ANNOTATION

Dissertation for the degree of Doctor of Philosophy (PhD)
Specialty: 8D10102 – «Medicine»

«Predictors of Ischemic and Hemorrhagic Events in Patients with Acute Coronary Syndrome and Atrial Fibrillation after Percutaneous Coronary Intervention»

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Relevance of the Study:

In the modern world, cardiovascular diseases (CVD) remain a leading cause of mortality. Endovascular interventions have opened a new stage in cardiology, significantly expanding treatment options for ischemic heart disease (IHD). At the same time, the widespread use of percutaneous coronary interventions (PCI) has raised the problem of recurrent adverse cardiovascular events (ACVE).
Among patients with IHD, approximately 10% have atrial fibrillation (AF). More than 30% of patients with AF have concomitant IHD, and 20–25% of patients with AF require PCI.
According to literature data and the 2023 guidelines of the European Society of Cardiology (ESC), patients with AF who have undergone PCI are recommended to receive dual antithrombotic therapy (DAT) consisting of an oral anticoagulant (OAC) at a dose approved for stroke prevention in combination with an antiplatelet agent. Clopidogrel is the most frequently used antiplatelet drug, selected in more than 90% of cases in clinical studies.
In patients with a combination of acute coronary syndrome (ACS) and AF, therapy requires a special approach: it is necessary to balance stroke prevention and the reduction of stent thrombosis risk while minimizing the likelihood of bleeding. To reduce bleeding risk while maintaining the desired antithrombotic effect, treatment should be individualized based on the balance between bleeding and thrombotic risks for each patient.
Variability in response to P2Y12 receptor blockers remains a key challenge. Approximately 20–40% of patients demonstrate a reduced response to therapy with P2Y12 receptor blockers, and the bleeding risk reaches 11%. A significant factor contributing to variability is genetic predisposition, particularly the presence of CYP2C19 gene polymorphisms, which regulate clopidogrel metabolism.
Ensuring the safety and efficacy of antithrombotic therapy in patients with AF after PCI remains an important clinical task. Therefore, the selection of safer and more effective regimens is the subject of current research and discussion, making this topic highly relevant.
This study was conducted under grant funding for scientific start-up projects by the academic staff of the National Academic Organization “Semey Medical University” for 2022–2025: “Optimization of Antithrombotic Therapy in Patients with Acute Coronary Syndrome after Percutaneous Coronary Intervention with Comorbid Conditions.” With financial support from the Committee of Science, Ministry of Science and Higher

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Aim of the Study:

To improve the prognosis of adverse cardiovascular events (ACVE) in patients with acute coronary syndrome (ACS) and atrial fibrillation (AF) after percutaneous coronary intervention (PCI) based on a comprehensive assessment of clinical and laboratory data, platelet function, and genotyping.

Objectives:

1. Determine the frequency of cardiovascular events and the clinical and laboratory factors associated with their development in patients with ACS and AF after PCI.
2. Identify residual platelet reactivity (RPR), the prevalence of CYP2C19 polymorphisms (CYP2C19*2 [G681A], CYP2C19*3 [Trp212Ter]) in the study population, and their correlations.
3. Develop prognostic risk scales for ischemic and hemorrhagic complications in patients with ACS and AF after PCI, incorporating platelet function testing and pharmacogenetic analysis.
4. Develop an algorithm for a personalized approach to antithrombotic therapy in patients with ACS and AF after PCI.

Object and Subject of the Study:

Object: Patients with ACS and AF who underwent PCI.
Subject: Clinical and laboratory parameters, platelet function indices, and genetic factors influencing the development of adverse cardiovascular events (ischemic and hemorrhagic), as well as the effectiveness of a personalized approach to antithrombotic therapy in this patient group.

Methods:

In patients with ACS and AF after PCI, residual platelet reactivity (RPR) and the area under the platelet aggregation curve (AUC) were measured using the AggRAM aggregometer (Helena Biosciences). Carriage of CYP2C19 polymorphisms (CYP2C19*2 [G681A], CYP2C19*3 [Trp212Ter]) was determined by real-time polymerase chain reaction (PCR) at the certified PCR laboratory "TreeGene" (Almaty). Using data from the Register of Attached Population, a comparative survival analysis was performed with a 12-month follow-up period. Statistical analysis was conducted in Excel, SPSS, and STATTECH with calculation of tests for differences and the construction of prognostic models.

Scientific Novelty:

• For the first time, predictors of adverse cardiovascular events in patients with ACS and AF who underwent PCI were established. Certificate of Authorship No. 37342 (Appendix A).

• For the first time, the prevalence of CYP2C19 polymorphisms (CYP2C19*2 [G681A], CYP2C19*3 [Trp212Ter]) in patients with ACS and AF after PCI and their correlations

with residual platelet reactivity while on clopidogrel were determined. Certificate of Authorship No. 56877 (Appendix A).
• For the first time, prognostic scales were created to assess the risk of ischemic and hemorrhagic complications in patients with ACS and AF after PCI. Implementation Act (Appendix B).
• For the first time, an algorithm for a personalized approach to antithrombotic therapy in patients with ACS and AF after PCI was developed based on an integrated assessment of clinical and laboratory parameters, platelet function testing, and pharmacogenetic analysis of CYP2C19 allelic variants (CYP2C19*2 [G681A], CYP2C19*3 [Trp212Ter]). Implementation Act (Appendix B).

Practical Significance:

1. An algorithm for a personalized approach to antithrombotic therapy in patients with ACS and AF after PCI has been developed and implemented, based on comprehensive clinical-laboratory assessment, platelet function testing, and pharmacogenetic analysis of CYP2C19 polymorphisms (CYP2C19*2 [G681A], CYP2C19*3 [Trp212Ter]). Implementation Act (Appendix B).
2. The algorithm was used to escalate and de-escalate antithrombotic therapy, enabling individualized selection of intensity and duration according to the level of residual platelet reactivity and the patient's genetic profile. Implementation Act (Appendix B).
3. The prognostic risk scales for ischemic and hemorrhagic complications allow prediction of treatment outcomes and dynamic assessment of the efficacy and safety of therapy over a 12-month follow-up. Implementation Act (Appendix B).
4. The results have been implemented in the clinical practice of the Cardiology Departments of the University Hospital of NAO "SMU" and the Semey Emergency Medical Care Hospital. Implementation Act (Appendix B).

Key Propositions Submitted for Defense:

1. In patients with ACS and AF after PCI, clinical and laboratory predictors of adverse cardiovascular events were identified.
2. High residual platelet reactivity on clopidogrel is significantly associated with carriage of CYP2C19*2 (G681A) and CYP2C19*3 (Trp212Ter) polymorphisms.
3. The developed prognostic scales, incorporating platelet function testing and pharmacogenetic analysis, enable assessment of the risk of ischemic and hemorrhagic complications in patients with ACS and AF after PCI and personalization of therapy.
4. Use of the algorithm for a personalized antithrombotic approach is associated with a reduction in the frequency of adverse cardiovascular events in patients with ACS and AF after PCI.

Conclusions:

1. The frequency of adverse cardiovascular events in patients with ACS and AF after PCI was 40.2%, including 25.0% ischemic and 15.2% hemorrhagic complications. Factors associated with ischemic events: prior myocardial infarction (OR 0.158; 95% CI 0.052–0.477; $p = 0.001$), higher ProBNP (OR 1.00; 95% CI 1.00–1.00; $p = 0.003$), lower left ventricular ejection fraction (LVEF) (OR 0.89; 95% CI 0.84–0.95; $p < 0.001$), reduced

glomerular filtration rate (eGFR) (OR 0.893; 95% CI 0.837–0.952; p < 0.001), and higher platelet count (OR 1.013; 95% CI 1.004–1.021; p = 0.003). Factors associated with hemorrhagic complications: male sex (OR 8.13; 95% CI 1.01–65.33; p = 0.030), active smoking (OR 4.44; 95% CI 1.36–14.50; p = 0.020), presence of anemia (OR 0.96; 95% CI 0.93–0.99; p = 0.039), anticoagulant use (OR 2.52; 95% CI 1.30–4.87; p = 0.007), and elevated INR (OR 3.10; 95% CI 1.25–7.68; p = 0.016).

2. Carriage of CYP2C19*2 and CYP2C19*3 polymorphisms in patients with ACS and AF was 34.2%. High residual platelet reactivity while on clopidogrel was significantly associated with CYP2C19*1/*2 and CYP2C19*2/*2 genotypes (p < 0.001).

3. Independent predictors of adverse events during dual antithrombotic therapy including clopidogrel were:

• Ischemic events: lower LVEF (OR 0.814; 95% CI 0.684–0.943; p = 0.001), higher creatinine (OR 0.741; 95% CI 0.569–0.914; p = 0.014), higher platelet count (OR 0.876; 95% CI 0.746–1.000; p < 0.001), high residual platelet reactivity (OR 1.17; 95% CI 1.08–1.26; p < 0.001), increased aggregation AUC (OR 1.05; 95% CI 1.02–1.08; p < 0.001), elevated D-dimer (OR 0.770; 95% CI 0.595–0.944; p = 0.006), and CYP2C19 polymorphism carriage (OR 6.03; 95% CI 2.12–17.17; p = 0.001).

• Hemorrhagic complications: lower hemoglobin (OR 0.880; 95% CI 0.764–0.997; p < 0.001), lower platelet count (OR 0.793; 95% CI 0.649–0.937; p = 0.001), reduced eGFR by CKD-EPI (OR 0.737; 95% CI 0.623–0.851; p = 0.010), low residual platelet reactivity (OR 0.919; 95% CI 0.768–1.000; p < 0.001), decreased aggregation AUC (OR 0.906; 95% CI 0.789–1.000; p < 0.001), and reduced LVEF (OR 0.704; 95% CI 0.589–0.818; p = 0.027).

4. Application of the personalized antithrombotic therapy algorithm—based on integrated assessment of clinical risk factors, residual platelet reactivity, and patients' genetic profiles—was associated with a lower frequency of adverse clinical events and no deaths over a 12-month follow-up (p < 0.001).

Practical Recommendations:

1. Use the prognostic scales incorporating platelet function testing and pharmacogenetic analysis to stratify patients with ACS and AF by risk of ischemic and hemorrhagic complications and to conduct dynamic monitoring of antithrombotic therapy efficacy and safety during the 12 months after PCI.

2. Use the developed algorithm to escalate or de-escalate the intensity and duration of antithrombotic regimens depending on residual platelet reactivity and the CYP2C19 genetic profile.

3. Incorporate assessment of residual platelet reactivity and pharmacogenetic testing into standard care pathways for patients with ACS and AF after PCI to optimize therapy and reduce adverse cardiovascular outcomes.