

# What is the best management for patients who have a TIA while on aspirin therapy?

## EVIDENCE-BASED ANSWER

Alternative antiplatelet therapy for stroke prevention is indicated for patients who experience transient ischemic attacks (TIAs) while on aspirin therapy (strength of recommendation [SOR]: **A**, based on 1 meta-analysis and 1 randomized controlled trial). The combination of aspirin and extended-release dipyridamole reduces the risk of stroke following a TIA (SOR: **A**). Thienopyridines (eg, clopidogrel and ticlopidine) are

an alternative for patients at high risk for a cardioembolic event. Ticlopidine reduces the risk of stroke following TIA, specifically showing benefit for patients previously on aspirin (SOR: **A**). Clopidogrel has not shown significant reduction in reoccurrence of stroke and has not been studied for patients with a previous TIA. Aspirin and a thienopyridine do not provide significant additional reduction in secondary strokes (SOR: **A**).

## CLINICAL COMMENTARY

### Modify risk factors not only for stroke but overall cardiovascular disease

No studies look specifically at patients already on aspirin, so we must extrapolate from other prevention trials how to best manage them. If aspirin therapy has failed, the choice of either aspirin and dipyridamole or clopidogrel should take into account cost, availability, side-effect profile, and a patient's comorbidities and preferences. There are no clear benefits of one over another. While the combination of aspirin and clopidogrel has shown benefit in acute coronary syndromes, what's good for the heart may not necessarily be good for the brain. The MATCH study

showed potential increases in bleeding from combination therapy; we should avoid the use of this combination for prophylaxis.

As primary care physicians concerned with our patients' overall health, we must aggressively modify those factors that put patients at risk not only for recurrent stroke or TIAs but overall cardiovascular disease. This means controlling hypertension, promoting smoking cessation and a healthy lifestyle, improving lipid parameters, and appropriate screening and management of diabetes.

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### Evidence summary

Patients who experience TIAs are at high risk for stroke and need adequate preventative therapies. A meta-analysis evaluated 158 randomized trials involving primary

and secondary prevention of stroke, concluding that antiplatelet therapy results in a 30% reduction in occurrence of ischemic stroke (95% confidence interval [CI], 24–35;  $P < .0001$ ).<sup>1</sup> Data that evaluate the

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antiplatelet efficacy following a TIA while on aspirin therapy are limited.

Combination aspirin and dipyridamole (Aggrenox) therapy reduces the risk of secondary stroke. Several randomized controlled trials (RCTs) that evaluated this combination for prevention of stroke included patients who had TIAs. Although the combination reduced the occurrence of a subsequent stroke, the difference was not significant compared with aspirin alone, possibly due to the use of high-dose aspirin in the comparison group.<sup>2,3</sup> A large-scale RCT including patients with previous stroke or TIA concluded that the combination of aspirin and extended-release dipyridamole reduced the occurrence of stroke by 23% ( $P < .001$ ) compared with aspirin (number needed to treat [NNT]=35; 95% CI, 20–130).<sup>4</sup> In this trial, patients with a prior TIA comprised only one quarter of the patients studied.<sup>4</sup> Subgroup analyses of patients on aspirin prior to experiencing a TIA have not been reported.

Thienopyridines may be considered for secondary stroke prevention for patients at high risk for a cardioembolic event. An RCT studying secondary prevention of stroke, in which 50% of the study population experienced a TIA as their qualifying event, concluded that ticlopidine (Ticlid) reduced the risk of stroke by 21% (95% CI, 0.04–0.38;  $P = .024$ ).<sup>5</sup> Subgroup analysis indicated that ticlopidine provided superior benefit for patients on aspirin or anticoagulant therapy at the time of their qualifying event.<sup>6</sup> Unlike ticlopidine, clopidogrel (Plavix) does not have significant hematologic side effects. An RCT comparing clopidogrel with aspirin found a nonsignificant risk reduction of 0.3% (95% CI, –0.03 to 0.9;  $P = .26$ ) in occurrence of stroke when compared with aspirin for patients with previous stroke, myocardial infarction, or peripheral arterial disease. A 0.9% absolute reduction in combined risk of cardioembolic events was reported for patients randomized to clopidogrel (NNT=111; 95% CI, 57–2454;  $P = .043$ ), but patients with TIA were excluded from the study population.<sup>7</sup>

A large-scale RCT concluded that the combination of clopidogrel and aspirin did not provide additional benefit in reducing a combined endpoint of cardioembolic events in comparison with aspirin alone for patients with prior stroke or TIA. The combination resulted in a significantly greater number of life-threatening and major bleeding complications.<sup>8</sup>

### Recommendations from others

The American Heart Association addresses the lack of evidence in treating patients who experience a TIA while on aspirin therapy. They recommend therapy be individualized for each patient to receive either the combination of extended-release dipyridamole and aspirin or clopidogrel daily for secondary prevention.<sup>9</sup> Clopidogrel 75 mg daily is recommended over ticlopidine 250 mg twice daily due to its favorable safety profile.<sup>10</sup> Similarly, the American College of Chest Physicians recommends use of dipyridamole and aspirin 200/25 mg twice daily or clopidogrel 75 mg daily.<sup>11</sup>

### FAST TRACK

**If aspirin therapy has failed, the choice of a combination therapy should take into account cost, side effects, and patient comorbidities**

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