Official Title: Efficacy of Transcutaneous Auricular Vagus Nerve Stimulation on Alleviating Major Depressive Disorder in Patients With Acute Coronary Syndrome After Percutaneous Coronary Intervention:A Prospective, Double-Blind,Randomized Controlled Study

NCT Number:

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1. Introduction

Acute Coronary Syndrome (ACS) is a clinical syndrome spectrum pathologically based on atherosclerotic plaque rupture or erosion, with subsequent complete or incomplete occlusive thrombus formation. It includes unstable angina and acute ST-segment elevation or non-ST-segment elevation myocardial infarction, representing a severe manifestation of coronary artery disease (CAD) and a leading cause of annual cardiovascular morbidity and mortality[1]. The incidence and mortality rates of ACS are substantial, with nearly half of CAD-related deaths occurring post-ACS, posing a severe threat to patients' quality of life[2].

Percutaneous coronary intervention (PCI) is a primary treatment for ACS. However, as an invasive procedure, PCI carries inherent procedural risks. Coupled with patients' lack of understanding, excessive concerns about postoperative complications, stent longevity, drug side effects, and treatment costs, patients diagnosed with ACS face a series of negative physical and mental health risks following PCI. A meta-analysis on anxiety and depression in post-PCI patients indicated[3] that varying degrees of anxiety and depression are prevalent, with rates ranging from 20% to 82%. Furthermore, these mental health issues, prone to occur after PCI, have been confirmed to significantly impact treatment adherence and prognosis[4]. Depression is estimated to be the second leading cause of global disability[5], and the mortality risk is substantially increased in patients with depression following an ACS event[6]. The onset, progression, and outcomes of cardiovascular disease are closely linked to psychological factors, characterizing it as a psychosomatic condition. Ample evidence indicates that psychological factors can promote the development of cardiovascular disease, while anti-anxiety and antidepressant treatments can significantly improve the prognosis of patients with cardiovascular disease[7].

The incidence of anxiety post-PCI ranges from 25% to 37%[8], and the prevalence of depression is as high as 20% to 40%. While PCI rapidly and effectively achieves vascular recanalization and reperfusion, the requirement for lifelong medication post-procedure imposes a substantial psychological and economic burden on patients and

society. Gu et al.[9] conducted Hospital Anxiety and Depression Scale (HADS) questionnaires on 170 patients one day before and one day after PCI. They found that on the day before PCI, 34.7% experienced anxiety and 23.5% experienced depression; whereas on the day after PCI, 54.7% experienced anxiety and 44.7% experienced depression. Concerns regarding surgical complications, quality of care, postoperative decline in cardiac function, and procedural failure contributed to a marked increase in anxiety and depression prevalence post-PCI. Most clinicians focus solely on resolving coronary obstruction, often overlooking patients' emotional disorders. However, patients with anxiety and depression frequently exhibit unhealthy lifestyles and poor medication adherence, leading to unfavorable prognoses. Kala et al.[10] analyzed the one-year rehospitalization rate and its influencing factors in 145 post-PCI patients, finding that the rate was associated with the presence of depressive symptoms. Li et al.[8] followed 303 PCI patients for one year to observe the incidence of major adverse cardiovascular events (MACE, e.g., new non-fatal myocardial infarction, stent restenosis, heart failure, arrhythmia, death). They found that the risk of MACE in anxious patients was 3.742 times that of non-anxious patients, and in depressed patients was 3.087 times that of non-depressed patients. Moreover, the risk for patients with both anxiety and depression was 7.303 times that of patients without these conditions, indicating that anxiety and depression are predictors of poor prognosis in CAD patients after stent implantation. Therefore, routine assessment of anxiety and depression in PCI patients and active measures to improve negative emotions are warranted in clinical practice to enhance patient outcomes.

Antidepressant medications are considered first-line treatment for depression. However, studies have found that one-third to one-half of patients do not respond to multiple antidepressants[11]. A response typically requires at least 4 weeks, and side effects such as nausea, cardiovascular issues, sexual dysfunction, and headaches are common, leading to low medication adherence[12]. Cognitive Behavioral Therapy (CBT) is a major psychotherapy, but its complexity and cost hinder accessibility for low-income patients with depression[13]. Thus, despite urgent need, current treatments for major depression remain far from satisfactory.

Vagus Nerve Stimulation (VNS) is an FDA-approved somatic therapy for treatment-resistant depression (TRD) that produces clinically significant antidepressant effects[14]. However, despite its efficacy, surgical risks, high procedural costs ($30,000 - $50,000), and potential side effects limit its appeal and result in low clinical utilization[15]. To overcome these barriers associated with invasive VNS (iVNS), a non-invasive transcutaneous auricular VNS (taVNS) method has been developed and is garnering increasing attention. Anatomical studies indicate that the ear is the only location on the human body surface with afferent vagus nerve distribution[16]. According to the "bottom-up" mechanism of the central nervous system, electrical stimulation propagation may follow a reverse pathway from peripheral nerves to the brainstem and central structures[17]. Therefore, direct stimulation of afferent nerve fibers on the ear should produce effects similar to classical VNS in alleviating depressive symptoms, without the burden of surgical intervention[18]. The first study on taVNS for depression was conducted in 2009. Since then, a series of clinical studies have demonstrated that taVNS can effectively improve depressive symptoms[19-21]. However, research on taVNS for treating depression in ACS patients after PCI is limited. We will employ a randomized controlled clinical trial to investigate the antidepressant effect of taVNS in post-PCI patients with moderate or severe depression.

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2. Objectives

2.1 Study Aims

Aim 1: To compare the improvement in depression, anxiety, and quality of life between patients receiving transcutaneous auricular vagus nerve stimulation or sham stimulation using a randomized controlled design.

Aim 2: To compare the improvement in multiple physiological indicators between patients receiving transcutaneous auricular vagus nerve stimulation or sham stimulation using a randomized controlled design.

2.2 Study Endpoints (or Evaluation Metrics)

2.2.1 Primary Endpoint (or Primary Evaluation Metric) and Definition

Hamilton Depression Rating Scale (HAMD) score at Week 8: The 17-item HAMD is convenient, has clear criteria, is easy to master, and can be used to assess depressive symptoms in various conditions including depression, bipolar disorder, and neurosis, being particularly suitable for major depressive disorder.

Scoring criteria:

No depressive symptoms: Total score ≤7； Mild depression: Total score ≥8 and ≤17； Moderate depression: Total score >17 and ≤24； Severe depression: Total score >24.

2.2.2 Secondary Endpoints (or Secondary Evaluation Metrics) and Definitions

1. Hamilton Anxiety Rating Scale (HAMA) score during follow-up: The total score effectively reflects the severity of anxiety symptoms and can be used to evaluate the severity of anxiety in patients with anxiety and depressive disorders and to assess the effects of various drug and psychological interventions.

According to data from the Chinese Scale Collaboration Group:Total score ≥29: Possible severe anxiety;Total score ≥21: Definite significant anxiety;Total score ≥14: Definite anxiety;Total score >7: Possible anxiety;Total score ≤7: No anxiety symptoms.

2. HAMD response rate: Reduction in HAMD-17 score ≥50%.

3. HAMD remission rate: Post-treatment HAMD-17 score ≤7.

4. Beck Depression Inventory (BDI) score: A tool specifically designed to assess depression severity. The entire questionnaire comprises 21 groups of items, each with 4 statements preceded by corresponding numbers as grade scores.

Scoring criteria: 0-4: (Essentially) no depressive symptoms;5-7: Mild depression;8-15: Moderate depression;≥16: Severe depression.

5. Generalized Anxiety Disorder 7-item (GAD-7) score: The GAD-7 consists of 7 items aiming to understand how often the respondent has been bothered by 7 problems including feeling nervous or anxious over the past 2 weeks.

Scoring rules: Each item scores 0-3, total score 21.0-4: No generalized anxiety;5-9: Mild generalized anxiety;10-14: Moderate generalized anxiety;15-21: Severe generalized anxiety

6. PTSD Checklist-Civilian Version (PCL-C) score: Developed in 1994 by the Behavioral Science Division of the US National Center for PTSD, translated into Chinese by Professors Jiang Chao and Zhang Jie in 2003. The scale includes 17 items categorized into 3 characteristic symptom clusters: re-experiencing (5 items), avoidance (7 items), and hyperarousal (5 items). Each item uses a Likert 5-point scale from 1 (not at all) to 5 (extremely). Total score range 17-85, with higher scores indicating a higher likelihood of PTSD.

Test results: 17-37: No significant PTSD symptoms;38-49: Some degree of PTSD symptoms; 50-85: Significant PTSD symptoms, possible PTSD diagnosis

7. Quality of Life Scale (SF-36) score: The 36-Item Short Form Health Survey (SF-36) is widely used, covering 8 domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Patients are scored on quality of life to assess changes in physical, energetic, emotional, and mental health, using a percentage system. Higher scores indicate better function and quality of life.

8. Heart Rate Variability (HRV): A 10-minute resting ECG is recorded. HRV analysis methods mainly include time-domain, frequency-domain, and non-linear methods.

Key time-domain parameters include:

SDNN (Standard Deviation of all Normal-to-Normal [NN] intervals): Reflects overall autonomic nervous system activity, primarily sympathetic tone. Normal value (141±39) ms; lower values suggest increased sympathetic activity and reduced adaptability.

- SDANN (Standard Deviation of the Averages of NN intervals in all 5-minute segments): Evaluates sympathetic nervous system activity. Normal value (127±35) ms.
- rMSSD (Root Mean Square of Successive Differences between adjacent NN intervals): Reflects parasympathetic (vagal) activity. Normal value (27±12) ms.
- pNN50 (Percentage of adjacent NN intervals differing by >50 ms): Lower values indicate lower parasympathetic activity.

Frequency-domain indicators include:

- Total Power (TP) (≤0.4 Hz): Reflects overall autonomic nervous system activity and regulatory capacity.
- High Frequency (HF) (0.15–0.40 Hz): A good indicator of parasympathetic (vagal) function, influenced by respiration depth.
- Low Frequency (LF) (0.04–0.15 Hz): Controlled by both sympathetic and parasympathetic systems; some studies consider it influenced by sympathetic activity, serving as a reliable indicator of cardiac sympathetic activity, affected by baroreflexes.
- Very Low Frequency (VLF) (0.003–0.040 Hz)
- Ultra-Low Frequency (ULF) (≤0.003 Hz)
- LF/HF ratio: Reflects the balance of sympathetic-parasympathetic tone.

9. Echocardiography: Includes left ventricular anterior-posterior diameter (diastolic/systolic) and left ventricular ejection fraction (LVEF).

10. Venous blood biomarkers: Levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), high-sensitivity C-reactive protein (hs-CRP).

11. Incidence of Major Adverse Cardiovascular Events (MACE): Including death, myocardial infarction, and target vessel revascularization (definitions based on Academic Research Consortium [ARC] criteria).

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3. Study Design

3.1 Overall Study Design

An investigator-initiated, single-center, prospective, randomized, double-blind, parallel-group controlled study.

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4. Study Population

4.1 Inclusion Criteria

- Age ≥18 years;
- Meets diagnostic criteria for ACS;

- 14 days to 12 months post-successful PCI, with stable vital signs;
- Meets Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) diagnostic criteria for Major Depressive Disorder;
- HAMD-17 score ≥7 and <24, with HAMA score < HAMD score;
- After full disclosure of condition, the patient or legal representative refuses psychiatric consultation and declines antidepressant medication or psychotherapy;
- Patient or legal representative voluntarily participates in the study and provides written informed consent.

4.2 Exclusion Criteria

- Severe heart failure (NYHA class ≥III);
- Uncontrolled hypertension (≥180/110 mmHg);
- First-degree atrioventricular block on awake ECG (PR interval ≥0.20s), or occurrence of Mobitz type II second-degree or third-degree AV block at any time;
- 24-hour average heart rate ≤50 beats per minute, RR interval ≥3s, or history of syncope unrelated to the current ACS;
- Patients on dialysis;
- History of renal denervation or vagal ganglion ablation therapy;
- Life expectancy less than 4 months;
- Pre-existing clinical diagnosis of other severe psychiatric disorders prior to PCI, including schizophrenia, severe intellectual disability, substance abuse;
- Patient currently taking antipsychotic medications;
- High suicide risk;
- Pregnant or lactating women;
- Left ear disease, acute exacerbation of asthma or chronic obstructive pulmonary disease, or other conditions precluding taVNS treatment;
- Presence of cardiac pacemaker, implantable cardioverter-defibrillator (ICD), or other implantable stimulators (e.g., VNS or deep brain stimulators).

4.3 Withdrawal Criteria

Desire to pursue other treatments or voluntary withdrawal from the trial without specific reason.

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5. Study Treatment Groups

- Group A (Active Stimulation Group): Patients receive standard ACS treatment plus active transcutaneous auricular vagus nerve stimulation (taVNS), twice daily for 20 minutes each session.
- Group B (Sham Stimulation Group): Patients receive standard ACS treatment plus sham taVNS treatment, twice daily for 20 minutes each session.

5.1 Randomization

5.1.1 Method for Generating Random Allocation Sequence

Stratified block randomization will be used: Eligible patients will be randomly assigned to Group A or B in a 1:1 ratio. Using R software, stratification will be based on age (two levels: 18-60 years, >60 years) and gender (two levels: male, female), resulting in 4 strata. Within each stratum, patients will undergo randomization with varying block sizes. The output will determine the stimulation device assigned to each patient.

5.1.2 Allocation Concealment

1. Personnel generating and safeguarding the random allocation sequence will not be involved in the trial. Research personnel will determine subject eligibility.

2. A central telephone randomization system will be used for allocation concealment. Once research personnel confirm a patient is eligible, they will notify the central randomization system (holder of the sequence) via telephone. The central system will record the subject's name and ID, then inform the researcher of the subject's group assignment.

5.2 Blinding and Unblinding

This is a double-blind study. Patients, research personnel, and data analysts will be blinded.

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6. Study Procedures

6.1 Study Intervention Implementation Steps

1. For outpatients or inpatients who are 2 weeks to 12 months post-ACS PCI, a psychiatrist will conduct assessments using DSM-V, HAMD, and HAMA scales. Patients meeting criteria for mild to moderate depression will be advised to receive appropriate treatment. If they refuse and meet inclusion/exclusion criteria, they will sign informed consent, enroll in the clinical trial, and baseline data will be collected.

2. Device Usage Method

Eligible patients will receive transcutaneous auricular non-invasive vagus nerve stimulation while awake. The electrode and the patient's left ear target area will first be disinfected with 75% alcohol. An abrasive gel will then be applied to the left concha cymba and tragus area for gentle abrasion, wiped off, and the area disinfected again with alcohol. Conductive gel will be applied to the electrode output points. The electrode will be placed on the patient's left ear, ensuring the output points are positioned on the left tragus. Pulses will be delivered via the Xidian Keyue brand (Product No.: BS-TVNS600) vagus nerve stimulator. The stimulation current will be gradually increased to the maximum intensity tolerable by the patient, defined as the threshold intensity.

Active Stimulation Group: Stimulation at threshold intensity, with parameters: pulse frequency 20 Hz, pulse width 250 μs, pulse current 0.5-3 mA. Stimulation cycle: 30 seconds ON, 30 seconds OFF.

Sham Stimulation Group: Device, parameter adjustment, and placement identical to the active group. The stimulator is programmed to deliver stimulation only for the first 5 seconds of each session, with no subsequent stimulation.

Both groups will undergo electrical stimulation twice daily for 20 minutes each session, for a total treatment duration of 8 weeks.

All patients will be trained on how to turn the stimulator on/off, attach the electrode to the ear and position it, and increase the intensity. All subsequent operations will be performed by the patient at home. Patients can obtain assistance via telephone

or site visits if they have questions. Each patient will be given a diary card to record usage date, duration, adverse reactions, and suggestions. Patients are required to complete daily entries, which will be checked during assessment visits.

Both groups will receive guidance on medication and lifestyle intervention during follow-up (including CAD knowledge education, diet/exercise, sleep guidance, smoking cessation/alcohol limitation, and weight control).

6.2 Concomitant Treatment and Follow-up Visits

All enrolled patients will receive standard post-PCI medication and strict secondary prevention for coronary artery disease.

Follow-up visits will occur at 4, 8, 12, and 16 weeks post-randomization. Follow-up content includes: HAMA, HAMD, BDI, GAD-7, PCL-C, and SF-36 scale assessments; HRV measurement; echocardiography; venous blood tests; assessment of smoking/alcohol cessation and lifestyle improvement; record of follow-up visits (time, location, results); presence of angina or heart failure-related symptoms; occurrence of MACE (time, management, outcome); adverse reactions.

6.3 Patient Adherence and Withdrawal

Adherence: A trusting relationship will be established to ultimately improve subject adherence.

Withdrawal: Subjects found during follow-up to have poor treatment adherence, including self-discontinuation of device use, heavy smoking, and severely poor lifestyle/dietary habits; development of other serious new illnesses post-procedure that may affect study endpoints; loss to follow-up.

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7. Evaluations

7.1 Efficacy Evaluation

HAMA score, HAMD response rate, HAMD remission rate, BDI score, GAD-7 score, PCL-C score, SF-36 score, heart rate variability parameters, echocardiography parameters, venous blood biomarkers, and incidence of MACE.

7.2 Safety Evaluation

7.2.1 Baseline Signs and Symptoms

Heart rate, respiratory rate, blood pressure, body temperature, chest tightness, chest pain, shortness of breath, wheezing, dyspnea.

7.2.2 Auxiliary Examination Safety Assessment

Myocardial injury markers, NT-proBNP, coagulation panel, complete blood count, echocardiography.

7.2.3 Physical Examination and Vital Signs

Consciousness, neurological reflexes, breath sounds, heart sounds, skin and mucous membrane condition.

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8. Adverse Event Reporting

8.1 Definition of Adverse Events

8.1.1 Definitions

- Adverse Event (AE): Any untoward medical occurrence in a subject administered an investigational treatment, which may manifest as signs, symptoms, disease, or laboratory abnormalities, but does not necessarily have a causal relationship with the treatment.
- Serious Adverse Event (SAE): Any AE occurring in a subject that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or other medically important events.

8.1.2 Severity

- Mild: Tolerable by the subject, does not affect prognosis, does not require special treatment, no impact on recovery.
- Moderate: Causes discomfort to the subject, requires special treatment, has a direct impact on recovery.
- Severe: Life-threatening, causing death or disability, requires immediate emergency treatment.

8.2 Recording and Reporting Pathway for Adverse Events

Any clinical AEs occurring during treatment will be recorded in detail in the source documents, including time of onset, clinical manifestations, management, duration, outcome, and relationship to the trial. For abnormal laboratory findings, follow-up will continue until results return to normal, baseline levels, or are determined unrelated to the investigational treatment. SAEs will be documented on an SAE form and reported to the clinical research center within 24 hours.

8.3 Risk Prevention and Management

The clinical trial application will be submitted according to regulatory requirements, and the trial will commence only after obtaining approval. Scientific rigor in trial design and strict adherence to inclusion/exclusion criteria will minimize risks. Patient guidance will be strengthened to reduce risks from improper operation. Reasonable safety indicators will be established to lower risk occurrence. Each center will designate a researcher familiar with taVNS procedures as a quality control supervisor responsible for managing risks during treatment.

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9. Statistical Analysis

9.1 Sample Size Determination

This is a randomized controlled trial. Significance level (α) is set at 0.05, and power (1-β) at 0.80. Based on literature, the effect size for taVNS alleviating depression is approximately 57%. Using PASS software, the calculated sample size per group is n1=n2=56. Considering a 10% dropout/loss-to-follow-up rate and the need for stratification by age and gender, the minimum sample size per group is determined to be 60, resulting in a total sample size of 120.

9.2 Analysis Populations

9.2.1 Full Analysis Set (FAS)

Based on the Intent-to-Treat (ITT) principle, includes all randomized subjects who received at least one treatment session from either the experimental or control group.

9.2.2 Per Protocol Set (PPS)

Includes all subjects who completed the treatment regimen as specified in the protocol without major protocol violations. The exact definition of major protocol violations will be finalized during data review and may include (but is not limited to): failure to meet inclusion criteria, receipt of interfering treatments post-enrollment, poor adherence, visits outside specified time windows.

9.3 Efficacy Analysis and Statistical Methods

9.3.1 Analysis of Primary Endpoint

Comparison of HAMD scores between groups will be performed using t-tests or non-parametric tests.

9.3.2 Analysis of Secondary Endpoints

Comparisons of HAMA scores, BDI scores, GAD-7 scores, PCL-C scores, SF-36 scores, HRV parameters, echocardiography parameters, and blood biomarkers between groups will be performed using t-tests or non-parametric tests. Comparison of HAMA response rates, remission rates, and MACE incidence between groups will be performed using chi-square tests.

9.4 Safety Analysis and Statistical Methods

Statistical analysis will be performed using SPSS 26.0 software. Categorical data will be presented as counts and percentages. Normally distributed continuous data will be presented as mean ± standard deviation; non-normally distributed continuous data will be presented as median and interquartile range. Differences between groups for normally distributed continuous data and categorical data will be compared using independent samples t-tests and chi-square tests, respectively. Non-parametric tests will be used for non-normally distributed continuous data. Bayesian analysis will be employed to further explore the impact of different stimulation modalities on outcome prognosis. All statistical tests will be two-sided, with a P-value <0.05 considered statistically significant.

9.5 Interim Analysis

This study does not involve interim analysis.

9.6 Data Monitoring Committee

Given the low incidence and mild nature of adverse reactions associated with this trial, and its high safety profile, a Data Monitoring Committee will not be established.

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10. Data Collection and Management

10.1 Case Report Form / Electronic Data Record

Table 1: Baseline Characteristics

Gender(%)	Male Female	Age ,mean (SD), y	
Marriage status(%)	Single Married	BMI (kg/m$^{2)}$	
Residential Area(%)	Urban Rural	Living alone(%)	Yes No
Education(%)	Primary education Secondary School Technical secondary school or higher	Occupation(%)	Retired Unemployed Employed
cigarette(%)	Yes No	Participant consumes alcoholic beverages(%)	Yes No
Type of health insurance(%)	New rural cooperative medical scheme Urban Employee Basic Medical Insurance Uninsured	Previous PCI.or CABG events(%)	Yes No

Previous cardiac events(%)	Yes No	Diagnosticn (%)	NSTEMI UA STEMI
Previous PCI.or CABG events(%)	Yes No	Hypertension(%)	Yes No
Diabetes(%)	Yes No	Yes No	Yes No
hsCRP(mg/L)		Total implanted stents mean (SD), pc	
NYHA_Class(%)	Ⅰ Ⅱ	EF (%)	
IL-1 (pg/ml)		IL-6 (pg/ml)	
TNF-α (pg/ml)		LVD (d/s)	
HAMA		HAMD	
BDI		GAD-7	
SF-36		PCL-C	
HbA1c (%)		HRV (SDNN) (ms)	
HRV (SDANN) (ms)		HRV (RMSSD) (ms)	
HRV (TP) (Hz)		HRV (HF) (Hz)	

HRV (LF) (Hz)		HRV (VLF) (Hz)	
HRV (ULF) (Hz)		NT-proBNP (ng/mL)	
hsCRP(mg/L)			

Note: BMI: Body Mass Index; NSTEMI: Non-ST-Elevation Myocardial Infarction; UA: Unstable Angina; STEMI: ST-Elevation Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; LVEF: Left Ventricular Ejection Fraction; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; hs-CRP: High-sensitivity C-Reactive Protein; IL-1: Interleukin-1; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-alpha; LVD (d/s): Left Ventricular Diameter (diastolic/systolic); HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale; BDI: Beck Depression Inventory; GAD-7: Generalized Anxiety Disorder 7-item; SF-36: 36-Item Short Form Health Survey; PCL-C: PTSD Checklist-Civilian Version; HRV: Heart Rate Variability; HbA1c: Glycated Hemoglobin; SDNN: Standard Deviation of NN intervals; RMSSD: Root Mean Square of Successive Differences; TP: Total Power; HF: High Frequency; LF: Low Frequency; VLF: Very Low Frequency; ULF: Ultra-Low Frequency.*

10.2 Data Management

Data will be entered, saved, and managed using Excel software. Data entry will be performed by two individuals simultaneously to enhance accuracy. Data will be subject to access control and dual backup to prevent tampering or loss.

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11. Research Ethics

11.1 Ethics Committee Review

This protocol, written informed consent form, and any materials directly related to subjects must be submitted to the Ethics Committee. The study may commence formally only after written approval is obtained. The investigator must submit an annual progress report (if applicable) to the Ethics Committee at least yearly. The investigator must notify the Ethics Committee in writing upon study termination and/or completion. The investigator must promptly report all changes to the research work (e.g., protocol and/or informed consent form revisions) to the Ethics Committee and must not implement these changes prior to obtaining Ethics Committee approval, except for changes necessary to eliminate apparent and immediate risks to subjects. In such cases, the Ethics Committee will be notified.

11.2 Informed Consent

Subjects or their legal guardians will be provided with comprehensible information regarding the study's purpose, potential benefits, and risks. They will be informed that the study has been approved by the Ethics Committee and provided with a photo or copy of the approval letter. Sufficient time will be given for consideration. Subjects may not be enrolled until signed written informed consent is obtained. During participation, subjects will be provided with all updated versions of the informed consent form and written information. Informed consent documents will be retained as essential trial documentation.

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12. Confidentiality Measures

The results of this research may be published in medical journals, but patient information will be kept confidential in accordance with legal requirements. Patient personal information will not be disclosed unless required by relevant laws. Government regulatory authorities and the hospital Ethics Committee and its relevant personnel may access patient data as stipulated by regulations when necessary.

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