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

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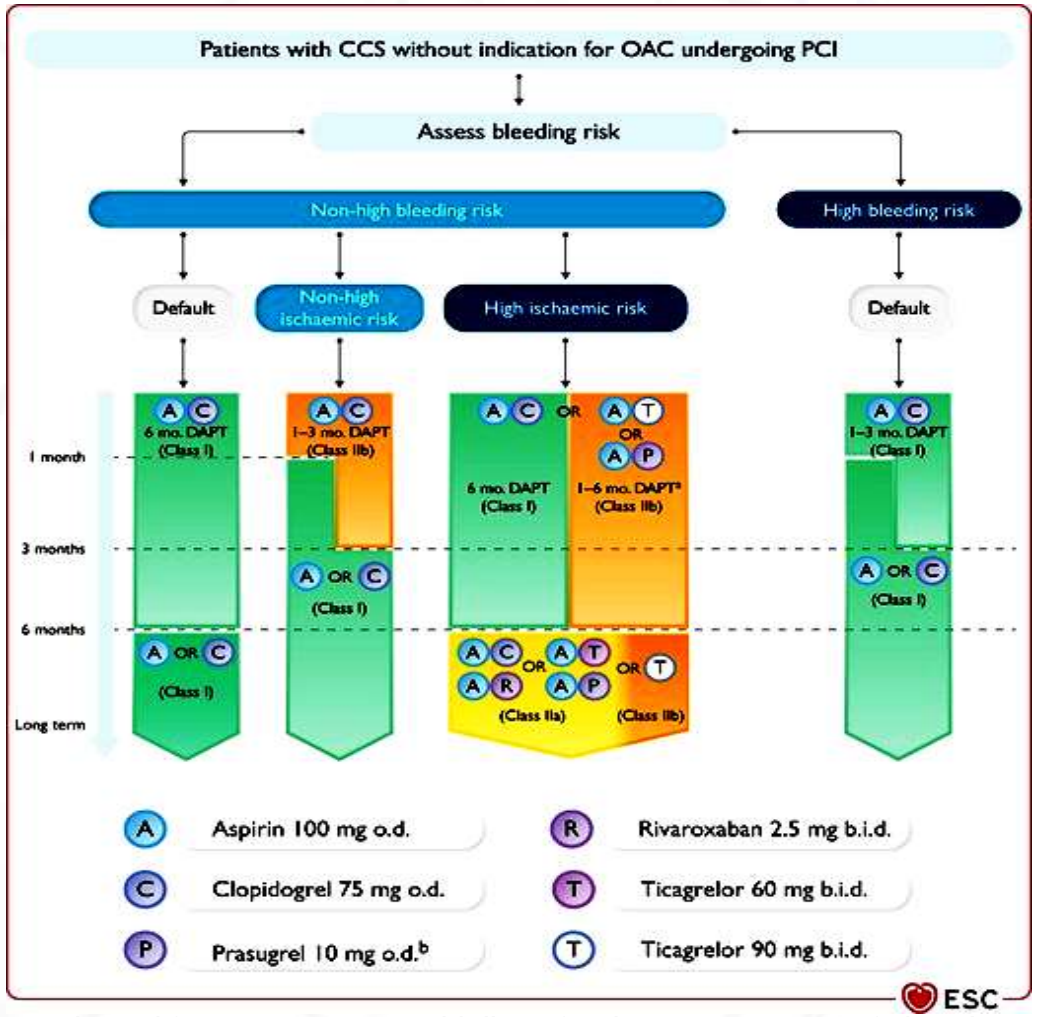
Focus:

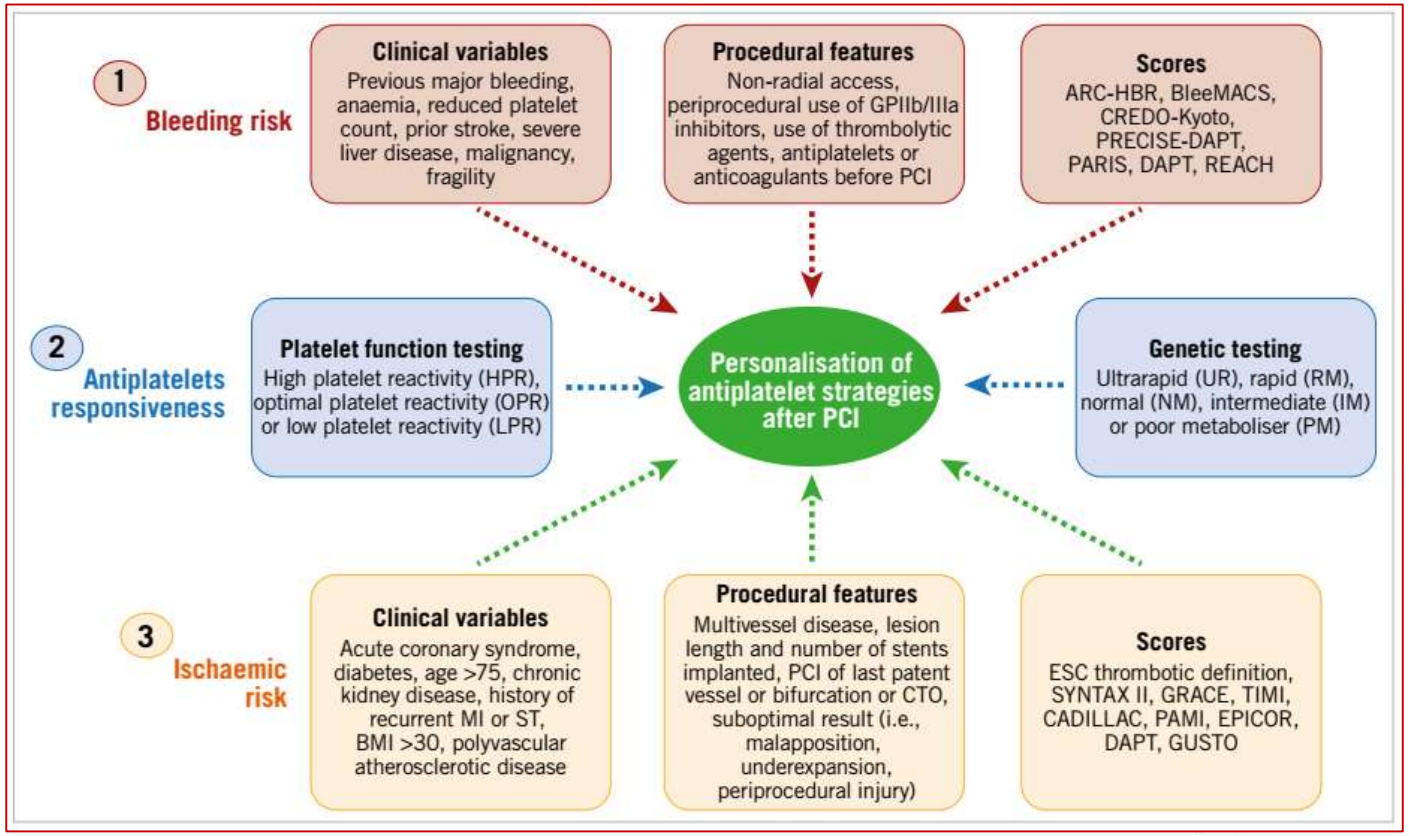
- Antiplatelet treatment (APT) efficiency and safety for preventing major adverse cardiovascular events (MACEs) in the post-PCI setting;
- Clopidogrel, the actionable PGx drug with a CYP2C19 genotype, remains the most commonly prescribed APT despite new potent P2Y12 inhibitors
  - Optimal Medical Treatment (OMT) of chronic coronary syndromes (CCS);
  - De-escalation of potent antiplatelet therapy;
  - Intolerance to potent P2Y12 inhibitors or aspirin.
- Personalised, risk-balanced APT for the reduction of disease-related adverse clinical events.

CPIC Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update
CYP2C19 Genetic Testing for Oral P2Y12 Inhibitor Therapy: A Scientific Statement from the American Heart Association
2024 ESC Guidelines for the management of chronic coronary syndromes



Adapted from 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024 Sep 29;45(36):3415-3537.

Risk assessment to guide antiplatelet therapy in the post-PCI setting



Adapted from Angiolillo DJ. et al. ***EuroIntervention 2022;17:e1371-e1396***

Object:

- CYP2C19 Loss of Function (LoF) alleles influence the pharmacokinetics and pharmacodynamics of the antiplatelet prodrug clopidogrel
  - alter the bioactivation in a graded fashion;
  - lower formation of its active metabolite;
  - maintain a higher on-treatment platelet reactivity;
  - experience reduced platelet inhibition and increased risk for MACE (MACCE) compared to Normal Function Allele (NFA) carriers in settings of:
    - ACS and/or PCI;
    - CCS with or without PCI;
  - impose a higher risk of MACE compared with prasugrel or ticagrelor.

Evidence from Systematic Review and Meta-analysis from the CPIC Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update

Evidence Base:

Systematic review and meta-analysis of 11 randomised controlled trials and 3 observational studies with data for 20 743 patients. *Adapted from Galli M, Benenati S, Capodanno D, et al. Lancet. 2021 Apr 17;397(10283):1470-1483. © 2021 The Lancet. Published by Elsevier.*

Superiority of guided (CYP2C19 genotyping and PFT) compared to standard, conventional selection of ATP improved both composite and individual efficacy clinical outcomes	reduced MACEs - RR 0·78, 95% CI 0·63–0·95, p=0·015; Bleeding - RR 0·88, 95% CI 0·77–1·01, p=0·069; CVD death - RR 0·77, 95% CI 0·59–1·00, p=0·049; MI - RR 0·76, 95% CI 0·60–0·96, p=0·021; Stent thrombosis - RR 0·64, 95% CI 0·46–0·89, p=0·011; Stroke - RR 0·66, 95% CI 0·48–0·91, p=0·010; Minor Bleeding - RR 0·78, 95% CI 0·67–0·92, p=0·0030;

Meta-analysis of 7 randomised controlled trails with data for 15,949 ACS patients. *Adapted from Pereira NL, Rihal C, Lennon R, et al. J Am Coll Cardiol Intv 2021;14:739–50. © 2021 the American College of Cardiology Foundation. Published by Elsevier.*

Non-inferiority of clopidogrel effects among CYP2C19 NFA allele carrier compared to ticagrelor/prasugrel among CYP2C19 LoF allele carrier patients with CAD in post-PCI setting.	reduction of ischemic events among CYP2C19 LoF carriers - RR: 0.70; 95% CI 0.59 - 0.83 CYP2C19 NFA carriers - RR: 1.00; 95% CI 0.80 - 1.25. The test of interaction - significant, p = 0.013

High level evidence from clinical models linked CYP2C19 to Clopidogrel Phenotype. *Adapted from Lee CR, Luzum JA, Sangkuhl K, et al. Supplement to Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. Clin Pharmacol Ther. 2022;112(5):959-967. © 2022 The Authors. Clinical Pharmacology & Therapeutics. © 2022 American Society for Clinical Pharmacology and Therapeutics*

Metabolism (PK)

- CYP2C19 phenotype influences the PK of clopidogrel: PMs have the lowest active metabolite levels and UMs have the highest active metabolite levels;
- IMs and PMs are associated with higher on-treatment platelet reactivity than NMs (might include RMs and UMs);

CVD Indications

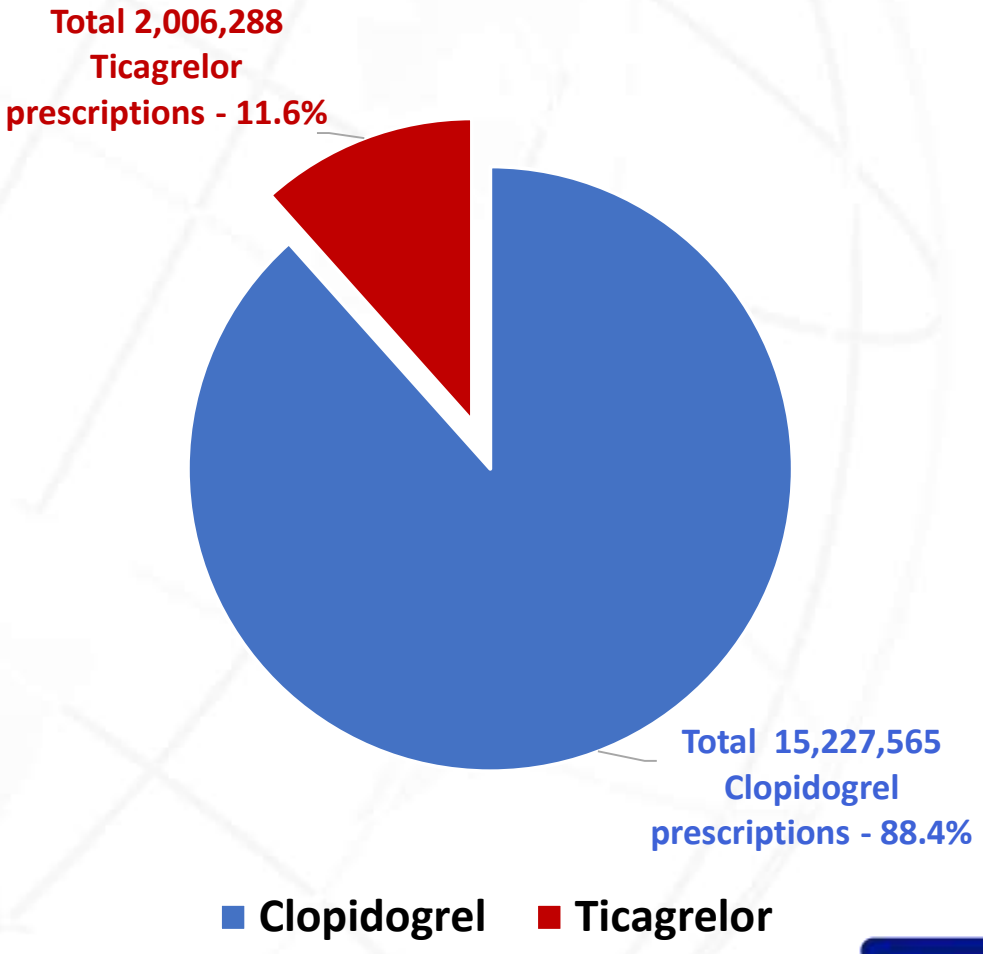
- IMs and PMs are associated with a higher risk of MACEs in ACS and/or PCI patients compared to NMs (might include RMs and UMs);
- High-dose clopidogrel (150 mg/day or higher) can increase the degree of platelet inhibition in ACS/PCI and stable CAD patients who are IMs or PMs compared with standard-dose clopidogrel (75 mg/day);
- IMs and PMs are associated with higher on-treatment platelet reactivity compared to NMs (might include RMs and UMs) in patients treated with high-dose clopidogrel;

ATP comparisons

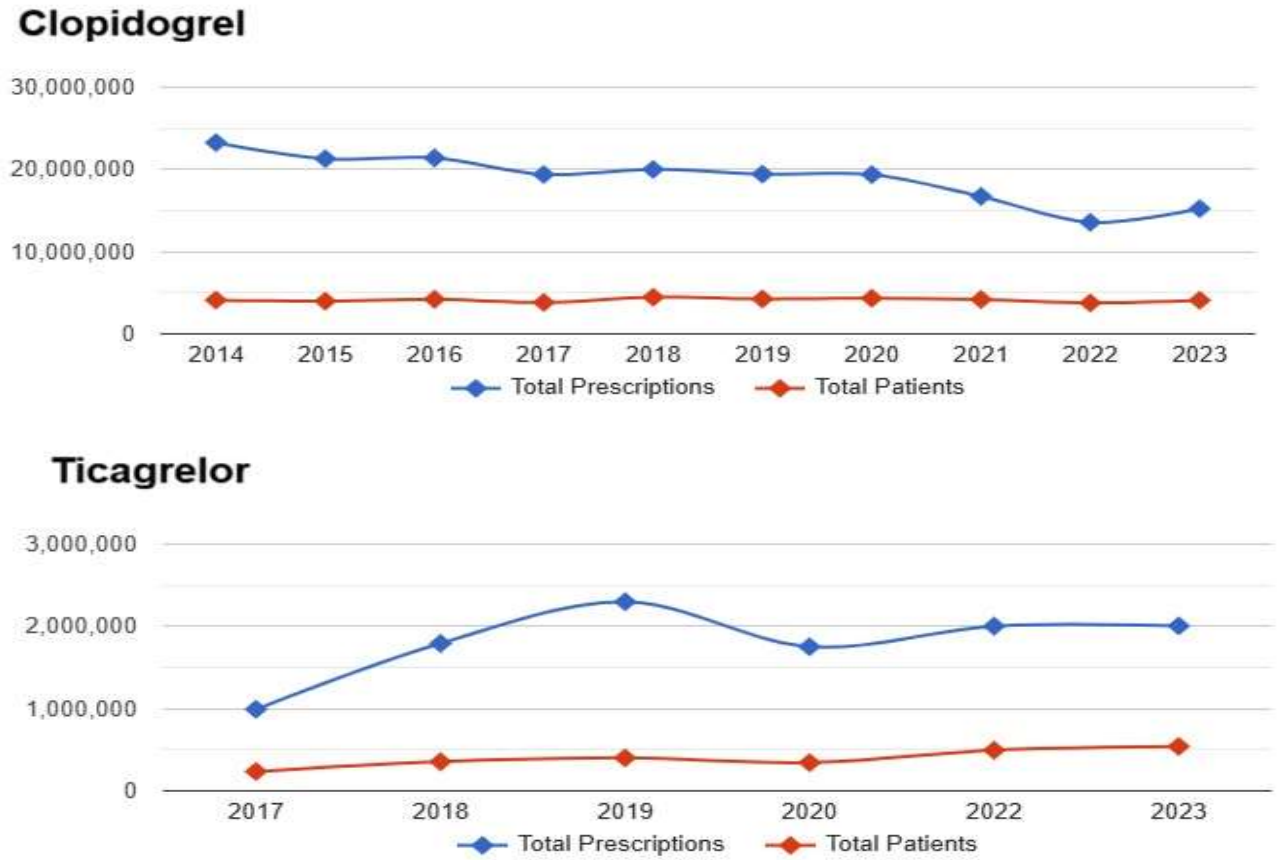
- Among IMs or PMs, treatment with clopidogrel is associated with a higher MACEs compared with treatment with prasugrel or ticagrelor.
- A guided ATP strategy (treatment with ticagrelor/prasugrel in IMs or PMs and treatment with standard-dose clopidogrel in NMs [may include RMs and UMs]) is associated with a decreased risk of MACEs when compared to a strategy of standard-dose clopidogrel in all patients.

ACS, acute coronary syndrome; CAD, coronary artery disease; MACE, major adverse cardiovascular event; IM, intermediate metabolizer; NM, normal metabolizer; PCI, percutaneous coronary intervention; PM, poor metabolizer; RM, rapid metabolizer; UM, Ultrarapid metabolizer

Total prescription of P2Y12 Inhibitor in United States, 2023



Total Prescriptions and Patients Per Year (2014 - 2023)



Prescription data source: Medical Expenditure Panel Survey (MEPS) 2014-2023. Agency for Healthcare Research and Quality (AHRQ), Rockville, MD. ClinCalc DrugStats Database version 2025.08.

Purpose:

Research QS:

Can CYP2C19 genotype-guided clopidogrel-based ATP remain superior to standard, conventional treatment when disease-related risk modifiers expose CCS progression, leading to MACEs in the post-PCI setting under OMT over one year?

Aim:

Evaluate CYP2C19 genotype-guided clopidogrel treatment outcomes against standard, conventional clopidogrel treatment by a one-year clinical outcomes study of CCS patients post-PCI under OMT.

Study:

Randomised, parallel-group controlled study for 12-month follow-up of 157 ‘normal’ and 83 ‘unspecified’ metabolizer CCS patients after ePCI setting

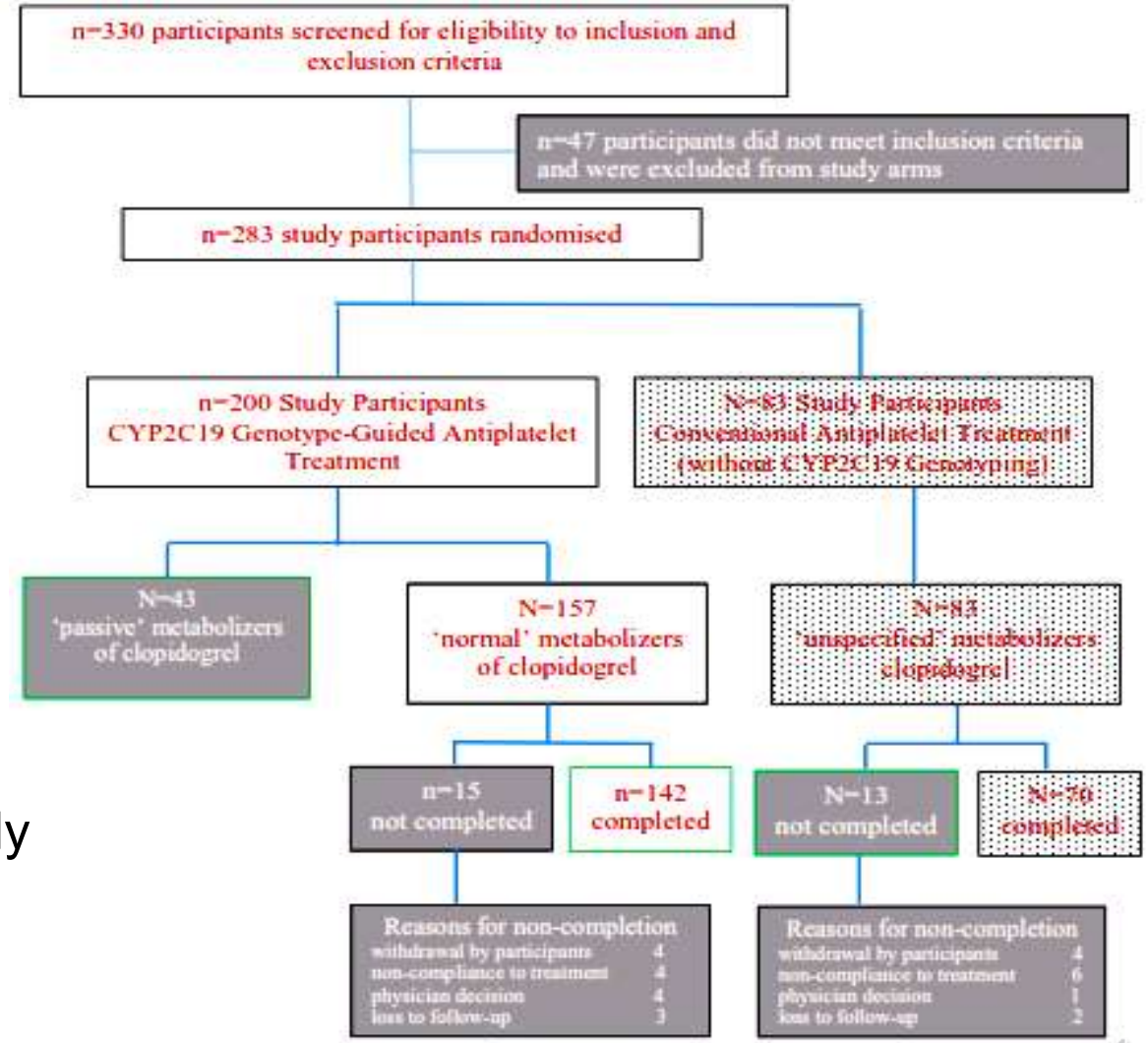
- comparing the clinical outcomes of CYP2C19 genotype-guided versus conventional clopidogrel APT;
  - — DAPT, clopidogrel combined with NOAC, Triple ATP, or monotherapy.
- examining the association of existing risk modifiers exposure on the clinical outcomes.

inclusion: *normal, mildly decreased, or preserved systolic function, clopidogrel-based ATP after ePCI.*

exclusion: *APT limitations, or pre-specified diseases/conditions adversely affect outcomes or alter the APT efficacy*

43 ‘passive’ metabolizers were excluded from the study analysis

- ! ATP with potent p2y12 inhibitors (ticagrelor or prasugrel)
- ! association with fewer MACE and frequent bleeding events



CYP2C19 *2, *3 genotyping

- RT-PCR-based allelic discrimination assay (TaqMan assay), for genotyping SNPs
  - rs4244285 and rs4986893;
- 3 mL of whole blood collected into a K3 EDTA tube was used as the sample.
- For DNA extraction, the custom commercial kit was used according to the manufacturer's instructions.
- Genotype differentiation by allelic discrimination plots constructed using respective homo- and heterozygous mutant reference DNAs for each SNP

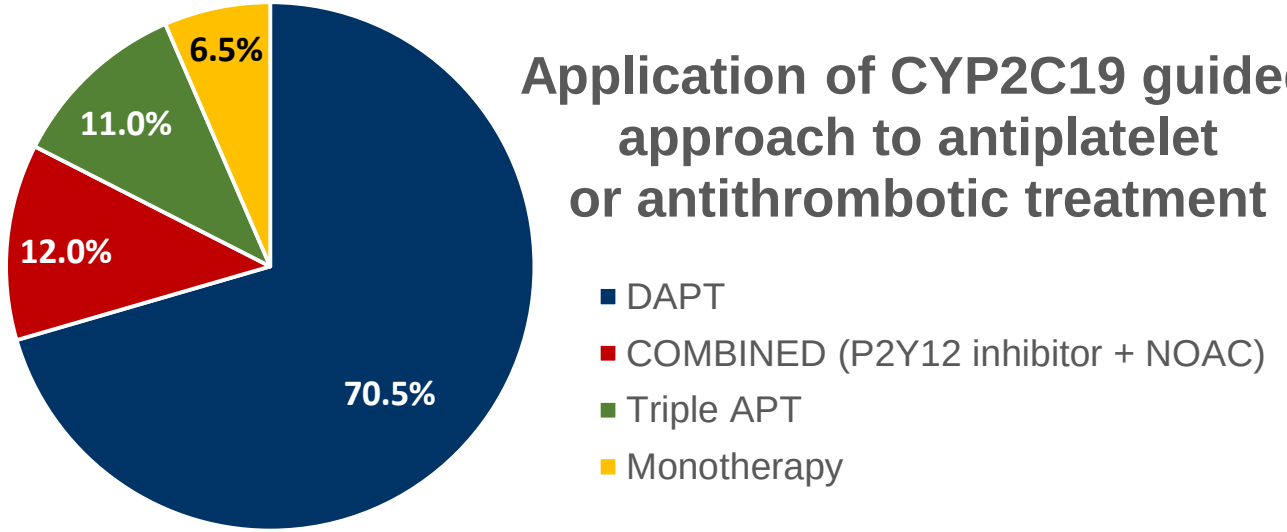
Phenotyping

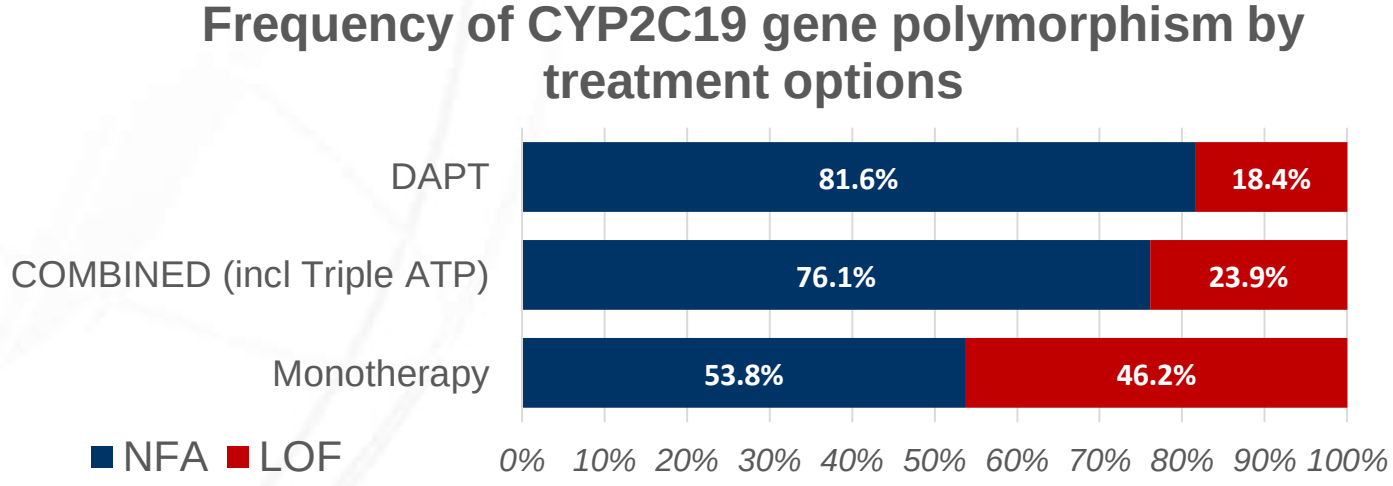
Allele		Clopidogrel Metabolizer
CYP2C19 *2	wt/wt	Normal (NFA)
	wt/mut	Passive (LoF)
	mut/mut	Passive (LoF)
CYP2C19 *3	wt/wt	Normal (NFA)
	wt/mut	Passive (LoF)
	mut/mut	Passive (LoF)

Wt – wild trait, mut – mutant, NFA – Normal Function Allele, LoF – Loss of Function Allele

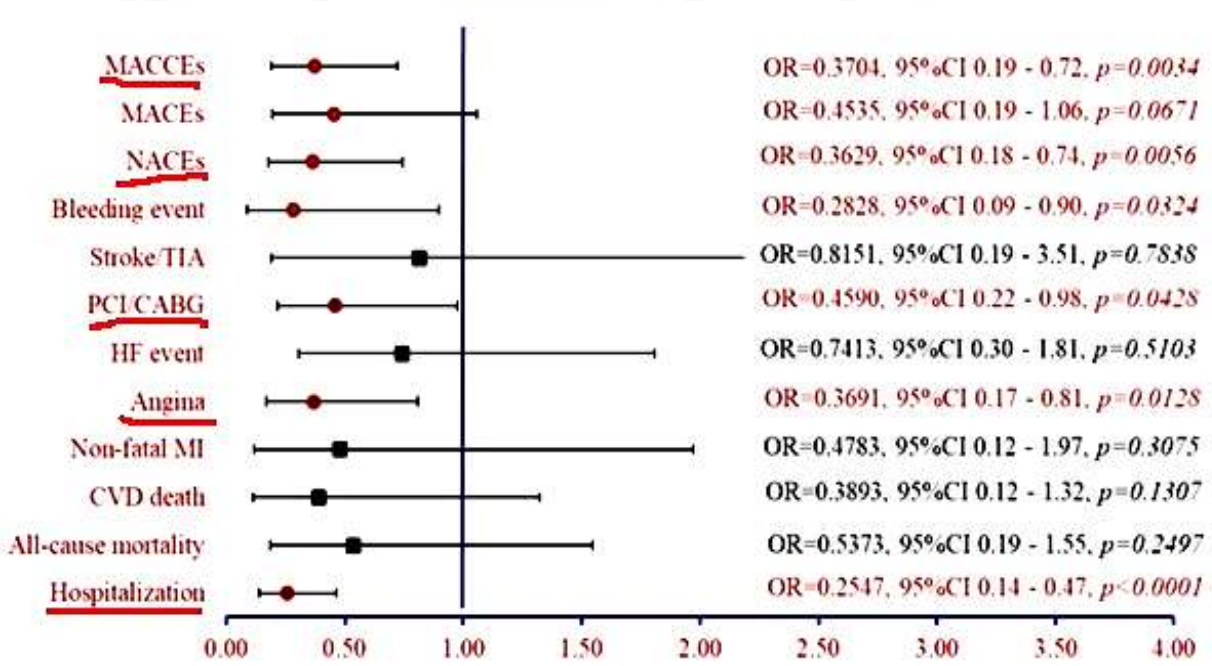
CYP2C19 Testing:

- 21.5% identified as carriers of the CYP2C19 LoF *2 or *3
  - 20.5% were heterozygous carriers of polymorphic CYP2C19 *2,
  - 0.5 – 0.5% (each) homozygous carriers of either CYP2C19 *2 or CYP2C19 *3.





Odds Ratios (OR) for the CYP2C19 genotype-guided clopidogrel-based ATP to clinical outcome associations

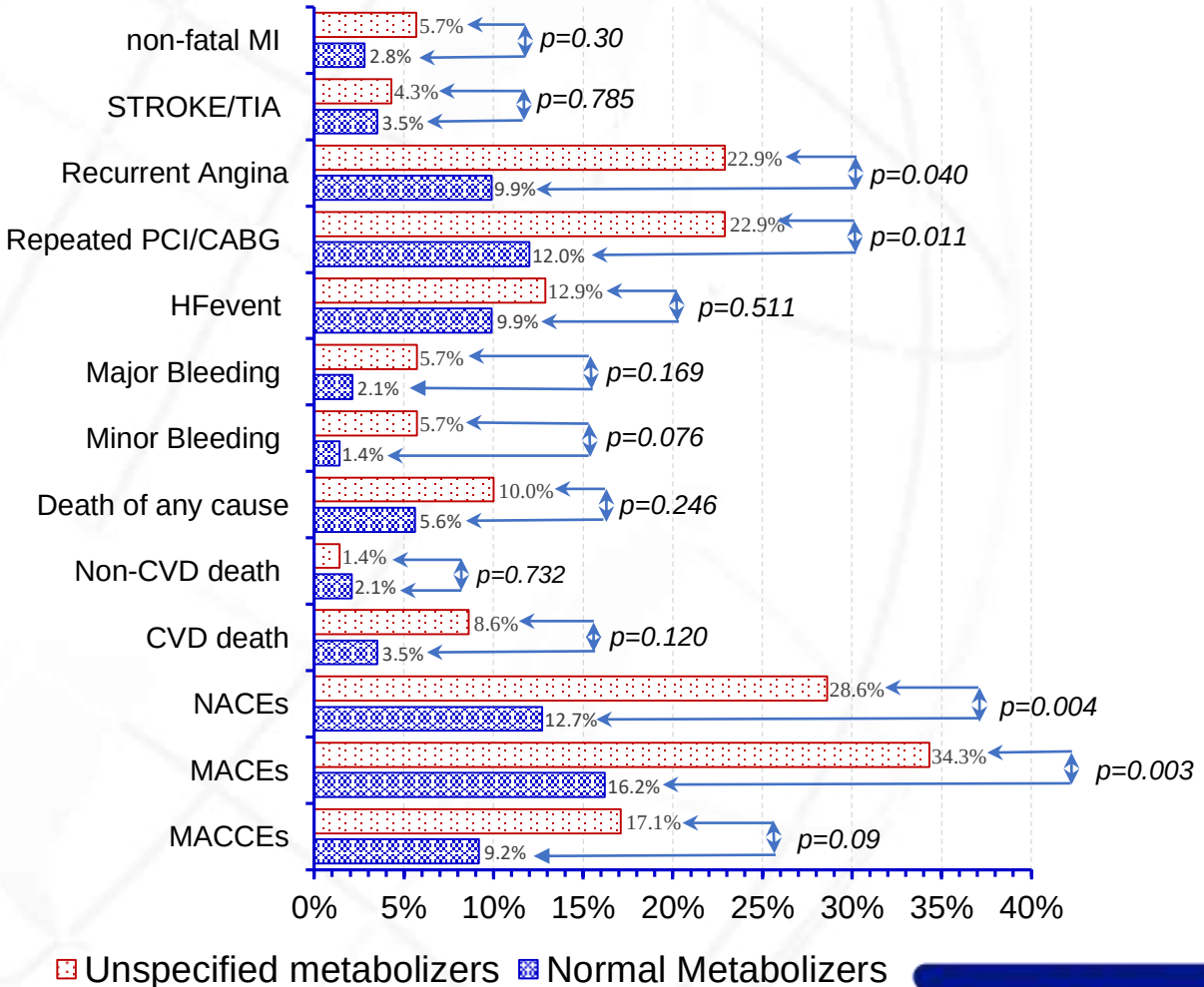


- Positive effects of CYP2C19 genotype-guided APT on clinical outcomes related to CCSs after ePCI setting
  - ORs below 0.5 were significant ($p<0.05$) for recurrent angina, repeated revascularisation (PCI/CABG), all-cause hospitalisation, and composite NACE or MACCE.
  - ORs below 1 were found for all-cause death or CVD death, nonfatal MI, HF event or Stroke/TIA, but w/o significant associations ($p>0.05$)

MACCE: *Major Adverse Cardio- and Cerebrovascular Events, the composite of death from any cause, non-fatal myocardial infarction, or stroke;* **MACEs**: *Major Adverse Cardiovascular Events, the composite of death from cardiovascular cause, non-fatal myocardial infarction, recurrent angina, or repeated revascularisation;* **NACEs**: *Net Adverse Clinical Events, the composite of death from any cause, non-fatal myocardial infarction, stroke, or bleeding event;* **Stroke/TIA**: *Stroke or Transitory Ischemic Attack as the major cerebrovascular event;* **PCI/CABG**: *percutaneous coronary intervention or coronary artery bypass graft;* **HF**: *heart failure event;* **Angina**: *recurrence of angina requiring hospitalization;* **Non-fatal MI**: *non-fatal myocardial infarction;* **CVD**: *cardiovascular disease*.

Risk modifiers exposure:

Adverse Clinical Outcomes of the 'normal' and 'unspecified' metabolizers within the 12 months of follow-up (per cent)



Risk Modifier	Hospitalization	Death of any cause	CVD death	Non-fatal MI	Recurrent Angina	HF Event	Repeated PCI/CABG	Stroke/TIA	Bleeding event	NACE	MACE	MACCE
Current Smoking												
Obesity												
Uncont. HTN History												
Uncont. LDL-C History												
Uncont. T2DM History		●	●							●	●	
PAD History	●					●	●					●
CAD History												
STROKE/TIA History												
COPD History												
CKD History		●	●	●		●				●	●	
SVTA						●					●	
VTA			●								●	●
LBBB	●	●										●
≥2 PCI												
OM1	●										●	●
PDA								●		●		
LVH												
RVD	●	●	●					●		●		●
LVEF <50%	●	●						●		●		●
Increased LVEDVi								●				●

● - OR over 2, p<0.05 at CI95%

Findings:

- A high frequency of the CYP2C19 LoF *2, affecting approximately one-fifth of the studied population and reflecting OMT schemes for drugs metabolised by the hepatic cytochrome P450 2C19 enzyme system.
- The efficiency of CYP2C19 genotype-guided ATP exceeds that of standard clopidogrel-based treatment for preventing early hospitalisation, NACE, MACCE, recurrent angina or repeated revascularisation (PCI/CABG) in CCSs at ePCI settings.
- The significant practical value of CYP2C19 Genotyping for precise ATP prescription positions it into routine laboratory diagnostic workflows.
- Clinical outcomes might be exposed with disease-related risk modifiers appeared due to dysmetabolism, comorbidities, structural and functional myocardial dysfunction, and coronary lesion anatomy.

Challenges:

Doubt & Lack of Willingness

- Unawareness of a personalised genotype-guided drug treatment approach;
  - Insufficient understanding of PGx, gene-drug interaction and the benefits of genotype-guided treatment among health professionals and patients;
    - *What and when to use? How to request and interpret? Why use it?*
  - Lack of strong guideline recommendations for the usual clinical practice.
- Misunderstanding of the role of laboratory diagnostic practices in personalised medicine and clinical decision-making.
  - Lack of effective bridging between medical and laboratory practices
- Costs and reimbursement pathways
  - Lack of cost to benefit analysis results.
    - *Who will pay? – Insurance, community or out-of-pocket?*

Implementation research for evaluating CYP2C19 genotype-guided antiplatelet treatment outcomes in real-world clinical practice

- Consolidation of valuable scientific evidence-based on
  - ATP for preventing MACEs in the post-PCI setting;
  - PGx of the clopidogrel and the actionable CYP2C19 gene;
  - CYP2C19 genotype-guided medication treatment;
- Pilot implementation of CYP2C19 genotype-guided, clopidogrel-based (or alternative) APT in real-world clinical practice of CCS cases at the post-PCI setting;
- Study clinical outcomes of genotype-guided versus standard APT;
- Improve awareness and understanding of gene-drug interaction and genotype-guided treatment;
- Informing the professional society, patients and other stakeholders on the critical role of laboratory services in achieving better outcomes

Project Initiation:

- Methodological and procedural application of CYP2C19 *2, *3 allele genotyping
  - Setting up for practical measurements – SNPs for identifying genetic variants using RT-PCR-based allelic discrimination method;
  - Probing - healthy volunteers and CVD patients from the expected study centres;
  - Defining Quality Assurance and Safety Standards
- The study protocol development
  - Fitting to the flowing clinical procedures and regulatory issues of real-world practice;
  - Adjusting pre-analytical issues and post-analytical CYP2C19 allele testing results;
  - Ensuring the scientific rigour of the expected clinical data for the CCS outcome study;
  - Obtaining ethical approval from the national level IRB;
  - Prospective registration of the study protocol (NIH NLM ClinicalTrial.gov NCT06665919)

Involvement:

- Facilities
  - The central diagnostic laboratory – performing CYP2C19 genotyping and other critical diagnostic tests required by the study protocol;
  - Four clinical centres - providing specialised, ambulatory and hospital CCS HC services at the post-PCI setting;
  - Study data collection and management team;
  - Scientific advisory group.
- Training
  - The study protocol;
  - Evidence Base from clinical studies;
  - CYP2C19 genotyping procedures/method

Publications:

- Clinical study protocol and results registration
  - NIH NLM ClinicalTrial.gov PRS, ID NCT06665919; the protocol registration date: 2024-10-30; the study results registration date: 2025-09-26
- Abstracts
  - 26th International Congress of Clinical Chemistry and Laboratory Medicine - IFCC WorldLab Dubai 2024 (May 26-30, 2024)

    Implementation of molecular markers targeting thrombosis-related conditions in real clinical practice. (Clinica Chimica Acta. 2024; 558(Suppl 1): 119263, https://doi.org/10.1016/j.cca.2024.119263)
  - 24th European Congress of Internal Medicine - ECIM 2026 (March 25-28, 2026).

    Cyp2c19 genetic polymorphism and comorbidity burden as ischemic risk determinants of chronic coronary syndrome after PCI (abstract reference: 0991, Poster presentation, 27.03.2026)
- Upcoming papers
  - CYP2C19 Genotype-Guided Antiplatelet Clopidogrel Treatment Among Subsequent Risk Modifiers of Chronic Coronary Syndromes After Elective Percutaneous Coronary Intervention – *Manuscript submission stage;*
  - Cost-Benefit Analysis of CYP2C19 Genotype-Guided Antiplatelet Clopidogrel Treatment of Chronic Coronary Syndromes After Elective Percutaneous Coronary Intervention – *Manuscript drafting stage*

Presentations:

- The regular seasonal (Winter Summer) Multi Profile Medical Conference provided by the Association of Medical Education and Evidence-Based Medicine (AME&EBM)
  - "Basic Principles and Clinical Application of Current Achievements of Pharmacogenomics" - 2023
  - "CYP2C12 allele Genotype Guided Clopidogrel Treatment – The Step Towards the Precision Medicine" - 2023
  - "Antiplatelet Treatment – Traditional Approaches and New Targets" - 2024
  - "CYP2C19 Genotype-Guided Antiplatelet Treatment Selection in the Real Clinical Practice" - 2024
  - "Risks of subsequent clinical events following established coronary heart disease" – 2025
- 5th Conference of Georgian Atherosclerosis Society "Modern Principles of Atherosclerosis and Cerebrovascular Syndromes Diagnosis and Treatment", October 18, 2024. Tbilisi, Georgia.
  - "CYP2C19 genotype-selected antiplatelet treatment models in real-world practice for the management of chronic coronary artery disease"
- 9th Congress of Georgian Society Cardiologists, October 4-5, 2025, Tbilisi, Georgia
  - "Challenges of de-escalating dual antiplatelet therapy following percutaneous coronary intervention"

Project Outcomes:

- Expanded knowledge on PGx approach to efficiency and safety of drug treatment, and CYP2C19 genotype-guided clopidogrel treatment after the ePCI;
- Piloted clinical and lab diagnostic procedures for genotype-guided treatment in real-world clinical practice;
- Improved awareness and involved stakeholders regarding the critical role of laboratory medicine in healthcare outcomes;
- Promoted PGx approach to medication treatment, precision medicine and personalised, patient-centred healthcare in the larger context;

Further research:

- Utility of a pharmacogenetic panel for strengthening genotyping strategies for OMT
  - Efficiency and safety of drug treatment in certain diseases/conditions, e.g. cardiac PGx panel [CYP2C9, CYP2C19, CYP2D6, VKORC1, SLCO1B1, ABCB1];
  - Drug interactions, for optimal clinical decision-making in medication treatment and prescription practice.
- Molecular markers of valued signalling systems of CCS risk modifiers and improved prediction of major adverse events.
- Harmonising and standardising the pharmacogenetic testing system;
  - Laboratory – methods, QA, analytics;
- Knowledge system building;
  - Evidence Base;
  - CPD programs;
  - Data registry;

For further information, visit
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