Stroke Literature Synopsis: Clinical Science

STROKE/2017/018510

October 2017

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Word Count: 890 in text

Disclosures: Nil

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Recent clinical stroke research has predominantly focussed on hyperacute interventions. These treatments are life-saving and life-changing at the individual level, but are only applicable to a proportion of those affected by stroke. At a population level, effective primary and secondary prevention of stroke is the most important intervention. Three recent studies have given us important insights into one of the fundamental aspects of prevention, antithrombotic treatment.

Cardiologists have been using increasingly potent antiplatelets for the management of acute coronary syndrome for years. A large randomised controlled trial of the P2Y12 receptor antagonist ticagrelor suggested that the benefits of intensive antiplatelet that have been seen in cardiology may not translate to stroke. Across 13,199 participants randomly allocated ticagrelor or aspirin following stroke or TIA, there was no statistically significant difference in rate of cardiovascular events between the groups, albeit there was a strong trend in favour of ticagrelor. In this new paper, the authors present a pre-planned subgroup analysis of the main trial, restricted to participants with large vessel atherosclerotic disease as defined by 'ASCO' grading. **Amerenco et al Efficacy and safety of ticagrelor versus aspirin in acute stroke or transient ischaemic attack of atherosclerotic origin: a subgroup analysis of SOCRATES, a randomised, double-blind, controlled trial. Lancet Neurol. 2017;16:301-310** http://dx.doi.org/10.1016/S1474-4422(17)30038-8 This time there was a significant between group difference with 168 (6·8%) patients in the ticagrelor group and 208 (8·3%) in the aspirin group having a cardiovascular event (HR:0.79[95%CI:0.65-0.97].) Analyses describing rates of recurrent stroke and mortality were also in favour of ticagrelor.

We always have to be wary of 'positive' subgroup analyses when the main trial is neutral. However, stroke is a syndrome and not a distinct disease process and so it makes sense that certain treatments may only show efficacy for certain types of stroke. Future trials of secondary prevention may wish to stratify or restrict inclusion by underlying stroke pathology. Ongoing trials of anticoagulant in presumed cardioembolic stroke are already adopting this approach. Of course, all of this is dependent on robust classification of the index stroke event and in the messy reality of acute stroke this is not always straightforward.

With increasing potency of antiplatelet comes increasing risk of adverse events. An elegant study from Oxford, UK suggests that we may be underestimating the risk associated with antiplatelet. **Linxin Li et al Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet 2017 online before print DOI: http://dx.doi.org/10.1016/S0140-6736(17)30770-5.** In this population based cohort study, the authors described rates of bleeding in patients prescribed antiplatelet (usually aspirin) following stroke, TIA or myocardial infarction. The average annual risk of bleeding was 3.36% (95%CI:3.04-3.70). Risk of major bleed, severity of bleeding and poor outcomes from bleeding were all also higher in older adults. The risk of bleeding did not substantial decrease with increasing duration of exposure.

There are many salutary lessons from this paper. The bleeding risk in this real world cohort was higher than described in previous clinical trials where recruitment has tended to focus on younger patients with less comorbidity. Risk of cardiovascular events following stroke and TIA is highest in the first days to weeks but risk of bleeding seems to be maintained over time. Perhaps for older

adults who are taking antiplatelet for a vascular event that occurred in the distant past we need to rethink the risk-balance of continuing the antiplatelet treatment.

Although the most common bleeding event in the Oxford study was gastrointestinal bleeding, the most feared bleeding event (amongst stroke physicians) is intracerebral haemorrhage (ICH). Patients with bleeding episodes are not immune to future cardiovascular events, in fact they may be at increased risk so any guidance on antithrombotic prescribing in this group is welcome. A recent meta-analysis looked at the evidence around antithrombotic treatment following an intracerebral bleeding event. **Perry LA et al Antithrombotic treatment after stroke due to intracerebral haemorrhage. Cochrane Database Syst Rev. 2017 DOI: 10.1002/14651858.CD012144.pub2** The authors collated all controlled trials looking at antithrombotic treatment following ICH. For such a common and important question, the available evidence was modest at best. Despite a rigorous search strategy, in total there were only two RCTs with a combined participant population of 121. Both studies were judged at risk of bias in a number of areas and generalizability was limited as the interventions studied were parenteral anticoagulants and follow up was limited to the short term.

Accepting all these caveats, the use of anticoagulants following ICH appeared safe with no increase in mortality or bleeding but equally there was no decrease in thrombotic events. Clearly the available evidence is not sufficient to guide practice and the review authors' call for large scale RCTS seems well founded. Several such trials are currently recruiting. One could argue that we don't need the trials as we have a number of studies from observational registries that report safety of reintroduction of anticoagulant following ICH. However, a properly conducted randomised trial remains the gold standard as stroke medicine has many examples of interventions that appeared efficacious or safe in observational cohorts but were subsequently proven to be ineffective or harmful in RCTs. For now, when we are faced with a patient who has ICH but also an indication for antiplatelet then perhaps the best course of action is to randomise to one of the trials.