Design and Rationale for a Cognitive Outcome Substudy in Ischemic Stroke Patients with High Risk of Cerebral Hemorrhage

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Goal: Cognitive impairment and dementia are common disabilities after stroke and are associated with increased risks of mortality and recurrent stroke. The prevention of dementia and preserving cognitive function are also important in stroke patients, but its strategy is not established yet. This PICASSO-COG (PreventIon of CArdiovascular events in iSchemic Stroke patients with high risk of cerebral hemOrrhage for reducing COGnitive decline) substudy aims to assess the effects of cilostazol and/or probucol on cognitive function. *Materials and methods:* The substudy aims to assess the reduction in cognitive decline of patients treated with cilostazol and/or probucol in the PICASSO trial. Patients will be assessed using the Korean version of mini-mental state examination and Montreal Cognitive Assessment at 4, 7, 10, 13, 25, 37, and 49 months after randomization. The primary outcome is the change in mini-mental status examination score, compared between treatment groups, with a modified intention-to-treat population using a restricted maximum likelihood-based mixed effects model repeat measurement. This will allow a within-subject correlation due to repeated cognitive tests as well as a different number of measurements among subjects at baseline and each follow-up period. *Conclusion:* PICASSO-COG is a novel study for assessing the effect on cognitive function of different antiplatelet regimens and the addition of a nonstatin lipid-lowering agent to the current standard statin therapy in patients who have a recent ischemic lesion and prior intracerebral macro- or microbleeds. **Key Words:** Cognitive impairment—vascular dementia—cilostazol—probucol—intracerebral hemorrhage—microbleeds—cerebral infarction—clinical trial.

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Introduction

Cognitive impairment after stroke is common and significantly increases disability and physical impairment.[1] Furthermore, stroke patients have a greater cognitive decline rate over time compared to the general population. Poststroke cognitive impairment is associated with increased risks of recurrent stroke and mortality.[2] The occurrence of recurrent stroke is a powerful predictor of cognitive impairment, and the prevalence of dementia is higher among persons with recurrent stroke than in those with first-ever stroke.[3,4] Therefore, the effects of secondary stroke prevention therapies on cognitive function and vascular events need to be tested.

Previously, the effect on cognitive function was assessed for blood pressure lowering and antiplatelet therapies in a clinical trial setting, but the results were conflicting or negative.[5-7] Furthermore, no trial has been conducted to assess the effects of lipid-lowering therapy, and observation studies and meta-analyses have not shown convincing data.[8]

A recent clinical trial reported that cilostazol, a phosphodiesterase-3 inhibitor, decreased the risk of recurrent stroke, especially hemorrhagic stroke (HS).[9] Therefore, cilostazol may be a reasonable antiplatelet agent for reducing cognitive decline in ischemic stroke patients at high risk of HS. The PICASSO (PreventIon of CArdiovascular events in iSchemic Stroke patients with high risk of cerebral hemOrrhage) trial is an ongoing 2×2 factorial design trial comparing cilostazol versus aspirin and probucol (nonstatin lipid-lowering agent) versus no treatment on top of the standard statin therapy for the prevention of HS and composite of major vascular events.[10] This trial recruited patients who had recent noncardioembolic ischemic stroke or transient ischemic attack (TIA) and prior intracerebral hemorrhage (ICH) or multiple cerebral microbleeds (CMBs).[10] Previous studies have reported that ischemic stroke with CMBs or lacunar stroke is associated with higher risk of poststroke cognitive impairment.[11-13] Therefore, the patients enrolled in PICASSO would be at particularly high risk of cognitive impairment. Our current substudy, PICASSO-COG (PICASSO for reducing COGnitive decline), aims to assess individual treatment effects on cognitive function, the loss of which substantially impacts the quality of life of individual patients and their caregivers and also increases socioeconomic burden.

Materials and Methods

The PICASSO trial is an ongoing randomized, double-blind, placebo-controlled multinational trial. Currently, 67 institutes from 3 countries (South Korea, the Philippines, and Hong Kong, China) have participated in this trial. However, the PICASSO-COG substudy is only being conducted in South Korea because the mini-mental state examination (MMSE) as a primary outcome measurement has not been validated by cross-cultural studies in each language. Detailed information on the design of the PICASSO trial has been published elsewhere,[10] and the trial is registered with ClinicalTrials.gov, no. NCT01013532.

Briefly, key inclusion criteria are as follows: (1) noncardioembolic ischemic stroke or TIA within 180 days; (2) age more than 20 years; (3) previous ICH based on clinical or radiological findings or multiple CMBs on gradient echo (GRE) imaging; (4) no history of recent clinical HS within 180 days; and (5) no contraindication for long-term antiplatelet therapy (Table 1). For the PICASSO-COG substudy, patients who were not able to perform the cognitive test because of severe dysphasia or severe neurological deficits will be further excluded.

Based on the factorial scheme, patients are randomized to cilostazol 100 mg twice daily or aspirin 100 mg once daily and probucol 250 mg twice daily or non-probucol. The trial is a double-blind and double-dummy study using matched placebo to compare cilostazol versus aspirin groups, and an open-labeled, blinded endpoint evaluation to compare probucol versus non-probucol groups. The scheduled visits of the trial are every 3 months after the first-month visit during the first year of enrollment (at 4, 7, 10, and 13 months) and then annually until the completion of the study (at 25, 37, and 49 months). The trial is planned to complete at 12 months after the enrollment of the last subject with his/her closing visit.

Cognitive Outcomes and Follow-Up

The aim of our PICASSO-COG substudy is to assess the reduction in cognitive decline of patients treated with cilostazol and/or probucol in the PICASSO trial. Cognitive functions will be evaluated in all patients with the Korean version of the Mini-Mental State Examination (K-MMSE) and the Korean-Montreal Cognitive Assessment (K-MoCA). The MMSE is a simple and widely used assessment tool for evaluating cognitive function,[14] which is scored by summing the points assigned to each successfully completed task (total score range 0-30). Lower scores indicate a greater degree of cognitive impairment. The K-MMSE is the validated version of the MMSE with standardized norms.[15] It usually takes less than 15 minutes to perform, making it applicable and practical in clinical practice settings. The K-MoCA can be executed within 15 minutes, and evaluates the following cognitive domains: visuospatial/executive functions, naming, verbal memory registration and learning, attention, abstraction, 5 minutes delayed verbal recall, and orientation. The K-MoCA has been previously validated in patients with stroke.[16]

Cognitive examination data will be obtained at baseline as well as during follow-up visits. The baseline cognitive function is evaluated at the second visit in patients who are randomized within 3 months after stroke onset (4 months after enrollment), or at the first visit for those randomized between 4 and 6 months after stroke