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# The Effect of CYP2C19 and Nongenetic Factors on Clopidogrel Responsiveness in the MENA Region: A Systematic Review

**Zainab Ali, Msc[1] and Hazem Elewa, PhD[1]**

**Abstract**

Clopidogrel is the cornerstone antiplatelet used in the treatment and prevention of thrombotic events. Some studies examined the effect of *CYP2C19* polymorphism and nongenetic factors on clopidogrel response in the Middle East and North Africa (MENA) region. However, the consistency among these studies is yet unknown. This study aims to estimate the prevalence of *CYP2C19* genetic variants in MENA region and to evaluate the effect of these variants as well as the nongenetic factors on clopidogrel responsiveness. A systematic literature search was performed to identify relevant articles. Only observational studies were included. A total of 20 studies in 8 different populations were included. The *CYP2C19*2* variant is the most prevalent loss-of-function (LOF) allele in the MENA region (1.7%-35%). The frequency of *CYP2C19*17* ranged from 5.3% to 26.9%. Of the 9 studies, 6 found an association between carriers of at least 1 LOF allele and clopidogrel resistance. Older age, high body mass index, females, and the use of calcium channel blockers were associated with clopidogrel resistance as well. Association between the *CYP2C19*2* allele and clopidogrel resistance is common among MENA populations. Future studies should focus on having larger sample sizes to detect other minor variant alleles and their effect on bleeding and cardiovascular outcomes.

**Keywords**

clopidogrel resistance, loss-of-function allele, gain-of-function allele, genetic

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## Introduction

Clopidogrel is the most widely used P2Y12 blocker worldwide, especially in the prevention of thrombotic events in patients with acute coronary syndrome (ACS) and/or stroke.[1-3] Nevertheless, not all patients respond to clopidogrel therapy adequately. This interpatient variability may compromise both efficacy and safety.[4] Some recent studies postulated that clopidogrel has a narrow therapeutic window where high on-treatment platelet reactivity (HTPR) is associated with thrombotic events while low on-treatment platelet reactivity is associated with bleeding events.[5,6] Therefore, several studies have investigated genetic and nongenetic factors that may be associated with clopidogrel response.[7,8]

Clopidogrel is a thienopyridine prodrug metabolized primarily through *CYP2C19* to form an active metabolite that selectively and irreversibly blocks P2Y12 receptor.[9] Most of the pharmacogenetic studies on clopidogrel have found an association between *CYP2C19* genetic variants and response to clopidogrel.[10] According to Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C19* Genotype and Clopidogrel Therapy (CPIC), individuals are categorized according to their *CYP2C19* genotype into ultrarapid (*1/*17, *17/*17), extensive (*1/*1), intermediate (*1/*2, *1/*3, *2/*17), and poor (*2/*2, *2/*3, *3/*3) metabolizers.[11] Based on the reduced efficacy reported for both *CYP2C19* intermediate and poor metabolizers, CPIC recommends using an alternative antiplatelet treatment (eg, prasugrel or ticagrelor) for patients in this category.[11] Additionally, US Food and Drug Administration has put a black box warning regarding *CYP2C19* poor metabolizers and the associated cardiovascular risk.[12] In regard to the genetic variants, the most common loss-of-function (LOF) allele is *CYP2C19*2*.[13] Two meta-analyses indicated that patients carrying 1 copy of the *CYP2C19*2* allele have increased risk of major cardiovascular

[1] College of Pharmacy, Qatar University, Doha, Qatar

**Corresponding Author:**
Hazem Elewa, College of Pharmacy, Qatar University, Doha 2713, Qatar.
Email: hazem.elewa@qu.edu.qa

adverse events (MACE; hazard ratio [HR]: 1.55; 95% confidence interval [CI], 1.11-2.17) and stent thrombosis (HR: 2.67; 95% CI, 1.69-4.22).[14,15] On the other hand, the most prevalent gain-of-function allele is *CYP2C19*17*. A meta-analysis has found that *CYP2C19*17* carriers had a significant protection against MACE in patients with coronary artery disease compared with noncarriers (10.0% vs 11.9%; odds ratio [OR], 0.82; 95% CI, 0.72-0.94; $P = .005$). However, *CYP2C19*17* carriers had also a higher incidence of bleeding (8.0% vs 6.5%; OR, 1.25; 95% CI, 1.07-1.47; $P = .006$).[16] Lastly, some nongenetic factors, such as old age (>65 years), type 2 diabetes mellitus, left ventricular dysfunction, and renal failure, were also found to affect clopidogrel responsiveness.[13]

Middle East and North Africa (MENA) involves unique populations with diverse ethnicities and genetic makeup due to the continuous migration in and out of its countries. This diversity created a heavily admixed population of Asian, Caucasian, Arab, and African Ancestry and made it important to have their own genetic studies. Thus, several studies from different countries of MENA examined the effect of *CYP2C19* polymorphism and nongenetic factors on clopidogrel response. Nevertheless, the consistency between these studies is not very well known. Therefore, we aimed to systematically review studies conducted in the MENA region to investigate the effect of genetic and nongenetic factors on clopidogrel responsiveness and its impact on cardiovascular outcomes.

## Methods

### Search Strategy

A search strategy was developed for each electronic database using a combination of Medical Subject Heading (MeSH) and free-text terms to identify the relevant observational studies with no date restrictions. The search was limited to articles published in English language. The search started on March 2016 and was completed by the second week of April 2016.

PubMed, EMBASE, Scopus, Google-Scholar, PharmGKB (Pharmacogenomics Knowledge Base), and HuGENet were searched using different MeSH (where appropriate) and key terms connected with Boolean operators (AND/OR).

EMBASE has an advantage of refining the search by country, which was very helpful in our case. The following are examples of combinations where both MeSH and key terms were used to search PubMed:

- Combination #1: "*CYP2C19*" AND "polymorphism" AND "Clopidogrel"
- Combination #2: "Pharmacogenomics" AND "Clopidogrel"
- Combination #3: "*CYP2C19*" AND "Clopidogrel" AND "Egypt"
- Combination #4: (("Cytochrome P-450 *CYP2C19*"[Mesh]) AND "clopidogrel" [Supplementary Concept]) AND ("Acute Coronary Syndrome/metabolism"[Mesh] OR "Acute Coronary Syndrome/therapy"[Mesh])
- Combination #5: (("Cytochrome P-450 *CYP2C19*"[Mesh]) AND "clopidogrel" [Supplementary Concept]) AND "Platelet Function Tests"[Mesh]

Additionally, Google Scholar was also searched without any language or date limits to identify gray literature. Furthermore, the reference lists of selected articles were hand-searched to identify additional relevant articles that were missed in the search strategy.

Our systematic review adhered to the PRISMA statements of reporting on systematic reviews and was published in Prospero at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=64369

### Study Types

Observational studies were included (prospective, retrospective, or cross-sectional). Reviews, letters, editorials, and commentaries were excluded from this review.

### Participants

Adults aged 18 years or older from the MENA region, with ACS who require percutaneous coronary intervention (PCI) and/or coronary-artery bypass grafting (CABG), and starting or continuing clopidogrel. Clopidogrel users for an indication other than cardiac indication, such as stroke secondary prevention, were included as well.

### Outcomes Measured

Studies that assessed the effect of *CYP2C19* polymorphism and/or nongenetic factors on clopidogrel responsiveness (based on platelet reactivity unit [PRU]/platelet inhibition/platelet aggregation and/or cardiovascular clinical outcomes) were included in this systematic review.

### Eligibility Criteria

To achieve the objectives of this systematic review, articles were included if they fulfilled any of the following criteria:

For the prevalence of *CYP2C19* genetic polymorphism in MENA countries without its impact on cardiovascular outcomes:

The study evaluated *CYP2C19* genetic polymorphism and their relevant genotypes in a population from the MENA region (either healthy or diseased using clopidogrel).

For the effect of *CYP2C19* genetic polymorphism and nongenetic factors on clopidogrel responsiveness and its impact on cardiovascular outcomes in the MENA region:

1. The study population included patients who had ACS (ST-elevation, non-ST-elevation myocardial infarction, or unstable angina) or revascularization (any type of PCI or CABG), with a consequent exposure to clopidogrel therapy (75 mg/d).

2. Patients taking clopidogrel for an indication other than cardiac indications, such as stroke secondary prevention, were included.
3. The study assessed the effect of *CYP2C19* polymorphism and/or nongenetic factors on clopidogrel responsiveness.
4. The clopidogrel responsiveness was assessed based on the PRU/platelet inhibition and/or MACE/stroke/fatal or nonfatal stent thrombosis.
5. The primary definition of MACE was the composite of death (either all-cause or cardiac), nonfatal myocardial infarction, and nonfatal stroke.[17]
6. These studies must be conducted on MENA region populations.

### Study Selection

There were 2 screening phases for the articles according to the prespecified inclusion and exclusion criteria. First, duplicates were removed and then title and abstract of the articles were screened to determine whether they were irrelevant. In the second screening phase, full text of the relevant articles was obtained and those that fulfilled the inclusion criteria were included. There were 2 independent reviewers involved in the screening process. Any disagreement was resolved by discussion and consensus.

### Data Extraction

A specific data extraction tool was developed by the 2 authors and used to collect data from the included articles. Extracted data were author and year of publication, sample size, indication, population studied, cardiovascular risk factors (smoking, diabetes, hypertensions, and dyslipidemia), clopidogrel-loading dose, clopidogrel maintenance dose and duration, follow-up, outcomes reported, genetic and nongenetic factors studied, and main results. For each eligible study, data of interest were extracted by 1 researcher. To ensure quality and accuracy, each data collection form was double-checked and verified by the other researcher.

### Quality Assessment

For assessing the quality of the included studies, the National Heart, Lung, and Blood Institute quality assessment tool for observational cohort and cross-sectional studies was used.[18]

## Results

### Selection of Studies

The search retrieved 4679 articles, 2070 from PubMed, 1121 from EMBASE, 975 from Scopus, 413 from PharmGKB, and 100 from HuGENet. Based on the inclusion criteria, a total of 20 studies were included in this systematic review. Figure 1 shows the flowchart of the included studies. Twenty-eight studies were eligible for full-text screening, 6 studies were excluded for studying patients outside the MENA region,[13,19-23] and 2 papers were excluded because they were reviews.[24,25] The 20 studies reviewed were from 8 different countries, including Egypt, Jordan, Iran, Lebanon, Turkey, Saudi Arabia, Palestine, and Qatar.

### Prevalence of Explored Genetic Variants

Minor allele frequency (MAF) was used to estimate the prevalence of *CYP2C19* genetic variants. Minor allele frequencies of *CYP2C19* genetic variants are presented in Table 1. *CYP2C19*1* variant (wild-type) had the highest frequencies among all populations, followed by the *2, *17, and *3. Minor allele frequency of *3 and *17 was not explored in all the studies. The *CYP2C19*2* variant was the most prevalent LOF allele in the MENA region and was highest among Jordanian (35%)[26] and lowest among Turkish (1.7%).[27] Eight studies estimated the prevalence of *CYP2C19*2* in Iranian populations. Five of these studies had similar MAF of *2 allele (13%),[28-32] but 2 studies had higher frequencies (27.9% and 19.1%).[27,33] The prevalence of *CYP2C19*2* varied among Saudi Arabians, with a range of 8.2% to 30%.[34,35]

The frequency of *CYP2C19*3* allele was found to be very low, with a maximum of 1% in Iranian population. The frequency of *CYP2C19*17* ranged from 5.3% to 26.9%. Hardy-Weinberg equilibrium was tested and reported in only 9 studies.[28,30-32,36-40]

### Characteristics of the Included Studies

The characteristics of the included studies are shown in Table 2. The primary objective of 11 included studies was to explore the prevalence of *CYP2C19* polymorphism in the MENA region. However, the rest of the studies investigated the association between *CYP2C19* polymorphism and other nongenetic factors on clopidogrel responsiveness in MENA region. Based on the quality assessment, 6 studies were of good quality, 2 of fair quality, and only 1 was considered of poor quality by Khalaf et al because the objective and the population were not defined clearly. Of the 9 studies, 5 were case–control studies while the other 4 were prospective observational studies.

### Clopidogrel Response Definition

The definition of clopidogrel responsiveness varied across the included studies. Among the 9 studies, the cutoff value for HTPR was expressed using platelet aggregation in 2 studies[26,40] whereas it was expressed as percentage of relative platelet inhibition in 1 study.[31] Two of the studies expressed the cutoff value for HTPR by the PRU.[35,43] The other 4 studies examined clopidogrel responsiveness by the clinical cardiovascular outcome, mainly MACE, stroke recurrence, and stent thrombosis.[27,36,41,44]

### Clopidogrel Responsiveness and the LOF Variants

Table 3 shows the association between *CYP2C19* genetic variants and clopidogrel responsiveness in the different

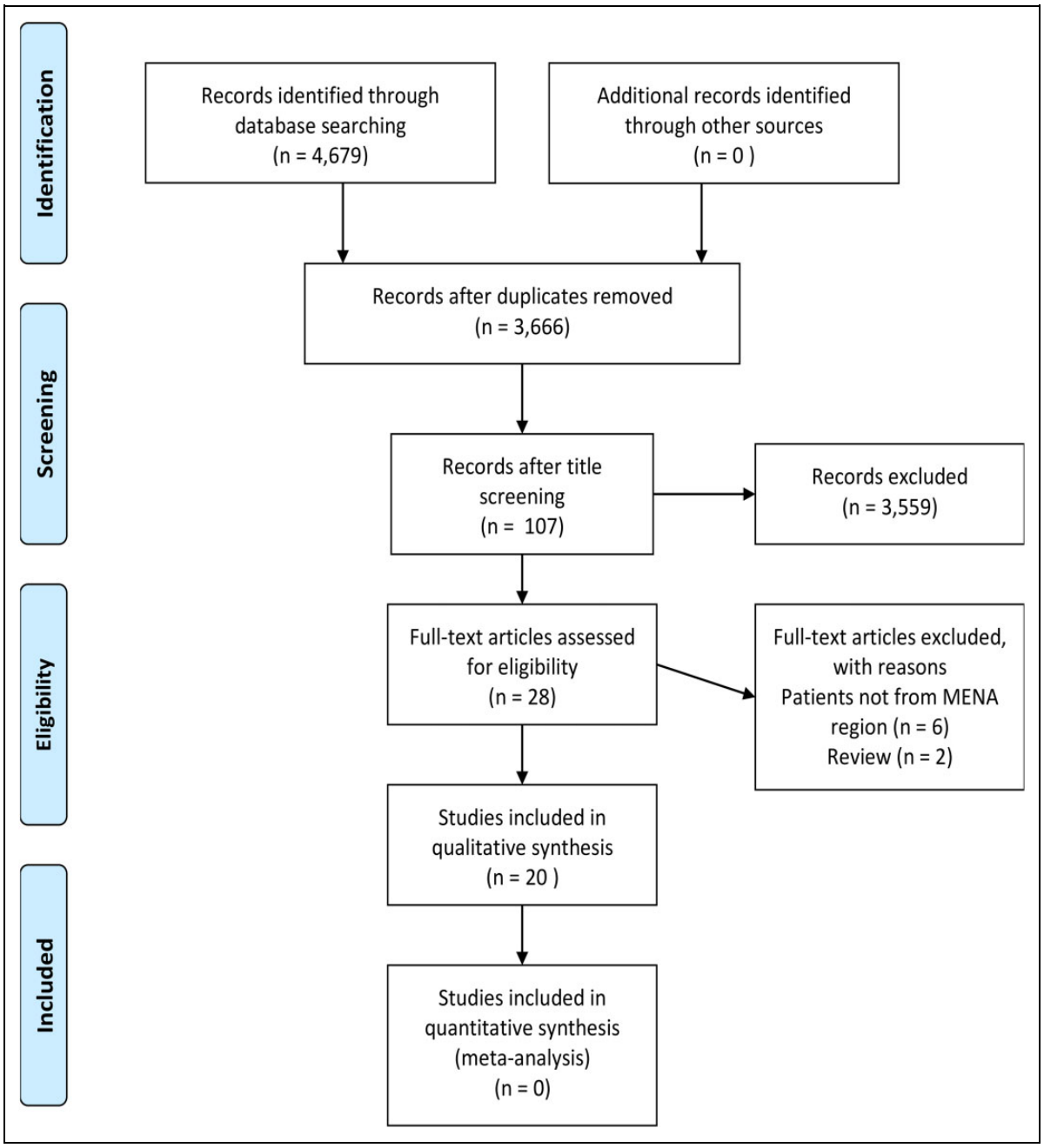


**Figure 1.** PRISMA flowchart of included studies.

populations. Of the 9 studies, 6 found an association between carriers of at least 1 LOF allele (*2 or *3) of *CYP2C19* and clopidogrel responsiveness. In 4 of these studies, the outcome assessed was the HTPR,[26,27,40,43] while clinical cardiovascular events were the measured outcomes in the other 2 studies.[36,41]

## *Clopidogrel Response Across Different Indications*

Among the 9 included studies, 2 had evaluated the association between having at least 1 LOF allele (*2 or *3) of *CYP2C19* and clopidogrel responsiveness in stroke prevention. The remaining 7 studies included patients who underwent PCI.[26,27,31,35,36,43,44] Sen et al evaluated the effect of *CYP2C19* polymorphism on the clinical outcomes of patients who began clopidogrel therapy after acute ischemic cerebrovascular disease.[41] However, the other study used platelet aggregation as a surrogate marker to study the effect of *CYP2C19* polymorphisms on clopidogrel response in patients with acute ischemic stroke.[40]

These studies found that carrying at least 1 LOF allele (*2 or *3) of *CYP2C19* is associated with recurrent stroke linked to insufficient response to clopidogrel.[40,41] Regarding clopidogrel responsiveness in patients who underwent PCI, 4 studies showed a significant association between LOF alleles and

**Table 1.** Minor Allele Frequency of *CYP2C19* Genetic Variants.

| Population | Sample Size | *CYP2C19* Alleles | | | |
|---|---|---|---|---|---|
| | | *1 | *2 (rs4244285) | *3 (rs4986893) or (rs57081121) | *17 (rs12248560) |
| Iranian[28] | 691 | 87.10% | 12.30% | 0.50% | NA |
| Turkish[41] | 51 | 83% | 17% | NA | NA |
| Saudi Arabians[34] | 192 | 64.9% | 8.20% | 0% | 26.90% |
| Egyptian[36] | 190 | 70.15% | 12.6% | 0.25% | 17% |
| Iranian[29] | 200 | 86.00% | 14.00% | 0% | NA |
| Iranian[30] | 150 | 86.73% | 13.00% | 1.00% | NA |
| Iranian[42] | 43 | 72.10% | 27.90% | NA | NA |
| Iranian[31] | 112 | 88.99% | 10.09% | 0.91% | NA |
| Iranian[32] | 180 | 65.30% | 13.10% | 0% | 21.60% |
| Lebanese[37] | 161 | 86.30% | 13.40% | 0.30% | NA |
| Palestinian and Turkish[38] | 200 | 90.5% in Palestinians and 86.5% in Turkish | 9.5% in Palestinian and 13.5% in Turkish | NA | NA |
| Saudi Arabians[39] | 201 | 62.90% | 11.20% | NA | 25.70% |
| Saudi Arabians[40] | 50 | 85.3% | 10.37% | 4.4% | NA |
| Turkish[43] | 347 | 89.50% | 5.1% | 0.1% | 5.30% |
| Saudi Arabians[35] | 90 | 70% | 30% | 0% | NA |
| Jordanian[26] | 270 | 65% | 35% | NA | NA |
| Turkish[27] | 100 | 92% | 1.7% | 0.3% | 6% |
| Iranian[44] | 100 | 94% | 6% | NA | NA |
| Iranian[33] | 118 | 80.90% | 19.10% | NA | NA |
| Qatari[45] | 100 | NA | NA | 0.02% | NA |

Abbreviation: NA, not applicable.

clopidogrel resistance.[26,27,36,43] On the other hand, 3 studies revealed that carrying at least 1 LOF is not a contributing factor in clopidogrel resistance in patients who were treated with clopidogrel after PCI.[31,35,44]

### *Clopidogrel Responsiveness and the Gain-of-Function Variant*

Of the 9 studies, 3 examined the effect of *CYP2C19*17* on clopidogrel responsiveness. One study found that PRU values in *CYP2C19*1/*17* carriers were significantly lower than in wild-type patients ($P = .029$).[43] Another study showed that *CYP2C19*17* mutation may have protective effect by preventing stent thrombosis.[27]

### *Clopidogrel Responsiveness and Nongenetic Factors*

Table 4 represents the association between the nongenetic factors and clopidogrel responsiveness. Only 4 studies examined the effect of nongenetic factors on clopidogrel response. Three of them showed a significant association between the nongenetic factors and clopidogrel response.[26,35,36] Two studies showed that females are at increased risk of clopidogrel resistance when compared to males.[26,35] In one of the former 2 studies, use of calcium channel blockers (CCBs) was also associated with clopidogrel resistance.[26] The third study showed that age and body mass index (BMI) were significantly associated with the incidence of MACE in patients taking clopidogrel.[36]

## Discussion

This systematic review was conducted to explore the prevalence of *CYP2C19* variants in MENA region and the different genetic and nongenetic factors associated with clopidogrel responsiveness.

Eleven of the included studies identified only the prevalence of *CYP2C19* polymorphism in the MENA region. Similar to Caucasians, MAF of *CYP2C19*2* was much higher than *CYP2C19*3* and it ranged from 1.7% to 35%.[11] There were some inconsistencies in the reported MAF of *CYP2C19*2* in Iranian populations and these variations maybe due to the differences in the studied sample size and the geographical distribution across the studied populations. The *CYP2C19*3* frequency was very low with a maximum of 1% in the Iranian population, which was similar to other racial groups (Caucasians and Africans).[11] In this systematic review, the frequency of *CYP2C19*17* ranged from 5.3% to 26.9%, which was marginally higher than the average multiethnic allele frequencies (3%-21%).[11]

The other studies in this review investigated the association between *CYP2C19* polymorphism along with nongenetic factors on clopidogrel responsiveness in the MENA region. Of the 9 studies, 6 found an association between carriers of at least 1 LOF allele (*2 or *3) of *CYP2C19* and clopidogrel responsiveness. Numerous studies conducted outside the MENA region have demonstrated similar findings.[46] Several factors can explain the inconsistency of results among the reviewed studies, including the small sample size (lack of power), study

**Table 2.** Study Characteristics.

| Study (Author, Year) | Design | Quality | Participants, n | Indication | Population | Cardiovascular Risk Factors (Smoking, DM, HTN, DYS) | Clopidogrel LD | Clopidogrel MD, Duration | Follow-Up |
|---|---|---|---|---|---|---|---|---|---|
| Sen et al, 2014[41] | Observational prospective | Fair | 51 | Stroke prevention | Turkish | NR | NA | 75 mg, 2 years | At least 1 year |
| Khalil et al, 2016[36] | Observational retrospective (case–control) | Good | 190 | ACS and/or PCI | Egyptian | Smoking: 33.3% in MACE vs 23.6% in non-MACE<br>HTN: 67.9% in MACE vs 51% in non-MACE group<br>DSY: NR<br>DM: 36.9% in MACE vs 24.5% in non-MACE | NR | 75 mg, at least 3 months and maximum 12 months | 3-12 months |
| Namazi et al, 2012[31] | Observational prospective (cross-sectional) | Fair | 112 | PCI with DES | Iranian | Smoking: 42%<br>HTN: 51%<br>DYS: 68%<br>DM: 19% | 600 mg | 150 mg/d for 2 weeks and 75 mg for 12 months | 1 month |
| Khalaf et al., 2016 [35] | Observational prospective | Poor | 90 | ACS | Saudi | Smoking: NR<br>HTN: 55%<br>DYS: 50%<br>DM: 59% | 300 mg | 75 mg, not documented | 2-3 days |
| Saydam et al, 2017[43] | Observational prospective | Good | 347 | ACS and PCI | Turkish | Smoking: 25.1%<br>HTN: 53.3%<br>DYS: 41.8%<br>DM: 40.3% | NR | 75 mg, at least 1 week | No follow-up |
| Alhazzani et al, 2017[40] | Observational retrospective (case–control) | Good | 50 | Stroke prevention | Saudi | Smoking: NR<br>HTN: 44% in responders vs 64% in nonresponders<br>DM: 52% in responders vs 68% in nonresponders | NA | 75 mg, not documented | No follow-up |
| Al-Azzam et al, 2013[26] | Observational prospective (cross-sectional) | Good | 270 | Cardiovascular disease | Jordanian | Smoking: 31.7%<br>HTN: 72.5%<br>DM: 46.3% | NR | 75 mg, at least 1 week | No follow-up |
| Kirac et al, 2016[27] | Observational retrospective (case–control) | Good | 100 | PCI and Stent Placement | Turkish | Smoking: 48% in control vs 46% in cases<br>HTN: 56% in control vs 74% in cases<br>DYS: 48% in control vs 46% in cases<br>DM: 28% in control vs 36% in cases | NR | 75 mg, 1 year | 180 days |
| Nozari et al, 2015[44] | Observational retrospective (case–control) | Good | 100 | PCI | Iranian | Smoking: 20%<br>HTN: 51.5%<br>DYS: 62.6%<br>DM: 26% | 600 mg | 75 mg, at least 1 month after | 1 year |

Abbreviations: ACS, acute coronary syndrome; DES, drug-eluting stent; DM, diabetes mellitus; DYS, dyslipidemia; HTN, hypertension; LD, loading dose; MACE, major cardiovascular adverse events; MD, maintenance dose; NA, not applicable; NR, not reported; PCI, percutaneous coronary intervention.

**Table 3.** *CYP2C19* Genetic Variants and Clopidogrel Responsiveness.[a]

| Population | Genetic Polymorphism Studied | Outcomes Reported | *CYP2C19* Polymorphism Association Results |
|---|---|---|---|
| Turkish[41] | *CYP2C19* (*2 and *3) | Recurrent Stroke | In *2 carriers, OR = 13.23; 95% CI, 6.45-27.11 for recurrent stroke. |
| Egyptian[36] | *CYP2C19* (*2, *3, *6, *8, *10, and *17) | MACE | In LOF alleles carriers, OR = 2.52; 95% CI, 1.23–5.15. |
| Iranian[31] | *CYP2C19* (*2 and *3) | Relative platelet inhibition | No significant associations between clopidogrel responsiveness and *CYP2C19* polymorphism, $P > .05$. |
| Saudi[35] | *CYP2C19* (*2, and *3) | PRU | No significant difference in PRU, $P = .349$. |
| Turkish[43] | *CYP2C19* (*2, *3, *4, *7, *8, and *17) | PRU | In *2 carriers, OR = 2.92; 95% CI, 1.91-4.46 for high PRU.<br>PRU values of *CYP2C19**1/*17 were lower ($P = .029$) vs *1/*1. |
| Saudi[40] | *CYP2C19* (*2 and *3) | Platelet aggregation | In *2 carriers, OR = 5.52; 95% CI, 2.42-12.83 for high platelet aggregation.<br>In *3 carriers, OR = 3.45; 95% CI, 1.57-7.70 high platelet aggregation. |
| Jordanian[26] | *CYP2C19**2 | Platelet aggregation | Patients with*2 allele were more resistant to clopidogrel than *1 allele ($P < .05$).<br>In *2 carriers, OR = 1.3; 95% CI, 0.6-2.6.<br>In *2/*2, OR = 4.6; 95% CI, 1.4-14.2. |
| Turkish[27] | *CYP2C19* (*2, *3, *4, *5, and *17) | Stent thrombosis | There were more *2 allele carriers in clopidogrel-resistant patients, $P = .000005$.<br>*17 allele may prevent ST, $P = .042$. |
| Iranian[44] | *CYP2C19**2 | Stent thrombosis | No significant associations between clopidogrel responsiveness and *CYP2C19* polymorphism. In *2 carriers, OR = 2.5; 95% CI, 0.49-12.89. |

Abbreviations: CI, confidence interval; LOF, loss of function; MACE, major cardiovascular adverse events; OR, odds ratio; PRU, platelet reactivity unit; ST, stent thrombosis.
[a]LOF allele carriers were *1/*2, *1/*3, *2/*3, and *2/*17.

**Table 4.** Nongenetic Factors and Clopidogrel Responsiveness.

| Population | Outcomes Reported | Nongenetic Factors Studied | Nongenetic Factors Association Results |
|---|---|---|---|
| Egyptian[36] | MACE | Age, BMI, smoking | A year older increases the odds of MACE by 3%, OR = 1.03; 95% CI, 1.003-1.07.<br>Every 1-unit increase in BMI increases the odds of MACE by 8%, OR = 1.08; 95% CI, 1.004-1.181. |
| Iranian[31] | Relative platelet inhibition | Age, BMI, sex | No significant associations between nongenetic factors and clopidogrel responsiveness ($P > .05$). |
| Saudi[35] | PRU | Sex | The PRU of the female patients was significantly higher than males ($255.6 \pm 68.8$ and $177.7 \pm 66.6$, $P = .000$, respectively). |
| Jordanian[26] | Platelet aggregation | Age, obesity, DM, HTN, smoking, and concomitant medication use | Females have higher risk of clopidogrel resistance. OR = 3.7; 95% CI, 1.8-7.7, $P < .001$.<br>Use of CCBs is associated with higher risk of clopidogrel resistance by 3.3 times, $P = .006$.<br>Elevated HDL level reduces the OR of clopidogrel resistance. OR = 0.97; 95% CI, 0.95-99, $P < .020$. |

Abbreviations: BMI, body mass index; CCBs, calcium channel blockers; CI, confidence interval; DM, diabetes mellitus; HDL, high-density lipoprotein; HTN, hypertension; MACE, major cardiovascular adverse events; OR, odds ratio.

design, variation in clopidogrel responsiveness definition, the studied *CYP2C19* variants, and the follow-up duration.

Among the 9 studies, clopidogrel resistance was measured based on a surrogate marker in 5 studies.[26,31,35,40,43] Two of these studies showed that carrying at least 1 LOF allele is not associated with clopidogrel resistance based on relative platelet inhibition or PRU measurement.[31,35] On the other hand, 4 studies examined clopidogrel responsiveness by the clinical cardiovascular outcome, mainly MACE, stroke recurrence, and stent thrombosis.[36,41,44] Of these 4 studies, 3 showed an association between LOF allele and MACE, stent thrombosis, or stroke recurrence.[27,36,41] In the remaining study, genetic variants were not associated with treatment failure, which was measured using stent thrombosis as an end point.[44] This insignificant result may possibly be due to the low prevalence of the *CYP2C19*2* allele in the studied population, the small sample size, and, consequently, low statistical power.

Regarding the nongenetic factors, in this systematic review, females were at increased risk of clopidogrel resistance. Additionally, older age, high BMI, and use of CCBs were associated

with the incidence of MACE in clopidogrel-treated patients. In previous studies, it was reported that females had poorer clopidogrel response.[47,48] In contrast, a meta-analysis found that there was no significant difference in clopidogrel response between males and females.[49] Results on the concomitant CCBs use and poor clopidogrel response were also replicated in previous studies.[50,51] This interaction could be due to the inhibition of *CYP3A4* by CCBs,[52] which may result in lower concentration of clopidogrel active metabolite.[50,51]

One may argue that studying clopidogrel pharmacogenetics is not that important, since we can use the more potent P2Y12 blockers (prasugrel and ticagrelor) that are also less likely to be associated with interpatient variability.[53] However, studies have shown that clopidogrel is still the most commonly prescribed antiplatelet.[54] This may be due to its reasonable price that may enhance patient adherence. Additionally, clopidogrel is associated with lower bleeding risk compared to prasugrel and ticagrelor.[55,56]

To overcome clopidogrel treatment failure, a study by Mega et al examined the effect of increasing clopidogrel dose in patients with *CYP2C19* polymorphism and found that doses up to 225 mg daily in heterozygous patients (*1/*2) would overcome the increase in platelet reactivity without any noticed side effects.[57] Hence, *CYP2C19*2* genetic testing might significantly improve the cardiovascular outcomes in patients treated with clopidogrel. In the same line, an ongoing prospective, randomized trial—tailored antiplatelet therapy following PCI (TAILOR-PCI)—is aiming to determine whether the best antiplatelet therapy can be identified based on genetic testing for patients undergoing coronary stent placement (ClinicalTrials.gov Identifier: NCT01742117). In this study, patient will be randomized to either conventional therapy arm (clopidogrel 75 mg once daily without prospective genotyping guidance) or to the prospective *CYP2C19* genotype-based arm (ticagrelor 90 mg twice daily in *CYP2C19 *2* or *3* carriers, clopidogrel 75 mg once daily in non-*2 or -*3 *CYP2C19* patients).

Our systematic review has some limitations. First of all, important SNPs like *CYP2C19*3* and *CYP2C19*17* were explored in a very limited number of the reviewed studies. Thus, it was difficult to come up with a conclusion regarding the effect of these variants on clopidogrel responsiveness in MENA populations. Additionally, the effect of *CYP2C19* genetic polymorphism was not studied in many populations of the MENA. Third, the bleeding outcome was not assessed in any of the studies as a clinical outcome. Lastly, some of the included studies had small sample sizes. Nevertheless, this is the first systematic review that assessed the effect of genetic and non-genetic factors in MENA region.

## Conclusion

Association between the *CYP2C19*2* allele as well as nongenetic factors and clopidogrel resistance has been replicated in MENA populations. Future studies should focus on having larger sample sizes to detect other minor variant alleles and their effect on bleeding and cardiovascular outcomes in clopidogrel users. Future studies in the region should have longer follow-up duration and consistent clopidogrel resistance outcome definitions, either in term of HTPR or the clinical cardiovascular outcomes. Finally, studies should evaluate the cost-utility of genotype-guided therapy, compared with standard clopidogrel dosing or the other novel antiplatelet agents without genotyping.

### Authors' Note

ZA and HE contributed to conceptualization, data collection, formal analysis, funding acquisition, investigation, methodology, project administration, and validation. HE supervised the manuscript.

### Data Availability

All relevant data are freely available and are within the paper.

### Declaration of Conflicting Interests

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### ORCID iD

Zainab Ali https://orcid.org/0000-0002-7667-2546

### Supplemental Material

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