The role of combination therapy, whether antiplatelet or antithrombotic, in secondary stroke prevention is controversial. The only widely accepted combination therapy is clopidogrel plus aspirin in patients with coronary, carotid, or intracranial artery stents. The duration of combination antiplatelet therapy in stent patients is, however, controversial, with a minimum of 3 months used in most patients. Permanent combination antiplatelet therapy is probably indicated in patients with drug eluting stents.

The combination of extended release dipyridamole and low-dose aspirin was superior to either agent alone for secondary stroke prevention in the ESPS2 and ESPRIT trials. This is in contradistinction to combined clopidogrel and aspirin, which was not superior to either clopidogrel alone or aspirin alone in the MATCH and CHARISMA trials, respectively. Perhaps paradoxically, the combination of low-dose aspirin and extended release dipyridamole was not superior to clopidogrel alone in the PROFESS trial. In these trials, bleeding complications, including intracerebral hemorrhage, were significantly increased with combination antiplatelet therapy.

The role of antiplatelet therapy combined with warfarin is even more controversial. Warfarin was not superior to aspirin for noncardioembolic stroke risk reduction in WARSS. In two substudies, there was no statistical benefit of warfarin compared to aspirin in patients with patent foramen ovale (PICSS) or antiphospholipid antibodies (APASS). Furthermore, warfarin was not superior to aspirin in patients with documented >50% intracranial atherostenosis in WASID.

Warfarin is superior to either aspirin or clopidogrel plus aspirin for stroke prevention in patients with atrial fibrillation. Warfarin is also superior to antiplatelet therapy in patients with mechanical heart valves and probably in patients with severe left ventricular dysfunction (although this concept is being tested in WARCEF).

It is well known that bleeding risks are higher with warfarin compared to antiplatelet therapy, and they are certainly further increased when warfarin is combined with aspirin or other antiplatelet agents.

Given this data, are there any patient populations remaining where the bleeding risk associated with combined warfarin and antiplatelet therapy may be justified? Despite the studies cited above, this remains a surprisingly common clinical dilemma. The most common scenario involves patients at risk for both cardioembolic (“red clot”) and atherosclerotic (“white clot”) stroke. Another scenario involves defining “maximal medical therapy” in patients with recurrent or fluctuating ischemic events related to high grade atherostenosis. A third scenario consists of so-called aspirin or antiplatelet “failure” patients. A fourth scenario includes patients with very recent events.

In a metaanalysis, Larson et al found that the combination of warfarin plus aspirin was beneficial only in patients with mechanical heart valves. In patients with mechanical heart valves, warfain plus aspirin significantly decreased thromboembolic events (relative risk [RR], 0.33; 95% confidence interval [CI], 0.19 to 0.58), increased major bleeding (RR,1.58; 95% CI, 1.02 to 2.44), and decreased all-cause mortality (RR, 0.43; 95% CI, 0.23 to 0.81) compared to warfarin alone. There was no evidence that adding aspirin to warfarin was beneficial in patients with recent myocardial infarction or atrial fibrillation.

However, an increasingly common clinical scenario involves patients with atrial fibrillation (or other classic cardioembolic source such as left ventricular failure) who also require a coronary, carotid, or intracranial artery stent for symptomatic atherostenosis. In such patients warfarin alone is insufficient to prevent in stent thrombosis. These patients are often treated with aspirin plus clopidogrel plus warfarin for 3
to 6 months and then aspirin plus warfarin long-term. In very high bleeding risk patients, warfarin is sometimes withheld for 3 months while the patient is on aspirin plus clopidogrel (ie, the higher cardioembolic risk is accepted for 3 months). There is no evidence available to suggest which approach is best in these patients.

Although WASID did not find any benefit of warfarin compared to high dose aspirin in patients with symptomatic >50% intracranial atherostenosis, combination therapy was not tested. Should a patient with 90% symptomatic basilar artery atherostenosis with recurrent events on aspirin alone (“failure”) be switched to clopidogrel (or extended release dipyridamole—an even lower dose of aspirin), or should warfarin, an antithrombotic, be added? How do we define “maximal medical therapy” in such high risk patients? Should they fail one antiplatelet agent, combined antiplatelet agents, or combined antithrombotic and antiplatelet agent(s) before proceeding to a stent? What is the role of platelet function monitoring in such patients, and what is the optimal INR?

The last group for consideration are patients with very recent events. There is evidence that more aggressive antiplatelet therapy is beneficial after acute myocardial infarction or recent stroke related to carotid artery atherostenosis. Patients with acute myocardial infarction benefit from multimodal antithrombotic and antiplatelet therapy. Presumably this reflects altered plaque anatomy with rupture or ulceration promoting both platelet and fibrin aggregation. Acute carotid artery occlusion is also associated with fresh platelet fibrin thrombus superimposed on a ruptured atherosclerotic plaque—is there a role for short term warfarin plus aspirin in these patients?

Does the combination of warfarin and aspirin have a place in secondary stroke prevention? The answer is “yes” for patients with mechanical heart valves and atherosclerotic risk factors. The answer is “probably” for patients with coronary, carotid, or intracranial artery stents and atrial fibrillation or other high risk cardioembolic source. The answer is “maybe” for antiplatelet “failure” patients with high-grade atherostenosis or patients with very recent stroke caused by large vessel atherothrombosis. The most certain answer is that we “definitely” need more evidence regarding combination antiplatelet and antithrombotic therapy in well-defined patient subgroups whom we seem to see everyday but somehow do not end up in clinical trials.

Disclosures

None.

References


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