New Perspectives on Clopidogrel Resistance Systematic Review and Meta-analysis

Abstract

Background: Clopidogrel resistance can be defined as failure of clopidogrel to inhibit its target of action. The prevalence of clopidogrel resistance in various studies ranges between 5%–44%. Clopidogrel resistance is a serious scary condition whereby clopidogrel drug is less or not effective for some patients than expected. Hence the present Systematic review was conducted to explore the new perspectives of Clopidogrel and to evaluate the effect of genetic polymorphisms CYP2C19 (CYP2C19*2, CYP2C19*3) of the key drug metabolizing enzymes on the response to the antiplatelet effect of clopidogrel. To provide insights into the commentary summarizes the clinical evidence on the pharmacokinetic determinants of clopidogrel efficacy.

Material and Method: Systematic review is a type of literature reviews that collects and critically analyzes multiple research studies using methods that are selected before one or more research questions are formulated and then finding and analyzing studies that relate to and answer those questions in a structured methodology.

Results: Accumulated information from suggested the presence of high incidence of clopidogrel resistance. Associated with acute coronary syndrome (ACS), Acute myocardial infarction (AMI) and stroke. There was no significant difference in the incidence of resistance according to the type of studies.

Conclusion: Accumulated information from previous studies and from the present systematic review suggested the presence of high incidence of clopidogrel resistance. This resistance was associated with serious complications such as acute coronary syndrome (ACS), Acute myocardial infarction (AMI) and stroke.

Key words: Anti platelet action, Clopidogrel, Clopidogrel resistance, coagulation

Introduction:

Coagulation is the process by which the blood changes from a liquid form to a form which seems like a gel, in other words, the blood clots. Usually, this occurs as a result of the body hemostasis in which a ruptured blood vessel needs to be closed up. The body hence activates the process of coagulation in collaboration of fibrin deposit and the action of the platelet, the blood clots to stop the bleeding[1].

Platelets are also known as thrombocytes; they work in collaboration with other mechanisms to stop bleeding during blood vessel injury. Anti-platelets are agents that are introduced in the body which reduce the capability of platelets to stick together. These agents are normally employed to help patients under high risk of myocardial infarction. Myocardial infarction may be caused by blood clotting in major heart artery blocking nutrients and oxygen to heart muscles[2].

Comment [1]: arteries

Some patients are under high risk of a heart attack and have the tendencies of having a blood clot in the blood vessels blocking important nutrients to vital organ muscles. In such situations anti-platelet medications are prescribed to reduce the platelet aggregation leading to reducing their capability to form a clot, which in turn reduces the risk of the patient experiencing any unwanted clotting in their blood vessels which may cause a stroke or heart attack[3].

One of the groups of Anti platelet action is the platelet aggregation inhibitor is Clopidogrel. This medicine is prescribed for the prevention of a high-risk occurrence of myocardial infarction and atrial fibrillation. The protease-activated receptor is the third group which also acts to inhibit important protease in the clotting process[4]. Clopidogrel is an antiplatelet medicine which is normally employed by medical professionals to reduce to risks of myocardial infarction and stroke. This medicine is however in most cases administered together with aspirin in the case of heart attacks and following placement of a coronary stent. It is administered orally and has side effects like nausea, heartburn, and headaches[5]. Clopidogrel, an oral irreversible P2Y12 receptor antagonist, is widely used in clinical practice in comparison to other P2Y12 antagonists such as ticagrelor or prasugrel. P2Y12 inhibitors are crucial for patients with acute coronary syndrome (ACS) and post percutaneous coronary intervention (PCI) to prevent future thrombotic events[6].

Comment [2]: proteases

Clopidogrel is a prodrug, which is activated in two steps, first by CYP2C19, CYP1A2 and CYP2B6, then by CYP2C19, CYP2C9, CYP2B6 and CYP3A. The active metabolite then specifically and irreversibly inhibits the P2Y12 subtype of ADP receptor, which is important in activation of platelets and eventual cross-linking by the protein fibrin[7].

Since there is dearth of information on clopidogrel and its resistance form and subsequent cardiovascular events, the present systematic review was conducted with to evaluate the effect of genetic polymorphisms CYP2C19 (CYP2C19*2, CYP2C19*3) of the key drug metabolizing enzymes on the response to the antiplatelet effect of clopidogrel and to provide insights into the commentary summarizes the clinical evidence on the pharmacokinetic determinants of clopidogrel efficacy. Along with this from the present systematic review it would be easy to

clarify the results of some studies that were carried out about the markers of the genetic effect of CYP2C19 on clopidogrel response.

Material and Methods:

The Five Steps to Conduct a Systematic Review

Based on Khan et al, 2003[8], a systemic review consists of five steps and they are;

Comment [3]: systematic

Step 1: Framing questions for a review

The problem to be addressed by the review will be specified in the form of clear structured questions before beginning the review work.

Step 2: Identifying relevant work

Studies from multiple resources will be searched with selection criteria that flow directly from the review questions. Reasons for inclusion and exclusion will be recorded.

Step 3: Assessing the quality of studies

Selected studies will be subjected to a more refined quality assessment by using general critical appraisal guidelines and design-based quality checklists.

Step 4: Summarizing the evidence

The study characteristics, quality and effects as well as the statistical methods will be tabulated to explore the differences between studies and combine their effects (meta-analysis).

Step 5: Interpreting the findings

The risk of publication bias will be explored. Exploration for heterogeneity will determine whether the overall summary can be trusted. Any recommendations will be graded by reference to the strengths and weaknesses of the evidence.

2. Registration

The research was registered with the REU (FPGRP/43739017/201)

3. Data collection

In this research we used open Meta analytic program.

The program is recommended by all academics for their students as well and I found a recommendation from my supervisor

The program helps the researcher (systemic review) to collect all data related to the study. (Authors, year of publication, gender of patients, number of patients)

During the study, all studies were added until they were analyzed accurately.

The information recorded during the research period was as follows:

1. Authors name.
2. Type of study.
3. Year of Publication.
4. Number of patients in the study.
5. The number of patient's incidence resistance.
6. Classification of patients by disease. (ACS, AMI, Stroke)

Comment [4]: used an open

Comment [5]: It is necessary to mention the name and version of the program used

Comment [6]: I think this information is not necessary

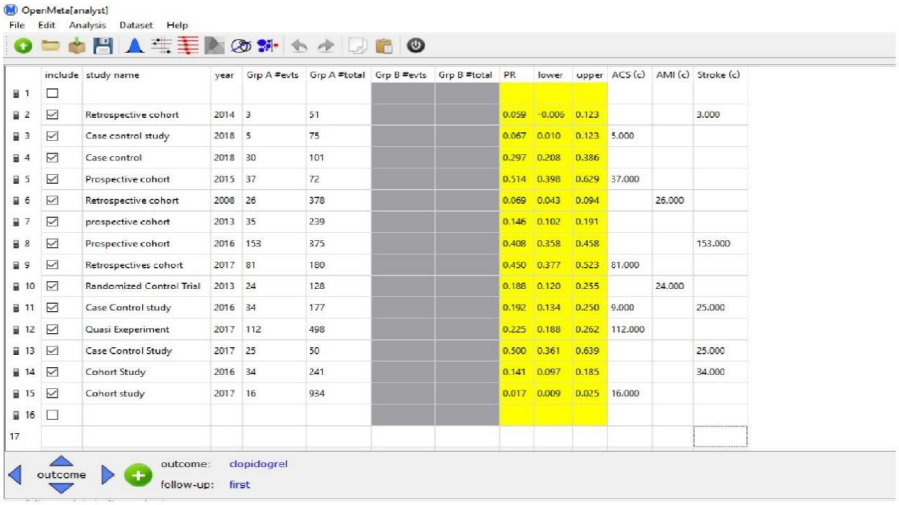
Comment [7]: This table did not include the presence of polymorphisms in the genes CYP2C19

Comment [8]: Author´s name

7. Gender of patient.

8. Number of males.

9. Number of females.



	include	study name	year	Grp A #evts	Grp A #total	Grp B #evts	Grp B #total	PR	lower	upper	ACS (c)	AMI (c)	Stroke (c)
1	☐												
2	☑	Retrospective cohort	2014	3	51			0.059	-0.009	0.123			3.000
3	☑	Case control study	2018	5	75			0.067	0.010	0.123	5.000		
4	☑	Case control	2018	30	101			0.297	0.208	0.386			
5	☑	Prospective cohort	2015	37	72			0.514	0.398	0.629	37.000		
6	☑	Retrospective cohort	2008	26	378			0.069	0.043	0.094		26.000	
7	☑	prospective cohort	2013	35	239			0.146	0.102	0.191			
8	☑	Prospective cohort	2016	153	375			0.408	0.358	0.458			153.000
9	☑	Retrospectives cohort	2017	81	180			0.450	0.377	0.523	81.000		
10	☑	Randomized Control Trial	2013	24	128			0.188	0.120	0.255		24.000	
11	☑	Case Control study	2016	34	177			0.192	0.134	0.250	9.000		25.000
12	☑	Quasi Experiment	2017	112	498			0.225	0.188	0.262	112.000		
13	☑	Case Control Study	2017	25	50			0.500	0.361	0.639			25.000
14	☑	Cohort Study	2016	34	241			0.141	0.097	0.185			34.000
15	☑	Cohort study	2017	16	934			0.017	0.009	0.025	16.000		
16	☐												
17													

Pic 1: Picture showing steps to use the program during the search (Open meta analytic)

Column 1: Type of studies used in systematic review.

Column 2: The year of publication for each study.

Column 3: The number of patient's incidence resistance.

Column 4: Number of total patients.

Column 5: Number of patient's incidence resistance with Acute coronary syndrome.

Column 6: Number of patient's incidence resistance with Acute Myocardial Infarction.

Column 7: Number of patient's incidence resistance with Stroke.

Results and Discussion:

Table 1 Summary of Studies Reviewed

Study Author	Year	Type of Study	Country	NO. Total of patients	Incidence of Resistance	No. Male	No. Female
Sen et al	2014	Retrospective cohort	Turkey	51	3	21	30
Hind Hassani Idrissi1 et al	2018	Case control study	Moroccan	75	5	42	33
Zhong-ling Zhuo et al	2018	Case control	China	101	30	28	73
V. ARYA et al	2015	Prospective cohort	India	72	37	60	12
Jean-Philippe Collet et al	2008	Retrospective cohort	France	378	26		
Mustapha M. El-Halabi et al	2013	prospective cohort	Lebanon	239	35	176	63
Xingyang Yi1 et al	2016	Prospective cohort	China	375	153	242	133
Jia Su1 et al	2017	Retrospective cohort	China	180	81	139	41
Kavita K. Shalia et al	2013	Randomized Control Trial	Mumbai, India	128	24	66	62
Alina Marginean, et al	2016	Case control study	Romania	177	34	98	79
Miaonan Li et al	2017	Quasi Experiment	China	498	112	310	188
Adel A. Alhazzani et al	2017	Case Control Study	Kingdom of Saudi Arabia	50	25	37	13
Wen-Yao Zhu et al	2016	Cohort Study	China	241	34	217	24
Zhixiong Zhong et al	2017	Cohort Study	China	934	16	717	217

1. **Summary of Studies Reviewed**

In a Retrospective cohort created by Sen et al (2014) in Turkey, 51 patients taken clopidogrel were included in this study (21 male, 30 female), 3 patients (5.8%) showed resistance to clopidogrel[9].

In a Case control study done by Hind Hassani Idrissi et al (2018) in Morocco, 75 patients taken clopidogrel were included in this study (42 male, 33 female), 5 patients (6.6%) showed resistance to clopidogrel [10].

In a Case control study created by Zhong-ling Zhuo et al (2018) in China, 101 patients taken clopidogrel were included in this study (28 male, 73 female), 30 patients (30%) showed resistance to clopidogrel[11].

In a Prospective cohort study created by V. ARYA et al (2015) in India, 72 patients taken clopidogrel were included in this study (60 male, 12 female), 37 patients (51%) showed resistance to clopidogrel[12].

In a Retrospective cohort study created by Jean-Philippe Collet et al (2008) in France, 378 patients taken clopidogrel were included in this study, 26 patients (6.8%) showed resistance to clopidogrel[13].

In a Prospective cohort study done by Mustapha M. El-Halabi et al (2013) in Lebanon, 239 patients taken clopidogrel were included in this study (176 male, 63 female), 35 patients (14.6%) showed resistance to clopidogrel[14].

In a Prospective cohort study created by Xingyang Yi et al (2016) in China, 375 patients taken clopidogrel were included in this study (242 male, 133 female), 153 patients (40.8%) showed resistance to clopidogrel[15].

In a Retrospective cohort study by Jia Su et al (2017) in China, 180 patients taken clopidogrel were included in this study (139 male, 41 female), 81 patients (45%) showed resistance to clopidogrel[16].

In a Randomized control trial by Kavita K. Shalia et al (2013) in India, 128 patients taken clopidogrel were included in this study (66 male, 62 female), 24 patients (19%) showed resistance to clopidogrel[17].

A Case control study by Alina Marginean, MD et al (2016) in Romania, 177 patients taken clopidogrel were included in this study (98 male, 79 female), 34 patients (19%) showed resistance to clopidogrel[18].

In a Quasi experiment created by Miaonan Li et al (2017) in China, 498 patients taken clopidogrel were included in this study (310 male, 188 female), 112 patients (22.5%) showed resistance to clopidogrel[19].

In a Case control study by Adel A. Alhazzani et al (2017) in Saudi Arabia, 50 patients taken clopidogrel were included in this study (37 male, 13 female), 25 patients (50%) showed resistance to clopidogrel[20].

In a cohort study created by Wen-Yao Zhu et al (2016) in China, 241 patients taken clopidogrel were included in this study (217 male, 24 female) 34 patients (14%) showed resistance to clopidogrel[21].

In a cohort study by Zhixiong Zhong et al (2017) in China, 934 patients taken clopidogrel were included in this study (717 male, 217 female), 16 patients (1.7%) showed resistance to clopidogrel [22].

Table 2: Specific Complications reported ACS; Acute Coronary syndrome.AMI; Acute Myocardial Infarction.

Study Author	Year	No. pt. w. ACS incidence resistance	No. pt. w. AMI incidence resistance	No. pt. w. stroke incidence resistance
Sen et al	2014			3
Hind Hassani Idrissi1 et al	2018	5		
V. ARYA et al	2015	37		
Jean-Philippe Collet et al	2008		26	
Xingyang Yi1 et al	2016			153
Jia Su1 et al	2017	81		
Kavita K. Shalia et al	2013		24	
Alina Marginean, MD et al	2016	9		25
Miaonan Li et al	2017	112		
Adel A. Alhazzani et al	2017			25
Wen-Yao Zhu et al	2016			34
Zhixiong Zhong et al	2017	16		

2. Complications reported to be associated with clopidogrel resentence

In addition to developing clopidogrel resistance these studies also reported a number of specific complications which when grouped showed that the incidence of Acute coronary syndrome was

the highest at 5 Patients (Hind et al,2018, case control study)[10], 37 patients (V.Arya et al,2015, cohort)[12],81 patients (Jia et al,2017,retrospectively study)[16], 9 patients (Alina et al,2016, case control)[18],112 patients (Miaonan et al,2017, case control)[19] and 16 patients (Zhixiong et al,2017, cohort study) [22] with a total of 260 patients incidence resistance with Acute coronary syndrome.

In one of the studies done among 24 patients (Kavita et al,2013, randomized control trial)[17] with a total 30 patients incidence resistance with Acute Myocardial Infarction was reported.

Also, other studies reported when grouped that there is a significant incidence of stroke at 3 patients (Sen et al, 2014, retrospective cohort)[9], 153 patients (xingyang, 2016, prospective cohort)[22], 25 patients (Alina et al,2016, case control study)[18], 25 patients (Adel et al,2017 case control study)[23] and with a total 240 patients incidence resistance with stroke.

This points towards a correlation trend between the development of resistance and Acute coronary syndrome (260 patients).

Table 3: Binary Random Effect Model for the incidence of Resistance

Estimate	**Lower Bound**	**Upper Bound**	**Std Error**	**P Value**
0.226	0.152	0.301	0.038	< 0.001

Heterogeneity

tau^2	**Q(df=13)**	**Heterogenity (p-Value)**	**I^2**
0.019	664.823	< 0.001	98.045

The mean probability of resistance using a binary random effect model was 0.226 (22.6%) with CI between 0.152 – 0.301. However, there is a large heterogeneity ($p<0.001$) (Table 3). This can be attributed to the significant variation in the studies as shown the forest plot (Figure 1)

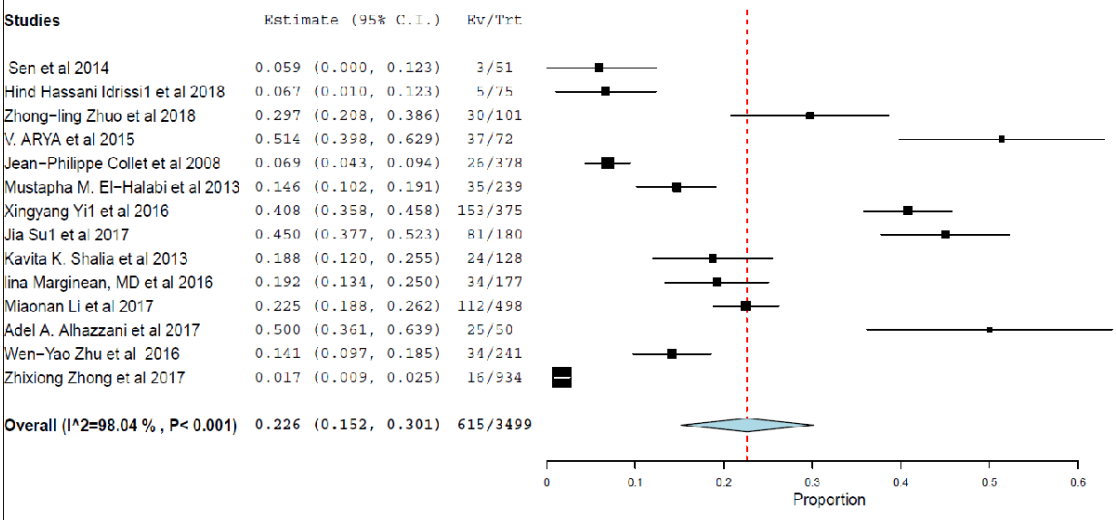


Figure 1: Forest plot of the different studies showing binary probability of resistance

The boxes show the effect estimates from the single studies, while the diamond shows the pooled result.

The horizontal lines through the boxes illustrate the length of the confidence interval. The longer the lines, the wider the confidential interval, the less reliable the study results.

The vertical line is the line of no effect (i.e. the position at which there is no clear difference between the intervention group and the control group).

The outcome of interest (resistance), the results to the left of the vertical line favor the development of resistance in the presence of the polymorphism.

The diamond at the bottom of the forest plot shows the result when all the individual studies are combined together and averaged. The horizontal points of the diamond are the limits of the 95% confidence intervals and are subject to the same interpretation as any of the other individual studies on the plot.

To combine it all, our systemic review of the studies chosen shows the following,

Comment [9]: systematic

1. There is a high probability to develop clopidogrel resistance in the presence of this specific gene polymorphism.

2. From the studies included, 9 showed small confidence interval in comparison to 5 that had a wide confidence interval. This indicates that the 9 studies have a more reliable result than the other 5. The 9 reliable studies were all showing a high correlation between the treatment, the polymorphism and the development of resistance.

Comment [10]: showed a small

3. Only one study, Miaonan Li et al., 2017[19] showed no difference or specifically no association between the development of resistance and the gene polymorphism.

4. Overall, from the diamond, there is a significant ($p<0.001$) association between the development of clopidogrel resistance and this specific gene polymorphism.

Table 4: Influence of the type of study on the incidence of resistance

Covariate	Level	Adjusted Means	Lower bound	Upper bound	Std. error	p-Value
Intercept						< 0.001
Type of Study	Cohort (n=8)	0.221	0.101	0.341	0.061	0.744
	Case Control (n=4)	0.256	0.083	0.429	0.088	

The meta-regression showed strong correlation between the cohort and the case control studies ($p<0.001$) and no significant difference in incidence of resistance according to the type of study.

Conclusion:

There was large heterogenicity due to significant variations in the studies involved in our meta-analysis which includes patient differences, data collection and analysis. There was strong correlation between the cohort & the case control studies but there was no significant difference in the incidence of resistance according to the type of study.

Comment [11]: heterogeneity

In conclusion, the presence of this polymorphism leads to high incidences of clopidogril resistance and the development of a number of complications as acute coronary syndrome (ACS), Acute myocardial infarction (AMI) and stroke. The studies included in this review that

Comment [12]: complications such as acute

signifies the development of resistance were both cohort and case control, with strong correlation between both, strengthening the outcome.

To conclude, I hereby quote from the works used in this paper that the prevalence of clopidogrel resistance in most parts of the world happens to be in accordance to the already reported cases in the western populations. The CYP2C19 polymorphisms including (*2/*2 & *1/*1) alleles showed greater levels of association with clopidogrel response. Patients deemed to be carriers of the allele CYP2C19*2/*2 presented with cases of elevated risks of not responding to clopidogrel treatment as compared to the wild-type allele (CYP2C19*1/*1).

Comment [13]: with the

Recommendation

The recommendations targeted the use of prasugrel or ticagrelor as the alternative anti-platelet agents. Publishing would be allowed if only the alternatives did not show any signs of contraindications in all the featured categories of patients like the PMs and IMs. These individuals have presented with reduced platelet inhibition, high risks associated with cardiovascular events as well as a high degree in terms of residual platelet aggregation. Due to lack of data and information concerning clopidogrel in the US and in Morocco as shown in the reports, it becomes very difficult to ascertain the loss of function (CYP2C19*2, CYP2C19*3) or even gain of function.

These findings lead to the breakthrough that genetic testing should be used so as to stratify who might need novel anti-platelet therapy. Additional research should also be carried out to characterize other genetic variations thus creating a platform for predicting clopidogrel resistance in a more diverse setting.

Strength and Weakness of this study

This research was conducted as a systematic review of clopidogrel resistance. This research was discussed after reviewing many of the topics that raise the question of health. The study was prepared after the study of similar topics related to the resistance of clopidogrel.

The research was prepared to be the first systematic review of clopidogrel resistance. It has not been done before.

References:

1. Taylor Jr FB, Toh CH, Hoots WK, Wada H, Levi M. Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Thromb Haemost. 2001;86(5):1327-30.

2. Born GVR, Cross MJ. The aggregation of blood platelets. J Physiol. 1963; 168(1): 178–95.

3. Lamberts M, Gislason GH, Olesen JB, Kristensen SL, Olsen AMS, Mikkelsen A et al. Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. J Am Coll Cardiol. 2013(10);62(11):981-9.

4. Darren Aw, Sharma JC. Antiplatelets in secondary stroke prevention: should clopidogrel be the first choice?. Postgrad Med J. 2012;88(1035):34-7.

5. Heemskerk JWM, Bevers EM, Lindhout T. Platelet activation and blood coagulation. Thromb Haemost. 2002;88(2):186-93.

6. Yusuf S Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Clopidogrel in unstable angina to prevent recurrent events trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001; 345, 494–502.

7. Cattaneo M. "Response variability to clopidogrel: is tailored treatment, based on laboratory testing, the right solution? Journal of Thrombosis and Haemostasis. March 2012; 10 (3): 327–36.

8. Khan KS, Kunz R, Kleijnen J, Antes G. Five steps to conducting a systematic review. Journal of the royal society of medicine. 2003;96(3):118-21

9. Sen HM, Silan F, Silan C, Degirmenci Y, Ozisik Kamaran HI. Effects of Cyp2c19 And P2y12 Gene Polymorphisms On Clinical Results Of Patients Using Clopidogrel After Acute Ischemic Cerebrovascular Disease. Balkan J Med Genet. 2015(10);17(2):37-41.

10. Idrissi HH, Hmimech W, El Khorb N, Akoudad H, Habbal R, Nadifi S. A synergic effect between CYP2C19*2, CYP2C19*3 loss of function and CYP2C19*17 gain of function alleles is associated with Clopidogrel resistance among Moroccan Acute Coronary Syndromes patients. BMC Res Notes. 2018 18;11(1):46.

11. Zhuo ling Z, Xian peng H, Long Y, Liu C, Sun Yy, Ma Yt, Gao H, Zhao Jz, Zhao tao X. Association between CYP2C19 and ABCB1 polymorphisms and clopidogrel resistance in clopidogrel treated Chinese patients. Anatol J Cardiol. 2018;19(2):123-129.

12. Arya V, Mahajan P, Saraf A, Mohanty A, Sawhney JPS, Bhargava M. Association of CYP2C19, CYP3A5 and GPIIb/IIIa gene polymorphisms with Aspirin and Clopidogrel Resistance in a cohort of Indian patients with Coronary Artery Disease. Int J Lab Hematol. 2015;37(6):809-18.

13. Collet JP, Hulot JS, Pena A, Villard E, Esteve JB, Silvain J et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet. 2009(24);373(9660):309-17.

14. El-Halabi MM, Zgheib N, Nabil M, Malli MA, Ghaith Ola A, Mahfouz R et al. CYP2C19 Genetic Polymorphism, Rabeprazole and Esomeprazole Have no Effect on the Antiplatelet Action of Clopidogrel. Anatol J Cardiol. 2013;6:80-89.

15. Yi X, Lin J, Wang Y, Zhou Q, Wang C, Cheng W. Association of Cytochrome P450 Genetic Variants with Clopidogrel Resistance and Outcomes in Acute Ischemic Stroke. J Atheroscler Thromb. 2016(1); 23(10): 1188–00.

16. Su J, Yu Q, Zhu H, Li X, Cui H, Du W et al. The risk of clopidogrel resistance is associated with ABCB1 polymorphisms but not promoter methylation in a Chinese Han population. PLoS One. 2017 (30);12(3):e0174511.

17. Shalia KK, Shah VK, Pawar P, Divekar SS, Payannavar S. Polymorphisms of MDR1, CYP2C19 and P2Y12 genes in Indian population: Effects on clopidogrel response. Indian Heart J. 2013;65(2):158-67.

18. Maˇrginean A, Baˇnescu C, Moldovan V, Scridon A, Maˇrginean M, Baˇlas¸a R et alThe Impact of CYP2C19 Loss-of-Function Polymorphisms, Clinical, and Demographic Variables on Platelet Response to Clopidogrel Evaluated Using Impedance Aggregometry. Clinical and Applied Thrombosis/Hemostasis. 2017; 23(3): 255-65

19. Li M, Wang H, Xuan L, Shi X, Zhou T, Zhang N et al. Associations between P2RY12 gene polymorphisms and risks of clopidogrel resistance and adverse cardiovascular events after PCI in patients with acute coronary syndrome. Medicine (Baltimore). 2017; 96(14): e6553.

20. Alhazzani AA, Munisamy M, Karunakaran G. Pharmacogenetics of CYP2C19 genetic polymorphism on clopidogrel response in patients with ischemic stroke from Saudi Arabia. Neurosciences (Riyadh). 2017; 22(1): 31–37.

21. Yao ZW, Zhao T, Yi XX, Li J, Li Wang, Yu Zhou, Association of CYP2C19 Polymorphisms with the Clinical Efficacy of Clopidogrel Therapy in Patients Undergoing Carotid Artery Stenting in Asia. Sci Rep. 2016(3);6:25478.

22. Zhong Z, Hou J, Zhang Q, Li B, Cunren Li, Liu Z et al. Effect of cytochrome P450 2C19 polymorphism on adverse cardiovascular events after drug-eluting stent implantation in a large Hakka population with acute coronary syndrome receiving clopidogrel in southern China. Eur J Clin Pharmacol. 2018;74(4):423-431.

23. Adel A. Munisamy AM, Karunakaran G. Pharmacogenetics of CYP2C19 genetic polymorphism on clopidogrel response in patients with ischemic stroke from Saudi Arabia. Neurosciences (Riyadh). 2018; 22(2): 57–62.