Editorial Commentary

Safety and efficacy of restarting antiplatelet therapy after intracerebral hemorrhage

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Intracerebral hemorrhage (ICH) develops as a result of bleeding from a small arterial rupture and can be included in the category of cerebral small vessel disease (1,2). Because the risk factors for ICH such as advanced age, hypertension, and cigarette smoking are also those for occlusive vascular diseases (3), many ICH patients have an accompanying ischemic stroke or coronary artery disease, which are significant causes of long-term morbidity and mortality in these cases (4-6). Hence, life-long antithrombotic therapy may be required in a considerable number of patients to prevent or/and treat occlusive vascular diseases even after ICH.

Most physicians however are reluctant to initiate antiplatelet therapy in patients who have a history of ICH. Firstly, ICH can recur and a prior use of antiplatelet agents is related to early hematoma growth in this disorder and a higher risk of mortality (7,8). The long-term use of antiplatelet agents itself may also increase the incidence of hemorrhagic stroke (9). In addition, although there have been observational studies, no randomized clinical trials of antithrombotic therapy after ICH have been conducted.

The recent REstart or STop Antithrombotics Randomised Trial (RESTART) is unique and meaningful in this context because it is the first multicenter, randomised, clinical trial to scrutinize the safety and efficacy of resuming antiplatelet agents compared to stopping (or withdrawing) them in patients who were given these drugs prior to ICH onset (10). The investigators of RESTART trial recruited 573 subjects with spontaneous ICH, 88% of whom had a prior occlusive vascular disease. A central computerized randomization system, including a minimization algorithm that evaluated five important variables (ICH location, time since symptom onset, antiplatelet therapy preference, age, and probability of being alive and independent at 6 months), was utilized to minimize the bias at randomization. The results indicated that restarting antiplatelet agents did not increase the rate of recurrent ICH and rather produced a trend towards a reduced risk of this outcome [adjusted HR 0.51 (95% CI, 0.25–1.03); P=0·060]. Major hemorrhagic events were found not to significantly differ between the restart and avoid-antiplatelet therapy groups. Major vascular events defined by the Antithrombotic Trialists' Collaboration were understandably fewer in the restart group [adjusted HR 0.65 (95% CI, 0.44–0.95); P=0.025].

These findings from the RESTART trial were interesting but somewhat counterintuitive. Although previous observational studies have indicated that antiplatelet therapy has a beneficial effect in preventing composite and detrimental vascular outcomes, this effect appeared to be primarily due to the prevention of thrombotic events (11-13). Antiplatelet therapy had generally seemed to be associated with an increased risk of bleeding events. However, the RESTART trial suggested the possibility of net beneficial effects of these treatments in preventing recurrent ICH as well as vascular composite outcomes. Although the explanation for these contradictory results is

still uncertain, we speculate that either antithrombotic or hidden pleiotropic effects of antiplatelet therapy may affect the recurrence of ICH directly or may alter the underlying pathophysiology of cerebral small vessel disease.

We should be cautious when generalizing these results. First, it must be noted that RESTART was conducted in ICH patients who had been taking antithrombotic drugs. Antithrombotics-related ICH has different characteristics to non-associated form. The former is related to early hematoma growth and an increased risk of mortality (8). The discontinuation of aspirin after ICH was associated with decreased survival rate (14). Therefore, the effect of commencing antiplatelet agents after ICH in antiplatelet-naïve patients has to be separately verified. Second, a considerable number of eligible patients could not be included in RESTART because the treating clinicians were not certain of the impacts of resuming antiplatelet therapy (15). The basic premise of this trial was to determine the benefits in ICH patients requiring antithrombotic medication of restarting antiplatelet treatments that has been discontinued at disease onset. Because there were no clear criteria for judging risk-benefits in this cohort, the trial needed to include as many patients as possible and only exclude cases involving definite contraindications for resuming antiplatelet drugs, such as significant hemorrhagic transformation. The subjective preferences of the treating clinicians may well have resulted in a selection bias although a minimization algorithm was employed in the study design. Furthermore, there was no limitation in the timing to randomization. The median time to randomization was 76 days and 25% of the participants was recruited about four months after the onset of ICH. However, occlusive vascular events occurred relatively frequently at the early stages in the avoid-antiplatelet therapy group in the trial. The recruitment of patients at the chronic and stable stages of ICH may have resulted in the exclusion of high-risk patients and thereby impacted on the findings regarding antiplatelet therapy effects. In addition, the trial failed to recruit its target number of participants and instead extended the follow-up period to reach the required patient-years. However, no recurrent ICH or major hemorrhagic events occurred after the first two years during the follow-up period in the RESTART cohort. On the other hand, occlusive vascular events occurred consistently. We cannot therefore exclude the possibility of an attrition bias. Finally, there was an issue with adherence to study medication. In some patients, antiplatelet or anticoagulation therapy was newly administered or discontinued according to medical needs regardless of treatment allocation. Consequently, the restart group received more anticoagulation medication and were less adherent to the treatment strategy than the avoid-antiplatelet group.

The selection of high-risk patients, determination of the optimal timing of resuming, and choice of appropriate antiplatelet agent, are issues that remained unresolved in relation to ICH. A lobar location, concomitant cerebral amyloid angiopathy, and the presence/location/number of cerebral microbleeds are correlated with recurrence of ICH (16,17). Although subgroup analyses have revealed no significant heterogeneity of the effects of antiplatelet therapy, it is doubtful that antiplatelet therapy would have similar effects against a lobar and non-lobar lesion (10). Subsequent subgroup analyses using MRI have also been inconclusive due to the insufficient number of patients (18). A larger study population is needed to confirm the treatment impacts in high-risk patients. In addition, because of the high prevalence of ICH in Asia, additional studies in populations from this region are warranted. The optimal timing for restarting antiplatelet therapy in ICH patients remains unclear. After the absorption of hematoma and improvement of secondary tissue injury due to such hematoma, an additional antiplatelet regimen could conceivably be attempted. However, the administration of antiplatelet agents might be as soon as possible required to prevent new ischemic lesions and subsequent vascular events (19). The size of the hematoma and surgical intervention status should also be considered. Further assessments are thus needed that take account of these factors.

It is also noteworthy that the antiplatelet effect may depend on the type of drug used, i.e., its mechanism of action. One prior study has revealed that low dose aspirin treatments after hemorrhagic stroke are associated with improved survival, but that clopidogrel did not have these beneficial effects (14). Cilostazol, which has a lower bleeding tendency, would be an alternative, particularly in Asian ICH patients (20). Besides antiplatelet therapy, direct oral anticoagulants are superior to warfarin in terms of complications of intracranial hemorrhage (21) and should be evaluated in ICH patients with non-valvular atrial fibrillation.

Despite its limitations, the RESTART trial has successfully demonstrated the safety and efficacy of resuming an antiplatelet regimen after spontaneous ICH and has thus paved the way for further clinical trials. We expect that the currently ongoing RESTART-Fr (NCT02966119) and STATCHI (NCT03186729) trials

will further expand our understanding of the effects of antithrombotic therapy on recurrent ICH.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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