Editorial Commentary

Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): are neurologists feeling more comfortable to RESTART antiplatelet?

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With an aging global population, the prevalence of chronic atherosclerotic diseases requiring antithrombotic medications has risen steadily (1). The worldwide incidence of haemorrhagic strokes has also been on the rise, as indicated by the Global burden of disease (GBD) study, which revealed a 47% increase in the absolute number of haemorrhagic strokes (2). Unfortunately, these two opposing disease processes can be encountered in the same patient with or without antithrombotic(s). The dilemma of whether or not to restart antithrombotic in someone with a recent history of intracerebral haemorrhage (ICH) is one of the most challenging clinical scenarios in daily neurology practice. The randomized, open-label trial "*Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART)*" by Al-Shahi Salman *et al.* provides the highest quality data available till date addressing this critical question (3). Before this trial, only data from observational studies were available to guide the decision-making process, and frequently, these studies were confounded by biases and not capable to provide convincing evidence to clinicians (4-7). For example, the latest American Heart Association (AHA) guideline vaguely recommended anticoagulant after non-lobar ICH or antiplatelet monotherapy after any ICH might be considered, particularly when there are strong indications for these agents (class IIb; level of evidence B) (8).

Overall, the methodology of the RESTART trial is pragmatic and scientifically sound. The authors approached the research question with a non-blinded, open-label, randomized trial in patients with primary ICH who survived for at least 24 hours post-haemorrhage. There was no upper time-limit after the ICH for the inclusion of patients in the study. The patients were randomized in hospital or clinic with an adaptive stratification to allow for balancing of important variables such as the location of ICH (lobar *vs.* non-lobar) and choice of antiplatelet agent (aspirin *vs.* non-aspirin). The primary outcome was identified as fatal or non-fatal recurrent symptomatic ICH. Several composite secondary endpoints were defined as well.

The trial fell short by 183 participants as only 537 participants were randomized instead of the planned 720. Baseline variables are well balanced in the two arms. Basic demographics of the study include average age of 76 years, only one third are female, and 62% of the ICHs were lobar in location. The median ICH-to-randomization interval is 76 days. After a 2-year median follow-up, 4% of participants receiving antiplatelet agent and 9% of participants not receiving antiplatelet therapy have recurrent symptomatic ICH [hazard ratio (HR), 0.51; 95% confidence interval (CI), 0.25–1.03; P=0.060]. The antiplatelet arm has significantly lower rates of composite arterial thrombotic events (non-fatal myocardial infarction, non-fatal ischemic or haemorrhagic stroke, and mortality from a vascular cause)

compared to the arm of no antiplatelet use (HR, 0.65; 95% CI, 0.44–0.95; P=0.025), but there is no difference in the two arms when composite endpoints of arterial and venous thrombotic events (ischemic stroke, myocardial infarction, mesenteric ischemia, peripheral arterial occlusion, deep venous thrombosis, pulmonary embolism, and coronary, carotid, or peripheral arterial revascularization procedure) are assessed (HR, 1.02; 95% CI, 0.65–1.60; P=0.92).

The trial provides important, but somewhat interesting results. In survivors after ICH, initiation of antiplatelet therapy at a median of 76 days post-ICH did not result in a greater risk of recurrent ICH or other haemorrhagic events. On the contrary, there is a non-significant trend towards fewer recurrent ICH in the antiplatelet arm, which is mostly driven by fewer recurrence in patients with index non-lobar ICH. It is difficult to ascertain the reason for such an unexpected finding. The pathophysiological relation of arterial thrombosis and haemorrhage may play a role in such a finding as the authors suggested in the publication. There are a few other explanations of such a finding. Firstly, the power of the study. The initial power calculation was based on an assumption of the primary outcome event rate of 4.5% per year based on historical data but it turned out that the real event rate is much lower. Furthermore, the study was unable to recruit 720 patients as originally planned and to compensate, the study follow-up period was increased from 2 to 5 years to cumulate more events. In general, the rate of recurrent ICH is higher in the first year after the indexed event (9), and in the RESTART trial, none of the participants in either of the arms had a recurrent ICH after 2 years post-randomization. Since most of the primary endpoint events occurred earlier in the study period, the extension of the follow-up period likely did not correct the underlying problem. Secondly, only 1 out of 12 eligible patients was recruited in the study. Authors report that 26% of the eligible patients were not recruited because the physicians were certain on whether the patient would or would not be using antithrombotic therapy in the future. Lack of granular information on these patients raises the possibility of an inadvertent introduction of selection bias to this study by excluding high-risk patients.

The second important point noted in the study is the results of the composite secondary end-point of non-fatal myocardial infarction, non-fatal ischemic stroke, non-fatal haemorrhagic stroke, and death from a vascular cause. These results are consistent with prior observational data (7) and are likely the consequence of being on antiplatelet and better control of vascular risk factors, such as blood pressure (BP) control which is the number one determinant for subcortical ICH. This study provides the highest quality evidence available till date of an overall benefit in restarting antiplatelet therapy in patients with a strong predisposition towards cardiovascular and cerebrovascular disease.

The subgroup analysis stratifying patients based on the location of haemorrhage (lobar *vs.* non-lobar) is interesting. Fundamentally, two different pathophysiological mechanisms are responsible for most lobar ICHs and non-lobar ICHs. While most of the lobar haemorrhages in the elderly population is likely secondary to amyloid deposition in the distal small and medium-sized arteries near the cortex, non-lobar or subcortical ICH are generally believed to arise from Charcot-Bouchard microaneurysm affecting the penetrating arterioles secondary to chronic hypertension. An interesting observation is that the primary endpoint of recurrent symptomatic ICHs is significantly lower in the antiplatelet treated arm when a subgroup of non-lobar ICHs (HR, 0.31; 95% CI, 0.10–0.96) is analyzed. The subgroup analysis, including only lobar ICHs results in a trend towards lower recurrent ICH rates in the antiplatelet treated arm, but the difference is non-significant (HR, 0.75; 95% CI, 0.30–1.87). Prior observational studies yielded conflicting results regarding the risk of recurrent ICHs in patients with lobar ICH after resuming aspirin (10,11). Although resuming antithrombotic agents in patients with lobar-ICH does not result in a significant increase in recurrent ICH, several confounders are not accounted for, for example, the number of cortical microbleeds at baseline, the degree of white matter disease/hyperintensity, and prior history of ICHs. A separate publication from the authors of RESTART trial examines recurrent ICHs in patients with strictly lobar microbleeds *vs.* other locations and does not find any significant interaction with this variable (12). The important point to consider, however, is that only 7/122 (15%) and 23/132 (29%) patients had strictly cortical microbleeds in the antiplatelet arm and no-antiplatelet arm, respectively. Patients with multiple cortical microbleeds are perceived to be at a greater risk of recurrent ICHs and were under-represented in the trial. Because of this, the results of the study cannot be broadly applied to patients with moderate to severe cerebral amyloid angiopathy (CAA), and further studies are needed in this patient population.

With regards to the global applicability of the study, the study is conducted in the UK with >90% of patients being Caucasians. Certain ethnicities have been associated with greater risk of haemorrhagic strokes (13-15), and underrepresentation of these ethnicities is a major

drawback of the RESTART trial. In a systematic review, the incidence rate of ICH was 51.8 per 100,000 person-years in Asians compared to 24.2 per 100,000 person-years in Caucasians (16). Furthermore, the Asian population has greater hypertensive related ICH and fewer CAA related ICH compared to the Caucasian population (17,18). Lastly, Asians appear to be at a greater risk of suffering from an ICHs in the presence of cerebral microbleeds compared to Caucasians (19). An observational study analyzing Chinese patients with a history of ICH reported initiation of aspirin did not lead to a greater risk of recurrent ICH and decreased rate of composite vascular events (recurrent ICH, ischemic stroke, and myocardial infarction) (20). Differentiation of ICH etiology, presence/number of cerebral microbleeds were not clear in the study, however. Because of such epidemiological, etiological, and pathophysiological variations in ICHs among Asian population compared to the majority Caucasian patients in the trial, one has to be careful in extrapolating the results of the RESTART trial to the Asian population. Perhaps, patients with hypertensive related non-lobar ICH with no significant cerebral microbleeds and a strong indication for antiplatelet therapy can be restarted on antiplatelet therapy safely, but in Asians with lobar ICH or several cerebral microbleeds, more research is warranted.

The RESTART trial provides valuable insight and new evidence on this challenging clinical scenario. Although questions about the ideal timing of initiation of antiplatelet therapy, interaction of antiplatelet therapy with factors such as ethnicity, cerebral microbleeds, and apolipoprotein E alleles remain unanswered, the RESTART trial lays a solid foundation on which future trials can be built. We are positive, in the near future, neurologists will feel more comfortable about the decision to restart antiplatelet after an ICH.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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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