Patients with transient ischemic attack or ischemic stroke have a high risk of recurrent stroke. Antiplatelet therapy has shown efficacy in secondary stroke prevention and is recommended by guidelines.\(^1\) In patients without cardiac source of embolism aspirin, clopidogrel or the combination of aspirin and dipyridamole is recommended.

In cardiology, the combination of aspirin and clopidogrel was superior to aspirin monotherapy in the prevention of vascular events after acute coronary syndrome\(^4\) but carried a higher bleeding risk. In patients with atrial fibrillation the combination of aspirin plus clopidogrel was superior to aspirin alone in preventing strokes,\(^5\) but was again associated with a significant higher risk of major bleeds. In early secondary stroke prevention after transient ischemic attack or minor stroke combination, antiplatelet therapy seems to be superior to monotherapy, but larger randomized trials are needed.\(^6,5\)

Combination antiplatelet therapy carries a consistent higher risk of major bleeding complications than monotherapy. Therefore, the possible benefit of a reduction in vascular events has to be balanced against the bleeding risk, especially in stroke patients. In the Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) trial, aspirin plus clopidogrel was investigated against aspirin monotherapy in high-risk patients with recent transient ischemic attack or ischemic stroke.\(^6\) Similar to the Secondary Prevention of Small Subcortical Strokes (SPS3) trial, patients with a cardiac source of embolism and significant carotid stenosis requiring surgery were excluded. About 50% of patients were categorized to have small vessel disease with suspected lacunar strokes, but in contrast to the SPS3 trial, no magnetic resonance imaging was required to demonstrate the lacunar lesion. MATCH showed no benefit of combination over monotherapy for the prevention of vascular events but a significant increase in major bleeding complications.

The SPS3 trial was a double-blind, multicentre trial with 3020 patients with recent symptomatic subcortical lacunar ischemic strokes identified by central-reading magnetic resonance imaging.\(^9\) All patients received 325 mg aspirin daily, and 1517 patients were randomized to receive in addition 75 mg clopidogrel daily. The primary outcome was any recurrent stroke, including ischemic and hemorrhagic stroke. SPS3 was an investigator-initiated trial sponsored by the National Institute of Neurological Disorders and Stroke. Of note, as SPS3 was designed in a 2-by-2 factorial design to study also the effect of intensive (<130 mm Hg) versus usual systolic blood pressure lowering (130–149 mm Hg), patients were not randomized in the first 2 weeks after their qualifying stroke to avoid blood pressure lowering in the acute stroke phase.

The study was terminated prematurely at the recommendation of the data safety monitoring board because of a significant increase in major bleeding complications.\(^10\) The mean age of the patients was 63 years, and 63% were men. After a mean follow-up of 3.4 years, the risk of recurrent stroke was not significantly reduced with dual antiplatelet therapy (125 strokes; rate, 2.5% per year) as compared with aspirin monotherapy (138 strokes; 2.7% per year) (hazard ratio, 0.92; 95% confidence interval, 0.72–1.16). This was also true for recurrent ischemic stroke. The risk of major hemorrhage was significantly increased with dual antiplatelet therapy (105 hemorrhages; 2.1% per year) as compared with aspirin alone (56, 1.1% per year) (hazard ratio, 1.97; 95% confidence interval, 1.41–2.71; \(P<0.001\)). 13 versus 21 patients experienced intracranial hemorrhage (hazard ratio, 1.65; 95% confidence interval, 0.83–3.31; \(P=0.15\)). Mortality was significantly increased among patients on dual antiplatelet therapy (77 deaths in the group receiving aspirin alone versus 113 in the group receiving dual antiplatelet therapy) (hazard ratio, 1.52; 95% confidence interval, 1.14–2.04; \(P=0.004\)).

**Critique**

SPS3 replicated the results of the MATCH trial in secondary stroke prevention\(^4\) and the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial,\(^11\) a mixed trial of primary and secondary prevention. Was it ethical to continue with SPS3 once the results from MATCH and CHARISMA were available? MATCH recruited patients from 2000 to 2002 and reported the results in 2004. CHARISMA recruited...
patients from 2002 to 2003 and reported outcomes in 2006. SPS3 started recruitment in 2003 and reached the anticipated number of patients in 2011. In principle, new treatment paradigms need to be investigated in at least 2 independent randomized trials. This principle was fulfilled by the well-designed SPS3 trial. MATCH and CHARISMA did not enrol only patients with lacunar stroke and did not require magnetic resonance imaging evidence of such an infarction. Theoretically, patients with lacunar strokes could respond differently to combination antiplatelet therapy than patients with other stroke mechanisms. The negative result of all 3 trials shows the opposite, namely that more powerful inhibition of platelet function has no additional benefit. The local occlusion of small penetrating arteries with vessel wall hyalinosis is obviously not primarily owing to platelet activation and aggregation.

SPS3 adds to the repeated observation that combination antiplatelet therapy increases the risk of extracranial and intracranial bleeding in long-term follow-up. This is not only true in secondary stroke prevention but also in the prevention of vascular events after acute coronary events or in stroke prevention in patients with atrial fibrillation. In SPS3 the rate of major bleeding complications was increased with combination antiplatelet therapy. This was primarily because of an increase in gastrointestinal bleeding. The same was true in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial. In PRoFESS, the combination of aspirin and dipyridamole had a higher risk of major bleeds compared with clopidogrel monotherapy. Therefore, the higher dose of aspirin in SPS3 (325 mg/d) cannot account for this effect. In PRoFESS, a dose of 25 mg aspirin bid was used.

Finally, there is a disconnect between patients with cardiac disease and stroke. In acute coronary syndrome, the benefit of combination antiplatelet therapy has been shown and the benefit outweighs the bleeding risk. The same is true for more potent new antiplatelet drugs. Voroxapar plus aspirin is superior to aspirin monotherapy in patients with prior myocardial infarction but not in patients with transient ischemic attack or stroke.

Is there still a place for combining aspirin and clopidogrel in secondary stroke prevention? In our opinion, there are 2 scenarios to still prescribe this combination antiplatelet therapy in stroke patients: patients with stroke owing to intracranial atherosclerotic stenosis and, as mentioned earlier, in the acute and early postischemic period (ie, first 3 months). The same dose of aspirin and clopidogrel was administered for 90 days as part of aggressive medical therapy in the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) study and has been shown to reduce microembolic signals in the small randomized clopidogrel plus aspirin versus aspirin alone for reducing embolization in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR) study. Similar to the results of MATCH, the Kaplan–Meier curves for major hemorrhages in SPS3 first started to diverge after the initial couple of months. But of course, these 2 indications have to be again investigated in specially designed and adequately powered randomized trials.

Acknowledgments

Hans-Christoph Diener received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Abbott, Allergan, AstraZeneca, Bayer Vial, BMS, Boehringer Ingelheim, CoAxia, Corimmun, Coviden, Daiichi-Sankyo, D-Pharm, EV3, Fresenius, GlaxoSmithKline, Janssen-Cilag, Knoll, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plow, Servier, Solvay, Thrombogenics, Wyeth and Yamanouchi. Financial support for research projects was provided by AstraZeneca, GSK, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis and Takeda. The Department of Neurology at the University Duisburg-Essen received research grants from the German Research Council (DFG), German Ministry of Education and Research (BMBF), European Union, National Institutes of Health, Bertelsmann Foundation and Heinz-Nixdorf Foundation. H.C. Diener has no ownership interest and does not own stocks of any pharmaceutical company.

Disclosures

None.

References


**Key Words:** aspirin ■ clopidogrel ■ lacunar stroke ■ randomized trial ■ stroke prevention
Clopidogrel Added to Aspirin Adds No Benefit but Bleeding Risk in Patients With Recent Lacunar Stroke
Hans-Christoph Diener and Ralph Weber

Stroke. 2013;44:861-863; originally published online January 22, 2013; doi: 10.1161/STROKEAHA.112.680751

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