Do Platelet Function Test and Monitoring Based Antiplatelet Preparation Reduce Thromboembolic Complication Related with Neurointerventional Surgery?

Subtitle
Standard vs Modified Antiplatelet Preparation for Preventing Thromboembolic Event in Patients with High on-Treatment Platelet Reactivity Undergoing Coil Embolization for an Unruptured Aneurysm.

Protocol Version 1.3
Synopsis

<table>
<thead>
<tr>
<th>Title</th>
<th>Do Platelet Function Test and Monitoring Based Antiplatelet Preparation Reduce Thromboembolic Complication Related with Neurointerventional Surgery?</th>
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<tbody>
<tr>
<td>Purpose</td>
<td>The most frequent complication in coil embolization for an unruptured aneurysm is a thromboembolic event. For its prevention, antiplatelet preparation is performed, but patients with high on-treatment platelet reactivity (HTPR) are detected. Therefore, we evaluate whether modification of antiplatelet preparation reduces the thromboembolic events in patients with HTPR undergoing coil embolization.</td>
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<tr>
<td>Design</td>
<td>Prospective, randomized, open-labeled, active-control trial with blinded outcome assessment</td>
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<td>Study period</td>
<td>One year after IRB approval</td>
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| Sample size                                                        | Candidate size: 240  
Target size: 126, considering a dropout rate 10% (standard preparation group, 63; modified preparation group, 63) |
| Study candidate                                                     | Patients with unruptured intracranial aneurysm |
| Study drugs                                                        | Aspirin, clopidogrel, cilostazol |
| Drug dose                                                          | Aspirin – high dose, 300mg; usual dose, 100mg daily  
Clopidogrel – high dose, 300 ~ 600mg; usual dose, 100mg daily  
Cilostazol – loading dose, 200mg; usual dose, 200mg bid |
| Methods                                                             | 1. Standard antiplatelet preparation (100mg aspirin, 75 mg clopidogrel) is prescribed for more than 5 days in patients undergoing coil embolization.  
2. Platelet function test with VerifyNow is performed before coiling. Based on its results, patients with HTPR are randomly assigned to the standard or modified preparation group in a 1:1 ratio.  
3. For the modified preparation group, modification of antiplatelet preparation using high-dose aspirin or loading dose cilostazol is performed. For the standard preparation group, standard preparation is maintained.  
4. Thromboembolic events and bleeding complications are evaluated for 30 days after coiling. |
| Inclusion criteria                                                  | • Patients with unruptured aneurysm who plan to undergo coil embolization  
• Patient aged 20 – 80 years at the day of enrollment  
• Patient with less than 2 of modified Rankin scale score at the day of enrollment  
• Patient who agrees and writes out a consent form |
| Exclusion criteria                                                  | • Patient with history of hypersensitivity of aspirin, clopidogrel, or cilostazol  
• Patient with a high possibility of active bleeding such as symptomatic intracranial hemorrhage or active gastric ulcer  
• Patient with bleeding tendency or coagulopathy  
• Patient with thrombocytopenia (< 100,000/mm$^3$ of platelet count within three months before enrollment)  
• Patient with liver disease (> 100 of AST or ALT within three months before enrollment)  
• Patient with renal disease (> 2mg/dL of serum creatinine within three months before enrollment)  
• Patient using anticoagulants  
• Patients with congestive heart failure or angina unable to be controlled  
• Patients with malignant tumor requiring treatment  
• Pregnant or breast-feeding woman  
• Patient in whom physician decision is disqualification |
| Efficacy endpoints                                                  | A thromboembolic event within 7 and 30 days after coil embolization  
* A thromboembolic event is defined as (1) a thromboembolism detected during the coiling procedure or (2) a transient ischemic attack or ischemic stroke with evidence of infarction on diffusion weighted imaging, which occurs in vascular territory consistent with the treated aneurysm location. |
| Safety endpoint                                                     | Bleeding complication within 30 days after coil embolization |
| Evaluation schedule                                                 | Platelet function test – 1 day before coiling  
Neurological status – 1 day before coiling, from coiling to discharge to home, and 7 and 30 days after coiling |
<table>
<thead>
<tr>
<th>Visiting schedule – 7 and 30 days after coiling</th>
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<tr>
<td><strong>Statistical analysis</strong></td>
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<td><strong>Sponsor</strong></td>
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</table>
1. **Study Title**
Do Platelet Function Test and Monitoring Based Antiplatelet Preparation Reduce Thromboembolic Complication Related with Neurointerventional Surgery?

2. **Study Institute and Location**
Seoul National University Bundang Hospital
300 Gumi-dong, Bundang-gu, Seongnam, Gyeonggi, Korea

3. **Investigators**

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
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<tbody>
<tr>
<td>Principle investigator</td>
<td>Gyojun Hwang</td>
<td></td>
<td>Assistant professor</td>
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<tr>
<td>Co-investigator</td>
<td>O-Ki Kwon</td>
<td></td>
<td>Professor</td>
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<tr>
<td>Co-investigator</td>
<td>Won Huh</td>
<td></td>
<td>Clinical fellow</td>
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<tr>
<td>Co-investigator</td>
<td>Jin Soo Lee</td>
<td></td>
<td>Clinical fellow</td>
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<tr>
<td>Co-investigator</td>
<td>Eun-A Jeong</td>
<td></td>
<td>Physician assistant</td>
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<tr>
<td>Co-investigator</td>
<td>Nam Mi Park</td>
<td></td>
<td>R.N.</td>
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<tr>
<td>Coordinator</td>
<td>Soo Joo Park</td>
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<td>R.N.</td>
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4. **Source of Funding**
The Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (HI10C2020)

5. **Background and Purpose**

5.1. **Current status and problems of coil embolization for an unruptured intracranial aneurysm**

Cerebrovascular disease is the second cause of the death in Korea. If the patient survive from the cerebrovascular disease, its prognosis is usually very poor. Therefore, active attempts for preventing the cerebrovascular disease are being considered and neurointerventional surgery is playing an important role for this purpose. As devices for neurointerventional surgery are rapidly developing, patients undergoing neurointerventional surgery are gradually increasing. Particularly, in elective surgery, more patients with cerebrovascular disease are selecting neurointerventional surgery, because of its less invasiveness. In neurointerventional surgery, however, because all procedures are proceeded in the vessel, thrombosis or embolism can develop and lead to serious neurological deficits or even death.

In coil embolization for an intracranial aneurysm, a recent development of coils and stents, and their related techniques have reduced procedural complication rate significantly. Nevertheless, thromboembolic event still occurs substantially. So the thromboembolic event is the most frequent complication in coil embolization of intracranial aneurysm, especially unruptured one.
For preventing the thromboembolic event in coil embolization of unruptured aneurysm, antiplatelet preparation was introduced. This short-time antiplatelet preparation before coil embolization was found to reduce the thromboembolic event rate without increasing bleeding complication in several studies. Based on these results, the antiplatelet preparation has been accepted as a standard preparatory step in coil embolization of unruptured aneurysm. However, a 4-7% of the thromboembolic event rate is still being reported. As a reason for not reducing the thromboembolic event rate even after antiplatelet preparation, high on-treatment platelet reactivity (HTPR) to standard antiplatelet regimen (aspirin and clopidogrel) was pointed out. However, no strategies for patients with HTPR are available.

5.2. Purpose of this study
In cardiovascular disease, a tailored antiplatelet therapy based on platelet function test is being investigated. This strategy needs to be considered in coil embolization of unruptured intracranial aneurysm. Therefore, in patients with HTPR undergoing coil embolization for an unruptured aneurysm, we will investigate whether modification of antiplatelet preparation based on platelet function test before procedure reduces the thromboembolic event rate (effect) and increases the bleeding complication rate (safety).

6. Antiplatelet Drugs and Platelet Function Test used in This Study

6.1. Aspirin
Aspirin protect (capsule, aspirin 100mg, Boryung, Beyer Korea)

6.1.1. Mechanism
Aspirin has an ability to suppress the production of prostaglandins and thromboxanes. It is due to its irreversible inactivation of the cyclooxygenase (COX) enzyme required for prostaglandin and thromboxane synthesis. Low-dose aspirin use irreversibly blocks the formation of thromboxane A2 in platelets, producing an inhibitory effect on platelet aggregation during the lifetime of the affected platelet (about 7 days).

6.1.2. Major side effect
Bleeding requiring medical treatment (intracranial hemorrhage, pulmonary hemorrhage, gastrointestinal bleeding, epistaxis, fundus hemorrhage), shock, anaphylaxis, mucocutaneous ocular syndrome, toxic epidermal necrolysis, exfoliative dermatitis, aplastic anemia

6.1.3. Minor side effect
Gastritis, ulcer, bleeding not requiring medical treatment (gastrointestinal bleeding, hematoma, retinal hemorrhage), skin rash, dizziness, hematologic dysfunction

6.2. Clopidogrel
Plavitor (tablet, clopidogrel 75mg, Donga ST, Korea)
6.2.1. **Mechanism**
Clopidogrel is a prodrug, which requires CYP2C19 for its activation. It acts on the ADP receptor on platelet cell membranes. The drug specifically and irreversibly inhibits the P2Y12 subtype of ADP receptor, which is important in activation of platelets and eventual cross-linking by the protein fibrin.

6.2.2. **Major side effect**
Bleeding requiring medical treatment (intracranial hemorrhage, gastrointestinal bleeding, joint hematoma, fundus hemorrhage), hepatic disorder requiring medical treatment, thrombotic thrombocytopenic purpura, interstitial pneumonitis, agranulocytosis, aplastic anemia, pancytopenia, mucocutaneousocular syndrome, erythema multiform syndrome, toxic epidermal necrolysis

6.2.3. **Minor side effect**
Bleeding not requiring medical treatment (subcutaneous bleeding, epistaxis, clotting time prolongation, gingival bleeding, ophthalmorrhagia, bloody sputum, puncture site bleeding), anemia, purpura, decrease of hemoglobin, red blood cell, hematocrit, white blood cell, or neutrophil, increase of neutrophil, skin rash, itching sense, urticarial, eczema, erythema

6.3. **Cilostazol**
Pletaal (tablet, cilostazol 100mg, Otsuka Korea)

6.3.1. **Mechanism**
Cilostazol is a selective inhibitor of 3-type phosphodiesterase (PDE3) with therapeutic focus on increasing cAMP. An increase in cAMP results in an increase in the active form of PKA, which is directly related with an inhibition in platelet aggregation.

6.3.2. **Major side effect**
Bleeding requiring medical treatment (intracranial hemorrhage, pulmonary hemorrhage, gastrointestinal bleeding, epistaxis, fundus hemorrhage), congestive heart failure, myocardial infarction, ventricular tachycardia, pancytopenia, agranulocytosis, thrombocytopenia, interstitial pneumonitis, hepatic disorder requiring medical treatment, jaundice

6.3.3. **Minor side effect**
Tachycardia, hot flush, headache, dizziness, insomnia, tingling sense, rash, abdominal pain, nausea, vomiting, diarrhea, anorexia, epigastric discomfort, subcutaneous bleeding, increase of liver enzymes, sweating, edema, chest pain

6.4. **VerifyNow™** (Accumetrics, San Diego, CA)
6.4.1. Test principle
Turbidometry

6.4.2. Aspirin assay
The test incorporates the agonist arachidonic acid to activate platelets, and it measures platelet function based upon the ability of activated platelets to bind to fibrinogen. Fibrinogen-coated microparticles aggregate in whole blood in proportion to the number of activated platelet GP IIb/IIIa receptors. If aspirin has produced the expected antiplatelet effect, such aggregation will be reduced. The VerifyNow aspirin assay reports the extent of platelet aggregation as aspirin reaction units (ARU).

6.4.3. P2Y12 assay
The test incorporates the agonist ADP to activate platelets. The VerifyNow P2Y12 test also uses PGE1 to increase intraplatelet cAMP and reduce the contribution of the P2Y1 receptor on activation. This makes the test more specific for the effects of ADP on the P2Y12 receptor. It measures platelet function based upon the ability of activated platelets to bind to fibrinogen. Fibrinogen-coated microparticles aggregate in whole blood in proportion to the number of activated platelet GP IIb/IIIa receptors; and if the P2Y12 inhibitor has produced the expected antiplatelet effect, such aggregation will be reduced. The VerifyNow PRU Test reports the extent of platelet aggregation in P2Y12 reaction units (PRU).

6.4.4. Definition of high on-treatment platelet reactivity (HTPR) in this study
HTPR to aspirin: ARU ≥ 550, according to manufacturer’s guideline
HTPR to clopidogrel: PRU > 213
For defining HTPR to clopidogrel, there are several methods and cut-off values. In neurointerventional surgery, PRU was found to better predict the thromboembolic events. Additionally, the cut-off value of 213 was selected based on the results in a correlation study between VerifyNow and flow cytometry, which is one of the criterion standard platelet response tests. One of possible explanation for failure in a large prospective cardiology trial (GRAVITAS) may be that the usual cut-off value of 230 in cardiology trials is too high to improve outcomes. Therefore, we will use a lower cut-off value, 213 in this study. The necessity of lower PRU value is also supported by a post hoc analysis of the GRAVITAS trial.

7. Candidate Disease for This Study
Unruptured aneurysms which plan to be treated with elective coil embolization.

8. Study Period
One year after Institutional Review Board (IRB) approves the study protocol

9. Study Methods
9.1. Study design
A prospective, randomized, open-labeled, active-control trial with blinded outcome assessment

9.2. Overview
Detail general workup, treatment decision, preparation, and patient management will follow a routine protocol for coil embolization of unruptured aneurysm in our hospital, except platelet function testing and modification of antiplatelet preparation at the coiling day.

The standard antiplatelet preparation (100mg aspirin and 75 mg clopidogrel, daily) will be performed for more than 5 days in patients who plan to undergo elective coil embolization of unruptured aneurysm. At 1 day before coiling, platelet function test is performed with VerifyNow. Based on results of platelet function test, patients with HTPR are randomly assigned to the standard or modified preparation groups in a 1:1 ratio. Patients without HTPR are also assigned to no-HTPR group. At the coiling day, for the modified preparation group, high-dose (300mg) aspirin or adding loading-dose (200mg) cilostazol will be prescribed. For the other groups, standard preparation is maintained. During 30 days after coiling, thromboembolic event and bleeding complication will be evaluated.

9.3. Inclusion and exclusion criteria

9.3.1. Inclusion criteria
- Patients with unruptured aneurysm who plan to undergo coil embolization
- Patient aged 20 – 80 years at the day of enrollment
- Patient with less than 2 of modified Rankin scale score at the day of enrollment
9.3.2. Exclusion criteria

- Patient with history of hypersensitivity of aspirin, clopidogrel, or cilostazol
- Patient with a high possibility of active bleeding such as symptomatic intracranial hemorrhage or active gastric ulcer
- Patient with bleeding tendency or coagulopathy
- Patient with thrombocytopenia (< 100,000/mm³ of platelet count within three months before enrollment)
- Patient with liver disease (> 100 of AST or ALT within three months before enrollment)
- Patient with renal disease (> 2mg/dL of serum creatinine within three months before enrollment)
- Patient using anticoagulants
- Patients with congestive heart failure or angina unable to be controlled
- Patients with malignant tumor requiring treatment
- Pregnant or breast-feeding woman
- Patient in whom physician decision is disqualification

9.4. Sample size calculation

9.4.1. The calculated size of the standard and modified preparation groups

In a recent cohort study, symptomatic thromboembolic event rate within 7 days after neurointervention was 16.8% in patients with HTPR and 0% in patients without HTPR. In estimating the power for determining efficacy, we assumed that the effect of the modified antiplatelet preparation for reducing thromboembolic events would be similar to the difference in thromboembolic event rates between patients with and without HTPR. Therefore, we assumed that the anticipated events rates in the standard and modified preparation groups would be 15% and 1%, respectively (rate difference, 14%).

To have 80% power to detect this rate difference in the primary outcome (thromboembolic event within 7 days after coiling) at the two-sided 0.05 significant level, the calculated sample size is 114 patients with HTPR (57 in each group).

9.4.2. The expected size of candidates who are evaluated with platelet function testing

In Korean population, 47.5–72.3% of patients undergoing neurointervention were found to have HTPR. Considering this incidence, no-HTPR group size is expected to be maximum 126 patients. Therefore, the total number of patients who will be evaluated with platelet function test is expected to be less than 240.

9.4.3. The target size of the standard and modified preparation groups

Considering a dropout rate of 10%, we will enroll patients with HTPR targeting 126 patients with HTPR (63 in each group) for this study. This calculation was performed with STATA Statistical Software (release 13, StataCorp LP, College Station, TX).
9.4.4. Estimated power of the target sample size

When the target sample size of 126 patients is successfully enrolled, estimated power will be as follows

- Person chi-square test: estimated power = 0.834

- Fisher’s exact test: estimated power = 0.802

9.5. Routine protocol of patients with unruptured intracranial aneurysm

For confirmation and future plan of patients with unruptured intracranial aneurysm, conventional cerebral angiography is performed. All patient and radiographic information are discussed by vascular neurosurgeons and neurointerventionists in a weekly conference. Treatment is considered for patients with an symptomatic unruptured intracranial aneurysm or unruptured aneurysm at high risk of rupture, according to the guidelines of the Korean Stroke Society (www.stroke.or.kr/CPGstroke.html): (1) aneurysm ≥ 5 mm, (2) aneurysm located in the posterior circulation, anterior communicating artery, or posterior communicating artery, (3) history of previous subarachnoid hemorrhage or family history of aneurysm, (4) aneurysm increasing in size or changing in morphology during follow-up, (5) patients with ages less than 50 years, hypertension, and multiple aneurysms,
(6) aneurysm with a high dome-to-neck ratio, multi-lobule, or bleb. The choice of clipping vs. coiling is made by considering the risk of each method.

9.6. Antiplatelet preparation before admission

As a routine protocol, for all patients with unruptured aneurysm which plans to be treated with coil embolization, the standard antiplatelet preparation using daily 100mg aspirin and 75 mg clopidogrel is prescribed at outpatient clinic for more than 5 days, based on results of studies showing the effect and safety of the antiplatelet preparation.2-4

9.7. Admission, platelet function test, and check for enrollment

The patient is admitted 1 day before coiling. Blood sampling for platelet function test is performed. According to inclusion and exclusion criteria, study subject eligibility for the study is finally confirmed.

9.8. Patient agreement and informed consent

We will provide information as follows to the patient and family members and obtain written informed consent.

- The purpose of this study
- The methods of this study
- All procedures in each group will be performed within guideline of Korea National Health Insurance.
- Enrollment in this study is made by a voluntary agreement, and if patient do not want enrollment, there will be no disadvantage.
- If patient wants, patient can stop at any time.
- Even when patient stop this study, follow-up results can be evaluated.
- Individual information are protected.
- This study and protocol were reviewed and approved by the IRB.

9.9. Randomization and antiplatelet preparation according to the study groups

Based on results of platelet function test, patients with HTPR are assigned to the standard or modified preparation groups in a 1:1 ratio with random number generated by a web site program (www.randomizer.org). Patients without HTPR are assigned to the no-HTPR group.

9.9.1. Antiplatelet preparation for the standard preparation and no-HTPR groups

On the morning at coiling day, 100mg aspirin and 75mg clopidogrel are maintained.

9.9.2. Antiplatelet preparation for the modified preparation group

At the coiling day, the modified antiplatelet preparation is performed at least before 4 hours. For patients with HTPR to aspirin, high-dose (300mg) aspirin and 75mg clopidogrel are prescribed. For patients with HTPR to clopidogrel, loading-dose (200mg) cilostazol is added to the standard preparation. Because high-dose clopidogrel failed to reduce the thromboembolic event rate related with neurointervention in
a previous cohort study, we selected adding cilostazol to the standard regimen for the modified antiplatelet preparation.

9.10. Routine protocol of coil embolization for an unruptured aneurysm

All aneurysm coil embolization procedures will be performed under general anesthesia using a biplane angiographic unit (Integris Allura; Philips Medical Systems, Best, the Netherlands). Systemic heparinization is administered after placing a femoral introducer sheath. Rotational angiography, followed by three-dimensional image reconstruction by volume rendering, is performed before embolization in all patients, using the Integris 3D-RA software package (release 3.2, Philips Medical Systems). On the basis of the images generated using rotational acquisition, at least two working projections that provided the best achievable view of the aneurysm neck are defined. Stent-assisted coiling will be employed for aneurysms unfavorable for standard coiling. The stents used for stent-assisted coiling will be the Neuroform (Stryker Neurovascular, Fremont, CA) or Enterprise stents (Cordis, Miami Lakes, FL). In this study, only detachable bare platinum coils, which included the GDC (Stryker Neurovascular), MicroPlex (MicroVention, Aliso Viejo, CA), Orbit Galaxy (Cordis), and Axium (Covidien, Irvine, CA) coils will be used. During coiling procedure, a coil suitable for safe packing is selected among these coils at every step. Final postembolization angiography is performed in the working projection to evaluate occlusion grade and detect any complications. Frontal and lateral projections are also acquired at the end of the procedure. All femoral puncture sites are closed using Femoseal (St. Jude Medical, St Paul, MN) and manual compression is applied for an additional 5 minutes.

9.11. Routine protocol for patients after coil embolization

After procedures, the patients will be observed in a recovery unit for 30 - 60 minutes. If coiling procedure was successful and the patient is fully recovered from general anesthesia without any problem, the patient is transferred to general ward. During 24 hours, the patient will be monitored by attending nurses, as a routine protocol. Physician assistants (day time, every 2 hours) or on-duty residents (night time, every 4 hours) also check the patient status.

If any events occur, attending nurse will call physician assistants, on-duty residents, or operating neurointerventionists, who will check the patient status, again. In cases of transient ischemic attack (TIA) and stroke, Critical Pathway for in-hospital stroke is activated. MRI including diffusion weighted imaging is performed. If necessary, conventional angiography and intervention can be included for evaluation and management. In general, thrombus or embolus causing flow disturbance is evident, intra-arterial fibrinolytics or antiplatelet drugs (tirofiban or abciximab) can be used. In other cases, including bleeding complication, a proper management will be selected according to the severity of cases.

Patients without any event during 24 hours after coiling are discharge to home. They will visit our outpatient clinic on days 7 and 30 days after coiling. Before discharge, we will instruct the patients to visit our hospital regardless of an appointment after a medical care at primary or secondary care center near their home, if any problem related to coil embolization occurs.

The standard or modified antiplatelet regimen is maintained after coiling in patients treated with stent-assisted coiling. However, it is discontinued in patients treated with standard coiling without a stent, including single or
multiple microcatheter techniques and balloon-assisted coiling, if the patients do not have diseases requiring continuous antiplatelet medication.


Although thromboembolic events occurs, the assigned antiplatelet regimen should be maintained without additional modification for patients treated by stent-assisted coiling until 30 days after coiling. For patients treated by standard coiling without stent-assistance, antiplatelet medication is not allowed except in patients with diseases requiring continuous antiplatelet therapy.

However, fibrinolytics or antiplatelet drugs for intra-arterial infusion can be used for patient safety, when thrombus or embolus causing flow disturbance is evident on angiography.

9.13. Study withdrawal

The study can be withdrawn in cases as follows.

- Patient disagreement or agreement withdrawal
- Severe adverse effect occurred by antiplatelet drugs
- When physician decision is that the study is difficult to continue.


Baseline clinical (sex, age, weight, body mass index, smoking, alcohol intake, medication, and medical history), laboratory (complete blood count, clotting test, lipid panel, and platelet function test), and aneurysmal data (aneurysm diameter, neck size, dome-to-neck ratio, aneurysm volume, location, and cerebral artery status) will be collected. Procedural data (coil volume, coiling method, occlusion grade, packing density, procedure time, and procedural complications) are also collected. Aneurysm volume is measured with the Integris 3D-RA volume measuring tool, and coil volume is calculated at a web site (www.angiocalc.com). Using these two volumes, packing density (%, coil/aneurysm volume × 100) can be obtained. Occlusion grade is evaluated according to the Raymond grade.\(^16\)

<table>
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<th>Procedure Time period</th>
<th>Screening Day -90 ~ -1 (admission)</th>
<th>Coiling Day 0</th>
<th>Follow-up 1 Day 1 (discharge)</th>
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9.15. Outcomes

9.15.1. Primary outcome
A thromboembolic event during the early periprocedural period (within 7 days after coil embolization).

* A thromboembolic event is defined as (1) a thromboembolism detected during the coiling procedure or (2) a transient ischemic attack or ischemic stroke with evidence of infarction on diffusion weighted imaging, which occurs in vascular territory consistent with the treated aneurysm location. Because the most thromboembolic events is known to occur within the first 7 days after coiling, we selected 7 days as a time window of the primary outcome.

9.15.2. Secondary outcomes
1. Bleeding complications according to Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria within 30 days after coil embolization
2. A thromboembolic event that occurred during the periprocedural period (within 30 days after coil embolization)

TIMI bleeding criteria

Non-CABG related bleeding

Major
- Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)
- Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL
- Fatal bleeding (bleeding that directly results in death within 7 d)

Minor
- Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL

Requiring medical attention
- Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above
- Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)
- Leading to or prolonging hospitalization
- Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

Minimal
- Any overt bleeding event that does not meet the criteria above
Bleeding in the setting of CABG
- Fatal bleeding (bleeding that directly results in death)
- Perioperative intracranial bleeding
- Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding
- Transfusion of \( \geq 5 \) U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products.
- Chest tube output >2 L within a 24-h period

9.16. Data and safety committee
The independent data and safety committee blinded to the treatment assignments and patient information adjudicates all primary and secondary outcomes. Procedural imaging and clinical monitoring data of the study subjects including only subject number for identification will be stored to a computer in our hospital. Using GetSync program (www.getsync.com), only members of the committee can access these data in our computer at their remote sites.

9.16.1. Members of data and safety committee
Kyeong Sun Song, MD (neurosurgeon, New Korea Hospital, Kimpo, Korea)
Young Jin Lee, MD (neurosurgeon, Pohang Stroke and Spine Hospital, Pohang, Korea)
Arham Abrar, MD (neurointerventionist, Dr Cipto Mangunkusumo National Hospital, Jakarta, Indonesia)
Nur Setiawan Suroto, MD (neurointerventionist, Dr Sutomo General Hospital, Surayaba, Indonesia)

9.17. Statistical analysis
The Wilcoxon rank-sum test was used for continuous variables, and the \( \chi^2 \) or Fisher’s exact tests were used for nominal factors in comparisons of baseline characteristics.

9.17.1. Exploratory analysis
Before principle analyses, comparison of primary and secondary outcomes between the modified and standard preparation groups, the primary outcome of the standard preparation group will be compared to that of the no-HTPR group, to explore whether patients with HTPR have a high risk of thromboembolic events under the standard preparation. This step is important, because the principle analyses will be meaningless, if this exploratory analysis shows no association of HTPR with thromboembolic event. Additionally, it can be a solution for multiple comparison.

9.17.2. Principle analyses
If exploratory analysis shows a significant association of HTPR with primary outcome, we will perform principle analyses, comparisons of primary and secondary outcomes between the modified and standard preparation groups, to evaluate the effect and safety of the modified antplatelet preparation.

9.17.3. Outcome comparisons and adjustment
All comparisons will be performed by logistic regression analysis adjusted for factors with clinical relevance among variables showing a baseline group difference at a p-value of less than 0.2, and provided with an adjusted risk difference and 95% confidence interval.

Because event rates are expected to be low, the number of variables which can be included in logistic regression model will be restricted. Therefore, clinical relevance is important for selecting the variables. Risk factors or potential confounders which are supported by theory, empirical findings, or previous studies have a priority. Extraneous, redundant, or intervening variables can be excluded.

Furthermore, risk difference is more informative in the study with rare event rate rather than odds ratio, so that we will provide results of comparisons as a risk difference. However, when zero event occurs, only crude risk difference without adjustment will be provided.

9.17.4. Subgroup analyses
Subgroup analyses are performed to explore the uniformity of the primary outcome difference found overall. The primary outcome will be compared in the subgroups by aneurysm diameter and coiling method, which are known to have a high risk of thromboembolic events. The test for heterogeneity will be performed with Q-statistics.

9.18. Definition, evaluation, and report of adverse events related with drugs

9.18.1. Definition
Adverse event refers to an undesirable and unintended sign or symptom, or disease, which occurs in the study subject during the study. It does not have causal relationship to the investigated drugs or devices.

Serious adverse event refers to one of the followings among adverse events.
- Results in death or life threatening
- If hospitalization or extension of hospitalization is needed
- If causing continuous or significant disability or malfunction
- If causing congenital malformation or abnormality

9.18.2. Evaluation of severity
Adverse event shall be reported under the criteria for severity evaluation below:
- Mild, if least inconvenience is caused without impairing the subject’s normal daily life (function) and the subject is readily endurable.
- Moderate, if inconvenience is caused which significantly impairs the subject’s normal daily life (function).
- Severe, if the subject’s normal daily life (function) is disable.

9.18.3. Evaluation of causal relationship
Upon an adverse event, its relationship with the investigated device or drugs shall be evaluated by the investigator under the following criteria, and the investigator’s opinion shall be described.
10. Measures for Safety and Protection of Subjects

- The procedures specified in this protocol is established so that the investigator observe the spirit of the ICH-GCP and Declaration of Helsinki when performing and evaluating the study and recording the results.
- Before starting the study, the investigator shall submit the protocol, informed consent form, and other related documents to IRB for examination and approval.
- Any modification in the protocol will be reported to the IRB.
- Prior to conducting the study, an informed consent form shall be obtained from each subject.
- If a subject is damaged from the use of clinical procedure, the subject will receive all treatment under the standard procedure of our hospital.

11. Other Requirements for Safe and Scientific Execution of Study

- The investigator shall keep confidential all the information related to the essence of the protocol.
- Anonymity of the subject who participated in the study shall be secured.
- Data for identification of the subject will be strictly secured by the investigator.
- The investigator prepared a subject list including subject number and name to find out documents.
- On CRF, no information which can identify the subject are allowed and only subject number can be used.
- When the subject list and CRF will be submitted to other institutes, new identifier shall be provided.

12. Study Schedule

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13. References


