

## **ANTITHROMBOTIC THERAPY IN PATIENTS SUFFERING RECENT CEREBRAL ISCHEMIA AND A HISTORY OF INTRACEREBRAL HEMORRHAGE: TO INITIATE OR NOT TO INITIATE?**

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Should a patient with recent cerebral ischemia who in addition exhibits thromboembolic risk factors for ischemic events, be treated with antithrombotic drugs if he has suffered prior intracerebral hemorrhage (ICH)?

On the one hand such drugs may reduce the risk for stroke, on the other they can increase the risk of intracerebral bleeding because of previous ICH. This issue has yet to be resolved by relevant randomized controlled trials.

The use of antiplatelet medication is well established in secondary prevention as a means of reducing risk for myocardial infarction, ischemic stroke and ultimately death. In addition the use of either antiplatelet or anticoagulant medication has been shown to increase the risk for ICH. However, according to two large (extensive?) meta analyses, randomized trials, antiplatelet therapy, administered to subjects with no history of ICH, did not increase the risk of cerebral bleeding.

The consensus is that having an ICH infers increased risk of a recurrent hemorrhage event. Risk of ischemic stroke in patients with primary ICH is not very well established. A systematic review showed that while there is an annual recurrence risk of 4-15% of all stroke types following a primary ICH, most recurrences are hemorrhages; ( 2.4% a year ICH; versus 1.1% a year ischemic). For this reason the use of antithrombotic medication is avoided in such cases.

However, there are subgroups of people who are at high risk for developing ischemic stroke for example, those with advanced age, hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease or atrial fibrillation. In this group the risk for ischemic stroke was > 6.5% per year and risk for recurrent ICH was < 1.4% per year. These patients tend to have deep brain bleeding, may be at particularly high risk for thromboembolic event and at low risk for recurrence of ICH, and may benefit from long term anticoagulation or antithrombotic therapy even after prior ICH.

Flynn et al reported a systematic review of published observational studies dealing with prescribing antithrombotic meds following ICH where such a dilemma exists. The primary endpoint was recurrent ICH and the second end point was serious ischemic stroke or myocardial infarction.

The data concerning antiplatelet medicines following ICH comes from a single observational study reported by Viswanathan et al. It is a prospective observational case controlled study that discovered that use of antiaggregant therapy after ICH was not associated with increased risk of recurrent intracerebral bleeding, in either lobar or deep brain.

Other studies have shown that the risk for recurrent ICH is higher in lobar ICH versus deep ICH and is more prevalent in patients with cerebral asymptomatic microbleeds (MB) (detected on MRI) treated with aspirin.

Clinical asymptomatic micro-bleeding, detected by MRI, is a potential risk factor for ICH but whether it is a contraindication to using antithrombotic drugs, is unclear.

Lovelock et al performed a systematic review of published data regarding presence of micro bleeding among ICH or ischemic stroke patients receiving vs. not receiving antithrombotic meds , and whether ICH or ischemic events intensified by antithrombotic use. He concluded that there is no consistent association between microbleeding and antiplatelet associated ICH. But there was evidence that the risk for recurrent ICH is in correlation with the number of MB on a baseline scan. In addition it was concluded that lobar MB may be a marker for amyloid angiopathy. Amyloid angiopathy and/or the possession of the apo E, ε2 or ε4 allele are associated with increased risk for lobar ICH and recurrent bleeding. In these cases use of antiplatelet medications is usually avoided .

Should anticoagulants be used in patients with cardioembolic stroke and history of ICH?

The benefits of anticoagulation must be weighed against the serious risk presented in ICH.

Eckman et al used a decision making model (Markov state transition decision model) to measure quality adjusted life years with and without anticoagulation therapy in a hypothetical 69 year old man with a history of primary ICH and newly diagnosed non valvular atrial fibrillation. His conclusion was not to give anticoagulate for survivors from lobar ICH, although there is a high risk for embolic stroke. The risk and benefits of anticoagulation were more closely balanced when applied to patients with deep ICH in which the risk of recurrent bleeding is substantially lower and risk for thromboembolic event is greater. This subgroup may benefit from long term anticoagulation or antithrombotic therapy.

Hypertensive vasculopathy seems to be the most important mechanism for deep hemispheric ICH. A patient with ischemic stroke should receive anti thrombotic therapy even if he has suffered prior deep ICH. Some commentators have taken a more cautious interpretation and suggested that antiplatelet treatment should be used only in patients at high risk for thrombo-embolism.