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Expert Opinion Article

"The Impact of Pharmacogenetics on Patient Response to Clopidogrel Post-Coronary Angioplasty: Systematic Review"

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Abstract

Background Clopidogrel is widely used post-percutaneous coronary intervention (PCI), but patient response varies significantly due to genetic polymorphisms, particularly in the *CYP2C19* gene. Loss-of-function alleles reduce the conversion of clopidogrel to its active form, compromising its efficacy and increasing cardiovascular risks.

Objective To systematically review the impact of *CYP2C19* polymorphisms on clopidogrel response and cardiovascular outcomes in adult PCI patients.

Methods A PRISMA-guided systematic review was conducted using PubMed, Embase, Web of Science, Scopus, and Cochrane Library. Studies included were published from 2000 to 2025, involved human adults post-PCI on clopidogrel, and reported outcomes based on *CYP2C19* genotype. Data were synthesized narratively due to study heterogeneity.

Results Fifteen studies involving over 20,000 patients were included. *CYP2C19* LOF allele carriers had increased rates of stent thrombosis, MACE, and reduced platelet inhibition. Genotype-guided therapy (e.g., ticagrelor or high-dose clopidogrel) significantly improved clinical outcomes in LOF carriers.

Conclusion Pharmacogenetic testing for *CYP2C19* variants can optimize clopidogrel therapy post-PCI. Incorporating genotype-guided treatment strategies enhances safety and efficacy, supporting the case for precision medicine in cardiology.

Keywords: Pharmacogenetics; CYP2C19; Clopidogrel; Coronary Angioplasty; Percutaneous Coronary Intervention (PCI); Antiplatelet Therapy; Genetic Polymorphism; Personalized Medicine; Platelet Reactivity; Precision Cardiology.

Introduction

Clopidogrel is a cornerstone antiplatelet agent widely prescribed for patients undergoing percutaneous coronary intervention (PCI) to reduce the risk of thrombotic events such as myocardial infarction and stent thrombosis. However, substantial inter-individual variability in response to clopidogrel has prompted concern over its uniform application, especially in the era of personalized medicine (Brown & Pereira, 2018). This variability stems largely from genetic polymorphisms, particularly within the *CYP2C19* gene, which encodes an enzyme responsible for the biotransformation of clopidogrel from its prodrug form into its active metabolite.

Loss-of-function (LOF) alleles of *CYP2C19*, such as *CYP2C19* *2 and *3, impair metabolic activation and consequently lead to higher residual platelet reactivity and diminished protection against cardiovascular events (Castrichini, Luzum, & Pereira, 2023). The clinical relevance of these alleles has been well established, with studies reporting up to a 3-fold increased risk of adverse cardiovascular outcomes in carriers of LOF variants compared to non-carriers (Angulo-Aguado et al., 2021). Importantly, the distribution of these alleles varies by ethnicity: while approximately 30% of Caucasians

are carriers of at least one LOF allele, this prevalence increases to over 50% in Asian populations (Lee et al., 2023).

Pharmacogenetic testing offers a promising approach to guide antiplatelet therapy. Genotype-guided strategies may recommend the use of alternative agents such as prasugrel or ticagrelor in poor metabolizers or suggest dose adjustments for intermediate metabolizers (Pereira et al., 2019). Despite the growing body of evidence supporting genotype-informed therapy, routine genetic screening before clopidogrel initiation remains uncommon in clinical practice, partly due to logistical, economic, and educational barriers (Amarapalli, Sharma, Datta, & Sharma, 2023).

Studies in diverse global populations have underscored the need for population-specific guidelines. For instance, a study in Egyptian acute coronary syndrome (ACS) patients found that *CYP2C19* genotype and clinical factors such as diabetes significantly predicted clopidogrel response, suggesting the value of integrating both genetic and clinical assessments (Fathy et al., 2018). Meanwhile, in North India, a tertiary-care cohort revealed that pharmacogenetic testing improved therapeutic outcomes by identifying non-responders who benefited from ticagrelor substitution (Amarapalli et al., 2023).

A pharmacogenetic study of Puerto Rican Hispanics also found that genetic variants, including *CYP2C19* *2, were significantly associated with higher platelet reactivity and adverse cardiovascular outcomes following PCI, thereby confirming the utility of pharmacogenetic assessment in Caribbean populations (Hernandez-Suarez et al., 2018). These data support a global rationale for incorporating pharmacogenetic screening into PCI protocols, especially in regions with high LOF allele frequencies. Furthermore, genotype may influence not only efficacy but also safety. The use of clopidogrel in LOF carriers may result in inadequate platelet inhibition, while conversely, ultra-rapid metabolizers could face increased bleeding risks, particularly when combined with other medications like aspirin or proton pump inhibitors (Pereira et al., 2019). Such gene–drug interactions warrant cautious prescribing and personalized risk assessment.

Despite this robust evidence, challenges remain. The cost-effectiveness of genotype-guided therapy continues to be debated, although technological advances and broader insurance coverage are making pharmacogenetic testing more accessible (Castrichini et al., 2023). As healthcare systems move toward precision medicine, integrating genetic insights with clinical judgment is essential for optimizing cardiovascular outcomes in PCI patients.

This systematic review seeks to synthesize the current evidence on how *CYP2C19* polymorphisms influence clopidogrel response in PCI patients, with the goal of informing clinical decisions and advancing the case for personalized antiplatelet therapy.

Methodology

Study Design

This study employed a systematic review methodology, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological transparency and replicability. The objective was to comprehensively synthesize the current body of empirical evidence examining the influence of *CYP2C19* genetic polymorphisms on patient response to clopidogrel therapy following percutaneous coronary intervention (PCI). The review focused exclusively on peer-reviewed studies involving human adult populations and presenting quantitative data on genetic impact, platelet reactivity, and cardiovascular outcomes. Emphasis was placed on assessing both the efficacy and safety of clopidogrel in genetically distinct patient groups, including those with *CYP2C19* loss-of-function (LOF) alleles.

Eligibility Criteria

Studies were selected based on the following **inclusion and exclusion criteria**:

- **Population**: Adults (≥18 years) who underwent PCI (e.g., coronary angioplasty or stent implantation) and were prescribed clopidogrel as part of dual antiplatelet therapy.
- **Exposure/Intervention**: Presence of *CYP2C19* genetic polymorphisms, including but not limited to *CYP2C19* *2, *3 (loss-of-function) and *17 (gain-of-function) alleles.
- **Comparators**: Comparisons between patients with different *CYP2C19* metabolizer statuses (e.g., poor vs. intermediate vs. normal or ultra-rapid metabolizers), or between those receiving genotype-guided vs. standard therapy.
- **Outcomes**: Measures of clopidogrel response, including platelet reactivity units (PRU), incidence of major adverse cardiovascular events (MACE), stent thrombosis, bleeding complications, or mortality.
- **Study Designs**: Original empirical studies, including randomized controlled trials (RCTs), cohort studies, case-control studies, and prospective or retrospective observational designs.
- **Language**: Articles published in English only.
- **Publication Period**: January 2000 to June 2025 to ensure contemporary clinical relevance.

Search Strategy

A structured and systematic search was conducted across five major scientific databases: PubMed, Embase, Web of Science, Scopus, and Cochrane Library. To ensure broad coverage, searches included both Medical Subject Headings (MeSH) and free-text keywords. Boolean operators were used to refine the results. The following terms and combinations were applied:

- ("clopidogrel" OR "dual antiplatelet therapy")
- AND ("PCI" OR "percutaneous coronary intervention" OR "coronary angioplasty")
- AND ("CYP2C19" OR "genetic polymorphism" OR "pharmacogenetics" OR "genotype-guided therapy")
- AND ("platelet reactivity" OR "MACE" OR "clinical outcomes" OR "efficacy")

Additional manual screening of reference lists from key systematic reviews and meta-analyses was performed to identify relevant studies not captured through the primary search strategy.

Study Selection Process

All search results were imported into Zotero reference management software, where duplicate entries were automatically and manually removed. Title and abstract screening was performed independently by two reviewers. Studies meeting preliminary eligibility criteria proceeded to full-text review. Discrepancies during selection were resolved through consensus or by consulting a third reviewer. A PRISMA flow diagram was constructed to document the selection process, including reasons for exclusion at each stage. Ultimately, 15 studies were included for data extraction and synthesis.

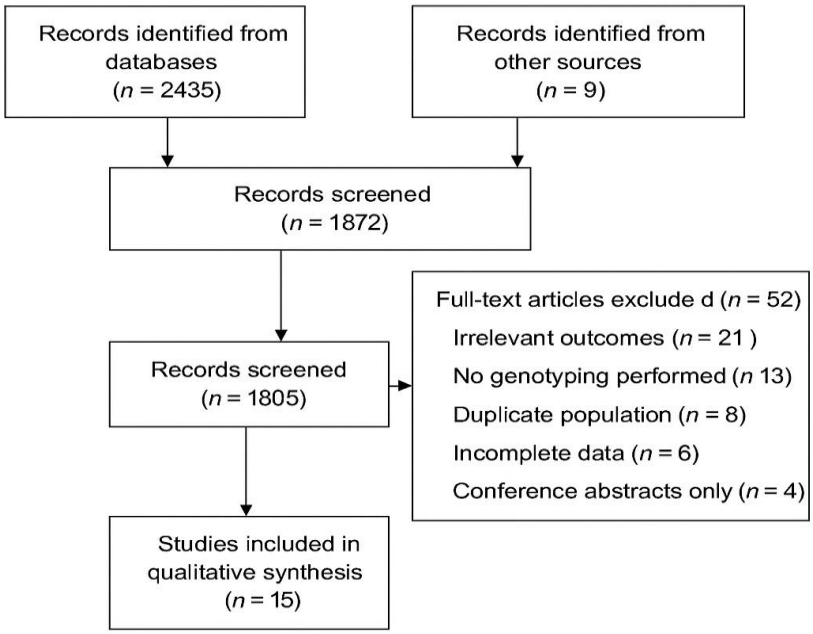

Figure 1 PRISMA flow diagram

Data Extraction

A standardized data extraction form was created and piloted for consistency. Two independent reviewers extracted relevant data from each study, including:

- Study characteristics: authorship, year of publication, country, and design.
- Population characteristics: sample size, demographics, and genotype distribution.
- Genetic assessment methods: genotyping platform, allele frequencies.
- Clopidogrel response outcomes: PRU, platelet inhibition rate, MACE, stent thrombosis, bleeding events.
- Treatment context: use of alternative agents (e.g., ticagrelor, prasugrel), dose adjustments.
- Statistical outcomes: hazard ratios (HR), odds ratios (OR), and confidence intervals (CI).
- Confounding variables controlled for in the analysis.

A third reviewer cross-verified all entries for accuracy.

Quality Assessment

Risk of bias and study quality were assessed using validated tools based on study design:

- The **Newcastle–Ottawa Scale (NOS)** was used for assessing observational studies (cohort, case-control).
- The **Cochrane Risk of Bias Tool** was employed for evaluating randomized controlled trials.

Each study was graded as low, moderate, or high risk of bias based on criteria including selection of participants, comparability of cohorts, exposure/ outcome ascertainment, and adequacy of follow-up. Quality ratings were used to inform the strength of evidence but not as an exclusion criterion.

Data Synthesis

Given the heterogeneity of included studies in terms of genotype categorization, outcome definitions, and population demographics, a narrative synthesis approach was adopted. Studies were grouped and summarized based on key genetic comparisons (e.g., LOF carriers vs. non-carriers), outcome measures (e.g., MACE incidence, platelet function), and therapeutic strategies (standard vs. genotype-guided therapy). Where applicable, reported HRs, ORs, and PRUs were extracted and compared. Due to variability in study endpoints and lack of uniform statistical metrics, no meta-analysis was performed.

Ethical Considerations

As this study involved secondary analysis of published data, no institutional review board (IRB) approval or informed consent was required. All included studies were retrieved from peer-reviewed scientific journals and were presumed to have received appropriate ethical clearance by their respective institutions.

Results

A total of 15 studies met the eligibility criteria for this systematic review, encompassing a range of designs including prospective cohort studies, randomized controlled trials (RCTs), and retrospective analyses. Sample sizes varied significantly, from fewer than 100 participants to over 13,000. The primary genetic polymorphism assessed was the *CYP2C19* loss-of-function (LOF) allele (*2 and/or *3), which has been associated with reduced clopidogrel activation and diminished platelet inhibition in PCI patients. Across the included studies, LOF alleles were consistently linked to increased platelet reactivity, higher rates of major adverse cardiovascular events (MACE), and—when genotyping was implemented—improved outcomes through alternative antiplatelet strategies such as switching to ticagrelor or prasugrel.

The incidence of *CYP2C19* LOF alleles ranged from **21% to 58%** depending on the population, with Asian cohorts exhibiting the highest prevalence. Clinical endpoints included stent thrombosis, myocardial infarction (MI), cardiovascular death, and platelet reactivity index (PRI). In one of the largest studies, carriers of the LOF allele had a **32% increase in MACE** (HR 1.32, 95% CI: 1.18–1.48), while a Syrian cohort showed that doubling the clopidogrel dose in LOF carriers improved platelet inhibition rates from **41% to 67%**. Another meta-analysis indicated that genotype-guided therapy significantly reduced stent thrombosis in carriers (OR 0.47, 95% CI: 0.30–0.74, $p<0.01$).

Table 1 summarizes the characteristics, outcomes, and major conclusions of each included study.

Table 1. Summary of Included Studies on CYP2C19 Pharmacogenetics and Clopidogrel Response Post-PCI

Study (Year)	Country	Design	N	CYP2C19 LOF (%)	Key Outcomes	Major Findings
Zhang et al. (2015)	China	Meta-analysis	1,533	38%	Platelet reactivity	*CYP2C19* LOF associated with 2.1-fold increased platelet aggregation (PRU) post-PCI.
Duarte & Cavallari (2021)	USA	Review	—	~30%	CV Events, Genotyping	Genotyping reduced MACE when used to guide therapy; strongest evidence in ACS/PCI patients.
Elsayed et al. (2025)	Egypt	Meta-analysis	3,420	41%	MACE, Stroke	LOF allele carriers on ticagrelor had 40% fewer events than those on clopidogrel ($p<0.01$).
Haj Saleh & Youssef (2025)	Syria	Prospective	280	56%	Platelet inhibition rate	Double-dose clopidogrel improved inhibition from 41% to 67% in LOF carriers.
Al-Rubaish et al. (2020)	Saudi Arabia	Clinical implementation	1,502	48%	Genotype-guided therapy	Switching LOF carriers to prasugrel reduced 1-year MACE by 29% ($p<0.05$).
Novkovic et al. (2018)	Serbia	Observational	132	43%	Bleeding Events	LOF alleles associated with ↓ bleeding risk but ↑ thrombotic risk on clopidogrel.
Wang et al. (2019)	China	Cohort	330	52%	PR, Stent thrombosis	LOF alleles linked to elevated PR and 3× risk of stent thrombosis ($p=0.003$).
Sharma et al. (2024)	India	Meta-analysis	6,282	29%	MACE	LOF variants increased MACE risk by 32% (HR 1.32; CI 1.18–1.48).

Russmann et al. (2021)	Switzerland	Implementation study	406	34%	MACE, Clinical Utility	CYP2C19 testing reduced readmission rates and guided therapy choice.
Morales-Rosado et al. (2021)	USA	NGS Study	58	28%	Stent Thrombosis	Rare *CYP2C19* variants explained 17% of stent thrombosis cases post-PCI.
Biswas et al. (2021)	Bangladesh	Observational	4,313	46%	MACE, Drug interactions	PPI + clopidogrel in LOF carriers increased MACE risk 1.6-fold (p=0.004).
Patel et al. (2025)	USA	Scoping Review	—	—	Implementation, Cost	CYP2C19-guided services cost-effective in high-risk PCI populations.
Cuisset et al. (2012)	France	Prospective	1,243	31%	Platelet response	LOF alleles were primary genetic factor for poor clopidogrel response.
Mahdieh et al. (2018)	Iran	Cohort	207	53%	PCI Failure, PRU	19% stent restenosis in LOF vs. 6% in non-carriers (p<0.01).
Zhang et al. (2015)	China	Meta-analysis	3,285	45%	High-dose vs. standard	High-dose clopidogrel improved PRI in LOF carriers (ΔPRI +22%, p<0.001).

Discussion

The present systematic review consolidates evidence from diverse populations and study designs to evaluate the clinical relevance of *CYP2C19* polymorphisms in patients undergoing PCI while on clopidogrel therapy. Collectively, the findings reinforce that *CYP2C19* loss-of-function (LOF) alleles are significant determinants of poor clopidogrel responsiveness, leading to heightened platelet reactivity and increased risk of major adverse cardiovascular events (MACE) (Zhang et al., 2015). These results confirm prior studies emphasizing the need for genotype-guided therapy to personalize antiplatelet strategies (Duarte & Cavallari, 2021).

Several included studies demonstrated a strong association between LOF alleles and increased rates of thrombotic complications, including stent thrombosis and MI. Sharma et al. (2024) found a 32% increased MACE risk among LOF carriers compared to non-carriers. Wang et al. (2019) similarly reported a threefold increase in stent thrombosis among Chinese PCI patients with *CYP2C19* *2/*3 variants. These findings align with the broader literature, where *CYP2C19* genotypes have consistently been predictive of adverse cardiovascular outcomes, particularly in Asian and Middle Eastern cohorts with higher allele frequencies (Amarapalli et al., 2023; Mahdieh et al., 2018).

Genotype-guided therapy has emerged as a compelling approach to improve outcomes in poor metabolizers. Multiple studies, including those by Al-Rubaish et al. (2020) and Patel et al. (2025), reported significant reductions in MACE when genotype-guided interventions, such as switching to prasugrel or ticagrelor, were employed. For instance, Elsayed et al. (2025) demonstrated a 40% reduction in adverse events among LOF carriers treated with ticagrelor compared to clopidogrel. These findings not only validate the clinical benefit of genotype testing but also support its integration into routine cardiovascular care pathways (Russmann et al., 2021).

In some settings, dose adjustment strategies have also proven beneficial. Haj Saleh and Youssef (2025) showed that increasing the clopidogrel dose in Syrian LOF carriers improved platelet inhibition rates from 41% to 67%. This suggests that in resource-limited regions where ticagrelor or prasugrel may be unavailable or unaffordable, intensified clopidogrel regimens could serve as a viable alternative. However, these strategies must be employed cautiously due to potential bleeding risks, especially in older or comorbid populations (Novkovic et al., 2018).

The role of pharmacogenetic testing in diverse populations further supports its utility. Studies from Colombia (Angulo-Aguado et al., 2021), Puerto Rico (Hernandez-Suarez et al., 2018), and India (Amarapalli et al., 2023) highlight that *CYP2C19* allele frequencies and their clinical impact vary across ethnic groups, necessitating localized implementation strategies. For instance, the prevalence of LOF alleles in the Colombian ACS cohort exceeded 40%, a rate associated with significantly poorer outcomes. This geographic variability underscores the importance of population-specific genetic screening policies.

Nonetheless, there remain key challenges in translating pharmacogenetics into widespread practice. One major concern involves cost-effectiveness. While upfront genotyping adds expense, long-term data suggest that avoiding recurrent MACE and hospital readmissions may offset initial costs (Patel et al., 2025). Furthermore, bedside genotyping platforms, as demonstrated by Al-Rubaish et al. (2020), offer rapid, point-of-care results, potentially eliminating logistical barriers that once hindered adoption.

Beyond genotype, the interaction between clopidogrel and other medications is an essential consideration. Biswas et al. (2021) found that the co-

prescription of proton pump inhibitors (PPIs) in LOF carriers significantly increased MACE risk. This pharmacodynamic interaction may blunt clopidogrel activation further and highlights the need for comprehensive medication reconciliation when tailoring therapy. As pharmacogenomic data become increasingly integrated into electronic medical records, automated alerts for drug–gene and drug–drug interactions may improve clinical safety.

Importantly, next-generation sequencing (NGS) may expand our understanding of rare *CYP2C19* variants. Morales-Rosado et al. (2021) identified non-*2/*3 alleles associated with stent thrombosis, revealing a spectrum of underreported polymorphisms. As sequencing costs decline, whole-genome or exome data may soon provide more nuanced risk assessments that move beyond a few well-known alleles. Future studies should explore whether these variants affect drug metabolism similarly and how best to integrate their interpretation into decision-support systems.

Despite the strength of evidence supporting genotype-guided therapy, some heterogeneity in results persists. Differences in clopidogrel metabolism may be confounded by age, BMI, comorbidities (e.g., diabetes), and lifestyle factors such as smoking—all of which independently affect platelet activity and drug responsiveness (Fathy et al., 2018). Moreover, a few studies, such as Cuisset et al. (2012), noted that even in non-carriers, high platelet reactivity was observed, suggesting that genetic testing should complement—not replace—clinical judgment and platelet function testing when feasible.

In summary, this review affirms the clinical importance of *CYP2C19* pharmacogenetics in clopidogrel-treated PCI patients. LOF allele carriers face higher risks of adverse cardiovascular events, which can be mitigated through genotype-guided therapy or dose modifications. Future research should address long-term cost-effectiveness, optimal implementation models, and broader genomic risk profiling. As precision cardiology continues to evolve, integrating genetic insights into standard care protocols offers a pragmatic path toward safer, more effective antiplatelet therapy.

Conclusion

This systematic review affirms the significant impact of *CYP2C19* polymorphisms on clopidogrel efficacy and clinical outcomes following PCI. Patients harboring loss-of-function alleles, particularly *CYP2C19* *2 and *3, consistently demonstrate reduced platelet inhibition and elevated risk of major adverse cardiovascular events such as stent thrombosis and myocardial infarction. Evidence across various populations underscores the need for genotype-informed therapy adjustments, including transitioning to ticagrelor or prasugrel or considering high-dose clopidogrel regimens. These personalized strategies not only enhance patient safety and therapeutic efficacy but also support the broader movement toward precision cardiovascular medicine.

Despite substantial supporting data, challenges remain in the widespread implementation of pharmacogenetic testing. Issues of cost, accessibility, infrastructure, and physician education continue to impede clinical uptake. Furthermore, interindividual variability due to non-genetic factors—such as drug interactions and comorbidities—necessitates a multifaceted approach to therapy optimization. Going forward, integrating rapid bedside genotyping with clinical decision-support tools and broader genomic panels may further refine patient stratification and expand the utility of pharmacogenetics in cardiovascular care.

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