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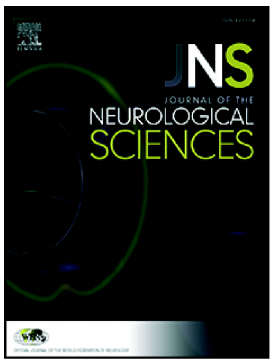

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EDITORIAL

Resumption of Antiplatelet Therapy in Patients with Primary Intracranial Haemorrhage: Balancing Benefits and Risks

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Intracranial or intracerebral haemorrhage (ICH) can be primary ICH (in the absence of a single clear underlying lesion) and secondary ICH (as a complication of a pre-existing lesion, such as vascular malformation or tumour; or antithrombotic therapy). Primary ICH is the most common type of ICH, and overall, is the second most common subtype of stroke accounting for approximately 10 to 20% of all strokes.

Antiplatelet therapies, particularly aspirin has been the cornerstone for primary and secondary prevention of ischaemic events such as myocardial infarction and ischaemic stroke for over 100 years. As the population ages, the prevalence of cardiovascular and cerebrovascular diseases is rising, leading to an increased use of antiplatelet agents. Conditions such as myocardial infarction and ischaemic stroke have a considerable risk of recurrence, thus necessitating continued use of antiplatelet therapy.

As antiplatelet therapy results in reduction of functioning platelets, theoretically it can predispose to bleeding or delay haemostasis to be achieved after a bleeding event. A systematic review by McQuaid *et al* showed that the use of antiplatelet therapy is associated with an increased risk of haemorrhage, including ICH [1]. People with ICH tend to have significant associated morbidity and mortality and due to the perceived risk of ICH recurrence, primary ICH is usually considered as a relative contraindication for antiplatelet therapy. Thus, the majority of clinicians have adopted a cautious approach in starting or resuming antiplatelet therapy in patients with confirmed diagnosis of ICH. This has serious implications for patients on antiplatelet therapy for a cardiovascular or cerebrovascular indication, who develop primary ICH.

Although few cohort studies have taken place to assess the risk of resuming antiplatelet therapy, these have involved small numbers [2-4]. Therefore, the meta-analysis by Ding and colleagues in this issue of *Journal of the Neurological Sciences* is timely. They performed a methodical and thorough search of major databases and found 6 relevant cohort studies with 1916 patients in total. Their results showed a significantly reduced risk of ischaemic or thromboembolic events following resumption of antiplatelet therapy (relative risk, RR 0.61; 95% confidence interval (CI), 0.48 - 0.79; $P<0.01$), which perhaps comes as no big surprise. More crucially, they found no significant difference in the risk of ICH recurrence or

haematoma expansion between patients with or without antiplatelet therapy resumption (RR 0.84; 95% CI, 0.47 - 1.51; P=0.56).

These findings are similar to the study by Risselada *et al* which provided evidence that the use of antiplatelets was not associated with an increased risk of ICH [5]. Furthermore, a systematic review performed by Hawryluk *et al* looking at resumption of anticoagulation following central nervous system (CNS) haemorrhage found that early re-initiation of anticoagulants may be prudent [6]. Another meta-analysis of controlled studies by Paciaroni *et al* looking at efficacy and safety of anticoagulants for the prevention of venous thromboembolism in patients with acute haemorrhagic stroke found that early anticoagulation is associated with a significant reduction in PE and a non-significant increase in haematoma enlargement [7].

This meta-analysis by Ding *et al* has several positive aspects addressing an important and clinically relevant issue. Nevertheless, limitations of this meta-analysis should be recognised. The cohort studies did not include patients on dual antiplatelet therapy, which is widely used in the context of primary coronary intervention (PCI) for myocardial infarction and shown to have increased risk of ICH [8, 9]. Only 6 cohort studies were included, and the limited studies and numbers of patients (n=1916) may decrease the reliability of the results. Furthermore, this may underestimate the risk of ICH recurrence or haematoma expansion.

The included studies used different antiplatelet agents, each with a varying bleeding profile. Indeed, 2 of the 6 studies' results showed heterogeneity when assessing the relationship between antiplatelet resumption and risk of ICH recurrence or haematoma expansion [10, 11]. In one of these studies, only aspirin was used which is associated with higher risk of adverse effects including haemorrhagic events when compared with other antiplatelet agents [10]. One other study conducted on patients with atrial fibrillation (AF) found that patients with AF who resumed antiplatelet therapy had decreased risk of ICH recurrence compared to those who did not resume [11]. However, baseline risks of haemorrhagic event between the two groups in the AF study was unknown, and it is possible that the patients with antiplatelet resumption may have had a lower risk of ICH recurrence at baseline due to potential selection bias. Also differences in timing of antiplatelet resumption, location of ICH

and the duration of follow-up and other factors may contribute to the heterogeneity. In addition, the studies included were all observational studies and patients may have difficulty in maintaining adequate adherence to the antiplatelet therapy. Lastly, differences in demographics, ethnicity, lifestyle and comorbidities cannot be avoided in cohort studies leading to potential bias.

What are the future considerations from this work? The meta-analysis by Ding and colleagues has shown that resuming antiplatelet therapy is generally safe in the setting of primary ICH with no significant increase in risk of recurrence or haematoma expansion, whilst providing significant reduction in the risk of ischaemic and thromboembolic events. Clearly, there are several limitations thus warranting a need for well-designed randomised controlled trials to provide better evidence. One such trial, REstart or STop Antithrombotics Randomised Trial (RESTART) is currently underway looking at this particular therapeutic dilemma. The data completion is set to complete by May 2018 and will provide stronger evidence.

For the time being, each individual patient's risks and benefits should be evaluated to enable appropriate management of these patients. Accurate assessment of bleeding risks (and addressing modifiable bleeding risk factors e.g. uncontrolled blood pressure, etc) may help clinicians to identify those patients for whom the benefits of antiplatelet therapy outweigh the risks. A limited number of prediction models are available that predict ICH or major bleeding in patients on antiplatelet therapy [12]. Unfortunately, external validation showed poor performance and thus none can be recommended for use in clinical practice [12]. Biomarkers may offer some insights, but would need to be balanced against the simplicity and practicality of clinical scores [13, 14]. Thus, there is still a great need to develop clinically validated risk scores according to current standards to help guide clinical management, such as those used successfully in the setting of AF and anticoagulation for stroke prophylaxis (e.g. CHA_2DS_2VASc and HAS-BLED risk scores).

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