RESEARCH ARTICLE

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY
(ФАРМАЦИЯ И ФАРМАКОЛОГИЯ)

Systematic review of the influence of DNA methylation level on the efficacy of P2Y12 receptor antagonists

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Received 29 Sep 2025 After peer review 30 April 2026 Accepted 20 May 2026

The prescription of antiplatelet agents is an important part of the therapy for acute coronary syndrome and other cardiovascular diseases. The risk of recurrent ischemic events depends on the efficacy of these drugs.

The aim. To summarize and analyze current scientific data on the influence of DNA methylation level on the efficacy of therapy with P2Y12 receptor antagonists.

Materials and methods. A search for scientific articles was conducted in the PubMed database. The systematic review included studies reflecting the relationship between DNA methylation and the efficacy of clopidogrel. No studies were found concerning the influence of DNA methylation on the efficacy of next-generation P2Y12 receptor antagonists.

Results. The review included 17 studies with a total of 3 441 participants. The influence of methylation of 20 genes was analyzed: *ABCB1, ABCC3, ALOX12, ALOX15, BTG2, CD80, COX1, COX2, CREB5, CYP2C19, GCK, GNAQ, P2Y12, PEAR1, PER3, PON1, PRG2, TRAF3, TBXAS1, VTRNA2-1*. In 9 studies, a bond was found between methylation levels and the risk of developing clopidogrel resistance. In 5 studies, a bond was found between DNA methylation and the risk of developing adverse reactions such as bleeding or recurrent ischemic events. It was found that patients with hypomethylation of the *CYP2C19* gene promoter have a higher risk of developing clopidogrel resistance (methylation level in the clopidogrel resistance group is 8.8 ± 22.7 %, in the control group — 76.7 ± 32.9 %, $p = 0.03$). Hypermethylation of the *P2Y12* promoter also increases the risk of developing resistance to the drug (0.48 ± 0.14 % vs. 0.86 ± 0.13 %, $p < 0.001$).

Conclusion. The products of DNA methylation of genes are involved in clopidogrel metabolism, platelet aggregation, and other processes affects clopidogrel efficacy. DNA methylation level is a promising biomarker. Additional confirmatory studies are needed, as well as studies on the relationship between the methylation level and the efficacy of next-generation P2Y12 receptor antagonists.

Keywords: methylation; epigenetics; clopidogrel; antiplatelet agents; P2Y12 receptor antagonists; resistance; platelet aggregation; acute coronary syndrome; ischemia

Abbreviations: MPA — maximum platelet aggregation; PRI — platelet Reactivity Index; PRU — platelet reactivity unit; ADP — adenosine diphosphate; DAT — dual antiplatelet therapy; IHD — ischemic heart disease; ACS — acute coronary syndrome; DM — diabetes mellitus.

For citation: S.N. Tuchkova, Sh.P. Abdullaev, N.P. Denisenko, K.B. Mirzaev, D.A. Sychev. Systematic review of the influence of DNA methylation level on the efficacy of P2Y12 receptor antagonists. *Pharmacy & Pharmacology.* 2026;14(3):218-235. **DOI:** 10.19163/2307-9266-2026-14-3-218-235

Для цитирования: С.Н. Тучкова, Ш.П. Абдуллаев, Н.П. Денисенко, К.Б. Мирзаев, Д.А. Сычев. Систематический обзор влияния уровня метилирования ДНК на эффективность антагонистов рецепторов P2Y12. *Фармация и фармакология.* 2026;14(3):218-235. **DOI**: 10.19163/2307-9266-2026-14-3-218-235

and prasugrel, it remains relevant in clinical practice, especially in the non-acute phase of ACS, including as part of DAT [2]. Currently, there are studies showing that therapy with new inhibitors is often more effective in preventing ischemic events; however, their use increases the risk of bleeding and other adverse reactions, such as dyspnea [4, 5]. Clopidogrel is also cheaper. The adverse side effects of ticagrelor and prasugrel are a reason for de-escalation of therapy, which involves switching to clopidogrel.

A significant problem with clopidogrel use is the risk of developing drug resistance. Thus, the efficacy of the inhibitor is influenced by other drugs that inhibit cytochromes [6]. It has also been shown that mutations in the *CYP2C19* gene, leading to reduced activity of the encoded enzyme, result in clopidogrel resistance [3].

Ticagrelor does not require prior activation. This drug, along with prasugrel, is preferred for preventing recurrent ischemic events after percutaneous coronary intervention for ACS [7]. Since the efficacy of the drug does not depend on *CYP2C19* activity, it can be used to treat patients with genetically determined clopidogrel resistance.

Prasugrel is also a third-generation inhibitor, but it is used less frequently in the Russian Federation. This is partly due to its limitations: the drug is not recommended for patients over 75 years of age, and it should be noted that, unlike ticagrelor, there is no antidote for this drug [8].

Personalization of antiplatelet therapy is an important issue in cardiology. Gene polymorphisms encoding enzymes involved in drug metabolism and concomitant therapy alone cannot fully explain interindividual variability in drug response, so scientific research continues to search for genetic and epigenetic biomarkers for predicting response to P2Y12 inhibitors. In this regard, it is important to also assess the DNA methylation level of genes that may affect drug efficacy. Candidate genes whose methylation level may affect the risk of developing resistance to antiplatelet agents include genes whose products are involved in drug metabolism or platelet aggregation, as well as those not related to these processes. In the studies included in the final analysis, the relationship between DNA methylation and clopidogrel efficacy was studied, as there are no similar articles for other drugs in the database.

For pharmacogenetic markers, there is the PharmGKB database[1], which catalogs studies on the relationship between polymorphisms. However, there is no such resource for epigenetic data, so the issue of systematization remains relevant.

[1] PharmGKB. Available from: https://www.pharmgkb.org

Thus, **THE AIM** of this systematic review is to identify and present epigenetic factors that influence the efficacy of P2Y12 antagonists.

MATERIALS AND METHODS

Inclusion criteria

1. Original clinical studies in humans: cohort studies and case-control studies;
2. Studies evaluating the association between DNA methylation and the efficacy of P2Y12 receptor antagonists;
3. Availability of data on the method of assessing antiplatelet therapy efficacy. Acceptable efficacy assessment methods: maximum platelet aggregation (MPA), platelet reactivity units (PRU), risk of ischemic events, platelet reactivity index (PRI).

Exclusion criteria

1. RNA or DR methylation;
2. Literature reviews.

Search strategy

A search was conducted in PubMed in January 2025. Articles on the topic published in 2014 and later were reviewed. To minimize the risk of losing relevant studies, standard PubMed filters were not applied. All search steps were performed manually in the standard PubMed web interface without the use of specialized software add-ons.

Search terms:

- “DNA methylation” OR “methylation” OR “hypomethylation” OR “hypermethylation”;
- AND (“antiplatelet” OR “clopidogrel” OR “ticagrelor” OR “prasugrel” OR “P2Y12 inhibitor”);
- AND (“response” OR “resistance” OR “efficacy” OR “reactivity”).

The study selection process included an initial screening of article titles and abstracts. The full text of selected manuscripts was evaluated. During the full-text analysis, the study type, patient clinical data, method of DNA methylation determination, criterion for determining antiplatelet resistance, and genes were determined.

Data analysis

For each article, the gene, its region where methylation was determined (if region data was available), and the association between methylation level and antiplatelet efficacy are indicated. After annotating the articles, it was determined how the

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methylation level of different DNA regions affects the efficacy of antiplatelets. A table was then compiled, noting the genes, their regions where methylation levels were determined, and their impact on the risk of resistance.

Quantitative meta-analysis was not performed due to significant heterogeneity of the included studies in terms of design, nosological populations: IHD, ACS, methods of resistance assessment, and different analyzed DNA regions.

Study selection

Figure 1 shows the flow diagram for study selection for the systematic review. In the final search in PubMed, conducted in January 2025, 36 articles were found. During the initial selection based on abstracts, 18 articles were excluded. The full text of the remaining 18 articles was then studied, and one article was excluded due to the absence of an analysis of the relationship between DNA methylation and the risk of developing resistance to antiplatelet agents.

Study characteristics

In the 17 studies included in the systematic review, the association between the efficacy of P2Y12 receptor antagonists and DNA methylation level was analyzed. The efficacy of antiplatelet therapy in patients with ACS was most frequently studied (7 articles); the second most frequently mentioned disease in the articles was ischemic stroke (5 articles); followed by IHD (2 articles); myocardial infarction and transient ischemic attack were studied in one scientific study each, and one study reported on both patients with ischemic stroke and patients with transient ischemic attack.

In the described studies, DNA methylation level was mostly determined by bisulfite pyrosequencing. The criterion for clopidogrel resistance was most often PRU (P2Y12 reactivity units) > 240.

Statistical methods used: Pearson's chi-square or Fisher's exact test for categorical variables, t-test for comparing means, Wilcoxon rank-sum test for non-parametric analysis, logistic regression.

The risk of bias for each study was assessed using the Newcastle-Ottawa Scale. Studies scoring 4 to 6 points had a moderate risk of systematic error, and those scoring 7 points or more had a low risk. No studies with a high risk of bias, scoring less than 4 points, were found among the articles included in the review. The results of the risk of bias assessment are presented in Table 1.

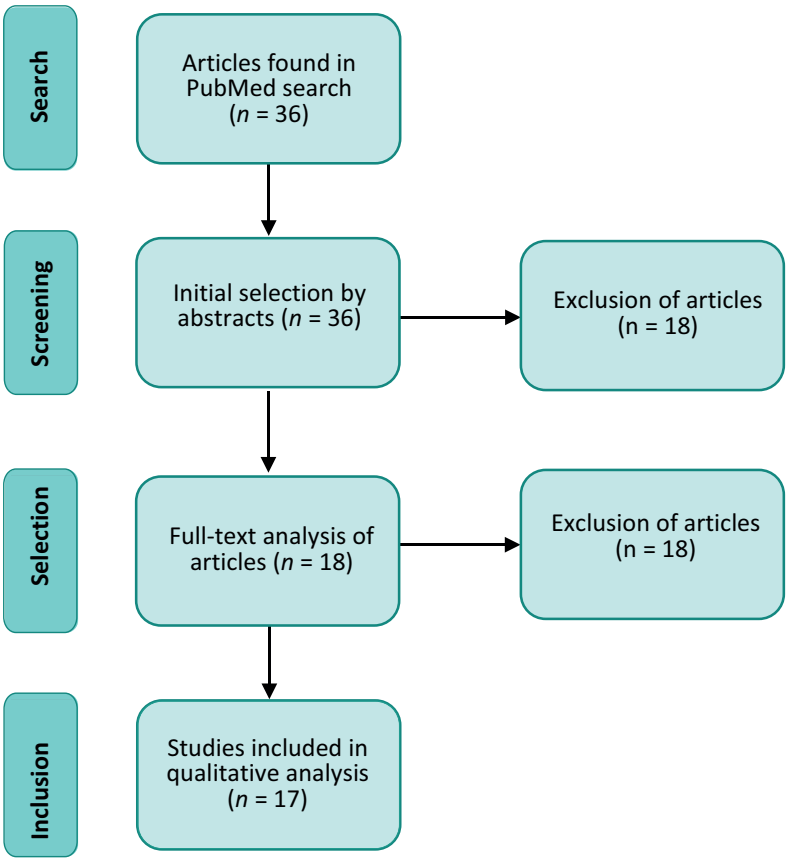

Figure 1 — PRISMA flow diagram.

Table 1 — Assessment of risk of bias in scientific works included in the study

First author (year of publication)	Article title	Newcastle-Ottawa Scale Score	Risk level	References
Yang J. (2015)	*ABCB1* hypomethylation is associated with decreased antiplatelet effects of clopidogrel in Chinese ischemic stroke patients	5/9	medium	[10]
Li D. (2022)	Association between *GNAQ* Gene DNA Methylation and Vascular Recurrence in Patients with Acute Ischemic Stroke or Transient Ischemic Attack	8/9	low	[19]
Su J. (2014)	«Association of *P2Y12* gene promoter DNA methylation with the risk of clopidogrel resistance in coronary artery disease patients	5/9	medium	[20]
Su J. (2019)	Association of *PON1* gene promoter DNA methylation with the risk of Clopidogrel resistance in patients with coronary artery disease	7/9	low	[24]
Su J. (2020)	Association of *GCK* gene DNA methylation with the risk of clopidogrel resistance in acute coronary syndrome patients	7/9	low	[18]
Song P.Y. (2023)	CD80 DNA methylation and single-nucleotide polymorphism associated with clopidogrel response: a whole-genome DNA methylation analysis in acute coronary syndrome	8/9	low	[14]
Yang J. (2023)	Clopidogrel Resistance Is Associated with DNA Methylation of Genes from Whole Blood of Humans	7/9	low	[13]
Lei H.P. (2018)	Effects of *PON1* Gene Promoter DNA Methylation and Genetic Variations on the Clinical Outcomes of Dual Antiplatelet Therapy for Patients Undergoing Percutaneous Coronary Intervention	6/9	medium	[23]
Yang J. (2023)	Impact of platelet endothelial aggregation receptor 1 genotypes and DNA methylation on platelet reactivity in patients with recurrent ischemic stroke treated with clopidogrel	6/9	medium	[22]
Sukmawan R. (2021)	Increase in the risk of clopidogrel resistance and consequent TIMI flow impairment by DNA hypomethylation of *CYP2C19* gene in STEMI patients undergoing primary percutaneous coronary intervention (PPCI)	5/9	medium	[17]
Kim J. (2024)	Molecular genomic and epigenomic characteristics related to aspirin and clopidogrel resistance	7/9	low	[12]
Yang J. (2014)	The association of *ABCC3* promoter methylation with clopidogrel response in Chinese ischemic stroke patients	5/9	medium	[11]
Li J. (2022)	The DNAm levels of *CREB5* (cg11301281) were associated with clopidogrel resistance	6/9	medium	[15]
Li X.G. (2016)	The impact of *P2Y12* promoter DNA methylation on the recurrence of ischemic events in Chinese patients with ischemic cerebrovascular disease	9/9	low	[21]
Su J. (2017)	The risk of clopidogrel resistance is associated with *ABCB1* polymorphisms but not promoter methylation in a Chinese Han population	7/9	low	[9]
Giantini A. (2023)	The role of clopidogrel resistance-related genetic and epigenetic factors in major adverse cardiovascular events among patients with acute coronary syndrome after percutaneous coronary intervention	8/9	low	[16]
Gallego-Fabrega C. (2016)	TRAF3 Epigenetic Regulation Is Associated with Vascular Recurrence in Patients with Ischemic Stroke	8/9	low	[25]

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DOI: 10.19163/2307-9266-2026-14-3-218-235

Table 2 — Association between DNA methylation level and the risk of developing clopidogrel resistance

Gene	Region	Nosology	Method / criterion for determining resistance	Sample size	Nature of the association between methylation level and response to clopidogrel, numerical characteristics	References
ABCB1	Promoter CpG1	ACS	PRU > 240	106	No, case vs. control: 90.84 ± 3.42 % vs. 91.18 ± 2.27 % (p = 0.545)	[9]
	Promoter CpG2				No, case vs. control: 92.65 ± 4.52 % vs. 93.53 ± 4.12 % (p = 0.408)	
ABCB1	promoter	ischemic stroke	MPA	183	Inverse, correlation of ABCB1 methylation with MPA (R = -0.764, p < 0.001)	[10]
ABCC3	promoter	ischemic stroke	MPA	87	No, association of methylation with MPA (R = 0.100, p = 0.358)	[11]
ALOX12, COX1, ALOX15, COX2, TXAS1	promoter	transient ischemic attack and ischemic stroke	> 270 PRU and > 550 ARU	988	No*	[12]
BTG2	cg23371584	ACS	PRU > 240	72	Direct, 10.598 ± 4.396 % in the group of patients with clopidogrel resistance and 8.063 ± 5.085 % in the control group (p = 0.043)	[13]
PRG2	cg15971518				Reverse, 4.633 ± 14.445 % in the group of patients with clopidogrel resistance and 35.263 ± 20.422 % in the control group (p = 0.023)	
VTRNA2-1	cg04481923				Reverse, 28.401 ± 14.699 % in the group of patients with clopidogrel resistance and 35.421 ± 12.142 % in the control group (p = 0.048)	
PER3	cg22507406				Reverse, 71.532 ± 2.474 % in the group of patients with clopidogrel resistance and 73.576 ± 3.5 % in the control group (p = 0.011)	
CD80	cg06300880	ACS	PRI > 75 %	330	Reverse, high methylation level is associated with lower odds of high platelet reactivity during treatment, OR = 0.31, 95 % CI 0.13–0.75 p = 0.009 in the overall patient group, OR = 0.25, 95 % CI 0.092–0.67, p = 0.006 in the group of patients with STEMI without ST-segment elevation	[14]
CREB5	cg01534253	ACS	PRU ≥ 240	72	Reverse, in patients with HbA1c ≥ 6.5 % case vs. control: 98.01 ± 2.55 % vs. 95.04 ± 3.84 % (p = 0.050); in patients with GLU ≥ 7 mmol/L 99.33 ± 1.51 vs. 93.85 ± 4.37 (p = 0.020)	[15]
CYP2C19	body	ACS	MPA > 59%	200	Reverse, OR = 2.13, 95 % CI 1.04–4.37, p = 0.037	[16]
P2Y12	promoter				No, OR = 1.59, 95 % CI 0.62–4.06, p = 0.334	
CYP2C19	—	ST-elevation myocardial infarction	PRU > 208	122	Reverse, case vs. control 8.8 ± 22.7 % vs. 76.7 ± 32.9 % (p = 0.03)	[17]

Gene	Region	Nosology	Method / criterion for determining resistance	Sample size	Nature of the association between methylation level and response to clopidogrel, numerical characteristics	References
GCK	cg18492943 chr7:44203220-44203435, тело	ACS	PRU ≥ 240	72	Direct, in men, case vs. control — 88.16 ± 4.32 % vs. 84.86 ± 6.29 % (p = 0.032); in patients without DM, case vs. control: 88.16 ± 4.17 % vs. 84.66 ± 6.18 % (p = 0.029); in patients with dyslipidemia, case vs. control: 88.39 ± 4.74 % vs. 83.81 ± 6.96 % (p = 0.042)	[18]
GNAQ	CpG 32–39	Acute ischemic stroke or transient ischemic attack	Association with the risk of ischemic events	152	An inverse association with the risk of ischemic events was found: OR = 73.82, 95 % CI 20.33–268.01, p < 0.001	[19]
P2Y12	2 CpG from the fragment GRCh37. p13:151103600-151101600	CAD	PRU ≥ 240	106	Cases vs. control: 36.67 ± 7.25 % vs. 46.70 ± 7.42 % (p = 0.009); CpG2, cases vs. control: 31.89 ± 5.18 % vs. 38.70 ± 6.48 % (p = 0.022); in smoking patients, cases vs. control: CpG1 38.53 ± 6.87 % vs. 44.90 ± 10.03 % (p = 0.026); patients with albumin level < 35 g/L, cases vs. control: 34.14 ± 7.24 % vs. 44.70 ± 4.45 % (p = 0.002)	[20]
P2Y12	promoter CpG11	Stroke	Association with the risk of ischemic events	60	Inverse association with the risk of ischemic events, case vs. control: 0.48 ± 0.14 vs. 0.86 ± 0.13 (p <0.001)	[21]
	promoter CpG12+13				Inverse association with the risk of ischemic events, case vs. control: 0.52 ± 0.15 vs. 0.79 ± 0.21 (p < 0.001)	
PEAR1	—	Acute minor ischemic stroke	Association with platelet reactivity level	90	Direct association with platelet reactivity level, 33.53 ± 14.28 % in the high platelet reactivity group vs. 26.11 ± 14.53 % in the low platelet reactivity group (p = 0.044)	[22]
PON1	CpG -142 from transcription start site	CAD	PRU > 208	653	Reverse, bleeding risk, OR = 0.98, 95 % CI 0.96–1.00, p = 0.028	[23]
	CpG -170 from transcription start site				Reverse, bleeding risk, OR = 0.99, 95 % CI 0.97–1.00, p = 0.048	
	CpG -163 from transcription start site				Reverse, bleeding risk, OR = 0.98, 95 % CI 0.96–1.00, p = 0.29	
	CpG -161 from transcription start site				Reverse, bleeding risk OR = 0.98, 95 % CI 0.97–1.00, p = 0.026	
	CpG -142 from transcription start site				Reverse, bleeding risk OR = 0.98, 95 % CI 0.97–1.00, p = 0.042	
PON1	promoter	ACS	PRU > 240	106	Direct, cases vs. control: 51.500 ± 14.742 % vs. 43.308 ± 10.891 % (p = 0.036)	[24]
TRAF3	cg03548645	Stroke	Association with the risk of ischemic events	42	Inverse association with the risk of vascular recurrence (p = 0.034)	[25]

Note: ACS, acute coronary syndrome; CAD, coronary artery disease; DM, diabetes mellitus; OR, odds ratio; CI, confidence interval; MPA, maximal platelet aggregation; PRI, platelet reactivity index; PRU, platelet reactivity units; *, no statistically significant association with the risk of resistance development, but the inclusion of gene methylation data in mathematical models increased the sensitivity of models for predicting the recurrence of ischemic events, PRU and ARU levels.

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DOI: 10.19163/2307-9266-2026-14-3-218-235

RESULTS

Association between DNA methylation level and the risk of developing resistance to P2Y12 receptor antagonists

The 17 studies included in the systematic review involved 3,441 patients who suffered from the following types of cardiovascular diseases: ACS, including ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction, and stroke. Clopidogrel efficacy was most often assessed by P2Y12 reaction units (PRU), but other methods were also used, such as platelet reactivity index (PRI) or maximal platelet aggregation (MPA). All patients received clopidogrel. In some studies, participants received DAPT.

The studies investigated the effect of methylation of 20 genes on clopidogrel efficacy: *ABCB1, ABCC3, ALOX12, ALOX15, BTG2, CD80, COX1, COX2, CREB5, CYP2C19, GCK, GNAQ, P2Y12, PEAR1, PER3, PON1, PRG2, TRAF3, TBXAS1, VTRNA2-1.*

The following information is summarized and presented in Table 2.

ABCB1

The *ABCB1* gene encodes P-glycoprotein, an ABC transporter family membrane protein, also known as multidrug resistance protein. It plays an important role in the excretion of various xenobiotics, including drug, through cell membranes. The protein is involved in the absorption of clopidogrel from the intestine, which determines the effect of P-glycoprotein on the bioavailability and absorption of clopidogrel [26]. The effect of promoter methylation level of this gene on the risk of developing clopidogrel resistance was studied in two studies [9, 10]. J. Su et al. showed that hypomethylation of the promoter increased the risk of clopidogrel resistance by increasing the mRNA expression activity of the *ABCB1* gene [9]. In the study by J. Yang et al., a similar association was not found. It is possible that the difference in results is due to the method of determining clopidogrel therapy efficacy: measurement of maximal platelet aggregation induced by ADP (MPA) vs.measurement of P2Y12 reaction (PRU) [10]. Also, in the study that did not find an association, patients received DAPT, which could also have affected the study results.

ABCC3

The product of the *ABCC3* gene is multidrug resistance protein 3 (MRP3), which, like P-glycoprotein, belongs to the ATP-binding cassette (ABC) transporter superfamily. Some studies show that low mRNA expression of ABCC3 is associated with increased clopidogrel efficacy [27]. However, in a study investigating the effect of gene promoter methylation level on drug efficacy, no association was found between this epigenetic factor and the risk of resistance development [11].

ALOX12 and ALOX15

The *ALOX12* gene encodes the arachidonate-12-lipoxygenase protein. This protein has a high expression level in megakaryocytes. It is involved in the metabolism of arachidonic acid, leading to its conversion into thromboxane A2, which promotes the activation of previously intact platelets. Thus, arachidonate-12-lipoxygenase is important for ensuring the platelet aggregation mechanism [28, 29]. The *ALOX15* protein, the product of the gene of the same name, is also involved in arachidonic acid metabolism. It catalyzes the conversion of arachidonic acid to 15-hydroperoxyeicosatetraenoic acid (15-HPETE) [30]. The role of this metabolite in platelet aggregation is not fully understood. Some studies show that the compound inhibits the release of tissue-type plasminogen activator (t-PA) and promotes the release of plasminogen activator inhibitor-1 (PAI-1), which reduces the binding capacity of antithrombin III on endothelial surfaces [31]. Also, at low collagen concentrations, 15-HPETE can negatively affect platelet aggregation, as it inhibits enzymes involved in arachidonic acid metabolism: cyclooxygenases, lipoxygenases, and prostacyclin synthase [32]. In a study of the methylation level of *ALOX12* and *ALOX15* genes, no statistically significant difference was found between patients who experienced recurrent ischemic stroke and patients who did not experience a recurrence. However, the inclusion of methylation level in the regression model increased the accuracy of predicting clopidogrel resistance in patients. Thus, hypermethylation (increased DNA methylation level due to excessive addition of methyl groups to cytosine in DNA) of the *ALOX12* promoter increased the risk of resistance development, while *ALOX15* decreased it [12].

BTG2

The *BTG2* gene encodes the protein of the same name, which regulates the cell cycle. BTG2 functions as a transcriptional coregulator by stimulating or inhibiting the activity of transcription factors, participating in the control of the G1/S transition of the cell cycle. Despite

the absence of a direct link between the gene and platelet aggregation, as well as with the metabolism of antiplatelet agents, it has been found that the gene expression level, which depends on DNA methylation, including the cg23371584 locus, affects the risk of developing clopidogrel resistance. Hypermethylation of cg23371584 is also associated with an increased risk of clopidogrel resistance [13].

CD80

The *CD80* molecule belongs to the immunoglobulin superfamily. It stimulates *CD28*, leading to T-cell activation and clonal expansion. *CD80* also participates in B-lymphocyte activation. A cancer cell in which this immunoglobulin is suppressed is not attacked by the immune system [33]. As there is no direct link described between this compound and platelet aggregation, there are no studies investigating the connection between its methylation and the risk of developing resistance to antiplatelet agents. However, during whole-genome methylation analysis, it was found that hypermethylation of the cg006300880 site, located in the promoter region of the *CD80* gene, reduces the risk of developing resistance to clopidogrel. Currently, the influence of the methylation level of this site on gene activity has not been established, although existing data suggest that hypermethylation of the CD80 promoter affects gene expression levels [14].

COX1 and COX2

Cyclooxygenases *COX1* (COX-1) and *COX2* (COX-2) are involved in the synthesis of prostaglandins, prostacyclins, and thromboxanes from arachidonic acid. Both enzymes are involved in inflammation. COX-1 is constitutive and is responsible for the synthesis of prostaglandins with homeostatic functions in the stomach, kidneys, and platelets. COX-2, on the other hand, is an inducible enzyme, and its synthesis is activated during inflammation. A small amount of *COX*-2 is produced in platelets even in the absence of a pathological process: both mRNA and the enzyme itself have been detected. Increased expression of this isoform is also characteristic of malignant cells [34]. Its function is the synthesis of pro-inflammatory prostaglandins. Thus, COX-1 is involved in the immediate prostanoid response to inflammatory stimuli, while COX-2 is a factor in prostanoid synthesis as inflammation progresses [35]. Cyclooxygenases also play an important role in the synthesis of thromboxane A2, which is responsible for stimulating and aggregating platelets. The antiplatelet action of acetylsalicylic acid, to which the enzyme is sensitive, is based on the blockade of COX-1 [36].

As with *ALOX12* and *ALOX15*, no statistically significant differences were found between groups of patients who experienced recurrent ischemic stroke while taking clopidogrel and patients without recurrence. However, incorporating methylation levels into the regression model improved the accuracy of predicting clopidogrel resistance in patients [12].

CREB5

The product of the *CREB5* gene belongs to a family of proteins that bind to CRE DNA sequences and regulate the transcription of genes containing these regions. CREB5 protein itself is a CRE-dependent trans-activator. Members of the CREB family are involved in regulating the expression of genes encoding transcription factors involved in protein import and mitochondrial homeostasis. They also regulate the synthesis of transporter and chaperone proteins [37]. *CREB5* regulates processes such as embryonic development, including cartilage formation, and is involved in nuclear signaling and neuroplasticity associated with dopamine receptors. In addition to physiological processes, this protein plays an important role in tumor development and progression [38, 39]. Aberrant overexpression of CREB5 is associated with an unfavorable prognosis in Pancoast tumor of the lung. The expression level can also be a prognostic criterion for the course and response to drugs in patients with glioma [40]. One study showed that hypomethylation (a reduced level of DNA methylation due to a low number of methyl groups attached to cytosine in DNA) of *CREB5* increased the risk of clopidogrel resistance in patients with a glycated hemoglobin concentration ≥ 6.5 % or blood glucose level ≥ 7 mmol/L. It is likely that reduced response to clopidogrel may be related to the fact that a hyperglycemic state contributes to a decrease in gene methylation levels, which leads to a change in response to antiplatelet agents [15].

CYP2C19

The *CYP2C19* enzyme belongs to the superfamily of hepatic cytochrome P450 enzymes. The primary function of *CYP2C19* is xenobiotic metabolism. It is involved in the metabolism of a wide range of drugs, including clopidogrel. This enzyme is key to

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DOI: 10.19163/2307-9266-2026-14-3-218-235

clopidogrel pharmacokinetics, as it is responsible for converting the drug into its active thiol metabolite. It has been shown that carrying mutant alleles *CYP2C19**2 and *CYP2C19**3 leads to the formation of a non-functional protein. For example, a mutation in rs4244285 (CYP2C19*2) or rs4986893 (*CYP2C19**3) results in an additional stop codon, causing the RNA chain and subsequently the enzyme itself to become shorter. Since such a protein cannot fully perform its functions, the level of clopidogrel biotransformation to the active metabolite decreases, leading to lower efficacy of clopidogrel therapy [41]. In this regard, the Clinical Pharmacogenetics Implementation Consortium (CPIC)[2] has developed recommendations for the use of pharmacogenetic testing for *CYP2C19* gene variants to adjust oral anticoagulant pharmacotherapy. The relationship between *CYP2C19* gene methylation levels and clopidogrel efficacy has been studied in two studies, both of which noted that methylation levels were inversely correlated with the risk of developing clopidogrel resistance. It has been shown that methylation level is an independent risk factor for resistance development. It is likely that hypermethylation of the gene body increases its activity, which positively affects clopidogrel activation and, consequently, therapy efficacy [16, 17].

GCK

Glucokinase, encoded by the *GCK* gene, is a hexokinase that catalyzes the first step of the glycolytic metabolic pathway—the phosphorylation of glucose to glucose-6-phosphate. This enzyme also serves as a link between blood glucose levels and the initiation of insulin secretion [42]. Mutations in this gene are associated with type 2 diabetes in young patients (MODY2). Identifying mutations in the *GCK* gene is the "gold standard" for diagnosing this type of diabetes [43]. In a diagnosis of 144 patients under 18 years of age with confirmed GCK-MODY, it was found that 80.2% of patients had missense mutations in this gene, the most frequent being p.G261R (n = 7) and p.G258C (n = 6) [44]. Since diabetes leads to increased platelet aggregation and reduces the effectiveness of antiplatelet therapy [45], assessing the epigenetic parameters of the gene may be promising for predicting clopidogrel efficacy. A CpG site of the gene has been included in one study. Hypermethylation of cg18492943, located in the GCK gene body, increased the risk of resistance in male patients with dyslipidemia. It has also been shown that high levels of DNA methylation lead to decreased GCK mRNA expression [18].

GNAQ

The Gaq protein, encoded by the *GNAQ* gene, is part of the heterotrimeric G protein complex and is responsible for regulating signaling pathways. Protein activation occurs through the binding of the G protein complex to G protein-coupled receptors, followed by binding to guanosine triphosphate, causing Gaq to dissociate from the complex and initiate signaling pathways that affect the development and function of blood vessels[3]. *GNAQ* is also a mediator of melanopsin, which is necessary for the normal development of retinal blood vessels in the fetus [46]. Aberrant Gaq protein activity can lead to cardiac hypertrophy, resulting in heart failure [47]. *GNAQ* also participates in platelet aggregation. It is involved in the secretion of von Willebrand factor, which ensures platelet adhesion to damaged blood vessel sites [48]. One study investigated the association between the methylation levels of several CpG sites in the gene and the risk of recurrent ischemic events while taking clopidogrel. Recurrent ischemic events while taking antiplatelet agents are the most dangerous consequence of developing drug resistance. It has been shown that low methylation levels of CpG 32-39 increased the risk of recurrent ischemic events, although the mechanism by which methylation levels affect therapy efficacy is currently unknown [19].

P2Y12

The *P2Y12* receptor, encoded by the gene of the same name, is located on the platelet membrane and plays a crucial role in platelet aggregation. Under the action of ADP, released from damaged cells or other activated platelets, *P2Y12* transmits a signal through intracellular pathways, leading to changes in platelet shape and activation [49]. This occurs through the activation of glycoprotein IIb / IIIa (integrin αIIbβ3), which binds fibrinogen and promotes platelet adhesion to each other. Furthermore, *P2Y12* activation promotes the involvement of previously intact platelets in thrombus formation, as

[2] CPIC® Guideline for Clopidogrel and CYP2C19. – [Электронный ресурс]. – Режим доступа: https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19

[3] Ген GNAQ. ГЕНОКАРТА Генетическая энциклопедия, 2019. – [Электронный ресурс]. – Режим доступа: https://www.genokarta.ru/gene/GNAQ

dense granules containing serotonin, among other substances, are released. The receptor is a target for antiplatelet agents—*P2Y12* antagonists—which block this receptor by irreversibly binding to it [50]. The influence of the epigenetic characteristics of the *P2Y12* gene on the risk of developing resistance to antiplatelet agents has been studied in three studies. In each of them, the CpG islands where methylation was determined were located in the gene's promoter region [17, 20, 21]. Two of these studies found a link between promoter methylation levels and the risk of clopidogrel resistance. In the second study, a link was found only in groups of patients who consumed alcohol, smoked, or had an albumin concentration in their blood below 35 g/L. Additionally, some clinical factors, including albumin, influenced methylation levels. The obtained data suggest a common inverse correlation between methylation levels in the promoter region and the transcriptional activity of the studied receptor gene, which is observed for many genes.

PEAR1

The platelet receptor *PEAR1* is located on the surface of platelets and in α-granules. The concentration of the receptor and its ligand on the cell surface increases upon activation due to their release from α-granules. The binding of the receptor on one platelet and its ligand on another promotes the formation of a complex consisting of at least two receptors, leading to the phosphorylation of *PEAR1*. This triggers a cascade of signals, resulting in the activation of phosphoinositide 3-kinase, which in turn increases the activity of integrin αIIbβ3 [51]. The latter mediates the binding of platelets to each other and to fibrinogen, leading to the formation of a stable thrombus. Hypermethylation of CpG sites in the gene has been shown to be associated with increased platelet reactivity and the risk of recurrent ischemic stroke in patients taking clopidogrel [22].

PER3

PER3 is a circadian gene. It is expressed in the suprachiasmatic nucleus and is responsible for the rhythmicity of many bodily processes. Variants of the gene, particularly differences in the number of tandem repeats, influence inter-individual variability in peak activity times, the risk of mental disorders, non-visual light responses, and brain and cognitive responses to sleep loss or circadian phase shift [52]. Furthermore, impaired function of this gene negatively affects cellular processes related to carcinogenesis, including proliferation, cell cycle, and apoptosis. Consequently, mutations in the *PER3* gene and reduced expression are linked to an increased risk of oncological diseases, particularly colorectal cancer and prostate cancer [53, 54]. No direct link has been found between the efficacy of antiplatelet agents and PER3; however, the rs2797685 polymorphism of this gene has been shown to influence the risk of clopidogrel resistance in patients with a platelet count greater than 0.19 [55]. In a study by J. Yang et al., it was found that the methylation level of the cg22507406 site negatively correlates with the risk of developing clopidogrel resistance [13].

PON1

Paraoxonase 1, encoded by the *PON1* gene, belongs to the paraoxonase enzyme family. It is synthesized in the liver and kidneys, then secreted into the bloodstream where it binds to high-density lipoproteins (HDL). It participates in the metabolism of many xenobiotics and lipids. The gene also contributes to vascular protection against atherosclerosis by preventing the oxidation of low-density lipoproteins (LDL) and HDL, thereby reducing the risk of atherosclerotic lesions [56]. A mutation in the SNP L55M A > T is associated with the progression of atherosclerosis in patients with coronary artery disease (CAD) [57]. PON1 is involved in the second stage of clopidogrel metabolism. Carriage of the Q192R substitution has been shown to be associated with higher platelet reactivity in patients after neurointerventional surgery taking clopidogrel [58]. The influence of methylation levels on the efficacy and safety of antiplatelet agents has been studied in two investigations. Promoter hypermethylation is associated with a reduced risk of clopidogrel resistance [24]. In the work by H.P. Lei et al., bleeding, an adverse event much rarer for clopidogrel compared to ticagrelor and prasugrel, is noted. Hypomethylation of five CpG sites (CpG -184, -170, -163, -161, -142 from the transcription start site) has been shown to increase the risk of bleeding when taking clopidogrel. Therefore, their methylation level directly correlates with the risk of bleeding, an adverse effect opposite to bleeding [23].

PRG2

The *PRG2* gene encodes proteoglycan 2. This protein is a major component of the crystalline core

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of eosinophil granules and likely contributes to the protective function of eosinophils against parasites. Additionally, proteoglycan 2 is toxic to Gram-positive and Gram-negative bacteria and mammalian cells. Immature proteoglycan 2 synthesized by other tissues does not possess these properties but is responsible for inhibiting proteolysis and activating prohormones [59]. The effect of CpG site methylation levels of this gene on the risk of clopidogrel resistance has been studied in one investigation. Hypermethylation of cg15971518 has been shown to reduce the risk of clopidogrel resistance [13].

TRAF3

TNF receptor-associated factor 3 is a member of the *TRAF* family. *TRAF3* is crucial for T-lymphocyte function, influencing T-cell proliferation, survival, differentiation, and cytokine production [60]. In B-lymphocytes, it performs an opposing function, acting as an inhibitor of signaling pathways that promote cell survival and proliferation. It also hinders antigen recognition and antibody production by suppressing B-cell receptor signaling [61, 62]. Impaired synthesis of this factor leads to immune dysregulation, which can manifest as recurrent infections, autoimmune diseases, and an increased risk of B-cell malignancies [63]. Low DNA methylation levels of the gene at the CpG site cg03548645 have been associated with higher platelet aggregation during clopidogrel therapy. This effect may be explained by the involvement of *TRAF* family proteins in CD40 signaling, which is elevated in individuals with cardiovascular diseases. It has also been shown that TRAF3 is linked to therapeutic interventions, and reduced expression leads to an anti-inflammatory effect [25].

TXAS1

Despite the structural similarity of thromboxane A synthase 1 to other members of the P450 superfamily, it performs different functions. It plays a significant role in platelet aggregation by catalyzing the conversion of prostaglandin H2 to thromboxane A2, which is involved in vasoconstriction and platelet aggregation [64]. Variations in this gene are associated with cardiovascular diseases and other disorders. For instance, a mutation in g.139985896 C > T increases the risk of ischemic stroke [65]. Mutation of both copies of the gene also leads to hematodiaphyseal dysplasia [66]. In a study by J. Kim et al., no statistically significant difference in methylation levels was found between patient groups with and without clopidogrel resistance; however, including TXAS1 methylation levels in a mathematical model improved its accuracy [12].

VTRNA2-1

The product of the *VTRNA2-1* gene is a RNA polymerase III transcript. It can adopt two RNA conformations. The first inhibits the phosphorylation of protein kinase R stress response element and the α subunit of the downstream eukaryotic translation initiation factor 2, which is involved in regulating protein synthesis levels in the cell. The second acts as a pseudo-inhibitor of protein kinase R when competing with other double-stranded RNA molecules [67]. It also plays a role in the development of oncological diseases. In acute myeloid leukemia, *VTRNA2-1* acts as a tumor suppressor. Hypomethylation of the gene, leading to increased expression levels, predicts a better prognosis for this disease [68]. However, in cervical cancer, this gene promotes cancer cell proliferation and reduces apoptosis [69]. One study showed that hypermethylation of cg04481923 in this gene reduces the risk of clopidogrel resistance [13].

Assessment the certainty of the evidence

The certainty of the body of evidence was assessed using the GRADE approach. The review included 17 studies, of which 6 were characterized by a low risk of bias, scoring 7–9 points on the Newcastle-Ottawa scale, and 11 had a moderate risk (4–6 points). No studies with a high risk were found.

For the association between promoter methylation levels of P2Y12 and the risk of clopidogrel resistance (3 studies, 2 with low risk of bias), the certainty of evidence was rated as moderate. The reduction in certainty is due to heterogeneity in PRU threshold values and the absence of standardized resistance assessment criteria. For the association between CYP2C19 methylation and clopidogrel efficacy (2 studies with low risk), the certainty of evidence was rated as moderate, as both studies showed a negative correlation between gene methylation levels and the risk of resistance, but only two studies were used, employing different criteria for resistance assessment. For the association between ABCB1 promoter methylation and clopidogrel efficacy, the certainty of evidence is low, as only one of the two studies found a

link between promoter methylation levels and the risk of resistance, and different criteria for drug resistance were used.

For the association between PON1 promoter methylation and clopidogrel efficacy, the certainty of evidence is low, as one of the two studies examined an adverse event opposite to resistance—bleeding.

DISCUSSION

Interindividual differences in the efficacy of antiplatelet agents are only partially explained by demographic and clinical patient characteristics. This systematic review evaluated 17 scientific works investigating the association between DNA methylation levels and the risk of developing clopidogrel resistance. In 9 of them, a direct link was found between methylation levels and the risk of developing clopidogrel resistance; in 5 articles, a link was found between methylation levels and the risk of adverse reactions: bleeding, recurrent ischemic events, and unfavorable platelet reactivity. In 3, no direct correlation was found. No scientific studies dedicated to the influence of this epigenetic DNA modification on the efficacy of other P2Y12 antagonists, which are commonly used in clinical practice, were found in the PubMed database. Most of the analyzed studies examined the relationship between clopidogrel efficacy and genes whose products are involved in its action (see Table 1). These include ADME genes (Absorption, Distribution, Metabolism, Excretion), such as *CYP2C19*, a key enzyme for converting the prodrug into its active substance, as well as genes related to platelet aggregation, such as P2Y12 and PEAR1 receptors, enzymes involved in arachidonic acid metabolism, and others. However, the influence of DNA methylation levels of genes not directly related to platelet aggregation and xenobiotic metabolism on drug efficacy was also found: circadian genes, genes responsible for immune response, and lipid and carbohydrate metabolism. Some studies indicate that patients with type 2 diabetes mellitus exhibit a weaker response to clopidogrel [70]; this may be explained by the influence of DNA methylation levels of genes responsible for insulin secretion and carbohydrate metabolism.

In the case of genes associated with platelet function (e.g., P2Y12), changes in CpG island methylation levels in regulatory regions, correlating with increased transcriptional activity, may lead to a decrease in the therapeutic efficacy of clopidogrel. The opposite situation is observed with the *CYP2C19* gene: epigenetic changes that increase its activity reduced the risk of developing clopidogrel resistance. These results are consistent with pharmacogenetic data, where single nucleotide polymorphisms that alter gene activity are associated with therapy efficacy or drug concentration in patient plasma. For example, carriage of the mutant alleles *CYP2C19*2* and *CYP2C19*3*, mentioned above, reduces enzyme activity and negatively affects clopidogrel efficacy. *CYP2C19*17*, on the other hand, is an allele with increased function. Carriers of this mutation have a high level of clopidogrel biotransformation into its active metabolite, but if an individual is a carrier of the *CYP2C19*2/*17* or *CYP2C19*3/*17* haplotype, they have a reduced level of clopidogrel metabolism[4]. The presence of a mutation in rs12041331 of the PEAR2 gene, which reduces its activity, is associated with a higher therapeutic effect when treated with clopidogrel, prasugrel, or ticagrelor [71, 72]. Carriage of the mutant allele rs6809699, which likely leads to increased PEAR2 activity, is associated with higher platelet reactivity when taking clopidogrel [73]. This is consistent with the results of the study presented in Section 3, which showed that hypomethylation of the promoter, leading to increased gene expression levels, negatively affects clopidogrel efficacy [9].

At present, it is impossible to explain the mechanism of the link between genes responsible for cell cycle, circadian rhythm, and other processes not related to the formation of atherosclerotic plaques, platelet aggregation, and antiplatelet metabolism, and the risk of developing resistance to P2Y12 receptor antagonists.

Review Limitations

This systematic review has several methodological limitations. There is heterogeneity in the criteria for defining clopidogrel resistance: in most studies, patients were considered resistant to clopidogrel if PRU > 240, but other indicators were also used, such as PRI > 75 % [15] or PRU > 208, which complicates direct comparison of study results. Furthermore, the analyzed studies did not measure methylation levels dynamically [74]. It is possible that during long-term antiplatelet therapy, gene methylation levels also change, which

[4] CPIC® Guideline for Clopidogrel and CYP2C19: [электронный ресурс]. URL: https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19

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could lead to changes in treatment response, such as the occurrence of resistance or bleeding with prolonged drug intake.

CONCLUSION

Most studies have identified a link between the methylation level of a gene responsible for platelet aggregation or antiplatelet metabolism, leading to altered activity, and the efficacy of P2Y12 antagonist therapy. There is also data on the link between methylation levels of other genes and therapy efficacy, but these need further verification. Studies are also needed on the impact of methylation levels on the efficacy of next-generation P2Y12 antagonist therapy. The inclusion of epigenetic biomarkers in diagnostic panels alongside genetic markers may allow for more accurate prediction of response to antiplatelet therapy in patients.

FUNDING

This work was carried out with the financial support of the Ministry of Health of the Russian Federation, the subject of the state assignment “Development of a pharmacogenetic test system to improve the effectiveness and safety of pharmacotherapy for patients with cardiological and psychiatric profiles” (EGISU R&D I124020600064-1).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR’S CONTRIBUTION

Svetlana N. Tuchkova — data curation, formal analysis, writing—original draft, visualization; Sherzod P. Abdulaev — data curation, formal analysis, writing—original draft; Natalia P. Denisenko — writing—review & editing; Karin B. Mirzaev — conceptualization, methodology, writing—review & editing; Sychev D.A. — scientific guidance, writing—review & editing. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved of the final version before the publication).

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ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2026-14-3-218-235

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