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ORIGINAL RESEARCH

The Frequency of *CYP2C19*2* Gene Polymorphisms in Burkina Faso Patients Treated with Clopidogrel

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Purpose: The hepatic cytochrome P450 2C19 (CYP2C19) superfamily plays a crucial role in converting clopidogrel into its active form. Polymorphisms in *CYP2C19* significantly contribute to the interindividual variability observed, often resulting in persistent thromboembolic complications. This study aimed to assess the frequency of the *CYP2C19*2* (*rs4244285*, 681 G>A1) polymorphism among patients with cardiovascular diseases undergoing clopidogrel therapy.

Patients and Methods: This cross-sectional study recruited a total of seventy-three (73) patients from the Cardiology Department of the Centre Hospitalier Universitaire Yalgado Ouédraogo (CHU-YO) between January and June 2023. DNA was extracted from blood samples for *CYP2C19*2* genotyping using PCR-RFLP.

Results: Genetic analysis revealed frequencies of 65.8% for the wild-type CYP2C19*1/*1, 28.8% for the heterozygous CYP2C19*1/*2, and 2.7% for the homozygous variant CYP2C19*2/*2. The distribution of the genotypic frequencies was consistent with Hardy-Weinberg equilibrium ($p > 0.05$). The overall frequency of the *CYP2C19*2* allele in the study population was 16.4%, with 12.5% observed in females and 19.5% in males.

Conclusion: This study provides valuable insights into the frequency of the CYP2C19*2 polymorphism among cardiovascular patients in Burkina Faso, contributing to the limited data available on *CYP2C19* polymorphisms in sub-Saharan Africa. The presence of loss-of-function alleles suggests a potential risk for reduced drug efficacy in a subset of individuals. As one of the pioneering studies in the region, these findings emphasize the importance of further research to understand the clinical implications of *CYP2C19* polymorphisms.

Keywords: *CYP2C19*, polymorphism, PCR-RFLP, cardiovascular diseases, clopidogrel, Burkina Faso

Introduction

Cardiovascular disease (CVD), which has gender differences in prognosis, is the leading cause of morbidity and mortality worldwide.[1,2] CVDs disproportionately burdened low- and middle-income countries.[3,4] In Burkina Faso, the burden of CVDs has been escalating due to rapid urbanization, lifestyle changes, and limited access to healthcare resources.[5,6] Effective management of CVDs often involves antiplatelet therapy to prevent thrombotic events, with clopidogrel being one of the most commonly prescribed antiplatelet agents.[7]

Clopidogrel is a prodrug that requires hepatic biotransformation to produce its active metabolite, which inhibits the platelet $P2Y_{12}$ receptor and reduces platelet aggregation.[8,9] The cytochrome P450 (CYP) enzyme system, particularly the CYP2C19 isoenzyme, plays a crucial role in this metabolic activation.[7,10] The *CYP2C19* gene, located at chromosome 10q23.33, has been found to have over 39 different alleles and approximately 2000 identified single nucleotide

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polymorphisms (SNPs) to date.[11] Genetic polymorphisms in the *CYP2C19* gene can lead to variations in enzyme activity, affecting the therapeutic efficacy of clopidogrel.[12–14]

One of the most significant polymorphisms is the *CYP2C19*2* allele (G681A, *rs4244285*), a loss-of-function variant that results in reduced enzyme activity.[15,16] Carriers of the *CYP2C19*2* allele [$p < 0.001$; OR: 3.37 (95% CI 1.93–5.53) for GA genotype and ($p = 0.009$; OR: 4.81 (95% CI: 1.47–5.53) for AA genotype in non-responder versus responder) have been shown to exhibit decreased responsiveness to clopidogrel, leading to higher rates of adverse cardiovascular events such as stent thrombosis, myocardial infarction, and stroke.[15] The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides guidelines to interpret *CYP2C19* genotypes and their corresponding metabolic phenotypes.[17] Ultrarapid metabolizers (UM) (~5–30% of patients) have normal (*1/*17) or increased enzyme activity (*17/*17) due to alleles like *CYP2C19*17*. Extensive metabolizers (EM) (~35–50% of patients) exhibit normal enzyme activity, typically possessing two *CYP2C19*1* alleles. Intermediate metabolizers (IM) (~18–45% of patients) carry one functional allele and one loss-of-function allele (eg, *CYP2C19*1/*2* or *CYP2C19*1/*3*), resulting in reduced enzyme activity. Poor metabolizers (PM) (~2–15% of patients) have two loss-of-function alleles (eg, *CYP2C19*2/*2, CYP2C19*2/*3 or CYP2C19*3/*3*), leading to significantly impaired enzyme activity.[17] Understanding these genetic variations is essential in pharmacogenomics and precision medicine.

Pharmacogenomics, a key pillar of precision medicine, aims to tailor drug therapy based on an individual genetic makeup.[18] Among the critical genes influencing drug metabolism, *CYP2C19* plays a pivotal role in modulating the efficacy and toxicity of several widely prescribed medications, including antiplatelet agents, proton pump inhibitors, and antidepressants.[17] Variations in CYP2C19 activity have been linked to altered drug response, underscoring the importance of pharmacogenomic testing in clinical decision-making. Studies have shown that carriers of at least one *CYP2C19* reduced-function allele exhibit a 32.4% decrease in plasma exposure to clopidogrel active metabolite,[19] with the *CYP2C19*2/*2* genotype being a significant risk factor for multi-site arteriosclerosis[20] and strongly associated with clopidogrel resistance.[21] However, a Malaysian study demonstrated that genotype information does not correlate with clopidogrel response, suggesting that platelet activity testing may be a more reliable approach than genotyping in guiding clopidogrel therapy.[22] The prevalence of the *CYP2C19*2* variant varies across populations, with studies indicating higher frequencies in certain ethnic groups.[23] Despite the global recognition of pharmacogenetics in optimizing clopidogrel therapy, data on the impact of the *CYP2C19*2* variant in Sub-Saharan Africa populations, including those in Burkina Faso, remain scarce. Understanding the distribution of this genetic variant and its clinical implications is essential for tailoring antiplatelet therapy to individual patients, thereby improving clinical outcomes. This study reports the distribution of the CYP2C19*2 gene variant among patients undergoing clopidogrel treatment in Ouagadougou, Burkina Faso.

Materials and Methods

Ethical Considerations

All patients gave informed consent to participate in the study according to the Helsinki Declaration, and permission was obtained from the Ethics Committee for Health Research (CERS) of Burkina Faso (Deliberation no. 2022–11-244).

Study Population

This cross-sectional study enrolled 73 patients with cardiovascular diseases and undergoing clopidogrel treatment at the cardiology department of the Centre Hospitalier Universitaire Yalgado OUEDRAOGO (CHU-YO), Ouagadougou, Burkina Faso, from January to June 2023.[7] Burkina Faso, a landlocked country in West Africa, has an estimated population of approximately 24 million people as of mid-2025.[24] The nation is characterized by a diverse ethnic composition, with the Mossi ethnic group constituting about half of the population. The country exhibits a young demographic profile, with a median age of 17.7 years. The population density is approximately 88 individuals per square kilometer, with urban residents accounting for 33.7% of the total population.[24] The sample size was determined based on resource availability and prior studies of similar scope. Selection bias was minimized by recruiting consecutive patients meeting the eligibility criteria. Each case was included in the study if the patient has been under clopidogrel treatment for at least 6 months, is being followed in the Cardiology Department of the Centre Hospitalier Universitaire Yalgado Ouédraogo (CHU-YO) and has voluntarily agreed to participate

in the study by signing the informed consent form. Patients treated with clopidogrel for conditions such as acute coronary syndrome, arterial hypertension, ischemic stroke, pulmonary embolism with ischemic or mixed heart disease, decompensated myocarditis, chronic renal failure, and myocardial infarction were included in the study. A case was excluded from the study if the patient has refused to participate.

Sample Collection

Venous blood samples (5 mL) were collected in ethylenediaminetetraacetic acid (EDTA) tubes and sent to Laboratoire de Biologie Moléculaire et de Génétique (LABIOGENE), Université Joseph KI-ZERBO (UJKZ) for processing. Samples were centrifuged at 1500 rpm for 15 minutes to separate plasma and cellular pellets. Aliquots of both plasma and pellet components were then prepared and stored at −20 °C for subsequent molecular analyses.

DNA Isolation and Genotyping of CYP2C19 rs4244285

For molecular genetic analysis, DNA was isolated from pellet blood samples using the salting-out method as previously described.[25] Genotyping for the G681A variant of the CYP2C19 gene was conducted following an established protocol, using the polymerase chain reaction (PCR) method followed by restriction fragment length polymorphism (RFLP) analysis as described elsewhere.[26] The DNA fragments of the CYP2C19 gene were amplified using the commercial FIREPol® Master Mix 5X (Solis BioDyne, Europe) and specific oligonucleotide primers (Genecust, Boynes, France) in compliance with the conditions of the reaction (Table 1). The amplification products of DNA fragments were subjected to hydrolytic cleavage by restriction endonuclease *MspI* (New England Biolabs, Beverly, Mass., USA).

Statistical Analyses

Statistical data processing was performed using Microsoft Excel 2019 and Statistical Package for Social Sciences (SPSS) v.27 software (SPSS Inc., Chicago, IL, USA). In the analysis of the sociodemographic characteristics, the percentages and mean value ± standard deviation was calculated. Expected genotypic frequencies were calculated using the Hardy–Weinberg equilibrium (HWE) equation within a 95% confidence interval, and deviations from HWE were assessed with the chi-square test (χ^2), setting statistical significance at a P-value < 0.05. Patients with incomplete demographic or genetic data were excluded from analysis to ensure validity.

Results

Socio-Demographic and Clinical Characteristics of the Study Population

The study involved a total of 73 patients, 41 men (56.2%) and 32 (43.8%) women, diagnosed with cardiovascular diseases who were receiving clopidogrel as antiplatelet therapy for at least six months. Almost all patients reported having a good response to clopidogrel treatment. The detailed sociodemographic and clinical characteristics of patients are provided in our previous papers (Ouattara et al, 2024).

CYP2C19*2 Polymorphism

Hydrolytic cleavage of PCR products by the restriction endonuclease *MspI* yielded fragments of 120 bp and 49 bp for the GG genotype (extensive metabolizer), a single fragment of 169 bp for the AA genotype (poor metabolizer), and three fragments of 169 bp, 120 bp, and 49 bp for the GA genotype (intermediate metabolizer) of the *CYP2C19**2 allelic variant (Figure 1). The results revealed frequencies of 65.8% for the wild-type GG genotype, 28.8% for the heterozygous AG

Table 1 Sequences of Primers and Annealing Temperature

Name	Polymorphisms	Exon	Primers	Annealing	Size
CYP2C19*2	rs4244285, **681 G>A**	4	F5'-AATTACAACCAGAGCTTGGC-3' R5'-TATCACTTTCCATAAAAGCAAG-3'	57 °C	169 bp

Notes: 636 G>A: Guanine by Adenine substitution polymorphism at position 681.

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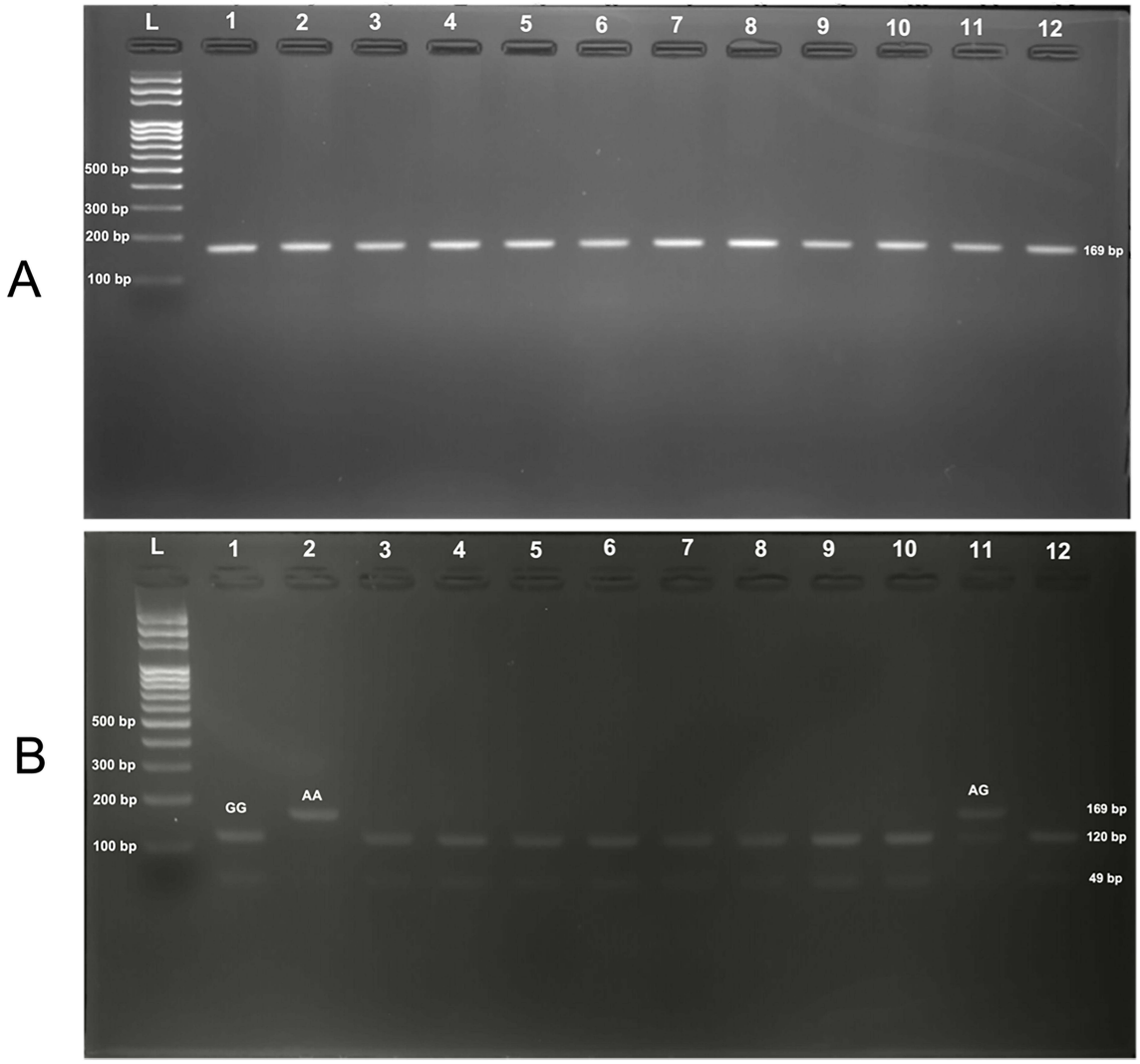

Figure 1 Gel electrophoresis of the PCR products. (**A**) PCR products before enzymatic digestion with *MSPI*. (**B**) PCR products after enzymatic digestion. L = ladder. Samples 1, 3–10 and 12 are wild type CYP2C19*1/*1 (GG) while sample 2 is homozygous variant CYP2C19*2/*2 (AA) and sample 11 is heterozygote CYP2C19*1/*2 (AG).

genotype, and 2.7% for the homozygous variant AA genotype (Table 2). The distribution of genotypes in the study population was in accordance with Hardy-Weinberg equilibrium. The comparison of these genotype frequencies between males and females was not statistically significant ($p > 0.05$).

Table 2 Allele and Genotype-Phenotype Distribution of CYP2C19*2 Gene in Burkina Faso Patients

***CYP2C19*2* Gene**	**Gender**		**HWE**		
Genotypes / phenotypes	**Females n (%)**	**Males n (%)**	**Total n (%)**	**Expected n (%)**	**P-value**
GG (*1/*1) / EM	25 (78.1)	25 (61.0)	50 (68.5)	50 (68.5)	0.908
GA (*1/*2) / IM	6 (18.8)	15 (36.6)	21 (28.8)	21 (28.8)	
AA (*2/*2) / PM	1 (3.1)	1 (2.4)	2 (2.7)	2 (2.7)	
Alleles					
G (*1)	28 (87.5)	33 (80.5)	61 (83.6)		0.532
A (*2)	4 (12.5)	8 (19.5)	12 (16.4)		

Abbreviations: EM, Extensive metabolizer; IM, Intermediate metabolizer; PM, Poor metabolizer.

Discussion

The present study investigated the prevalence of the *CYP2C19*2* gene variant (G681A, rs4244285) among patients undergoing clopidogrel therapy in Ouagadougou, Burkina Faso. The key findings indicate that the genotype distribution of *CYP2C19*2* in the study population was in accordance with Hardy-Weinberg equilibrium, suggesting a stable allele frequency within the population. We previously reported a high frequency of *CYP2C19*3* heterozygotes in the same population.[7] Additionally, there was no significant difference in genotype distribution between male and female patients, suggesting that both male and female patients are equally likely to carry the *CYP2C19*2* allele. This is important for clinical considerations, as it implies that gender-specific dosing adjustments of clopidogrel based on *CYP2C19*2* genotype may not be necessary in this population.

The *CYP2C19*2* allele is a well-documented loss-of-function variant that impairs the conversion of clopidogrel into its active metabolite, potentially leading to decreased antiplatelet efficacy and an increased risk of adverse cardiovascular events.[8,9] The frequency of the *CYP2C19*2* allele was 16.4% in the present study. These findings are consistent with previous studies conducted in African populations, which have reported varying frequencies of the *CYP2C19*2* allele but generally indicate a significant presence of this variant.[27] This variability underscores the importance of population-specific genetic studies to inform clinical decision-making. For instance, a study in Nigeria reported a *CYP2C19*2* allele frequency of 15.5%, while research in Tanzania and Uganda found frequencies of 12.6% and 17.9% respectively.[28,29] A comparison with other populations reveals notable interethnic differences in *CYP2C19*2* and *CYP2C19*3* allele frequencies. In the Thai population, *CYP2C19*2* was found at a frequency of *25.36*%, while *CYP2C19*3* was observed in 4.50% of individuals.[30] Interestingly, CYP2C19*3 was absent in several other populations, including Caucasian, Hispanic, African, Italian, Macedonian, Tanzanian, and North Indian populations. The presence of *CYP2C19*3* in the Thai population suggests a higher genetic diversity in certain Asian populations, which may influence drug response profiles.[30]

The high prevalence of the *CYP2C19*2* GG (68.5%) genotype (extensive metabolizer) in the present study population suggests that most patients possess normal CYP2C19 enzyme activity, which is crucial for the metabolic activation of clopidogrel into its active form. However, the presence of the heterozygous (intermediate metabolizer) AG genotype (28.8%) of patients and the homozygous variant AA (2.7%) genotype (poor metabolizer) indicates that a notable proportion of the population carries at least one copy of the loss-of-function *CYP2C19*2* allele. The c.681G>A mutation in exon 5 of *CYP2C19*2* disrupts a splice site, resulting in a frameshift that causes premature termination of translation.[31] This polymorphism is known to reduce the enzymatic activity of CYP2C19, potentially leading to decreased formation of clopidogrel's active metabolite and, consequently, reduced antiplatelet efficacy.[32] This has significant implications for the management of cardiovascular diseases, as inadequate platelet inhibition can result in serious complications such as stent thrombosis, myocardial infarction, or stroke.[33] Interestingly, despite the presence of the *CYP2C19*2* allele, almost all patients reported having a good response to clopidogrel treatment. This could be attributed to several factors such as: (i) individuals with the heterozygous AG genotype for *CYP2C19*2* (intermediate metabolizer) may retain sufficient CYP2C19 activity to effectively metabolize clopidogrel, although possibly at a reduced rate compared to those with the GG genotype (extensive metabolizer); (ii) alternative metabolic pathways involving other cytochrome P450 enzymes, such as CYP3A4 and CYP2B6,[34] may compensate for reduced CYP2C19 activity, aiding in the activation of clopidogrel; (iii) variability in clinical response assessment because patient-reported outcomes may not fully capture subtle differences in drug efficacy. Without objective measures like platelet aggregation tests or monitoring of adverse cardiovascular events, it is challenging to conclusively determine the clinical impact of the *CYP2C19*2* variant. Given these findings, there is a compelling case for considering pharmacogenetic testing for CYP2C19 variants in patients scheduled to receive clopidogrel, especially in regions where the *CYP2C19*2* allele is prevalent. Alternative antiplatelet agents that are not metabolized by CYP2C19, such as prasugrel or ticagrelor, could be considered for patients identified as carriers of loss-of-function alleles to enhance therapeutic outcomes. However, the implementation of routine genetic testing in resource-limited settings like Burkina Faso poses challenges, including cost, availability of testing facilities, and healthcare infrastructure limitations. Therefore, it may be necessary to develop cost-effective strategies, such as targeted testing for high-risk patients or population-specific guidelines that account for the genetic makeup of the patient population.

In addition to genetic variations, several non-genetic factors significantly influence clopidogrel response, including drug-drug interactions, physiological conditions, lifestyle factors, platelet function variability, and treatment adherence. Proton

pump inhibitors (PPIs), calcium channel blockers (CCBs), certain statins, antifungal agents, and SSRIs can inhibit CYP enzymes, reducing clopidogrel activation and efficacy.[35] Obesity, diabetes, chronic kidney disease (CKD), and liver dysfunction also impair clopidogrel metabolism, leading to reduced platelet inhibition.[36] Interestingly, smoking enhances clopidogrel efficacy by inducing CYP1A2 and CYP2B6, while grapefruit juice and excessive alcohol consumption may inhibit CYP enzymes, limiting drug activation.[35] Inflammation, particularly in acute coronary syndrome (ACS) and infections, increases platelet reactivity, diminishing clopidogrel's effect. Additionally, poor adherence to therapy and suboptimal dosing regimens (eg, using a 300 mg loading dose instead of 600 mg) can result in insufficient platelet inhibition, raising thrombotic risks. Given these multiple influencing factors, a personalized approach considering both genetic and non-genetic variables is crucial for optimizing clopidogrel therapy and improving cardiovascular outcomes.[35,36]

The study involved a relatively small cohort of patients, which may limit the generalizability of the findings. Larger studies are needed to confirm the prevalence of the *CYP2C19*2* allele in the broader population. The *CYP2C19*17* allele, a gain-of-function variant, was also not assessed. Individuals carrying CYP2C19*17 exhibit ultrarapid metabolism (UM), which could impact clopidogrel effectiveness and increase bleeding risks. The assessment of clopidogrel response was based on patient reports rather than objective clinical endpoints or laboratory measurements. Future studies should include comprehensive genotyping of all relevant *CYP2C19* alleles, platelet function tests and monitoring of cardiovascular events to accurately evaluate the impact of the *CYP2C19*2* polymorphism on treatment outcomes.

Conclusion

This study highlights a significant prevalence of the *CYP2C19*2* polymorphism among patients receiving clopidogrel in Ouagadougou, Burkina Faso. While most patients reported a good response to treatment, the presence of loss-of-function alleles suggests a potential risk for reduced drug efficacy in a subset of individuals. These findings emphasize the need for increased awareness of genetic factors influencing clopidogrel metabolism and support the consideration of personalized therapeutic approaches.

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Disclosure

The authors report no conflicts of interest in this work.

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