BMC Cardiovascular Disorders

RESEARCH Open Access

The frequencies of CYP2C19*2, *3, and *17 alleles and their impact on the clinical efficacy of doubled maintenance dose of clopidogrel in Syrian patients with coronary artery disease

Nour Haj Saleh[1] and Lama A. Youssef[1,2*]

Abstract

Background Genetic variations in the *CYP2C19* gene, which encodes the major enzyme responsible for activating clopidogrel, may influence response to Clopidogrel antiplatelet therapy. This study aimed to assess the prevalence of *CYP2C19* variants in Syrian patients with coronary artery disease (CAD) and evaluate the impact of these variants on the clinical efficacy of a doubled maintenance dose of clopidogrel following percutaneous coronary intervention (PCI).

Methods This study included 50 Syrian CAD patients on dual antiplatelet therapy (DAPT) with a doubled maintenance dose of clopidogrel. *CYP2C19* genotypes were determined by PCR, followed by Sanger sequencing. Clinical outcomes, including major acute cardiovascular events (MACE) and bleeding events, were monitored over 18–24 months.

Results The allele frequencies were 8% for *CYP2C19*2*, 0% for *CYP2C19*3*, and 17% for *CYP2C19*17*. The distribution of our study population by CYP2C19 genotype-predicted metabolizer phenotypes was 56% for normal metabolizers (NMs), 26% for intermediate metabolizers (IMs), 12% for rapid metabolizers (RMs), and 2% for ultra-rapid metabolizers (UMs). No association was found between the *CYP2C19*2* allele and recurrent ischemic events or between the *CYP2C19*17* allele and bleeding complications in patients treated with a doubled maintenance dose of clopidogrel.

Conclusions In Syrian patients undergoing PCI, a doubled maintenance dose of clopidogrel (150 mg/day) may help mitigate variability in response due to *CYP2C19*2* carrier status, offering potential benefits in optimizing antiplatelet therapy. However, given the study's limited sample size, these findings should be interpreted with caution, and larger studies are needed to confirm this potential benefit.

Keywords Clopidogrel, Doubled maintenance dose, *CYP2C19*, Genotyping, *CYP2C19*2*, *CYP2C19*3*, *CYP2C19*17*, Syria

*Correspondence:
Lama A. Youssef
ylama@hotmail.com; lama.youssef@damascusuniversity.edu.sy
[1]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Damascus University, April 17th street, Al-Mazzeh, Damascus, Syria
[2]National Commission for Biotechnology, Damascus, Syria

Background

Coronary artery disease (CAD), also known as ischemic heart disease (IHD), is a widespread health condition and one of the leading causes of death worldwide. This condition is characterized by an imbalance between myocardial oxygen supply and demand, primarily arising due to atherosclerosis of the coronary arteries [1]. Percutaneous coronary intervention (PCI) is a minimally invasive, nonsurgical procedure utilized in the management of IHD, with the aim of relieving the stenosis or obstruction of coronary arteries by restoring blood flow to the affected area, commonly achieved by inflating a balloon or deploying a stent [2]. Following stenting, a dual antiplatelet therapy (DAPT) is administered to patients, comprising aspirin and an oral P2Y12 receptor antagonist (clopidogrel, prasugrel, or ticagrelor), to prevent stent thrombosis and reduce the likelihood of major acute cardiovascular events (MACE) [3].

Clopidogrel, a second-generation thienopyridine, is a prodrug absorbed through the intestines via the P-glycoprotein pump following oral administration. Once absorbed, it undergoes metabolism via two primary pathways. The first pathway involves esterase enzymes, resulting in the hydrolysis of clopidogrel to a non-active carboxylic acid derivative, which accounts for 85% of the parent drug. The second pathway involves two sequential oxidative steps mediated by a group of cytochrome P450 enzymes, mainly CYP2C19. The initial step involves the oxidation of clopidogrel to an intermediate metabolite, 2-oxo-clopidogrel, followed by a second step in which an active thiol metabolite is formed [4]. The resulting metabolite specifically and irreversibly binds to the P2Y12 adenosine diphosphate receptors on platelets, inhibiting platelet aggregation and preventing blood clot formation [5]. Despite the well-established benefits of clopidogrel, a considerable portion of patients exhibit a limited response to its antiplatelet effect, leading to recurrent ischemic events after PCI [6].

The response to clopidogrel has substantial interpatient variability, which has received close attention. Several potential mechanisms have been proposed, likely to be multifactorial, depending on pharmacokinetic, pharmacodynamic, and pharmacogenomic factors. Considering that the CYP2C19 enzyme plays a pivotal role in the hepatic activation of clopidogrel, the examination of CYP2C19 polymorphisms has come to the forefront of clopidogrel pharmacogenetic research [7].

The *CYP2C19* gene is located on chromosome 10q23.33 within the *CYP2C* gene cluster and comprises nine coding exons and eight introns. This gene is highly polymorphic, with the Pharmacogene Variation (PharmVar) Consortium cataloging over 35 different star alleles, each with varying levels of evidence. The majority of these alleles result from specific combinations of single nucleotide polymorphisms (SNPs), while a few arise from copy number variation (CNV), such as the **36* and **37* alleles, which represent complete and partial deletion of the *CYP2C19* gene, respectively [9, 10]. The most common non-functional alleles that contribute to poor and intermediate metabolizer phenotypes are *CYP2C19*2* (rs4244285; c.681G > A) and *CYP2C19*3* (rs4986893; c.636G > A). In contrast, *CYP2C19*17* (rs12248560; -806 C > T) is a gain-of-function allele associated with increased gene transcription, resulting in rapid metabolizers (RMs) or ultra-rapid metabolizers (UMs) depending on the copy number of the *CYP2C19*17* allele that the individual carries [9].

Considering the absence of studies reporting the prevalence of *CYP2C19* polymorphisms in the Syrian population, a highly admixed Mediterranean population, our study aimed to determine the frequencies of the most clinically relevant *CYP2C19* alleles among Syrian patients undergoing PCI and assess the impact of these genetic variations on the clinical response to a double maintenance dose of clopidogrel presented by patients' cardiovascular outcomes.

Methods

Study design and ethics approval

This prospective cohort study was approved by the Scientific Research Bioethics Committee of the Faculty of Pharmacy, Damascus University, in accordance with the World Medical Association Declaration of Helsinki. Informed consent was obtained from all individuals who participated in the study in compliance with ethical standards.

Sample collection

Between June 2020 and January 2021, patient eligibility assessments were conducted at three medical institutions in Damascus, Syria: Martyr Bassel al-Assad Heart Hospital, Damascus Hospital, and Al Fayhaa Hospital. The inclusion criteria were CAD patients aged 18 years or older who underwent PCI and were prescribed DAPT with a double maintenance dose of clopidogrel 150 mg/day (for at least one month after PCI). Patients were excluded if they were prescribed the standard dose of Clopidogrel (75 mg/day), or if they were taking other adenosine diphosphate (ADP) receptor antagonists like Ticagrelor or Prasugrel. Eligible patients participated in face-to-face interviews, during which relevant information (Additional File 1), such as age, gender, body weight, height, smoking status, medical history, and concomitant medication use, were recorded. Furthermore, a peripheral blood sample (5 mL) was collected from each participant using an EDTA tube.

DNA extraction

Genomic DNA (gDNA) was extracted from whole blood samples using a Blood DNA Preparation Solution Kit (Jena Bioscience®, Jena, Germany) following the manufacturer's protocol. The quality and purity of the extracted gDNA were assessed using a NanoDrop device (MaestroGen®, Hsinchu City, Taiwan). For analysis, two µL of gDNA were loaded onto the lens of the NanoDrop and measured at a wavelength of 260/280 nm. The NanoDrop lens was meticulously cleaned with distilled water and a cotton swab after each measurement to ensure accuracy and prevent contamination. Subsequent measurements were performed on the remaining samples.

*CYP2C19 *2, *3* and **17* genotyping

Genotyping of *CYP2C19*2* (rs4244285), *CYP2C19*3* (rs4986893), and *CYP2C19*17* (rs12248560) was performed using polymerase chain reaction (PCR), followed by Sanger sequencing of the amplicons. The PCR reactions were carried out using the Labcycler Basic (011–103) device (SensoQuest GmbH®, Göttingen, Germany), using specific primers and implementing the conditions outlined in Table 1. The targeted locations of the forward and reverse primers for each investigated SNP are illustrated in Fig. 1. a. Each PCR reaction had a final volume of 20 µl and included 50 ng of gDNA, five pmol of 10 pmol/µL of each the forward and reverse primer, and ten µl of 2X Master Mix (Kapa Biosystems®, Wilmington, USA). The resulting PCR products were separated by gel electrophoresis using a (1.5%) agarose gel, stained with ethidium bromide, and visualized under ultraviolet (UV) light (Additional File 2). The observed bands were documented using a digital camera and compared to a 100-bp DNA ladder for identification purposes. Subsequently, 150 PCR amplification products were sent to Macrogen (Seoul, South Korea) for sequencing.

Sequencing reactions were performed using the MJ Research PTC-225 Peltier Thermal Cycler device and ABI PRISM®BigDyeTM Terminator Cycle Sequencing Kit with AmpliTaq® DAN polymerase (Applied Biosystems®, Waltham, USA). The resulting fluorescently labeled fragments were purified to remove unincorporated terminators using the BigDye® XTerminator™ purification protocol. The purified samples were resuspended in distilled water and subjected to electrophoresis using an ABI 3730xl sequencer (Applied Biosystems®, Waltham, USA). Geneious Prime® software (Biomatters Ltd, Auckland, New Zealand) was used to analyze the sequencing chromatograms and to identify the frequencies of the studied alleles (Additional File 3). Moreover, by using the length of the PCR products, we were able to screen for four additional core SNPs (rs6413438, rs140278421, rs375781227, and rs370803989) that define the **10*, **22*,**26*, and **33* alleles, respectively.

Phenotype prediction

Patient phenotypes were classified according to the guidelines established by the Clinical Pharmacogenetics Implementation Consortium (CPIC) for CYP2C19 Genotype and Clopidogrel Therapy, updated in January 2022. According to these guidelines, individuals who carry two copies of the gain-of-function allele *CYP2C19*17* are considered ultrarapid metabolizers (UMs). Those with one copy of the *CYP2C19*17* allele and one copy of the normal function allele *CYP2C19*1* are classified as rapid metabolizers (RMs). Individuals carrying two copies of the normal function allele *CYP2C19*1* are designated as normal metabolizers (NMs). In contrast, individuals with

Table 1 Primers sequences and PCR conditions

Allele	Primers		PCR Conditions				Product Size
			Step	Tm°C	Time	# of Cycles	
*CYP2C19*2*	F	5′-ACAACCAGAGCTTGGCATATT-3′	Initial Denaturation	95	5 min		203 bp
			Denaturation	95	20 s	40	
			Primer Annealing	54.4	30 s		
	R	5′-TGTCCATCGATTCTTGGTGT-3′	Extension	72	30 s		
			Final Extension	72	10 min		
*CYP2C19*3*	F	5′-ATTGTTTCCAATCATTTAGCTTCAC-3′	Initial Denaturation	94	5 min		269 bp
			Denaturation	94	1 min	37	
			Primer Annealing	52	45 s		
	R	5′-ACTTCAGGGCTTGGTCAATA-3	Extension	72	30 s		
			Final Extension	72	5 min		
*CYP2C19*17*	F	5′-GCCCTTAGCACCAAATTCTC-3′	Initial Denaturation	95	3 min		473 bp
			Denaturation	94	1 min	35	
			Primer Annealing	56.3	1 min		
	R	5′-ATTTAACCCCCTAAAAAAACACG-3′	Extension	72	1 min		
			Final Extension	72	10 min		

Abbreviations: F = forward; R = reverse; Tm = temperature

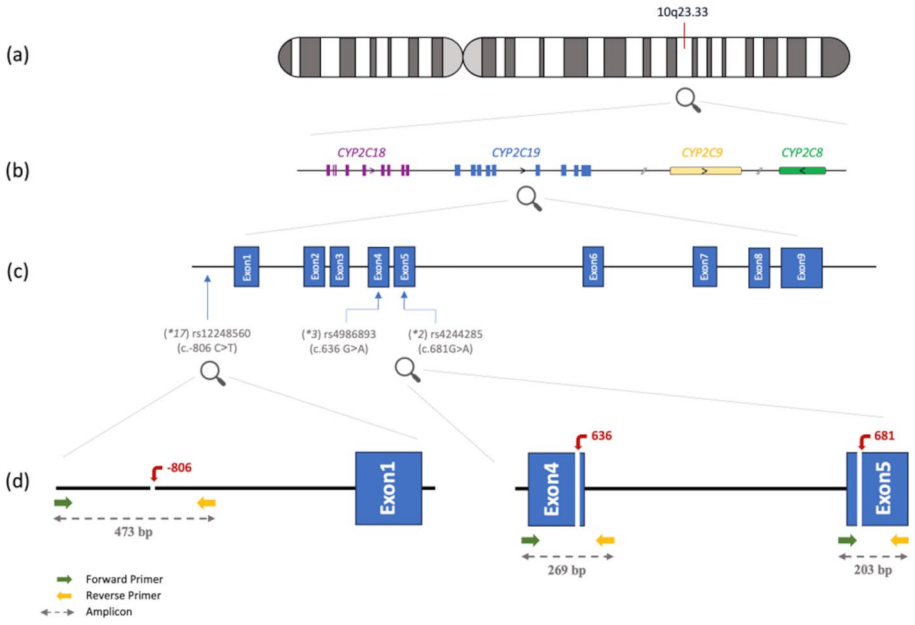

Fig. 1 Schematic representation of the *CYP2C19* gene location, structure, studied SNPs, and primer positions. (**a**) Human chromosome 10 with the 10q.23.33 band marked by a red vertical line. (**b**) A cluster of four cytochrome P450 genes including *CYP2C18*, *CYP2C19*, *CYP2C9*, and *CYP2C8*. (**c**) Core sequence variations defining *CYP2C19*2*, **3* and, **17* alleles. (d) Targeted locations of the forward and reverse primers for each of the studied SNPs. Forward and reverse primers are represented by green and yellow arrows, respectively. The arrow's tip indicates the 5′➔3′ orientation of the primers. The dotted lines depict the PCR product lengths for each primer set

one copy of a non-functional allele (either *CYP2C19*2* or *CYP2C19*3*) along with either a normal function or gain-of-function allele are designated as intermediate metabolizers (IMs). Finally, patients with two copies of a non-functional allele are categorized as poor metabolizers (PMs).

Follow-up

A follow-up period of 18-24 months was conducted for patients, during which they were contacted via phone calls. The purpose of this follow-up was to assess adherence to the prescribed medication regimen and evaluate the occurrence of any subsequent cardiovascular events following the PCI procedure. The assessed cardiovascular events included refractory angina symptoms, MACE, and bleeding events.

Statistical analysis

Data were analyzed using GraphPad Prism® 9.2.0 (283) (GraphPad Software Inc., California, USA) and SPSS® version 26 (IBM Corp, NY, USA). Categorical data were represented as frequency and percentage, while quantitative data that showed a normal distribution were expressed as the mean ± standard deviation. Genotype frequencies were tested for deviations from Hardy–Weinberg equilibrium (HWE) using chi-square analysis. The relationship between genetic and non-genetic variables and clinical responsiveness to clopidogrel was analyzed using the chi-square or Fisher's exact test. A two-sided P-value of less than 0.05 was considered to indicate statistical significance in all performed tests.

Results

Patients' characteristics

59 CAD patients undergoing PCI were evaluated, and 51 of these subjects met the inclusion criteria, as illustrated in Fig. 2. The general characteristics of the study population in the current research were summarized and categorized in Table 2. The study population comprised 32 males and 18 females. The mean age of the patients was 57.67 ± 9.26 years. The study investigated other clinical features of patients and found that (56%) had hypertension, (28%) had diabetes, and (52%) had a family history of CAD. Furthermore, (12%) of the patients reported a previous PCI, (50%) reported being smokers, and (44%) had a sedentary lifestyle.

Allelic and genotypic distribution of the CYP2C19 polymorphisms

Table 3 displays the allelic distribution frequencies of the investigated SNPs within the *CYP2C19* gene. The frequency of the *CYP2C19*2* allele was found to be (8%) with only one individual homozygous for this non-functional allele, resulting in a frequency of (2%) for the (**2/*2*) genotype. The allelic frequency of *CYP2C19*17* was determined to be (17%), with (4%) of the participants

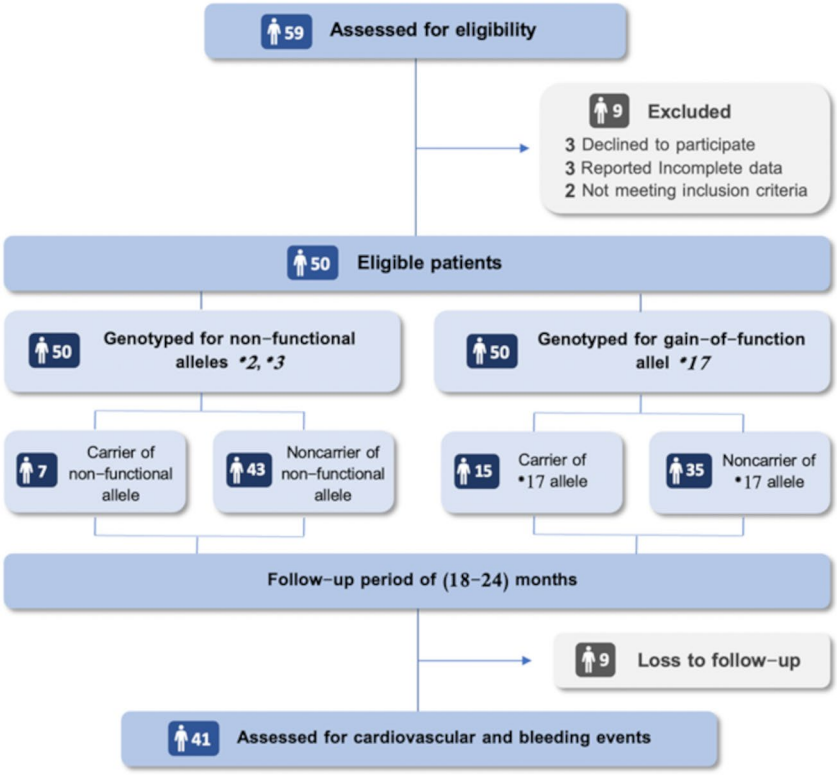

Fig. 2 Flow diagram for study participants

Table 2 Baseline demographics of study participants

Mean age, y (SD)	57.67 (1.35)
Gender	
Male	32 (64%)
Female	18 (32%)
BMI by class	
Normal	15 (30%)
Overweight	20 (40%)
Obese	15 (30%)
Current smoker	25 (50%)
Sedentary lifestyle	22 (44%)
Medical history	
Hypertension	28 (56%)
Diabetes	14 (28%)
CAD FH	26 (52%)
Previous PCI	6 (12%)
Comedications	
Statin	50 (100%)
ACEIs/ARBs	26 (52%)
Beta blocker	37 (74%)
CCB	12 (24%)
Aspirin	50 (100%)
PPIs	24 (48%)

Table 3 Studied *CYP2C19* gene polymorphisms

Allele	rsID number	Nucleis Acid Base Substitution	Frequency
*CYP2C19*2*	rs4244285	19,154 G > A	0.08
*CYP2C19*3*	rs4986893	17,948 G > A	0
*CYP2C19*10*	rs6413438	19,153 C > T	0
*CYP2C19*17*	rs12248560	–806 C > A / C > T	0.17
*CYP2C19*22*	rs140278421	17,869 G > A / G > C / G > T	0
*CYP2C19*26*	rs375781227	19,239 G > A	0
*CYP2C19*33*	rs370803989	17,874 G > A	0

carrying the homozygous (**17/*17*) genotype, and (26%) were heterozygous wild-type (**1/*17*). The other examined alleles (*CYP2C19*3*, **10*, **22*, **26*, and **33*) were not detected in the study population. The genotype frequencies were not significantly different from those predicted by the Hardy–Weinberg equation ($Rx^2 = 3.023$; P value = 0.082; Table 4). The distribution of patients by CYP2C19 phenotypes was as follows: UMs (4%), RMs (26%), NMs (56%), IMs (12%), and PMs (2%) (Table 4).

Follow-up

Out of all the patients initially included in the study, nine individuals could not be followed up. Among the remaining 41 patients for whom data were available, 16 patients (39%) reported experiencing recurrent angina symptoms.

Table 4 Observed versus expected genotype distribution of *CYP2C19*

Phenotype	*N* (%)	Genotype	*N* (%) Observed	*N* (%) Expected	HWE x^2	HWE *P* value
UMs	2 (4%)	**17/*17*	2 (4%)	1.44 (2.89%)	0.2131	0.64
RMs	13 (26%)	**1/*17*	13 (26%)	12.75 (25.5%)	0.0049	0.94
NMs	28 (56%)	**1/*1*	28 (56%)	28.13 (56.25%)	0.00055	0.98
IMs	6 (12%)	**1/*2*	6 (12%)	6 (12%)	0	1
		**1/*3*	0 (0%)	0 (0%)	NA	NA
		**17/*2*	0 (0%)	1.36 (2.72%)	1.36	0.24
		**17/*3*	0 (0%)	0 (0%)	NA	NA
PMs	1 (2%)	**2/*2*	1 (2%)	0.32 (0.64%)	1.445	0.22
		**2/*3*	0 (0%)	0 (0%)	NA	NA
		**3/*3*	0 (0%)	0 (0%)	NA	NA

HWE x2 Hardy–Weinberg equation test ($P=0.05$)

NA, not applicable

Table 5 Distribution of recurrent cardiac ischemic events by *CYP2C19*2* polymorphism

Allele *CYP2C19*2*	Refractory angina symptoms		*P* value	Major adverse cardiac events		*P* value
	Yes	No		Yes	No	
Yes	2 (%33.33)	4 (%66.67)	>0.9999	1 (%16.67)	5 (%83.33)	0.2744
No	14 (%38.89)	22 (%61.11)		1 (%2.86)	34 (%97.14)	

Table 6 Distribution of recurrent cardiac ischemic events by non-genetic factors

Variables		Refractory angina symptoms		*P* value	Major adverse cardiac events		*P* value
		Yes	No		Yes	No	
Gender	Male	4 (14.81%)	23 (85.19%)	> 0.9999	0 (0%)	27 (100%)	0.1228
	Female	2 (14.28%)	12 (85.71%)		2 (14.28%)	12 (85.71%)	
BMI	Normal	1 (7.69%)	12 (92.31%)	0.19134	0 (0%)	13 (100%)	0.1317
	Overweight	1 (7.14%)	13 (92.86%)		0 (0%)	14 (100%)	
	Obese	4 (28.57%)	10 (71.42%)		2 (14.28%)	12 (85.72%)	
Hypertension	Yes	4 (12.90%)	27 (87.10%)	0.6221	1 (4.76%)	20 (95.24%)	> 0.9999
	No	2 (10%)	18 (90%)		1 (5%)	19 (95%)	
Diabetes	Yes	3 (27.27%)	8 (72.73%)	0.3162	1 (9.1%)	10 (90.9%)	0.4695
	No	3 (10%)	27 (90%)		1 (3.33%)	29 (96.77%)	
Proton Pump Inhibitor Use	Yes	4 (18.18%)	18 (81.82%)	0.6681	0 (0%)	22 (100%)	0.2085
	No	2 (10.52%)	17 (89.47%)		2 (10.53%)	17 (89.47%)	
Calcium Chanel Blockers Use	Yes	3 (30%)	7 (70%)	0.1435	0 (0%)	10 (100%)	> 0.9999
	No	3 (9.67%)	28 (90.33%)		2 (6.45%)	29 (93.55%)	

Additionally, two individuals (4.88%) experienced MACE, and four patients (9.76%) reported bleeding events.

Refractory angina symptoms and *CYP2C19* polymorphism

As represented in Table 5, it was found that two patients (33.33%) from the *CYP2C19*2* allele carrier group exhibited symptoms of refractory angina. However, this result did not demonstrate a statistically significant difference when compared with the non-carrier group, in which 14 patients (%38.89) exhibited similar symptoms ($P > 0.9999$).

Major adverse cardiac events and *CYP2C19* polymorphism

Overall, two of the 41 patients who were followed up in the study experienced at least one MACE after PCI. One case was from the *CYP2C19*2* allele carrier group and the other was from the non-carrier group. In terms of the distribution of MACE based on *CYP2C19*2* status, there was no statistically significant correlation ($P = 0.2744$).

Recurrent cardiac ischemic events and non-genetic factors

The distribution of refractory angina symptoms and MACE among patients according to various demographic and clinical factors is presented in Table 6. Statistical analyses were conducted to investigate the association between these factors and the clinical response to Clopidogrel, particularly regarding the incidence of recurrent cardiovascular events. The results indicated that the P-value in all tests exceeded 0.05, suggesting no significant association between these factors and cardiovascular events. Specifically, no significant relationship was found between MACE and factors such as gender,

body mass index (BMI), hypertension, diabetes mellitus, proton pump inhibitor use, or calcium channel blocker use. These findings highlight the absence of a clear link between these non-genetic factors and major cardiovascular events in the studied population.

Bleeding events and *CYP2C19* polymorphism

Our results indicated that carriers of the *CYP2C19*17* variant experienced a higher incidence of bleeding events (16.67%) compared to non-carriers (6.9%). Despite this observed difference, it is important to note that the statistical analysis found no significant difference between the two groups ($P = 0.567$; see Table 7). Similarly, there was no statistically significant difference in bleeding events between *CYP2C19*2* carriers and non-carriers ($P = 0.0952$; see Table 7), although a higher proportion of bleeding events was observed among carriers.

Discussion

Dual antiplatelet therapy, consisting of aspirin and a P2Y12 inhibitor, is the current recommended treatment strategy for patients with CAD undergoing PCI with stent implantation to reduce the risk of recurrent MACE [27]. Although novel P2Y12 inhibitors, such as prasugrel and ticagrelor are becoming more popular due to their strong antiplatelet effects [28–30], clopidogrel remains the most widely prescribed drug of P2Y12 inhibitors in Syria. This preference is primarily due to its lower cost and reduced risk of bleeding. However, most Syrian physicians tend to duplicate the maintenance dose of clopidogrel for at least one month after stenting to provide additional prevention of recurrent ischemic events, including stent thrombosis. However, despite clopidogrel's general effectiveness, various studies have shown that a significant number of patients (between 5% and 44%) may not respond adequately to this medication [31]. Clopidogrel response has been attributed to be affected by several factors, which can be categorized as clinical, cellular, and genetic. Polymorphism of *CYP2C19* gene is one of the key genetic factors influencing individual responses to clopidogrel [32, 33].

To the best of our knowledge, this is the first study in Syria reporting allelic frequencies of *CYP2C19*2*, **3*, and **17* and assessing their impact on the clinical efficacy and safety of a double maintenance dose of clopidogrel as part of DAPT in CAD patients undergoing PCI. The Syrian population is a highly admixed community with diverse ethnic, cultural, and religious groups, resulting from historical factors such as immigration, political occupations, and trade relations with various countries over the centuries. This diversity has created a unique genetic makeup, making it important to conduct genetic studies specific to this population.

The frequency of *CYP2C19*2* allele in our study population (8%) was found to be compatible with that of other populations in the Middle East and North Africa (MENA) region, such as the Jordanian (9.8%) [11], Iraqi (11.7%) [14], Saudi (9.9%) [17], Egyptian (12.6%) [15], and Tunisian (9%) [18]. However, a noteworthy variation was observed when comparing our results to East Asian populations, such as Chinese (24.7%) [25] and Japanese (27.9%) [24]. The *CYP2C19*3* allele was absent in our study population, which aligns with the low or diminished frequencies reported in European and Middle Eastern populations. In contrast, this allele has a higher prevalence in Asian populations, ranging from 3.3% in China [25] to 12.8% in Japan [24]. This suggests a notable ethnic difference between Caucasian and Oriental populations, indicating that this genetic variant likely emerged relatively recently after the differentiation of these groups [21]. For the *CYP2C9*17* allele, the frequency was found to be (17%), which is close to that reported in European and Middle Eastern populations but higher than those found in other studies on Asians (from 0.3% in Koreans [26] to 1.3% in Japanese [23]). Table 8 summarizes the frequencies of the studied alleles across different countries and populations.

The present study did not confirm an association between MACE incidence and the carrier status of the non-functional *CYP2C19*2* allele, which has been established in many previous studies and meta-analyses [34–39]. Numerous prominent international medicine and regulatory agencies, including the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada/Santé Canada (HCSC), and Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, have incorporated pharmacogenomics (PGx)-relevant annotations into the clopidogrel drug label under the "Prescribing" section. These annotations indicate that the antiplatelet efficacy of clopidogrel may be impaired or absent in certain patient groups carrying loss-of-function alleles of the *CYP2C19* gene [40–43]. Furthermore, extensive literature reviews have been conducted, leading to the development of clinical practice guidelines by professional organizations such as the Clinical Pharmacogenetics Implementation Consortium,

Table 7 Distribution of bleeding events by *CYP2C19* polymorphism

Allele *CYP2C19*17*	Bleeding events		*P* value	Allele *CYP2C19*2*	Bleeding events		*P* value
	Yes	No			Yes	No	
Yes	2 (16.67%)	10 (83.33%)	0.567	**Yes**	2 (33.33%)	4 (66.67%)	0.0952
No	2 (6.9%)	27 (93.1%)		**No**	2 (5.71%)	33 (94.29%)	

Table 8 Comparison of allele frequencies of *CYP2C19*2, *3, and *17* reported from different ethnic populations

Country	*2 allele frequency (%)	*3 allele frequency (%)	*17 allele frequency (%)	Ref.
Syria	8	0	17	Current study
Lebanon	13.4	0.3	NE	[1]
Jordan	9.8	0	28.72	[2, 3]
Palestine	15.5	2.3	NE	[4]
Iraq	11.7	0	27.6	[5]
Egypt	12.6	0.25	17	[6]
Qatar	13	0.4	21	[7]
Saudi Arabia	9.9	0.1	25.7	[8]
Tunisia	9	0	21.3	[9]
Turkey	15.27	0.43	15.85	[10]
Iran	16.5	0.1	21.78	[11]
Italy	11	0	20.3	[12]
Greek	13.07	0	19.61	[13]
Japan	27.9	12.8	1.3	[14, 15]
China	24.7	3.3	1.2	[16]
Korea	28	11	0.3	[17]

the Dutch Pharmacogenetics Working Group (DPWG), and the French National Network of Pharmacogenetics (RNPGx). These guidelines specifically address clopidogrel and *CYP2C19* genotyping, recommending various approaches based on the patient's CYP2C19 phenotype [44–46]. The recommendations provided by the DPWG team suggest considering alternative antiplatelet treatments or doubling the dose of clopidogrel for patients with the Intermediate Metabolizer (IM) phenotype [45]. This may explain the findings of our study. In our study population, all patients who carried the *CYP2C19*2* allele and were followed up demonstrated the IM phenotype of the CYP2C19 enzyme, as they carried a single copy of the *CYP2C19*2* allele. These patients were prescribed a double maintenance dose of clopidogrel (150 mg/day) for at least one month following (PCI) procedure, as directed by their treating physician. It is possible that by increasing the clopidogrel dosage in individuals with the IM phenotype, sufficient platelet inhibition could have been achieved, potentially reducing the occurrence of recurrent ischemic events.

Our study revealed a noteworthy observation regarding the incidence of bleeding events among the patients we investigated. Despite 30% of the individuals carrying the gain-of-function *CYP2C19*17* allele and receiving a double maintenance dose of clopidogrel after stent placement, the occurrence of hemorrhagic events remained relatively low, not exceeding (9.7%). Several potential explanations for these findings include limitations related to the study population size, medication adherence, loss to follow-up, and various clinical and genetic factors.

The *CYP2C19*17* allele is well-known to be associated with increased CYP2C19 enzyme activity. However, the clinical significance of this allele remains a topic of ongoing controversy. Although several studies, including a comprehensive meta-analysis, have confirmed that individuals carrying the *CYP2C19*17* allele are at an elevated risk of bleeding events when treated with a standard dose of clopidogrel [47–49], conflicting evidence has been reported [50]. In addition to the conflicting evidence, therapeutic recommendations vary among different guidelines issued by professional organizations in the field of pharmacogenetics for patients undergoing (PCI) and carrying the *CYP2C19*17* allele [44–46]. Given these controversies and inconsistencies, further research is needed to gain a more comprehensive understanding of the clinical implications of the *CYP2C19*17* allele and its impact on treatment outcomes, particularly in patients undergoing PCI.

In addition to the extensively studied *CYP2C19*, several other genes have been investigated in the literature because of their potential impact on the metabolism and effective concentration of the active metabolites of clopidogrel. These genes included *ABCB1* [51], *CYP2C9* [52], *CYP3A4/5* [53], *PON1* [54], and *CES1* [55]. Within the *ABCB1* gene, a SNP known as C3435T (rs1045642) has been associated with a higher incidence of ischemic cardiac events in patients with acute myocardial infarction treated with clopidogrel. This SNP has been linked to potential sub-therapeutic concentrations of clopidogrel, primarily resulting from decreased intestinal absorption of the drug [51]. The frequency of this genetic variant varies among populations. High frequencies have been observed in nearby Middle Eastern populations, such as Jordanians (58%) [56], Palestinians (46%) [57], and Lebanese (50.8%) [58], making it possible that this SNP could be present in a substantial percentage within our study population.

One of the main limitations of this study was the small number of participants, which may restrict the generalizability of the findings. Additionally, the study did not include laboratory evaluation of Clopidogrel responsiveness through platelet function testing. Such testing could have provided valuable insights into the pharmacodynamic effect of clopidogrel in relation to *CYP2C19* polymorphisms and further strengthened the interpretation of our findings. It is crucial to acknowledge that this research represents an initial step towards investigating the genetic profile of the Syrian community in relation to the double maintenance dose of clopidogrel. The utilization of a robust genotyping method (amplicon Sanger sequencing) bolsters the reliability of the genetic data obtained. As such, the findings of this study should be interpreted as modest contributions to the existing literature rather than definitive evidence. Further research

with larger sample sizes, more diverse populations, and rigorous study designs is necessary to gain a comprehensive understanding of the genetic factors influencing clopidogrel response within the Syrian community.

Conclusions

Among patients who underwent PCI and were treated with a double maintenance dose of clopidogrel, the carrier status of the *CYP2C19*2* allele does not appear to be associated with an increased risk of MACE. This finding could potentially support the increased clopidogrel dosing strategy depending on the *CYP2C19* genotype. Nonetheless, given the widespread use of clopidogrel for the treatment of patients undergoing PCI, further evidence regarding the impact of adjusting clopidogrel dosage or utilizing alternative antiplatelet therapy for *CYP2C19* non-functional alleles carriers is necessary.

Abbreviations

CAD	Coronary artery disease
CNV	Copy number variation
CPIC	The Clinical Pharmacogenetics Implementation Consortium
DAPT	Dual antiplatelet therapy
DPWG	Dutch Pharmacogenetics Working Group
EMA	European Medicines Agency
FDA	Food and Drug Administration
gDNA	Genomic DNA
HCSC	Health Canada/Santé Canada
HWE	Hardy–Weinberg equilibrium
IHD	Ischemic heart disease
IMs	Intermediate metabolizers
MACE	Major acute cardiovascular events
MENA	Middle East and North Africa
NMs	Normal metabolizers
PCI	Percutaneous coronary intervention
PGx	Pharmacogenomics
PharmVar	Pharmacogene Variation
PMDA	Pharmaceuticals and Medical Devices Agency
PMs	Poor metabolizers
RMs	Rapid metabolizers
RNPGx	French National Network of Pharmacogenetics
SNPs	Single nucleotide polymorphisms
UMs	Ultra-rapid metabolizers
UV	Ultraviolet

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04768-8.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements

We would like to express our sincere appreciation to Professor Majd N. Aljamali for his invaluable technical guidance. We also acknowledge the Department of Pharmaceutical Biotechnology at the National Commission for Biotechnology for granting us access to their laboratory equipment and facilities.

Author contributions

LAY contributed to the conception and design of the study, data interpretation, and revisions of the manuscript. NHS was responsible for assessing eligibility, collecting data, conducting laboratory work, performing statistical analyses, interpreting the data, and drafting the manuscript.

Funding

This research was partially supported by special funding from Damascus University and a grant awarded by The Ministry of Higher Education and Scientific Research-Fund to support scientific research and technological development.

Data availability

The datasets generated and/or analysed during the current study are available in the ClinVar repository, with the accession numbers SCV005438651 to SCV005438653.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Scientific Research Ethics Committee at the Faculty of Pharmacy, Damascus University in accordance with the Declaration of Helsinki (1964). All patients provided written informed consent.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 24 January 2025 / Accepted: 14 April 2025
Published online: 28 April 2025

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