaction suggesting genotype-modified effect (p=0.013)*

These trials used point-of-care genotyping. VA is extrapolating this strategy through outpatient re-evaluation of $P2Y_{12}$ therapy post-PCI.
[§] Not significant likely due to trial being underpowered.

Utilize PGx testing in patients undergoing PCI to optimize antiplatelet therapy efficacy and safety.

Care coordination

PGx test results may take 10 to 20 days to come back. Care coordination between peri-procedural and outpatient cardiology providers is essential as results are likely to come back after discharge.

Consider consulting your PGx Clinical Pharmacy Practitioner (CPP) (https://tinyurl.com/47zzsb8p) or entering an interfacility PGx consult when test results come back.

PGx test results

Table 3. *CYP2C19* phenotype and clinical implications[8]

CYP2C19 phenotype	Active metabolite formation	Event risk
Intermediate or likely intermediate metabolizer	⬇ Reduced clopidogrel active metabolite formation	⬆ Increased risk for adverse cardiac and cerebrovascular events
Poor or likely poor metabolizer	⬇⬇ Significantly reduced clopidogrel active metabolite formation	⬆⬆ Significantly increased risk for adverse cardiac and cerebrovascular events
All other phenotypes	**Normal or increased** clopidogrel active metabolite formation	**Normal event risk**, no increased bleed risk

The prevalence of *CYP2C19* intermediate or poor metabolizers varies widely between 1% and 57% in certain ancestral populations.[15] Actionable phenotypes are present, to varying degrees, in all major ancestries and only PGx testing can confirm metabolizer status.

Escalation to prasugrel or ticagrelor may be suboptimal in some circumstances due to increased bleeding risk or other patient-specific factors despite metabolizer status. There are no definitive guidelines on alternative dosing regimens or non-$P2Y_{12}$ therapies in this patient population.

Consult your PGx CPP (https://tinyurl.com/47zzsb8p) **or enter an interfacility consult** for recommendations.

Applying PGx test results to antiplatelet therapy selection

Table 4. ESCALATING antiplatelet therapy from clopidogrel to prasugrel or ticagrelor in intermediate and poor *CYP2C19* metabolizers[1]

	Prasugrel	Ticagrelor
Pathway for active metabolite formation	Primarily metabolized by other P450 enzymes	Orally active
Transitioning from clopidogrel: **≤ 30 days after PCI[1]**	**≥ 60 kg:** 60 mg loading dose once, then 10 mg once daily; **< 60 kg:** 5 mg once daily irrespective of last clopidogrel dose	180 mg loading dose irrespective of last clopidogrel dose, then 90 mg twice daily starting 12 hours later
> 30 days after PCI[1]	**≥ 60 kg:** 10 mg once daily; **< 60 kg:** 5 mg once daily starting 24 hours after last clopidogrel dose	90 mg twice daily starting 24 hours after last clopidogrel dose
Other considerations	• Higher bleeding risk and reduced net clinical benefit in patients ≥ 75 years and those weighing < 60 kg[1,5,6] • Caution with concomitant use of anticoagulants[5]	• Higher bleeding risk[1,4,7] • Caution with concomitant use of anticoagulants[2] • Compliance concerns with twice daily dosing • Avoid concomitant simvastatin and lovastatin doses > 40 mg[4]

Note that local prior authorization may be required. The patient must meet both the inclusion and exclusion criteria for prasugrel and ticagrelor.

Table 5. DE-ESCALATING antiplatelet therapy from prasurgrel or ticagrelor to clopidogrel in normal or rapid *CYP2C19* metabolizers[1]

	Prasugrel	Ticagrelor
Transitioning to clopidogrel: ≤ 30 days after PCI	600 mg loading dose 24 hours after last prasugrel dose, then 75 mg daily	600 mg loading dose 24 hours after last ticagrelor dose, then 75 mg daily
> 30 days after PCI	75 mg daily maintenance dose, starting 24 hours after last prasugrel dose	

For patients with bleeding or particularly high bleeding risk de-escalating to clopidogrel, the loading dose of clopidogrel may be withheld or reduced to 300mg.[1]

See these guides for information on antiplatelet pharmacotherapy duration *(titles abbreviated).*

- 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization... (https://pubmed.ncbi.nlm.nih.gov/34882435/)
- 2020 ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy... (https://www.sciencedirect.com/science/article/pii/S0735109720366158?via%3Dihub)
- 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for ...Chronic Disease (https://www.ahajournals.org/doi/10.1161/CIR.0000000000001168)

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