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Research Article
High Frequency of CYP2C19*3 Heterozygotes Among Patients Under Clopidogrel Treatment in Ouagadougou, Burkina Faso

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Abstract

Background and Objective: Despite its widespread use in cardiology, patient's response to clopidogrel exhibits significant interindividual variability, often leading to persistent thromboembolic complications. The hepatic Cytochrome P450 2C19 (CYP2C19) superfamily plays a pivotal role in clopidogrel's conversion to its active form and CYP2C19 polymorphisms significantly contribute to this variability. This study aimed to evaluate the prevalence and impact of the CYP2C19 rs4986893 polymorphism on clopidogrel treatment response. **Materials and Methods:** Seventy-three patients with Cardiovascular Diseases (CVD) undergoing clopidogrel antiplatelet therapy for a minimum of six months were recruited from Centre Hospitalier Universitaire Yalgado Ouédraogo (CHU-YO). Sociodemographic data were collected and DNA was extracted from blood samples for CYP2C19 rs4986893 genotyping using PCR-RFLP. **Results:** The patient's mean age was 62.56±13.45 years, ranging from 23 to 94 years, with a male-to-female sex ratio of 1.28. Most patients came from the informal sector, primarily of Mossi ethnicity and residing in Ouagadougou. Acute coronary syndromes (ACS) and hypertension were the predominant reasons for consultation, with clopidogrel showing efficacy in 97.3% of cases. While 72.6% had no family history of CVD, hypertension was prevalent among those with familial cardiovascular conditions. Genetic analysis revealed a 65.8% frequency of heterozygotes CYP2C19*1/*3, with no mutant homozygotes CYP2C19*3/*3 detected. The results of the present study underscore a high prevalence of heterozygotes CYP2C19*1/*3 among patients with cardiovascular diseases. **Conclusion:** This intermediate metabolic phenotype, along with a good response to clopidogrel, suggests that CYP2C19*1/*3 genotype promotes a favourable response to clopidogrel therapy.

Key words: CYP2C19, polymorphism, PCR-RFLP, cardiovascular diseases, clopidogrel, Burkina Faso

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Coronary heart diseases, including chronic coronary syndrome (CCS), stable angina and acute coronary syndrome (ACS), are associated with high mortality and morbidity rates leading to disability[1]. It is estimated that more than 7 million people experience ACS worldwide each year, with over 1 million patients hospitalized in the United States due to ACS[2]. Dual antiplatelet therapy with aspirin and clopidogrel is the standard treatment recommended in many guidelines for managing type I ACS[2]. Clopidogrel (Plavix®) is a thienopyridine prodrug that undergoes activation in the liver through a 2-step oxidative biotransformation process[3]. The hepatic enzyme CYP2C19 plays a crucial role in the activation of clopidogrel to its active thiol metabolite (MTA), known as R130964 (clop-AM). This metabolite irreversibly binds to the P2Y12 adenosine diphosphate (ADP) receptor, exerting its antiplatelet activity[4]. Despite its widespread use in cardiology, patient's response to clopidogrel exhibits significant interindividual variability, leading to persistent thromboembolic complications. This variability has prompted the consideration of "resistance" to treatment, for which several mechanisms are proposed. One such mechanism is genetic mutations affecting CYP2C19, contributing to the multifactorial origin of interindividual variability in response to clopidogrel[3,4]. The CYP2C19 gene is highly polymorphic, with over 35 star allele haplotypes (*) that include rare gene deletions[5]. The mutations responsible for genetic polymorphisms can result in a reduced function (CYP2C19*9), loss of function (CYP2C19*2 and *3), or gain of function (CYP2C19*17) of the mutant enzyme compared to the normal enzyme (CYP2C19*1)[2,5].

Among the polymorphisms associated with a loss of function of the enzyme, the CYP2C19*2 SNP (rs4244285) is the most common, with an allele frequency estimated at approximately 15% in Africans and Caucasians and 29-35% in Asians[2]. Other known loss-of-function alleles are much less common, with an allele frequency of less than 1% each, except CYP2C19*3 in Asians (2-9%)[6]. Despite its use in cardiology, to the best of our knowledge, there is no data on the effect of CYP2C19 polymorphisms and the response to clopidogrel treatment in patients with cardiovascular diseases in Burkina Faso. This study aimed to evaluate the prevalence and impact of the CYP2C19 rs4986893 polymorphism on clopidogrel treatment response. A high frequency of CYP2C19*1/3 heterozygotes was observed in patients under clopidogrel treatment, with almost all showing no poor response after 6 months of treatment.

MATERIALS AND METHODS

Study design: This study was conducted in Ouagadougou, the capital of Burkina Faso. Samples were collected at the Cardiology Department of the Center Hospitalier Universitaire Yalgado Ouédraogo. The various molecular analyses were performed at the Laboratory of Molecular Biology and Genetics of the Training and Research Unit in Life and Earth Sciences at Joseph KI-ZERBO University, Burkina Faso.

Type and period of the study: This was a descriptive-analytical study that took place over a period of 6 months, from January to June, 2023 and aimed at determining the prevalence of rs4986893 (CYP2C19*3) as well as the correlation between these polymorphisms and the response to clopidogrel.

Ethical considerations: The study received approval from the Ethics Committee for Health Research (CERS) of Burkina Faso (Deliberation no. 2022-11-244). Each study participant gave his or her free and written informed consent according to the Helsinki Declaration. Anonymity and confidentiality were strictly maintained throughout the collection and analysis of samples.

Study population: The present study recruited patients undergoing clopidogrel treatment at the Cardiology Department of Ouagadougou University Hospital during the collection period. Patients who met the inclusion criteria had previously provided their voluntary and informed consent to participate in the study, adhering to the principles outlined in the Declaration of Helsinki. Subsequently, these patients were administered a questionnaire to gather sociodemographic data, including age, gender, treatment duration, response to treatment, level of study/schooling, parental ethnicity, occupation, place of residence and medical data.

Table 1: Primer sequences and PCR conditions

Name	Polymorphisms	Exon	Primer	Annealing	Size
CYP2C19*3	rs4986893, 636 G>A[1]	4	F5'-AAATTGTTTCCAATCATTTAGCT-3' R5'-ACTTCAGGGCTTGGTCAATA-3'	57°C	271 bp[1]

636G>A: Guanine by adenine substitution polymorphism at position 636

Sample collection: Venous blood samples (5 mL) were collected in Ethylenediaminetetraacetic Acid (EDTA) collection tubes. The collected samples were subsequently sent to the LABIOGENE, UJKZ for processing. Upon arrival, the samples were centrifuged at 1500 rpm for 15 min to separate the plasma and pellet components. Aliquots of both plasma and pellets were then prepared and stored at -20°C for subsequent molecular analyses.

DNA extraction: The genomic DNA was extracted from the blood pellet using the salting-out method as previously described by Miller *et al.*[7] and Ouattara *et al.*[8]. The quantity and purity of the DNA extracts were evaluated using a spectrophotometer, specifically the NanoDrop (Isogen Life Science, Utrecht, The Netherlands). The DNA samples with an A260/A280 absorbance ratio falling within the range of 1.8 to 1.9 were considered to have good purity and were used for genotyping purposes. Any DNA extracts with an absorbance below 1.8 or above 1.9 were subjected to re-extraction to ensure optimal purity before proceeding with genotyping.

PCR-RFLP: Genotyping of CYP2C19*3 variants (rs4986893, 636 G>A) was performed using PCR-RFLP (Polymerase Chain Reaction-Restriction Fragment Length Polymorphism) following the protocol outlined by Babalola *et al.*[9] (Table 1). The PCR amplification of exon 4 (CYP2C19*3) was carried out according to the following program: Initial denaturation step at 95°C for 5 min. Followed by 40 cycles of amplification with denaturation at 94°C for 1 min. Hybridization at 56°C for 1 min. Elongation at 72°C for 1 min. Final extension step at 72°C for 7 min[8,9]. The PCR was carried out in a reaction volume of 25 µL consisting of 4 µL of Master Mix (2X), 0.5 µL of sense and antisense primers (1 µM) and 2 µL of DNA (50-100 ng/µL) of each sample then make up to 25 µL with sterile water. The PCR products were subjected to enzymatic digestion using the restriction enzyme BamHI at 37°C for 1 hr to detect the CYP2C19*3 variants. Subsequently, these digested products underwent electrophoresis on a 3% agarose gel. The bands were visualized under UV light following electrophoretic migration to determine and discriminate wild-type alleles from mutants.

Statistical analysis: Data were recorded in Excel 2019 and analyzed using Statistical Package for Social Sciences (SPSS) 17.0 and Epi Info version 7 software. Results were presented as percentages and Mean±Standard Deviation, with observed frequencies considered and represented using a 95% confidence interval. Expected genotypic frequencies were determined using the Hardy-Weinberg equation (HWE) and the Chi-square test (χ^2) assessed the deviation of genotypic frequencies from HWE, with statistical significance set at a p-value below 0.05.

RESULTS

Socio-demographic characteristics of the study population: The study population consisted of 73 patients with cardiovascular diseases undergoing antiplatelet treatment with clopidogrel. The sex ratio favored men, with a ratio of 1.28. The mean age of the patients was 62.56±13.45 years, ranging from 23-94 years. Most patients resided in Ouagadougou (59/73, 80.8%), were over 60 years old (46/73, 63.0%) and worked in the informal sector (52/73, 71.2%). Additionally, most patients belonged to the Mossi ethnic group (50/73, 68.5%) (Table 2).

Table 2: Sociodemographic characteristics of the study population

Characteristics	Number	Percentage
Age group (years)		
20-40	3	4.1
40-60	24	32.9
60-94	46	63.0
Gender		
Male	41	56.2
Female	32	43.8
Profession		
Formal sector	21	28.8
Informal sector	52	71.2
Ethnic groups		
Mossi	50	68.5
Non-Mossi	23	31.5
Residence		
Ouagadougou	59	80.8
Others	14	19.2

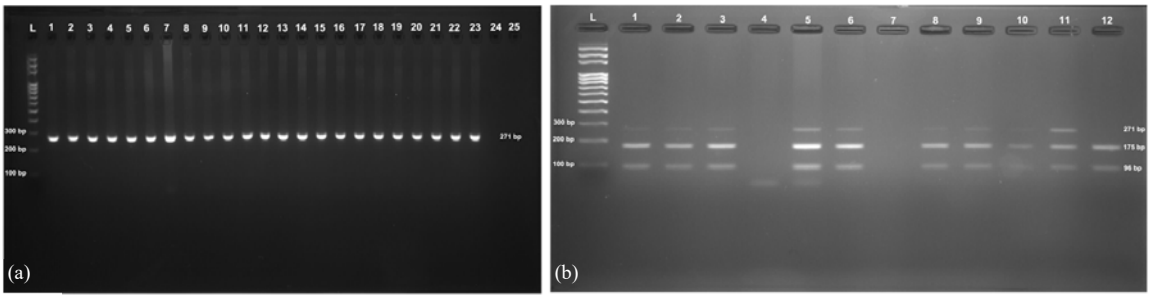

Fig. 1(a-b): Gel electrophoresis of the PCR products, (a) PCR products before enzymatic digestion with BamHI and (b) PCR products after enzymatic digestion

Samples 1-3, 5,6 and 8-11 are heterozygotes CYP2C19*1/*3 while sample 12 is wild type CYP2C19*1/*1 and L: Ladder

Table 3: Clinical data of the study population

Characteristics	Number	Percentage
Reason for consultation		
Ischemic heart disease (post-ACS)	22	30.1
High blood pressure	19	26.0
Ischemic stroke	11	15.1
Hypertensive heart disease	10	13.7
Myocardial infarction	7	9.6
Other cardiovascular diseases	4	5.5
Treatment effectiveness	50	68.5
Yes	71	97.3
I don't know	2	2.7
Family history		
None	53	72.6
High blood pressure	16	21.9
Ischemic stroke	2	2.7
Stroke	2	2.7

Table 4: Allelic and genotypic frequencies of CYP2C19*3 by sex and comparison of the total with the expected numbers using the Hardy-Weinberg equation

CYP2C19*3	Gender		HWE			
Genotypes	Female n (%)	Male n (%)	Total n (%)	Expected n (%)	χ^2	p-value
GG (*1/*1)	11 (34.4)	14 (34.1)	25 (34.2)	33 (45.2)	-	-
GA (*1/*3)	21 (65.6)	27 (65.9)	48 (65.8)	32 (43.8)	17.5127	< 0.001
AA (*3/*3)	0 (0.0)	0 (0.0)	0 (0.0)	8 (11.0)	-	-
Alleles						
G (*1)	43 (67.2)	55 (67.1)	98 (67.1)	-	-	-
A (*3)	21 (32.8)	27 (32.9)	48 (32.9)	-	-	-

Clinical data: Coronary syndromes and high blood pressure (hypertension) were the two main reasons for consultation and clopidogrel was effective in almost all patients (71/73, 97.3%). Most patients (53/73, 72.6%) had no family history, while among those who did, hypertension was the predominant familial association (Table 3).

CYP2C19*3 polymorphism: The amplification of the CYP2C19 gene exon 4 with specific primers results in the generation of a 271 bp fragment. Enzymatic digestion of PCR products with BamHI yields two bands of 175 and 96 bp for the wild CYP2C19*1 allele and a single band of 271 bp for the mutant CYP2C19*3 allele, while heterozygotes will exhibit 3 bands (Fig. 1a-b).

The results revealed a high frequency (65.8%) of heterozygotes (*1/*3), with no mutant homozygotes (*3/*3) detected within the current study population (Table 4). It's worth noting that the comparison of genotype frequency between men and women did not show statistical significance ($p<0.05$).

DISCUSSION

The incidence of cardiovascular and cerebrovascular diseases is steadily rising worldwide, particularly in developing countries like Burkina Faso. These diseases are multifactorial in nature and their treatment can be influenced by drug-metabolizing enzymes such as cytochromes P450 (CYP)[10].

Here, the frequency of the rs4986893 (636G>A) polymorphism of CYP2C19 was evaluated, as well as its impact on the response to treatment of patients on clopidogrel followed in the cardiology department of the CHU-YO.

The age of the patients in the present study population ranged from 23-94 years with a mean of 62.56±13.45 years. The majority (63.01%) of these patients were also aged between 60 and 94 years, with aging being a contributing factor to the development of cardiovascular diseases[11]. Previous studies conducted by the present research team have reported average ages of 48.98±11.32 years[12,13] and 51±10.01 years in hypertensive patients in Burkina Faso[14]. Most patients in the present study population resided in urban areas (80.8%), with a sex ratio of 1.28 in favor of men, while the informal sector was the most affected (71.23%). It's worth noting that the study was conducted in Ouagadougou, the largest urban center in Burkina Faso. The lower participation of rural populations could be attributed to factors such as distance and lack of financial means. Sex differences in cardiovascular diseases stem from the combined expression of genetic and hormonal variances between women and men[14]. Cardiovascular diseases can be classified into those that are sex-specific and those that exhibit differences in terms of incidence, prevalence, etiology, symptomatology, response to treatment, morbidity and mortality between genders[14]. In the context of Burkina Faso, it's important to note that men are more exposed to stress and intense activities, particularly in the informal sector. The Mossi, the majority ethnic group in Burkina Faso, were predominant in the present study population.

Elevated systolic blood pressure (SBP) is one of the main risks to global health[15]. Acute coronary syndromes (ACS) and high blood pressure (hypertension) were the primary reasons for patients seeking consultation in the present study. Hypertension was noted as the predominant family history. Indeed, hypertension continues to be recognized as the most significant cardiovascular risk factor[15]. All patients in the present study were undergoing clopidogrel treatment for a minimum of 6 months, which proved effective in 97.3% of cases. Genetic analyses revealed a high frequency (65.8%) of heterozygotes (CYP2C19*1/*3) and an absence of homozygous mutants (CYP2C19*3/*3) within the present study population. The CYP2C19*2 (rs4244285, 681G>A) and CYP2C19*3 (rs4986893, 636G>A) are considered loss-of-function (LOF) alleles associated with reduced platelet response to clopidogrel or an increased incidence of resistance to clopidogrel[16]. These findings indicate that the metabolic phenotype of mutant heterozygotes (CYP2C19*1/*3), considered intermediate, leads to a favorable response to clopidogrel treatment. A recent study examining the association between CYP2C19 polymorphisms and cardiovascular diseases suggested that the CYP2C19*1/*3 genotype could serve as an independent protective factor against atherosclerosis[17]. The allele frequencies were 67.1% for the wild-type allele (G) and 32.9% for the mutant allele (A). The absence of the CYP2C9*3 allele has been previously reported in studies conducted in Benin *et al.*[18] and Ghana *et al.*[19]. The high frequency of the CYP2C9*3 mutant allele in the present study population necessitates further investigation into its role in cardiovascular diseases in Burkina Faso.

One of the limitations of the present study was the absence of patients who showed a poor response to clopidogrel, which prevented an analysis of the association between subgroups of poor and normal metabolizers. It would have been valuable to conduct plasma MTA dosage, the active metabolite of clopidogrel and compare levels between groups carrying and not carrying the SNP. While determining the frequency of CYP2C19*3, which is crucial for clopidogrel response, it's important to note that several other alleles influencing loss or gain of function, such as CYP2C19*2 and CYP2C19*17, were not studied and their contribution cannot be ruled out. Nonetheless, to the best of our knowledge, this study represents one of the first in Burkina Faso to shed light on the frequency of CYP2C19 polymorphisms in cardiovascular disease patients and their impact on clopidogrel response.

CONCLUSION

The present study highlights a high prevalence of CYP2C19*3 heterozygotes (rs4986893, 636G>A) among patients with cardiovascular diseases undergoing clopidogrel treatment. Despite the significant number of intermediate metabolizers, most patients exhibited a good response to treatment, suggesting that heterozygosity for CYP2C19*3 enables a favorable response to clopidogrel. Extending the analyses to include CYP2C192* (rs4244285, 681G>A) as well as CYP2C19*17 (rs12248560, -806 C>T), would have provided valuable insights into the role of the enzyme CYP2C19 in clopidogrel metabolism within the present study population.

SIGNIFICANCE STATEMENT

Variations leading to changes in the activity of drug-metabolizing enzymes such as CYP2C19 can categorize individuals into fast, intermediate or poor metabolizers, thereby affecting treatment. This study investigated how a specific genetic variation in CYP2C19 affects the effectiveness

of clopidogrel, a medication used to prevent blood clots in people at high risk of cardiovascular events. The CYP2C19 variations were assessed in patients with cardiovascular disease who had been treated with clopidogrel for at least 6 months. Although most patients were intermediate metabolizers, clopidogrel treatment was effective in almost all of them. No poor metabolizers were found in this study. This pioneering study in Burkina Faso suggests that individuals with normal and intermediate metabolism potentially have a good response to clopidogrel treatment.

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