INVITED COMMENTARY

Mirror Mirror on the Wall, Which Is the Most Protective Antithrombotic Therapy of Them All?

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Antiplatelet therapy remains a matter of controversy in patients undergoing carotid endarterectomy (CEA). It is still not clear whether the benefit of dual antiplatelet therapy (DAPT) in terms of peri-procedural stroke is counterbalanced by the increased risk of bleeding. To answer this question, Ku *et al.*[1] aimed to add new information compared with a recently published meta-analysis.[2,3] Overall data from 47 411 patients (30% receiving DAPT; mixed symptomatic status) reported in 11 studies (two randomised controlled trials [RCTs]) were included. Although DAPT substantially reduced the number of intra-operative microemboli compared with aspirin alone (OR 0.19, 95% CI 0.10 − 0.35), neurological events in the two treatment groups did not differ statistically significantly (stroke OR 0.87, 95% CI 0.72 − 1.05, TIA OR 0.78, 95% CI 0.52 − 1.17). Subgroup analysis found no difference for symptomatic status although separate data for timing of intervention were lacking. DAPT was, however, associated with an increased risk of relatively subjective endpoints such as neck hematoma (OR 2.79, 95% CI 1.87 − 4.18) and need for re-operation for bleeding (OR 1.98, 95% CI 1.77 − 2.23).

In patients with asymptomatic carotid stenosis (ACS), guidelines recommend aspirin monotherapy. The COMPASS trial suggested a potential benefit of dual pathway inhibition (DPI) by adding low dose rivaroxaban to aspirin. Most probably because of a lack of statistical power (only 7% [1.919] of COMPASS patients had carotid disease), there was only a trend towards a reduction in the composite endpoint (stroke, myocardial infarction, or cardiovascular death) from 6.1% (aspirin) to 3.9% with DPI (HR 0.63, 95% CI 0.38 − 1.05, $p = .070$).[4] Therefore, aspirin monotherapy remains the treatment of choice for patients with ACS (undergoing CEA or not).

In contrast, patients with symptomatic stenosis obviously benefit from the addition of clopidogrel or dipyridamole immediately after symptom onset to reduce the recurrent neurological event rate. All RCTs selected conservatively treated patients only. The controversy in this context therefore is the management of DAPT in patients undergoing revascularisation and especially the early peri-operative period. In the meantime, guidelines increasingly recommend continuing aspirin + clopidogrel for a 21 day course from the index event irrespective of the indication for undergoing CEA. Based on non-randomised studies, the analysis by Ku *et al.* confirmed the higher bleeding risk with DAPT without showing a benefit in terms of neurological outcome. Importantly, the overall quality of the included studies was low while missing high quality data on crucial clinical endpoints such as post-operative haemorrhagic stroke. Interestingly, the only RCTs both focused on the surrogate endpoint of intra-operative embolisation while an RCT on clinical endpoints is still lacking. The Ku analysis is directive but several important questions remain unanswered: 1) safety of DAPT in early CEA; Does a wound hematoma really outbalance the protective effect of DAPT concerning recurrent stroke in the 48 − 72 hour time period?[5] 2) optimal antithrombotic therapy in patients with comorbidities such as atrial fibrillation? 3) effect of protamine reversal on wound haematoma? In practical terms, predefined outcome reporting standards in prospective registry based analyses may provide a refined answer to these open questions. Until standardised analysis from a prospective registry is available, the current guideline recommendation on DAPT in the early three week period may offer the most balanced and pragmatic approach.

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