Alkattan *et al.*
Egyptian Journal of Medical Human Genetics (2022) 23:101
https://doi.org/10.1186/s43042-022-00313-w

Egyptian Journal of Medical Human Genetics

REVIEW

Open Access

The efficacy of clopidogrel in preventing recurrent cardiovascular events among Arab population carrying different *CYP2C19* mutations: systematic review and meta-analysis

Abdullah N. Alkattan[1*], Nashwa M. Radwan[2,3*], Nagla E. Mahmoud[3], Amjad F. Alfaleh[1], Amal H. Alfaifi[3] and Khaled I. Alabdulkareem[4]

Abstract

Background: The prevalence and the role of CYP2C19 gene mutations concerning recurrent Cardiovascular Events (CVEs) among patients treated with clopidogrel is still controversial especially among Arab people. Therefore, this review aimed to determine the frequency of CYP2C19 polymorphic alleles among the Arab population and to investigate the efficacy of clopidogrel as an antiplatelet drug among those carrying different variants of this gene.

Methodology: Two authors independently searched in PubMed, Google Scholar, and EMBASE databases at any year for studies related to the role of CYP2C19 gene on the prognosis of patients with CVEs treated with clopidogrel. The review included Arab people who were genotyped to determine the frequency of CYP2C19 genotypes and alleles (the qualitative part). Concerning the quantitative part (meta-analysis), only patients who previously had CVEs and using clopidogrel as secondary prophylaxis had been included. The Newcastle Ottawa Scale for non-randomizes Studies was utilized to consider the risk of bias among included studies. We analyzed the data using odds ratio at 95% confidence interval and the quality of evidence of each outcome measure was judged using GRADE approach.

Results: The current study revealed that 4% of Arabs reported in the included studies are homozygous, and 25% are heterozygous for the *CYP2C19*2* allele. While 3% and 18.5% of them are homozygous and heterozygous of *CYP2C19*17* alleles, respectively. A significant increased risk of recurrent CVEs by about threefold was associated with *CYP2C19*2* or *CYP2C19*3* allele carriers (OR = 3.32, CI = 1.94–5.67, and OR = 3.53, CI = 1.17–10.63, respectively). However, no significant increased risk among carriers of *CYP2C19*17* mutation (OR = 0.80, (CI = 0.44–1.44) was documented.

Conclusion: The present study revealed that Arabs carrying *CYP2C19*2* and *CYP2C19*3* alleles could be at increased risk of decreasing the antiplatelet efficacy of clopidogrel and an alternative drug should be prescribed for those patients to avoid recurrent CVEs. However, few available studies were included in the quantitative part of the analysis and further studies with large sample size are recommended to confirm our results.

*Correspondence: abdullahalkattan@gmail.com; radwan.n.m@gmail.com

[1] Department of Research and Development, General Directorate of School Health, Ministry of Health, Riyadh, Saudi Arabia
[3] Department of Research, Assisting Deputyship for Primary Health Care, Ministry of Health, Riyadh, Saudi Arabia
Full list of author information is available at the end of the article

Keywords: *CYP2C19* genotypes, Pharmacogenetics, Clopidogrel, Arab population, Platelet reactivity, Cardiovascular events

Background

Cardiovascular disease (CVD) is a medical term that describes any disorder, which affects the blood vessels, the heart, or both. CVDs, including stroke, coronary artery disorder, and venous thromboembolism, are usually caused by blood coagulation which blocks the vessels from supplying oxygen, glucose, minerals, and microminerals to the cardiac or other tissues. Patients with CVD should be subjected to antiplatelet or anticoagulant medications to avoid further blood coagulation [1, 2].

Despite the availability of various clinically effective antiplatelet drugs to prevent blood clots, some patients may have either a hyper-response or resistance to these medications owing to genetic factors. For instance, Higashi et al. reported that warfarin users who are CYP2C9*2 or CYP2C9*3 allele carriers could suffer from bleeding due to the poor metabolism of this drug [3]. Also, Wu et al. showed that dabigatran users carrying the *rs2244613* allele of the *CES-1* gene are at high risk of recurrent cardiovascular events (CVEs) because of a lower response to the drug [4].

Clopidogrel is an antiplatelet medication frequently used in Middle-Eastern countries as a protective agent to avoid recurrent CVEs [5]. The effect of several mutations related to *the CYP2C19* gene on the prognosis of patients with CVDs treated with clopidogrel is still controversial. Most studies suggest that some *CYP2C19* variants among specific ethnicities cause weak antiplatelet activity [6].

Pharmacokinetic studies showed that the clopidogrel prodrug is activated by several metabolic enzymes, which is converted to 2-oxo-clopidogrel (inactive metabolite) by CYP1A2, CYP2C19, and CYP2B6 oxidative enzymes. Moreover, 2-oxo-clopidogrel is further converted to cis-thiol-clopidogrel (active metabolite) by CYP3A4, CYP2C19, CYP2C9, and CYP2B6 oxidative enzymes [7, 8]. Therefore, some genetic mutations related to these oxidative enzymes (e.g., CYP2C19) could affect the metabolism of clopidogrel and consequently affect its plasma concentration levels and efficacy [9].

At least 30 variants of *CYP2C19* have been identified [10]; however, only three variants have been described as most familiar, including *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* alleles. *CYP2C19*2* and *CYP2C19*3* mutant alleles encode an inactive CYP2C19 enzyme, and the *CYP2C19*17* mutant allele is known to express a more active form of CYP2C19 enzyme [11]. *CYP2C19*1* is described as the wild-type allele and encodes a normal active form of the CYP2C19 enzyme.

Previous studies revealed that *CYP2C19*2 and CYP2C19*3* alleles are related to poor clinical outcomes among Asian and European CVD patients treated with clopidogrel [12–14]. Nevertheless, few studies have discussed the efficacy of clopidogrel in preventing recurrent CVEs among Arab (as an ethnic group) carriers of *CYP2C19* mutations. Therefore, this systematic review aimed to investigate the efficacy of clopidogrel as an antiplatelet drug among *CYP2C19* gene mutation carriers. In addition, a qualitative assessment was conducted to determine the frequency of *CYP2C19* polymorphic alleles and genotypes among the Arab population.

Methods

Search methods

Two authors (N.R. and A.K.) independently searched PubMed, Google Scholar, and EMBASE databases for studies published in any year in the English language and related to clopidogrel efficacy in Arabic CVD patients carrying *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* alleles. Studies related to *CYP2C19* gene polymorphisms frequency among Arabs were reviewed. Manuscripts that included non-Arab populations, non-clopidogrel users, or patients with any contraindication for clopidogrel (i.e., intracranial hemorrhage) were excluded. The following terms were used for the search; *CYP2C19* genotypes; OR *CYP2C19* polymorphic alleles; OR *CYP2C19* gene mutations; AND clopidogrel response; OR antiplatelet activity; AND Arabs.

Type of participants

The qualitative section of this systematic review included Arab people genotyped to determine the frequency of *CYP2C19* genotypes and alleles. For the quantitative section (meta-analysis), only patients with previous CVEs on clopidogrel as secondary prophylaxis were included. These patients were categorized into carriers of (cases) and non-carriers (controls) of *CYP2C19* mutations, including *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17*. Cardiovascular patients on other drugs rather than clopidogrel were excluded from the study.

Outcome measures

The outcome of the quantitative part of the study was to predict the antiplatelet efficacy of clopidogrel among CYP2C19 mutation carriers and non-carriers who previously had CVEs by measuring the frequency of the recurrent CVDs or high platelet aggregation reported.

On the other hand, the qualitative part aimed to determine the frequency of genotypes and alleles related to the *CYP2C19* gene among Arabs.

Data collection and extraction

Two authors (N.R. and A.K.) independently reviewed the abstracts of potential articles to determine the inclusion criteria and identify all the relevant articles. In addition, they extracted the specific characteristics from the included studies, including study setting, duration, design, participants' age, sex, and outcome measures. Disagreement or variation in judgment was resolved by discussion; thus, it is not likely that this method could introduce bias in this systematic review.

Assessment of the risk of bias

Two authors (N.R., N.M.) independently judged the risk of bias in the included studies. They graded each risk as high, low, or unclear according to The Newcastle Ottawa Scale for non-randomized Studies [15].

Assessment of the quality of evidence

According to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach, the quality of evidence for each outcome measure was judged as high, moderate, low, or very low [16].

Measures of treatment effect

A random-effect model of the Review Manager 5.3 program [17] was used for data analysis. The prevalence of different studied alleles was determined. To assess the role of CYP2C19*2, *3, and *17 alleles on recurrent CVEs, Odds Ratio (OR) with 95% Confidence Interval (CI) was conducted between carriers (cases) and non-carriers (controls) of these different CYP2C19 variants with the level of significant was considered at < 0.05.

Dealing with heterogeneity

The I^2 statistic was used to assess heterogeneity among the included studies in each analysis [18].

Results

Results of search

The search included one hundred and eighty-eight potentially relevant articles, of which 97 were identified after the removal of duplicates. Nineteen full-text articles were assessed for eligibility; ten met the inclusion criteria (10 in the qualitative and 6 in the quantitative analysis). Details of the search are given in the PRISMA flow diagram (see Fig. 1).

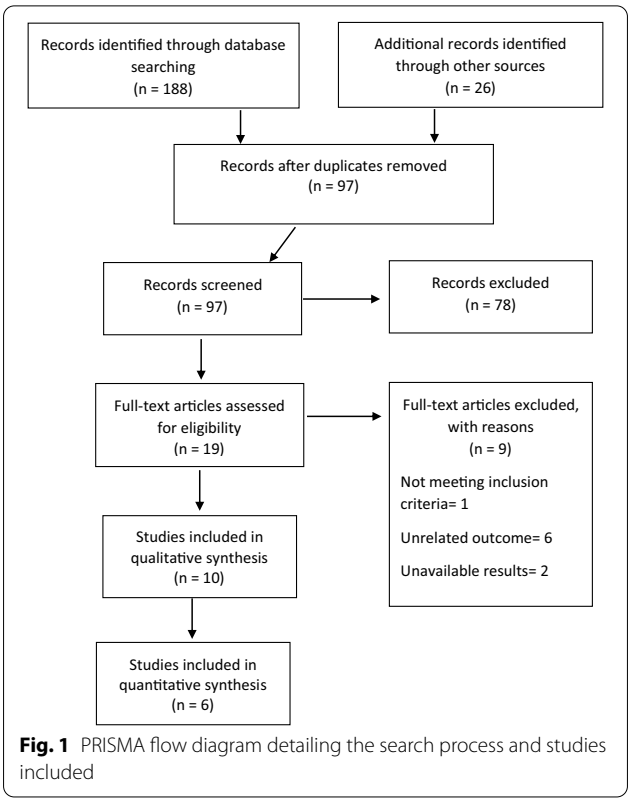

Fig. 1 PRISMA flow diagram detailing the search process and studies included

Included studies

In the quantitative part of the study, the review included 6 observational studies (2 retrospectives, 3 prospective, and one cross-section) [13, 19–23], which reported data on clopidogrel antiplatelet efficacy in the presence of different *CYP2C19* gene variations.

On the other hand, the qualitative part included 10 studies, four case series, and 6 observational studies. These ten studies reported the frequency of *CYP2C19* polymorphisms among Arabs [24–27].

Two authors independently (N.R. and A.K.) extracted characteristics of the included studies, including study title, journal, study design, duration, setting, aim, participants' age, sex, number, and outcome measures (see Table 1).

Trial participants

The quantitative part of the review included 878 Araba (Saudis, Egyptians, Jordanians, Tunisians, Iraqis, and Palestinians) patients who were previously diagnosed with CVDs. For the qualitative part, 1417 Arabs, either healthy or non-healthy, were included. The participants in the qualitative were from 7 different Arabic

Table 1 Characteristics of the included studies

Author	Title	Setting/duration	Design	Participants	Aim	Outcome
1- Adel Alhazzani et al. [13]	Pharmacogenetics of *CYP2C19* genetic polymorphism on clopidogrel response in patients with ischemic stroke from Saudi Arabia	Neurology Clinics at Aseer Central Hospital, Abha, Kingdom of Saudi Arabia, between October 2015 and January 2016	Retrospective study	50 patients on 75 mg maintenance dose of clopidogrel therapy suffering from stroke	To assess the influence of *CYP2C19* genetic polymorphisms on the response to clopidogrel in ischemic stroke in Saudi Arabian population	The variant allele (homozygous and homozygous Mutant) showed significant influence on platelet inhibition and the antiplatelet effect of clopidogrel in ischemic stroke
2-Khalil et al. [22]	Genetic and Nongenetic Factors Affecting Clopidogrel Response in the Egyptian Population	Hospital network in Chicago, Illinois between 5 March and 6 April 2020	Retrospective study	190 patients with acute coronary syndrome (ACS) treated with clopidogrel (75 mg/day) for at least a month	To investigate genetic and non-genetic factors associated with clopidogrel response in Egyptians	*CYP2C19* loss-of-function (LOF) alleles carriers had increased risk of recurrent CVES vs. noncarriers (odds ratio 2.52; 95% confidence interval 1.23–5.15, P = 0.011)
3-Abid et al. [19]	Impact of cytochrome P450 2C19*2 polymorphism on the clinical cardiovascular events after stent implantation in patients receiving clopidogrel of a southern Tunisian region	Department of Cardiology of Sfax (Tunisia) May 2009 and September 2010	Prospective study	100 consecutive patients admitted to the cardiology department for percutaneous coronary stenting. 2 groups: those with at least one *CYP2C19*2* allele (*2 carriers) and non-carriers	to investigate the genetic variant of the gene CYP 2C19 in our population To assess the involvement of this genetic profile in the occurrence of major cardiovascular events	The prevalence of *CYP2C19*2* allele was 11.5%. No statistically significant differences were noted between the two groups regarding the occurrence of intra hospital recurrent CVES
4- Mohammad et al. [23]	*CYP2C19* genotype is an independent predictor of Adverse Cardiovascular Outcome in Iraqi Patients on Clopidogrel Post Percutaneous Coronary Intervention	Duhok Heart center, Kurdistan-Iraq, in the period between Jan 2014 to Mar 2017	Prospective study	201 unselected patients undergoing percutaneous coronary intervention (PCI) aged 35–82 (M:F = 1.9:1) 186 patients had regular follow up	To determine the impact of *CYP2C19* genotyping on the occurrence of major adverse cardiovascular events (recurrent CVES)	The risk of recurrent CVES is 8.6% after a median follow-up of 12 months,
5- Ayesh et al. [21]	The clinical effects of *CYP2C19*2* allele frequency on Palestinian patients receiving clopidogrel after percutaneous coronary intervention	The cardiology department of the European Gaza Hospital (EGH). March and the end of May 2014	Prospective study	110 consecutive unrelated post-PCI patients	To determine the prevalence of *CYP2C19*2* and *3 alleles in Palestinian patients with percutaneous coronary intervention	The frequency of *CYP2C19 *1*, **2* and **3* alleles was 82.3%, 15.5% and 2.3%, respectively
6- Al-Azzam et al. [20]	Factors that contribute to clopidogrel resistance in cardiovascular disease patients: environmental and genetic approach	King Abdullah University Hospital (KAUH) and Jordan University Hospital (JUH) in the period between November 2010 and June 2011	Cross-section study	270 cardiovascular disease patients	To investigate factors that contribute to clopidogrel resistance	Gender, concomitant use of calcium channel blockers, HDL and *CYP2C19*2* polymorphism are significant factors
7- Ahmad et al. [26]	Analysis of Gene Polymorphism *CYP2C19* in the Lebanese Population Who Reside in Colombia	three Lebanese volunteers residents of Colombia	Cross-section study	109, 38 women and 71 men between 18 and 75 years	To determine the polymorphism of the *CYP2C19* gene in the Lebanese	Similar behavior with the alleles frequencies of the previous studies made in Colombia, Africa, Europe and other American population

Table 1 (continued)

Author	Title	Setting/duration	Design	Participants	Aim	Outcome
8-Rjoub et al. [25]	Allelic frequency of *PON1 Q192R*, *CYP2C19*2* and *CYP2C19*17* among Jordanian patients taking clopidogrel	among Jordanian patients in University of Jordan	Cross-section study	148 unrelated Jordanian patients who were taking clopidogrel (55 females and 95 males)	To investigate the influence of allelic frequencies of *PON1 Q192R*, *CYP2C19*2* and *CYP2C19*17* genetic polymorphisms on the response to clopidogrel	The *CYP2C19*2*, *CYP2C19*17*, and *PON1 Q192R* allele frequencies were 9.8, 28.72 and 28.7%, respectively
9- Khalaf et al. [27]	Impact of *Cytochrome P450 2C19*2* and **3* on Clopidogrel Loading Dose in Saudi Patients with Acute Coronary Syndrome	Prince Sultan Cardiac Center, Buraidah, Saudi Arabia	Prospective study	90 patients underwent coronary angioplasty with drug eluting stents	To evaluate the impact of *CYP2C19* allele **2* and allele **3* on PRU and the potential clinical consequences of such interaction	Genotypes **1/*1*, **2/*2*, and **1/*2* were expressed by 60, 28, and two patients (67, 32, and 3%), respectively
10- Al-Jenoobi et al. [24]	*CYP2C19* Genetic Polymorphism in Saudi Arabians	King Saud University, Riyadh, Saudi Arabia Different geographic regions	Cross-section study	192 healthy unrelated Saudi Arabians	To evaluate *CYP2C19* genetic polymorphism in a Saudi Arabian population by determining frequencies of *CYP2C19*2*, **3*, **4*, **6*, **7* and **17* alleles	The allelic frequency of heterozygous *CYP2C19*2* was 8.2% with only one individual carry the homozygous genotype of this defective allele

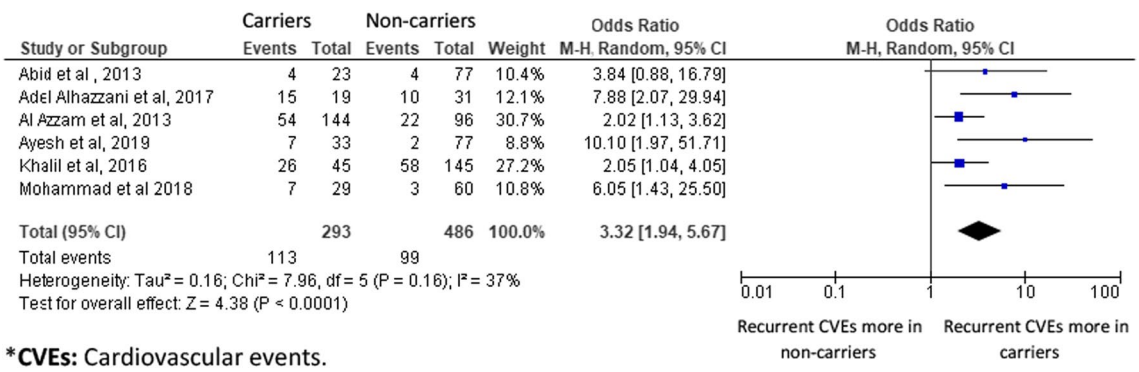

Fig. 2 Forest plot showing the frequency of recurrent CVEs among carriers and non-carriers of *CYP2C19*2* mutation, and results of odds ratios

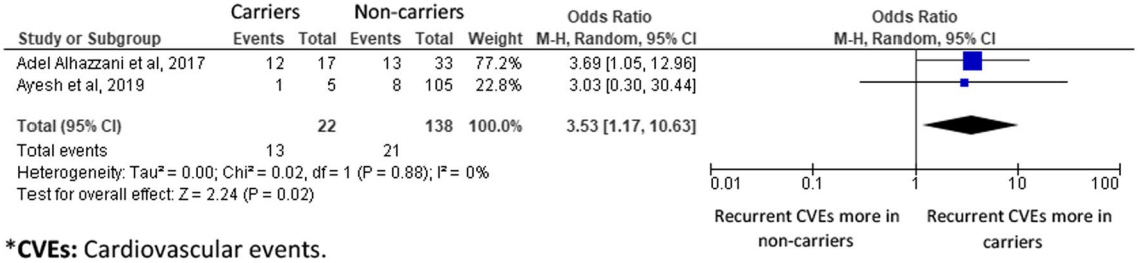

Fig. 3 Forest plot showing the frequency of recurrent CVEs among carriers and non-carriers of CYP2C19*3 mutation

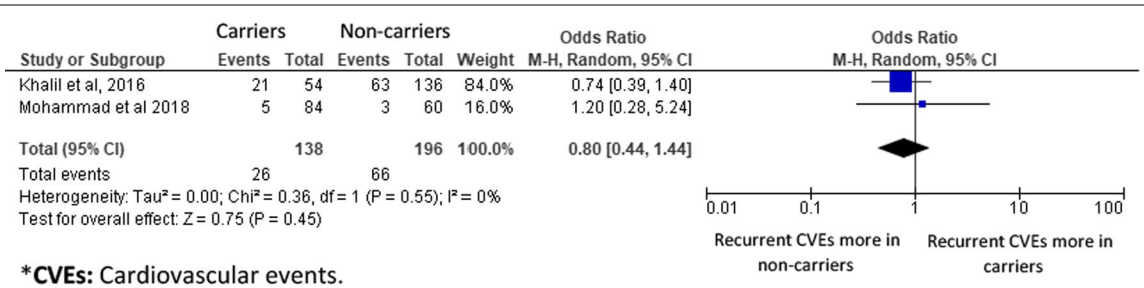

Fig. 4 Forest plot showing the frequency of recurrent CVEs among carriers and non-carriers of CYP2C19*17 mutation, and results of odds ratios

countries, including Saudi Arabia, Egypt, Jordan, Lebanon, Tunisia, Iraq, and Palestine.

Risk of bias among included studies

Overall, no high risk of bias was recorded among the included studies in this review. Regarding {adequate case definition} bias and {comparability of cases and control} bias, it was unclear in Rjoub et al. study. In addition, the {same representative rate for cases and control} bias was low risk in all included studies. While {consecutive representative of cases} bias and {independent outcome assessment} bias were unclear in most of the included studies (Additional file 1: Fig. S1).

Outcomes

Outcomes of the quantitative part

Figures 2, 3, and 4 present the forest plots of the frequency of recurrent CVD events among Arab patients who are clopidogrel users and are either carriers or non-carriers of *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* mutations. The results showed a significantly increased risk of recurrent CVDs events by about threefold

associated with *CYP2C19*2* and *CYP2C19*3* mutations compared to non-carriers (OR = 3.32, CI = 1.94–5.67, and OR = 3.53, CI = 1.17–10.63, respectively). However, no significant difference was recorded between both studied groups regarding the presence of *CYP2C19*17* mutation (OR = 0.80, (CI = 0.44–1.44).

Outcomes of the qualitative part

This part included 1417 Arab people, which were genotyped in order to determine the *CYP2C19* gene variations and to detect the availability of any well-known mutated alleles, including *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* alleles among Arab populations, including Saudis, Egyptians, Jordanians, Iraqis, Palestinians, Lebanese, and Tunisians people. The results revealed that 59 (4.16%) of these carried two *CYP2C19*2* alleles (homozygous), and 356 (25.12%) had one *CYP2C19*2* allele and one *CYP2C19*1* allele (heterozygous). Moreover, 42 (2.96%) carried two *CYP2C19*17* alleles (homozygous), and 262 (18.49%) carried one *CYP2C19*17* allele, and one wild-type allele of *CYP2C19* gene (heterozygous).

The most common CYP2C19 genotype reported among Arabs was the wild type **1/*1*, of which 49.26% of them had the homozygous form of the *CYP2C19*1* allele. The frequency of the *CYP2C19*1* allele was 71.07%, followed by the *CYP2C19*2* allele (16.73%) and *CYP2C19*17* (12.21%), respectively. The *CYP2C19*3* allele was rarely detected among Arabs (< 1%) compared to *CYP2C19*1*, **2*, and **17* alleles.

Based on the frequencies of genotypes, about half of the Arab people (> 49%) could be described as CYP2C19 extensive metabolizers. Other common *CYP2C19* gene phenotypes identified among Arabs were intermediate metabolizers (25%), rapid metabolizers (18%), poor metabolizers (4%), and ultra-rapid metabolizers (3%), respectively.

Discussion

Many studies genotyped the *CYP2C19* gene to assess clopidogrel's efficacy among specific ethnic groups. However, few studies correlated *CYP2C19* gene mutation and clopidogrel efficacy among Arab ethnic groups.

In the quantitative part, the present study recorded significant differences between carriers (cases) and non-carriers (controls) of *CYP2C19*2 and CYP2C19*3* alleles regarding the number of recurrent CVEs among Arabs using clopidogrel (OR = 3.32, CI = 1.94, 5.67, and OR = 3.53, CI = 1.17, 10.63, respectively). However, there was no significant difference among carriers and non-carriers of the *CYP2C19*17* allele concerning the same aspect (OR = 0.80, CI = 0.44, 1.44).

The included studies regarding the recurrent CVEs among carriers and non-carriers of *CYP2C19*2* and *CYP2C19*17* alleles showed low or insignificant heterogeneity. Therefore, we judged the quality of evidence of these outcomes to be high. This strong evidence indicates high confidence that the evidence reflects the actual effect. Meanwhile, we judged the quality of evidence of the pooled estimate of the included studies related to the recurrent CVEs among carriers and non-carriers of *CYP2C19*3* to be moderate. We downgrade the evidence by one level due to imprecision, as indicated by a wide confidence interval due to the small sample size. Moderate evidence indicates moderate confidence that the evidence reflects the actual effect, and further research is likely to change the results.

These results indicate that carrying *CYP2C19*2* and *CYP2C19*3* alleles may decrease the antiplatelet activity of clopidogrel among Arab patients and could lead to recurrent CVEs. The present outcomes were consistent with more than 18 high-quality clinical trials and 6 meta-analysis studies. These revealed that *CYP2C19*2* and **3* alleles have a significant role in causing recurrent CVEs among patients using clopidogrel [28–47].

On the other hand, 3 previous meta-analysis concluded that loss-of-function alleles (*CYP2C19*2* and *CYP2C19*3*) have no significant effect in causing recurrent CVEs while using clopidogrel. However, they showed a significant effect in leading to other complications (e.g., ST-elevation and stent thrombosis) [48–50]. This could be explained by the presence of other genetic factors that may affect both the clopidogrel bioactivation process and recurrent CVEs, including specific *CYP2C9*, *CYP3A4*, *CYP1A2*, and *CYP2B6* genes' mutations.

Regarding the qualitative part, the study revealed that *CYP2C19* alleles including *1 (71%), *2 (17%), *17 (12%), and *3 (< 1%), respectively, are commonly distributed among Arabs. Compared with some other ethnic groups (Caucasians, Africans, and Asians), the frequency of *CYP2C19*1* allele among Arabs was more or less similar to Caucasians (59%), Africans (70%), and Asians (65%). Besides, the frequency of the *CYP2C19*2* allele is similar to that of Caucasians (15%) and Africans (13%) but less than Asians (35%). Concerning the frequency of the *CYP2C19*17* allele among some different ethnic groups, it could be described that Caucasians were the most ethnic group to carry this allele (26%), followed by the Africans (17%), Arabs (12%), and Asians (0.5%). While the *CYP2C19*3* allele was rare among all reported ethnic groups, this allele is commonly detected in Asians (9%) [23].

Conclusion and future perspective

This study revealed that the *CYP2C19* genotypes including *1/*1, *1/*2, *1/*17, *2/*2, and *17/*17 are commonly distributed among Arabs. In addition, most Arab patients carrying *CYP2C19*2* or *CYP2C19*3* mutated alleles are at a significantly higher risk of recurrent CVEs, and could be described as non-responders to clopidogrel. However, few available studies were included in the quantitative part of the analysis, and further studies with a large sample size are recommended to confirm our results.

Abbreviations

CES-1: CArboxylesterase 1; CVD: Cardiovascular disease; CVDs: Cardiovascular diseases; CVE: Cardiovascular event; CVEs: Cardiovascular events; CI: Confidence interval; CYP2C9: Cytochrome P450 2C9 family 2 subfamily C member 9; CYP2B6: Cytochrome P450 family 2 subfamily B member 6; CYP2C19: Cytochrome P450 family 2 subfamily C member 19; CYP3A4: Cytochrome P450 family 3 subfamily A member 4; GRADE: Grading of recommendations assessment, development, and evaluation; OR: Odds ratio; PRISMA: Preferred reporting items for systematic reviews and meta-analyses.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43042-022-00313-w.

Additional file1. **Figure S1**: Risk of bias among included studies regarding adequate case definition, consecutive representativeness of cases, selection of community controls, adequate control definition, ascertainment of exposure/independent blind assessment of outcome, comparability of cases and controls, ascertainment of cases and controls/adequacy of the follow-up period, and complete follow-up period/same response rate.

Acknowledgements

The researchers would like to thank Dr. Yousef Almutairi (Saudi Ministry of Health, Riyadh, Saudi Arabia) for their assistance in reviewing the manuscript.

Author contributions

AK and NR contributed in conceptualization. AK, NR and NM contributed in writing—original draft preparation. NM, AF, and KA contributed in writing—review and editing. NR, NM, AK, and AF contributed in resources. All authors have read and agreed to the published version of the manuscript.

Funding

Not funded.

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no conflict of interest.

Author details

[1]Department of Research and Development, General Directorate of School Health, Ministry of Health, Riyadh, Saudi Arabia. [2]Department of Public Health and Community Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt. [3]Department of Research, Assisting Deputyship for Primary Health Care, Ministry of Health, Riyadh, Saudi Arabia. [4]Department of Family Medicine, College of Medicine, Al-Imam Mohammad Bin Saud Islamic University, Riyadh, Saudi Arabia.

Received: 8 February 2022 Accepted: 25 May 2022
Published online: 11 June 2022

References

1. Malaguarnera G, Latteri S, Catania VE, Malaguarnera M (2017) Reduction of cardiovascular risk in subjects with high lipoprotein (a) levels. J Thorac Dis 9(8):2332
2. Gradolí J, Vidal V, Brady AJ, Facila L (2018) Anticoagulation in patients with ischaemic heart disease and peripheral arterial disease: clinical implications of COMPASS study. Eur Cardiol Rev 13(2):115
3. Higashi MK, Veenstra DL, Kondo LM, Wittkowsky AK, Srinouanprachanh SL, Farin FM, Rettie AE (2002) Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. JAMA 287(13):1690–1698
4. Tingting W, Xia X, Jinglan F, Chen W, Zhang J (2020) Left atrial appendage thrombus formation in a patient with atrial fibrillation on dabigatran therapy associated with CES1 and ABCB1 genetic polymorphisms: a case report. Medicine 99(36):e22084
5. Al-Rubaish AM, Al-Muhanna FA, Alshehri AM, Al-Mansori MA, Alali RA, Khalil RM, Al-Faraidy KA, Cyrus C, Sulieman MM, Vatte C, Loza B-L (2021) Bedside testing of CYP2C19 vs. conventional clopidogrel treatment to guide antiplatelet therapy in ST-segment elevation myocardial infarction patients. Int J Cardiol 343:15–20. https://doi.org/10.1016/j.ijcard.2021.08.051
6. Xi Z, Fang F, Wang J, AlHelal J, Zhou Y, Liu W (2019) CYP2C19 genotype and adverse cardiovascular outcomes after stent implantation in clopidogrel-treated Asian populations: a systematic review and meta-analysis. Platelets 30(2):229–240
7. Damman P, Woudstra P, Kuijt WJ, de Winter RJ, James SK (2012) P2Y12 platelet inhibition in clinical practice. J Thromb Thrombolysis 33(2):143–153
8. Frelinger AL, Bhatt DL, Lee RD, Mulford DJ, Wu J, Nudurupati S, Nigam A, Lampa M, Brooks JK, Barnard MR, Michelson AD (2013) Clopidogrel pharmacokinetics and pharmacodynamics vary widely despite exclusion or control of polymorphisms (CYP2C19, ABCB1, PON1), noncompliance, diet, smoking, co-medications (including proton pump inhibitors), and pre-existent variability in platelet function. J Am Coll Cardiol 61(8):872–879
9. Zhu WY, Zhao T, Xiong XY, Li J, Wang L, Zhou Y, Gong ZL, Cheng SY, Liu Y, Shuai J, Yang QW (2016) Association of CYP2C19 polymorphisms with the clinical efficacy of clopidogrel therapy in patients undergoing carotid artery stenting in Asia. Sci Rep 6(1):1–7
10. Drögemöller BI, Wright GE, Niehaus DJ, Koen L, Malan S, Da Silva DM, Hillermann-Rebello R, La Grange AM, Venter M, Warnich L (2010) Characterization of the genetic profile of CYP2C19 in two South African populations. Pharmacogenomics 11(8):1095–1103
11. Liu J, Nie XY, Zhang Y, Lu Y, Shi LW, Wang WM (2015) CYP2C19* 2 and other allelic variants affecting platelet response to clopidogrel tested by thrombelastography in patients with acute coronary syndrome. Chin Med J 128(16):2183–2188
12. Tabari RG, Marjani A, Ataby OA, Mansourian AR, Samai NM (2013) Genetic polymorphism of cytochrome p450 (2C19) enzyme in Iranian Turkman ethnic group. Oman Med J 28(4):237
13. Alhazzani AA, Munisamy M, Karunakaran G (2017) Pharmacogenetics of CYP2C19 genetic polymorphism on clopidogrel response in patients with ischemic stroke from Saudi Arabia. Neurosci J 22(1):31–37
14. Kim S, Yun YM, Chae HJ, Cho HJ, Ji M, Kim IS, Wee KA, Lee W, Song SH, Woo HI, Lee SY (2017) Clinical pharmacogenetic testing and application: laboratory medicine clinical practice guidelines. Ann Lab Med 37(2):180–193

15. WELLS G (2001) The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
16. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336:924
17. Collaboration C (2014) Review Manager (RevMan)[Computer Program] Version 5.2. 3, The Nordic Cochrane Centre, Copenhagen, 2012. Health Psychol Rev. 17
18. Higgins JPT, Thompson SG, Deeks JJ (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
19. Abid L, Laroussi L, Bahloul A, Siala A, Abdelhédi R, Kharrat N, Hentati M, Kammoun S (2013) Impact of cytochrome P450 2C19* 2 polymorphism on the clinical cardiovascular events after stent implantation in patients receiving clopidogrel of a southern Tunisian region. World J Cardiovasc Dis 3:4–10
20. Al-Azzam SI, Alzoubi KH, Khabour OF, Nusair MB, Al-Hadidi H, Awidi A, Saleh A (2013) Factors that contribute to clopidogrel resistance in cardiovascular disease patients: environmental and genetic approach. Int J Clin Pharmacol Ther 51(3):179–186
21. Ayesh BM, Al-Astal IR, Yassin MM (2019) The clinical effects of CYP2C19* 2 allele frequency on palestinian patients receiving clopidogrel after percutaneous coronary intervention. Int J Clin Pharm 41(1):96–103
22. Khalil BM, Shahin MH, Solayman MH, Langaee T, Schaalan MF, Gong Y, Hammad LN, Al-Mesallamy HO, Hamdy NM, El-Hammady WA, Johnson JA (2016) Genetic and nongenetic factors affecting clopidogrel response in the Egyptian population. Clin Transl Sci 9(1):23–28
23. Mohammad AM, Al-Allawi NA (2018) CYP2C19 genotype is an independent predictor of adverse cardiovascular outcome in Iraqi patients on clopidogrel after percutaneous coronary intervention. J Cardiovasc Pharmacol 71(6):347–351
24. Al-Jenoobi FI, Alkharfy KM, Alghamdi AM, Bagulb KM, Al-Mohizea AM, Al-Muhsen S, Halwani R, Parvez MK, Al-Dosari MS (2013) CYP2C19 genetic polymorphism in Saudi Arabians. Basic Clin Pharmacol Toxicol 112(1):50–54
25. Rjoub M, Saleh A, Hakooz N, Imraish A, Jarrar Y, Zihlif M (2018) Allelic frequency of PON1 Q192R, CYP2C19* 2 and CYP2C19* 17 among Jordanian patients taking clopidogrel. Trop J Pharm Res 17(11):2275–2280
26. Ahmad M, Navarro-Quiroz E, García Moreno AM, Rios Anillo MR, Silvera Redondo CA, Fernandez PC (2018) Analysis of gene polymorphism CYP2C19 in the Lebanese population who reside in Colombia. Global J Health Sci 10(7):1–36
27. Khalaf H, Al Meman AA, Rasool S (2016) Impact of cytochrome P450 2C19*2 and *3 on clopidogrel loading dose in saudi patients with acute coronary syndrome. Drug Metab Lett 10(1):65–70. https://doi.org/10.2174/1872312810666151117122841
28. Mirzaev KB, Zelenskaya EM, Barbarash OL, Ganyukov VI, Apartsin KA, Saraeva NO, Nikolaev KY, Ryzhikova KA, Lifshits GI, Sychev DA (2017) CYP2C19 polymorphism frequency in Russian patients in Central Russia and Siberia with acute coronary syndrome. Pharmacogenom Personal Med 10:107
29. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS (2009) Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 360(4):354–362
30. Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, Horenstein RB, Damcott CM, Pakyz R, Tantry US, Gibson Q, Pollin TI (2009) Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA 302(8):849–857
31. Harmsze AM, van Werkum JW, Bouman HJ, Ruven HJ, Breet NJ, Ten Berg JM, Hackeng CM, Tjoeng MM, Klungel OH, de Boer A, Deneer VH (2010) Besides CYP2C19* 2, the variant allele CYP2C9* 3 is associated with higher on-clopidogrel platelet reactivity in patients on dual antiplatelet therapy undergoing elective coronary stent implantation. Pharmacogenet Genom 20(1):18–25
32. Gong IY, Crown N, Suen CM, Schwarz UI, Dresser GK, Knauer MJ, Sugiyama D, DeGorter MK, Woolsey S, Tirona RG, Kim RB (2012) Clarifying the importance of CYP2C19 and PON1 in the mechanism of clopidogrel bioactivation and in vivo antiplatelet response. Eur Heart J 33(22):2856–2864
33. Simon T, Bhatt DL, Bergougnan L, Farenc C, Pearson K, Perrin L, Vicaut E, Lacreta F, Hurbin F, Dubar M (2011) Genetic polymorphisms and the impact of a higher clopidogrel dose regimen on active metabolite exposure and antiplatelet response in healthy subjects. Clin Pharmacol Ther 90(2):287–295
34. Varenhorst C, James S, Erlinge D, Brandt JT, Braun OÖ, Man M, Siegbahn A, Walker J, Wallentin L, Winters KJ, Close SL (2009) Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. Eur Heart J 30(14):1744–1752
35. Sibbing D, Gebhard D, Koch W, Braun S, Stegherr J, Morath T, Von Beckerath N, Mehilli J, Schömig A, Schuster T, Kastrati A (2010) Isolated and interactive impact of common CYP2C19 genetic variants on the antiplatelet effect of chronic clopidogrel therapy. J Thromb Haemost 8(8):1685–1693
36. Kelly RP, Close SL, Farid NA, Winters KJ, Shen L, Natanegara F, Jakubowski JA, Ho M, Walker JR, Small DS (2012) Pharmacokinetics and pharmacodynamics following maintenance doses of prasugrel and clopidogrel in Chinese carriers of CYP2C19 variants. Br J Clin Pharmacol 73(1):93–105
37. Collet JP, Hulot JS, Anzaha G, Pena A, Chastre T, Caron C, Silvain J, Cayla G, Bellemain-Appaix A, Vignalou JB, Galier S (2011) High doses of clopidogrel to overcome genetic resistance. JACC: Cardiovasc Interv 4(4):392–402. https://doi.org/10.1016/j.jcin.2011.03.002
38. Jinnai T, Horiuchi H, Makiyama T, Tazaki J, Tada T, Akao M, Ono K, Hoshino K, Naruse Y, Takahashi K, Watanabe H (2009) Impact of CYP2C19 polymorphisms on the antiplatelet effect of clopidogrel in an actual clinical setting in Japan. Circ J 73(8):1498–1503
39. Hochholzer W, Trenk D, Fromm MF, Valina CM, Stratz C, Bestehorn HP, Büttner HJ, Neumann FJ (2010) Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. J Am Coll Cardiol 55(22):2427–2434
40. Jeong YH, Kim IS, Park Y, Kang MK, Koh JS, Hwang SJ, Kwak CH, Hwang JY (2010) Carriage of cytochrome 2C19 polymorphism is associated with risk of high post-treatment platelet reactivity on high maintenance-dose clopidogrel of 150 mg/day: results of the ACCEL-DOUBLE (accelerated platelet inhibition by a double dose of clopidogrel according to gene polymorphism) study. JACC Cardiovasc Interv 3(7):731–41
41. Kang MK, Jeong YH, Yoon SE, Koh JS, Kim IS, Park Y, Hwang SJ, Kwak CH, Hwang JY (2010) Pre-procedural platelet reactivity after clopidogrel loading in korean patients undergoing scheduled percutaneous coronary intervention. J Atheroscler Thromb. https://doi.org/10.5551/jat.4564
42. Bouman HJ, Harmsze AM, van Werkum JW, Breet NJ, Bergmeijer TO, Ten Cate H, Hackeng CM, Deneer VH, Ten Berg JM (2011) Variability in on-treatment platelet reactivity explained by CYP2C19* 2 genotype is modest in clopidogrel pretreated patients undergoing coronary stenting. Heart 97(15):1239–1244
43. Yamamoto K, Hokimoto S, Chitose T, Morita K, Ono T, Kaikita K, Tsujita K, Abe T, Deguchi M, Miyagawa H, Saruwatari J (2011) Impact of CYP2C19 polymorphism on residual platelet reactivity in patients with coronary heart disease during antiplatelet therapy. J Cardiol 57(2):194–201
44. Kim IS, Jeong YH, Park Y, Yoon SE, Kwon TJ, Park JR, Hwang SJ, Koh EH, Kwak CH, Hwang JY, Kim S (2012) Interaction analysis between genetic polymorphisms and pharmacodynamic effect in patients treated with adjunctive cilostazol to dual antiplatelet therapy: results of the ACCEL-TRIPLE (accelerated platelet inhibition by triple antiplatelet therapy according to gene polymorphism) study. Br J Clin Pharmacol 73(4):629–640
45. Tang XF, Wang J, Zhang JH, Meng XM, Xu B, Qiao SB, Wu YJ, Chen J, Wu Y, Chen JL, Gao RL (2013) Effect of the CYP2C19* 2 and* 3 genotypes, ABCB1 C3435T and PON1 Q192R alleles on the pharmacodynamics and adverse clinical events of clopidogrel in Chinese people after percutaneous coronary intervention. Eur J Clin Pharmacol 69(5):1103–1112
46. Wu H, Qian J, Xu J, Sun A, Sun W, Wang Q, Ge J (2012) Effects of CYP2C19 variant alleles on postclopidogrel platelet reactivity and clinical outcomes in an actual clinical setting in China. Pharmacogenet Genom 22(12):887–890
47. Zou JJ, Xie HG, Chen SL, Tan J, Lin L, Zhao YY, Xu HM, Lin S, Zhang J, Wang GJ (2013) Influence of CYP2C19 loss-of-function variants on the antiplatelet effects and cardiovascular events in clopidogrel-treated Chinese patients undergoing percutaneous coronary intervention. Eur J Clin Pharmacol 69(4):771–777
48. Zabalza M, Subirana I, Sala J, Lluis-Ganella C, Lucas G, Tomás M, Masiá R, Marrugat J, Brugada R, Elosua R (2012) Meta-analyses of the association

between cytochrome CYP2C19 loss-and gain-of-function polymorphisms and cardiovascular outcomes in patients with coronary artery disease treated with clopidogrel. Heart 98(2):100–108
49. Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP (2011) CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. JAMA 306(24):2704–2714
50. Bauer T, Bouman HJ, van Werkum JW, Ford NF, Ten Berg JM, Taubert D (2011) Impact of CYP2C19 variant genotypes on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis. BMJ 4:343

Publisher's Note