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Prognostic Factors And Efficacy Of Antiplatelet Therapy In Patients With Chronic Ischemic Heart Disease

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ABSTRACT

Background: Vascular diseases, primarily chronic ischemic heart disease (CIHD) and cerebrovascular pathology, remain leading causes of mortality in Uzbekistan and Central Asia. Atherothrombosis, resulting from plaque destabilization and subsequent thrombosis, is the key mechanism underlying disease progression and cardiovascular complications. Biomarkers of coagulation, fibrinolysis, and extracellular matrix remodeling, as well as genetic determinants, may improve risk prediction; however, their prognostic value in regional populations has not been sufficiently studied.

Objective: To identify clinical, biochemical, and genetic predictors of cardiovascular complications in patients with CIHD, to develop a long-term risk stratification scale, and to evaluate factors influencing the efficacy of antiplatelet therapy.

Methods: A prospective observational study was conducted in 2023–2024 at the Republican Specialized Scientific-Practical Medical Center of Cardiology (Tashkent) and included 503 patients with stable CIHD. Clinical characteristics, biochemical markers of coagulation and fibrinolysis (D-dimer, plasmin–α2-antiplasmin complexes [PAP], matrix metalloproteinases MMP-2 and MMP-9), platelet reactivity, and genetic polymorphisms related to hemostasis, homocysteine metabolism, and antiplatelet drug response were assessed. Patients received aspirin, clopidogrel, or dual antiplatelet therapy according to clinical indications. Follow-up duration was at least 12 months. Primary endpoints included vascular death, acute coronary syndrome (ACS), ischemic stroke/transient ischemic attack (IS/TIA), peripheral arterial thrombosis, and revascularization. Statistical analysis was performed using Cox proportional hazards models and Kaplan–Meier survival analysis.

Results: During follow-up (mean 1.5 years), cardiovascular events occurred in 31% of patients. Independent clinical predictors included angina pectoris class II–III, previous myocardial infarction, multivessel coronary disease, history of IS/TIA, abnormal ankle–brachial index, body

mass index ≥31.6 kg/m², creatinine clearance <67 mL/min, and erosive gastritis. Based on these variables, a risk scale stratified patients into low-, intermediate-, and high-risk categories with event rates of 13%, 20%, and 39%, respectively. Percutaneous coronary intervention did not demonstrate superiority over optimal medical therapy and was associated with worse outcomes in the low-risk subgroup. Elevated D-dimer (OR 3.1), MMP-2 (OR 2.1), and PAP levels showed prognostic significance, with the highest risk observed when MMP-2 and PAP were elevated simultaneously (OR 3.6). Polymorphisms in homocysteine metabolism genes (MTHFR C677T, A1298C; TCN2 C776G) were associated with increased risk in a folate-dependent manner. Reduced clopidogrel efficacy was observed in carriers of CYP2C19*2 alleles, while dose escalation to 150 mg improved outcomes in poor metabolizers after PCI. Proton pump inhibitor co-administration was associated with increased thrombotic risk. Prolonged dual antiplatelet therapy beyond 12 months did not provide additional benefit.

Conclusion: An integrated approach combining clinical parameters, biomarkers, and pharmacogenetic testing improves long-term risk stratification and enables personalized antiplatelet therapy in patients with CIHD in Uzbekistan. Routine incorporation of genetic and biochemical markers may enhance secondary prevention strategies in stable coronary disease,

Keywords: chronic ischemic heart disease, atherothrombosis, antiplatelet therapy, pharmacogenetics, coagulation biomarkers, Uzbekistan

INTRODUCTION

Chronic ischemic heart disease (CIHD) remains one of the leading causes of morbidity and mortality worldwide and represents a particularly significant public health burden in Central Asian countries, including Uzbekistan [1–3]. According to global and regional epidemiological data, high prevalence of traditional cardiovascular risk factors, delayed diagnosis, and limited implementation of personalized preventive strategies contribute to unfavorable long-term outcomes in this population [15].

The pathophysiological basis of CIHD progression is atherothrombosis, a complex process involving endothelial dysfunction, inflammatory activation, plaque destabilization, and subsequent thrombus formation [4–6]. Histopathological and clinical studies have demonstrated that acute and chronic coronary events are frequently triggered not by progressive luminal narrowing alone, but by plaque rupture or erosion followed by platelet activation and coagulation cascade engagement [4,5].

In recent decades, increasing attention has been paid to circulating biomarkers reflecting activation of coagulation and fibrinolysis systems as potential predictors of adverse cardiovascular events in patients with stable coronary disease. Large prospective studies, including ARIC, Caerphilly, AtheroGene, and the Edinburgh Heart Study, have shown that elevated levels of D-dimer, fibrinogen, plasminogen activator inhibitor-1, and other fibrinolytic markers are associated with an increased risk of myocardial infarction, stroke, and cardiovascular death, even in clinically stable patients [7]. Nevertheless, the optimal combination of biomarkers and their incremental prognostic value beyond established clinical risk factors remain a subject of ongoing debate [8].

Another important mechanism contributing to plaque vulnerability and disease progression is extracellular matrix remodeling, mediated primarily by matrix metalloproteinases (MMPs). MMP-2 and MMP-9 play a key role in degradation of collagen and elastin within the fibrous cap of atherosclerotic plaques, thereby promoting plaque instability [6]. Elevated circulating levels of MMPs have been associated with adverse cardiovascular outcomes in several observational studies, although their clinical utility in routine risk stratification has not been fully established [6,7].

In parallel with biochemical markers, genetic

determinants of thrombosis and drug response have gained increasing importance in cardiovascular research. Polymorphisms in genes involved in homocysteine metabolism, particularly MTHFR and TCN2, have been linked to hyperhomocysteinemia and increased cardiovascular risk, especially in populations with insufficient folate intake [5]. At the same time, classical hereditary thrombophilias appear to play a limited role in arterial thrombosis compared with venous events [7].

The effectiveness of antiplatelet therapy, which constitutes the cornerstone of secondary prevention in CIHD, is characterized by marked interindividual variability. Clopidogrel resistance, largely mediated by loss-of-function polymorphisms of the CYP2C19 gene, has been consistently associated with higher rates of ischemic events after both acute coronary syndromes and percutaneous coronary intervention [12–14]. Despite the availability of platelet function testing, its prognostic value in routine clinical practice remains controversial due to methodological limitations and multiple confounding factors [14].

The role of invasive strategies in stable CIHD also remains a subject of extensive discussion. Large randomized trials, including COURAGE and BARI 2D, demonstrated that routine elective percutaneous coronary intervention does not improve long-term prognosis compared with optimal medical therapy in stable patients, although it may provide symptomatic relief in selected cases [9,10]. Subsequent meta-analyses confirmed the absence of a mortality benefit and emphasized the importance of careful patient selection for invasive treatment [11].

Taken together, current evidence suggests that effective long-term management of CIHD requires an integrated approach that combines clinical assessment with biochemical, genetic, and therapeutic response markers. However, data on the prognostic value of such an integrated strategy in Central Asian populations remain scarce. Therefore, the present study was designed to evaluate clinical, biochemical, and genetic predictors of cardiovascular complications, as well as factors influencing antiplatelet therapy efficacy, in a cohort of patients with stable CIHD in Uzbekistan.

METHODS

Study Design and Population

This prospective observational study enrolled 503 patients aged over 35 years with stable CIHD. Diagnosis was confirmed by a documented history of acute coronary syndrome occurring more than one month prior to enrollment, previous coronary revascularization, positive stress testing, or coronary angiography. Exclusion criteria included recent thrombotic events, severe angina or advanced heart failure, mandatory use of nonsteroidal anti-inflammatory drugs or oral anticoagulants, intolerance to antiplatelet agents, and severe comorbid conditions limiting life expectancy. All patients received guideline-directed medical therapy, including beta-blockers, statins, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Antiplatelet therapy consisted of aspirin (75–150 mg/day), clopidogrel (75 mg/day, with dose escalation to 150 mg/day after PCI when indicated), or dual antiplatelet therapy for 12–18 months following ACS or PCI. Upper gastrointestinal endoscopy was performed to detect erosive lesions, and proton pump inhibitors were prescribed when clinically indicated. Decisions regarding PCI or coronary artery bypass grafting were made by the treating physicians. Patients were followed every 3–6 months for at least 12 months or until the occurrence of a study endpoint.

Endpoints

The composite endpoint included vascular death, ACS, ischemic stroke or transient ischemic attack, peripheral arterial thrombosis, and revascularization procedures. A thrombotic endpoint was defined as the composite endpoint excluding revascularization. Bleeding events were classified according to TIMI criteria.

Assessments

Clinical assessment included evaluation of cardiovascular risk factors, extent of vascular disease, and gastrointestinal pathology. Biochemical measurements comprised D-dimer (n=494), PAP, plasminogen activator inhibitor-1, tissue plasminogen activator/PAI-1 complexes, MMP-2 and MMP-9 (n=440), as well as homocysteine, folate, and vitamin B12 levels. Genetic analysis included polymorphisms in genes related to thrombophilia, platelet function, homocysteine metabolism, and antiplatelet drug transport and metabolism, including CYP2C19*1, *2, *3, and *17 alleles. Platelet function testing was performed using optical aggregometry with adenosine diphosphate and arachidonic acid in a subset of patients (n=241).

Statistical Analysis

Statistical analyses were performed using Cox proportional hazards regression, Kaplan–Meier survival curves, chi-square tests, Mann–Whitney U tests, and Fisher's exact tests as appropriate. Biomarkers were analyzed by quintiles. A p-value <0.05 was considered statistically significant.

RESULTS

The mean follow-up duration was 1.5 years, during which composite cardiovascular events occurred in 31% of patients.

Clinical Predictors and Risk Stratification

Eight independent clinical predictors were identified: angina pectoris class II–III, previous myocardial infarction, multivessel or left main coronary disease, history of IS/TIA, abnormal ankle–brachial index (≤0.9 or ≥1.3), body mass index ≥31.6 kg/m^2, creatinine clearance <67 mL/min, and erosive gastritis. A cumulative risk score stratified patients into low-risk (≤1 factor), intermediate-risk (2–3 factors), and high-risk (≥4 factors) groups with corresponding event rates of 13%, 20%, and 39%.

Comparison of invasive and conservative management strategies demonstrated no overall difference in thrombotic or composite outcomes. However, in the low-risk group, PCI was associated with a significantly higher incidence of adverse events.

Genetic and Biochemical Predictors

No significant associations were observed for classical thrombophilia mutations. In contrast, polymorphisms in homocysteine metabolism genes (MTHFR C677T and A1298C, TCN2 C776G) were associated with increased risk, particularly in the presence of folate deficiency. Elevated levels of D-dimer (≥250 ng/mL), MMP-2 (≥213.7 ng/mL), and PAP (≥173.1 ng/mL) were associated with an increased risk of thrombotic events. PAP demonstrated a trend toward increased risk. The combination of elevated MMP-2 and PAP conferred the highest prognostic risk.

Antiplatelet Therapy Efficacy

Bleeding events occurred in 8% of patients and were predominantly minor. Clopidogrel monotherapy was associated with a higher rate of adverse events compared with aspirin. Carriers of CYP2C19*2 alleles exhibited significantly reduced clopidogrel efficacy, whereas dose escalation to 150 mg improved outcomes in poor metabolizers following PCI. Co-administration of proton pump inhibitors was associated with increased thrombotic risk. Extension of dual antiplatelet therapy beyond 12 months did not improve outcomes. Optical aggregometry demonstrated limited prognostic value due to multiple clinical and pharmacological confounders.

DISCUSSION

The present study demonstrates that activation of coagulation, fibrinolysis, and extracellular matrix remodeling pathways contributes significantly to long-term cardiovascular risk in stable CIHD. Integration of biochemical markers and genetic testing with clinical assessment improves prognostic accuracy. In stable CIHD, PCI did not confer a prognostic advantage over optimal medical therapy, whereas variability in clopidogrel response was largely determined by genetic and clinical factors. These findings support a personalized, biomarker-guided approach to secondary prevention.

CONCLUSION

Chronic ischemic heart disease is characterized by substantial heterogeneity in thrombotic risk and response to therapy. The present study demonstrates that integration of clinical characteristics, biomarkers of coagulation and vascular remodeling, and pharmacogenetic information provides a robust framework for individualized risk stratification and management. Adoption of this personalized approach may significantly enhance secondary prevention and long-term outcomes in patients with stable coronary disease, particularly in Central Asian populations.

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