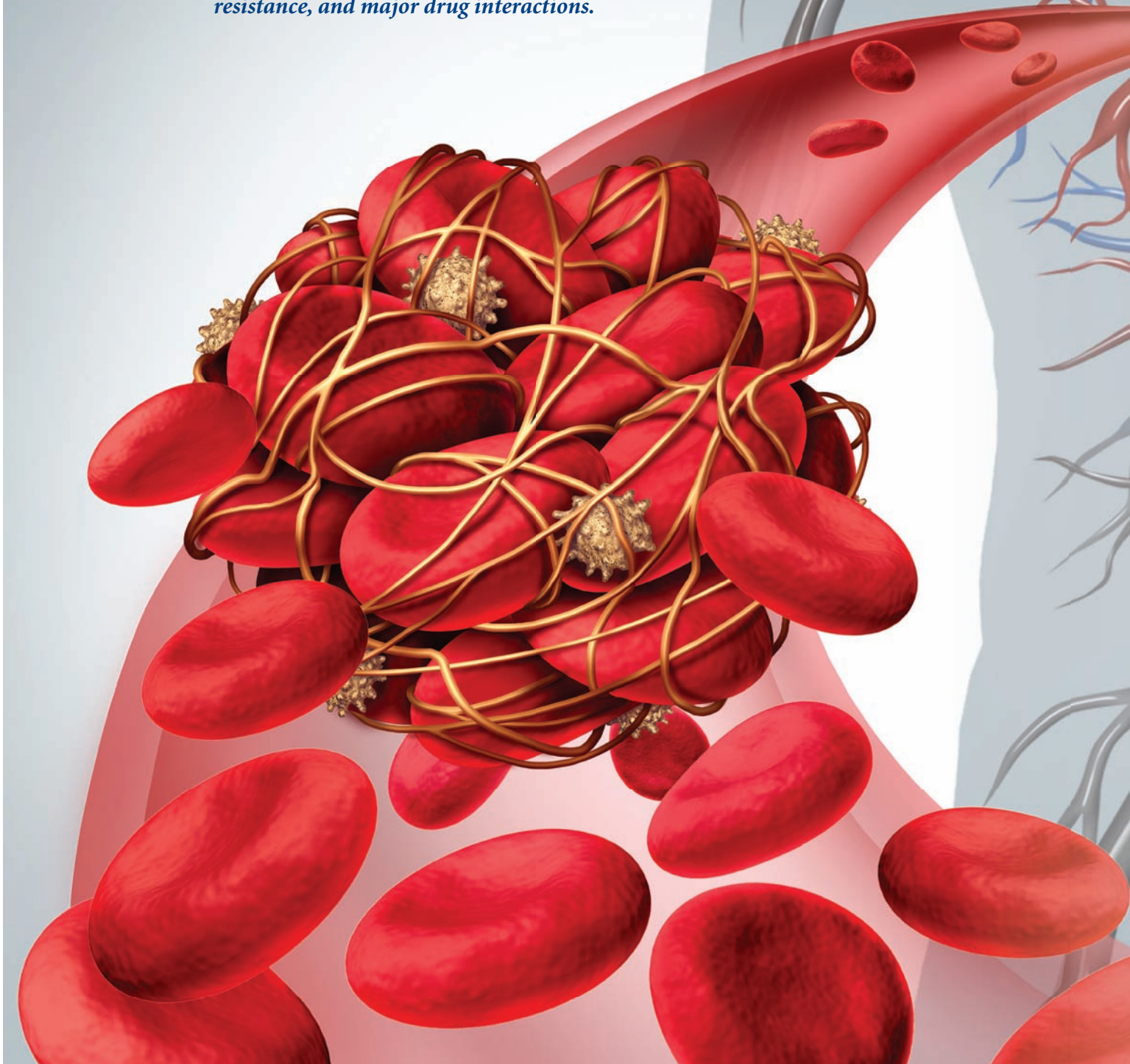


Abstract: New and more potent oral antiplatelet agents have shown better clinical outcomes over the last few years. This article reviews the latest oral antiplatelet therapies available, their indications and contraindications, genetic resistance, and major drug interactions.





New oral antiplatelet medications

By Travis Jeffords, BSN-RN, CCRN

Antiplatelet therapy consists of several medication combinations. The acronym DAPT (dual antiplatelet therapy) has been used to refer to the combination of aspirin and a P2Y₁₂-receptor inhibitor, such as clopidogrel, prasugrel, or ticagrelor.¹ Clopidogrel in combination with aspirin has been the foundation of DAPT for patients with acute coronary syndrome since its approval by the FDA in 1997.²

Prasugrel and ticagrelor are more potent and have a more rapid onset of action, which has shown improved clinical outcomes by reducing the risk of recurrent ischemic events in patients with acute coronary syndrome (ACS) or who have undergone a percutaneous coronary intervention (PCI).³ The latest evidence suggests a change in the current treatment of choice, reflecting that in the early period of ACS, treatment should include DAPT with a combination of aspirin and either prasugrel or ticagrelor as opposed to clopidogrel.^{1,3-6}

The use of newer medications has an inherent risk and cost associated, so treatment must be individualized to each patient regarding the patient's overall medical condition and financial capabilities. The evidence associated with newer oral antiplatelet medications has been largely limited to cardiology.

This article discusses four of the newest FDA-approved oral antiplatelet agents and simplifies the latest research and guidelines to provide a better understanding of the latest oral antiplatelet therapy available, the indications and contraindications, genetic considerations in relation to resistance, and drug interactions.

Keywords: antiplatelet therapy, clopidogrel, clopidogrel resistance, cyclopentyl-triazolopyrimidine agents, CYP2C19 genetic variance, DAPT, dual antiplatelet therapy, oral antiplatelet comparison, oral antiplatelets, prasugrel, protease-activated receptor-1 antagonists, thienopyridines, ticagrelor, vorapaxar

■ Pathophysiology and pharmacokinetics

The pathophysiology of platelet activation pathways is a complex intracellular signaling process. Thrombus formation is a key concept, and there are similarities and

differences in the mechanism utilized by the different oral antiplatelet medications in order to inhibit platelet activation. differences in the mechanism utilized by the different oral antiplatelet medications in order to inhibit platelet activation. tions may cause vascular changes and a disturbance in blood flow, resulting in an arterial occlusion, which is typically seen in atherosclerotic vessels of the heart or brain, resulting in a myocardial infarction (MI) or stroke.⁷



The P2Y₁₂ receptor plays a central role in platelet activation and is the primary target of the novel antiplatelet agents.

Antiplatelet therapy is the attempt to decrease the formation of arterial thrombi by inhibiting adhesion, activation, and aggregation of platelets through one of the signaling pathways at the site of vascular injury.^{3,7} Clopidogrel and prasugrel are first- and second-generation thienopyridines,

respectively.^{8,9} Ticagrelor is a cyclopentyl-triazolo-pyrimidine agent.¹⁰

Platelet adhesion and aggregation are the response to vascular injury. Single platelets bind through membrane receptors located on the vessel walls and tissues.⁷ This adhesion is viewed as the first step of thrombus formation. Typically, this response is positive and beneficial, preventing hemorrhage and permitting wound healing. These condi-

tioned by the different oral antiplatelet medications in order to inhibit platelet activation.

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Oral antiplatelet comparison⁸⁻¹¹

	Clopidogrel	Prasugrel	Ticagrelor	Vorapaxar
Class	Second-generation thienopyridine	Third-generation thienopyridine	Cyclopentyl-triazolo-pyrimidine	PAR-1 antagonist
Mechanism of platelet inhibition	Irreversible inhibition of P2Y ₁₂ component of ADP receptor; prevention of ADP binding and activation of platelets	Irreversible inhibition of P2Y ₁₂ component of ADP receptor; prevention of ADP binding and activation of platelets	Reversible modification of P2Y ₁₂ component of ADP receptor; prevention of ADP binding and activation of platelets	Blocks thrombin-mediated platelet activation by selectively inhibiting PAR-1
Adverse reactions	<ul style="list-style-type: none"> • Bleeding • Thrombotic thrombocytopenic purpura 	<ul style="list-style-type: none"> • Bleeding • Hypertension • Hyperlipidemia • Headache • Back pain 	<ul style="list-style-type: none"> • Dyspnea • Bleeding • Avoid use in patients with severe hepatic impairment 	<ul style="list-style-type: none"> • Bleeding
Duration of therapy	See latest ACC/AHA guidelines	See latest ACC/AHA guidelines	See latest ACC/AHA guidelines	See latest ACC/AHA guidelines
Pregnancy category	B	There is no data with prasugrel use in pregnant women to determine drug-associated risk	C	B
Oral bioavailability	>50% (active metabolite)	>78% (active metabolite)	30% to 42%	100% (fasting)
CYP drug interaction	CYP2C19	No	CYP3A4	CYP3A4
Half-life	0.5 h	7 h (2–15 h)	9 h (6.7–9.1 h)	159–311 h
Hold prior to surgery	5 days	7 days	5 days	8 days (terminal elimination)

■ Comparing oral antiplatelet medications

DAPT is currently indicated in a multitude of conditions. This includes secondary prevention of stroke and MI, peripheral arterial disease (PAD), ACS, and after PCI.⁸⁻¹¹ Current evidence and treatment guidelines released by the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Clinical Practice Guidelines support the use of prasugrel or ticagrelor when not contraindicated or when patient adherence is not a concern.¹

Patient adherence may be a concern due to cost, frequency of administration, and potential adverse reactions. Prasugrel and ticagrelor have shown to be superior to clopidogrel with improved clinical outcomes (see *Oral antiplatelet comparison*).¹²

Clopidogrel. Approved by the FDA in 1997, clopidogrel is a second-generation thienopyridine that causes irreversible inhibition of the P2Y₁₂ protein component of the adenosine diphosphate (ADP) receptor, which prevents ADP binding and activation of platelets.⁸ Clopidogrel is considered to be prodrug and requires enzymatic activation. It is metabolized by cytochrome P450 2C19, and the prescribing information carries a warning about drug interactions associated with the 2C19 isoform.⁸

Indications include reduction of stroke and MI risk in patients with ACS, PAD, and PCI in conjunction with aspirin. Contraindications include a history of intracranial hemorrhage (ICH) or active pathologic bleeding; bleeding is the most commonly reported adverse reaction.⁸ Avoid concomitant use of clopidogrel with omeprazole or esomeprazole because these drugs significantly reduce the antiplatelet activity of clopidogrel.⁸

Prasugrel. Approved by the FDA in 2009, prasugrel is a third-generation thienopyridine that causes irreversible inhibition of the P2Y₁₂ protein component of the ADP receptor.⁹ This prevents ADP binding and activation of platelets.⁹ Indications include reduction of thrombotic cardiovascular events in patients with ACS treated with PCI in conjunction with aspirin. Prasugrel cannot be used for medical management of ACS.⁹

Prasugrel is considered to be pro-drug and requires enzymatic activation. It is metabolized quickly using cytochrome P450 3A4 and 2B6, although it carries no drug interactions associated with those isoforms.⁹ Contraindications include patient's active pathologic bleeding, ICH, and a history of transient ischemic attack (TIA) or stroke.⁹ Prasugrel is not recommended for use in patients age 75 or older because of the increased risk of bleeding.⁹ No dose adjustments are needed for patients

DAPT risk factors¹³

Increased ischemic risk

- Advanced age
- ACS presentation
- Multiple prior MIs
- Extensive CAD
- Diabetes mellitus
- Chronic kidney disease (CKD)

Risk of stent thrombosis

- ACS presentation
- Diabetes mellitus
- Left ventricular ejection fraction <40%
- First-generation drug-eluting stent
- Stent undersizing
- Stent underdeployment
- Small stent diameter
- Greater stent length
- Bifurcation stents
- In-stent restenosis

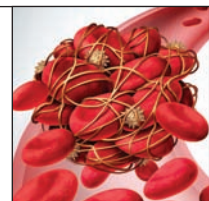
Bleeding risk

- History of prior bleeding
- Oral anticoagulant therapy
- Female gender
- Advanced age
- Low body weight
- CKD
- Diabetes mellitus
- Anemia
- Chronic corticosteroid or nonsteroidal anti-inflammatory drug therapy

with mild-to-moderate hepatic impairment; however, the drug has not been studied in patients with severe hepatic impairment.⁹ Due to an increased bleeding risk, a lower maintenance dose is considered for patients with a body weight under 132 lb (60 kg).

Ticagrelor. Approved by the FDA in 2011, ticagrelor is a cyclopentyl-triazolo-pyrimidine that reversibly modifies the P2Y₁₂ protein component of the ADP receptor, which

Prasugrel, a third-generation thienopyridine, causes irreversible inhibition of the P2Y₁₂ protein component of the ADP receptor.



prevents ADP binding and activation of platelets.^{7,10} Indications include reduction of cardiovascular death, MI, and stroke in patients with ACS in conjunction with aspirin.¹⁰ The drug also reduces the risk of stent thrombosis in

patients with ACS who received a stent. Ticagrelor carries a box warning to avoid aspirin doses above 100 mg because higher aspirin doses reduce the effectiveness of ticagrelor. Ticagrelor is metabolized primarily in the liver using cytochrome P450 3A4 and the prescribing information carries a warning about drug interactions associated with the 3A4 isoform.¹⁰

Contraindications include a history of ICH and active pathologic bleeding. Ticagrelor should not be used in patients with severe hepatic impairment because of the risk of increased drug concentrations due to hepatic dysfunction.¹⁰

Vorapaxar. Approved by the FDA in 2014, vorapaxar is the newest oral antiplatelet medication. The first of its kind (a PAR-1 antagonist), vorapaxar blocks thrombin-mediated platelet activation by selectively inhibiting PAR-1.¹¹ Indications include the reduction of thrombotic cardiovascular events in patients with a history of MI or PAD.¹¹ Vorapaxar is not to be used as antiplatelet monotherapy and should be used in conjunction with aspirin and/or clopidogrel. Vorapaxar is metabolized primarily in the liver using cytochrome P450 3A4, and the prescribing information carries a warning about drug interactions associated with the 3A4 isoform.¹¹

Contraindications include a history of ICH, active pathologic bleeding, and TIA or stroke. The only notable adverse reaction is bleeding.¹¹

■ **DAPT duration**

The ACC/AHA Task Force on Clinical Practice Guidelines released an update on duration of DAPT in patients with

coronary artery disease (CAD) in 2016 with a master treatment algorithm.¹ The algorithm is broken into two sides: stable ischemic heart disease and acute/recurrent ACS followed by a color correspondence to the class of recommendations based on the evidence. The patient's presentation and medical treatment or therapy dictate the minimum recommendations, which may range from 1 month to over 1 year for DAPT.¹

Duration of oral antiplatelet therapy always requires a balance between decreasing ischemic risk and increasing bleeding risk. The guidelines point out that aspirin therapy is indicated for an indefinite duration with CAD, and the recommendations on duration are applied to P2Y₁₂ inhibitors. A shorter duration can be considered for patients with a low ischemic risk or high risk of bleeding.¹

In contrast, a longer duration can be considered for patients with a high ischemic risk or low risk of bleeding.¹ An individual approach should be used when making a decision regarding duration.¹ Yeh and colleagues analyzed DAPT study data and created a new risk score, the Clinical Prediction Score, which may be useful in understanding the thought process behind prolonged DAPT.¹⁴ Providers need to take into account the patient's age, smoking history, history of type 2 diabetes mellitus, MI at presentation, prior MI or PCI, the presence of a drug-eluting stent, the stent diameter, a vein graph stent, heart failure, or a left ventricular ejection fraction less than 30%. Each item is assigned a point value. A score of 2 or greater is associated with a higher benefit for prolonged DAPT, whereas a score of less than 2 is associated with a higher bleeding risk for prolonged DAPT.¹⁴

Oral antiplatelet medication interactions and associated effects^{8-11,20,21}	
<p>Omeprazole and esomeprazole CYP2C19 inhibitors (proton pump inhibitors) have shown that concomitant use results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition.</p> <p>Non-steroidal anti-inflammatory drugs (NSAIDs) NSAIDs have been shown to increase the risk of gastrointestinal bleeding, and concomitant use would increase these risks. There is a black box warning from the FDA against NSAID use in patients with CAD due to the increased risk of MI and stroke.</p> <p>Ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, and telithromycin Strong CYP3A inhibitors (antifungals, macrolide antibiotics, and antivirals) substantially increase ticagrelor and vorapaxar exposure and increase the risk of dyspnea, bleeding, and other adverse events.</p>	<p>Rifampin, phenytoin, carbamazepine, and phenobarbital Strong CYP3A inducers substantially reduce ticagrelor and vorapaxar exposure, decreasing their efficacy.</p> <p>Simvastatin/lovastatin Doses over 40 mg paired with ticagrelor increase serum concentrations and higher bleeding risks because both of these drugs are metabolized by CYP3A4.</p> <p>Selective serotonin reuptake inhibitors and selective serotonin-norepinephrine reuptake inhibitors These classes of drugs affect platelet activation. Concomitant administration with clopidogrel increases the risk of bleeding.</p> <p>Warfarin Warfarin is only approved to be used with clopidogrel. Concurrent use with any DAPT increases the risk of bleeding, and the risk versus benefit should be thoroughly evaluated.</p>

Case examples

Scenario A

Ms. L, a 68-year-old female has a history of hypertension, hypercholesterolemia, type 2 diabetes mellitus (T2DM), general anxiety disorder, and a non-ST-segment elevation MI 14 months ago with a drug-eluting stent placed. She is a current smoker and reports only drinking socially. Ms. L was placed on prasugrel during her hospital stay 14 months ago and subsequently prescribed at discharge. She is no longer following up with her cardiologist and presented in the primary care office for her annual visit. Ms. L has recently run out of her prasugrel and questions the NP on the necessity of continuing to take the medications. She is currently taking 81 mg aspirin daily, 20 mg lisinopril, 25 mg metoprolol XL, 80 mg atorvastatin nightly, and 500 mg metformin twice daily.

Based on the information provided (the patient's age, smoking status, history of T2DM, and MI), Ms. L would need further evaluation, and more questions would need to be asked regarding the type of stent, heart function including the ejection fraction, and any prior history of PCI to accurately determine her clinical prediction score and evaluate her risk versus benefit for continued antiplatelet therapy.

Scenario B

Mr. J is a 68-year-old White male with a history of hypercholesterolemia, gastroesophageal reflux disease (GERD), T2DM, and multiple non-ST-elevated MIs (with the most recent being 6 months ago with a drug-eluting stent placed). The patient was loaded on and prescribed prasugrel at discharge. Mr. J is also prescribed a daily 81 mg aspirin, 50 mg metoprolol XL,

10 mg lisinopril, 80 mg atorvastatin nightly, and 1,000 mg metformin twice daily.

The patient presents at the primary care clinic for a routine follow-up. During his exam, Mr. J questions the necessity of taking "such an expensive medicine." He goes on to state that his friend is taking clopidogrel and "it is a lot cheaper, plus he only takes it once a day." The patient wants to know if he can switch his medication and if there is any risk in doing so. The NP considers Mr. J to be a reasonable candidate for CYP2C19 genotyping and contacts Mr. J's cardiologist. The NP and cardiologist concur that CYP2C19 genotyping is not currently recommended by the ACC/AHA for routine use to guide therapy, although ongoing studies are being conducted to show the efficacy. However, Mr. J is presenting with concerns of medication costs and possible adherence issues moving forward. Knowing the high prevalence of genetic resistance to clopidogrel, the NP and cardiologist agree that genotyping may be beneficial, and the results concur that clopidogrel would be appropriate therapy. The NP, in conjunction with the cardiologist, agrees to switch him to clopidogrel.

Drug interactions should be evaluated with the initiation of any new medication therapy. This includes any additional diagnoses and over-the-counter medications the patient may be taking. A diagnosis of GERD alerts the NP to discuss that concomitant use of omeprazole or esomeprazole (a common treatment for GERD) and clopidogrel would result in a decrease in platelet inhibition and a higher risk of stent rethrombosis. These medications should be avoided. DAPT should remain for at least 1 year based on the ACC/AHA guidelines.

Referring patients back to the cardiologist for this more complex decision using the Clinical Prediction Score is advisable (see *DAPT risk factors*).

■ Switching a patient's oral antiplatelet medications

Switching between inhibitors has become more common in clinical practice since the approval of the newer oral antiplatelet agents. The driving forces behind changing antiplatelet agents range from genetic resistance and socioeconomic factors to increased bleeding risks and secondary ischemic events.² It is important to note that drug interactions have been described when switching oral antiplatelet agents.²

These medications have different receptor-binding properties and are currently being researched for optimal switching strategies.² The current available data stem from registries and pharmacodynamics studies, and the clinical effects of switching agents are not clear.²

Pharmacologic properties, including binding site, half-life, speed of onset and offset, and the timing of the

disease presentation, are important factors to consider and understand prior to switching medications.² The provider should be well educated on the evidence available and preferably experienced in prescribing oral antiplatelet medications.

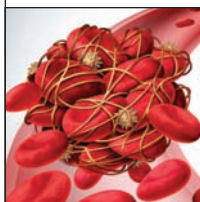
In the primary care setting, it is acceptable to refer the patient to a cardiologist or at least make medication adjustments in collaboration with a cardiologist who is familiar with the patient and medications.

■ Genetic variations and clopidogrel resistance

Genetic variance on the cytochrome P450 enzyme 2C19 has been found in relation to the efficacy of clopidogrel. In 2010, the FDA released a black box warning to alert providers of its reduced effectiveness in certain patients (2% to 14% of the population) who metabolize clopidogrel poorly.⁸ It was also noted that the rate varies based on racial background. A rate of loss-of-function carrier status is lower in White Americans (15%) and higher in Asians (29% to 35%).¹⁵ The loss of function is in reference to a mutation

on the genetic allele resulting in a change in the end function associated.¹⁵

Gain-of-function allele is present in about 30% to 40% of White Americans and Black Americans and approximately 6% of Asians.¹⁵ Polymorphisms of the CYP2C19 enzyme are divided according to their metabolizing status: ultrarapid, extensive, intermediate, and poor metabolizers. An ultrarapid metabolizer results in a normal or increased platelet inhibition. Extensive metabolizers result in a normal or decreased residual platelet aggregation.¹⁵



Cytochrome P450 2C19 genotyping can be completed in the outpatient setting and is available as a whole blood or buccal swab kit.

Both ultrarapid and extensive metabolizers would be recommended to stay on clopidogrel. Intermediate and poor metabolizers result in reduced platelet inhibition (poor metabolizers more significantly) and increased residual platelet aggregation, placing patients at a higher risk for stent thrombosis. Both intermediate and poor metabolizers are not good candidates for clopidogrel therapy; prasugrel or ticagrelor should be initiated instead.¹⁵

Randomized control trials have not demonstrated that genetic testing can be used as a guide for P2Y₁₂ inhibitor therapy with improved outcomes.¹ Therefore, the ACC and AHA are not recommending the routine use of genetic testing.¹ Currently, multiple studies are being conducted that address genetic resistance to determine if genetic testing can identify the best antiplatelet therapy.

These trials are assessing the value of platelet-function testing using both serum and point-of-care genetic tests.¹⁵ Cytochrome P450 2C19 genotyping can be completed in the outpatient setting and is available as a whole blood or buccal swab kit specimen.¹⁶ Platelet testing could be used in specific situations, such as high-risk patients or those who have had stent thrombosis while on clopidogrel. Genetic testing can also identify those who have an ideal response to clopidogrel and can avoid the higher cost of newer agents.

■ Drug interactions


The focus of drug interactions is based mostly on a reduction or increase of platelet inhibition. Fluctuation of platelet inhibition presents the patient with an increased risk of bleeding or stent thrombosis. Information regarding drug interactions is significant considering a majority of patients

prescribed oral antiplatelet medications would likely have had a recent stent placement (see *Oral antiplatelet medication interactions and associated effects*).

■ Staying up-to-date

It is necessary to be up-to-date with the latest developments in medical therapy regarding the provider's patient population. (See *Case examples*.) Interventional cardiology is continuing to expand, and medical therapy associated with interventions grows concurrently. Future developments regarding DAPT include genotyping for therapy, increased evidence on switching antiplatelet medications, and increased indications for the newer oral antiplatelet agents. Providers should be competent in the ability to manage these patients while maintaining sound judgment within their scope of practice. The costs associated with the more novel oral antiplatelet medications

can be significant, ranging from \$295 to \$475 for brand only. Clopidogrel (generic) is available for lower out-of-pocket costs at most pharmacies.¹⁷ All oral antiplatelet medications are covered under most major private- and government-funded insurances with manufacturer discounts available.¹⁷⁻²⁰

The ACC has produced the Guideline Clinical app, which is available for free via iTunes and Google Play.²² This user-friendly app provides a resource to quickly disseminate guideline-related content and tools for any provider treating patients with cardiovascular disease. The Guideline Clinical app includes a resource for DAPT information, clinician tools, and patient resources.²² 

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