# Clinical Study Protocol

**Anti-platelet Precision Medicine to Prevent Stroke Early Progression and Recurrence (PRECISE)**

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| **Protocol Number** | PRECISE |
| **Protocol Version** | 3.1 |
| **Version Date** | July 23, 2018 |
| **Study Center** | Asan Medical Center and 21 Other Institutions |
| **Study Coordinator** | Dong-Wha Kang, Dept. of Neurology, Asan Medical Center |

**※ PROTOCOL SYNOPSIS**

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| **Study title** | Anti-platelet Precision Medicine to Prevent Stroke Early Progression and Recurrence (PRECISE) |
| **Study phase and design** | Pragmatic, multi-center, non-interventional, non-random trial based on prospective observational study |
| **Study center** | Asan Medical Center and 21 other institutions |
| **Study coordinator** | Dong-Wha Kang of Department of Neurology, Asan Medical Center |
| **Study sponsor** | Dong-Wha Kang of Department of Neurology, Asan Medical Center |
| **Study funder** | Chong Kun Dang Holdings |
| **Study objectives** | **Primary objectives:** To predict the clinical prognosis according to the antiplatelet treatment regime (aspirin as first-line treatment or in combination with clopidogrel), develop an AI that will search for and retrieve similar cases to each patient, and assess benefits of the technology:<br>1) To establish a stroke clinical-imaging library (big data) and develop Deep Learning-based AI that understands the relationship between anti-platelet agents and prognosis (progression or recurrence). AI will present the probability of stroke progression or recurrence following each treatment regime. AI will also help physicians make treatment decisions by searching for and retrieving existing cases with similar clinical conditions to the patients concerned.<br>2) To prove AI's merit in predicting prognosis by applying it to different patient groups.<br><br>**Secondary objective:** To analyze practical results of antiplatelet agents:<br>The aspirin alone group and the clopidogrel plus aspirin group will be compared against each other directly to help find the link between early progression and recurrence of stroke. Although this is a non-randomized trial, different statistical methodologies, including propensity score matching (PSM) should address confidence issues. |
| **Study subjects** | Acute ischemic stroke patients:<br>Transient ischemic attack with confirmed acute ischemic stroke by brain imaging |

<table>
<tr><td>Inclusion criteria</td><td>1) Male and/or female subjects who are aged 19 or over.<br>2) Patients with acute noncardiac stroke or transient ischemic attack within 72 hours of the onset (in the case of a transient ischemic attack, presence of ischemic/ischemic lesion on DWI or PWI).<br>3) Patients whose informed consent document within 72 hours of onset was signed and submitted.<br>4) Patients who were treated with aspirin alone or aspirin plus clopidogrel resinate following stroke.</td></tr>
<tr><td>Exclusion criteria</td><td>1) Patients who need anticoagulants for cardiac ischemic stroke or other reasons.<br>2) Patients who suffered severe stroke (National Institutes of Health Stroke Scale> 16).<br>3) Patients who received emergency remission therapies such as tPA and thrombolysis.<br>4) Patients with neurological deterioration prior to signing an informed written consent document.<br>5) Patients who have undergone patency procedures (surgery or stent insertion) in the cerebrovascular or carotid arteries following stroke or are expected to do so.<br>6) Patients who are scheduled to undergo major surgery.<br>7) Patients who developed stroke during procedure/surgery.<br>8) Patients with recent history (in the past three months) of cerebral hemorrhage.<br>9) Patients with active internal bleeding.<br>10) Patients with severe anemia (Hb <10 g / dL) or bleeding tendency (platelet <100,000 / uL or PT-INR> 1.7).<br>11) When a patient’s life expectancy is less than 6 months due to other systemic disease.</td></tr>
<tr><td>Number of target study subjects</td><td><table><tr><th></th><th>Aspirin alone group</th><th>Aspirin + Clopidogrel resinate group</th><th>Total No. of target subjects</th></tr><tr><td>No. of subjects</td><td>1,000</td><td>1,000</td><td>2,000</td></tr></table></td></tr>
<tr><td>Study duration</td><td>1) Study duration: Approximately 36 months from IRB approval (subject to change depending on subject enrollment speed)<br>2) Study duration for each subject: 90 days (± 15 days)</td></tr>
<tr><td>Study drug and dose</td><td><table><tr><th>Study drug</th><th>Route of administration/dose</th></tr><tr><td>Aspirin (monotherapy or concomitant therapy)</td><td>75~100mg once per day, initial loading dose of 300~500mg/d is allowed</td></tr></table></td></tr>
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| | Clopidogrel resinate (Concomitant therapy) — 75mg once per day, initial loading dose of 300mg/d is allowed |
| **Study description** | This is a pragmatic, multi-center, non-interventional, non-randomized prospective observational study.<br><br>■ Study procedures<br>This is a prospective study of patients with acute stroke or transient ischemic attack within 72 hours of symptom onset. It is to mainly observe the patients' prognosis following the prescription of clopidogrel resinate and aspirin, collect relevant data and create big data for stroke. Based on this data, an AI, using various advanced statistical methodologies and deep learning techniques will be developed, and offer information regarding stroke prognosis by extracting markers that are characteristic of the relationship between stroke and the study drug.<br><br>These analyses and results will include information on which drug regimen will better prevent the progression or recurrence of stroke by considering individual patient conditions. This is a pragmatic trial based on the prescription and treatment processes of routine clinical practice. Thus, there is no major restriction and with only the minimum exclusion criteria in place, it does not hinder usual clinical practices. Therefore, selecting and changing a patient's antiplatelet agents should be a rational medical judgment made by the patient's attending physician. The study will proceed without any major change in the sequence of routine clinical examinations, prescriptions, treatments, observations, etc. Provided, the process of storing and analyzing relevant information will be added to each study procedure in accordance with study methodologies and conditions no other special efforts or limitations will be required.<br><br>The data will be collected prospectively, and the AI will generate brain imaging data and prognostic indicators for 3-months after stroke has occurred. The performance of the AI will be verified with independent test sets. |
| **Dropout criteria** | Because the subjects will receive usual stroke care practice, there will be no subject withdrawal or dropout due to issues related to the study description and design.<br>However, if a research subject withdraws his/her consent to participate in the study (informed consent to have his/her personal information utilized), participation of the research subject will be suspended, and the data concerned |

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| | will not be used in the study. |
| **Endpoints** | **<u>Primary study endpoints</u>**<br>AI will learn and predict the occurrence of the following outcome variables (up to 3 months after stroke onset) according to the antiplatelet regimen (aspirin alone, or aspirin plus clopidogrel). An independent investigator, without knowledge of individual patient treatment regimens, will evaluate the same outcome variables separately and compare the results with those predicted by the AI:<br>1) Neurological deterioration<br>2) New ischemic stroke<br>3) Symptomatic hemorrhagic transformation of an ischemic stroke<br>4) Symptomatic intracranial hemorrhage<br>5) Myocardial infarction<br>6) Coronary revascularization without myocardial infarction<br>7) Major hemorrhage other than intracranial hemorrhage (life threatening or non-life-threatening)<br>8) Minor hemorrhage other than intracranial hemorrhage<br>9) Ischemic vascular death<br>10) Hemorrhagic vascular death<br>11) Other serious adverse events<br><br>**<u>Secondary study endpoints</u>**<br>A direct comparison between the aspirin alone group and the aspirin and clopidogrel combination therapy group for the incidence of 11 outcome variables evaluated by an independent investigator at the primary endpoints will be conducted. |
| **Statistical Methodology** | **<u>General principle</u>**<br>All the enrolled study subjects whose results are confirmed will be subject to analysis, and they will be selected and classified according to the study methodologies and objectives prior to analysis. During the study period, data will be regularly checked and managed so that the number of datasets and their levels will be maintained appropriately.<br><br>**<u>Analyses of endpoints</u>**<br>**Analysis of primary endpoints**<br>1) The stroke clinical and imaging library (big data), that includes all the |

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| | clinical/imaging information related to clinical prognoses, will be established, and based on a deep learning algorithm, AI that has learned the relationship between antiplatelet agents and the following prognostic information will be developed.<br>2) A probability of prognosis according to each treatment option prior to using antiplatelet agents will be offered. This information will help physicians select an antiplatelet agent by searching for and retrieving similar cases that match each patient.<br>3) The stroke clinic and imaging library (big data) regarding the effect of antiplatelet agents that are being prescribed mainly to stroke patients in the clinical setting and the prognostic information of the patients concerned will be constructed. The relationship and prognostic features of antiplatelet agents in preventing early progression and recurrence of stroke will be extracted and analyzed from the "Big Data."<br>4) The development of AI using deep learning techniques will provide the basis for analysis of internal and external variables of stroke. This technique will change the model composition in line with the features and numbers extracted from the data. The depth and structure of the model will segment and materialize the characteristics of the target subjects and will be accompanied by the optimal design and verification processes of the model to simultaneously consider clinical/image information.<br>5) The research analysis using the trained AI that will be developed will need to have its results clearly verified as to their quality/accuracy. The delivered outcome will be used directly or indirectly by physicians, but the performance and reliability of the results that will be generated are of significant importance. Therefore, the AI will learn and have its performance assessed based on the data that will continue to accumulate throughout this study. However, because of the features of deep learning technology, training and verification, using the same data may cause major issues such as overfitting. Therefore, a new dataset will be created to evaluate the performance of the AI.<br><br>**Analysis of secondary endpoints**<br>1) The propensity score matching (PSM) technique will be used to select either the aspirin monotherapy, or the clopidogrel resinate and aspirin combination therapy group which have matched important clinical/imaging parameters that affect the prognosis of stroke. |

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| | 2) Compare the prognosis of each treatment group to determine which prescription method is superior. |