Secondary prevention by stroke subtype: impact of the Korean experience

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This editorial refers to ‘Secondary prevention by stroke subtype: a nationwide follow-up study in 46 108 patients after acute ischaemic stroke’, by D. Kim et al., on page 2760

The next best thing to a properly powered randomized trial in patients with vascular diseases is a large population-based prospective registry. Such a registry exists since 2002 in South Korea for stroke patients with vascular diseases is a large population-based prospective registry. The authors grouped the stroke aetiology according to the TOAST criteria. The most important subgroups were large vessel disease (34%), small vessel disease (24%), cardio-embolic stroke (16%), other defined causes (1.7%), undetermined cause (14.2%), and transient ischaemic attack (TIA; 7%). Large vessel disease is defined by a stenosis of >50% or occlusion of a brain-supplying artery. Small vessel disease causes small strokes in the deep white matter of the brain in patients with diabetes or hypertension (Figure 1). Patients were followed up on average for 2.4 years, and mortality, the primary endpoint, was 22.5%. Other endpoints, e.g. stroke recurrence, were not assessed.

Based on large vessel disease as a reference, the mortality was increased by 47% in cardio-embolic stroke and decreased by 45% in small vessel disease. This information is not new, but underlines the importance of atrial fibrillation as a risk factor with poor prognosis and the importance of stroke prevention by anticoagulation.

The second part of the paper investigates the possible association between different antithrombotic medications and all-cause and vascular mortality. The authors claim that compared with antiplatelet monotherapy, antiplatelet polytherapy, anticoagulation, and the combination of antiplatelet therapy plus anticoagulation all decrease vascular death by 7–20%. The risk of fatal haemorrhagic stroke is increased by 3–61%. The risk was high for patients receiving anticoagulation who had large artery atherosclerosis or small vessel occlusion. Another group with an increased risk of fatal cerebral bleeds were patients on the combination of anticoagulation plus antiplatelet therapy without cardio-embolic aetiology of stroke.

One disturbing aspect of the study is the fact that obviously a whole country and healthcare system neglects the results from randomized trials and treatment guidelines. Three randomized trials have been performed investigating monotherapy with either aspirin or clopidogrel against the combination of aspirin and clopidogrel in secondary stroke prevention in patients without cardio-embolic strokes. All three trials (MATCH, CHARISMA, and SP3) showed that combination antiplatelet therapy had no benefit in preventing vascular events including stroke, but resulted in a significant increase in major bleeds. The MATCH trial was published in 2004 and the CHARISMA trial in 2006, giving stroke physicians in South Korea ample time to change their approach of using antiplatelet polytherapy. In addition treatment guidelines from the USA and Europe discouraged the use of combination antiplatelet therapy in stroke prevention.

Despite all this information, 13 990 patients (30%) were treated with combination antiplatelet therapy including aspirin + clopidogrel, aspirin + cilostazol, aspirin + ticlopidine, aspirin + triflusal, clopidogrel + cilostazol, and aspirin + clopidogrel + cilostazol. I want to reiterate that we only have scientific evidence for the combination of aspirin plus clopidogrel (negative outcome), but none for the other combinations. The only combination therapy which has proven efficacy over aspirin monotherapy, namely the combination of aspirin and slow-release dipyridamole, was not used. The authors provide no information on whether the outcome of the randomized trials resulted in a change in treatment strategies in South Korea. One could argue that the large number of patients in this data set could provide results that are different from the results of randomized trials simply due to a higher power. We have to admit that in none of the randomized trials so far performed with single vs. polytherapy has a decrease or increase in mortality been observed. Avoiding cerebral haemorrhage in patients on antithrombotic treatment has a high priority, due to the poor prognosis of these events, with a mortality of up to 50%.

On the positive side, 60% of all patients with cardio-embolic strokes were anticoagulated. This is by far the most effective way to prevent strokes in patients with atrial fibrillation. But again, 10%...
of the patients were treated with antiplatelet polytherapy. We showed in the ximelagatran studies that the addition of aspirin to either warfarin or ximelagatran in patients with atrial fibrillation will not decrease the number of vascular events, but will increase the risk of major bleeding complications. Similar observations were made in the recently concluded trials with novel anticoagulants vs. warfarin in patients with atrial fibrillation. Hopefully the feedback from this editorial will help the stroke physicians in South Korea to reconsider the use of antiplatelet combination therapy in secondary stroke prevention.

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