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REVIEW

Advances in the Clinical Use of Clopidogrel: A Review of Individualized Treatment Strategies and Monitoring Optimization Based on Genetic Polymorphisms

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Abstract: This paper systematically reviews recent advances in clopidogrel clinical applications to optimize therapeutic precision and medication safety. Using a literature review methodology, we elucidate clopidogrel's pharmacokinetic properties and pharmacodynamic mechanisms, while evaluating its clinical efficacy and adverse reactions in disease management. Recent studies have emphasized the key role of genetic polymorphisms in regulating the efficacy and safety of clopidogrel. Polymorphisms in the *CYP2C19* gene have a significant effect on the metabolism of clopidogrel, with loss-of-function (LOF) alleles (**2, *3*) reducing the production of active metabolites, leading to elevated platelet reactivity and increasing the risk of major adverse cardiovascular events (MACE), particularly in the Asian populations, where the prevalence of LoF alleles is as high as 29–35%. In contrast, the gain-of-function allele *CYP2C19*17* results in a reduced risk of cardiovascular events but increases the risk of bleeding. This article summarizes the latest research progress and monitoring methods of clopidogrel, and suggests that clinics should combine genotyping and platelet function testing with monitoring of blood levels to optimize treatment and provide data reference for clinical administration of clopidogrel.

Keywords: clopidogrel, indications, adverse effects, genetic polymorphism, drug monitoring

Introduction

The primary prevention strategy for acute coronary syndromes (ACS) after percutaneous coronary intervention (PCI) is mainly based on dual antiplatelet therapy (DAPT), whose standard regimen consists of aspirin in combination with a P2Y12 receptor inhibitor (eg, clopidogrel, prasugrel, or ticagrelor). As a widely used antiplatelet drug, clopidogrel can be used to treat coronary heart disease and stroke by inhibiting adenosine diphosphate (ADP) receptors to reduce platelet activation and aggregation. However, poor control of platelet activity, known as clopidogrel resistance (CR), may occur in some patients after clopidogrel therapy,[1] which may lead to in-stent thrombosis and myocardial infarction. In addition, the most common adverse effect caused by clopidogrel is the risk of bleeding, especially gastrointestinal bleeding. One study found that among patients who underwent PCI and drug-eluting stents (DES) and completed 12 months of DAPT, complications such as gastrointestinal bleeding and cerebral hemorrhage could be induced in both the aspirin and clopidogrel groups (incidence: 1.5% in the aspirin group vs 1.7% in the clopidogrel group, P=0.160), but the clopidogrel group was superior to the aspirin group in terms of secondary prevention.[2] Other studies have shown that P2Y12 receptor inhibitors, specifically clopidogrel, were superior in reducing the incidence of myocardial infarction (RR=0.77, 95% CI: 0.67–0.89) and hemorrhagic stroke (RR=0.53, 95% CI: 0.30–0.92) and did not significantly increase the risk of major bleeding (RR=0.96), as compared with aspirin alone (RR=0.96, 95% CI: 0.71–1.30).[3] Notably, in ACS patients treated with PCI, ticagrelor and prasugrel were associated with a high risk of bleeding compared to clopidogrel, with prasugrel exhibiting a higher risk of short-term bleeding at 90 days (HR=1.66, 95% CI: 1.11–2.48).[4] In recent years, several studies

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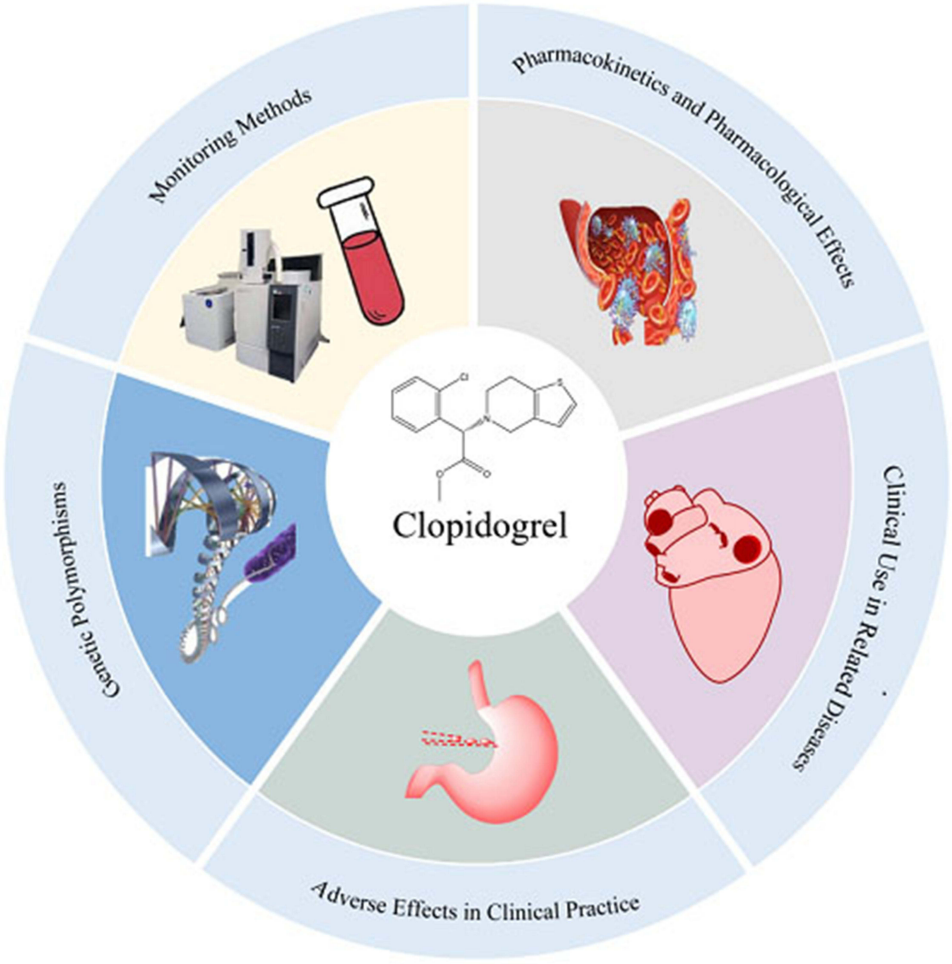
Graphical Abstract



have found that with clopidogrel, patients may also suffer from rare adverse effects such as severe fatigue and bleeding from small bowel ulcers. In clinical individualised treatment, drug efficacy can be assessed by means of genetic polymorphism testing, platelet function testing and plasma concentration monitoring, so that dosage can be adjusted to achieve better therapeutic effects and reduce the occurrence of adverse reactions.[5–7]

Although new antiplatelet agents are emerging, clopidogrel remains important in the treatment of cardiovascular disease (CVD). Current clinical practice guidelines (2023 ACC/AHA and 2023 ESC) point to clopidogrel as an alternative choice for patients at high bleeding risk and actively recommend genetic testing to guide clopidogrel use. As the precision medicine paradigm advances, dynamic dose adjustment based on pharmacogenomics may further reshape its clinical status, which provides an important direction for future research.

Pharmacokinetics and Pharmacological Effects of Clopidogrel

Clopidogrel, with the molecular formula $C_{16}H_{16}ClNO_2S$, acts as an ADP receptor inhibitor and is an inhibitor of platelet aggregation, platelet inhibition results from irreversible binding of the P2Y12 receptor. Clopidogrel inhibits platelet aggregation by selectively inhibiting ADP binding to platelet receptors and inhibiting ADP-mediated activation of the glycoprotein IIb/IIIa (GPIIb/IIIa) complex.

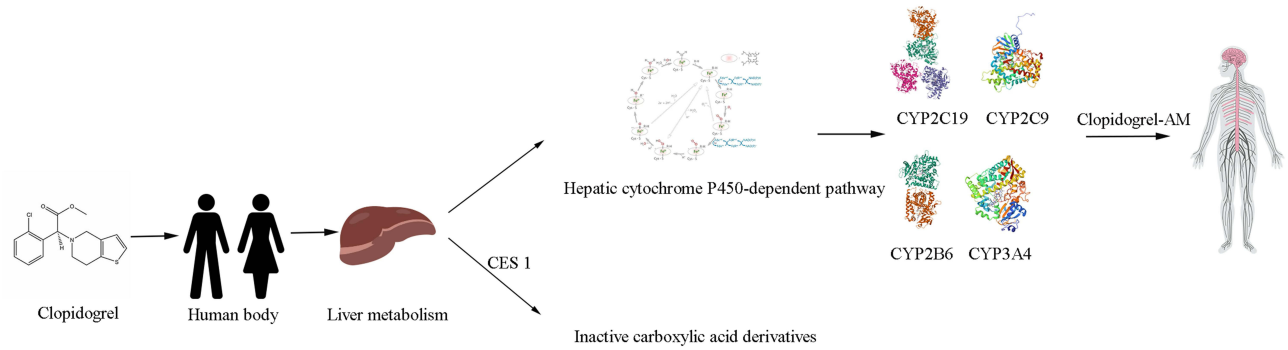


Figure 1 Mechanism of action of clopidogrel in humans. Clopidogrel, as a precursor drug, needs to be metabolized by the liver before it can exert its antiplatelet effect. There are two metabolic pathways, one of which is hydrolyzed to inactive carboxylic acid derivatives by an esterase-dependent pathway (CES 1). The other is bioactivation via the hepatic cytochrome P450-dependent pathway (mainly catalyzed by CYP2C19, CYP2C9, and CYP3A4 enzymes) to produce the active metabolite clopidogrel-AM. This figure summarizes the key enzymatic steps and metabolic transformations that underlie the pharmacological activity of clopidogrel.

Clopidogrel, a thienopyridine prodrug, is inactive in vitro and must be biotransformed in vivo to be effective, with a number of different genetically encoded metabolising enzymes involved in the multi-step biotransformation of clopidogrel.[8] Clopidogrel is mainly metabolised by the liver after ingestion by two metabolic pathways, one is hydrolysed to inactive carboxylic acid derivatives via an esterase-dependent pathway (CES 1). The other is through the hepatic cytochrome P450-dependent pathway *(CYP2C19*: 44.9%, *CYP2B6*: 19.4%, *CYP1A2*: 35.8%), which first converts clopidogrel to the 2-oxo-clopidogrel intermediate, and then to clopidogrel-AM through *CYP2C9, CYP2B6, CYP2C19* and *CYP 3A 4/5* which ultimately acts systemically[9] (Figure 1 and Table 1).

Clinical Use of Clopidogrel in Related Diseases

Coronary Artery Disease

Coronary artery disease (CAD) is defined as a condition with one or more of the following: a history of myocardial infarction, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), coronary artery stenosis of ≥50%, and chest pain accompanied by myocardial ischaemia.[10] CAD includes acute coronary syndrome (ACS) and stable coronary heart disease. According to the 2023 ESC Guidelines for the management of acute coronary syndromes, DAPT needs to be initiated as early as possible after ACS, and clopidogrel in combination with aspirin reduces the risk of early ischemic events. The guidelines emphasize that in the acute phase of ACS, ticagrelor or prasugrel are preferentially recommended for their more potent antiplatelet effects, but clopidogrel remains the logical choice for patients at high risk of bleeding or with contraindications, such as advanced age, prior history of bleeding, and inability to tolerate ticagrelor (eg, dyspnea) or prasugrel (eg, prior history of stroke). In patients requiring long-term anticoagulation after atrial fibrillation or mechanical valve replacement, clopidogrel in combination with an anticoagulant (eg, rivaroxaban) is associated with a lower risk of bleeding than ticagrelor/ prasugrel (Class I recommendation, Level of Evidence A).[11] In 2020, the safety and efficacy of clopidogrel, ticagrelor, and prasugrel were compared in patients with st-segment

Table 1 Summary of Pharmacokinetics of Clopidogrel

Process	Description
Absorption	It is absorbed through the gastrointestinal tract into the bloodstream
Distribution	The main target is platelets, but it can also enter other cellular spaces and body fluids
Metabolism	One: hydrolysis to inactive carboxylic acid derivatives by esterase dependent pathway (CES 1) The other: through the hepatic cytochrome P450-dependent pathway
Excretion	Within 5 days, about 50% is excreted by urine and about 46% by feces

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elevation myocardial infarction. All-cause mortality and ischaemic event rates were reduced with ticagrelor and prasugrel compared to clopidogrel. However, since clopidogrel is cheaper, it will still dominate in the clinic.[12,13] In 2023, Kim, MC et al[14] found that in the treatment of patients with acute myocardial infarction with a high risk of bleeding, clopidogrel, as compared to ticagrelor, would reduce adverse clinical outcomes, such as bleeding, and was safer to use. In 2024, Kim, SH et al[15] found that patients with acute myocardial infarction often experienced dyspnoea with the use of ticagrelor, and that switching to clopidogrel in patients with such symptoms resulted in an improvement in dyspnoea without increasing the risk of ischaemic events.In 2024, Li et al[16] found that in dual-risk ACS patients who completed 9 to 12 months of DAPT after drug-eluting stent implantation (DAPT) and were free of adverse events for at least 6 months prior to randomization to a subgroup, a 9-month extension of the clopidogrel monotherapy regimen was superior to continuation of clopidogrel DAPT in reducing clinically relevant bleeding without increasing ischemic events.

In 2021, clopidogrel was found to reduce morbidity and mortality in stable coronary heart disease and has been widely used in such patients.[17] According to the 2024 ESC Guidelines and the 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guidelines for the management of chronic coronary syndromes, clopidogrel monotherapy (75 mg/d) is the standard alternative (Class I recommendation) to aspirin in chronic coronary disease (CCS) for those who are not aspirin tolerant patients (Class I recommendation), and there is insufficient evidence to support the superiority of novel P2Y12 inhibitors over clopidogrel in long-term monotherapy, which is more suitable for long-term management because of its lower cost and lower bleeding risk. In patients at high bleeding risk for PCI, especially those with normal *CYP2C19* genes, clopidogrel is the first choice for switching to monotherapy after a short period of dual resistance (1–3 months) (Class I recommendation).[18,19] Kang et al[20] found that clopidogrel monotherapy was superior to aspirin in reducing both thrombotic and bleeding risks in patients who were event-free 6–18 months after PCI and required long-term antithrombotic therapy, and that the advantages were independent of the patient's risk of bleeding or the complexity of PCI, with a wide range of applicability and without the need to adjust treatment strategies.

Stroke

Stroke is defined as the sudden onset of a focal neurological deficit at a site consistent with the extent of the large cerebral arteries.[12] Currently, clopidogrel is increasingly used for secondary prevention of ischaemic stroke, and can be used as a reasonable monotherapy option in patients with non-embolic ischaemic stroke or as a 21-day dual antiplatelet therapy in combination with aspirin after minor ischaemic stroke or transient ischaemic attack (TIA) in patients at high risk of stroke recurrence.[8] Carotid endarterectomy (CEA) improves carotid blood flow and reduces the risk of stroke. In 2023, a study found that patients with a history of symptomatic carotid artery disease were more likely to use clopidogrel at the time of surgery. From 2010 to 2017, a total of 1066 patients were treated with CEA. During the study period, clopidogrel use increased by 24.9% over these seven years, which equates to an annual increase of 11%, and clopidogrel was not associated with an increased risk of postoperative complications, including bleeding. These data suggest that clopidogrel should not be discontinued before CEA and should be considered part of the "optimal pharmacological treatment" for patients undergoing CEA.[21]

Central Retinal Vein Occlusion

Retinal vascular occlusions are the second most common vascular disorder in the retina after diabetic retinopathy.[22] There are two major forms of retinal vein occlusion: branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). Based on fundus fluorescein angiography (FFA), CRVO can also be classified into ischemic or nonischemic.[23] Al Ghaithi et al reported a case of a 54-year-old male with nonischemic CRVO and multiple systemic comorbidities, including diabetes, hypertension, and dyslipidemia. After initial treatment with aspirin failed, switching to clopidogrel demonstrated significant efficacy in improving visual acuity, resolving macular edema, and alleviating retinal vascular pathology, suggesting that clopidogrel may be superior to aspirin in select CRVO patients and providing strong evidence for its potential new indications in CRVO management.[24]

Adverse Effects of Clopidogrel in Clinical Practice

Gastrointestinal Bleeding

Clopidogrel inhibits platelet aggregation and increases the risk of bleeding, the most common is gastrointestinal bleeding. One study found 2,252 reports of clopidogrel adverse events through the US Food and Drug Administration Adverse Event Reporting System (FAERS) database, and clopidogrel leads to the highest rate of hospitalised gastrointestinal bleeding events.[25] Clopidogrel does not directly damage the gastric mucosa, but on the one hand inhibits platelet production of vascular endothelial growth factor, which in turn inhibits the proliferative capacity of gastric mucosal epithelial cells. On the other hand, it induces apoptosis of gastric mucosal cells, which reduces the expression of intercellular tight junction proteins, thus affecting the repair ability of gastric mucosa. Therefore, clopidogrel also has a damaging effect on the gastric mucosa to some extent, which increases with increasing dose.[26]

Liver Injury

Clopidogrel-induced liver injury has been seen in the form of hepatocellular or mixed cholestatic/hepatocellular patterns. The most common pattern of liver injury is mixed, followed by hepatocellular damage and cholestatic injury. It has been shown that hepatotoxicity occurs 35 days after initiation of clopidogrel (range 3–180 days) and the clinical presentation is more inclined to a dose-dependent response.[27]

Neutropenia

A PubMed search for "clopidogrel" and "neutropenia" revealed 17 cases since 2000. Clopidogrel administration resulted in a significant decrease in haemoglobin and white blood cells, leading to an increased risk of bleeding. An 84-year-old female patient with a previous asymptomatic acute myocardial infarction, who had coronary stenting, experienced a significant decrease in haemoglobin and white blood cells approximately 40 days after clopidogrel administration. Subsequent replacement administration of ticagrelor resulted in a rise in markers after the switch.[28,29]

Thrombotic Microangiopathy

Immune thrombocytopenic purpura, and thrombotic thrombocytopenic purpura are all thrombotic microangiopathies, which may be induced by the use of clopidogrel. Lizondo López, T et al[30] reported an example of thrombotic microangiopathy in a patient who developed microangiopathic haemolytic anaemia and thrombocytopenia after one month of treatment with clopidogrel and aspirin. After extensive clinical and laboratory investigations, it was shown that his thrombotic microangiopathy was induced by clopidogrel. Both Grossman, K and Távora, C et al[31,32] reported cases of clopidogrel-induced immune thrombocytopenic purpura, which can be considered to be caused by clopidogrel in patients presenting with isolated thrombocytopenia. Ndulue, CN et al[33] reported a case of thrombotic thrombocytopenic purpura triggered by clopidogrel in a Nigerian patient with chronic kidney disease (CKD), which resolved quickly after discontinuation of clopidogrel.

Rare Adverse Reactions

In addition to the common adverse reactions described above, many rare adverse reactions to clopidogrel have been reported. Severe fatigue syndrome is a rare but clinically significant side effect of overreaction to clopidogrel in patients undergoing neurovascular endovascular intervention. In 2021, Bass et al[34] assessed patient response to clopidogrel using the VerifyNow assay, which is expressed in terms of P2Y12 reaction units (PRUs), with lower PRU values equating to a greater degree of inhibition of the P2Y12 receptor and a lower presumed probability of platelet aggregation, with overresponse to clopidogrel defined as PRUs ≤60. The diagnosis of clopidogrel-induced severe fatigue was made when symptoms appeared after clopidogrel treatment and resolved with dose reduction.

To date, seven cases of insulin autoimmune syndrome (IAS) induced by clopidogrel have been reported, and the sulfhydryl group of clopidogrel metabolites can induce IAS with hypoglycemia as the main symptom. Shi Chen et al[35] conducted a meta-analysis of six trials involving a total of 61,399 participants and found that clopidogrel-associated hypoglycemia may occur in Asian participants. Du, W et al[36] reported recurrent hypoglycemic episodes in a patient after

23 days of antiplatelet therapy with clopidogrel, suggesting that physicians should be vigilant for hypoglycemia-related symptoms in clopidogrel users.

Clopidogrel-induced small bowel ulcers and bleeding are uncommon, and in 2021 Lee, SH. et al[37] reported a case of bleeding small bowel ulcers from clopidogrel use in an 86-year-old male clopidogrel-resistant patient, which was found to be expected to increase in older patients with risk factors. Rowell's syndrome, a combination of polymorphic lupus erythematosus and lupus erythematosus, was first reported in the literature in 2024 in a 52-year-old woman with sjogren's syndrome who was taking paquinimod for two months but developed this symptom when she mistakenly took clopidogrel for one week.[38] Clopidogrel induced arthritis is a rare instance, Faiza Javed et al[39] reported the development of inflammatory arthritis in a male patient after 5 days of clopidogrel, and after diagnosis by exclusion it was determined that clopidogrel was responsible for the development of the induced arthritis.

Impact of Genetic Polymorphisms on Clinical Use of Clopidogrel

Several genes are involved in the biotransformation of clopidogrel to the active drug, and their polymorphisms may interfere with the biotransformation, leading to a decrease or increase in the amount of active metabolite, thereby affecting the drug's efficacy.

CYP2C19 Gene Polymorphisms

Some patients develop residual high platelet reactivity (HPR) during antiplatelet therapy. HPR has been shown to be significantly associated with thrombotic events. One of the major causes of residual HPR after antiplatelet therapy is the *CYP2C19* polymorphism, the most common genetic variant associated with clopidogrel resistance. Recent studies have shown that patients with one or more *CYP2C19* loss-of-function alleles (LoF, **2* or **3*) with low levels of active metabolites have an increased incidence of HPR, clopidogrel resistance and major adverse cardiovascular events (MACE).[40] Clopidogrel efficacy decreases with increasing number of *CYP2C19* LoF alleles. Individuals carrying one *CYP2C19* LoF allele are referred to as intermediate metabolizers (IM) and those carrying two *CYP2C19* LoF alleles are referred to as poor metabolizers (PM).[41,42] Several studies have shown that increasing the dose of clopidogrel improves platelet inhibition and overcomes resistance to clopidogrel in patients with IM (**2*) but not in patients with PM (**2*).[43] According to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for clopidogrel treatment based on the *CYP2C19* genotype, replacement therapy is recommended for patients who are PM.[44] There are significant racial and regional differences in the distribution of *CYP2C19* polymorphisms, and it has been estimated that approximately 15% of white and black populations carry at least one LoF allele (**2* or **3*) compared to 29–35% in Asian populations.[8]

Mohitosh Biswas et al[45,46] compared the clinical efficacy of clopidogrel versus other P2Y12 receptor antagonist treatments after PCI in CAD patients who inherited the *CYP2C19* LoF allele. The results showed that CAD patients who inherited the *CYP2C19* LoF allele and were treated with clopidogrel had a significant 62% increased risk of MACE compared with patients treated with other P2Y12 receptor antagonists such as prasugrel or ticagrelor. In another article, he assessed the overall risk of recurrent stroke in stroke or TIA patients who carried the *CYP2C19* LoF allele and were taking clopidogrel, and the risk of recurrent ischemic stroke was significantly increased in Asian patients with stroke or TIA compared with non-carriers.[47] It has also been shown that in patients with coronary artery disease or stroke, clopidogrel users who carry the *CYP2C19* LoF allele have a significantly higher risk of MACE than clopidogrel-treated individuals alone who do not carry a defect in this gene.[48]

Fu et al[49] found that the proportion of clopidogrel-resistant individuals among carriers of one or more *CYP2C19* loss-of-function alleles was estimated to be 71.7%, which was significantly different from 32.1% among non-carriers. Similarly, Jia et al[50] demonstrated a higher incidence of platelet hyperreactivity during clopidogrel treatment of ischemic stroke in *CYP2C19 *2* or **3* carriers than in non-carriers.

Liu et al[51] demonstrated that the risk of clopidogrel resistance was higher in carriers of the *CYP2C19*2* allele than in non-carriers, but did not increase the risk of vascular events or recurrence rates.

A gain-of-function (GoF) allele, *CYP2C19*17*, was first described in 2006.[52] This variant allele increases gene transcription, thereby increasing enzyme activity and clopidogrel responsiveness. Individuals carrying one or both **17* alleles have been described as ultra-rapid metabolizers (UM) based on the genotype and phenotype of *CYP2C19*.[41,42] A meta-analysis by Li, Y et al[53] showed that carriers of the *CYP2C19*17* allele had better clinical outcomes with clopidogrel and a lower risk of cardiovascular events, but carriers of *CYP2C19*17* had a higher risk of bleeding. In 2010, the US Food and Drug Administration (FDA) recommended that individuals should be considered for alternative antiplatelet agents or higher doses of clopidogrel depending on their *CYP2C19* genotype or poor metabolism genotype.[54]

CYP3A4 Gene Polymorphisms

The *CYP3A4* enzymes plays a role in the metabolism of the clopidogrel prodrug molecule and is primarily responsible for the bioconversion of approximately 40% of 2-oxoclopidogrel (the inactive metabolite) to the active metabolite cis-thiol-clopidogrel, which is responsible for P2Y12 receptor inhibition.[55,56] The expression of the *CYP3A4* enzyme is derived from the *CYP3A4* gene, and the *CYP3A4*1G* mutation is thought to be a protective factor against clopidogrel resistance in ischemic stroke patients, as this mutation increases the concentration of the active clopidogrel-related substance, thereby increasing platelet inhibition. Liu[51] showed that the estimated risk of clopidogrel resistance was significantly lower in *CYP3A4*1G* carriers than in non-carriers.

ABCB1 Gene Polymorphisms

The p-glycoprotein (P-gp) encoded by the *ABCB1* gene regulates the absorption of clopidogrel in the small intestine.[57] P-gp is a transmembrane protein whose main function is to pump drugs out of cells and into the circulation, and this pumping mechanism may affect the bioavailability of the drug. Mega et al[58] found that *ABCB1* gene polymorphisms affect the degree of platelet inhibition, which is strongly correlated with the risk of MACE. Simon et al[59] reported an association between adverse events in patients taking clopidogrel and the *ABCB1* (C3435T, rs1045642) polymorphism, with carriers of the GG and AA genotypes showing a significantly increased incidence of adverse events. *ABCB1* polymorphisms have been found to influence ADP-induced platelet aggregation, and carriers of the G allele are more prone to exhibit hyporesponsiveness to antiplatelet therapy. The *ABCB1* C3435T polymorphism could be considered as a potential genetic biomarker for the risk of MACE in CAD patients on clopidogrel after receiving PCI. One study confirmed that patients carrying the *ABCB1* C3435T double mutation (TT) had a significantly increased risk of MACE compared with patients carrying the CC genotype or the CC+CT genotype.[60]

However, there are studies that suggest otherwise, Mugosa, S et al[61] conducted a study related to *ABCB1* gene polymorphisms in a population in Montenegro, Europe, but found no significant correlation between *ABCB1* gene polymorphisms and clopidogrel efficacy and safety.

CYP1A2 Gene Polymorphisms

A Korean study found an enhanced response to clopidogrel in smokers, which has been referred to as the "smoker's paradox". However, this phenomenon is not universal and was only observed in carriers of the cytochrome P450 *CYP1A2* allele, suggesting a genotype-dependent effect of smoking on clopidogrel response.[62] Cresci et al[63] recruited 2732 patients diagnosed with myocardial infarction and taking clopidogrel and evaluated the correlation between long-term clinical efficacy and safety of clopidogrel in patients carrying the *CYP1A2*1c* allele. The results showed that patients carrying the *CYP1A2*1c* allele were significantly more responsive to clopidogrel, but they had a worse prognosis and a significantly higher mortality rate due to major bleeding events.

PON1 Gene Polymorphisms

The paraoxonase 1 (*PON1*) gene may play an important role in clopidogrel resistance. The *PON1* gene is involved in high-density lipoprotein (HDL) antioxidant processes such as platelet-activating factor acetylhydrolase and lecithin-cholesterol acyltransferase, which has the ability to hydrolyse oxidised low-density lipoprotein (LDL) cholesterol and cleave phospholipid peroxidation adducts, leading to potential prevention of atherosclerosis. Several studies have shown

that reduced *PON1* activity affects serum glucose, increases the risk of diabetes and reduces platelet inhibition.[64,65] *PON1* is also involved in the esterification and subsequent inactivation of clopidogrel, which is more likely to lead to clopidogrel resistance.[66]

It has been shown that single nucleotide polymorphisms in the *PON1* gene are associated with lower clopidogrel responsiveness in patients with atherosclerosis, and that the *PON1* Q192R polymorphism is associated with clopidogrel biotransformation. However, the above conclusions have been challenged by a large number of studies that have failed to replicate these results, possibly due to epigenetic changes.[67,68] Mohitosh Biswas et al[69] in assessing the overall risk of MACE associated with harboring the *PON1* Q192R gene variant in patients taking clopidogrel, found that the *PON1* Q192R gene polymorphism did not have a significant effect on the risk of MACE or bleeding events in patients treated with clopidogrel.

KDR Gene Polymorphism

The *KDR* gene is responsible for the transcription of vascular endothelial growth factor receptor 2 (VEGFR2), which plays an important role in cardiovascular disease and platelet aggregation. Al Awaida, W. et al[70] found that the *KDR* (rs1870377) gene correlates with CR in cardiovascular disease (CVD) patients admitted for percutaneous coronary intervention as a potential genetic biomarker.

Clopidogrel-related gene polymorphisms and their clinical significance are shown in Table 2. A panel of experts assembled by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) has suggested that the current methodologies for genotyping are still a matter of considerable debate.[71] The main advantage of genotypic testing is that it does not require measurement after drug administration.[72] Proponents argue that there are common genetic polymorphisms that have been shown to affect platelet response to clopidogrel and its clinical efficacy in randomized clinical trials and registration experience, and that genotypic assessment is justified. In contrast, opponents argue that the available evidence does not demonstrate that *CYP2C19* carriers can improve efficacy by adjusting clopidogrel dosage or using alternative antiplatelet agents. Furthermore, in clinical practice, genotype-guided antiplatelet therapy selection strategies do not yield immediate results, which severely limits the usefulness of these data in the acute care setting.[50] In addition, further studies have recommended treating patients based on their clinical indications rather

Table 2 Clopidogrel-Related Gene Polymorphisms and Their Clinical Significance

Gene	Polymorphism Type	Metabolic Impact	Clinical Phenotype	Impact on Efficacy	Impact on Safety	Evidence Strength & Key Studies
CYP2C19	LoF, *2 or *3	Reduced active metabolite generation	Intermediate metabolizers (IM), poor metabolizers (PM)	Increased MACE risk (higher in Asians); clopidogrel resistance	Elevated thrombotic risk	Strong: LoF carriers have higher MACE risk (Asian LoF frequency 29–35%)[8]
CYP2C19	GoF, *17	Enhanced enzyme activity	Ultra-rapid metabolizers (UM)	Reduced cardiovascular risk	Increased bleeding risk	Strong: *17 improves efficacy but raises bleeding risk[52,53]
CYP3A4	*1G variant	Increased active metabolite levels	Normal metabolizers	Lower clopidogrel resistance	Not specified	Moderate: *1G is protective in stroke patients[51]
ABCB1	rs1128503, rs2032582, rs1045642	Altered transporter function	Not specified	No significant efficacy link	Not specified	Weak: Meta-analysis shows no clinical association[58–61]
CYP1A2	*1c allele	Enhanced smoker response	Not specified	Stronger platelet inhibition in smokers	Higher major bleeding risk	Conflicting: Supports "smoker's paradox" but poor prognosis[63]
PON1	Q192R	Alters active metabolite stability	Not specified	Unclear clopidogrel resistance link	No MACE/ bleeding impact	Controversial: Meta-analysis finds no clinical effect[69]
KDR	rs1870377	Potential CR link	Not specified	Needs validation	Not specified	Preliminary: Possible genetic marker for CR[70]

than genetic testing.[73] In conclusion, there are limited examples of pharmacogenomic testing requirements or recommendations in detailed clinical practice guidelines (CPGs), and the presence of a standardized method for assessing the evidence for clinical application of pharmacogenomic testing could increase the recommendation of pharmacogenomic testing in CPGs to some extent. Consistent recommendations for pharmacogenomic testing in CPGs may enhance the clinical utilization of testing, provide more effective treatments, and benefit society.[74]

Monitoring Methods

Platelet Function Test

The Platelet Function Test (PFT) provides a rapid assessment of platelet function and an estimate of the degree of platelet inhibition. Thus, the test is applicable for assessing clopidogrel-treated patients at elevated thrombotic risk to gauge antiplatelet therapy efficacy and residual platelet activity, guiding optimal medication and dosing selection.[13] Wadhwa et al[75] evaluated the economic viability of platelet function testing (PFT) in dual antiplatelet therapy (DAPT). They recommended PFT, followed by a switch from clopidogrel to prasugrel in combination with aspirin if resistance is identified, citing the reasonable cost of PFT for tailoring DAPT regimens to individual patients. The primary PFTs for clopidogrel include the VerifyNow assay, light transmission aggregometry (LTA), thromboelastography (TEG) platelet labelling system, rotational thromboelastography (ROTEM) and vasodilator-associated stimulated phosphoprotein (VASP) assay.

VerifyNow Assay

The VerifyNow assay is a whole blood point-of-care test that measures P2Y12 receptor activity by turbidimetric optical detection of platelet aggregation. The test is rapid bedside assay, completed in less than 5 minutes, which is an advantage over LTA and VASP phosphorylation assays. The VerifyNow assay also allows direct monitoring the effect from clopidogrel on P2Y12 receptors, helping determine the dosage of clopidogrel in patients due to undergo coronary artery stenting. In addition, the analysis is technically simple and the results are easy to interpret.[76] The results are expressed in PRUs and the effective therapeutic window for clopidogrel is $85 < \text{PRU} < 208$.[77]

Light Transmission Aggregometry (LTA)

LTA is considered gold standard in all PFTs. In LTA, the optical density of platelet aggregates in a sample is detected in the optical channel, whereas in the impedance aggregometry method, the change in resistance between two electrodes is measured. Although LTA has been included in many studies, it has been criticized for being time-consuming and lacking standardization and reproducibility.[78,79] The results of LTA are expressed as the maximum platelet aggregation rate. A study has shown that a maximum platelet aggregation rate greater than 40% is the optimal LTA platelet function threshold for clopidogrel when it is used to treat intracranial aneurysm shunts and prevent thromboembolic events.[80]

Thromboelastography (TEG) Platelet Labelling System and Rotational Thromboelastometry (ROTEM)

Thromboelastography combined with platelet mapping (TEG-PM) produces more complex data than PRU. The output of this test is four real-time curves of clot development as a function of time, showing clot initiation, expansion, and lysis. The values extracted from these curves represent multiple aspects of the coagulation cascade, with enzyme-promoted clot formation, intensity of clot formation, and rate of clot breakdown all being part of the underlying TEG curve. Under these conditions, platelet aggregation and the resulting clot intensity are determined exclusively by ADP-dependent platelet aggregation, mediated by the P2Y12 ADP receptor.[81] The rate of ADP-induced platelet inhibition was calculated from TEG to determine the incidence of CR and the factors influencing it.[82] Using the TEG-PM assay, the following reference values were formulated under the effective therapeutic window for clopidogrel, with amplitude (MA) values of 31 mm-47 mm; arachidonic acid (AA) greater than 50% and ADP greater than 30%. Individualized antiplatelet therapy based on TEG-PM results reduces the risk of ischaemic events in patients with non-cardioembolic ischaemic stroke without increasing the risk of bleeding events and mortality.[83]

Conventional TEG techniques can overproduce thrombin and therefore their lack of ability to determine ADP receptor inhibition is considered a major problem associated with conventional TEG. However, ROTEM is able to monitor clopidogrel without thrombin production and Schultz-Lebahn, A et al[84] used ROTEM to analyse platelet function.

Vasodilator-Associated Stimulated Phosphoprotein (VASP) Assay

The most pharmacologically specific assay for assessing clopidogrel therapy is VASP, which targets only the P2Y12 receptor.[79,85] The VASP assay is based on a physical principle: quantitative flow cytometry measures levels of phosphorylated and dephosphorylated VASP, which correlate with inhibition or activation of P2Y12. However, we must consider that VASP phosphorylation is regulated by a number of factors, which are impaired in certain comorbidities. In addition, VASP assays are time-consuming.[86,87] Aleil et al[88] implemented the first VASP assay in 2005 for the detection of clopidogrel-resistant patients with ischaemic cardiovascular events. The effective therapeutic window for clopidogrel is formulated with a reference platelet reactivity index (PRI) of 16–50 and requires the study of scatter plots to interpret the conditions.[76]

Therapeutic Drug Monitoring

High-performance liquid chromatography (HPLC) is usually used for the identification and quantification of compounds, and the determination of drug levels in patients' plasma using HPLC becomes difficult due to the low levels of prodrugs in plasma after clopidogrel ingestion and the instability of sulfhydryl derivatives. Therefore, liquid chromatography-tandem mass spectrometry (LC-MS/MS) has been used to assay the blood of three patients with coronary artery disease who underwent stent implantation, which allowed the simultaneous determination of clopidogrel, 2-oxo-clopidogrel and clopidogrel thiol metabolites in human plasma.[89] In 2024, Li et al[90] studied 100 patients with ischemic cerebrovascular disease diagnosed by a neurologist as needing clopidogrel therapy, and all the patients were genotyped for *CYP2C19*, the plasma concentration and plasma clopidogrel clearance of different groups of patients before and after clopidogrel treatment were detected by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS), the platelet aggregation rate of patients with different genotypes was determined by turbidimetric assay, and CR and stent thrombosis were analyzed in all the groups after 3 months of treatment.

Clinically, the genotypes of the patients were tested before administration, and after the end of the administration, the results of the PFT test were used to reflect the clinical results together with the plasma concentration determined by HPLC-MS/MS to provide a basis for judgement of the clinical administration of clopidogrel.[91]

Discussion

The clinical application of clopidogrel, as a major drug in antiplatelet therapy, requires a balance between optimization of efficacy and risk control. In this paper, we synthesized the available evidence that genetic polymorphisms and individual differences in drug metabolism are key factors contributing to CR and adverse events.The *CYP2C19* LOF allele has been identified as a major genetic marker affecting the production of active metabolites of clopidogrel, and gene-directed therapy significantly reduces the risk of in-stent thrombosis and myocardial infarction, especially in patients with CAD.[88] However, the association of *PON1* Q192R polymorphism with CR remains controversial, and a recent Meta-analysis showed that it had no significant effect on the risk of MACE and bleeding,[65] suggesting that future studies need to focus on epigenetic regulation and combined multigene effects.

In terms of clinical monitoring strategies, the combination of PFT and blood drug concentration provides a double guarantee for individualized treatment.VerifyNow and VASP assays can dynamically assess the level of P2Y12 receptor inhibition, whereas HPLC-MS/MS technology provides a direct basis for dosage adjustment by quantifying the concentration of active metabolites of clopidogrel.[71,72,86,87] Notably, the lack of harmonized standards for PFT thresholds and the limitations of VASP assays to be interfered by comorbidities need to be carefully considered in clinical interpretation. In addition, the applicability of genotype-guided immediate testing (eg, bedside *CYP2C19* rapid typing) for patients with acute PCI still needs to break through technical bottlenecks.[50]

The gene-efficacy relationship shows heterogeneity across the disease spectrum: switching to ticagrelor in *CYP2C19* LOF carriers in stroke patients reduces the risk of recurrence, whereas the genetic evidence for peripheral arterial disease (PAD) is not yet sufficient, suggesting that clinical decision-making needs to be combined with disease-specific evidence.[88] Notably, while novel P2Y12 inhibitors circumvent some of the metabolic defects, their bleeding risk (eg,

prasugrel short-term bleeding HR=1.66)[4] limits the advantages of their use in older or high-risk bleeding populations, highlighting the unique position of clopidogrel in balancing thrombotic/bleeding risk.

Conclusion

Recent studies have shown that platelet aggregation plays a key role in both the initiation and progression of thrombosis. Despite the emergence of new antiplatelet agents, clopidogrel remains the basic drug in current clinical practice due to its favorable safety profile, including a low risk of bleeding and high tolerability. However, the individual variability of this drug is of concern-gene polymorphisms leading to clopidogrel resistance can increase the risk of thrombotic events, suggesting the importance of precise dosing. In CAD, secondary prevention of ischemic stroke, gene-directed therapeutic strategies have shown significant benefits, with carriers of the *CYP2C19* LOF allele switching to ticagrelor or prasugrel experiencing a lower incidence of major ischemic events (myocardial infarction, in-stent thrombosis, etc.) compared with conventional regimens, while non-carriers continue to use clopidogrel to not only achieve comparable thrombotic efficacy to that achieved with the newer P2Y12 inhibitors but also significantly reduce the risk of major hemorrhage and significantly reduced the risk of major bleeding. Of particular note, in areas with limited medical resources, targeted genetic testing may be more cost-effective than "empirically reinforced antithrombotic" regimens. Clinical assessment of clopidogrel efficacy is currently based on the determination of optimal thresholds for platelet inhibition by light turbidimetric assay (LTA), platelet function assays such as VerifyNow, and in vivo measurement of active metabolite concentrations by HPLC-MS/MS. However, the standardization of these methods still faces challenges, with a lack of uniform consensus on critical values for functional assays and effective concentration thresholds for pharmacokinetic monitoring still requiring large-scale cohort validation.

In summary, this review aims to help achieve individualized and precise drug administration, reduce or avoid the occurrence of clinical adverse events, reduce the severity of the corresponding symptoms, and ensure that patients' treatment progresses smoothly, as well as to improve the quality of life and confidence of patients during the treatment period. Therefore, it has significant social and economic benefits.

Abbreviations

ADP, adenosine diphosphate; CR, clopidogrel resistance; GPIIb/IIIa, glycoprotein IIb/IIIa; CAD, Coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACS, acute coronary syndrome; TIA, transient ischaemic attack; CEA, carotid endarterectomy; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; FFA, fundus fluorescein angiography; FAERS, the US Food and Drug Administration Adverse Event Reporting System; CKD, chronic kidney disease; PRUs, P2Y12 reaction units; IAS, insulin autoimmune syndrome; HPR, high platelet reactivity; LOF, loss-of-function; GOF, gain-of-function; UM, ultra-rapid metabolizers; FDA, the US Food and Drug Administration; P-gp, p-glycoprotein; MACE, major adverse cardiovascular event; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CVD, cardiovascular disease; CPGs, clinical practice guidelines; PFT, platelet function test; DAPT, dual antiplatelet therapy; LTA, light transmission aggregometry; TEG, thromboelastography; ROTEM, rotational thromboelastography; VASP, vasodilator-associated stimulated phosphoprotein; AA, arachidonic acid; HPLC, High-performance liquid chromatography; LC-MS/MS, liquid chromatography-tandem mass spectrometry; HPLC-MS/MS, high-performance liquid chromatography-tandem mass spectrometry; CYP2C19, cytochrome P450 Family 2 Subfamily C Member 19 gene; CYP3A4, cytochrome P450 Family 3 Subfamily A Member 4 gene; ABCB1, ATP Binding CassetteSubfamily B Member 1 gene; CYP1A2, cytochrome P450 Family 1 Subfamily A Member 2 gene; PON1, paraoxonase 1; KDR, Kinase Insert Domain Receptor.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Qian L. Research Progress on Related Genes of Clopidogrel Resistance. *Adv Clin Med*. 2023;13(03):3828–3835. doi:10.12677/acm.2023.133549
2. Lan K, Gao H, Gong H. A retrospective study of the safety and efficacy of clopidogrel versus aspirin monotherapy one year after coronary stent implantation. *BMC Pharmacol Toxicol*. 2024;25(1):67. doi:10.1186/s40360-024-00796-w
3. Wang Z, Zhu S, Zhu J, et al. Comparison of P2Y12 inhibitors and aspirin in secondary prevention of coronary events: a meta-analysis of RCTs. *BMC Cardiovasc Disord*. 2025;25(1):207. doi:10.1186/s12872-025-04668-x
4. Kumar A, Lutsey PL, St Peter WL, et al. Comparative Risk of Hospitalized Bleeding of P2Y12 Inhibitors for Secondary Prophylaxis in Acute Coronary Syndrome After Percutaneous Coronary Intervention. *Clin Pharmacol Ther*. 2023;113(2):412–422. doi:10.1002/cpt.2806
5. Della Rocca DG, Horton RP, Di Biase L, et al. Incidence of Device-Related Thrombosis in Watchman Patients Undergoing a Genotype-Guided Antithrombotic Strategy. *JACC: Clinical Electrophysiology*. 2021;7(12):1533–1543. doi:10.1016/j.jacep.2021.04.012
6. DiLosa K, Wolinsky R, Harding J, et al. A Multi-Center Evaluation of Clopidogrel Resistance and its Role in Predicting Stent Thrombosis in Transcarotid Artery Revascularization. *Ann Vasc Surg*. 2024. doi:10.1016/j.avsg.2024.09.031
7. Seyfinejad B, Jouyban A. Overview of therapeutic drug monitoring of immunosuppressive drugs: analytical and clinical practices. *J Pharma Biomed Anal*. 2021;205:114315. doi:10.1016/j.jpba.2021.114315
8. Wiśniewski A, Filipska K. The Phenomenon of Clopidogrel High On-Treatment Platelet Reactivity in Ischemic Stroke Subjects: a Comprehensive Review. *Int J Mol Sci*. 2020;21(17):6408. doi:10.3390/ijms21176408
9. Chetty M, Ravenstijn P, Manchandani P. Clopidogrel Dosing: current Successes and Emerging Factors for Further Consideration. *Clin Pharmacol Ther*. 2021;109(5):1203–1211. doi:10.1002/cpt.2055
10. Wan H, Han W, Wu Z, et al. Whole blood dynamic platelet aggregation counting and 1-year clinical outcomes in patients with coronary heart diseases treated with clopidogrel. *Platelets*. 2020;32(7):968–974. doi:10.1080/09537104.2020.1817886
11. Byrne RA, Rossello X, Coughlan JJ, et al. ESC Guidelines for the management of acute coronary syndromes. *G ITAL CARDIOL*. 2023;25(Suppl 2):e1–e112. doi:10.1714/4191.41785
12. Ravn Jacobsen M, Engstroem T, Torp-Pedersen C, et al. Efficacy and safety of clopidogrel, ticagrelor, and prasugrel in an all-comers population of patients with ST-segment elevation myocardial infarction. *Eur Heart J*. 2020;41:Supple2. doi:10.1093/ehjci/ehaa946.1768
13. Jovanovic L, Antonijevic N, Novakovic T, et al. Practical Aspects of Monitoring of Antiplatelet Therapy. *Semin Thromb Hemost*. 2016;43(1):14–23. doi:10.1055/s-0036-1586230
14. Kim MC, Ahn SG, Cho KH, et al. De-escalation from ticagrelor to clopidogrel in patients with acute myocardial infarction: the TALOS-AMI HBR substudy. *Eurointervrntion*. 2023;19(10):e832–e843. doi:10.4244/EIJ-D-23-00427
15. Kim SH, Shin S, Choo EH, et al. Clinical Impact of Dyspnea after Ticagrelor Treatment and the Effect of Switching to Clopidogrel in Patients with Myocardial Infarction. *Thromb Haemostasis*. 2024. doi:10.1055/a-2299-4537
16. Li Y, Li J, Wang B, et al. Extended Clopidogrel Monotherapy vs DAPT in Patients With Acute Coronary Syndromes at High Ischemic and Bleeding Risk: the OPT-BIRISK Randomized Clinical Trial. *JAMA CARDIOL*. 2024;9(6):523–531. doi:10.1001/jamacardio.2024.0534
17. Biswas M, Kali SK. Association of *CYP2C19* Loss-of-Function Alleles with Major Adverse Cardiovascular Events of Clopidogrel in Stable Coronary Artery Disease Patients Undergoing Percutaneous Coronary Intervention: meta-analysis. *Cardiovasc Drug Ther*. 2021;35(6):1147–1159. doi:10.1007/s10557-021-07142-w
18. Vrints C, Andreotti F, Koskinas KC, et al. ESC Guidelines for the management of chronic coronary syndromes. *G ITAL CARDIOL*. 2023;25(12 Suppl 1):e1–e132. doi:10.1714/4375.43725
19. Virani SS, Newby LK, Arnold SV, et al. AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: a Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *CIRCULATION*. 2023;148(9):e9–e119. doi:10.1161/CIR.0000000000001168
20. Kang J, Chung J, Park KW, et al. Long-Term Aspirin vs Clopidogrel After Coronary Stenting by Bleeding Risk and Procedural Complexity. *JAMA CARDIOL*. 2023. doi:10.1001/jamacardio.2024.4030
21. Manunga J, Pedersen C, Stanberry L, et al. Impact of continued clopidogrel use on outcomes of patients undergoing carotid endarterectomy. *J Vascular Surg*. 2023;78(2):438–445. doi:10.1016/j.jvs.2023.04.016
22. Esmaili DD, Boyer DS. Recent advances in understanding and managing retinal vein occlusions. *F1000RES*. 2018;7:467.
23. Rehak M, Wiedemann P. Retinal vein thrombosis: pathogenesis and management. *J THROMB HAEMOST*. 2010;8:1886–1894.
24. Al Ghaithi H, Al Hinai A, Al Abri M, et al. Clopidogrel therapy in nonischemic central retinal vein occlusion: a case report and therapeutic insight. *OMAN J OPHTHALMOL*. 2024;17:1
25. Fahmy AI, Mekkawy MA, Abou-Ali A. Evaluation of adverse events involving bleeding associated with oral P2Y12 inhibitors use in the Food and Drug Administration adverse event reporting system. *Int J Clin Pharmacol Therap*. 2019;57(4):175–181. doi:10.5414/CP203365
26. Zongdan J, Yuyu L, Zhibing W, et al. The mechanism of miR-363-3p/DUSP10 signaling pathway involved in the gastric mucosal injury induced by clopidogrel. *Toxicol Mech Methods*. 2020;31(2):150–158. doi:10.1080/15376516.2020.1850960
27. Eslami V, Gheymati A. Clopidogrel-induced liver damage: a case report and review of the literature. *Clin Case Rep*. 2020;8(12):3024–3027. doi:10.1002/ccr3.3324
28. Pinto FMC, Victorino APOS. Clopidogrel-induced neutropenia in a 84-year-old patient: a case report. *Hematol Transfus Cell Therapy*. 2020;44(2):256–258. doi:10.1016/j.htct.2020.07.002
29. Nguyen KA, Eadon MT, Yoo R, et al. Risk Factors for Bleeding and Clinical Ineffectiveness Associated With Clopidogrel Therapy: a Comprehensive Meta-Analysis. *Clin Transl Sci*. 2020;14(2):645–655. doi:10.1111/cts.12926
30. Lizondo López T, Barceló FI, García Gutiérrez A, et al. Clopidogrel-induced thrombotic microangiopathy: a case report. *Eur J Hosp Pharm*. 2024. doi:10.1136/ejhpharm-2024-004209
31. Grossman K, Iftikhar M, Zhang R, et al. A Rare Case of Clopidogrel-Induced Immune Thrombocytopenic Purpura. *J Am College Cardiol*. 2024;83(13):3331. doi:10.1016/s0735-1097(24)05321-x
32. Távora C, Rodrigues Dos Santos J, Cruz D. Thrombocytopenia Induced by Clopidogrel: a Rare Adverse Effect. *Eur J Case Rep Intl Med*. 2023;10(11):004045. doi:10.12890/2023_004045

33. Ndulue CN, Jisieike-Onuigbo NN, Okwesa NJ, et al. Clopidogrel-induced thrombotic thrombocytopenic purpura: a case report. *Afr Health Sci*. 2023;23(1):592–595. doi:10.4314/ahs.v23i1.62
34. Bass DI, Young CC, Park MS, et al. Severe, Intolerable Fatigue Associated with Hyperresponse to Clopidogrel. *World Neurosurg*. 2021;156:e374–e380. doi:10.1016/j.wneu.2021.09.075
35. Chen S, Qiang J, Zhang Y, et al. Hypoglycemia as a potential risk for patients taking clopidogrel: a systematic review and meta-analysis. *Front Endocrinol*. 2023;14(1091933). doi:10.3389/fendo.2023.1091933
36. Du W, Wang H, Liu Y, et al. Recurrent hypoglycemia induced by clopidogrel: a case report and mini review. *J Diabetes Invest*. 2023;15(3):275–281. doi:10.1111/jdi.14110
37. Lee SH, Ryu DR, Lee SJ, et al. Small bowel ulcer bleeding due to suspected clopidogrel use in a patient with clopidogrel resistance: a case report. *World J Clin Cases*. 2021;9(15):3689–3695. doi:10.12998/wjcc.v9.i15.3689
38. Saad S, Soua Y, Belhadjali H, et al. Un syndrome de Rowell induit par le clopidogrel: à propos d'un premier cas. *Rev Med Interne*. 2020;2020:41A189. doi:10.1016/j.revmed.2020.10.321.
39. Javed F, Champaneria SU. The Mystery of Clopidogrel-Associated Inflammatory Arthritis. *Cureus*. 2023;15(12):e50564. doi:10.7759/cureus.50564
40. Biswas M, Sukasem C, Khatun Kali MS, et al. Effects of the CYP2C19 LoF allele on major adverse cardiovascular events associated with clopidogrel in acute coronary syndrome patients undergoing percutaneous coronary intervention: a meta-analysis. *Pharmacogenomics*. 2022;23(3):207–220. doi:10.2217/pgs-2021-0098
41. Amin AM, Sheau Chin L, Azri Mohamed Noor D, et al. The Personalization of Clopidogrel Antiplatelet Therapy: the Role of Integrative Pharmacogenetics and Pharmacometabolomics. *Cardiol Res and Pract*. 2017;2017:8062796. doi:10.1155/2017/8062796A
42. Uppugunduri CR, Daali Y, Desmeules J, et al. Transcriptional regulation of CYP2C19 and its role in altered enzyme activity. *Curr Drug Metabol*. 2012;13(8):1196–1204. doi:10.2174/138920012802850146
43. Zhang M, Wang J, Zhang Y, et al. Effects of individualized antiplatelet therapy, based on CYP2C19 genotyping, on platelet function in patients underwent percutaneous coronary intervention. *Perfusion*. 2020;37(1):78–85. doi:10.1177/0267659120978584
44. 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;112(5):959–967.
45. Biswas M, Murad MA, Ershadian M, et al. Risk of major adverse cardiovascular events in *CYP2C19* LoF genotype guided clopidogrel against alternative antiplatelets for CAD patients undergoing PCI: meta-analysis. *Clin Transl Sci*. 2025;18(2):e70080. doi:10.1111/cts.70080
46. Biswas M, Kali MSK, Biswas TK, et al. Risk of major adverse cardiovascular events of *CYP2C19* loss-of-function genotype guided prasugrel/ticagrelor vs clopidogrel therapy for acute coronary syndrome patients undergoing percutaneous coronary intervention: a meta-analysis. *Platelets*. 2021;32(5):591–600. doi:10.1080/09537104.2020.1792871
47. Biswas M, Hossain MS, Ahmed Rupok T, et al. The association of *CYP2C19* LoF alleles with adverse clinical outcomes in stroke patients taking clopidogrel: an updated meta-analysis. *Clin. Transl. Sci.* 2024;17(4):e13792. doi:10.1111/cts.13792
48. Biswas M, Rahaman S, Biswas TK, et al. Risk of major adverse cardiovascular events for concomitant use of clopidogrel and proton pump inhibitors in patients inheriting *CYP2C19* loss-of-function alleles: meta-analysis. *Int. J Clin Pharmacol*. 2021;43(5):1360–1369. doi:10.1007/s11096-021-01261-y
49. Fu H, Hu P, Ma C, et al. Association of clopidogrel high on-treatment reactivity with clinical outcomes and gene polymorphism in acute ischemic stroke patients. An observational study. *Medicine*. 2020;99(15):e19472. doi:10.1097/MD.0000000000019472
50. Jia DM, Chen ZB, Zhang MJ, et al. *CYP2C19* polymorphisms and antiplatelet effects of clopidogrel in acute ischemic stroke in China. *Stroke*. 2013;44(6):1717–1719. doi:10.1161/STROKEAHA.113.000823
51. Liu R, Zhou ZY, Chen YB, et al. Associations of *CYP3A4, NR1I2, CYP2C19* and *P2RY12* polymorphisms with clopidogrel resistance in Chinese patients with ischemic stroke. *Acta Pharmacol Sin*. 2016;37(7):882–888. doi:10.1038/aps.2016.41
52. Helsby NA, Burns KE. Molecular mechanisms of genetic variation and transcriptional regulation of *CYP2C19*. *Front Genetics*. 2012;3:1–8. doi:10.3389/fgene.2012.00206
53. Li Y, Tang HL, Hu YF, et al. The gain-of-function variant allele *CYP2C19*17*: a double-edged sword between thrombosis and bleeding in clopidogrel-treated patients. *J Thromb Haemost*. 2012;10(2):199–206. doi:10.1111/j.1538-7836.2011.04570.x
54. Zhang L, Yang J, Zhu X, et al. Effect of high-dose clopidogrel according to *CYP2C19*2* genotype in patients undergoing percutaneous coronary intervention- a systematic review and meta-analysis. *Thromb Res*. 2014;135(3):449–458. doi:10.1016/j.thromres.2014.12.007
55. Kazui M, Nishiya Y, Ishizuka T, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. *Drug Metab Dispos*. 2010;38(1):92–99. doi:10.1124/dmd.109.029132
56. Giusti B, Gori AM, Marcucci R, et al. Determinants to optimize response to clopidogrel in acute coronary syndrome. *Pharmacogenomics Personalized Med*. 2010;3:33–50. doi:10.2147/pgpm.s5056
57. Lock E, Saveliev A, Kennedy L. Methanol and Dimethyl Sulfide Removal by Pulsed Corona Part I: experiment. *Plasma Chemistry and Plasma Processing*. 2006;26(6):527–542. doi:10.1007/s11090-006-9011-9
58. Mega JL, Close SL, Wiviott SD, et al. Genetic variants in ABCB1 and *CYP2C19* and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet*. 2010;376(9749):1312–1319. doi:10.1016/S0140-6736(10)61273-1
59. Su Q, Li J, Tang Z, et al. Association of *CYP2C19* Polymorphism with Clopidogrel Resistance in Patients with Acute Coronary Syndrome in China. *Med Sci Monit*. 2019;25:7138–7148. doi:10.12659/MSM.915971
60. Biswas M, Rahaman S, Biswas TK, et al. Effects of the ABCB1 C3435T single nucleotide polymorphism on major adverse cardiovascular events in acute coronary syndrome or coronary artery disease patients undergoing percutaneous coronary intervention and treated with clopidogrel: a systematic review and meta-analysis. *Expert Opin Drug Saf*. 2020;19(12):1605–1616. doi:10.1080/14740338.2020.1836152
61. Mugosa S, Todorovic Z, Cukic J, et al. *ABCB1* polymorphism in clopidogrel-treated Montenegrin patients. *Open Life Sci*. 2021;16(1):142–149. doi:10.1515/biol-2021-0017
62. Kw P, Jj P, Jeon KH, et al. Enhanced clopidogrel responsiveness in smokers: smokers' paradox is dependent on cytochrome P450 *CYP1A2* status. *Arteriosclerosis Thrombosis Vasc Biol*. 2011;31(3):665–671. doi:10.1161/ATVBAHA.110.217182
63. Cresci S, Depta JP, Lenzini PA, et al. Cytochrome p450 gene variants, race, and mortality among clopidogrel-treated patients after acute myocardial infarction. *Circulation-Cardiovasc Genet*. 2014;7(3):277–286. doi:10.1161/CIRCGENETICS.113.000303

64. Gupta N, Binukumar BK, Singh S, et al. Serum paraoxonase-1 (PON1) activities (PONase/AREase) and polymorphisms in patients with type 2 diabetes mellitus in a North-West Indian population. *Gene*. 2011;487(1):88–95. doi:10.1016/j.gene.2011.07.011
65. Bouman HJ, Schömig E, van Werkum JW, et al. Paraoxonase-1 is a major determinant of clopidogrel efficacy. *Nat Med*. 2010;17(1):110–116. doi:10.1038/nm.2281
66. Farid NA, Kurihara A, Wrighton SA. Metabolism and disposition of the thienopyridine antiplatelet drugs ticlopidine, clopidogrel, and prasugrel in humans. *J Clin Pharmacol*. 2009;50(2):126–142. doi:10.1177/0091270009343005
67. Marchini JF, Pinto MR, Novaes GC, et al. Decreased platelet responsiveness to clopidogrel correlates with CYP2C19 and PON1 polymorphisms in atherosclerotic patients. *Braz J Med Biol Res*. 2017;50(1):e5660. doi:10.1590/1414-431X20165660
68. Sibbing D, Koch W, Massberg S, et al. No association of paraoxonase-1 Q192R genotypes with platelet response to clopidogrel and risk of stent thrombosis after coronary stenting. *Eur Heart J*. 2011;32(13):1605-1613. doi:10.1093/eurheartj/ehr155
69. Biswas M, Kali SK, Sarker AK, et al. Association between *Q192R PON1* genetic polymorphism and major adverse cardiovascular events in patients treated with clopidogrel: an updated meta-analysis. *Expert Opin Drug Saf*. 2023;22(9):807–817. doi:10.1080/14740338.2023.2212152
70. Al Awaida W, Ahmed AA, Hamza AA, et al. Association of *KDR* rs1870377 genotype with clopidogrel resistance in patients with post percutaneous coronary intervention. *Heliyon*. 2021;7(2):e06251. doi:10.1016/j.heliyon
71. Holmes DR, Dehmer GJ, Kaul S, et al. ACCF/AHA Clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. *Circulation*. 2010;122(5):537–557. doi:10.1161/CIR.0b013e3181ee08ed
72. Fontana P, Roffi M, Reny JL. Platelet Function Test Use for Patients with Coronary Artery Disease in the Early 2020s. *J Clin Med*. 2020;9(1):194. doi:10.3390/jcm9010194
73. Bhopalwala AM, Hong RA, Khan ZR, et al. Routine screening for CYP2C19 polymorphisms for patients being treated with clopidogrel is not recommended. *Hawai'i J Med Public Health*. 2015;74:16–20.
74. hertz DL, Bousman CA, McLeod HL, et al. Recommendations for pharmacogenetic testing in clinical practice guidelines in the US. *Am J Health-Syst Ph*. 2024;81(5):672–683. doi:10.1093/ajhp/zxae110
75. Wadhwa A, Ramirez-Velandia F, Mensah E, et al. Cost-effectiveness of platelet function testing in dual antiplatelet therapy decision-making after intracranial aneurysm treatment with flow diversion. *Neurosurgical Rev*. 2024;47:1. doi:10.1007/s10143-024-02668-7
76. Alvitigala BY, Gooneratne LV, Constantine GR, et al. Pharmacokinetic, pharmacodynamic, and pharmacogenetic assays to monitor clopidogrel therapy. *Pharmacol Res Perspect*. 2020;8(6):e00686. doi:10.1002/prp2.686
77. Lianos I, Varlamos C, Benetou DR, et al. Platelet function testing in atrial fibrillation patients undergoing percutaneous coronary intervention. *J Thrombosis Thrombolysis*. 2023;55(1):42–50. doi:10.1007/s11239-022-02723-4
78. Gremmel T, Koppensteiner R, Panzer S. Comparison of aggregometry with flow cytometry for the assessment of agonists -induced platelet reactivity in patients on dual antiplatelet therapy. *PLoS One*. 2015;10:e0129666. doi:10.1371/journal.pone.0129666
79. Garabedian T, Alam S. High residual platelet reactivity on clopidogrel: its significance and therapeutic challenges overcoming clopidogrel resistance. *Cardiovas Diagnosis Ther*. 2013;3(1):23–37. doi:10.3978/j.issn.2223-3652.2013.02.06
80. Enriquez-Marulanda A, Filo J, Ramirez-Velandia F, et al. Defining light transmission aggregometry cutoff values for clopidogrel and aspirin resistance in flow diversion treatment of intracranial aneurysms. *J Neurosurg*. 2024;2024:1–9. doi:10.3171/2024.3.JNS2487.
81. Corliss BM, Freedman R, Brennan MM, et al. Laboratory assessments of therapeutic platelet inhibition in endovascular neurosurgery: complication prediction using the VerifyNow P2Y12 assay and thromboelastography with platelet mapping. *J Neurosurg*. 2021;134(3):884–892. doi:10.3171/2019.12.JNS192396
82. Wei YN, Li MH, Liu J, et al. Risk Factors of Clopidogrel Resistance in the Elderly Patients with Atherosclerotic Cardiovascular Disease. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*. 2023;45(1):38–43. doi:10.3881/j.issn.1000-503X.15108
83. Zhang Y, Wang M, Su S. Individualized antiplatelet therapy for non-cardiogenic ischemic stroke. *J Stroke Cerebrovascular Dis*. 2024;33(6):107711. doi:10.1016/j.jstrokecerebrovasdis.2024.107711
84. Schultz-Lebahn A, Nissen PH, Pedersen TF, et al. Platelet function assessed by ROTEM® platelet in patients receiving antiplatelet therapy during cardiac and vascular surgery. *Scand J Clin Lab Invest*. 2022;82(1):18–27. doi:10.1080/00365513.2021.2012820
85. Geiger J, Teichmann L, Grossmann R, et al. Monitoring of clopidogrel action: comparison of methods. *Clin Chem*. 2005;51(6):957–965. doi:10.1373/clinchem.2004.047050
86. Sudo T, Ito H, Kimura Y. Phosphorylation of the vasodilator-stimulated phosphoprotein (VASP) by the anti-platelet drug, cilostazol, in platelets. *Platelets*. 2003;14(6):381–390. doi:10.1080/09537100310001598819
87. Aktas B, Utz A, Hoenig-Liedl P, et al. Dipyridamole enhances NO/cGMP-mediated vasodilator-stimulated phosphoprotein phosphorylation and signaling in human platelets: in vitro and in vivo/ex vivo studies. *Stroke*. 2003;34:764–769. doi:10.1161/01.STR.0000056527.34434.59
88. Aleil B, Ravanat C, Cazenave JP, et al. Flow cytometric analysis of intraplatelet VASP phosphorylation for the detection of clopidogrel resistance in patients with ischemic cardiovascular diseases. *J Thrombosis Haemostasis*. 2005;3(1):85–92. doi:10.1111/j.1538-7836.2004.01063.x
89. Xu L, Li R, Li J, et al. Simultaneous determination of clopidogrel, 2-oxo-clopidogrel, and the thiol metabolite of clopidogrel in human plasma by LC-MS/MS. *J Biomed Res*. 2022;36(2):109–119. doi:10.7555/JBR.36.20210125
90. Li P, Cao M, Liu L, et al. Analysis of the effect of CYP2C19 gene properties on the anti-platelet aggregation of clopidogrel after carotid artery stenting under network pharmacology. *BMC Pharmacol Toxicol*. 2024;25. doi:10.1186/s40360-024-00750-w
91. Akkaif M, Daud N, Noor D, et al. Platelet reactivity index after treatment of clopidogrel versus ticagrelor based on *CYP2C19* genotypes among patients undergoing percutaneous coronary intervention: results of a randomized study. *Eur Heart J*. 2024;44. doi:10.1093/eurheartj/ehac779.120