*Macedonian Pharmaceutical Bulletin*, 72 (Suppl 1) 529 - 530 (2026)
Online ISSN: 1857-8969
DOI: 10.33320/maced.pharm.bull.2026.72.03.255
*Short communication*

# *CYP2C19*2-AKR1D1*36* polymorphisms and long-term cardiovascular outcomes in clopidogrel treated patients with acute coronary syndrome from Kosovo

Nora Elshani[1*], Marija Staninova Stojovska[2], Nadica Matevska Geshkovska[2], Aleksandra Kapedanovska Nestorovska [2]

*[1]Alma Mater Europaea Campus College "REZONANCA", Glloku te Shelgjet"Veternik", 10000 Prishtina, Kosovo*
*[2]Ss Cyril and Methodius in Skopje, Faculty of Pharmacy, Mother Teresa 47, 1000 Skopje, Republic of N Macedonia*

## Introduction

Clopidogrel remains an important *P2Y12* receptor inhibitor in antiplatelet therapy for patients with acute coronary syndrome (ACS). As a prodrug, it requires hepatic bioactivation, mainly through *CYP2C19* enzymes, while variability in clopidogrel response has been partly attributed to *CYP2C19* genetic polymorphisms, with loss-of-function alleles such as *2 and *3 associated with reduced active metabolite formation and an increased risk of major adverse cardiovascular and cerebrovascular events (MACCE) (Lee et al., 2022). In addition, *AKR1D1* has been proposed as an upstream regulator of several CYP enzymes, including *CYP2C19* and *CYP3A4*, while the *AKR1D1*36* polymorphism has been associated with altered CYP450 expression and clopidogrel treatment outcomes (Chaudhry et al., 2013; Kapedanovska-Nestorovska et al., 2019). However, pharmacogenetic evidence from Western Balkan populations remains limited. Therefore, this study aimed to evaluate the individual and combined association of *CYP2C19*2* and *AKR1D1*36* polymorphisms with long-term cardiovascular outcomes in clopidogrel-treated patients with ACS in Kosovo.

## Materials and methods

This prospective observational study included 150 patients with ACS receiving clopidogrel therapy. Genotyping for *CYP2C19*2 (rs4244285)* and *AKR1D1*36 (rs1872930)* was performed using TaqMan allelic discrimination assays (Applied Biosystems, Foster City, CA, USA), according to the manufacturer's protocol. The primary clinical endpoint was the occurrence of MACCE during follow-up. Time-to-event outcomes were assessed using Kaplan–Meier survival analysis, while the association between genotype/metabolizer status and time to MACCE was evaluated using Cox proportional hazards regression models. Model discrimination was assessed using Harrell's C-index.

## Results and discussion

Regarding *CYP2C19*2* genotype-derived metabolizer status, normal metabolizers (NM; **1/*1*) predominated (66.0%), followed by intermediate metabolizers (IM; **1/*2*; 29.33%) and poor

*nora.elshani1@gmail.com

metabolizers (PM; **2/*2*; 4.67%). For *AKR1D1*, most patients carried the wild-type genotype (**1/*1*; 59.33%), while the heterozygous (**1/*36*; 34.0%) and homozygous variant (**36/*36*; 6.67%) were less frequent. During a median follow-up of 22 months, MACCE occurred in 18.7% of patients. No statistically significant association was observed between *CYP2C19*2* or *AKR1D1*36* polymorphisms and MACCE occurrence. Event rates were comparable across *CYP2C19* metabolizer groups, while *AKR1D1*36* carriers showed a numerically higher MACCE rate compared with non-carriers; however, this difference did not reach statistical significance. Kaplan–Meier analysis showed no significant differences in event-free survival according to *CYP2C19* metabolizer status, *AKR1D1* genotype, or combined genotype/allele groups. Minor numerical trends, including an earlier decline in event-free survival among *CYP2C19* PM, were observed but were not statistically significant. Cox proportional hazards analysis showed no significant association between *CYP2C19* metabolizer status and time to MACCE (HR = 1.40; 95% CI: 0.72–2.73; P = 0.326), with limited discriminative performance, as indicated by Harrell's C-index of 0.536. Similarly, *AKR1D1* genotype was not significantly associated with MACCE over time (HR = 1.01; 95% CI: 0.54–1.87; P = 0.984), and the predictive performance remained poor (C-index = 0.531).

Although *CYP2C19* loss-of-function alleles are established determinants of clopidogrel pharmacogenetics, their translation into long-term MACCE prediction across diverse ACS populations remains an area of active investigation. In this regard, the absence of statistically significant associations in the present cohort is consistent with studies reporting variable or non-uniform genotype–outcome relationships in clopidogrel-treated patients (Chanfreau-Coffinier et al., 2025). The present findings, however, differ from previous regional evidence from North Macedonia, where *CYP2C19*2* and *AKR1D1*36* were associated with adverse clinical outcomes in clopidogrel-treated patients (Kapedanovska Nestorovska et al., 2010; Kapedanovska-Nestorovska et al., 2019). Thus, this study contributes to the external validation of these pharmacogenetic markers in a Western Balkan ACS cohort and suggests that genotype-based prediction may require integration with clinical and population-specific factors.

## Conclusion

In this prospective cohort of clopidogrel-treated ACS patients from Kosovo, *CYP2C19*2* and *AKR1D1*36* polymorphisms were not significantly associated with long-term MACCE or event-free survival. These findings do not diminish the pharmacogenetic relevance of these markers but highlight the complexity of translating genotype information into long-term clinical risk prediction in real-world ACS populations. The results suggest that *CYP2C19*2* and *AKR1D1*36* may have limited standalone predictive value and should be interpreted within integrated models incorporating clinical, procedural, and population-specific factors. Given the modest sample size and limited number of events, larger multicenter studies are warranted. This study provides valuable population-specific evidence from the Western Balkans and supports regionally validated approaches to personalized antiplatelet therapy.

## References

Chanfreau-Coffinier, C. et al., 2025. CYP2C19 polymorphisms and clinical outcomes following percutaneous coronary intervention in the Million Veteran Program. Clin. Pharmacol. Ther. 118, 876–884. https://doi.org/10.1002/cpt.3741

Chaudhry, A.S. et al., 2013. Genetic variation in aldo-keto reductase 1D1 affects the expression and activity of multiple cytochrome P450s. Drug Metab. Dispos. 41, 1538–1547. https://doi.org/10.1124/dmd.113.051672

Kapedanovska Nestorovska, A. et al., 2010. Association between CYP2C19*2 variant and clinical outcome in clopidogrel-treated patients from Republic of Macedonia. Maced. Pharm. Bull. 56, 37–44. https://doi.org/10.33320/maced.pharm.bull.2010.56.005

Kapedanovska-Nestorovska, A. et al., 2019. The AKR1D1*36 (rs1872930) allelic variant is independently associated with clopidogrel treatment outcome. Pharmacogenomics Pers. Med. 12, 287–295. https://doi.org/10.2147/PGPM.S222212

Lee, C.R. et al., 2022. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update. Clin.Pharmacol. Ther. 112, 959–967.