*Case Report*

# Triple Antiplatelet Therapy for Secondary Prevention of Recurrent Ischemic Stroke

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Antiplatelet agents are effective for secondary prevention after ischemic stroke, although they do not always prevent recurrent events. Laboratory studies confirm that therapy with 3 antiplatelet agents is superior to dual therapy or monotherapy at inhibiting platelet and leucocyte function. We report here a 69-year-old man who had recurrent strokes despite single or dual antiplatelet agents, but who responded to a combination of aspirin, dipyridamole, and clopidogrel. Likewise, triple antiplatelet therapy was effective in a series of 8 additional patients during a period of 28 months of follow up. Because combining 3 agents runs the risk of major bleeding, clinical trials are essential to address issues of safety and efficacy in patients with stroke. **Key Words:** Antiplatelet therapy—ischemic stroke—secondary stroke prevention.


## Case Report

A 69-year-old right-handed man presented in 1999 with a series of 4 episodes of right-sided weakness, each lasting less than 1 hour (patient 6, Table 1). He had multiple risk factors including hypertension, type 2 diabetes, hypercholesterolemia, peripheral vascular disease, and smoking. At his first clinical assessment there were no abnormal neurologic findings. No abnormalities of the carotid arteries were found, and electrocardiographic and transthoracic echocardiographic results were normal. Computed tomography of the brain showed periventricular ischemia and well-defined infarcts located in the caudate nucleus, external capsule, and temperoparietal subcortical regions bilaterally. A diagnosis of recurrent transient ischemic attacks was made and he was treated with a combination of an angiotensin-converting enzyme inhibitor, statin, and clopidogrel (aspirin was avoided because of dyspepsia). In January 2001 he presented with another episode of right-sided weakness lasting 48 hours. Examination revealed a mild right hemiparesis. Carotid Doppler results were normal and head computed tomography scan showed widespread chronic ischemia with additional infarcts in the deep white matter of both cerebral hemispheres and the left occipital lobe. Secondary prevention was increased by addition of aspirin (75 mg once daily) and a calcium antagonist for hypertension. Subsequently, in September 2001 he presented with another transient episode of right-sided weakness lasting 1 hour. Clinical neurologic findings had resolved at the time of assessment when a diagnosis of left transient ischemic attack was made. Head magnetic resonance imaging found cerebral atrophy with areas of periventricular and deep white matter changes. Multiple areas of

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**Table 1.** *Patients receiving triple antiplatelet therapy*

| Patient | Comorbidity | Previous treatment | Recurrent strokes on previous treatment | Duration on triple therapy (mos) | Recurrent strokes on triple therapy | Status of triple therapy |
|---|---|---|---|---|---|---|
| 1 | Hypertension<br>PFO | A<br>A + D | 3 | 15 | 0 | Discontinued after closure of PFO |
| 2 | Carotid artery disease (bilateral)<br>Hypertension<br>Hypercholesterolemia | A<br>A + D | 3 | 25 | 0 | Continuing; no adverse events |
| 3 | Carotid artery disease (bilateral)<br>Ischemic heart disease<br>Hypertension | A<br>A + D | 2 | 28 | 0 | Continuing; no adverse events |
| 4 | Hypercholesterolemia<br>Hypertension<br>Ischemic heart disease | A<br>A + D | 2 | 10 | 0 | Continuing; no adverse events |
| 5 | Ischemic heart disease<br>Hypercholesterolemia<br>PE | A<br>W<br>W + A<br>D + C | 4 | 9 | 0 | Discontinued after further PE |
| 6 | Diabetes<br>Hypercholesterolemia<br>Hypertension | C<br>A + C | 4 | 19 | 0 | Continuing; no adverse events |
| 7 | Ischemic heart disease<br>Hypertension<br>Renal cysts | A<br>A + D | 2 | 1 | 0 | Discontinued after episode of hematuria |
| 8 | Hypertension<br>Hypercholesterolemia<br>Diabetes | A<br>A + D | 3 | 7 | 0 | Continuing; no adverse events |
| 9 | Hypertension<br>Carotid artery disease<br>Ischemic heart disease<br>PE | A<br>A + D | 2 | 12 | 0 | Continuing; no adverse events |

*A*, Aspirin; *C*, clopidogrel; *D*, dipyridamole; *PE*, pulmonary emboli; *PFO*, patent foramen ovale; *W*, warfarin.

high signal were demonstrated in the frontal lobe, basal ganglia, and thalamus on the right, and caudate and cerebellar hemisphere on the left. The patient was treated with the addition of dipyridamole (modified release, 200 mg twice daily) and a diuretic, and remained free from events during subsequent follow-up of 19 months.

## Discussion

Treatment with an antiplatelet agent is an essential part of the armamentarium for the secondary prevention of stroke, yet the relative effect is only modest. Aspirin and dipyridamole, and clopidogrel by extrapolation, each individually reduce stroke recurrence in patients with prior cerebrovascular disease by 15% to 20% as compared with no treatment.[1,2] Hence, it is not uncommon for patients to have a recurrent stroke event even when taking antiplatelet medication. Trials suggest the risk for recurrence at the primary follow-up when on aspirin is in the range of 2.8% to 21.8%.[1-7]

Aspirin, dipyridamole, and clopidogrel have independent modes of action: aspirin irreversibly inhibits cyclo-oxygenase; clopidogrel is an indirect antagonist of the adenosine diphosphate receptor; and dipyridamole prevents the uptake by red cells of adenosine (which has antiplatelet properties). One strategy that has been adopted in secondary prevention is the use of aspirin in combination with another antiplatelet agent[8] because it is presumed that the individual effects on platelets will be additive. In the case of cerebrovascular disease, two trials have assessed the use of the combination of aspirin and dipyridamole in the prevention of recurrent stroke.[1,9] Aspirin and dipyridamole were found to have an additive effect as compared with

aspirin alone.[1] Further work is ongoing in this area with alternative therapies (e.g., the combination of aspirin and clopidogrel is presently under investigation in the MATCH study).[10]

Because dual antiplatelet therapy is more effective than monotherapy,[1] triple therapy might be even more effective, provided that major bleeding is not a problem. We have used the combination of all 3 drugs (aspirin [75 mg/d], clopidogrel [75 mg/d], dipyridamole [modified release 200 mg twice daily]) in several additional patients who were resistant to single or dual antiplatelet therapy. In each case, recurrent cerebrovascular events only ceased with triple therapy, at least during a period of up to 28 months of follow up (Table 1). No episodes of intracranial hemorrhage occurred, however, one patient discontinued therapy after an episode of hematuria.

In laboratory studies we found that triple antiplatelet therapy with aspirin, dipyridamole, and AR-C69931 (a direct-acting adenosine diphosphate receptor antagonist, used because clopidogrel has no effect in vitro) was superior to dual treatment or monotherapy in respect of inhibiting platelet and leucocyte function and the formation of platelet-leucocyte conjugates in vitro.[11] Combining 3 antiplatelet agents runs the risk of major bleeding, although rates of this were not elevated significantly with the combination of aspirin and dipyridamole in the European Stroke Prevention Study-2.[1] We are currently studying the effects of triple antiplatelet therapy in two trials involving patients with prior ischemic cerebrovascular disease and acute ischemic stroke.

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