

# Antithrombotic Treatment in Secondary Prevention of Non-cardioembolic Ischemic Stroke

a report by

Els LLM De Schryver, MD<sup>1</sup> and Ale Algra, MD<sup>2</sup>

1. Department of Neurology, Rijnland Ziekenhuis Leiderdorp, The Netherlands;

2. Julius Center for Health Sciences and Primary Care, and Department of Neurology, University Medical Center Utrecht, The Netherlands

Age-standardized stroke incidence rates per 100,000 population vary between 88 in whites and 191 in blacks in the US,<sup>1</sup> and between 101 and 285 in men and between 47 and 198 in women in Europe.<sup>2</sup> After six months, about one-third of patients who survive stroke are dependent on others for activities of daily living.<sup>3</sup> The 10-year cumulative risk of major cerebrovascular and cardiovascular events after a transient ischemic attack (TIA) or stroke is about 45%.<sup>4</sup> Since patients with ischemic stroke have such a high risk of subsequent vascular events, effective secondary prevention will contribute to the reduction of morbidity, disability, and handicap and will provide better opportunities to preserve the level of quality of life.

Especially after a TIA or mildly disabling stroke, a large gain can be achieved by preventing subsequent (disabling) strokes or myocardial infarcts. Besides the individual benefit for patients and their families in terms of reducing the risk of subsequent vascular events, there will be a reduction of demands on health and social care, which will lead to practical and economic benefits. Because of the high incidence of this health problem, any improvement would benefit a large proportion of the population.

One of the means of secondary preventive treatment is antithrombotic drugs. This article provides a review of antithrombotic therapy in patients with a presumed arterial—i.e. non-cardioembolic—source of stroke to advise physicians on which antithrombotic they should prescribe to patients after ischemic stroke to prevent subsequent vascular events.

## Aspirin

In the secondary prevention of important vascular complications after ischemic stroke, the use of the antiplatelet drug acetylsalicylic acid (aspirin) in doses between 30 and 325mg per day is generally accepted.<sup>5,6</sup> Based on data from the AntiThrombotic Trialists' Collaboration Group<sup>7</sup> and the Dutch TIA Trial, which compared the efficacy of 30 versus 283mg aspirin daily in patients after cerebral ischemia,<sup>8</sup> it is estimated that 30–300mg aspirin daily prevents only 13% of vascular complications in patients who had an episode of cerebral ischemia (95% confidence interval (CI) 6–19).<sup>8,9</sup> This risk reduction is far from ideal as 87% of major arterial complications are not avoided.

## Clopidogrel

Other antiplatelet drugs are clopidogrel and ticlopidine, which are thienopyridine derivatives. In all patients with vascular disease included in the CAPRIE study—which included patients with cerebral ischemia, myocardial infarction, or peripheral arterial disease—there was a modest reduction with clopidogrel 75mg daily compared with aspirin 325mg daily in the secondary prevention of major vascular events. The relative risk reduction was 8.7% (95% CI 0.3–16.5). The relative risk reduction among those patients who presented with ischemic stroke was 7.3% (95% CI -5.7–18.7) in favor of clopidogrel, but this was not statistically significantly better than aspirin.<sup>10</sup> To prevent one vascular complication, about 200 patients would need to be treated with clopidogrel instead of aspirin for one year. In addition, clopidogrel is more expensive than aspirin. Since clopidogrel has a different adverse effect profile, it can be used in patients who cannot tolerate aspirin. In a systematic review, the thienopyridines appeared to be modestly more effective than aspirin in preventing serious vascular events in high-risk patients.<sup>11</sup> Clopidogrel appeared to be safer than ticlopidine and as safe as aspirin.

The MATCH trial, in which clopidogrel 75mg daily combined with aspirin 75mg daily was compared with clopidogrel 75mg alone in high-risk patients with cerebral ischemia, showed that combined treatment with clopidogrel and aspirin was not safe. There were more life-threatening bleeding complications than with clopidogrel alone, and there was no statistically significant benefit of the combination with regard to major vascular events or re-hospitalization for acute ischemia (relative risk reduction 6.4%, 95% CI -4.6–16.3).<sup>12</sup> In the CHARISMA study, patients with cardiovascular disease or multiple cardiovascular risk factors were randomized to either 75mg clopidogrel combined with 75–162mg aspirin or placebo combined with aspirin.<sup>13</sup> The combination therapy of clopidogrel plus aspirin reduced the risk of major vascular events by 7.1% (95% CI -5–17%) compared with aspirin alone, a non-significant difference; there were also significantly more moderate bleeding complications in the combination period. The subgroup analyses in the study show a large heterogeneity and different results:



Els LLM De Schryver, MD, is a Neurologist in the Department of Neurology at Rijnland Ziekenhuis Leiderdorp in The Netherlands. She was the trial co-ordinator and a member of the Steering Committee of the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT). She wrote her thesis on the rationale of antithrombotic treatment in secondary prevention after ischemic stroke, and has also written several publications and reviews on this subject.

E: e.d.schryver@rijnland.nl



Ale Algra, MD, is a Professor of Clinical Epidemiology with a shared appointment between the Departments of Neurology and Clinical Epidemiology of the University Medical Centre Utrecht in The Netherlands. In addition, he works one day a week in the Department of Clinical Epidemiology at the Leiden University Medical Center. Dr Algra has a long-term interest in the field of (cerebro)vascular disease and has been principal investigator of several secondary prevention studies.

patients with cardiovascular disease on combination therapy had a relative risk reduction of 12% (95% CI 0–23) and patients with multiple risk factors had an increase in risk of 20% (95% CI –9–59%). At present, there is no convincing evidence to prescribe clopidogrel combined with aspirin for secondary prevention in patients with non-cardioembolic ischemic stroke.

### Dipyridamole

Dipyridamole is another antithrombotic drug. For patients who present with arterial vascular disease, there is no evidence that dipyridamole alone is more efficacious than aspirin.<sup>14</sup> In 1996, the results of a large trial (ESPS-2) were reported in which the effect of combination treatment with dipyridamole 200mg extended-release twice-daily (bid) and aspirin 25mg bid was compared with that of aspirin 25mg bid alone.<sup>15,16</sup> This trial showed a statistically significant reduction of recurrent stroke in favor of the combination treatment, but no such reduction in mortality rate. There was a relative risk reduction of 22% of major vascular events over aspirin (95% CI 9–33). In the ESPRIT study, patients were randomized to either dipyridamole 200mg bid in 83% extended-release form combined with aspirin 30–325mg daily and aspirin 30–325mg daily alone. The combination therapy showed a relative risk reduction for major vascular events of 20% (95% CI 2–34) and no increased bleeding risk.<sup>17</sup> In addition, meta-analyses provide evidence that among patients presenting with non-cardioembolic stroke, the combination of dipyridamole plus aspirin is associated with a lower risk of further vascular events than aspirin alone.<sup>14,17</sup> In summary, there are currently enough data to conclude that combination therapy of dipyridamole with aspirin should be the first-choice treatment for secondary prevention after non-cardioembolic ischemic stroke.

### Thrombocyte-GPIIb/IIIa-receptor Antagonists

Thrombocyte-GPIIb/IIIa-receptor antagonists are yet another kind of antiplatelet drug. In the BRAVO trial, combination treatment of aspirin with an oral thrombocyte-GPIIb/IIIa-receptor antagonist was not effective and even more hazardous than aspirin alone in patients with cerebral ischemia.<sup>18</sup> In patients with an unstable coronary syndrome, thrombocytopenia was associated with oral thrombocyte-GPIIb/IIIa-receptor antagonist use and an increased risk of bleeding, death, and myocardial infarction.<sup>19</sup>

### Oral Anticoagulation

Oral anticoagulants such as acenocoumarol, phenprocoumon, or warfarin offer a different type of antithrombotic therapy that interferes with blood coagulation. In the secondary prevention of vascular complications in patients with cerebral ischemia and atrial fibrillation, anticoagulation is an effective and safe treatment.<sup>20,21</sup> The SPIRIT study showed that oral anticoagulation

(international normalized ratio (INR) 3.0–4.5) is not safe compared with aspirin 30mg daily in patients with a TIA or minor ischemic stroke of presumed arterial origin.<sup>22</sup> The trial was stopped after the first interim analysis because of an excess of major bleeding complications in the anticoagulant group. The WARSS trial, with a target INR of 1.4–2.8, failed to show a significant effect of oral anticoagulation compared with aspirin 325mg daily.<sup>23</sup> The comparison of oral anticoagulants (INR 2.0–3.0) versus aspirin in ESPRIT was halted earlier than planned because ESPRIT reported that the combination of aspirin and dipyridamole was more effective than aspirin alone;<sup>24</sup> the hazard ratio (HR) was 1.02 (95% CI 0.77–1.35). The HR for the primary outcome event comparing oral anticoagulants with the combination treatment of aspirin and dipyridamole was 1.31 (95% CI 0.98–1.75). Oral anticoagulants (target INR range 2.0–3.0) are not more effective than aspirin or the combination of dipyridamole with aspirin for secondary prevention after non-cardioembolic ischemic stroke. In the WASID trial, patients with transient ischemic attack or stroke caused by angiographically verified 50–99% stenosis of a major intracranial artery were randomized to either warfarin (INR 2.0–3.0) or aspirin 1,300mg daily.<sup>25</sup> The primary end-points were ischemic stroke, brain hemorrhage, or death from vascular causes. The HR was 1.04 (95% CI 0.73–1.48), with significantly more major hemorrhages in the warfarin group. We therefore conclude that there is insufficient evidence to justify the routine use of oral anticoagulants for the secondary prevention of further vascular events after non-cardioembolic ischemic stroke.

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### Conclusions

The consistent data from ESPRIT and ESPS-2 have now confirmed dipyridamole plus aspirin as the preferred first-choice antiplatelet therapy for the long-term prevention of serious vascular events in patients with non-cardioembolic ischemic stroke. Clopidogrel alone may be used in patients who cannot tolerate aspirin. There is insufficient evidence to recommend combination therapy of clopidogrel with aspirin for secondary prevention after non-cardioembolic ischemic stroke. There is also no place for secondary prevention with oral anticoagulants. ■

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