Clinical Research Protocol

(Version: V1.0, Date: August 1, 2025)

I. Title: Risk Prediction Model for Ischemic Stroke in Patients with Acute Myocardial Infarction Without Atrial Fibrillation

II. Background:

Patients with acute myocardial infarction (AMI) who do not have atrial fibrillation (AF) still exhibit a significantly higher risk of ischemic stroke compared to the general population. A multicenter retrospective study by Ferreira et al. found that among patients with reduced left ventricular ejection fraction (LVEF ≤ 35%) following AMI, the incidence of stroke was 5.97% in those with AF and 2.9% in those without AF over a median follow-up of 1.9 years. However, this study had important limitations: it focused on a restricted population (only those with LVEF ≤ 35%), making its findings unsuitable for extrapolation to the full range of LVEF; it did not distinguish between ischemic stroke and cerebral hemorrhage (despite the latter accounting for less than 10%); and it underestimated the annual stroke risk in non-AF patients, which remained as high as 1.5%, significantly higher than in healthy individuals.

Ischemic stroke dramatically worsens the prognosis of AMI patients. Evidence from clinical studies shows that the in-hospital mortality rate among patients with concomitant stroke is as high as 46.2%, compared to 6.3% in those without stroke, with a hazard ratio of 7.3. Even when stroke does not lead to death, it significantly reduces quality of life and increases public health expenditures.

The pathophysiology of ischemic stroke in non-AF AMI patients is complex and involves four major pathways:

1. Cardiogenic embolism: Detachment of left ventricular mural thrombi or spontaneous echo contrast (SEC) in the left atrium;

2. Arterio-arterial embolism: Thrombosis resulting from rupture of atherosclerotic plaques in cerebral arteries;

3. Paradoxical embolism: Deep vein thrombosis in the lower extremities passing through a patent foramen ovale;

4. Hypercoagulable state: Systemic inflammation leading to endothelial dysfunction.

For patients with sinus rhythm (excluding AF), anticoagulation combined with antiplatelet therapy can also provide significant benefits. The COMPASS trial demonstrated that in patients with stable atherosclerosis (including 22% with a history of MI), rivaroxaban (2.5 mg twice daily) combined with aspirin significantly reduced the risk of the composite endpoint of cardiovascular death, MI, or ischemic stroke by 24% (HR 0.76; 95% CI 0.66–0.86; $P < 0.001$), with a 40% reduction in the risk of ischemic stroke. However, this regimen also increased the risk of major bleeding by 70%, highlighting the necessity of precise risk stratification.

Current evidence indicates that advanced age, heart failure, left atrial enlargement, renal insufficiency, history of stroke, hypertension, and diabetes are independent predictors of stroke in non-AF AMI patients. However, current clinical practice faces a critical gap: although stroke prediction models for AF patients (such as CHA_2DS_2-VASc) are well established, there is no specific tool for predicting ischemic stroke in non-AF AMI patients. Non-AF AMI accounts for more than 85% of all AMI cases, and ischemic stroke in these patients constitutes more than 75% of all ischemic strokes in AMI

patients. This lack leads to under-recognition of high-risk patients and challenges in decision-making regarding anticoagulant therapy, underscoring the need to develop a dedicated predictive model for precise intervention.

Innovation and Rationale:

Based on the "multiple pathways of thrombosis after MI," we propose to integrate the following novel predictive factors:

Imaging features: Left atrial diameter

Biomarkers: D-dimer, LP(a)

Treatment parameters: Duration of dual antiplatelet therapy

III. Study Objectives:

To construct and validate a specialized risk prediction model for ischemic stroke in non-AF AMI patients (CAMI-Stroke Score), with the following goals:

1. Screening for high-risk patients for in-hospital stroke (positive predictive value > 85%)

2. Stratifying stroke risk at 3 months and 1 year post-discharge (C-index target > 0.80)

IV. Study Content:

A retrospective analysis of hospital records of AMI patients admitted between January 1, 2014, and December 31, 2023, will be conducted. Cases meeting the diagnostic criteria for AMI will be identified, and those with AF will be excluded. Baseline data, clinical information, and follow-up data will be collected. After retrieving and verifying the original medical records, a total of 3,832 AMI patients with completed follow-up will be analyzed.

Model Development:

Predictive variables: Significant factors will be selected using LASSO regression, followed by multivariate Cox regression modeling.

Validation methods: 70% of the sample will be used for training, and 30% for internal validation. Discrimination (AUC, C-index) and calibration (Hosmer-Lemeshow test) will be evaluated. Decision curve analysis (DCA) and clinical net benefit analysis will be performed. Key performance metrics will include uncertainty (e.g., confidence intervals). If public database data becomes available, external validation may be considered. The development of the model and feature selection must take into account the feasibility of clinical implementation and the availability of data. The impact of the model on patient outcomes (e.g., mortality, morbidity, quality of life) and healthcare costs in real-world clinical settings will be assessed. The goal is to establish a model development ecosystem that is data-driven, methodologically rigorous, clinically relevant, ethically sound, and continuously improved.

V. Quality Control and Assurance:

This study is a retrospective study. All patient identity information will be anonymized to protect privacy. To prevent the leakage of patient identity information, electronic medical records should be closed and screen protected when leaving the workstation. Medical records will be handled in accordance with the "Medical Records Management Regulations." When using patient imaging data, all patient identity information will be removed. During the model validation phase, the predictive performance across subgroups (e.g., age $\geq$ 75 years, eGFR $<$ 60 ml/min) will be analyzed. Fairness

indicators (e.g., equal opportunity difference) will be used to assess bias, and the algorithm will be adjusted to reduce discrimination risk.

Data Security Provisions:

Storage location: Encrypted server within the hospital network (physically isolated area)

Access control: Dual authentication (employee ID + dynamic password) + role-based access (researchers can only export aggregated data)

Data transmission: Secure SSL-VPN transmission; prohibited to use WeChat or email to transfer data

Device management: Data loss prevention (DLP) system installed on research-specific computers; USB ports disabled

VI. Ethical Considerations:

This study complies with Article 39 of the "Ethical Review Measures for Biomedical Research Involving Human Subjects" (2023):

(1) The study uses existing medical records and cannot identify specific individuals;

(2) The study does not involve the secondary use of sensitive personal information;

(3) The study protocol has been approved by the Ethics Committee.

The study only uses biochemical indicator concentrations and does not perform gene sequencing or genetic analysis, complying with Article 21 of the "Regulations on the Administration of Human Genetic Resources." The study protocol and related materials must be submitted to the Medical Ethics Committee for approval before the study begins. Researchers must submit annual reports to the Ethics Committee. Upon completion or termination of the study, researchers must notify the Ethics Committee

in writing. Any changes during the study must be reported to the Ethics Committee, and such changes cannot be implemented without prior approval, unless they are necessary to eliminate an obvious and direct risk to participants, in which case the Ethics Committee must be notified immediately.

VII. Conflict of Interest Statement:

The researchers declare no commercial conflicts of interest. This study has no funding support.

VIII. Additional Clauses:

This model is intended solely as a research tool and is not to be used for clinical decision-making. If the model is applied in clinical practice in the future, prospective validation and the development of informed consent procedures for patients and physicians will be required.

IX. Study Timeline:

August 1, 2025 – December 31, 2025

X. References:

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