A Multi-center Prospective Cohort Study on the Assessment of Carotid Plaque Vulnerability and Prediction of Cardiovascular and Cerebrovascular Event Risks through Ultrasound Imaging

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1. Research Background

Cardio-cerebrovascular diseases, collectively referring to diseases of heart vessels and cerebral vessels, manifest as systemic vascular disorders in the heart and brain. They have become the leading cause of death worldwide, including cardiovascular diseases such as coronary heart disease (angina pectoris, myocardial infarction, sudden cardiac death) and cerebrovascular diseases such as stroke (cerebral thrombosis, cerebral infarction, cerebral hemorrhage). These cardio-cerebrovascular events are characterized by high morbidity, high disability rate, and high mortality, causing an increasing economic burden on society and residents. Due to the poor prognosis of such diseases, risk stratification and early prevention of cardio-cerebrovascular diseases are crucial for improving outcomes.

Atherosclerosis, the main pathological basis of cardio-cerebrovascular diseases, is a systemic disorder of the arteries that often affects multiple arterial beds throughout the body. Atherosclerosis is closely related to traditional cardio-cerebrovascular risk factors (such as hypertension, hyperlipidemia, diabetes, age, overweight, smoking, etc.) and is also considered a major risk factor for cardio-cerebrovascular events. The carotid artery, which is superficial and easy to access, has been used as a "window" for clinical observation of systemic atherosclerosis. Its degree of hardening can indirectly reflect the extent of coronary artery, cerebral artery, and peripheral artery hardening. At the same time, studies have shown that the greater the carotid artery burden, the higher the risk of cardio-cerebrovascular events, and vulnerable plaques in the carotid artery are independently associated with the occurrence of stroke and cardiovascular events. Vulnerable plaques refer to all dangerous plaques with a tendency to rupture, prone to thrombosis, or rapid progression. The diagnostic criteria for vulnerable plaques include: extensive infiltration of inflammatory cells; thin fibrous cap and large lipid necrotic core; neovascularization within the plaque; causing over 90% stenosis of the vessel; intraplaque hemorrhage, rupture of the fibrous cap on the plaque surface, and thrombus formation. The presence of any one of these five features is sufficient for diagnosis. However, due to the inability to

perform pathological component diagnosis in vivo, imaging techniques for the detection of carotid plaque components and assessment of plaque burden have become the primary means of evaluating plaque vulnerability in recent years. In 2018, guidelines from the American Society of Neuroradiology (ASNR), European Society of Cardiology (ESC), and European Society for Vascular Surgery (ESVS) also pointed out that imaging assessment of plaque components can serve as an indication for drug treatment and carotid surgery intervention.

Currently, imaging techniques for detecting carotid artery plaques mainly include: ultrasound imaging, high-resolution MRI enhanced imaging, CT enhanced imaging, optical coherence tomography, PET-CT imaging, etc. High-resolution MRI enhanced imaging can identify various components such as lipid necrotic cores and intraplaque hemorrhage within plaques, while CT enhanced imaging has high sensitivity to plaque calcification and lumen stenosis rate. Optical coherence tomography can also identify lipid necrotic cores and other components within plaques. However, due to insufficient spatial resolution, high cost, long duration, poor patient tolerance, flow void effects affecting inspection accuracy, or radiation, contrast agent allergies, MRI and CT imaging have not yet become routine screening methods. PET-CT imaging has a significant characterization and quantification effect on intraplaque inflammation, but due to high cost and radiation, it cannot become a clinically commonly used detection method. Optical coherence tomography, on the other hand, is an invasive intravascular imaging technique with poor tissue penetration and cannot fully display the contour of plaques, and is currently not used clinically.

Ultrasound examination remains the most commonly used method for screening carotid artery plaques. It has the advantages of convenient operation, good reproducibility, non-invasiveness, and no radiation, and has become an effective tool for assessing carotid vulnerable plaques. Conventional duplex ultrasound examination includes B-mode ultrasound and Doppler ultrasound imaging, which can provide information on plaque location, morphology, echogenicity, and carotid artery stenosis rate. Contrast-enhanced ultrasound (CEUS) can accurately assess plaque surface

ulceration and intraplaque neovascularization (IPN), which is currently the most direct indicator of evaluating plaque vulnerability by ultrasound. Its diagnostic performance shows good consistency with pathological results and provides accurate indicators of carotid artery stenosis rate. Three-dimensional ultrasound imaging can accurately display plaque volume and surface smoothness. Shear wave elastography (SWE) can obtain information on plaque hardness, thus indicating plaque stability. Currently, studies have explored the value of ultrasound in assessing carotid vulnerable plaques and predicting the risk of future cardio-cerebrovascular ischemic events. Clinical application of conventional duplex ultrasound to detect carotid IMT not only serves as an assessment indicator of the severity of atherosclerosis, but several large clinical studies have also shown that increased carotid IMT is associated with future strokes or cardiovascular events. In many clinical trials, IMT has also been used as an imaging indicator to guide clinical intervention. Meanwhile, the use of conventional duplex ultrasound to detect unstable plaque morphologies such as hypoechoic areas, surface ulceration, and plaque mobility with blood flow has confirmed their correlation with future ischemic cardiovascular and cerebrovascular events. Furthermore, the application of conventional duplex ultrasound to examine the stenosis rate of the carotid artery is not only an important indicator for clinical screening, but also crucial for the management of patients with acute ischemic stroke. ESC-related guidelines recommend that surgical intervention should be considered for patients with atherothrombotic stroke accompanied by severe internal carotid artery stenosis. CEUS's quantitative assessment of carotid plaque IPN is currently an important means of evaluating plaque vulnerability. Research has shown that IPN in carotid plaques is an independent predictor of future cardiovascular and cerebrovascular events. Existing studies have demonstrated that the combined use of multiple ultrasound modalities provides a richer and more reliable basis for the examination of vulnerable carotid plaques. However, apart from IPN, which has been proven as a predictor of cardiovascular and cerebrovascular diseases, there is insufficient research to confirm the predictive effect of other ultrasound imaging markers of carotid plaque under multiple ultrasound modalities on cardiovascular and

cerebrovascular diseases. There is still no clinically applicable method for risk stratification of cerebrovascular events based on ultrasound multimodal imaging of carotid plaques.

In recent years, with the continuous updating of guidelines, carotid atherosclerotic stenosis rate is no longer the only diagnostic criterion for assessing patient risk. The 2019 ESC and European Atherosclerosis Society (EAS) guidelines for dyslipidemia management emphasize that in the risk assessment of asymptomatic patients, imaging examinations can serve as a defining criterion for extremely high/high-risk groups. It states that "both clinical and imaging examinations can clearly confirm cardiovascular and cerebrovascular diseases, including images that can predict clinical event outcomes, such as carotid ultrasound showing significant carotid atherosclerotic plaques, i.e., vulnerable plaques, which can be diagnosed as extremely high-risk patients with cardiovascular and cerebrovascular diseases." This shows that ultrasound examination for the diagnosis of vulnerable carotid plaques can provide a favorable basis for patient risk stratification. However, traditional methods for screening vulnerable carotid plaques based on ultrasound multimodal imaging rely on semi-quantitative or qualitative judgments based on image characteristics, but there is significant subjectivity in visual assessment, and there is a large amount of information in ultrasound images that cannot be recognized by the naked eye. Therefore, the accuracy of traditional ultrasound diagnosis in assessing plaque vulnerability solely relies on human assessment is limited, and the information provided about plaque composition is also very limited. Additionally, the latest guidelines from the American College of Cardiology (ACC) / American Heart Association (AHA) do not recommend the use of carotid ultrasound for cardiovascular risk stratification, mainly due to the difficulty in standardizing ultrasound examinations and the lack of large-scale studies to validate that combining traditional risk factors with the assessment of carotid plaque stenosis and vulnerability is more accurate than established traditional cardiovascular risk assessment tools (such as the 10-year cardiovascular risk prediction tools - SCORE score abroad, pooled cohort equations, and China-PAR score domestically).

In current research, deep learning models have been applied to analyze carotid ultrasound plaques, enabling automatic segmentation of plaques in carotid ultrasound images and extracting multi-dimensional information for the diagnosis of vulnerable plaques based on plaque morphology and composition characteristics, internal texture features, and plaque stiffness. This addresses issues such as the high subjectivity and difficulty in standardization of manual diagnosis. Currently, methods for marking vulnerable plaques based on ultrasound images are still in the research stage and are not widely used clinically, requiring large-scale prospective longitudinal studies to establish and validate image-based risk scores for carotid plaques and their clinical practicability. Therefore, this project aims to obtain prospective data from multi-center population cohorts, integrate ultrasound multimodal imaging with clinical risk factors and laboratory indicators, establish a new diagnostic model for vulnerable plaques, and establish a new method for risk stratification of cerebrovascular events in patients with carotid plaques, providing effective tools for patient risk management and improvement of prognosis.

1. Research Objectives and Endpoints

2.1 Research Objectives

(1) To establish a vulnerable plaque assessment model based on ultrasound imaging indicators, patient clinical history, and laboratory indicators.

(2) To establish a cardiovascular risk prediction model for patients with carotid plaques by combining clinical data and ultrasound multimodal imaging data.

(3) To screen ultrasound imaging indicators for predicting cardiovascular events.

2.2 Research Endpoints/Primary Observation Indicators

(1) Myocardial infarction;

(2) Cardiovascular-related death;

(3) After resuscitation from cardiac arrest;

(4) Unstable angina requiring hospitalization;

(5) Ischemic stroke.

2. Research Methodology

3.1 Research Design

This study is a multicenter prospective cohort study. The project intends to collect 600 cases of patients with carotid plaques from Shanghai First People's Hospital (the main center) and four sub-centers (Dongtai People's Hospital, Zhoupu Hospital in Pudong New Area, Minhang Central Hospital, and Shanghai Changzheng Hospital). Each patient will be followed up from the screening period until the occurrence of an endpoint event or the completion of the 36-month follow-up period, with a maximum follow-up period of 36 months. During the follow-up period, outpatient or telephone follow-ups will be conducted every 12 months to record the patient's condition, the occurrence of cardiovascular events, and the time of occurrence. The relationship between the vulnerability of carotid plaques assessed by ultrasound imaging and the occurrence of cardiovascular events will be explored, and a prediction model for cardiovascular events in patients with carotid plaques will be established.

3.2 Sample Size

Based on literature data and considering the feasibility of the experiment, the prevalence of carotid plaques in the population over 40 years old is 40%, with an allowable error of 10%. The sample size is estimated using sensitivity, and the larger value is selected as the required sample size, approximately 201 cases. Considering a dropout rate of approximately 50%, the minimum required sample size is 300 cases. This study plans to collect 600 samples, with 280 cases collected at the main center and 80 cases collected at each sub-center. The allocation of the 600 samples is as follows: 300 cases for the training and validation sets (180 cases for the training set and 120 cases for the validation set) and 300 cases for the external validation set.

The ultrasound multimodal imaging data includes: conventional duplex ultrasound image data (over 2400 images), CEUS dynamic videos (600 cases of dynamic videos, with a total of over 600,000 images converted from videos), ultrasound elastography image data (over 1800 images), and three-dimensional ultrasound imaging data (over 1800 images). These data will be used to establish carotid plaque segmentation and classification models for tasks such as plaque segmentation, plaque IPN grading,

carotid artery stenosis rate assessment, and plaque image classification. Based on the constructed plaque segmentation and classification models, traditional risk-related indicators such as clinical and laboratory indicators will be further integrated to establish plaque vulnerability models and cardiovascular risk prediction models.

3.3 Research Population

The research population included in this study is patients with carotid plaques who underwent carotid ultrasound examinations at outpatient clinics and hospitals of various research centers during the study period.

There are many risk factors for carotid plaques, but the carotid plaque patients included in this study do not have significant differences in risk factors, age, and other aspects compared with general carotid plaque patients, making them representative.

3.3.1 Inclusion Criteria

(1) Have a full understanding of the purpose and significance of this experiment, voluntarily participate, and sign the informed consent form;

(2) The patient's age is over 40 years old;

(3) Patients with carotid plaques ≥1.5 mm on conventional ultrasound undergo examinations such as conventional ultrasound, CEUS, SWE, and three-dimensional ultrasound imaging.

All patients agreed to participate in the experiment and signed the informed consent form.

3.3.2 Exclusion Criteria

(1) Severe cardiopulmonary dysfunction; allergy to sulfur hexafluoride; pregnant or lactating women; patients with advanced tumors;

(2) Poor ultrasound image quality;

(3) Patients who have previously undergone carotid stenting or endarterectomy on the same side as the carotid plaque.

3.3.3 Withdrawal Criteria

(1) The subject withdraws their informed consent to participate in the study and refuses to undergo carotid ultrasound examination;

(2) After assessment, it is not suitable for the subject to undergo carotid ultrasound examination.

3. Research Steps

4.1 Clinical Data

Collect clinical information from patients with mild carotid artery stenosis participating in this study, including:

(1) Demographic characteristics: Participant's name, hospitalization/clinic number, gender, age, contact information, etc.;

(2) Baseline clinical data: Blood pressure, height, weight, history of hypertension (defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg), history of diabetes (defined as two measurements of glycosylated hemoglobin ≥ 6.5% or two measurements of fasting blood glucose ≥ 7.0 mmol/L or two measurements of blood glucose 2 hours after an oral glucose tolerance test ≥ 11.1 mmol/L, or having typical hyperglycemic symptoms/hyperglycemic crisis with random blood glucose ≥ 11.1 mmol/L), history of hyperlipidemia, smoking history (defined as continuous or cumulative smoking for 6 months or more in one's lifetime), alcohol consumption history, medication history, family history, etc.

4.2 Laboratory Tests

Collect the following laboratory indicators from participants in a fasting state: Alanine transaminase (ALT), Aspartate aminotransferase (AST), Total cholesterol (TC), Triglyceride (TG), Low-density lipoprotein cholesterol (LDL-C), High-density lipoprotein cholesterol (HDL-C), Homocystein (HCY), Glucose (GLU), and Creatinine (Cr) levels. Record all laboratory data in detail and keep the original data properly.

4.3 Carotid Artery Ultrasonography

To ensure the safety of ultrasonography, this study adopts linear array probes and three-dimensional probes with a frequency range of 4-18 MHz, with the mechanical index (MI) set below 0.1 and the thermal index (TI) below 1.0. This configuration avoids cavitation and thermal effects, meeting the safety standards for ultrasonic

diagnosis specified by the US FDA's 510(k), China's SFDA, and the International Electrotechnical Commission (IEC) International Standard IEC60601-2-37 (the equivalent national standard in China is GB 9706.9). Ultrasound physicians operate strictly in accordance with the "Fundamentals and Examination Norms for Ultrasonic Diagnosis" and the "Working System for Ultrasonic Diagnostic Departments."

The operational steps and image acquisition standards for ultrasonography are as follows:

(1) Routine Ultrasonography: In a resting state, the patient lies supine with the head unsupported, fully exposing the neck. Using a high-frequency peripheral vascular probe, examine the right and left carotid arteries (including the common carotid artery, carotid bifurcation, and internal carotid artery) in sequence. Select the plaque with the greatest thickness and clear image on each side as the target plaque, and adjust the image parameters to optimize the plaque display.

Capture three cross-sectional and three longitudinal images of the plaque (including one with measurements for each); capture three cross-sectional, longitudinal, and measurement images of the largest area of surface ulceration and low-echo regions within the plaque (if present); measure the blood flow velocity at the thickest part of the plaque and the normal lumen at the distal end of the plaque, capture images, and record the data.

For the positioning of carotid plaques in different examination methods, the same plaque is identified based on markers such as calcification within the plaque or the carotid bifurcation.

(2) Ultrasound Elastography: After obtaining a stable grayscale image, select the shear wave elastography (SWE) mode and adjust the region of interest (ROI) to include the entire plaque. During the examination, ensure that the probe only has minimal contact with the skin to minimize compression artifacts. Freeze the image after stabilization, acquire the elastography image, and use the tracking tool to accurately outline the plaque boundary to obtain the average shear wave velocity (SWV).

(3) Three-Dimensional Ultrasonic Imaging: After obtaining a stable grayscale image, select the three-dimensional mode, capture three 3D image sets, record the size of any surface depression or ulceration (if present) within the plaque, and calculate the plaque volume (mm^3) using the software package provided with the ultrasound machine or post-processing software.

(4) CEUS: Dissolve 59 mg of SonoVue in 5 ml of normal saline, shake to mix evenly, and prepare for use. Inject 1.2 ml of SonoVue suspension through the elbow vein bolus, followed by a rapid flush with 5 ml of normal saline. Activate the ultrasound machine's built-in timer and record the dynamic CEUS images, with each plaque CEUS video lasting no more than 2 minutes. Adjust the mechanical index to less than 0.1 while adjusting the image depth and gain to achieve optimal imaging quality.

Observe whether the surface morphology of the plaque is regular or if there are depressions/ulcers; record IPN conditions, including the location of microbubble appearance (upper/lower shoulder, intimal surface, basal part, plaque core), IPN semi-quantitative grading (Grade 0: no microbubbles seen within the plaque; Grade 1: microbubbles limited to the plaque shoulder or adventitial surface; Grade 2: microbubbles visible at the thickest part of the plaque, the intimal surface, or extensive enhancement within the plaque), and the direction of microbubble movement (from outside to inside, from inside to outside).

4.4 Follow-up after Treatment

All subjects will undergo follow-up once each at the 12th, 24th, and 36th months after being enrolled in this study. Each follow-up visit should not exceed two weeks before or after the specified follow-up time. Follow-up visits at the 12th and 24th months can be conducted through outpatient clinics or telephone calls, during which the occurrence of endpoint events will be recorded. At the 36th month, carotid ultrasound examinations will be performed, and the occurrence of endpoint events will be recorded accordingly. The definition and diagnostic criteria for endpoint events are detailed in Appendix 1. The time of occurrence of endpoint events will be recorded.

5. Study Evaluation

The evaluation indicators are the occurrence of cardiovascular and cerebrovascular events, including: myocardial infarction, cardiovascular death, cardiac arrest after resuscitation, unstable angina requiring hospitalization, and ischemic stroke. The definition and diagnostic criteria are detailed in Appendix 1.

6. Withdrawal from the Study or Study Completion

Criteria for Withdrawal from the Study:

(1) Subjects who withdraw their informed consent to participate in the study and refuse to undergo carotid ultrasound imaging;

(2) Subjects who are deemed unsuitable for carotid ultrasound imaging after assessment.

Criteria for Study Completion:

Collect data from 600 eligible patients with carotid plaques, conduct statistical analysis, explore the value of ultrasound imaging in assessing carotid plaque vulnerability and predicting cardiovascular and cerebrovascular events, and establish a predictive model for the risk of future cardiovascular and cerebrovascular events among patients with carotid plaques.

7. Dropout Criteria

All patients who have completed the informed consent form and been screened as eligible to enter the trial have the right to withdraw from the clinical trial at any time, regardless of the reason. Subjects who do not complete the observation period specified in the study protocol are considered dropout cases.

For patients who have only signed the informed consent form, been screened as eligible, but have not been enrolled in the study, they are not considered dropout cases. For patients who drop out due to adverse reactions, if it is determined that the dropout is related to the trial examination, it must be recorded in the Case Report Form (CRF).

8. Statistical Analysis

Before database lock-in, statisticians will discuss with the principal investigators and the lead research institution to finalize the statistical plan based on the characteristics of the data. This protocol only provides general statistical requirements.

8.1 Baseline Demographic Analysis

(1) Continuous data: Described using mean, standard deviation, median, maximum, minimum, and quartiles.

(2) Categorical data: Described using frequency and composition ratio.

8.2 Analysis of Primary Endpoint Events

Univariate and multivariate logistic regression analysis will be used to identify risk factors and adjust the model for significant risk factors. Cox proportional hazards regression model will be employed to study independent predictors of cardiovascular and cerebrovascular events and to screen for ultrasonographic indicators that predict cardiovascular and cerebrovascular events. Kaplan-Meier method and log-rank test will be used to compare the cumulative incidence of cardiovascular and cerebrovascular events based on carotid plaque ultrasound parameters. Objective evaluation of the diagnostic performance of the model will be carried out using indicators such as accuracy, sensitivity, specificity, and precision. Additionally, ROC curves and AUC values will be used to assess the diagnostic performance of the model.

8.3 Statistical Software

SPSS, R software, SAS, and other software will be used for analysis. All statistical tests will be two-sided, and a P-value less than or equal to 0.05 will be considered statistically significant.

8.4 Operational Training and Consistency Assurance

(1) Operational Training: All ultrasound image acquisitions will follow the "Chinese Expert Consensus on Ultrasound Evaluation of Vulnerable Carotid Plaques (2023 Edition)". The lead center physicians will provide initial training on carotid multimodal ultrasound examination at the beginning of the project and conduct

regular assessments. Monthly case summaries will be reviewed by ultrasound experts for quality assessment, and centers that do not meet quality control standards will receive analysis and feedback. Specific methods for ultrasound data acquisition are detailed in "4.3 Carotid Artery Ultrasound Examination."

(2) Consistency Analysis: Inter-observer consistency analysis will be performed by two ultrasound physicians (with over 5 years of experience). For divergent diagnostic results, a final decision will be made by an ultrasound expert with 20 years of experience in vascular ultrasound. To assess intra-observer consistency, the same ultrasound physician (with over 5 years of experience) will reanalyze the data after an interval of 1 month, without referring to the initial results.

9. Data Management

This study uses paper-based CRFs to record data, strictly adhering to all aspects of the research protocol and conducting regular inspections of the original data. Additionally, study participants will undergo unified training, and consistency checks will be conducted when primary indicators may be subject to subjective influence.

10. Quality Control

Study participants will undergo unified training to ensure standardization in examination procedures, image acquisition, and interpretation. When primary indicators may be subject to subjective influence, consistency checks will be conducted. This study allows for inspection, audits, institutional review board or ethics committee, and regulatory agency reviews related to the trial, providing direct access to original data or documents. Clinical trial quality control and assurance measures will be implemented.

11. Ethical Protection and Informed Consent in Clinical Research

This study adheres to the Helsinki Declaration and ethical standards of the country where the trial is conducted.

This study has applied for and obtained approval from the ethics committee with the

necessary documents and procedures.

Before being enrolled in this study, it is the responsibility of the research physician to provide patients or their designated representatives with a complete and comprehensive written explanation of the study's purpose, procedures, and potential risks. Patients should be informed that they have the right to withdraw from the study at any time. Each patient will be given a copy of the informed consent form before enrollment, which will be retained as part of the clinical trial documentation.

The personal information and all identity information disclosed by the participants in this study will be strictly confidential and will not be disclosed. If the results of this study are published, the identities of the participants will be kept confidential.

This study is an observational diagnostic study. The carotid plaque-related examinations conducted will help assess the participants' carotid plaques and are non-invasive, with a low probability of serious adverse events. The results obtained from this study will benefit human health and society.

Appendix 1. Definition of Clinical Endpoint Events

I. Myocardial Infarction

1. Non-procedure-related Myocardial Infarction:

Fulfilling any of the following criteria:

(1) Ischemic symptoms (resting pain, shortness of breath, pressing discomfort; or gradually worsening of the above symptoms; confirmed by the investigator as secondary to ischemia);

(2) ECG changes consistent with myocardial infarction:

New significant Q waves (or significantly increased R waves in V1-V2) in 2 consecutive leads, in the absence of previous left ventricular hypertrophy or conduction abnormalities;

ST-T wave evolution in ≥2 consecutive leads;

New left bundle branch block;

ST-segment elevation requiring thrombolysis or PCI.

(3) Cardiac markers:

Troponin: Quantitative detection within the diagnostic range for myocardial necrosis, otherwise at least one of the other cardiac markers must be >2 times the ULN (upper limit of normal);

CK and CK-MB: Both ≥ULN; if CK < ULN, CK-MB must be ≥1.5 times the ULN; if only CK-MB is tested, CK-MB must be ≥1.5 times the ULN.

2. Procedure-related Myocardial Infarction:

(1) Post-PCI Myocardial Infarction:

New pathological Q waves (or other well-documented wall motion abnormalities excluding the interventricular septum) or cardiac markers ≥3 times the ULN within 24 hours after the procedure; if the previous measurement was ≥ULN, the cardiac marker should be ≥50% higher than the previous measurement within 24 hours after the procedure.

(2) Post-CABG Myocardial Infarction:

New pathological Q waves (or other well-documented wall motion abnormalities excluding the interventricular septum) or CK-MB ≥5 times the ULN within 24 hours after the procedure; if the previous measurement was ≥ULN, the CK-MB should be ≥50% higher than the previous measurement within 24 hours after the procedure.

3. Silent Myocardial Infarction:

Myocardial tissue necrosis attributed to myocardial infarction that is not clinically recognized. The time of the event should be determined as the time of the earliest ECG showing new Q waves.

II. Cardiovascular Death

Includes any of the following situations:

Sudden death: Death occurs suddenly; witnessed by someone, and the time of death is clear. The cause may be arrhythmia confirmed by ECG or electrocardiographic monitoring, or cardiac arrest.

Fatal myocardial infarction: Death occurs after myocardial infarction without evidence of other causes of death; patients who die suddenly during the treatment of myocardial infarction should be classified as myocardial infarction-related death; recent myocardial infarction confirmed by autopsy without evidence of other causes of death also falls into this category. Sudden death of patients with evidence suggestive of myocardial infarction but not meeting the strict definition of myocardial infarction (e.g., ECG suggesting myocardial injury, abnormal myocardial markers without evolution, evidence of new wall motion abnormalities) should also be classified as myocardial infarction-related death.

Heart failure death: Death due to heart failure without evidence of other causes such as ischemia, infection, or arrhythmia. Death due to cardiogenic shock.

Suspected cardiovascular death: Suspected death due to cardiovascular causes with supporting clinical evidence but not meeting other criteria (e.g., patients with typical chest pain characteristic of myocardial infarction but without ECG or enzymatic records meeting the criteria for myocardial infarction).

Death of unknown cause: If there is no clear evidence of other diseases, it is considered to be death due to cardiovascular events.

III. Unstable Angina

Includes:

New-onset effort angina: The presence of typical angina pectoris confirmed by provocative tests (ECG, echocardiography, or nuclear myocardial imaging).

Worsening effort angina: An increase in the frequency, duration, and/or severity of known angina attacks, requiring hospitalization and/or an increase in anti-anginal medication.

Other unstable angina:

Ischemic symptoms (pain, shortness of breath, pressing discomfort) occurring at rest or gradually worsening, lasting ≥10 minutes, with the researcher determining that the symptoms are secondary to ischemia, and:

ECG during ischemia compared to the most recent ECG or previous stable state ECG:

(a) Transient ST segment depression ≥0.5mm in 2 consecutive limb or chest leads;

(b) Transient ST segment elevation ≥1mm in 2 consecutive leads (or ST segment depression ≥1mm in V1 or V2);

(c) Transient T wave changes ≥2mm in 2 or more consecutive leads, or myocardial markers suggesting myocardial injury, ≥ULN but not meeting the criteria for myocardial infarction.

IV. Coronary Revascularization

Includes the following:

Percutaneous transluminal coronary angioplasty (PTCA);

PTCA with stent implantation;

Other types of percutaneous coronary interventions;

Coronary artery bypass grafting.

V. Ischemic Stroke

Diagnostic criteria for acute ischemic stroke:

Acute onset;

Focal neurological deficits (unilateral facial or limb weakness or numbness, speech disorders, etc.), with a few cases showing global neurological deficits;

Imaging showing responsible lesions or symptoms/signs lasting for more than 24 hours;

Exclusion of non-vascular causes;

Brain CT/MRI excluding cerebral hemorrhage.