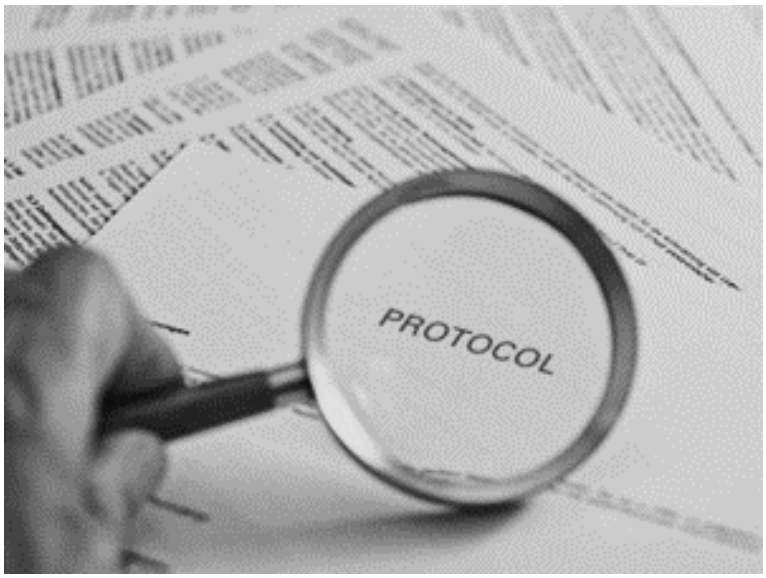
Clinical Study Protocol

Protocol BREC-TSMU#2-2023/103 - "The research implementation of the clinical model for evaluation of CYP2C19 alleles genotype-guided clopidogrel treatment"



June 7,

2023

Vistamedi Ltd.
Clinical Study Protocol
The research implementation of the clinical model for evaluation of the *CYP2C19* allele genotype-guided clopidogrel treatment

Protocol Number:	Protocol BREC-TSMU#2-2023/103. Revision of protocol version #2023/1.0 submitted to the Biomedical Research Ethics Committee of Tbilisi State Medical University for review with explanations and clarifications by the IRB conditions, and notes from May 24, 2023.
Date of the Version:	June 7, 2023
Study Object:	Human *CYP2C19 *2, *3* allele genotype as a pharmacogenetic marker of clopidogrel treatment efficacy
Gene ID:	NCBI entrez gene: 1557 (an update from March 15, 2023)
Study:	Randomized Parallel Group Controlled Trial for Evaluating CYP2C19 Allele Genotype-guided Clopidogrel Treatment Outcomes in Real-world Practice After the ePCI
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Co-funder:	International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Via Carlo Farini 81, 20159 Milan, Italy; Email: ifcc@ifcc.org
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Abbreviations

ACC	American College of Cardiology
ACG	American College of Gastroenterology
AHA	American Heart Association
ACS	Acute Coronary Syndrome
AE	Adverse Event
ASCVD	Atherosclerotic Cardiovascular Disease
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCs	Chronic Coronary Syndromes
CRF	Case Report Form
CVD	Cardiovascular Disease
CPIC	Clinical Pharmacogenetics Implementation Consortium
DAPT	Double Antiplatelet Treatment
DPWG	Dutch Pharmacogenetics Working Group
EACTS	European Association for Cardio-Thoracic Surgery
EMA	The European Medicines Agency
ePCI	elective Percutaneous Coronary Intervention
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ESVS	European Society for Vascular Surgery
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HF	Heart Failure
ICD-10	10^{th} version of the International Classification of Diseases
IRB	Institutional Review Board
MACE	Major adverse cardiovascular event
MACCE	Major adverse cardiac and cerebrovascular event
MI	Myocardial Infarction
mut	mutant allele
NACE	New Adverse Clinical Event
NCDC	National Centre for Disease Control and Public Health
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
PCI	Percutaneous Coronary Intervention
PCR	Polymerase chain reaction
P2Y12	G protein-coupled purinergic receptors of G_i class, adenosine diphosphate chemoreceptor
R_c	Frequency of occurrence of a control event (statistical calculation value)
R_t	Frequency of occurrence of an experimental event (a statistical calculation quantity)
RT-PCR	Real-Time Reverse Transcription–Polymerase Chain Reaction Assay
SAE	Serious adverse event
STE/NSTE-ACS	ST-Elevation or Non-ST-Elevation Acute Coronary Syndrome
wt	wild trait allele

SYNOPSIS

Title	The research implementation of the clinical model for evaluating CYP2C19 allele genotype-guided clopidogrel treatment.
Sponsor	Vistamedi Ltd. Ramazi str. 28, 0159. Tbilisi. Georgia. phone: (+995 32) 2 18 33 18, (+995 32) 2 22 47 77; Email: info@vistamedi.ge
Co-funder	International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Via Carlo Farini 81, 20159 Milan, Italy; Email: ifcc@ifcc.org
Sites	4 or more clinical practice centers that provide clinical case management of ACS and CCS, PCI procedures or post-PCI and follow-up activities for patients at risk of CVDs, including CAD, HF.
Relevance	Among the challenges of ASCVD, preventing recurrent MACCEs is a significant issue. Scientific evidence widely supports pharmacotherapeutic approaches for the routine use of a *P2Y12* inhibitor (clopidogrel or an alternative) within the framework of DAPT or other regimens of antiplatelet treatment. Clopidogrel remains the most commonly used *P2Y12* inhibitor in the post-PCI setting. Pharmacogenetic models of drug selection are also being introduced to optimize treatment. Currently, the selection of treatment with clopidogrel or an alternative *P2Y12* inhibitor by genotyping *CYP2C19* alleles is based on reliable evidence. The effects of treatment are influenced by the wide variability of *CYP2C19* genotype in the population, which, even under conventional treatment with clopidogrel, significantly increases the risk of MACCEs in carriers of non-functional alleles. The antiplatelet treatment paradigm faces a significant dilemma regarding the use of clopidogrel: on the one hand, existing practice guidelines (ESCARDIO and ACC/AHA) recommend the use of clopidogrel without *CYP2C19* genotyping. On the other hand, the Global Consensus Report of Industry Associations on the Possibility of Adapting *P2Y12* Inhibitor Treatment to *CYP2C19* Genotyping and the Selective Use of the Test (2019), as well as the FDA's so-called "black box warnings" on the use of clopidogrel, the EMA's precautionary statements, the CPIC and DPWG scientific reports and practice guidelines, and the evidence base UNC study, TAILOR-PCI, POPular Genetics, PHARMA-ACS, UK Biobank study, and other so-called "From New Prospective Studies" clearly demonstrates the advantages for guiding P2Y12 inhibitor treatment by *CYP2C19* genotype. In these circumstances, promising research directions are determined by the following critical questions: Is it possible to select *P2Y12* inhibitor treatment by genotype? This issue will be resolved by answering the main question: Are *CYP2C19* genetic variations associated with clinical outcomes of clopidogrel treatment, in interaction with other known influencing factors or independently of them?
Hypothesis	The research question is how antiplatelet treatment for preventing major adverse cardiovascular events after ePCI works in chronic coronary artery disease when guided by personal genetic characteristics for drug metabolism. The study aims to test two research hypotheses: • *CYP2C19* genotype-guided clopidogrel treatment ensures better clinical outcomes when compared with conventional treatment selection led without *CYP2C19* genotyping. • *CYP2C19* genotype-guided antiplatelet treatment could be beneficially applied in real-world clinical practice.
Design	Multicenter, randomized, parallel-group controlled study

Primary Objectives	The aim of the study is to evaluate *CYP2C19* allele genotype-guided antiplatelet treatment outcomes. The specific objectives of the study are: — Pre-assignment and randomization of study participants into study arms for conventional and *CYP2C19* genotype-guided antiplatelet treatment with clopidogrel or an alternative P2Y12 inhibitor; — providing RT-PCR-based pre-, analytical and post-analytical processes of the study to ensure *CYP2C19 *2, *3* allele profiling for detection of study participants with normal functioning (NFA) and loss of function (LOF) allele; — Observation of clinical outcomes of patients in the study groups during the 12 months of treatment; — Evaluation of processes and non-clinical outcomes of clinical case management;
Secondary Objectives	— Implementation of the methods and procedures provided by the research protocol into a real clinical practice pipeline; — Raising awareness and understanding of the role of laboratory services by bridging clinical, laboratory practice professionals and other stakeholders to achieve patient-centeredness and improve clinical outcomes; — Evaluation of clinical practice models based on assessments of molecular markers; — Disseminate study results through publishing a scientific paper in a peer-reviewed journal and abstracts for reporting study results.
Study Participants	240 patients requiring antiplatelet treatment with a *P2Y12* inhibitor after ePCI as a major cardiovascular clinical event for CAD, meeting clinical inclusion criteria and not meeting exclusion criteria.
Randomization	Inclusion in two parallel groups with a 1:2 allocation ratio of controls (active comparators) and experiments. Genotyping the *CYP2C19 *2, *3* alleles of experimental arm participants for separation of carriers of normal **2, *3* function alleles (NFA) and Carriers of loss of function **2, *3* alleles (LOF).
Study arms	3 arms of study participants: 1st arm - experimental: “Normal Metabolizers of Clopidogrel”, 110 study participants diagnosed with chronic coronary artery disease who had undergone elective PCI, tested with *CYP2C19* genotyping and identified as NFA **2, *3* carriers, who undergo *CYP2C19* Genotype-Guided Clopidogrel Treatment - Clopidogrel as a component of preventive antiplatelet treatment such as double antiplatelet treatment (DAPT), or an antiplatelet drug (clopidogrel) combined with the non-vitamin K antagonist oral anticoagulants (NOAC), incl. triple antiplatelet treatment (Aspirin, Clopidogrel and a NOAC), or antiplatelet monotherapy (Clopidogrel). 2nd arm - experimental: “Passive Metabolizers of Clopidogrel”, approximately‡ 50 study participants diagnosed with chronic coronary artery disease who had undergone elective PCI, tested with *CYP2C19* genotyping, identified as LOF **2, *3* allele carriers, who undergo *CYP2C19* Genotype Guided Antiplatelet Treatment Alternative to Clopidogrel - an antiplatelet drug alternative to clopidogrel in conventional dosing regimen, as a component of preventive antiplatelet treatment, such as double antiplatelet treatment (DAPT) with ticagrelor or prasugrel, or prasugrel combined with the nonvitamin K antagonist oral anticoagulants (NOAC), or antiplatelet monotherapy (ticagrelor, or prasugrel). 3rd arm - active comparator: “Unspecified Metabolizers of Clopidogrel”, 80 participants diagnosed with chronic coronary artery disease who had undergone elective PCI were allocated to the arm, without *CYP2C19* genotyping through simple randomization, and having an unspecified metabolism phenotype, who were assigned to the conventional

	clopidogrel treatment - clopidogrel as a component of preventive antiplatelet treatment, such as double antiplatelet treatment (DAPT), or clopidogrel combined with the non-vitamin K antagonist oral anticoagulants (NOAC), incl. triple antiplatelet treatment (Aspirin, Clopidogrel and a NOAC), or antiplatelet monotherapy (Clopidogrel). ǂ *in the Georgian population, the prevalence of CYP2C19 LOF carriers has not been studied and is unknown. For preliminary calculations of the study participants' number in the 1st arm and 2nd arm, known data from the European population study were used [21].*
Controls	2 study arms could be used for controlling participants' (study) outcome measures: 3rd study arm participants create the active comparators group for 1st and 2nd arm, and besides, 2nd study arm participants - as the comparators for 1st arm. Control 1: "Normal Metabolizers of Clopidogrel" - 110 study participants vs "Unspecified Metabolizers of Clopidogrel" - 80 participants; Control 2: "Passive Metabolizers of Clopidogrel" - approximately 50 participants vs "Unspecified Metabolizers of Clopidogrel" - 80 participants; Control 3: "Normal Metabolizers of Clopidogrel" - 110 study participants vs "Passive Metabolizers of Clopidogrel" - approximately 50 participants.
Selection criteria	Participants of both sexes aged between 35-79 years are eligible for the study. **Inclusion Criteria:** ▪ Diagnosed with chronic coronary artery disease; ▪ Completed informed consent form for participation in the study; ▪ Undergone elective PCI within the last 12 weeks without procedure-related complications; or the clinical challenge is to de-escalate post-PCI antiplatelet treatment from an alternative P2Y12 inhibitor to clopidogrel. ▪ LVEF≥38% after index PCI; **Exclusion Criteria:** ▪ Concomitant using of potent *CYP3A4* or *CYP2C19* inhibitors; ▪ Clinical obesity, BMI - 40 kg/sq.m or more; ▪ Type 1 diabetes mellitus; ▪ Poorly controlled type 2 diabetes mellitus, Hba1c - 9% or more; ▪ Acute Myocardial Infarction; ▪ Coronary artery bypass grafting was performed within the last 12 weeks. ▪ Valvular heart disease due to dysplasia, connective tissue disorders, or inflammatory disorders, or valvular disorders requiring cardiac surgery; ▪ History of severe hepatic impairment; ▪ Severe chronic kidney disease; ▪ Clinically important leucopenia, lymphopenia, thrombocytopenia or thrombocytosis; ▪ History of hemorrhagic diathesis or coagulopathy; ▪ An active or an obvious threat of bleeding (including GI bleeding): ▪ Bleeding within the past 6 months that required hospitalization; ▪ Blood transfusion during the past 6 months or its refusal; ▪ History of intracranial hemorrhage; ▪ Cardiac or non-cardiac degenerative disease, including: cardiomyopathy, restrictive lung disease, or neurodegenerative diseases; ▪ Malignant tumor (cancer) that limits life expectancy to less than one year; ▪ Current chemotherapy or immunosuppressive therapy; ▪ Ongoing immunosuppression or immunosuppressive conditions;

	▪ Pregnancy or lactation period; ▪ Any disease/condition for which control is not achieved; ▪ Personal (patient/physician dependent) or health care system-related circumstances that can restrict or limit any study procedures or operations.
Product	Selection of *P2Y12* inhibitor treatment by *CYP2C19* allele genotype. The investigational product development is based on the RT-PCR-based detection of normal or loss-of-function alleles of the human cytochrome P450 system 2c19 enzyme encoded by *CYP2C19 *2, *3*.
Expected use	Tailoring antiplatelet treatment to optimize MACCEs prevention in high-risk ASCVD patients.
Perspective arm	A clinical group of patients with ASCVD who require treatment with a P2Y12 inhibitor (including clopidogrel) after PCI for acute myocardial infarction, characterized by a more severe course of the disease and a significantly higher baseline risk of recurrent MACCEs compared with the participants group under the study. The perspective arm is clinically more heterogeneous and requires a different study design.
Duration of the study	Total duration of the study: 24 months. ▪ Expected duration of the study activities (from screening/randomization of the first patient to the end of follow-up of the last involved patient): 20 months; — Patient enrollment period: 8 months; — Follow-up period: 12 months; ▪ Study preparation period: 2 months; Study closure period: 2 months.
Follow-up	Follow-up of study end-points from the start of the study intervention: ▪ 3 months (±1 week); ▪ 6 months (±1 week); ▪ 12 months (±1 week); Follow-up evaluation within 72 hours in cases of early withdrawal within 12 months from the study for any reason. Reasons for the early withdrawal are defined as: ▪ Withdrawal by study participant; ▪ Non-compliance with treatment intervention; ▪ Loss of follow-up; ▪ Physician's decision. Routine observations of the study cases by the institutional standards and protocols for long-term disease control, as accepted for the real practice of clinical centers enrolling the study participants.
Clinical management and medication treatment	The ongoing management and treatment of patients in the study group, as well as those withdrawn from the study following the ESC, ESC/ESH, ESC/EACTS, ESC/ESVS, ACC/AHA, ACC/AHA/ASA, ACG, ISTH guidelines and recommendations for CAD and concomitant ASCVDs. Treatment of other concomitant diseases/conditions following the recommendations provided by national protocols and guidelines, and taking into account the contraindications and limitations of the use of individual medications.
Primary clinical end-points for outcome measures	— Death from any cause within a 12-month of the study follow-up; — Death from any cardiovascular cause within a 12-month of the study follow-up;

Secondary clinical end-points of outcome measures	— Non-fatal myocardial infarction within a 12-month of the study follow-up; — Unstable angina or angina requiring hospitalization within a 12-month of the study follow-up; — Stroke or transitory cerebral ischemic event within the study follow-up period within a 12-month of the study follow-up; — Major bleeding within a 12-month of the study follow-up; — Non-major bleeding within a 12-month of the study follow-up; — Heart failure event within a 12-month of the study follow-up; — Percutaneous coronary intervention or coronary artery bypass-grafting within a 12-month of the study follow-up
Other end-points of outcome measures	— Composite of death from any cause, non-fatal myocardial infarction, stroke, or major bleeding within a 12-month of the study follow-up (Net adverse clinical events - NACEs); — Composite of death from any cause, non-fatal myocardial infarction, or stroke within a 12-month of study follow-up (Major adverse cardio or cerebrovascular events - MACCEs); — Composite of death from cardiovascular cause, non-fatal myocardial infarction, recurrent angina, or repeated revascularization (PCI or CABG) within a 12-month of study follow-up (Major adverse cardiovascular events - MACEs); — Number of study participants whose health status was defined as good or satisfactory, or with the appearance of CVD symptoms, or with a significant inability to self-care (Patient-Reported Health Status) reported by the patient or patient caregiver at 3, 6 and 12 months of the study follow-up; — Participants self-reported (or patient's caregiver reported) angina not required hospitalization (Patient-Reported Angina Not Required Hospitalization at 3, 6 and 12 months of the study follow-up; — Participants reported (or patient's caregiver reported) last week's shortness of breath due to heart failure not requiring hospitalization (Patient-Reported Heart Failure Severity) at 3, 6 and 12 months of the study follow-up; — Withdrawal for any reason within a 12-month of the study follow-up; — Costs of clinical service utilization for case management during the study follow-up; — Incremental costs incurred for real-world health care services, including costs for the MACCEs, MACEs and NACEs;
Other measures	— Cardiometabolic risk factors and their control status; — Total number of hospitalizations for any reason within 12 months of the study follow-up; — Comorbidities;
Safety	The risk of the study is minimal. The clinical diagnostic procedures for screening, randomization (incl. CYP2C19 *2, *3 allele genotyping) and follow-up are safe for study participants. Health-related risks are associated with major adverse cardio- and cerebrovascular risks (MACCEs) of the CAD and possible known adverse effects of the drugs used in medication control of the diseases/conditions. However, they cannot be significantly related to adverse events/effects caused by the study procedures. They can appear in the routine processes of clinical case management outside the scope of the study activities in real clinical practice. The follow-up assessments at the 3rd, 6th and 12th month follow-up and the selection and management of medication treatment provided across the study are likely to reduce the risks.

	Equally, risks to the health of study participants can be contributed to or neutralized by medical care procedures provided in real practice outside the scope of the study, because on the one hand, it may be erroneous or incomplete, on the other hand, it may be timely and targeted. Risks to the health of study participants can be attributed to non-compliance with clinical management and treatment measures. The study's follow-up assessment processes can effectively prevent these risks. Threats may arise from possible violations of the confidentiality of study participants and possible illegal access to and processing of personal data. Consistently conducted study procedures provide special measures to protect confidentiality and personal data. Deviations in the implementation of procedures and activities may cause study-related risks. However, ongoing monitoring of research processes will make it possible to assess and prevent risks caused by research deviations. Researchers/investigators, the management team and the IRB will carry out research risk assessments and mitigation measures.
Effectiveness	Effectiveness will be assessed by analyzing the incidence and the difference appearing between the clinical endpoints of the study in the experimental and control arms. Study bias will be reduced by the random selection of the experimental and the control arms. The overlap of effects will be reduced by homogenizing the experimental and control clinical cases, which is achieved by using inclusion and exclusion criteria for all study patients. This will equalize the baseline risks, and eliminate the effects due to age, sex, risk factors and high-risk comorbidities. Study bias will be eliminated by consistent measures of monitoring and evaluation of the study-specific processes, including procedures for data entry, validation and protection in the electronic database used.
Primary statistical analysis	Descriptive statistical analysis methods will be used to evaluate the values (mean, median) and distribution (standard deviation) for quantitative and a probability and frequency of distribution of clinical features and events determine outcomes for qualitative characteristics of variables to detect significant central tendencies and summarize features (for 95% confidence level and ±5% confidence interval, when the p-value of statistical significance <0.05) according to the experimental and control arms. The frequency of detection of the study clinical endpoints in the experimental treatment intervention (R_t) and control arms (R_{c1} and R_{c2}) will be calculated. To analyze the difference between the frequencies of detection of the endpoints and the effectiveness of the selected treatment intervention, the Hazard Ratio (OR), Relative Risk (RR), Relative Benefit (RB), and Absolute Benefit (AB) indicators will be measured. By reviewing the results obtained, those indicators of effectiveness will be selected that can determine the applicability of the study findings for the translation of the study results.
Sample size	The sample size for the study was determined to be 240 patients. Calculations were made using two instruments that provided two approximate sample sizes. The median of these values (considering that the better the odds ratio could be achieved from the larger the sample size) was taken as the sample size. (1) Calculate the sample size for scientific studies using a standard numerator based on the proportion of the population that is likely to have the demographic characteristics of the study sample and the size (number) of the population with the clinical characteristics expected for the study, with a 95% confidence level and a ±5% confidence interval for the results of the statistical calculations.

	(2) Sample size calculation for a randomized, parallel case-control study with a two-sided statistical significance level, at a confidence interval of α – 0.05, at statistical power of $(1-\beta)$ – 0.8, at case/control ratio of 2, at probability of occurrence of an event in the experimental arm of p0 – up to 0.4, and at probability of occurrence of an event in the control arm of p1 – up to 0.6.
Data processing	The study data will be processed in stages when: I - More than 50% of patients are enrolled in the study; II - The study group is fully formed, and by this time, more than 50% of patients have completed the 3-month observation period, and some patients have completed the 6-month observation period. III - all patients included in the study have completed the 6 months, and some have completed the 12 months; IV - All patients included in the study have completed the 12-month observation period. The following will be carried out during the follow-up periods: — Observation of MACCEs and collection of information about them; — Monitoring and evaluation of the project; — Observation and analysis of study activities, procedures, non-clinical outcomes and safety data.

Content

1.0 Study Aim

1.1. The Investigational Product

The investigational product is a *P2Y12* inhibitor treatment selection assay based on the *CYP2C19* allele genotype.

The development of the investigational product is based on assessing resistance to clopidogrel treatment by RT-PCR-based detection of impaired/non-functional alleles of the human cytochrome P450 system *2c19* enzyme encoded by the *CYP2C19 *2, *3*.

The *CYP2C19 *2, *3* wild-type (wt) and mutant (mut) alleles will be determined, and heterozygous or homozygous carriers of *CYP2C19 *2, *3* normal alleles or altered alleles will be determined.

Clopidogrel *CYP2C19* metabolism phenotypes are determined according to the rule provided in the table below.

<table>
<tr><th rowspan="2">Alleles</th><th colspan="2">Haplotypes</th><th rowspan="2">Test results</th><th colspan="2">Metabolizing Phenotypes of the CYP2C19 Gene</th></tr>
<tr><th>wt</th><th>mut</th><th>Active</th><th>Passive</th></tr>
<tr><td rowspan="3">CYP2C19 *2</td><td>✓</td><td>—</td><td>wt/wt</td><td rowspan="6">▪ Normal Function Alleles;
➥ CYP2C19 *2 wt/wt and *3 wt/wt</td><td rowspan="6">▪ Loss of Function alleles (Heterozygous)
➥ CYP2C19 *2 wt/wt and *3 wt/mut
or
➥ CYP2C19 *2 wt/mut and *3 wt/wt
or
➥ CYP2C19 *2 wt/mut and *3 wt/mut

▪ Loss of Function alleles (Homozygous)
CYP2C19 *2 wt/wt and *3 mut/mut
or
➥ CYP2C19 *2 mut/mut and *3 wt/wt
or
➥ CYP2C19 *2 mut/mut and *3 wt/mut
or
➥ CYP2C19 *2 wt/mut and *3 mut/mut
or
➥ CYP2C19 *2 mut/mut and *3 mut/mut</td></tr>
<tr><td>✓</td><td>✓</td><td>wt/mut</td></tr>
<tr><td>—</td><td>✓</td><td>mut/mut</td></tr>
<tr><td rowspan="3">CYP2C19 *3</td><td>✓</td><td>—</td><td>wt/wt</td></tr>
<tr><td>✓</td><td>✓</td><td>wt/mut</td></tr>
<tr><td>—</td><td>✓</td><td>mut/mut</td></tr>
</table>

1.2. Anticipated Use of the Investigational Product

The investigational product can be used for CYP2C19 *2, *3 genotype-guided clopidogrel or an alternative P2Y12 inhibitor treatment of high-risk ASCVD patients for tailoring antiplatelet therapy to optimize the prevention of MACCE.

1.3. Relevance of the Study

Despite the progress of modern health systems, ASCVD remains the leading cause of global disease burden and mortality [1, 2]. The dramatic nature of the situation is due to the development of MACCEs in the course of ASCVD. Through complex interactions with genetic and other multiple risk factors and comorbid conditions, the disease/conditions exacerbate structural and functional disorders, manifest different clinical phenotypes of the disease, and affect treatment efficacy and outcomes [3].

Current evidence presents preventive treatment approaches for recurrent MACCEs in ASCVD, the implementation of which in routine practice allows for patient-specific and personalized clinical decisions and, as a result, improved outcomes. The pharmacotherapeutic approach to the prevention of MACCEs in CAD [4, 5] involves the routine use of aspirin and a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) as part of DAPT based on a risk-benefit assessment. Current recommendations also provide a choice between newer and more potent P2Y12 inhibitors (ticagrelor and prasugrel) and clopidogrel to optimize their use at different stages of CAD management.

Nevertheless, clopidogrel remains the most commonly used P2Y12 inhibitor, including in the primary and post-elective PCI period [6]. This trend is supported by the significant risk-benefit of the use of new-generation antiplatelet agents and the higher risk of other, non-MACCEs, and adverse clinical events, such as bleeding [7].

To increase the effectiveness of clopidogrel and optimize the use of alternative, new-generation P2Y12 inhibitors, models for assessing the pharmacogenetic feasibility of drug treatment are currently being introduced into practice [8]. The hypothesis, which has been actively discussed over the past decade, that the decision to treat with clopidogrel for the prevention of MACCE is significantly more effective in meeting risk reduction goals if it is based on the results of CYP2C19 allele genotyping, is now supported by reliable clinical evidence [9-16]. Therefore, clopidogrel has become a suitable target for pharmacogenetic evaluation of P2Y12 inhibitor use, as its effects are influenced by the variability of CYP2C19 genotype in the population, which, even with conventional treatment with clopidogrel, significantly increases the risk of MACCE, especially in carriers of non-functional alleles [17].

The current paradigm for clopidogrel use faces a dilemma. Existing practice guidelines (ESCARDIO, 2017 and ACC/AHA, 2016) provide recommendations for the use of clopidogrel or other P2Y12 inhibitor treatment without CYP2C19 genotyping. A larger evidence base supporting the efficacy of the pharmacogenetic approach is required to guide treatment recommendations based on CYP2C19 genotyping, including genome-wide associations between CYP2C19 genotype variability and MACCE of recurrent ASCVD on clopidogrel treatment [8, 10]. On the other hand, the 2019 Global Consensus Report of the industry associations presented the possibility of tailoring P2Y12 inhibitor treatment based on CYP2C19 genotype and general recommendations for the selective use of CYP2C19 genetic testing [10]. The FDA's so-called "Clopidogrel" "Black box warnings" [18], EMA precautionary statements, CPIC and DPWG scientific reports [19-21], as well as the evidence base from new pragmatic and prospective studies [9-16], support the approach of CYP2C19 allele-specific P2Y12 inhibitor treatment and determine its efficacy. Approximately 30% of the European population and 60% of Asians carry CYP2C19 non-functional alleles [21], which are associated with resistance to clopidogrel treatment and a significantly increased risk of MACCE [21-24].

At this stage, the directions of scientific development can be determined by the following research questions: Can CYP2C19 allele genotypes be routinely used for P2Y12 inhibitor treatment? The answer to the main question will make a significant contribution to resolving this issue: Are CYP2C19 genetic variations associated with clinical outcomes of clopidogrel treatment independent of interactions with other known factors?

1.4. Study Objectives

1.4.1. Primary Objectives

The aim of the study is to evaluate *CYP2C19* allele genotype-guided antiplatelet treatment outcomes.

The specific objectives of the study are:

- Pre-assignment and randomization of study participants into study arms for conventional and *CYP2C19* genotype-guided antiplatelet treatment with clopidogrel or an alternative P2Y12 inhibitor;
- providing RT-PCR-based pre-, analytical and post-analytical processes of the study to ensure *CYP2C19 *2, *3* allele profiling for detection of study participants with normal functioning (NFA) and loss of function (LOF) allele;
- Observation of clinical outcomes of patients in the study groups during the 12 months of treatment;
- Evaluation of processes and non-clinical outcomes of clinical case management;

By responding to these objectives, the effectiveness of CYP2C19 genotype-guided clopidogrel treatment in selected cases will be assessed, clinical approaches for the use of CYP2C19 genotyping in existing, real-world clinical practice will be determined, the implementation of treatment measures tailored to the results of CYP2C19 genotype testing will be analyzed, and the possibilities of using these approaches in real-world clinical practice for treatment personalization will be analyzed.

1.4.2 Secondary Objectives

Secondary objectives are set to explore and evaluate opportunities for implementing research findings:

- Implementation of the methods and procedures provided by the research protocol into a real clinical practice pipeline;
- Raising awareness and understanding of the role of laboratory services by bridging clinical, laboratory practice professionals and other stakeholders to achieve patient-centeredness and improve clinical outcomes;
- Evaluation of clinical practice models based on assessments of molecular markers;
- Disseminate study results through publishing a scientific paper in a peer-reviewed journal and abstracts for reporting study results.

By responding to these objectives, the feasibility and applicability of the clinical and laboratory procedures for CYP2C19 genotype-guided treatment selection to optimize the treatment with clopidogrel or alternative P2Y12 inhibitors in real clinical practice will be assessed, obstacles and acceptability of the studied approaches by stakeholders groups will be determined, the perception of the problems will be strengthened, and the effectiveness of the use of dissemination channels for research results will be determined.

1.4.3 Expected Duration of the Study

The total expected duration of the study is 24 months. The implementation will conditionally include 4 stages.

Preparatory work will be carried out during the first 2 months of the project implementation to initiate the study.

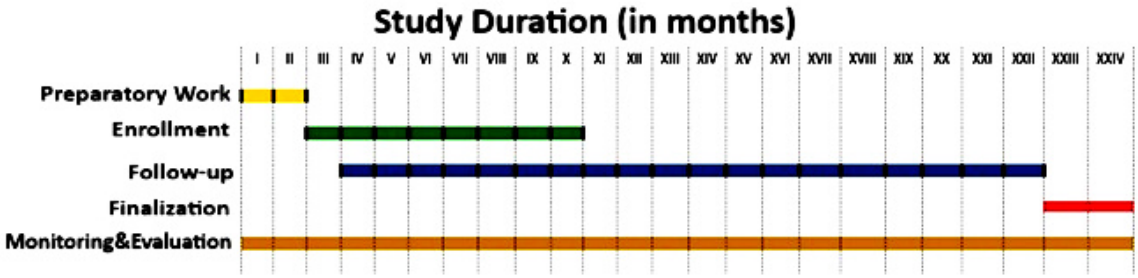
The expected duration of the study component itself is 20 months from the screening/randomization of the first study participant to the end point of observation of the last involved study participant.

During this period, the inclusion of participants in the study will continue for approximately 8 months.

Follow-up visits and relevant examinations will begin 1 month after the inclusion of the first patient, which will continue for 12 months after the inclusion of the last participant in the study and continue throughout the follow-up of clinical outcomes and related clinical case management processes.

The analysis of the final results of the study, the formulation of assessments, the preparation of the scientific paper, submission for peer-reviewed publications and the preparation of the final scientific and technical reports of the study will be carried out during the last 2 months of the project.

Monitoring and evaluation activities will be carried out throughout the 24-month project period.



The overall duration of the research project can be reduced by condensing the study components separately. In particular, the intensification of study participants' enrolment activities can be achieved by increasing the frequency (accelerating) of study participants' screening, pre-assignment and randomization in study centers and, accordingly, by shifting the calendar end of the follow-up component period. In such a case, it is expected that the reasonable duration of the calendar term for the study activities for study participants enrollment will be 6 months instead of 8 months, and accordingly, by shifting the calendar end of the 12-month follow-up period, the overall duration of the research project will be shortened up to 22 months instead of 24 months.

2.0 Study Protocol

2.1 Protocol ID and Title

Protocol: BREC-TSMU#2-2023/103.

The research implementation of the clinical model for evaluation of the CYP2C19 allele genotype-guided clopidogrel treatment.

2.2 Protocol Version and the Date

Version: #2-2023/103

The revision of protocol version #2023/1.0, which was primarily submitted to the Biomedical Research Ethics Committee of Tbilisi State Medical University for review by May 24, 2023, was revised with additional explanations and clarifications by the IRB conditions and notes, and finally approved on June 7, 2023.

The definitions and clarifications presented in this protocol version do not change the essence of study participants' selection criteria and do not reflect the study design, methodology, study procedures, the measures for observing effects and safety, or the expected results, either qualitatively or quantitatively.

The revisions and updated definitions presented only increase the pool of patients from whom study participants should be selected in real clinical practice, and facilitate and support researchers/investigators in conducting subject selection, study procedures, and monitoring efficacy and safety in a targeted manner.

2.3 Study Design

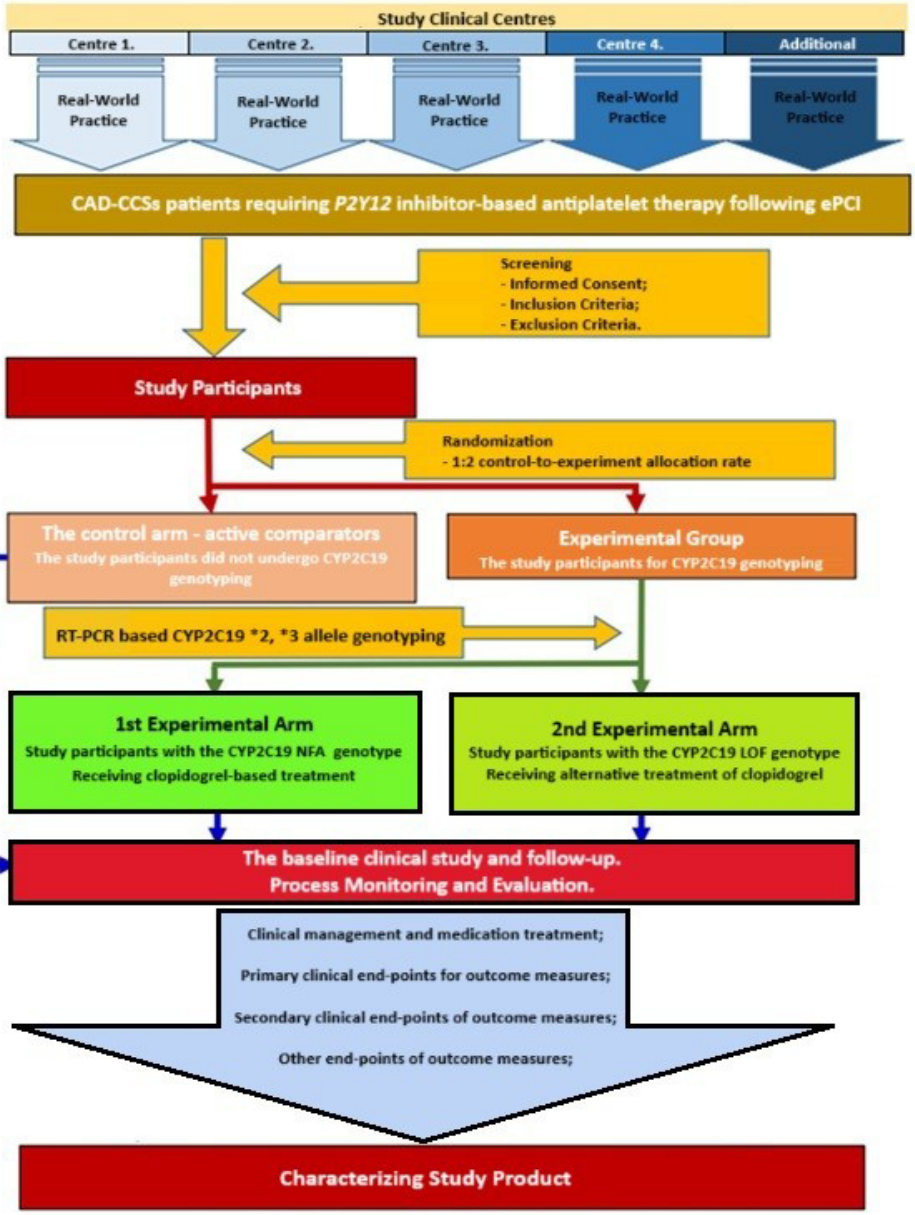
2.3.1 General Design

Randomized Parallel Group Controlled Trial for Evaluating CYP2C19 Allele Genotype-guided Clopidogrel Treatment Outcomes in Real-world Practice After the ePCI.

2.3.2 Structural Design

Study participants will be recruited from 4 or more clinical centers. Based on informed consent, these centers will be selected and employed to provide study-specific activities under the condition that they provide CAD-specific diagnostic, treatment, and prevention services as recommended by current guidelines in their real-world clinical practice. They must provide GCP-compliant care based on current quality standards, patient best interests, and safety.

A logical model of study.



A population of patients who require antiplatelet therapy with a *P2Y12* inhibitor following ePCI in CAD CCs cases within the framework of the recommendations for the use of DAPT (ESC, ACC/AHA) will be pre-assigned from the centers' real-world practice. Eligible patients will be considered for participation in the study after formal informed consent for inclusion in the specific clinical study measures.

Screening measures will be implemented for these patients to establish study inclusion and exclusion criteria. In conditions of the existence of inclusion criteria and absence of exclusion criteria, study participants will be randomized to the study or control arm by control-to-experiment allocation rate 1:2.

Study participants randomly allocated to the experimental arm will undergo laboratory blood testing for *CYP2C19 *2, *3* genotyping using the RT-PCR-based allele discrimination method. According to the results of genotyping, the study participants will be assigned to two experimental treatment arms:

1st experimental arm will consist of the study participants with the active metabolizing phenotype of CYP2C19 (a normal function CYP2C19 *2, *3 allele (NFA) genotype), who will receive clopidogrel-based antiplatelet treatment;

2nd experimental arm will consist of study participants with the passive metabolizing phenotype of CYP2C19 (a loss-of-function CYP2C19 *2, *3 allele (LOF) genotype, heterozygous or homozygous), who will receive alternative antiplatelet treatment of clopidogrel.

Study participants allocated to the control arm – 3rd arm of active comparators will not undergo laboratory blood testing for CYP2C19 *2, *3 genotyping, will be considered as study participants with unspecified metabolizing phenotype of CYP2C19 and receive the P2Y12 inhibitor clopidogrel-based antiplatelet treatment according to current clinical practice recommendations, without genotyping for CYP2C19 *2, *3 alleles as by real-world practice.

All study participants assigned to the study arms will undergo baseline and ongoing clinical follow-up to assess clinical endpoints as study clinical outcomes.

All clinical cases will be followed up with the primary, secondary and other prespecified clinical endpoints of the study and routine clinical indicators of safety at 3, 6, and 12 months. Non-clinical study outcomes will be assessed and compiled with other results of the outcome measures.

Study monitoring and evaluation procedures will be implemented alongside the study activities to assess safety and efficacy, and outputs.

2.4 Study Participant Selection

2.4.1 General Characteristics of Study Participants

Study participants are patients requiring treatment with clopidogrel or an alternative P2Y12 inhibitor following ePCI as a major cardiovascular clinical event for CAD.

Study participants will be selected based on a clinical model defined by stable CAD confirmed by ePCI. They have undergone coronary stenting within the past 12 weeks to reduce their risk, and despite this reduction, they are still at risk of developing recurrent MACCEs. To reduce the risk of subsequent MACCE, the patient with these clinical characteristics requires antiplatelet therapy with clopidogrel after coronary stenting. Carriers of CYP2C19 *2, *3 LOF alleles, as patients at complement risk due to expected resistance to clopidogrel treatment, will be given antiplatelet therapy with an alternative P2Y12 inhibitor to clopidogrel for prevention.

In contrast to primary PCI for the management of CAD STE/NSTE-ACS or coronary artery bypass grafting, patients selected with the study clinical model have a relatively lower risk of developing recurrent MACCEs. By equalizing or excluding complementary cardiovascular risky conditions, and co-morbidities, which will be achieved by using study participants' inclusion and exclusion criteria, precise antiplatelet therapy using P2Y12 inhibitors and ensuring adherence to treatment at baseline the probability of recurrent MACCE cases will be equal for the experimental and control arm of study participants. Thus, it will be possible to follow-up and evaluate the clinical outcomes of CYP2C19 genotype-guided as well as conventional treatment with P2Y12 inhibitors (clopidogrel or alternative) which is the aim of the study.

2.4.2 Expected Number of Study Participants

Patients with stable CAD who have undergone ePCI coronary artery stenting without clinically significant procedural complications, require conventional antiplatelet therapy with a P2Y12 inhibitor, meet inclusion criteria, do not present exclusion criteria, and provide informed consent for participation will be selected and randomized for the study.

The sample size of 240 study participants is determined for inclusion in the study. Calculations were made using two instruments that provided two approximate sample sizes. The median of these values (considering that the greater level of significance of the odds ratio and the relative absolute risk values could be achieved with the larger sample size) was taken as the sample size.

(1) Calculate the sample size for scientific studies using a standard numerator based on the proportion of the population that is likely to have the demographic characteristics of the study sample and the size (number) of the population with the clinical characteristics expected for the study, with a 95% confidence level and a ±5% confidence interval for the results of the statistical calculations.

(2) Sample size calculation for a randomized, parallel case-control study with a two-sided statistical significance level, at a confidence interval of α – 0.05, at statistical power of $(1-\beta)$ – 0.8, at case/control ratio of 2, at probability of occurrence of an event in the experimental arm of p0 – up to 0.4, and at probability of occurrence of an event in the control arm of p1 – up to 0.6.

Study participants will be randomly assigned to two parallel groups, control and experimental, with a 1:2 allocation ratio and selected 3 study arms for participants by CYP2C19 genotyping results:

1st arm – experimental: “Normal Metabolizers of Clopidogrel”, 110 study participants diagnosed with chronic coronary artery disease who had undergone elective PCI, tested with *CYP2C19* genotyping and identified as NFA **2, *3* carriers, who undergo *CYP2C19* Genotype-Guided Clopidogrel Treatment - Clopidogrel as a component of preventive antiplatelet treatment such as double antiplatelet treatment (DAPT), or an antiplatelet drug (clopidogrel) combined with the non-vitamin K antagonist oral anticoagulants (NOAC), incl. triple antiplatelet treatment (Aspirin, Clopidogrel and a NOAC), or antiplatelet monotherapy (Clopidogrel).

2nd arm - experimental: “Passive Metabolizers of Clopidogrel”, approximately‡ 50 study participants diagnosed with chronic coronary artery disease who had undergone elective PCI, tested with *CYP2C19* genotyping, identified as LOF **2, *3* allele carriers, who undergo *CYP2C19* Genotype Guided Antiplatelet Treatment Alternative to Clopidogrel - an antiplatelet drug alternative to clopidogrel in conventional dosing regimen, as a component of preventive antiplatelet treatment, such as double antiplatelet treatment (DAPT) with ticagrelor or prasugrel, or prasugrel combined with the nonvitamin K antagonist oral anticoagulants (NOAC), or antiplatelet monotherapy (ticagrelor, or prasugrel).

3rd arm - active comparator: “Unspecified Metabolizers of Clopidogrel”, 80 participants diagnosed with chronic coronary artery disease who had undergone elective PCI were allocated to the arm, without *CYP2C19* genotyping through simple randomization, and having an unspecified metabolism phenotype, who were assigned to the conventional clopidogrel treatment - clopidogrel as a component of preventive antiplatelet treatment, such as double antiplatelet treatment (DAPT), or clopidogrel combined with the non-vitamin K antagonist oral anticoagulants (NOAC), incl. triple antiplatelet treatment (Aspirin, Clopidogrel and a NOAC), or antiplatelet monotherapy (Clopidogrel).

‡ *The prevalence of carriers of CYP2C19 *2, *3 non-functional alleles in the Georgian population has not been studied and is unknown. To estimate the number of patients in subgroup II arm 1 and arm 2, we used the extrapolation of known data from a European population study [12].*

2 study arms could be used as control for analyzing and comparing study outcome measures: 3rd study arm participants create the active comparators’ group for 1st and 2nd arm, and besides, 2nd study arm participants - as the comparators for 1st arm:

Control 1: “Normal Metabolizers of Clopidogrel” - 110 study participants vs “Unspecified Metabolizers of Clopidogrel” - 80 participants;
Control 2: “Passive Metabolizers of Clopidogrel” - approximately 50 participants vs “Unspecified Metabolizers of Clopidogrel” - 80 participants;
Control 3: “Normal Metabolizers of Clopidogrel” - 110 study participants vs “Passive Metabolizers of Clopidogrel” - approximately 50 participants.
It is reasonable to assume that 75% of the selected study subjects will complete the study activities in full by 12 months of follow-up after enrollment. A portion of the 25% of patients are expected to drop out of the study for various reasons. Withdrawal by study participants, non-compliance with treatment, loss to follow-up and physician decisions are expected as the possible reasons for the study's non-completion.
Some of the dropped-out study participants will undergo appropriate clinical assessments at the interim follow-up periods (before 3, 6, or 12 months) or at the time of early withdrawal from the study and are therefore also considered a source of study data.

2.4.3 Inclusion Criteria

Inclusion criteria define the clinical model according to which the study subject will be selected. The criteria will equalize cardiovascular risk disease/condition and co-morbidities that may distinguish and exclude CAD severity.

A patient will be selected for the study participation if they meet all of the following inclusion criteria:

- Participants of both sexes aged between 35-80 years are eligible for the study.

[*and*]

- Diagnosed with chronic coronary artery disease;

[*and*]

- Completed informed consent form for participation in the study;

[*and*]

- Undergone elective PCI within the last 12 weeks without procedure-related complications; or the clinical challenge is to de-escalate post-PCI antiplatelet treatment from an alternative P2Y12 inhibitor to clopidogrel.

[*and*]

- LVEF≥38% after index PCI;

Atherosclerotic coronary artery lesion confirmed by coronary angiography and coronary artery stenting performed within 12 weeks without clinically significant procedural complications are determined by the results of relevant PCI. De-escalation of antiplatelet treatment from an alternative P2Y12 inhibitor to clopidogrel can be easily detected by the prescription order from routine clinical practice. Complementary, this inclusion criterion also represents clinical evidence of CAD medication treatment.

The selected participant should be characterized by echocardiographically confirmed normal or clinically mild left ventricular systolic dysfunction or preserved systolic function after the index PCI. Assessment of systolic function should be assessed by the standard echocardiographic measurements of left ventricular ejection fraction. Echocardiography should be performed as part of the screening measures of the potential study participant before randomization.

2.4.4 Exclusion Criteria

Exclusion criteria are defined as diseases, clinical conditions, risks or treatment limitations, and contraindications that increase the severity and risks of the study cases. These conditions may have

additional negative prognostic effects on the study subject's disease/condition, interfere with the development of study endpoints, or alter the effectiveness of the treatment interventions included in the study.

Exclusion criteria are used to identify and exclude potential study participants with clinical severity characteristics to ensure homogeneity of treatment effects. They also prevent bias, confounding, and unintended effects.

The use of criteria ensures the safety of subjects in the study by identifying diseases/conditions that require clinical observation, evaluation, and treatment measures other than those specified in the study.

Any of the following should be considered as exclusion criteria from the study:

- Concomitant using of potent CYP3A4 or CYP2C19 inhibitors;
- Clinical obesity, BMI - 40 kg/sq.m or more;
- Type 1 diabetes mellitus;
- Poorly controlled type 2 diabetes mellitus, Hba1c - 9% or more;
- Acute Myocardial Infarction;
- Coronary artery bypass grafting was performed within the last 12 weeks.
- Valvular heart disease due to dysplasia, connective tissue disorders, or inflammatory disorders, or valvular disorders requiring cardiac surgery;
- History of severe hepatic impairment;
- Severe chronic kidney disease;
- Clinically important leucopenia, lymphopenia, thrombocytopenia or thrombocytosis;
- History of hemorrhagic diathesis or coagulopathy;
- An active or an obvious threat of bleeding (including GI bleeding):
- Bleeding within the past 6 months that required hospitalization;
- Blood transfusion during the past 6 months or its refusal;
- History of intracranial hemorrhage;
- Cardiac or non-cardiac degenerative disease, including: cardiomyopathy,
- restrictive lung disease, or neurodegenerative diseases;
- Malignant tumor (cancer) that limits life expectancy to less than one year;
- Current chemotherapy or immunosuppressive therapy;
- Ongoing immunosuppression or immunosuppressive conditions;
- Pregnancy or lactation period;
- Any disease/condition for which control is not achieved;
- Personal (patient/physician dependent) or health care system-related circumstances that can restrict or limit any study procedures or operations.

Concomitant use of other drugs that inhibit CYP3A4 or CYP2C19 with clopidogrel may reduce the expected positive effects of treatment and induce negative ones, since the hepatic metabolism of clopidogrel is also mainly mediated by CYP2C19 and to a lesser extent by CYP3A4. The concomitant use of drugs that inhibit CYP3A4 or CYP2C19 can be assessed by reviewing the patient's medical history. Their use is prohibited during the study and must be discontinued 2 weeks before enrollment, otherwise, it will constitute an exclusion criterion from the study. Below is a list of drugs that inhibit CYP3A4 or CYP2C19 and their use is prohibited during the study period. If the use of these medications is necessary, the patient will be considered for withdrawal from the study.

— CYP3A4 inhibitors:

Omeprazole, clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, grapefruit;

— CYP2C19 inhibitors:

Omeprazole, fluvoxamine, ticlopidine, efavirenz, chloramphenicol, fluoxetine, delavirdine, gemfibrozil, stiripentol, bortezomib.

The PPI of choice for patients included in the study is pantoprazole. However, according to the CPIC CYP2C19 genotype-based PPI dosing guidelines and recommendations [25], carriers of CYP2C19 *2, *3 LOF alleles are at increased plasma concentrations of this PPI and increased risk of toxicity with prolonged treatment (>12 weeks). Despite the expected increase in treatment efficacy, the drug dose should be reduced by 50% for use >12 weeks and continued monitoring for maintenance of efficacy.

BMI is determined by calculating the results of simple anthropometry. BMI≥40 kg/m^2 defines clinical obesity/fatty states. They are considered an independent risk factor for repeated MACCE in CAD cases. Prevention of this risk factor requires consistent, intensive measures of lifestyle changes (diet, physical activity) and drug treatment for at least 6-12 months, during which it is impossible to achieve results during the study inclusion and observation period. The excess of risks due to this factor during the study may be an important reason for the dispersion of the study effects. Including patients with this clinical characteristic in the study group, only with the drug treatment provided by the study, would be ethically unjustified. Accordingly, BMI≥40 kg/m^2 is an important exclusion criterion from the study.

Type 1 Diabetes mellitus and uncontrolled or poorly controlled type 2 diabetes mellitus are considered important independent risk factors for recurrent MACCE in CAD cases. High glycemia levels will act as an important cause of excess risk and may cause dispersion of effects in the course of the study. Additionally, randomization of study participants with uncontrolled glycemia without CYP2C19 genotyping (control arm) and the possible presence of CYP2C19 *2, *3 LOF allele genotype cannot be assessed. Such study participants will be at higher risk than participants randomized in experimental arms, which would be unjustified, allow unequal risk in the study and raise ethical concerns.

Clinical evidence of Type 1 Diabetes mellitus can be assessed by obtaining the patient's medical history. Uncontrolled or poorly controlled diabetes mellitus can be specifically defined as a history of diabetes mellitus, clinical evidence of inadequate glycemic control, elevated glycated hemoglobin (HbA1c ≥9%), or clinical evidence of vascular complications of diabetes.

Patients with type 2 diabetes mellitus may be included in the study if the results of the screening test:

- HbA1c <9%;

[*and*]

- are receiving optimal medical treatment to control glycemic levels;

[*and*]

have no evidence of progressive vascular complications of diabetes other than CAD;

Such assessment results should also be demonstrated by the 6th and 12-month follow-up of the study. If these key criteria for diabetes control are not met, the subject should be withdrawn from the study early after appropriate investigations have been conducted.

Acute myocardial infarction, valvular heart disease, or previous valvular heart surgery are high-risk conditions for recurrent MACCE.

Interstitial lung disease, neurodegenerative diseases, agranulocytosis (leukopenia, lymphopenia), pancytopenia, thrombocytopenia or thrombocytosis, and any other uncontrolled disease or clinical condition in the course of CAD are associated with high risks of other serious clinical conditions and a poor prognosis.

These diseases/conditions may serve as important causes of biases and confounding effects during analyzing study outcomes. They can be easily identified as part of screening measures based on the patient’s medical history and the results of routine clinical examinations.

Certain conditions should be routinely considered for the determination of study exclusion criteria.

Thrombocytopenia is a condition that increases the risk of bleeding complications and thrombotic thrombocytopenic purpura (TTP) during treatment with clopidogrel or an alternative P2Y12 inhibitor. Therefore, thrombocytopenia is considered an important limitation of antiplatelet therapy and an exclusion criterion of the study. This important side effect of treatment can be clinically manifested by thrombocytopenia, microangiopathic hemolytic anemia (schistocytosis - fragmented erythrocytes), neurological symptoms, renal failure, and fever.

Treatment with an NSAID and warfarin is a significant limitation of treatment with clopidogrel or an alternative P2Y12 inhibitor and is an exclusion criterion from the study. Nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a significant increase in the risk of gastrointestinal bleeding when used concomitantly with clopidogrel or alternative P2Y12 inhibitors. This effect is particularly pronounced when NSAIDs are used in the setting of DAPT.

The interaction of warfarin and clopidogrel does not change the pharmacokinetic properties of the drugs, since during the process of liver metabolism, they are substrates of different enzyme systems (CYP2C9 and CYP2C19, respectively) and do not act by reducing INR in cases of long-term use of warfarin. However, the simultaneous use of warfarin and clopidogrel or alternative P2Y12 inhibitors during treatment critically increases the risk of clinically significant bleeding (gastrointestinal or intracerebral), since they independently suppress coagulation.

Hemorrhagic diathesis, coagulopathy, significant bleeding within the past 6 months, blood transfusion within the past 6 months (or refusal of blood transfusion), active gastrointestinal bleeding or threat of bleeding, and a history of intracranial hemorrhage pose clinical conditions that determine a high risk of recurrent bleeding complications. Therefore, these conditions carry an obvious threat of recurrent bleeding events during treatment with P2Y12 inhibitors, clopidogrel or alternatives, due to inhibiting platelet aggregation. Platelet inhibition occurs throughout their life cycle (7-10 days), and in the event of bleeding, simply stopping the drug will not have a significant effect on pro-coagulation treatment. However, due to the short half-life of the active metabolite of clopidogrel, hemostasis can be restored by infusion of exogenous platelets. The effects of platelet transfusion are significantly reduced within 4 hours of a loading dose of clopidogrel and within 2 hours of a maintenance dose.

When conducting antiplatelet therapy with clopidogrel, prasugrel or ticagrelor, it is necessary to take into account the following conditions that are not direct contraindications, but which nevertheless determine important limitations.

After surgical operations, the expected antiplatelet effects in response to treatment with P2Y12 inhibitors are undesirable. Therefore, treatment with P2Y12 inhibitors should be discontinued at least 5 days before surgery and should be resumed as soon as the operative risk of bleeding has decreased.

In patients with moderate and severe renal insufficiency (creatinine clearance from 30 ml/min to 60 ml/min and <30 ml/min, respectively), clopidogrel reduces the effects of ADP-induced platelet aggregation by an average of 25%. Such effects are associated with an increased risk of thrombosis despite clopidogrel treatment. Increasing the dose of clopidogrel to reduce the risk of thrombotic complications is unreasonable and significantly increases the risk of bleeding and TTP. Therefore, cases of moderate and severe chronic kidney disease are exclusion criteria from the study.

In cases of liver failure, the effects of clopidogrel treatment on ADP-induced platelet aggregation are the same as in healthy individuals. However, in conditions of liver failure, due to the addition of the effects of impaired metabolism of clotting proteins (factors), clopidogrel treatment causes more profound hemostasis disorders, and in cases of thrombocytopenia, it leads to a significantly increased risk of TTP. The risk of major bleeding increases. Therefore, clinically significant liver diseases are exclusion criteria from the study.

Malignant tumor (cancer), ongoing chemotherapy or immunosuppressive therapy, as well as immunosuppressive or autoimmune disease and any uncontrolled disease, constitute clinical conditions under which observation of patients according to the study plan will be impossible, or these diseases/conditions may cause a severe outcome of the clinical case under study. Such conditions may serve as objects of biases and confounding effects when analyzing study outcomes. In this regard, malignant tumor (cancer), ongoing chemotherapy or immunosuppressive therapy, as well as immunosuppressive or autoimmune disease and any uncontrolled disease are considered exclusion criteria from the study.

Under the special clinical discussion, certain diseases/conditions could not be routinely considered as study exclusion criteria:

- A prior myocardial infarction >3 months, or old myocardial infarction, is not considered an exclusion criterion if the clinical characteristics of the study participants meet the inclusion criteria.
- Cases of valvular heart disease that meet the inclusion criteria and are not caused by rheumatic heart disease, and valvular heart disease that does not require cardiac surgery, could not be considered for exclusion from the study.
- Cases of obstructive/interstitial lung disease that meet the inclusion criteria and are not treated by systemic immunosuppressive drugs, or do not show a clinically significant immunosuppressive condition and do not have a life expectancy <1 year due to the disease, could not be considered for exclusion from the study.

2.5 Study Procedures

2.5.1 Screening

All patients

- must present having undergone ePCI within the past 12 weeks, documented by imaging and a report form,

[*or*]

- a practical clinical task must be defined to de-escalate antiplatelet therapy from an alternative P2Y12 inhibitor to clopidogrel or initiate clopidogrel.

eICA data must meet the criteria for CAD, and ePCI results must determine the indication for treatment with clopidogrel or an alternative P2Y12 inhibitor:

- Coronary artery stenosis;

[and]

- Coronary artery stenting with DES;

Study subjects must have formally confirmed informed consent to participate in the study, as approved by the ethics committee.

Study subjects should undergo baseline clinical assessments that will determine:

- Demography data:
  - Sex; Age; Race, Ethnicity, Country of residence.
- Cardiometabolic risk factors and their control status:
  - BMI; Obesity; Systolic and Diastolic Blood Pressure, Hypertension; T2 Diabetes Mellitus; HbA1c Measures; LDL-C, Dyslipidemia;
- History of Cardiovascular Morbidity. The patient must undergo all clinical-diagnostic examinations that confirm inclusion criteria and deny exclusion criteria:
  - Clinical indications for the most recent PCI;

- Angina
- No Angina: Heart Failure Event, Supraventricular Tachycardia, Atrial Fibrillation, Premature Ventricular Complex or Ventricular tachycardia, Left Bundle Branch Block;
- Other non-specific symptoms;

- History of any Cardiovascular Morbidity and their control status:
  - Prior Myocardium Infarction, Number of Prior MIs; Chronic Heart Failure; Supraventricular Tachycardia; Atrial Fibrillation; Premature Ventricular Complex; Ventricular Tachycardia; Ventricular Fibrillation Event; Sinus Node Dysfunction; AV Block; Left Bundle Branch Block; Right Bundle Branch Block; Coronary artery bypass graft;
- History of prior PCI:
  - Number of prior PCIs; Number of Coronary Artery Lesion Sites – total and obstructive; Number of Stents Ever Placed; Sites of Coronary Artery Lesions – obstructive and non-obstructive

— History of Co-morbid Diseases/Conditions and their control status. The patient must undergo all clinical-diagnostic examinations that confirm inclusion criteria and deny exclusion criteria:
- Peripheral Artery Disease; Carotid Artery Disease; Cerebrovascular Disease;
- Other co-morbid diseases/conditions:
  - Chronic Obstructive Pulmonary Disease; Chronic Kidney Disease; Peptic Ulcer Disease/Chronic Gastritis; GI Bleeding Event; Cured Cancer; Thyroid Disease

— Doppler-, Echocardiography characteristics of heart remodeling:
- Left ventricle
  - PW, IVS thickness; Hypertrophy; Relative Wall Thickness; end-diastolic diameter; end-diastolic volume index; Mass index; Ejection fraction; Filling pressure;
- Left atrium
  - transverse diameter; volume index;
- Right Ventricular
  - Diameter, Dilatation; Pulmonary Artery Systolic Pressure (PASP); Tricuspid annular plane systolic excursion (TAPSE);
- Mitral, Aortic, Tricuspid valve disorders
  - Mitral annular calcification (MAC); Secondary (functional) mitral regurgitation (FMR); Aortic valve calcification; Secondary (functional) aortic regurgitation (FAoR); Secondary (functional) Tricuspid Regurgitation (FTR).

— Ongoing medication treatment application:
- Antiplatelet Treatment Selection:
  - DAPT; TRIPLE; Combined; Monotherapy
- Antiplatelet Medications:
  - Aspirin; Clopidogrel; P2Y12 inhibitor, Alternative of Clopidogrel; NOAC;
- Lipid-lowering Medications:
  - STATIN; STATIN plus EZETIMIBE; STATIN plus EZETIMIBE plus PCSK9i;
- Hypoglycemic Medications:
  - Insulin; SGLT-2; Metformin; GLP1-AG; DPP4;
- Other Medications:
  - ACEi; ARB; ARNI; Beta-Blocker; Calcium Channel Blocker; Anti-arrhythmics; Ivabradine; Loop Diuretic; Thiazide Diuretic; MCRA

Clinical examinations conducted as part of screening should not identify diseases/conditions included in the exclusion criteria (see Chapter 2.4.4 Exclusion criteria) or their specific laboratory and instrumental investigation findings:

- Complete blood count should not reveal:
  - Clinically significant anemia - Hb<10g/dl; RBC<3.5; HCT<32L/L;
  - Leukopenia - <3.0 x 109/L, or neutropenia - ≤1.5 x 109/L;
  - Lymphopenia - <1.1 × 109/L;
  - Thrombocytopenia - <100×109/L or <50% compared to previous measurement;
  - Thrombocytosis - ≥500×109/L;
- Coagulation tests should not reveal:
  - Thrombocytopenia - < 100×109/L or <50% compared to previous measurement data;
  - Prolongation of APTT - >45";
  - Prolongation of PT - >16"
  - Prolongation of TT - >19";
  - Decreased fibrinogen level - <200mg/dl or <50% compared to previous measurement data;
  - Hypocalcemia ionized calcium (iCa) < 0.89 mM/L;
- Blood biochemical tests should not reveal:
  - Hba1c ≥ 9%, in patients with type 2 diabetes;
  - eGFR ≤30% (according to the MDRD formula for kidney disease) or creatinine > 1.7mg/dl;
  - ALT, AST, GGT ≥3 times the upper limit of normal or ALT-to-AST ratio ≥2.0;
  - TBIL >20.0 mg/dl and DBIL ≥ 4.0mg/dl;
  - LDH > 400U/L;
  - K^{+}<3.2mmol/l and >5.3mmol/l, Na^{+}<132mmol/l and >147mmol/l, Ca^{+2}<1.05mmol/l and >1.40mmol/l;
- A complete urinalysis should not reveal:
  - Gross hematuria or clinically significant microhematuria - >25 erythrocytes/field of view;
  - Clinically significant proteinuria - >300 mg/dl or albumin-to-creatinine ratio >300 mg/g;

Screening tools are required for the initial clinical evaluation and the study baseline data generation. Diagnostic tests that are used for baseline clinical evaluation are regularly applied in everyday, real-life clinical practice for routine observation of patients with the clinical features of interest.

2.5.2 Management of Clinical Study Cases

Clinical judgments for management and personalized preventive treatment of study participants are based on estimates of the ratio between expected MACCE and bleeding risks, as recommended in the ESCARDIO/EACTS 2017 revised guideline for the treatment of CAD with DAPT[†‡].

† - The ESCARDIO/EACTS 2017 revised guideline recommendations for the treatment of CAD with DAPT [ESC GUIDELINES] present approaches and tools for assessing the relationship between MACCE and bleeding risks.

‡ - The selection of patients for clopidogrel treatment based on the results of CYP2C19 allele genotyping is clearly stated by the FDA in the form of warnings related to the use of clopidogrel ("Black Box of Warnings"), as "reduced efficacy of clopidogrel in poor metabolizers" [FDA. PLAVIX (clopidogrel bisulfate) tablets. Initial U.S. Approval: 1997. FULL PRESCRIBING INFORMATION. WARNINGS AND PRECAUTIONS (5.1), CYP2C19 Poor Metabolizers (2.3), Pharmacogenomics (12.5). 2010.]

Ongoing management of clinical study cases and appropriate treatment, including clinical cases of all early withdrawn study participants, should be conducted following the guidelines and recommendations provided by ESCARDIO for ASCVDs group diseases, AHA for ischemic and hemorrhagic strokes, ACG for GI bleeding, and ISTH for thrombocytopenic thrombotic purpura:

- 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS - doi:10.1093/eurheartj/ehx419;
- 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes - doi:10.1093/eurheartj/ehz425;
- 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice - doi:10.1093/eurheartj/ehab484;
- 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD – doi:10.1093/eurheartj/ehz486;
- 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk - doi:10.1093/eurheartj/ehz455;
- 2018 ESC/ESH Guidelines for the management of arterial hypertension - doi:10.1093/eurheartj/ehy339;
- 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation - doi:10.1093/eurheartj/ehx393;
- 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation - doi:10.1093/eurheartj/ehaa575;
- Fourth universal definition of myocardial infarction (2018) - doi:10.1093/eurheartj/ehy462;
- 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death - doi.org/10.1093/eurheartj/ehac262;
- 2018 ESC/EACTS Guidelines on myocardial revascularization - doi:10.1093/eurheartj/ehy394;
- 2018 ESC Guidelines for the diagnosis and management of syncope - doi:10.1093/eurheartj/ehy037;
- 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS) - doi:10.1093/eurheartj/ehx095;
- Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association - doi.org/10.1161/STR.0000000000000211;
- 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association - doi.org/10.1161/STR.0000000000000407;
- 2021 ACG Clinical Guideline: Upper Gastrointestinal and Ulcer Bleeding - DOI: 10.14309/ajg.0000000000001245;
- 2020 ISTH guidelines for treatment of thrombotic thrombocytopenic purpura - doi.org/10.1111/jth.15010

Treatment of concomitant diseases/conditions should be carried out according to national protocols and recommendations. Contraindications and restrictions should be taken into account when prescribing medications.

These measures of drug treatment and management of a clinical case are routinely used in established, routine clinical practice.

2.5.3 Other Perspective Arms of the Study

In the case of equal distribution of study participants by gender and inclusion of 50% more than the planned number, it will be possible to evaluate the gender-related CYP2C19 allele genotype-guided clopidogrel treatment outcomes.

The study participants' selection process will form a clinical group of CAD STE/NSTE-ASC patients who require treatment with a P2Y12 inhibitor (including clopidogrel) after PCI, characterized by a more severe course of the disease and a significantly higher baseline risk of recurrent MACCEs compared with the participants group under the study. The perspective arm is clinically more heterogeneous and requires a different study design. This group differs from the study participants group in terms of inclusion and exclusion criteria, but requires treatment with a P2Y12 inhibitor (including clopidogrel) after PCI.

The concept of study P2Y12 inhibitor preventive antiplatelet treatment of this perspective study arm cases may be based on the clinical outcomes of CYP2C19 genotype-guided drug selection. In real-world practice, the patients with primary PCI after CAD STE/NSTE-ASC are more prevalent than current study group patients. Despite their similarity to the study group, they are characterized by a significantly higher baseline risk and a more severe course of the disease. Patients of Perspective Arms of the Study are clinically more heterogeneous and require a different study design.

In the future, a study with similar goals and objectives, albeit with a different design, could be planned for this group of patients and conducted, provided the necessary resources are raised, which would be justified from a scientific point of view, clinical feasibility, and ethical considerations.

2.5.4 Disclosure of Study Results

The allocation of patients to the experimental and control groups will be carried out by double-blind randomization. At this stage, the results of the randomization will be hidden from the study participants, the medical care team, and the clinical outcome assessors. However, after randomization and CYP2C19 genotyping, the results will be disclosed to the study participants and the medical care team, and the results of both the baseline and ongoing clinical assessments of the study subject will be known throughout the study.

2.5.5 Compliance with Treatment

The study does not use new medications or treatments and does not investigate their previously unknown effects. The subject of the study is the selection of the most commonly used antiplatelet drug regimens after PCI in CAD cases in current, real-world clinical practice based on the results of CYP2C19 allele genotyping.

The use of the drugs of interest, P2Y12 inhibitors - clopidogrel or an alternative P2Y12 inhibitor, in patients with selected clinical characteristics has already been tested, studied and recommended by the European Society of Cardiology guidelines and recommendations as part of routine DAPT in patients with CAD after PCI for the prevention of recurrent MACCE events.

Thus, these drugs are prescribed and used in everyday, real-world clinical practice, even without research interests and ensure the prevention of MACCE cases of ASCVD. This circumstance is an important basis for patient motivation, study participation and adherence to treatment. In addition, other drugs are used to treat patients with selected clinical characteristics, which can be prescribed to the study group patients. Today, both the drug of interest in the study (clopidogrel) and alternative antiplatelet drugs are available for regular use, which is one additional component of treatment adherence.

The patient's informed consent form, which explains the treatment measures to be carried out within the framework of the study and the patient's formal expression of consent (signing the informed

consent form), is an important criterion for inclusion in the study and, at the same time, represents an important basis for treatment adherence.

A 12-month clinical follow-up during the treatment will also be a prerequisite to patient motivation and treatment adherence. To this end, patients will undergo clinical assessments supporting adherence and motivation to therapy during the 3rd and 6th month follow-up visits.

2.5.6 Withdrawal from the Study due to Non-adherence to Treatment

Non-adherence to the study of treatment with clopidogrel, alternative antiplatelet or other prescribed medication or a patient's decision to avoid or discontinue study procedures is grounds for withdrawal from the study due to non-adherence.

Evaluations for medication non-adherence should be performed at each study-planned follow-up visit using the Brief Medication Use Questionnaire (BMQ) [26].

No single (so-called “gold standard”) tool is presented for assessing non-adherence to medication treatment. The highly specific and sensitive BMQ, currently being developed, was selected for the assessment of non-adherence to treatment. Based on characteristics of drug consumption by evaluating (scaling) the responses to nine simple questions and amounts of medication taken “during the past week” and the patient’s opinion on the effects, adherence to medication treatment can be calculated. Assessments carried out during the observation period will reveal possible barriers that lead to non-adherence. The results of the assessment of the medication regimen, trust in treatment, and attitude determine the state of repeated or sporadic non-adherence or adherence. To influence the identified factors of non-adherence, the patient will be consulted during the observation period, and it will be possible to overcome sporadic non-adherence cases.

In the event of repeated non-adherence, procedures for withdrawing the patient from the study will be considered.

These procedures include:

- Informing the patient about his/her withdrawal from the study;
- Justification of the decision to withdraw the patient from the study;
- Conducting follow-up assessments of clinical outcomes;
- Clinical examinations are conducted to assess the patient's current condition and safety;

In cases where a patient is withdrawn from the study due to non-adherence to medication treatment during the 3rd, and 6th month of follow-up, a new study subject may be included in the study in his/her place, with allocation to the appropriate experimental or control group. After the 6-month follow-up period, a patient withdrawn from the study should not be replaced by a new study subject.

Withdrawal from the study will be reviewed by the study center investigator, principal investigator, and data management team. The patient will be informed of the non-adherence case and the decision to withdraw from the study.

2.5.7 Efficiency Assessment

The efficiency of the study is assessed based on the results of investigational product application, the *CYP2C19* genotype-guided preventive treatment with P2Y12 inhibitor and the effectiveness of application of study procedures in real-world clinical practice.

At the 3rd, 6th and 12th months of follow-up, the incidence of the study's primary, secondary and other clinical endpoints (see Chapter 2.6.1 Study Endpoints) will be determined. At the final evaluation, quantitative calculations of their frequency and risk-adjusted clinical outcomes will be performed in the experimental treatment intervention and control arms of the study. Odds Ratio (OR), Relative Risk (RR), Relative Benefit (RB), and Absolute Benefit (AB) indicators will be determined. The efficacy of the study product will be evaluated by considering by evaluation study indicators presented in Appendix 2. Measuring more than three-fourths (>75%) of these indicators will consider the efficiency of the study.

Biases in the study and related evaluations will be avoided by random selection of study participants for intervention and control arms and by excluding confounder variables from the statistical analysis. See study participants' selection procedures in Chapter 2.3.2, Structural Design.

After randomization of the study participants will be allocated into experimental and control arms. 2 experimental arms will be formed based on the results of CYP2C19 genotyping results, one of which will be used as a parallel control group as well. Each arm of the study participants will differ from each other according to the principal characteristic, which is determined by the results of CYP2C19 genotyping, and treatment with a P2Y12 inhibitor will be selected based on the results of CYP2C19 genotyping:

- Clopidogrel treatment in patients with the genotype of CYP2C19 *2, *3 normal alleles, "active metabolizers" - experimental arm;
- Clopidogrel treatment without CYP2C19 genotyping, "Unspecified metabolizers group" - experimental arm;
- Clopidogrel alternative P2Y12 inhibitor treatment group, CYP2C19 *2, *3 loss-of-function allele genotype, "passive metabolizers" – comparator (control) arm;

Reduction of overlap/confounding of effects will be achieved by homogenized clinical characteristics of experimental and control clinical cases, which will be achieved by strict application of inclusion and exclusion criteria for the selection of all study subjects. This approach equalizes baseline risks and eliminates additional effects due to age, sex, other risk factors and high-risk comorbidities.

The effectiveness of study procedures and possible deviations will be excluded by consistent monitoring and evaluation measures, using the data management system and the validation function of data entry into the electronic database.

2.5.8 Security Assessment and Control

The health risks of the research subjects are not related to the interventions and procedures envisaged in the study. The clinical-diagnostic and treatment approaches used in the research process are routinely used in real-life medical care for patients with the clinical characteristics of interest in the study. Diagnostic tools and treatments are standardized.

The genotyping of CYP2C19 *2, *3 alleles performed on randomly selected patients in the experimental group belongs to the category of laboratory-diagnostic procedures and does not pose a health risk.

The antiplatelet drugs such as clopidogrel or alternative P2Y12 inhibitors selected for treatment in this laboratory study are commonly prescribed drugs in everyday, real-world clinical practice. Their use is recommended by current guidelines in the setting of routine PCI. Patient-tailored treatment selection of these drugs based on the results of CYP2C19 *2, *3 genotyping increases the chances of preventing MACCE and, therefore, cannot be considered as an additional health hazard for the study subjects.

Health risks are not related to the initial assessment and ongoing follow-up of study subjects, which are conducted to determine inclusion and exclusion criteria, and to monitor clinical outcomes of the study.

Health risks to study subjects are primarily related to the development of the disease under study, such as CAD, MACCEs (cardiovascular death, nonfatal myocardial infarction, recurrent angina, repeated PCI, stent thrombosis, ischemic stroke, transient ischemic attack, intracerebral hemorrhagic stroke), and known, expected, adverse effects of drug treatment (intracerebral hemorrhage, GI bleeding, other bleeding, thrombotic thrombocytopenic purpura).

In some cases, health risks may also be due to the results of medical care measures taken outside the scope of the study, including inappropriate or erroneous.

During the observation period, patients will undergo the following clinical-diagnostic examinations, the results of which will assess health risks related to the study disease and treatment:

At each follow-up visit or withdrawal, patients will undergo a medical examination and clinical tests:

- to assess the disease/condition of interest;
- to identify the risk of known, expected, adverse events of MACCE and drug treatment;
- to assess possible comorbidities/conditions;
- to control lifestyle-related risks;
- to review the results of diagnostic tests and treatment interventions performed outside the study;

These diagnostic measures of clinical case observation are routinely used in real-life clinical practice.

To assess the risks posed by the results of potentially inappropriate or erroneous medical care performed outside the scope of the study, the results of clinical and laboratory tests available at that time will be used. The possible effects of medical care provided to the patient outside the study on the health status and study processes will be assessed within the framework of the study's planned monitoring measures. Such effects may include:

- medical care;
- place of care;
- medication;
- diagnostic or treatment procedure;
- diagnosis.

Health risks for study subjects may be associated with non-adherence to medication treatment. Using the BMQ, potential barriers and risks to the use of prescribed treatment will be assessed at all points of observation included in the study. This will make it possible to avoid risks associated with sporadic cases of non-adherence.

The results of monitoring and evaluation during the study will reveal possible deviations from the study procedures, which may be associated with other unforeseen health hazards and will make it possible to avoid them.

In order to avoid threats to the right to choose, freedom of choice and confidentiality of research subjects, the following research-related procedures should be implemented in all cases:

- Providing complete written and narrative information about research operations
  - Detailed explanations of the study protocol;
  - Objectives, measures and procedures;
  - Expected risks, benefits and consequences;
  - Collection, storage and processing of patient identification and clinical data in accordance with the objectives of the research;
  - Measures for the protection of personal data and conditions for transfer;

- Obtaining informed consent from the patient to participate in the research based on an independent decision following the principles of the Declaration of Helsinki;
- Implementing data collection and processing procedures following the conditions set out in the 2018 EU General Data Protection Regulation (GDPR)
  - Identification of the persons conducting the research, legal processing and controlling of the data and authorization for access to the processing of the study data;
  - Coding of the study participants' personal identification data within the framework of the research with its other unique identifier, which will be stored confidentially, on paper and in an electronic file during the research period, in a physical space, on a personal computer or domain and will be accessible only to personnel authorized in the study;
  - Storage and protection of primary medical documents (clinical, laboratory or imaging examination results, reports, images, instrumental records or other, produced in digital or paper form) in the medical card following the current rules, conditions, forms and practices;
  - Entering the data of study interest into a data record form (CRF) without personal data identifying the study participants, with a subject-specific, coded, unique identifier (e.g., number) and protecting it in a physical space that will be accessible only to authorized study personnel;
  - Entering the data of study interest into an electronic database by encoding the names of the data (including variables) and without study participants personal data identifiers with subject-specific, coded, unique study identifiers and protecting it in an electronic file or domain, in such a way that it is accessible only to authorized study personnel;
  - Processing and transmitting the study data without the study participants' personal identifiers in an encrypted (coded) form and through a protected communication channel only to authorized study personnel;
  - Transfer of own data to the research subject in aggregate form, in the form of a report and based on a formal request;
  - Storage of the results of legal data processing, de-identified data for an indefinite period and for the purposes of the study;
  - Destruction of the blood sample taken for the CYP2C19 genotype testing in accordance with the established procedure upon completion of the laboratory analysis provided for in the study;
  - Deletion of the study participants' personal identification data on paper and from electronic databases and data collection forms within 1 year after the study completion;

The results of monitoring and evaluation carried out throughout the study period will reveal the risks of possible deviations from operational procedures, which may be associated with unforeseen threats of data breaches and illegal processing, and will make it possible to avoid them.

2.5.9 Processing of Biological Study Material

As part of the study, blood samples from study participants will be processed for *CYP2C19* genotyping. In addition, during the observation period, study subjects may undergo routine clinical tests by processing blood and urine samples.

Laboratory testing for CYP2C19 genotyping should be performed on at least 160 patients randomized to the study treatment arm for clopidogrel or an alternative P2Y12 inhibitor treatment intervention and for allocation to the appropriate study arm. Blood samples will be processed for this analysis only once during the study period.

The sample laboratory examination for CYP2C19 *2, *3 allele genotyping will be carried out in the Ltd "Vistamedi" diagnostic laboratory.

The analysis requires a 3 ml venous blood sample, obtained by simple venipuncture manipulation. The blood sample will be collected at the research center. The blood sample is immediately placed in a K3 EDTA type tube.

The tube label must be marked with the patient's unique number in the study. Along with the blood sample preparation, a sample form (paper) must be filled out, accompanying the sample during transportation to the laboratory. The sample form must include:

- The patient's unique number or code in the current study;
- The sample tube number (or the tube barcode must be marked.
- Sample volume;
- Purpose of the sample, name of the test.
- Place of sample collection;
- Time of sample collection;
- Time of sample shipment;
- Method of transportation;

The sample should be transported to the laboratory in a special blood sample transport container that ensures compliance with the transportation temperature (from -20° to -80°) regime.

Upon receipt in the laboratory, the sample with the accompanying form will be stored in a storage space (refrigerator) with a temperature regime from -20° to -80°, accessible to authorized study personnel.

The obtained sample will be subjected to analysis for *CYP2C19 *2, *3* allele genotyping using the RT-PCR-based allele discrimination method. The analytical procedures include the stages of DNA extraction from the obtained blood sample, pre-PCR and PCR, which are performed using DNA extraction reagents and appropriate primers. Appendix 2 presents the main procedural descriptions of the analytical phase of *CYP2C19 *2, *3* allele genotyping that should be applied in the study.

The procedures of the post-analytical stage of the laboratory study include the analysis of the measurement results obtained at the RT-PCR stage, the formation of the final test result, and the documentation of the study result in the form of a report.

The laboratory study report will be transmitted to the researcher, authenticated in the study and the patient. The study investigator will enter the result reflected in the report into the clinical case registration form.

After that, the remains of the biological material sample will be destroyed according to the procedures adopted in the laboratory.

During the initial assessment and follow-up period, blood and urine samples of the study participants involved can be collected and processed by the medical care team and the study center investigator for various laboratory-diagnostic tests as part of the ongoing clinical assessments - at the end of the 3rd, 6th and 12th months and in case of early withdrawal of the participant from the study or at any time during the follow-up. These laboratory tests may be performed as routine diagnostic tests in real-world practice in an accredited diagnostic laboratory of the study center or other medical institution using conventional (generally accepted) methods for performing these tests.

The results of the tests performed in the laboratory of the study center or other medical institution within the follow-up period can be collected in the patient's outpatient medical record as a routine practice. The investigator may transfer the results of these diagnostic tests to the study case registration form and then use them for the purposes of the study.

The patient's outpatient medical record will also include the results of other laboratory tests used for routine management of the patient's condition, which are not of interest to the study, although they can be used to characterize the study's endpoints.

2.5.10 Schedule of Study Visits

A schematic description of the screening, randomization, and follow-up procedures is provided in Appendix 4 in tabular form.

2.6 Evaluation of Study Results

2.6.1 Study Endpoints

The study follow-up results will be discussed and presented by study arms, as well as concerning the primary and secondary endpoints of the study.

The study results will also be discussed concerning other endpoints, which will be represented by clinical or non-clinical data and characterize the factors that affect the efficacy of antiplatelet treatment and determine the clinical and non-clinical outcome in the course of the CCSs both with and without the results of CYP2C19 genotyping.

The indicators for assessing the effectiveness of the study are presented in Appendix 5.

In the study, the selection of treatment regimens with clopidogrel and an alternative P2Y12 inhibitor will be carried out by determining the genotype of the CYP2C19 *2, *3 non-functional alleles. Clopidogrel will be used in study participants with CYP2C19 *2, *3 normal allele genotypes and in the control arm of study participants not undergone CYP2C19 genotyping – unspecified CYP2C19 genotype. Study participants with CYP2C19 *2, *3 non-functional allele genotypes will be given alternative antiplatelet therapy.

In cases of CAD, regardless of treatment with P2Y12 inhibitors after ePCI, the clinical endpoints will be represented with MACCEs and other clinical conditions related to CAD or the potential adverse events of antiplatelet drug treatment. The incidence of the primary, secondary and other study endpoints defined as clinical outcomes of CYP2C19 genotype-guided P2Y12 inhibitor treatment will be assessed in the study arms.

The primary endpoints of the study are defined as:

- Number of study participants who died from any cause (Death from Any Cause) within a 12-month of the study follow-up;
- Number of study participants who died from any cardiovascular cause (Death from Cardiovascular Cause) within a 12-month of the study follow-up;

The secondary endpoints of the study are defined as:

- Number of study participants who experienced non-fatal myocardial infarction (Non-fatal Myocardial Infarction)
  within a 12-month of the study follow-up;
- Number of study participants who experienced unstable angina or angina requiring hospitalization (Unstable Angina) within a 12-month of the study follow-up;
- Number of study participants who experienced a stroke or transitory cerebral ischemic event (Stroke or TIA) within a 12-month of the study follow-up;
- Number of study participants who experienced major bleeding (Major Bleeding) within a 12-month of the study follow-up;

- Number of study participants who experienced non-major bleeding (Non-major Bleeding) within a 12-month of the study follow-up;
- Number of study participants who experienced a heart failure event (Heart Failure Event) within a 12-month of the study follow-up;
- Number of study participants who experienced percutaneous coronary intervention or coronary artery bypass-grafting (Repeated Coronary Revascularization) within a 12-month of the study follow-up;

Pre-specified endpoints of the study are defined as:

- Number of study cases in each arm with a composite of death from any cause, myocardial infarction, stroke, or major bleeding (Net adverse clinical events - NACEs) within a 12-month of the study follow-up;
- Number of study cases in each study arm with a composite of death from any cause, myocardial infarction, or stroke (Major adverse cardiac or cerebral events - MACCEs) within a 12-month of the study follow-up;
- Number of study participants who reported their health status as good or satisfactory, or with the appearance of CVD symptoms, or with a significant inability to self-care (Patient-Reported Health Status) at 3, 6 and 12 months of the study follow-up;
- Number of study participants self-reported angina not required hospitalization (Patient-Reported Angina Not Required Hospitalization) at 3, 6 and 12 months of the study follow-up;
- Number of study participants reported last week's shortness of breath due to heart failure not requiring hospitalization (Patient-Reported Heart failure Severity) at 3, 6 and 12 months of the study follow-up;
- Number of study participants withdrawn from the study for any reason within a 12-month of the study follow-up;
- Costs of clinical service utilization for case management during the study follow-up;
- Costs incurred for incremental services, including costs for the major adverse cardiovascular and cerebrovascular event;

Along with studying the effectiveness of CYP2C19 genotype-guided treatment selection with clopidogrel and an alternative P2Y12 inhibitor, clinical case management processes in the real-life healthcare system and factors that positively and negatively impact the processes will be evaluated: healthcare processes, place of care, delivery of medical procedures, medication use, and management of comorbidities.

2.6.2 Determining the Study Sample Size

The study sample size was determined at 240 patients.

In order to achieve representativeness of the sample, strength of evidence, high level of reliability and cost-effectiveness of the study, the minimum sample size calculations were performed using two tools that provided two approximate sample sizes. It is assumed that for the subsequent statistical analysis of the study results for calculating the odds ratio, relative risks and benefits, a larger number of variables would be better, and if the average of these two sizes of the study sample deviates towards the larger one, it was taken as the sample size.

The calculations were performed using the following tools:

(1) Sample size calculation for scientific studies using a standard calculator[*]

According to the population size data, the proportion of the population that may have the demographic characteristics characteristic of the study sample (men and women aged 35-79) is 24%[†].

In addition, the size (number) of the population with the clinical characteristics required for the study, from which the sample is directly selected, was calculated based on the rates of new cases of the disease/condition. According to the NCDC data for 2022, there were 2056 new cases registered in the categories of other forms of angina [ICD-10, I20.8] and angina unspecified [ICD-10, I20.9], for which ePCI and subsequent treatment with a P2Y12 inhibitor (clopidogrel or alternative) were likely to be performed‡.

Using this population data and statistical calculations performed with a 95% confidence level and a ±5% confidence interval for the results, the calculated sample size is a minimum of 251 study participants.

** There are no direct, structured data on ePCI performed in men and women aged 40-75 years in Georgia or on the prescription/prescription of clopidogrel or alternative P2Y12 inhibitors in patients with this condition. Therefore, the study sample size was determined by indirect calculation of the data.*

† According to the 2021 demographic data of the National Statistics Service, the number of men and women aged 40-75 years in the general population of Georgia is 932,000, which is 24% of the general population.

‡ Among the eligible new cases of CAD in 2022 by the NCDC, the number of patients registered under the categories of other forms of angina [ICD-10, I20.8] and angina unspecified [ICD-10, I20.9], for whose management post-ePCI treatment with P2Y12 inhibitors is likely, is 2,056.

(2) Sample size calculation for a randomized, parallel, case-control study.

This tool for calculating the study sample size in a selected population will demonstrate reliable statistical relationships and estimate the effects of factors on the development of disease outcomes.

With a two-sided statistical relationship, a confidence interval of - α - 0.05, a power of (1−β) - 0.8, a case/control ratio of - 2, a probability of developing an event in the case group - p0 - up to 0.4, and a probability of developing an event in the control group - p1 - up to 0.6, the calculated sample size is determined as a minimum 221 patients.

2.6.3 Statistical Analysis of Study Results

Primary statistical analysis will be carried out using descriptive statistics methods. The values and distribution of quantitative and qualitative variables from the study participants' initial clinical assessment and follow-up results will be evaluated according to the experimental and control arms. The magnitudes and trends of the variations of the data values will be analyzed.

Quantitative variable data will be calculated by mean, standard deviation, and median. For comparative statistical analysis, differences between the variable values will be calculated using the t-test or the Wilcoxon signed-rank test.

Categorical variable data will be calculated as frequencies and percentages (%). For comparative statistical analysis, differences between the variable values will be calculated using the chi-square or Fisher’s exact tests.

To analyze the effectiveness of selected study interventions, the frequency of detection of clinical endpoints in the experimental treatment intervention arms (Rt1 and Rt2) and the comparator arm (Rc) will be calculated. According to the frequencies of clinical endpoint-positive and -negative cases detected in the study arm, the odds ratio (OR), hazard ratio - Cox proportional hazards regression (HR), relative risk (RR), relative benefit (RB) and absolute benefit (AB) indicators at 95%CI will be calculated.

The obtained results and indicators of treatment intervention effectiveness will be selected to consider the applicability of the study findings and the possibility of the study results translation into real-world clinical practice.

Data evaluation will be carried out continuously, immediately after they enter the registration form and the database. Preliminary statistical calculations and analysis for study evaluation and monitoring will be provided in several stages, when:

I - More than 50% of patients will be included in the study;

II - The study arms will be fully formed, and more than 50% of patients will complete a 3-month and a 6-month follow-up;

III - All study participants will be included in the study, and at a minimum, half of them will complete a 6-month and a 12-month observation period;

IV - All study participants included in the study will complete a 12-month follow-up.

The development of clinical endpoints will be monitored, and the relevant data will be collected in a special data registration form.

Observation and analysis of study activities, procedures, non-clinical outcomes and safety measures will be carried out continuously according to the monitoring and evaluation plan and procedures. Clinical case management processes in real-life medical care practice and factors that positively and negatively impact these processes will be assessed and characterized.

2.6.4 Data and Safety Monitoring

Study data monitoring will be carried out throughout the study as part of the monitoring and evaluation activities.

The practical monitoring and evaluation activities and the structuring and processing of data will be carried out by a group formed within the framework of the management of the research project - representatives of the research centers, the sponsor and the research team.

The study sponsor will discuss the results of the study data monitoring. Because the study contains minimal risks and dangers for the study participants, but provides for double-blind randomization for the selection of the study-specific treatment interventions, includes concerns on a highly-specialized clinical practice area, considers a 12-month observation period for the study participants and may have an impact on current clinical practice monitoring process will also be cooperated by the Institutional Review Boards (IRBs) of the study centers involved.

The study monitoring and evaluation team observes study activities at study centers and assesses the safety, scientific and practical relevance, consistency and continuity of data collected. IRBs monitor and evaluate the confidentiality of data collection and management, ethical issues of clinical case management and safety at clinical centers.

The study monitoring and evaluation team consists of specialists with experience in conducting research and evaluations, data management, issuing recommendations and advice on the scientific aspects of research, who are not directly involved in the implementation of this research, do not have intellectual and financial conflicts of interest and formed preconceived ideas and biases concerning the research problem.

The functions of the study monitoring and evaluation team are to observe and evaluate the following processes:

- Involvement of research participants;
- Compliance of research procedures with the research protocol;
- Safety of collected data and their scientific processing;
- Research progress;
- Compliance of the collected data on important adverse clinical events with the clinical endpoints;
- Follow-up management needs of the trial participants;

The IRBs' roles and responsibilities concerning the trial monitoring and evaluation team are defined by oversight of the ethical issues and the safety of the trial participants. In addition, they also discuss the safety of data management procedures and relevant data protection issues.

The monitoring and evaluation team operating within the study management will regularly submit reports for the sponsor's review.

Safety monitoring will be carried out as part of the monitoring and evaluation activities throughout the study. Study monitoring and evaluation procedures address the assessment and avoidance of threats to the safety of study participants, restrictions on freedom of choice, and breaches of confidentiality. Chapter 2.5.8 - Safety Assessment and Control presents the framework for these activities.

3.0 Risk Analysis

3.1 Expected Risks

No specific health risks are associated with study activities or procedures for study participants.

CYP2C19 *2, *3 genotyping with the RT-PCR-based allele discrimination method, applied on randomly selected patients in the experimental arm, belongs to the category of diagnostic procedures that do not involve health risks.

Investigational medicinal products used in the study also do not pose additional health risks to patients. Antiplatelet drugs selected for treatment interventions are real-world clinical practice drugs for the study participants' treatment in conditions with clinical characteristics of study interest. Current guidelines recommend routine use of these medications in post-PCI settings. The use of the investigational product, based on the results of CYP2C19 *2, *3 genotyping, is a patient-centered and precision treatment selection approach that increases the chances for prevention of MACCE. Thus, it represents a significant benefit to patients and cannot be considered a health risk determinant.

Non-adherence is a significant problem in the use of long-term antiplatelet treatment with P2Y12 inhibitors. As part of the clinical follow-up provided by the study investigators and healthcare team, patients included in the study will be assessed for adherence to treatment using the BMQ. The questionnaire will assess adherence not only to P2Y12 inhibitors but also to other medications used to reduce the risk of CAD in the patients included in the study. Accordingly, this study procedure will make it possible to identify and prevent non-adherence to drug treatment (sporadic or recurrent), which will significantly reduce the possibility of developing MACCE and thus be beneficial for the subjects included in the study.

The health risks for study participants are related to the development of the disease/condition under study, CAD, MACCE (cardiovascular death, nonfatal myocardial infarction, recurrent angina, repeat PCI, stent thrombosis, ischemic stroke, transient ischemic attack, intracerebral hemorrhagic stroke), and known, expected, adverse effects of drug treatment (intracerebral hemorrhage, GI bleeding, other bleeding, thrombotic thrombocytopenic purpura). However, these cannot be considered as health risks related to the study. Such adverse events may develop in real-world practice even outside of research interventions.

Health risks may arise from inappropriate or erroneous medical care outside the study's scope and centers. The study procedures include follow-up of results from health care provided outside of study centers and scope for preventing related adverse effects.

Risk management procedures are outlined in the study protocol in Chapter 2.5.8, Safety Assessment and Control.

Additionally, diagnostic tests for the initial assessment and follow-up of study participants allow for identifying, assessing, and preventing risks from other comorbidities. Significant comorbidities that are difficult to control with the study measures or that may contribute to adverse drug reactions are excluded from the study, see Chapter 2.4.4 Exclusion Criteria.

The main study objectives include following up MACCE after ePCI in CAD cases over 12 months using widely used clinical diagnostic methods in real-world practice. These measures significantly increase the ability to identify and prevent MACCE risks and, therefore, will benefit the study participants.
The study may involve risks of limiting study participants' independence of choice and breaching confidentiality. To avoid it, special study data management operations will be implemented:

- Achieving the study participants' informed consent to participate in the study, based on complete written and verbal information about the study operations and making an independent decision;
- Data collection and processing procedures by the 2018 EU General Data Protection Regulation (GDPR);
- Monitoring and evaluation
    - Measures that will identify possible deviations from the study protocol and make it possible to prevent them.
    - Results and risks related to individual clinical cases that will be reviewed;

With consistent implementation of the study procedures, the expected benefits of the study will significantly outweigh the risks.

3.2 Adverse Event Reporting

3.2.1 Definition of an Adverse Event

Major Adverse Cardiovascular and Cerebrovascular Events (MACCEs): A clinically significant adverse cardiovascular and cerebrovascular clinical event that occurs in CAD cases, which may be recurrent, incidental, with a frequency consistent with that expected in the course of the disease and the natural history of the disease (Hazard Ratio [HR], 1.26–5.68, 95%CI [4,5,7,18,23]), is quite common (1–10%) in terms of its probability, is severe in terms of its outcome, is associated with the impact of the risks associated with the disease even under optimal management, is clinically serious, may lead to death, may change the course of the disease/clinical condition, and is not preventable. MACCE determines the outcome of the clinical cases in the study and is, therefore, considered a study clinical endpoint. These include: Cardiovascular death, Nonfatal myocardial infarction, Recurrent angina, Stent thrombosis, Repeated PCI, CABG, Ischemic stroke, Transient ischemic attack, Intracerebral hemorrhage, Atrial fibrillation, Heart failure.
Anticipated Adverse Medication Effect (AAME): A serious adverse effect on the patient's health or a life-threatening problem or death associated with a medicinal product, in cases where the cause of the clinical effect, problem or death is already established and is consistent with previously studied possible effects of the medicinal product in its nature, severity or frequency of occurrence; an expected serious problem with the medicinal product that is related to the safety of the study participant. Possible adverse effects associated with treatment with clopidogrel, prasugrel, or ticagrelor are expected and are considered clinical outcomes and are considered clinical endpoints of the study: Bleeding requiring hospitalization, Thrombotic thrombocytopenic purpura, Minor or minimal bleeding, Change/discontinuation of P2Y12 inhibitor.

3.2.2 Information on Adverse Effects

In accordance with the study follow-up plan procedures (Chapter 2.5.8 Safety Assessment and Control; Chapter 2.5.9 Schedule of Study Visits and its Appendix 4. and Section 2.6 Evaluation of Study Outcomes), all study subjects will undergo a medical examination, routine, conventional laboratory and instrumental examinations, and adherence to the treatment will be assessed. Results of clinical and laboratory examinations and treatments performed outside the study center and the study protocol will be reviewed (see Chapter 2.5.2 Randomization and Treatment Procedures; Chapter 2.5.8 Safety Assessment and Control). These results will allow for the assessment of significant adverse events and effects.

Information on the results of medical care provided outside the study center (medical record) will be retrieved by the investigator and recorded in a special form for recording adverse effects.

3.2.3 Recording and Assessing Adverse Effects

All observable and voluntary adverse events ("serious" or "non-serious") and abnormal test results during the study, regardless of treatment intervention arm allocation and presumed causal relationship or relationship to the investigational product or other therapeutic agent or diagnostic test, will be recorded in the study data registration form.

Information on the volume and purpose necessary to describe and evaluate all adverse events will be obtained from the study site or outside the study site and collected from the study subject's observation procedures, including diagnostic and therapeutic procedures. The volume and content of the information obtained from the adverse event or abnormal test result should ensure:

- Identification of possible clinical outcomes;
- Classification of severity and randomness;
- Establishing a causal relationship
  - to the investigational product;
  - to a disease/concomitant, or comorbid condition;
  - to other therapeutic or diagnostic agents;

An adverse effect or abnormal test result, whether related to the investigational product, another therapeutic agent, or a disease/concomitant or comorbid condition, will be followed up until it resolves or stabilizes to a level acceptable to the investigator or medical team.

3.2.4 Abnormal Test Results

An individual abnormal result of a study alone cannot be considered an adverse event. An abnormal result of the study is classified as an adverse event if it meets one or more of the following criteria:

- accompanied by relevant clinical symptoms;
- requires specific diagnostic evaluations, or therapeutic measures, such as surgical intervention, or additional drug or non-drug treatment, which is not recommended and considered for the treatment of the disease/condition of study interest and provided in the framework of study procedures;
- an effect changes or terminates the treatment intended for the study or the conditions of participation of the study subject (for example, when an abnormal study result determines the study exclusion criteria);
- considered as an adverse event by the sponsor or investigator of the study;

3.2.5 An Event Causality Assessment

The investigator shall review a described and documented adverse event or abnormal study result if:

- The abnormal study result is classified as an adverse event;
- There is a proven relationship between the adverse event to the use of the investigational product or the study drug treatment;
- Meets the definition of a MACCE or AAME.

In such circumstances, the adverse event or abnormal study result is recorded in the patient's medical record, the study data collection form, and reported to the principal investigator and the study sponsor for review. The adverse event or abnormal study result is monitored and managed by the patient's medical care team.

In cases when the causality is initially determined by the investigator or sponsor as "unknown but unrelated to the investigational product or study treatment," it is recorded in the patient's medical record and the study data registration form with appropriate explanations. The patient's medical care team will continue to monitor and respond to it.

In cases where the causality will be assessed by the investigator or the study sponsor, as MACCE or AAME, even if there is a probable or doubtful relationship with the disease/condition of study interest or the investigational product, the adverse event/effect will still be classified as associated with the disease/condition or investigational product. The patient's medical care team will continue to monitor and respond to the adverse event/effect. The concluded results will be recorded in the study data registration form following assessments and the health care team discussions.

3.2.6 Adverse Event Reporting

Any MACCE or AAME observed or voluntary adverse event occurring in a trial is identified by the investigator or sponsor. Information about it is submitted to the trial participant's medical care team, who should then direct the clinical case management.

A MACCE or AAME event is recorded:

- In the study data registration form;
- A description and significance of the event are recorded in the routine medical documentation;

After the registration of the MACCE or AAME event, the participant will be withdrawn from the study.

3.2.7 Adverse Event Reporting to the IRB

Any adverse event that is assessed as MACCE or AAME will be reported by the investigator or sponsor to the IRB of the study center, along with a description and an analysis of the adverse event. The IRB will review the reported adverse event, evaluate it, and make recommendations for further clinical trial follow-up or withdrawal of the subject from the study.

3.3 Early Withdrawal of a Study Participant

A study participant may withdraw from the study at any time during the study and for any reason, whether identifiable or not, by their own free will. This decision and the patient's independent choice are presented in the informed consent form.

A study participant may also be withdrawn early from the study if there is persistent non-adherence to the study follow-up and treatment procedures (see Chapter 2.5.6, Withdrawal from the Study Due to Non-Adherence to Treatment.

A study participant may be withdrawn early from the study based on a clearly stated justification by the investigator or the study sponsor if it is in the patient's best interests to discontinue the study.

The basic reasons for withdrawal from the study are considered as follows:

- If any abnormal study result, symptom, or measurement parameter is detected and resolution, improvement, correction or stabilization of which may require a long period of treatment and/or observation and will change the course of the study-defined follow-up and treatment;
- Any adverse event that may persist during the follow-up period, or require a change or discontinuation of the study-defined treatment, or disrupt the study-defined clinical evaluation plan, or be associated with a severe outcome.
- Any adverse event that may be masked by the use of different medical care regimens than those specified in the study protocol;
- If study treatment intervention, it may pose an expected AAME, a health threat, requiring discontinuation and modification. These conditions require modified treatment measures and regimens other than those specified in the study, including hospitalization. In addition, clinical conditions that may be characteristic of AAME may be exclusion criteria from the study.
- An adverse event related to treatment with P2Y12 inhibitors is a study endpoint, after which the study-planned follow-up is no longer required.
- The MACCE determines the study endpoint, and further measures are no longer required.

In these cases, study participants are discontinued from the study-planned follow-up; the necessary assessments of early withdrawal from the study should be conducted, and the reason for early withdrawal from the study should be determined (evaluated). In these cases, the patient continues to be monitored and treated by the medical support team.

The investigator will describe and analyze the reason for the study participant's early withdrawal, which is part of the routine medical records. An adverse clinical event will be registered in the study data form.

The investigator will inform the study participant of the decision to withdraw from the study early and about further follow-up and treatment measures.

Patient data collected before withdrawal will be used for study purposes, with confidentiality, following the procedures provided and the terms presented to the patient in the informed consent form.

3.4 Definition of Study Completion

The expected end of the study for a participant is determined by the date at the end of the 12-month follow-up period. However, in cases of early withdrawal, this period may be shorter.

Generally, the end of the study is determined by the end of the 12-month follow-up period for the last subject in the study.

4.0 Study Monitoring and Evaluation

The study is monitored and evaluated by a team established by the study sponsor.

Monitoring and evaluation activities include communication with the principal investigator and study personnel, follow-up of study processes, data collection and registration at selected clinical centers (sites), control of the accuracy and quality of data collection, assessment, and reporting of adverse events that occurred during the study to the study sponsor.

Centralized and on-site monitoring procedures at study sites will be aimed at:

- Assessing the risks of data collection and collection -

  - Assessing the data collection process using routine medical records, data registration forms, electronic databases, and communication tools;
- Identifying deviations and inconsistencies from the protocol of the current study procedures -
  - Observing the operational processes of the study sites and processing and analyzing the accompanying information;
- Reviewing the adequacy, quality, and effectiveness of research data sources -
  - Assessing the adequacy and effectiveness of the use of study center resources (including personnel) for research data collection;
- Monitoring the implementation of legal communication, rights, and security measures with research participants -
  - Monitoring and evaluating the medical care and documentation of subjects related to the research.

Monitoring and evaluation activities carried out in these areas will

- Avoid or reduce potential risks to data quality and integrity and research processes.
- Identify additional measures to ensure the safety of research procedures and data quality for research participants.
- Avoid data collection anomalies (e.g., non-random or inappropriate data sources) and risks of patient rights or safety violations;

Various monitoring methods will be used to eliminate the risks of errors in the study: the collection, integrity and processing of critically important data. To this end, during the implementation of the study, the sponsor

- identifies critical data and research processes for monitoring;
- develops a monitoring and evaluation plan;
- assesses possible risks;
- implements monitoring procedures;
- evaluates the monitoring results and again identifies critical processes and conditions for adjustment/improvement.

Critical data and processes for monitoring and evaluation in all cycles will be considered:

- Procedures for obtaining informed consent from the subject to participate in the study;
- Screening measures, application of inclusion and exclusion criteria;
- Processes for random allocation of research subjects and disclosure of research results;
- Compliance and reporting of the use of the investigational product;
- Documentation and reporting of study endpoints;
- Assessment and reporting of abnormal study results and adverse effects/events (serious or non-serious) within the study;
- Collection and documentation of medical care and study results outside the study;
- Assessment and reporting of procedures for early withdrawal from the study;
- Protection of confidentiality and security of study data;

Planned monitoring activities at study sites will be carried out at 4-6 week intervals. Its procedures will enable the collection of data on study processes, the detection of errors in the processing of study data, the detection of inconsistencies between primary data sources and study data forms, the review of study documentation, the observation of procedures, and the assessment of compliance with the study protocol.

The monitoring processes at the study sites will be based on the following procedures:

- Communication with investigators and research personnel -
  - To review and monitor research activities at various stages of initiation and progress of the study. Centralized monitoring can enhance and support communication through teleconferencing, videoconferencing, and email.
  - Communication with research personnel does not discuss the clinical context, diagnosis, or treatment approaches of an individual patient (research subject);
- Review of the appropriateness of processes, procedures, and data records at the research site -
  - From screening, randomization, use of the study product, and determination of study endpoints;
  - Review the appropriateness of informed consent forms for participation in the study.
  - Evaluation and validation/rejection of primary sources of research data;
  - Reporting of medical care and examination results outside the scope of the study in primary sources of research data;
  - Response to abnormal results and adverse events (serious or non-serious) of the study as part of the study safety assessment measures and procedures (Chapter 2.5.8 Safety Assessment and Control) will assess all cases of risk:
    - Abnormal results of the study, MACCEs and AAMEs;
    - Medical care or diagnostic tests performed outside the scope of the study;
    - Non-adherence to medical treatment;
    - Early withdrawal of the subject from the study;
    - Violation of independent choice, confidentiality and illegal processing of study data;

5.0 Informed Consent

Study participant informed consent is obtained by the Declaration of Helsinki, the International Conference on Harmonisation of Clinical Research (ICH) Good Clinical Practice (ICH GCP for Clinical Research), the laws of Georgia [27-30] and this study protocol.

The study sponsor prepares the informed consent form. After approval by the Medical Ethics Council (the Biomedical Research Ethics Committee of Tbilisi State Medical University), it is submitted to the IRB of the study centers. Its written form and verbal consent constitute a formal document for obtaining the study participant's informed consent.

The study centers will maintain the informed consent forms and relevant protocols approved by the National Medical Ethics Council, along with other documents.

To obtain consent, study participants (or their legal representatives) will be provided with narrative, explanatory information and a written informed consent form, and explanations about the study will be provided upon request before participating in the study.

Properly completed, written informed consent will be obtained from study subjects before they participate in the study activities.

According to Georgian legislation [28,31], the legal representative of the research subject is considered to be family members (spouse, children, parents, grandparents - from the circle of first-degree heirs), relatives (sister, brother - in cases where there are no first-degree heirs) or a person who is legally supported by the person, a guardian or a person entrusted with trust, who will be known by the assignment agreement - power of attorney or trustee.

6.0 Informing the IRB

The study protocol, the participant consent form and, upon request, all documents regulating the study activities and procedures approved by the Medical Ethics Board will be submitted to the study center’s IRB.

All documents issued by the IRB will be kept throughout the study period, along with other study documents. Through them, the investigator will receive confident evidence of compliance with existing regulations of the study procedures.

Throughout the study period, any MACCE, UAME, and all observable or voluntary adverse clinical events will be reviewed by the study center’s IRB. It will review these events and, if necessary, present a position on ethical issues of study case management.

Before the start of the study, the investigator must have a written study protocol and informed consent form approved by the IRB, which will then be used to initiate the activities envisaged by the study.

If changes to the protocol and informed consent form are necessary, they will not be used in the research process until the IRB has reviewed the changes, if necessary, with the participation of the study sponsor, eliminated provisions containing risks to the study participant, and approved the changes to the documents in written form.

In addition to making changes, updates or additions to the research protocol and informed consent form, the IRB should, as necessary, review, indicate to the study sponsor, and amend other previously received documents that may be affected by the changes to the research protocol and informed consent form.

The IRB may request revisions to the protocol or other research documentation if content received from various information channels will be related to risks for study conducting activities or present conditions

that may affect study participant's safety. In addition, the IRB may require an annual review of research documents for the purpose of updating them or completing the study.

7.0 Study Records and Reports

7.1 Record Keeping and Data Processing

The data record form (DRF) will be filled in with the data from the study results of each study participant, the form and structure of which will be the same for all subjects and study centers.

At the study center, the data provided in the DRF will be collected and recorded by the study center investigator, who is directly involved in the study participant screening, randomization and follow-up. The study center investigator confirms the completeness, accuracy and authenticity of the entered study data by signature and date.

The principal investigator reviews, signs and dates each completed form. His signature will confirm the responsibility of the study sponsor for the completeness and relevance of the study data (clinical, laboratory, other) entered in the DRF.

The fields allocated for data recording in the DRF are structured according to the name, periods of study activities and the entry date. It provides spaces for recording clarifications, comments or conclusions. Data is entered into the form from primary sources of clinical information and medical documentation used in real-world practice.

In case of omission, non-use or inaccuracy of study data in the DRF, a record confirming their existence is checked in the primary source of data (medical record, authenticated result of the conducted examination, other source of registration of the study result, e.g., result registration journals, electronic databases). In such cases:

- If there are records in the primary data sources, they are transferred to the clinical data report form and the data are marked as "filling in the omission".
- If there are no corresponding records in the primary data sources, within a reasonable time frame (+2 weeks), it can be conducted through the corresponding examination and recording of the results in the DRF by the envisaged plan. In such a case, the data is marked as "filling in the unused".
- If there are no relevant records in the primary data sources and it is not possible to conduct the relevant examination and obtain the data within a reasonable time frame (+2 weeks) according to the research plan, "omission" is indicated in such a case.
- If data is entered in the DRF, but there is no such data in the primary source and it is possible to conduct the relevant examination and record the results as data within a reasonable time frame (+2 weeks) according to the study plan, the recorded result is considered true data, transferred to the DRF as "modified, true". The previous data will be cancelled, which will be confirmed by the investigator's signature and date.
- If data is entered in the clinical case registration form, but there is no such data in the primary source, and it is not possible to conduct the corresponding examination and record the results in the form of data within a reasonable time frame (+2 weeks) according to the study plan, the data entered in the registration form will be marked as "false".

False data will not be processed, used neither for the study, nor for reporting, nor for the discussions planned for the study. During the monitoring and evaluation period, the number of missing and false data will be calculated for each CRF and will be reported if the number of such data exceeds 10% of the unique data planned for the study.

The primary source of data is considered to be the study participant's medical record, which must be produced in accordance with applicable regulations and must chronologically reflect the results of clinical examinations and interventions conducted both within and outside the scope of the study, clinical findings and observation results, laboratory/instrumental diagnostic examination results (including diagnostic examinations included in this study), results of specialized consultations, clinical judgments, medical prescriptions (including treatment included in this study), treatment results, and results of medical care provided outside the research center (in other institutions) throughout the entire period of the study.

Within the study, the patient's medical record is considered the primary documentary source of study data. Its constituent documents will include original medical records, including, but not limited to: hospital care records, medical care charts and forms produced by a doctor's or clinic's office, doctor's notes, diaries, checklists, drug prescription forms and prescriptions, treatment regimens and regimens, printouts of automated diagnostic instruments, laboratory and instrumental examination reports and forms reflecting the results. All records in the DRF must be searchable, readable and consistent with the medical record.

The study data will be collected, stored and processed in a special electronic database. It will include a data entry platform with a similar design to the DRF, however, data entry validation will be carried out not by the name of the data, but by its encrypted code. Once in the database, the name of each data variable will be reflected only in encrypted code without a readable name or textual explanation, so that the data cannot be identified.

The electronic database file will be located away from the research centers. Authorized investigators and study monitoring and evaluation team members will have access to enter and process data through electronic signature authorization.

Data will be entered into the electronic database under the DRF design. Data will be placed with a unique study participant number and without patient identification data, it will not be possible to read the identifiers.

The electronic database will not be connected to the Internet or any other network. The aggregation and import of data collected in the study centers will be carried out from working files. Such an interim file will only collect data from individual subjects enrolled in a single study center, and for the current period. In these files, the subject will be identified only by their unique study number. After data aggregation in the electronic database, the working file will be destroyed.

The identifiers of the study participant, marked with a unique code, and the names and descriptions of the data variables marked with unique codes will be placed in separate files and remotely from the main study database. They will be fully protected. Only authorized investigators will be allowed to access them.

The study database will be processed only for the purposes of the study and for the performance of procedures specified in the protocol.

After the completion of the study data collection, the electronic files containing the personal identification data of the study participants will be deleted. Subsequently, this data will be stored in a secure space only in hard copy for 1 year after the end of the study.

After the study is completed, the DRFs, filled in with the relevant data and confirmed by signatures, will be collected by the sponsor from the study centers and stored centrally for 2 years.

The electronic database of the study data, without the identifiers of the study subjects, will be stored for further processing for scientific purposes for an indefinite period after the study is completed.

7.2 Maintaining and Storing Study Records and Documentation

The sponsor will maintain the following records and documentation of the study:

- The study design and its approval documents;
- Correspondence related to the approval of the study design;
- Documentation of the participation of partners in the study design;
- Copies of documents submitted for review by the Medical Ethics Board, correspondence regarding the review of the study protocol, notifications of approval of the study protocol and informed consent form;
- The version of the approved study protocol;
- The approved informed consent form for participation in the study;
- A list of centers participating in the study;
- A list of investigators (principal investigator and sub-investigators);
- Correspondence with the IRB of the study centers;
- Certificates of the laboratory performing the CYP2C19 *2, *3 allele genotyping (accreditation, quality control);
- Description of the pre-analytical, analytical and post-analytical procedures for determining the genotype of CYP2C19 *2, *3 alleles;
- Randomization plan and list study participants randomization;
- Completed DRFs of study clinical cases;
- Correspondence of the principal investigator, reports and forms with information on adverse effects;
- Coding list of identification data of study participants;
- Coding list of names and definitions of study data variables;
- Results of interim data analysis and interim study reports;
- Final study report;
- A research protocol submitted for peer review, with a plan for analyzing the results and research results;
- Scientific papers submitted for peer-review publication;

Personal information identifying research subjects will not be reflected in reports, open documents, or scientific and public publications that disclose research results.

Research records and documentation will be protected by the research initiator, ensuring the confidentiality of research participants, protecting against illegal data processing, and will be stored for 1 year after the end of the research. Individual Participant Data expected for sharing. After deidentification of the data records, the deidentified IPD used for the results section intended for article publication will be shared. The data set will contain certain demographics, risk factors, cardiovascular morbidity, co-morbidity, coronary angiography, doppler-echocardiography, medication selection records of intervention and control group patients as well as CYP2C19 gene *2, *3 allele profiles of the intervention group patients.

Meta-data in the form of tables, figures, text or appendices will be available as well. The study protocol, variable and recorded data coding, statistical analysis plan and informed consent form will be shared as well. Supporting Information contains: the Study Protocol, the Statistical Analysis Plan (SAP); the Informed Consent Form (ICF) and the Clinical Study Report (CSR).

The IPD will be available 1 month following the publication of the article containing the study results. The anticipated date of final data collection for the primary outcome measures is April 2025.

At this time two manuscripts for publication submission are expected to be completed and the study IDP will be available for sharing. Before this time supporting information will be shared. After sharing IPD,

supporting information will be available for researchers in the field related to this study. The study IPD will remain available for sharing 36 months after the article's publication.

IPD and supportive information will be accessible for researchers who will provide a methodologically sound proposal and whose proposed use of the data will be approved by the independent review and ethics boards. The proposal should display the aims and types of IPD analysis, and show intentions for IPD meta-analysis.

The proposal can be submitted up to 36 months following the study article's publication. After 36 months the IPD will be available in the VistaMedi Ltd data warehouse but without investigators' support other than deposited metadata.

Information regarding proposal submission, IPD accessing procedures and a more detailed plan for sharing IPD, Study Protocol, Statistical Analysis Plan (SAP), Informed Consent Form (ICF) and Variable Data codes will be released on the VistaMedi Ltd official website http://vistamedi.ge/en/

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31. 31. “General Civil Code of Georgia” #786;

Appendix 1. Main procedures of the analytical phase of genotyping of CYP2C19 *2, *3 alleles using the RT-PCR-based allele discrimination method

The CYP2C19 *2, *3 genotyping method involves performing analytical procedures in 3 stages: DNA extraction, pre-PCR and PCR stages.

The first stage of DNA extraction, the analysis, requires the isolation of DNA from a 3 ml venous blood sample, which is taken in a K3 EDTA tube. For DNA extraction, we use the corresponding reagent according to the protocol, which includes lysis of the blood sample, lysis of proteins in the sample using a special lysis buffer, their subsequent removal using washing buffers and obtaining pure nucleic acids in the elution stage.

The next stage of extraction is the preparation of pre-PCR, i.e. master mix and mixing of the obtained DNA samples. To determine the polymorphism of CYP2C19 *2, *3 alleles, TaqManâ master mix is used.

The final stage includes the PCR stage, after mixing all the PCR components in a small volume tube (tablet), 10 µl of PCR mix. The reaction is performed using a thermal cycler (QuantStudio5 Real-Time PCR System (Applied Biosystems, USA)), which performs a rapid change in temperature regime. The first stage is known as the denaturation stage, the second stage - annealing and the third - polymerization stage. Each such cycle doubles the matrix in the array and produces NM copies. The process involves 45 denaturation cycles to obtain an allelic discrimination plot.

Appendix 2. Schedule of Visits to Study Participants Included in the Study

Research Procedures	Screening	Randomization	3rd month follow-up	6th month follow-up	12th month follow-up	Study withdrawal follow-up
Informed consent to participate in the study	—	✓	—	—	—	—
Medical examination/evaluation	✓	✓	✓	✓	✓	✓
Clinical criteria for CAD	✓	—	—	—	—	—
Inclusion/Exclusion Criteria	✓	—	—	—	—	—
Inherited risks	✓	—	—	—	—	—
Cardiometabolic risks	✓	—	—	—	—	—
Patient medical history	✓	—	—	—	—	—
Hospitalization history	✓	—	—	—	—	—
History of comorbidities	✓	—	—	—	—	—
Outcomes of medical care outside the scope of the study	✓	—	✓	✓	✓	✓
Adherence to medication treatment (BMQ)	✓	—	✓	✓	✓	✓
Data collection and processing procedures	✓	✓	✓	✓	✓	✓
Evaluation of clinical end-points	—	—	✓	✓	✓	✓
*CYP2C19 *2, *3* genotiping	—	✓	—	—	—	—
Anthropometry	✓	—	—	—	—	—
Standard 12-lead ECG	✓	—	✓	✓	✓	✓
Doppler-, Echocardiography	✓	—	—	✓	✓	✓
Complete Blood Count (CBC)	✓	—	✓	✓	✓	✓
Glycated Hemoglobin (Hba1c)	✓	—	—	✓	✓	✓
Creatinine, eGFR (MDRD)	✓	—	✓	✓	✓	✓
Study Monitoring Evaluation	✓	✓	✓	✓	✓	✓

Appendix 3. Indicators for evaluating the effectiveness of the study product

Indicator	Statistical Analysis
Number of study participants (n) with genotype of heterozygous and homozygous mutation of *CYP2C19 *2, *3 alleles*	**Counting:** *Number of study participants with wt/mut or mut/mut alleles by CYP2C19 *2, *3 genotyping*
Percentage (%) of study having heterozygous or homozygous mutations of *CYP2C19 *2, *3* genotype	**Numerator:** *Number of study participants with wt/mut or mut/mut alleles by CYP2C19 *2, *3 genotyping* **Denominator:** *Total number of experimental arms study participants, tested for CYP2C19 genotype*
The rate (percentage - %) of death from any cause among study participants	**Numerator:** *Number of study participants dead from any cause* **Denominator:** *Total number of study participants*
The rate (percentage - %) of death from any cause among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants dead from any cause* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of death from any cause among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants dead from any cause* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of death from any cause among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants dead from any cause* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of death from any cause for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from any cause of death of 'normal metabolizer' study participants, calculated as the proportion of any cause of death among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from any cause of death of 'unspecified metabolizer' study participants, calculated as the proportion of any cause of death (%) among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of death from any cause for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from any cause of death of 'normal metabolizer' study participants, calculated as the proportion of any cause of death among 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from any cause of death of 'unspecified metabolizer' study participants, calculated as the proportion of any cause of death (%) among 'unspecified metabolizer' study participants*
The relative risk (RR) of developing death from any cause for 'normal metabolizer' study participants' arm vs 'unspecified metabolizer' study participants' arm	**Numerator:** *the probability of developing death from any cause in the 'normal metabolizer' study participants arm, calculated as the number of 'normal metabolizer' study participants dead from any cause divided by the sum of the number of 'normal metabolizer' study participants dead from any cause and number of 'normal metabolizer' study participants not dead from any cause;* **Denominator:** *the probability of developing death from any cause in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants dead from any cause divided by the sum of the number of 'unspecified metabolizer' study participants dead from any cause and number of 'unspecified metabolizer' study participants not dead from any cause;*
The relative risk (RR) of developing death from any cause for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *the probability of developing death from any cause in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants dead from any cause divided by the sum of the aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants dead from any cause and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants not dead from any cause;*

	Denominator: *the probability of developing death from any cause in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants dead from any cause divided by the sum of the number of 'unspecified metabolizer' study participants dead from any cause and number of 'unspecified metabolizer' study participants not dead from any cause;*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding death from any cause	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of developing death from any cause for 'normal metabolizer' study participants' arm vs 'unspecified metabolizer' study participants' arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding death from any cause	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of developing death from any cause for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding death from any cause	**Calculating:** *The absolute benefit (%) = the rate (%) of death from any cause among 'unspecified metabolizer' study participants – the rate (%) of death from any cause among 'normal metabolizer' study participants*
The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding death from any cause	**Calculating:** *The absolute benefit (%) = the rate (%) of death from any cause among 'unspecified metabolizer' study participants – the rate (%) of death from any cause among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of death from non-cardiovascular causes among study participants	**Numerator:** *Number of study participants dead from non-cardiovascular causes* **Denominator:** *Total number of study participants*
The rate (percentage - %) of death from non-cardiovascular causes among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants dead from non-cardiovascular causes* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of death from non-cardiovascular causes among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants dead from non-cardiovascular causes* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of death from non-cardiovascular causes among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants dead from non-cardiovascular causes* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of death from non-cardiovascular causes for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from non-cardiovascular death of 'normal metabolizer' study participants, calculated as the proportion of non-cardiovascular death among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from non-cardiovascular cause of death of 'unspecified metabolizer' study participants, calculated as the proportion of non-cardiovascular death (%) among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of death from non-cardiovascular causes for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from non-cardiovascular death of 'normal metabolizer' study participants, calculated as the proportion of non-cardiovascular death among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from non-cardiovascular death of 'unspecified metabolizer' study participants, calculated as the proportion of non-cardiovascular death (%) among 'unspecified metabolizer' study participants*
The relative risk (RR) of developing death from non-cardiovascular causes for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of developing death from non-cardiovascular cause in the 'normal metabolizer' study participants arm, calculated as the number of 'normal metabolizer' study participants dead from non-cardiovascular cause divided by the sum of number of 'normal metabolizer' study participants dead*

	from non-cardiovascular cause and number of 'normal metabolizer' study participants not dead from any cause; **Denominator:** *probability of developing death from non-cardiovascular cause in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants dead from non-cardiovascular cause divided by the sum of the number of 'unspecified metabolizer' study participants dead from any non-cardiovascular and the number of 'unspecified metabolizer' study participants not dead from non-cardiovascular cause;*
The relative risk (RR) of developing death from non-cardiovascular causes for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of developing death from non-cardiovascular cause in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants dead from non-cardiovascular cause divided by the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants dead from non-cardiovascular cause and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants not dead from non-cardiovascular cause;* **Denominator:** *probability of developing death from non-cardiovascular cause in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants dead from non-cardiovascular cause divided on the sum of number of 'unspecified metabolizer' study participants dead from non-cardiovascular cause and number of 'unspecified metabolizer' study participants not dead from non-cardiovascular cause;*
The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding death from non-cardiovascular cause	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of developing death from non-cardiovascular cause for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding death from non-cardiovascular cause	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of developing death from non-cardiovascular cause for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding death from non-cardiovascular cause	**Calculating:** *The absolute benefit (%) = the rate (%) of death from non-cardiovascular cause among 'unspecified metabolizer' study participants – the rate (%) of death from non-cardiovascular cause among 'normal metabolizer' study participants*
The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding death from non-cardiovascular cause	**Calculating:** *The absolute benefit (%) = the rate (%) of death from non-cardiovascular cause among 'unspecified metabolizer' study participants – the rate (%) of death from non-cardiovascular cause among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of death from cardiovascular causes among study participants	**Numerator:** *Number of study participants dead from cardiovascular causes* **Denominator:** *Total number of study participants*
The rate (percentage - %) of death from cardiovascular causes among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants dead from cardiovascular causes* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of death from cardiovascular causes among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants dead from cardiovascular causes* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of death from cardiovascular causes among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants dead from cardiovascular causes* **Denominator:** *Total number of 'unspecified metabolizer' study participants*

The hazard ratio (HR) of death from cardiovascular causes for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from cardiovascular death of 'normal metabolizer' study participants, calculated as the proportion of cardiovascular death among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from cardiovascular cause of death of 'unspecified metabolizer' study participants, calculated as the proportion of cardiovascular death (%) among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of death from cardiovascular causes for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from cardiovascular death of 'normal metabolizer' study participants, calculated as the proportion of cardiovascular death among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from cardiovascular death of 'unspecified metabolizer' study participants, calculated as the proportion of cardiovascular death (%) among 'unspecified metabolizer' study participants*
The relative risk (RR) of developing death from cardiovascular causes for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of developing death from cardiovascular cause in the 'normal metabolizer' study participants arm, calculated as the number of 'normal metabolizer' study participants dead from cardiovascular cause divided on the sum of number of 'normal metabolizer' study participants dead from cardiovascular cause and number of 'normal metabolizer' study participants not dead from any cause;* **Denominator:** *probability of developing death from cardiovascular cause in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants dead from cardiovascular cause divided by the sum of number of 'unspecified metabolizer' study participants dead from cardiovascular cause and number of 'unspecified metabolizer' study participants not dead from cardiovascular cause;*
The relative risk (RR) of developing death from cardiovascular causes for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of developing death from cardiovascular cause in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants dead from cardiovascular cause divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants dead from cardiovascular cause and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants not dead from cardiovascular cause;* **Denominator:** *probability of developing death from cardiovascular cause in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants dead from cardiovascular cause divided on the sum of number of 'unspecified metabolizer' study participants dead from cardiovascular cause and number of 'unspecified metabolizer' study participants not dead from cardiovascular cause;*
The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding death from cardiovascular cause	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of developing death from cardiovascular cause for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding death from cardiovascular cause	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of developing death from cardiovascular cause for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding death from cardiovascular cause	**Calculating:** *The absolute benefit (%) = the rate (%) of death from cardiovascular cause among 'unspecified metabolizer' study participants – the rate (%) of death from any cardiovascular among 'normal metabolizer' study participants*

The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding death from cardiovascular cause	**Calculating:** *The absolute benefit (%) = the rate (%) of death from cardiovascular cause among 'unspecified metabolizer' study participants – the rate (%) of death from cardiovascular cause among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of non-fatal myocardial infarction among study participants	**Numerator:** *Number of study participants with non-fatal myocardial infarction* **Denominator:** *Total number of study participants*
The rate (percentage - %) of non-fatal myocardial infarction among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants with non-fatal myocardial infarction* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of non-fatal myocardial infarction among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants with non-fatal myocardial infarction* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of non-fatal myocardial infarction among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants with non-fatal myocardial infarction* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of non-fatal myocardial infarction for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from non-fatal myocardial infarction of 'normal metabolizer' study participants, calculated as the proportion of non-fatal myocardial infarction events among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from non-fatal myocardial infarction of 'unspecified metabolizer' study participants, calculated as the proportion of non-fatal myocardial infarction events among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of non-fatal myocardial infarction for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from non-fatal myocardial infarction of 'normal metabolizer' study participants, calculated as the proportion of non-fatal myocardial infarction events among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from non-fatal myocardial infarction of 'unspecified metabolizer' study participants, calculated as the proportion of non-fatal myocardial infarction events among 'unspecified metabolizer' study participants*
The relative risk (RR) of non-fatal myocardial infarction for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of non-fatal myocardial infarction in the 'normal metabolizer' study participants arm, calculated as the number of 'normal metabolizer' study participants with non-fatal myocardial infarction divided on the sum of number of 'normal metabolizer' study participants with non-fatal myocardial infarction and number of 'normal metabolizer' study participants without non-fatal myocardial infarction;* **Denominator:** *probability of non-fatal myocardial infarction in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with non-fatal myocardial infarction divided by the sum of number of 'unspecified metabolizer' study participants with non-fatal myocardial infarction and number of 'unspecified metabolizer' study participants without non-fatal myocardial infarction;*
The relative risk (RR) of non-fatal myocardial infarction for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of non-fatal myocardial infarction in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants with non-fatal myocardial infarction divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants with non-fatal myocardial infarction and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants without non-fatal myocardial infarction;*

	Denominator: *probability of non-fatal myocardial infarction in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with non-fatal myocardial infarction divided on the sum of number of 'unspecified metabolizer' study participants with non-fatal myocardial infarction and number of 'unspecified metabolizer' study participants without non-fatal myocardial infarction;*
The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding non-fatal myocardial infarction	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of non-fatal myocardial infarction for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding non-fatal myocardial infarction	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of non-fatal myocardial infarction for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding non-fatal myocardial infarction	**Calculating:** *The absolute benefit (%) = the rate (%) of non-fatal myocardial infarction events among 'unspecified metabolizer' study participants – the rate (%) of non-fatal myocardial infarction among 'normal metabolizer' study participants*
The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding non-fatal myocardial infarction	**Calculating:** *The absolute benefit (%) = the rate (%) of non-fatal myocardial infarction among 'unspecified metabolizer' study participants – the rate (%) of non-fatal myocardial infarction among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of stroke/TIA among study participants	**Numerator:** *Number of study participants with stroke/TIA* **Denominator:** *Total number of study participants*
The rate (percentage - %) of stroke/TIA among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants with stroke/TIA* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of stroke/TIA among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants with stroke/TIA* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of stroke/TIA among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants with stroke/TIA* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of stroke/TIA for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from stroke/TIA of 'normal metabolizer' study participants, calculated as the proportion of stroke/TIA events among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from stroke/TIA of 'unspecified metabolizer' study participants, calculated as the proportion of stroke/TIA events among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of stroke/TIA for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from stroke/TIA of 'normal metabolizer' study participants, calculated as the proportion of stroke/TIA events among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from stroke/TIA of 'unspecified metabolizer' study participants, calculated as the proportion of stroke/TIA events among 'unspecified metabolizer' study participants*
The relative risk (RR) of stroke/TIA for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of stroke/TIA in the 'normal metabolizer' study participants arm, calculated as the number of 'normal metabolizer' study participants with stroke/TIA divided on the sum of number of 'normal metabolizer' study participants with stroke/TIA and number of 'normal metabolizer' study participants without stroke/TIA*;

	Denominator: *probability of stroke/TIA in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with stroke/TIA divided by the sum of number of 'unspecified metabolizer' study participants with stroke/TIA and number of 'unspecified metabolizer' study participants without stroke/TIA;*
The relative risk (RR) of stroke/TIA for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of stroke/TIA in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants with stroke/TIA divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants with stroke/TIA and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants without stroke/TIA;* **Denominator:** *probability of stroke/TIA in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with stroke/TIA divided on the sum of number of 'unspecified metabolizer' study participants with stroke/TIA and number of 'unspecified metabolizer' study participants without stroke/TIA;*
The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding stroke/TIA	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of stroke/TIA for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding stroke/TIA	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of stroke/TIA for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding stroke/TIA	**Calculating:** *The absolute benefit (%) = the rate (%) of stroke/TIA events among 'unspecified metabolizer' study participants – the rate (%) of stroke/TIA among 'normal metabolizer' study participants*
The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding stroke/TIA	**Calculating:** *The absolute benefit (%) = the rate (%) of stroke/TIA events among 'unspecified metabolizer' study participants – the rate (%) of stroke/TIA events among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of hemorrhagic stroke among study participants	**Numerator:** *Number of study participants with hemorrhagic stroke* **Denominator:** *Total number of study participants*
The rate (percentage - %) of hemorrhagic stroke among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants with hemorrhagic stroke* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of hemorrhagic stroke among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants with hemorrhagic stroke* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of hemorrhagic stroke among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants with hemorrhagic stroke* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of hemorrhagic stroke for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from hemorrhagic stroke of 'normal metabolizer' study participants, calculated as the proportion of hemorrhagic stroke events among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from hemorrhagic stroke of 'unspecified metabolizer' study participants, calculated as the proportion of hemorrhagic stroke events among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of hemorrhagic stroke for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from hemorrhagic stroke of 'normal metabolizer' study participants, calculated as the proportion of hemorrhagic stroke events among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*

	Denominator: *the hazard rate from hemorrhagic stroke of 'unspecified metabolizer' study participants, calculated as the proportion of hemorrhagic stroke events among 'unspecified metabolizer' study participants*
The relative risk (RR) of hemorrhagic stroke for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of hemorrhagic stroke in the 'normal metabolizer' study participants arm, calculated as the number of 'normal metabolizer' study participants with hemorrhagic stroke divided on the sum of the number of 'normal metabolizer' study participants with hemorrhagic stroke and number of 'normal metabolizer' study participants without hemorrhagic stroke;* **Denominator:** *probability of hemorrhagic stroke in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with hemorrhagic stroke divided by the sum of number of 'unspecified metabolizer' study participants with hemorrhagic stroke and number of 'unspecified metabolizer' study participants without hemorrhagic stroke;*
The relative risk (RR) of hemorrhagic stroke for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of hemorrhagic stroke in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants with hemorrhagic stroke divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants with hemorrhagic stroke and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants without hemorrhagic stroke;* **Denominator:** *probability of hemorrhagic stroke in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with hemorrhagic stroke divided on the sum of number of 'unspecified metabolizer' study participants with hemorrhagic stroke and number of 'unspecified metabolizer' study participants without hemorrhagic stroke;*
The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding hemorrhagic stroke	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of hemorrhagic stroke for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding hemorrhagic stroke	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of hemorrhagic stroke for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding hemorrhagic stroke	**Calculating:** *The absolute benefit (%) = the rate (%) of hemorrhagic stroke events among 'unspecified metabolizer' study participants – the rate (%) of hemorrhagic stroke among 'normal metabolizer' study participants*
The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding hemorrhagic stroke	**Calculating:** *The absolute benefit (%) = the rate (%) of hemorrhagic stroke events among 'unspecified metabolizer' study participants – the rate (%) of hemorrhagic stroke events among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of MACCE among study participants	**Numerator:** *Number of study participants with MACCE* **Denominator:** *Total number of study participants*
The rate (percentage - %) of MACCE among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants with MACCE* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of MACCE among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants with MACCE* **Denominator:** *Total number of 'passive metabolizer' study participants*

The rate (percentage - %) of MACCE among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants with MACCE* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of MACCE for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from MACCE of 'normal metabolizer' study participants, calculated as the proportion of MACCE among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from MACCE of 'unspecified metabolizer' study participants, calculated as the proportion of MACCE among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of MACCE for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from MACCE of 'normal metabolizer' study participants, calculated as the proportion of MACCE among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from MACCE of 'unspecified metabolizer' study participants, calculated as the proportion of MACCE among 'unspecified metabolizer' study participants*
The relative risk (RR) of MACCE for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of MACCE in the 'normal metabolizer' study participants' arm, calculated as the number of 'normal metabolizer' study participants with MACCE divided by the sum of the number of 'normal metabolizer' study participants with MACCE and the number of 'normal metabolizer' study participants without MACCE;* **Denominator:** *probability of MACCE in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with MACCE divided by the sum of the number of 'unspecified metabolizer' study participants with MACCE and the number of 'unspecified metabolizer' study participants without MACCE;*
The relative risk (RR) of MACCE for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of MACCE in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants with MACCE divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants with MACCE and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants without MACCE;* **Denominator:** *probability of MACCE in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with MACCE divided by the sum of the number of 'unspecified metabolizer' study participants with MACCE and the number of 'unspecified metabolizer' study participants without MACCE;*
The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding MACCE	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of MACCE for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding MACCE	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of MACCE for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding MACCE	**Calculating:** *The absolute benefit (%) = the rate (%) of MACCE among 'unspecified metabolizer' study participants – the rate (%) of MACCE among 'normal metabolizer' study participants*
The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding MACCE	**Calculating:** *The absolute benefit (%) = the rate (%) of MACCE among 'unspecified metabolizer' study participants – the rate (%) of MACCE among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of recurrent angina among study participants	**Numerator:** *Number of study participants with recurrent angina* **Denominator:** *Total number of study participants*

The rate (percentage - %) of recurrent angina among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants with recurrent angina* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of recurrent angina among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants with recurrent angina* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of recurrent angina among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants with recurrent angina* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of recurrent angina for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from recurrent angina of 'normal metabolizer' study participants, calculated as the proportion of recurrent angina among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from recurrent angina of 'unspecified metabolizer' study participants, calculated as the proportion of recurrent angina among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of recurrent angina for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from recurrent angina of 'normal metabolizer' study participants, calculated as the proportion of recurrent angina among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from recurrent angina of 'unspecified metabolizer' study participants, calculated as the proportion of recurrent angina among 'unspecified metabolizer' study participants*
The relative risk (RR) of recurrent angina for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of recurrent angina in the 'normal metabolizer' study participants' arm, calculated as the number of 'normal metabolizer' study participants with recurrent angina divided by the sum of the number of 'normal metabolizer' study participants with recurrent angina and the number of 'normal metabolizer' study participants without recurrent angina;* **Denominator:** *probability of recurrent angina in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with recurrent angina divided by the sum of the number of 'unspecified metabolizer' study participants with recurrent angina and the number of 'unspecified metabolizer' study participants without recurrent angina;*
The relative risk (RR) of recurrent angina for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of recurrent angina in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants with recurrent angina divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants with recurrent angina and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants without recurrent angina;* **Denominator:** *probability of recurrent angina in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with recurrent angina divided by the sum of the number of 'unspecified metabolizer' study participants with recurrent angina and the number of 'unspecified metabolizer' study participants without recurrent angina;*
The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding recurrent angina	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of recurrent angina for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding recurrent angina	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of recurrent angina for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*

The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding recurrent angina	**Calculating:** *The absolute benefit (%) = the rate (%) of recurrent angina among 'unspecified metabolizer' study participants – the rate (%) of recurrent angina among 'normal metabolizer' study participants*
The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding recurrent angina	**Calculating:** *The absolute benefit (%) = the rate (%) of recurrent angina among 'unspecified metabolizer' study participants – the rate (%) of recurrent angina among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of repeated PCI among study participants	**Numerator:** *Number of study participants with repeated PCI* **Denominator:** *Total number of study participants*
The rate (percentage - %) of repeated PCI among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants with repeated PCI* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of repeated PCI among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants with repeated PCI* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of repeated PCI among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants with repeated PCI* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of repeated PCI for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from repeated PCI of 'normal metabolizer' study participants, calculated as the proportion of repeated PCI among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from repeated PCI of 'unspecified metabolizer' study participants, calculated as the proportion of repeated PCI among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of repeated PCI for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from repeated PCI of 'normal metabolizer' study participants, calculated as the proportion of repeated PCI among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from repeated PCI of 'unspecified metabolizer' study participants, calculated as the proportion of repeated PCI among 'unspecified metabolizer' study participants*
The relative risk (RR) of repeated PCI for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of repeated PCI in the 'normal metabolizer' study participants' arm, calculated as the number of 'normal metabolizer' study participants with repeated PCI divided by the sum of the number of 'normal metabolizer' study participants with repeated PCI and the number of 'normal metabolizer' study participants without repeated PCI;* **Denominator:** *probability of repeated PCI in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with repeated PCI divided by the sum of the number of 'unspecified metabolizer' study participants with repeated PCI and the number of 'unspecified metabolizer' study participants without repeated PCI;*
The relative risk (RR) of repeated PCI for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of repeated PCI in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants with repeated PCI divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants with repeated PCI and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants without repeated PCI;* **Denominator:** *probability of repeated PCI in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with repeated PCI divided by the sum of the number of 'unspecified metabolizer' study participants with repeated PCI and the number of 'unspecified metabolizer' study participants without repeated PCI;*

The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding repeated PCI	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of repeated PCI for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding repeated PCI	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of repeated PCI for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding repeated PCI	**Calculating:** *The absolute benefit (%) = the rate (%) of repeated PCI among 'unspecified metabolizer' study participants – the rate (%) of repeated PCI among 'normal metabolizer' study participants*
The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding repeated PCI	**Calculating:** *The absolute benefit (%) = the rate (%) of repeated PCI among 'unspecified metabolizer' study participants – the rate (%) of repeated PCI among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of CABG among study participants	**Numerator:** *Number of study participants with CABG* **Denominator:** *Total number of study participants*
The rate (percentage - %) of CABG among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants with CABG* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of CABG among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants with CABG* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of CABG among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants with CABG* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of CABG for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from CABG of 'normal metabolizer' study participants, calculated as the proportion of CABG among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from CABG of 'unspecified metabolizer' study participants, calculated as the proportion of CABG among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of CABG for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from CABG of 'normal metabolizer' study participants, calculated as the proportion of CABG among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from CABG of 'unspecified metabolizer' study participants, calculated as the proportion of CABG among 'unspecified metabolizer' study participants*
The relative risk (RR) of CABG for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of CABG in the 'normal metabolizer' study participants' arm, calculated as the number of 'normal metabolizer' study participants with CABG divided by the sum of the number of 'normal metabolizer' study participants with CABG and the number of 'normal metabolizer' study participants without CABG;* **Denominator:** *probability of CABG in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with CABG divided by the sum of the number of 'unspecified metabolizer' study participants with CABG and the number of 'unspecified metabolizer' study participants without CABG;*
The relative risk (RR) of CABG for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of CABG in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants with CABG divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants with CABG and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants without CABG;*

	Denominator: *probability of CABG in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with CABG divided by the sum of the number of 'unspecified metabolizer' study participants with CABG and the number of 'unspecified metabolizer' study participants without CABG;*
The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding CABG	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of CABG for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding CABG	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of CABG for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding CABG	**Calculating:** *The absolute benefit (%) = the rate (%) of CABG among 'unspecified metabolizer' study participants – the rate (%) of CABG among 'normal metabolizer' study participants*
The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding CABG	**Calculating:** *The absolute benefit (%) = the rate (%) of CABG among 'unspecified metabolizer' study participants – the rate (%) of CABG among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of MACE among study participants	**Numerator:** *Number of study participants with MACE* **Denominator:** *Total number of study participants*
The rate (percentage - %) of MACE among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants with MACE* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of MACE among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants with MACE* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of MACE among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants with MACE* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of MACE for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from MACE of 'normal metabolizer' study participants, calculated as the proportion of MACE among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from MACE of 'unspecified metabolizer' study participants, calculated as the proportion of MACE among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of MACE for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from MACE of 'normal metabolizer' study participants, calculated as the proportion of MACE among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from MACE of 'unspecified metabolizer' study participants, calculated as the proportion of MACE among 'unspecified metabolizer' study participants*
The relative risk (RR) of MACE for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of MACE in the 'normal metabolizer' study participants' arm, calculated as the number of 'normal metabolizer' study participants with MACE divided by the sum of the number of 'normal metabolizer' study participants with MACE and the number of 'normal metabolizer' study participants without MACE;* **Denominator:** *probability of MACE in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with MACE divided by the sum of the number of 'unspecified metabolizer' study participants with MACE and the number of 'unspecified metabolizer' study participants without MACE;*

The relative risk (RR) of MACE for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of MACE in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants with MACE divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants with MACE and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants without MACE;* **Denominator:** *probability of MACE in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with MACE divided by the sum of the number of 'unspecified metabolizer' study participants with MACE and the number of 'unspecified metabolizer' study participants without MACE;*
The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding MACE	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of MACE for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding MACE	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of MACE for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding MACE	**Calculating:** *The absolute benefit (%) = the rate (%) of MACE among 'unspecified metabolizer' study participants – the rate (%) of MACE among 'normal metabolizer' study participants*
The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding MACE	**Calculating:** *The absolute benefit (%) = the rate (%) of MACE among 'unspecified metabolizer' study participants – the rate (%) of MACE among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of major bleeding among study participants	**Numerator:** *Number of study participants with major bleeding* **Denominator:** *Total number of study participants*
The rate (percentage - %) of major bleeding among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants with major bleeding* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of major bleeding among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants with major bleeding* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of major bleeding among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants with major bleeding* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of major bleeding for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from major bleeding of 'normal metabolizer' study participants, calculated as the proportion of major bleeding among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from major bleeding of 'unspecified metabolizer' study participants, calculated as the proportion of major bleeding among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of major bleeding for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from major bleeding of 'normal metabolizer' study participants, calculated as the proportion of major bleeding among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from major bleeding of 'unspecified metabolizer' study participants, calculated as the proportion of major bleeding among 'unspecified metabolizer' study participants*
The relative risk (RR) of major bleeding for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of major bleeding in the 'normal metabolizer' study participants' arm, calculated as the number of 'normal metabolizer' study participants with major bleeding divided by the sum of the*

	number of 'normal metabolizer' study participants with major bleeding and the number of 'normal metabolizer' study participants without major bleeding; **Denominator:** *probability of major bleeding in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with major bleeding divided by the sum of the number of 'unspecified metabolizer' study participants with major bleeding and the number of 'unspecified metabolizer' study participants without major bleeding;*
The relative risk (RR) of major bleeding for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of major bleeding in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants with major bleeding divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants with major bleeding and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants without major bleeding;* **Denominator:** *probability of major bleeding in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with major bleeding divided by the sum of the number of 'unspecified metabolizer' study participants with major bleeding and the number of 'unspecified metabolizer' study participants without major bleeding;*
The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding major bleeding	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of major bleeding for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding major bleeding	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of major bleeding for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding major bleeding	**Calculating:** *The absolute benefit (%) = the rate (%) of major bleeding among 'unspecified metabolizer' study participants – the rate (%) of major bleeding among 'normal metabolizer' study participants*
The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding major bleeding	**Calculating:** *The absolute benefit (%) = the rate (%) of major bleeding among 'unspecified metabolizer' study participants – the rate (%) of major bleeding among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of NACE among study participants	**Numerator:** *Number of study participants with NACE* **Denominator:** *Total number of study participants*
The rate (percentage - %) of NACE among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants with NACE* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of NACE among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants with NACE* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of NACE among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants with NACE* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of NACE for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from NACE of 'normal metabolizer' study participants, calculated as the proportion of NACE among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from NACE of 'unspecified metabolizer' study participants, calculated as the proportion of NACE among 'unspecified metabolizer' study participants*

The hazard ratio (HR) of NACE for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from NACE of 'normal metabolizer' study participants, calculated as the proportion of NACE among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from NACE of 'unspecified metabolizer' study participants, calculated as the proportion of NACE among 'unspecified metabolizer' study participants*
The relative risk (RR) of NACE for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of NACE in the 'normal metabolizer' study participants' arm, calculated as the number of 'normal metabolizer' study participants with NACE divided by the sum of the number of 'normal metabolizer' study participants with NACE and the number of 'normal metabolizer' study participants without NACE;* **Denominator:** *probability of NACE in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with NACE divided by the sum of the number of 'unspecified metabolizer' study participants with NACE and the number of 'unspecified metabolizer' study participants without NACE;*
The relative risk (RR) of NACE for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of NACE in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants with NACE divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants with NACE and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants without NACE;* **Denominator:** *probability of NACE in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with NACE divided by the sum of the number of 'unspecified metabolizer' study participants with NACE and the number of 'unspecified metabolizer' study participants without NACE;*
The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding NACE	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of NACE for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding NACE	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of NACE for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding NACE	**Calculating:** *The absolute benefit (%) = the rate (%) of NACE among 'unspecified metabolizer' study participants – the rate (%) of NACE among 'normal metabolizer' study participants*
The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding NACE	**Calculating:** *The absolute benefit (%) = the rate (%) of NACE among 'unspecified metabolizer' study participants – the rate (%) of NACE among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of TTP among study participants	**Numerator:** *Number of study participants with TTP* **Denominator:** *Total number of study participants*
The rate (percentage - %) of TTP among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants with TTP* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of TTP among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants with TTP* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of TTP among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants with TTP* **Denominator:** *Total number of 'unspecified metabolizer' study participants*

The hazard ratio (HR) of TTP for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from TTP of 'normal metabolizer' study participants, calculated as the proportion of TTP among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from TTP of 'unspecified metabolizer' study participants, calculated as the proportion of TTP among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of TTP for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from TTP of 'normal metabolizer' study participants, calculated as the proportion of TTP among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from the TTP of 'unspecified metabolizer' study participants, calculated as the proportion of TTP among 'unspecified metabolizer' study participants*
The relative risk (RR) of TTP for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of TTP in the 'normal metabolizer' study participants' arm, calculated as the number of 'normal metabolizer' study participants with TTP divided by the sum of the number of 'normal metabolizer' study participants with TTP and the number of 'normal metabolizer' study participants without TTP;* **Denominator:** *probability of TTP in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with TTP divided by the sum of the number of 'unspecified metabolizer' study participants with TTP and the number of 'unspecified metabolizer' study participants without TTP;*
The relative risk (RR) of TTP for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of TTP in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants with TTP divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants with TTP and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants without TTP;* **Denominator:** *probability of TTP in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with TTP divided by the sum of the number of 'unspecified metabolizer' study participants with TTP and the number of 'unspecified metabolizer' study participants without TTP;*
The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding TTP	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of TTP for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding TTP	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of TTP for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding TTP	**Calculating:** *The absolute benefit (%) = the rate (%) of TTP among 'unspecified metabolizer' study participants – the rate (%) of TTP among 'normal metabolizer' study participants*
The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding TTP	**Calculating:** *The absolute benefit (%) = the rate (%) of TTP among 'unspecified metabolizer' study participants – the rate (%) of TTP among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of HF event among study participants	**Numerator:** *Number of study participants with HF event* **Denominator:** *Total number of study participants*
The rate (percentage - %) of HF event among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants with HF event* **Denominator:** *Total number of 'normal metabolizer' study participants*

The rate (percentage - %) of HF event among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants with HF event* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of HF event among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants with HF event* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of the HF event for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from the HF event of 'normal metabolizer' study participants, calculated as the proportion of HF events among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from the HF event of 'unspecified metabolizer' study participants, calculated as the proportion of HF events among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of HF event for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from the HF event of 'normal metabolizer' study participants, calculated as the proportion of HF events among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from the HF event of 'unspecified metabolizer' study participants, calculated as the proportion of HF events among 'unspecified metabolizer' study participants*
The relative risk (RR) of HF event for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of the HF event in the 'normal metabolizer' study participants' arm, calculated as the number of 'normal metabolizer' study participants with HF events divided by the sum of the number of 'normal metabolizer' study participants with HF events and the number of 'normal metabolizer' study participants without HF events;* **Denominator:** *probability of HF event in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with HF event divided by the sum of the number of 'unspecified metabolizer' study participants with HF event and the number of 'unspecified metabolizer' study participants without HF event;*
The relative risk (RR) of HF event for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of the HF event in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants with HF event divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants with HF event and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants without HF event ;* **Denominator:** *probability of HF event in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with HF event divided by the sum of the number of 'unspecified metabolizer' study participants with HF event and the number of 'unspecified metabolizer' study participants without HF event;*
The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding HF event	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of HF event for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding HF event	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of HF event for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding HF event	**Calculating:** *The absolute benefit (%) = the rate (%) of HF event among 'unspecified metabolizer' study participants – the rate (%) of HF event among 'normal metabolizer' study participants*

The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding HF event	**Calculating:** *The absolute benefit (%) = the rate (%) of HF event among 'unspecified metabolizer' study participants – the rate (%) of HF event among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of minor bleeding among study participants	**Numerator:** *Number of study participants with minor bleeding* **Denominator:** *Total number of study participants*
The rate (percentage - %) of minor bleeding among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants with minor bleeding* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of minor bleeding among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants with minor bleeding* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of minor bleeding among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants with minor bleeding* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of the minor bleeding for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from the minor bleeding of 'normal metabolizer' study participants, calculated as the proportion of minor bleeding among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from the minor bleeding of 'unspecified metabolizer' study participants, calculated as the proportion of minor bleeding among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of minor bleeding for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from the minor bleeding of 'normal metabolizer' study participants, calculated as the proportion of minor bleeding among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from the minor bleeding of 'unspecified metabolizer' study participants, calculated as the proportion of minor bleeding among 'unspecified metabolizer' study participants*
The relative risk (RR) of minor bleeding for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of the minor bleeding in the 'normal metabolizer' study participants' arm, calculated as the number of 'normal metabolizer' study participants with minor bleeding divided by the sum of the number of 'normal metabolizer' study participants with minor bleeding and the number of 'normal metabolizer' study participants without minor bleeding;* **Denominator:** *probability of minor bleeding in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with minor bleeding divided by the sum of the number of 'unspecified metabolizer' study participants with minor bleeding and the number of 'unspecified metabolizer' study participants without minor bleeding;*
The relative risk (RR) of minor bleeding for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of the minor bleeding in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants with minor bleeding divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants with minor bleeding and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants without minor bleeding;* **Denominator:** *probability of minor bleeding in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with minor bleeding divided by the sum of the number of 'unspecified metabolizer' study participants with minor bleeding and the number of 'unspecified metabolizer' study participants without minor bleeding;*

The relative benefit (RB) of CYP2C19 *2, *3 genotype-guiding clopidogrel treatment application for avoiding minor bleeding	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of minor bleeding for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm*
The relative benefit (RB) of *CYP2C19 *2, *3* genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding minor bleeding	**Calculating:** *The relative benefit = 1 – the relative risk (RR) of minor bleeding for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm*
The absolute benefit (AB) of *CYP2C19 *2, *3* genotype-guiding clopidogrel treatment application for avoiding minor bleeding	**Calculating:** *The absolute benefit (%) = the rate (%) of minor bleeding among 'unspecified metabolizer' study participants – the rate (%) of minor bleeding among 'normal metabolizer' study participants*
The absolute benefit (AB) of CYP2C19 *2, *3 genotype-guiding any P2Y12 inhibitor antiplatelet treatment application for avoiding minor bleeding	**Calculating:** *The absolute benefit (%) = the rate (%) of minor bleeding among 'unspecified metabolizer' study participants – the rate (%) of minor bleeding among aggregated 'normal metabolizer' and 'passive metabolizer' study participants*
The rate (percentage - %) of repeated non-adherence to medication treatment among study participants	**Numerator:** *Number of study participants with repeated non-adherence to medication treatment* **Denominator:** *Total number of study participants*
The rate (percentage - %) of repeated non-adherence to medication treatment among 'normal metabolizer' study participants	**Numerator:** *Number of 'normal metabolizer' study participants with repeated non-adherence to medication treatment* **Denominator:** *Total number of 'normal metabolizer' study participants*
The rate (percentage - %) of repeated non-adherence to medication treatment among 'passive metabolizer' study participants	**Numerator:** *Number of 'passive metabolizer' study participants with repeated non-adherence to medication treatment* **Denominator:** *Total number of 'passive metabolizer' study participants*
The rate (percentage - %) of repeated non-adherence to medication treatment among 'unspecified metabolizer' study participants	**Numerator:** *Number of 'unspecified metabolizer' study participants with repeated non-adherence to medication treatment* **Denominator:** *Total number of 'unspecified metabolizer' study participants*
The hazard ratio (HR) of the repeated non-adherence to medication treatment for 'normal metabolizer' study participants vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from the repeated non-adherence to medication treatment of 'normal metabolizer' study participants, calculated as the proportion of repeated non-adherence to medication treatment among 'normal metabolizer' study participants* **Denominator:** *the hazard rate from the repeated non-adherence to medication treatment of 'unspecified metabolizer' study participants, calculated as the proportion of repeated non-adherence to medication treatment among 'unspecified metabolizer' study participants*
The hazard ratio (HR) of repeated non-adherence to medication treatment for study participants of 'normal metabolizer' and 'passive metabolizer' vs 'unspecified metabolizer' study participants	**Numerator:** *the hazard rate from the repeated non-adherence to medication treatment of 'normal metabolizer' study participants, calculated as the proportion of repeated non-adherence to medication treatment among aggregated 'normal metabolizer' and 'passive metabolizer' study participants* **Denominator:** *the hazard rate from the repeated non-adherence to medication treatment of 'unspecified metabolizer' study participants, calculated as the proportion of repeated non-adherence to medication treatment among 'unspecified metabolizer' study participants*
The relative risk (RR) of repeated non-adherence to medication treatment for 'normal metabolizer' study participants arm vs 'unspecified metabolizer' study participants arm	**Numerator:** *probability of the repeated non-adherence to medication treatment in the 'normal metabolizer' study participants' arm, calculated as the number of 'normal metabolizer' study participants with repeated non-adherence to medication treatment divided by the sum of the number of 'normal metabolizer' study participants with repeated non-adherence to medication treatment and the number of 'normal metabolizer' study participants without repeated non-adherence to medication treatment;*

	Denominator: *probability of repeated non-adherence to medication treatment in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with repeated non-adherence to medication treatment divided by the sum of the number of 'unspecified metabolizer' study participants with repeated non-adherence to medication treatment and the number of 'unspecified metabolizer' study participants without repeated non-adherence to medication treatment;*
The relative risk (RR) of repeated non-adherence to medication treatment for aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Numerator:** *probability of the repeated non-adherence to medication treatment in the aggregated 'normal metabolizer' and 'passive metabolizer' study participants arm, calculated as the aggregated number of 'normal metabolizer' metabolizer' and 'passive metabolizer' study participants with repeated non-adherence to medication treatment divided on the sum of aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants with repeated non-adherence to medication treatment and aggregated number of 'normal metabolizer' and 'passive metabolizer' study participants without repeated non-adherence to medication treatment;* **Denominator:** *probability of repeated non-adherence to medication treatment in the 'unspecified metabolizer' study participants' arm, calculated as the number of 'unspecified metabolizer' study participants with repeated non-adherence to medication treatment divided by the sum of the number of 'unspecified metabolizer' study participants with repeated non-adherence to medication treatment and the number of 'unspecified metabolizer' study participants without repeated non-adherence to medication treatment;*
Costs associated with the utilization of medical care services of real-world clinical practice in the study cases (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Costs associated with the utilization of medical care services of real-world clinical practice in the 'normal metabolizer' study arm cases (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Costs associated with the utilization of medical care services of real-world clinical practice in the 'passive metabolizer' study arm cases (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Costs associated with the utilization of medical care services of real-world clinical practice in the 'unspecified metabolizer' study arm cases (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Difference in costs associated with the utilization of medical care services of real-world clinical practice between 'normal metabolizer' study participants' arm vs 'unspecified metabolizer' study participants' arm	**Measuring:** *Statistical significance of the difference between the means two study arms in the 95% confidence interval by p value using Student's Two-sample t-test*
Difference in costs associated with the utilization of medical care services of real-world clinical practice between aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm	**Measuring:** *Statistical significance of the difference between the means two study arms in the 95% confidence interval by p value using Student's Two-sample t-test*

Incremental costs associated with the utilization of medical care services of real-world clinical practice in the study cases manifested MACCEs (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Incremental costs associated with the utilization of medical care services of real-world clinical practice in the 'normal metabolizer' study arm cases manifested MACCEs (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Incremental costs associated with the utilization of medical care services of real-world clinical practice in the 'passive metabolizer' study arm cases manifested MACCEs (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Incremental costs associated with the utilization of medical care services of real-world clinical practice in the 'unspecified metabolizer' study arm cases manifested MACCEs (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Difference in incremental costs associated with the utilization of medical care services of real-world clinical practice between 'normal metabolizer' study participants' arm vs 'unspecified metabolizer' study participants' arm cases manifested MACCEs	**Measuring:** *Statistical significance of the difference between the means two study arms in the 95% confidence interval by p value using Student's Two-sample t-test*
Difference in incremental costs associated with the utilization of medical care services of real-world clinical practice between aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm cases manifested MACCEs	**Measuring:** *Statistical significance of the difference between the means two study arms in the 95% confidence interval by p value using Student's Two-sample t-test*
Incremental costs associated with the utilization of medical care services of real-world clinical practice in the study cases manifested MACEs (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Incremental costs associated with the utilization of medical care services of real-world clinical practice in the 'normal metabolizer' study arm cases manifested MACEs (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Incremental costs associated with the utilization of medical care services of real-world clinical practice in the 'passive metabolizer' study arm cases manifested MACEs (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Incremental costs associated with the utilization of medical care services of real-world clinical practice in the 'unspecified metabolizer' study arm cases manifested MACEs (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Difference in incremental costs associated with the utilization of medical care services of real-world clinical practice between 'normal metabolizer' study participants' arm vs 'unspecified metabolizer' study participants' arm cases manifested MACEs	**Measuring:** *Statistical significance of the difference between the means two study arms in the 95% confidence interval by p value using Student's Two-sample t-test*
Difference in incremental costs associated with the utilization of medical care services of real-world clinical practice between	**Measuring:** *Statistical significance of the difference between the means two study arms in the 95% confidence interval by p value using Student's Two-sample t-test*

aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm cases manifested MACEs	
Incremental costs associated with the utilization of medical care services of real-world clinical practice in the study cases manifested NACEs (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Incremental costs associated with the utilization of medical care services of real-world clinical practice in the 'normal metabolizer' study arm cases manifested NACEs (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Incremental costs associated with the utilization of medical care services of real-world clinical practice in the 'passive metabolizer' study arm cases manifested NACEs (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Incremental costs associated with the utilization of medical care services of real-world clinical practice in the 'unspecified metabolizer' study arm cases manifested NACEs (*in USD, m±Std*)	**Calculating:** *Mean value of the costs (m) and standard deviation (Std) in the 95% confidence interval*
Difference in incremental costs associated with the utilization of medical care services of real-world clinical practice between 'normal metabolizer' study participants' arm vs 'unspecified metabolizer' study participants' arm cases manifested NACEs	**Measuring:** *Statistical significance of the difference between the means two study arms in the 95% confidence interval by p value using Student's Two-sample t-test*
Difference in incremental costs associated with the utilization of medical care services of real-world clinical practice between aggregated 'normal metabolizer' and 'passive metabolizer' study participants' arms vs 'unspecified metabolizer' study participants' arm cases manifested NACEs	**Measuring:** *Statistical significance of the difference between the means two study arms in the 95% confidence interval by p value using Student's Two-sample t-test*