DUAL OR MONO ANTIPLATELET EARLY AFTER TIA OR MINOR STROKE?: MONO

Christian Weimar
Department of Neurology and Stroke Center, University Duisburg-Essen, Essen, Germany

Patients with a transient ischaemic attack (TIA) or minor ischaemic stroke are at high risk of (recurrent) stroke, particularly during the first few days after the index event. Aspirin is effective in preventing early recurrence, but its treatment effect is small. A recent meta-analysis by Palacio *et al.* analysed four trials that investigated the addition of clopidogrel to aspirin in 1,930 patients with recent (≤30 days) brain ischaemia. Fourty-eight recurrent strokes occurred within the first 90 days in the combination therapy group, compared with 73 in the aspirin mono-therapy group (OR 0.67, 95% CI 0.46–0.97). Major haemorrhage (*n* = 21) was not significantly increased by dual antiplatelet therapy in these trials. A total of seven intracerebral haemorrhages were reported in the four trials: four with combination therapy and three with aspirin alone (meta-analysis OR 1·12, 96% CI 0·29–4·32). Thus, there might be a benefit of early antiplatelet combination therapy in patients with TIA or minor stroke—a concept that has recently been investigated in the Chinese CHANCE trial.

The randomized, double-blind, placebo-controlled CHANCE trial randomized 5,170 patients within 24 h of onset of minor ischaemic stroke or high-risk TIA. Both groups received open-label aspirin on day 1, at doses of 75-300 mg at the discretion of the treating physician. Patients in the clopidogrel–aspirin group received a loading dose of 300 mg of clopidogrel on day 1, followed by a dose of 75 mg per day on from day 2 to 90, aspirin at a dose of 75 mg per day on days 2 to 21, and placebo aspirin on days 22 to 90. Patients in the aspirin-only group received a placebo version of clopidogrel on days 1 to 90 and aspirin at a dose of 75 mg per day on days 2 to 90. The primary outcome (ischaemic or haemorrhagic stroke during 90 days of follow-up) occurred in 8.2% of patients in the clopidogrel-aspirin group compared with 11.7% in the aspirin group (hazard ratio [HR] 0.68; 95% CI 0.57–0.81; *P* <0.001). Notably, the rate of haemorrhagic stroke was 0.3% in both groups.

However, the question that arises is whether these results can be readily transferred to non-Chinese populations: should we change existing guidelines and implement combination antiplatelet therapy early after TIA or minor ischaemic stroke based on this well planned and executed trial? The pathophysiology of TIA and ischaemic stroke in Chinese patients is quite different to that in caucasian patients, as the former have a much higher incidence of intracranial atherosclerosis. In addition, Asian populations have different genetic polymorphisms for liver enzymes, which are important for the metabolism of clopidogrel. Patients were not treated according to Western standards. The very high recurrence rate in this trial could therefore be explained by the fact that secondary prevention other than antiplatelet therapy was not routinely offered to all patients included in this study. Only about 42% received lipid-lowering drugs, about 35% received antihypertensive treatment, and only 0.4% received heparins for prevention of deep venous thrombosis. How many patients with high-grade carotid stenosis were included in the trial rather than received carotid endarterectomy or stenting was not reported.

Studies from TIA clinics in Oxford, UK and Paris, France, with an early in-depth diagnostic work-up and initiation of secondary prevention (including dual antiplatelet therapy in presumed high-risk patients only) have shown markedly reduced rates of recurrent stroke (1–2% vs 8–12% in CHANCE) within 90 days following the index event. CHANCE had a 90 day observation period with only 3 weeks of dual antiplatelet treatment. The rates of recurrent stroke were particularly high in the first few days, during which the curves representing the treatment groups diverged dramatically. Subsequently, the rates of stroke were similar in both treatment arms, suggesting that the individually chosen loading dose of aspirin may have been insufficient compared to the combination of aspirin and the fixed loading dose of clopidogrel employed in this study.

Evidence from the MATCH, CHARISMA and SPS3 trials clearly indicate that the combination of aspirin and clopidogrel is not superior to aspirin or clopidogrel in long-term secondary stroke prevention, and that combination treatment carries a higher bleeding risk. One possible reason for this finding was the inclusion of many patients with a low recurrent stroke risk. By contrast, patients with recently symptomatic intracranial or extracranial atherosclerotic lesions might particularly benefit from dual antiplatelet therapy. Only the latter group has been previously investigated in a phase II study, which was not sufficiently powered to detect a clinical benefit of dual antiplatelet therapy. It would, therefore, be of great interest to know the presumed stroke aetiology of patients included in CHANCE in order to define which patient subgroup is most likely to benefit from early dual antiplatelet therapy. Before advocating dual antiplatelet therapy in unselected patients with TIA or minor stroke in the acute phase, we should therefore await the results of the ongoing North American POINT trial. Nevertheless, because the early recurrent stroke rate in Western populations is considerably lower, it will be much harder to show a significant and clinically relevant benefit of combination antiplatelet therapy.