

# Antiplatelet therapy in ischemic stroke: evidence-based review

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## ABSTRACT

Antiplatelet therapy is indicated for long-term secondary stroke prevention in ischemic stroke due to atherothrombosis. Aspirin is the well-known antiplatelet agent and best studied for stroke prevention. It inhibits platelet activation by irreversibly inhibiting platelet cyclooxygenase and thromboxane production. Recent meta-analysis suggests that the benefit of aspirin is independent of dosage and now, lower dosage is favored due to low side-effect profiles. The adenosine diphosphate (ADP) receptor antagonists which are ticlopidine and clopidogrel are slightly more effective than aspirin in high-risk patients. However, they have different side effect profile and higher price. There no clearer role for other agents such as dipyridamole or oral GP IIb / IIIa receptor antagonist as single agent for prevention. Therefore, the choice for antiplatelet therapy need to be individualized due to their efficacy, side effect profiles, availability and cost.

**Key words :** Ischemic stroke, antiplatelet therapy

## Introduction

The Healthcare burden from stroke is considerable. Stroke ranks as the third leading cause of death in the united states and it is estimated to have 700,000 New strokes annually and 4.4 million stroke survivors.<sup>1</sup> In Thailand, the estimated annual incidence is 150,000 new cases and the trend is on the rise.<sup>2</sup> Ischemic stroke accounts for approximately 80% of all strokes, while the remaining are due to cerebral hemorrhage. The process of large-vessel atherothrombosis and small vessel occlusion, each account for 20% of all strokes<sup>3</sup>. Antiplatelet therapy is indicated for both subtypes.

## Current evidence for oral antiplatelet agents

Antiplatelet Trialists' Collaboration (APT) analyzed the effectiveness and safety of antiplatelet

therapy from various trials and categorized qualifying condition of patients as symptomatic vascular disease of the brain, heart or limbs<sup>4</sup>.

The analyses showed that the effects of antiplatelet agents were effective for all above qualifying conditions but the magnitude of the favorable effect varied. These data indicate that atherothrombosis is a global disease that affects different vascular beds and respond to similar way to antiplatelet therapy, regardless of which vascular bed is symptomatic.

The results of meta-analysis are generally expressed in the same terms, as are the results of clinical trials. The effect of treatment is most commonly described using the relative risk (RR), and the relative risk reduction (RRR). RR is calculated as the incidence rate in the treatment group divided

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by the incidence rate in the control group. The RRR is simply one minus the RR expressed as a percent. RRR is quite independent of the baseline risk and to some degree is also independent of the study duration. This measure is particularly useful for describing population benefits, but its meaning for the individual is less clear<sup>5</sup>.

Absolute risk reduction (ARR) is the difference in event rates between the treatment and control groups, expressed in percent. This may be more meaningful to the individual patient. And can be calculated to another measure, number needed to treat (NNT). It is the events avoided per 1,000 patients treated. However, they are quite sensitive to differences in study duration and baseline risk.

## Aspirin

Aspirin is the most economical and frequently chosen antiplatelet agent. In 11 randomized placebo - controlled trials of aspirin in more than 10,000 patients with prior transient ischemic attacks (TIA) or ischemic stroke, aspirin reduced the odds of a serious vascular event by 17%. This is a RRR of 13% (95% CI 6-19%) and ARR of 3% over about 3 years, or about 1% per year<sup>6</sup>. The NNT with aspirin to prevent one serious vascular event each year is therefore about 100.

Aspirin doses, ranging from 25 mg 2 times per day<sup>7</sup> to 325 mg 4 times per day<sup>8</sup> have shown to be efficacious for prevention of stroke after TIA. Meta-analysis can also be used to clarify the relationship between the benefit of aspirin and the dose. Separate analysis of trials using 900-1,500 mg daily (high dose) versus 300 mg daily (medium dose) versus 50-75 mg daily (low dose) for prevention of vascular events in patients with prior stroke or TIA showed a very similar RR for

each dose category (Table1)<sup>5</sup>. In summary, aspirin provides a 13% RRR and we can avoid 28 events for every 1,000 patients treated for 2 years. Therefore, the benefit of aspirin alone is rather modest.

**Table 1** Efficacy of aspirin versus placebo by dose for prevention of stroke, MI, or vascular death among patients with prior stroke or TIA<sup>5</sup>

| Dose (mg) | Relative risk | 95 % CI     |
|-----------|---------------|-------------|
| 900-1,500 | 0.87          | (0.76,0.98) |
| 300       | 0.91          | (0.76,1.09) |
| 50-75     | 0.87          | (0.78,0.97) |
| overall   | 0.87          | (0.81,0.95) |

MI=myocardial infarction

TIA=transient ischemic attack

The gastrointestinal toxicity of aspirin is dose related, even low dose aspirin (50-75 mg/d) slightly increases the risk of major bleeding, particularly gastrointestinal hemorrhage<sup>9</sup>. Enteric coating reduces gastrointestinal toxicity and appears to inhibit thromboxane synthetase similarly to equal doses of uncoated preparation .

In a recent survey of US physicians, the use of aspirin 325 mg/d is favored<sup>10</sup>. If one cannot tolerate aspirin 325 mg/d because of minor dyspepsia, the options include taking aspirin with meals, using an enteric coated preparation, or taking a lower dose. The American Heart Association (AHA) guideline recommended a dosage range of 50-325 mg of aspirin per day for most TIA patients<sup>11</sup>.

In patients who were already on aspirin, then suffered a first or recurrent TIA or stroke, (aspirin failure), there is no clinical trial to investi-

gate this problem. The possible strategies are to continue aspirin, add dipyridamole, or switch to ticlopidine or clopidogrel or to use anticoagulation with an INR of 2.0 to 3.0<sup>12</sup>. Nevertheless, prior use of low dose aspirin may be associated with a small but significant reduction in stroke mortality. Beneficial effects was seen in atherosclerotic and cardioembolic strokes, but not in small vessel disease. The effect of prior aspirin use on mortality was independent of age, gender, other risk factors, and use of other medication<sup>13</sup>.

## ADP receptor antagonists (Ticlopidine, Clopidogrel)

### Ticlopidine

Ticlopidine prevents platelet aggregation by inhibiting the binding of ADP to its receptor on platelets, independent of any effects on prostaglandins. The efficacy of ticlopidine was demonstrated in two clinical trials, described below.

The Canadian American Ticlopidine Study (CATS)<sup>14</sup> studied the efficacy of Ticlopidine hydrochloride 250 mg twice a day versus placebo in stroke patients. The relative risk reduction, in intention-to-treat analysis, was 23.3% for combined outcome of stroke, MI and vascular death. Another trial, Ticlopidine Aspirin stroke study (TASS)<sup>15</sup>, assessed the efficacy of ticlopidine 250 mg twice a day versus aspirin 650 mg twice a day. In the first year, the event rates clearly diverged, favoring ticlopidine over aspirin. However, at 3 years, the overall risk reduction from ticlopidine was 21% in fatal or non-fatal stroke risk. And the differences between two agents were not statistically significant.

Diarrhea was the most common adverse event but the more severe side effect was neutrope-

nia. Severe neutropenia was found in 0.8% of patients, therefore, complete blood count screening is recommended every 2 weeks for the first 3 months of treatment. Thrombotic thrombocytopenic purpura (TTP) is another serious hematologic problem that may occur in the first 3 months of treatment<sup>16</sup>. The post marketing surveillance about the use of ticlopidine with aspirin after coronary angioplasty and stenting was complicated by TTP approximately once in every 4,184 patients and was total in >20% of cases<sup>17</sup>.

### Clopidogrel

Clopidogrel is a new thienopyridine derivative that also acts by inhibiting platelet aggregation induced by ADP and affecting ADP dependent activation of the GP IIb/IIIa complex, which is the major receptor of available fibrinogen.

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Event (CAPRIE) trial<sup>18</sup> evaluated the relative safety and efficacy of clopidogrel 75 mg/d versus aspirin 325 mg/d in 19,185 patients with stroke, MI, or peripheral arterial disease. The results showed that clopidogrel was more effective than aspirin in preventing a combined endpoint of ischemic stroke, MI or vascular death. Intention-to-treat analysis showed a small RRR of 8.7% in favor of clopidogrel ( $p=0.043$ ) For the 6431 patients in the stroke subgroup, the RRR was a non-significant 7.3% in favor of clopidogrel ( $p=0.26$ ), however the CAPRIE trial was not initially powered for subgroup analysis.

The side effect of clopidogrel and aspirin appeared to be similar, although diarrhea and rash are more common. Additionally, the neutropenia occurred about 0.1% and routine CBC monitoring is not recommended as it is for ticlopidine. Therefore, clopidogrel is another alternative to aspirin in

patients who are aspirin intolerance or have ischemic event despite aspirin therapy<sup>7,11</sup>.

## Dipyridamole

Dipyridamole is an antiplatelet agent with inhibition of cyclic nucleoside phosphodiesterase and blockade of the uptake of adenosine. The European Stroke Prevention Study (ESPS) compared placebo with aspirin 975 mg/d plus dipyridamole 225 mg/d. The combination regimen reduced the risk of stroke and death by 33%, and the risk of fatal and nonfatal stroke by 38%<sup>19</sup>. In this trial, the effect of each agent alone cannot be determined.

ESPS-2 was designed to assess the efficacy of aspirin and an extended release dipyridamole by 2x2 factorial designs which allowed comparisons between 4 treatment groups : placebo, aspirin alone (25 mg twice daily), extended release dipyridamole (200 mg twice daily) , and the combination therapy<sup>7</sup>. The trial showed 37% RR in favored of combination therapy compared to placebo. For monotherapy versus placebo, each agent showed statistically significant reduction in stroke risk: 18% for aspirin and 16% for dipyridamole. The most common side effects of dipyridamole were headache (7-8%) and gastrointestinal disturbances (6-7%).

## Future perspectives

As stated earlier, the maximal risk reduction from antiplatelet monotherapy seems modest. Based on the promising results obtained with ADP-aspirin combination in coronary stenting, several additional trials with clopidogrel plus aspirin are undergoing, such as MATCH (Management of Atherothrombosis with Clopidogrel in High - risk patients) However, the combination of oral GP IIb/IIIa receptor antagonist plus aspirin versus aspi-

rin seems less promising due to excess death from earlier reports of the combination treatment in cardiac patients (orbofiban, xemilofiban and sibrafiban)<sup>20,21</sup>.

The other important aspect of stroke prevention is risk factor modification in each patient. Most risk factors are modifiable to achieve maximal stroke risk reduction independent of antiplatelet therapy. The important ones are hypertension, diabetes mellitus, smoking, hyperlipidemia, obesity , poor nutrition/diet, physical inactivity, and alcohol/drug abuse<sup>22,23</sup>.

Despite recent advances in acute stroke management and promising new approaches to improving post-stroke recovery, prevention remains the cornerstone of therapy for these devastating disease. The understanding of antiplatelet therapy will facilitate physician in improving stroke care and maximally protect patients from recurrent event.

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### บทคัดย่อ

#### การใช้ยาต้านเกล็ดเลือดในโรคหลอดเลือดสมองตีบหรืออุดตัน

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ยาค้านเกล็ดเลือดเป็นยาที่ใช้ในการป้องกันการกลับเป็นซ้ำของโรคหลอดเลือดสมองตีบเนื่องจากภาวะหลอดเลือดแข็ง แอสไพรินเป็นยาหลักและได้รับการศึกษาในกรณีนี้มากที่สุด และออกฤทธิ์โดยการยับยั้งการทำงานของเกล็ดเลือดผ่านทางสารผลิตไซโคลออกซีจีเนส และพรอมบ็อกเซน การวิเคราะห์ผลการวิจัยหลายชิ้นพบว่าประสิทธิภาพของแอสไพรินไม่ขึ้นกับขนาดของยา ดังนั้นในปัจจุบันจึงมักจะใช้ยาในขนาดที่ต่ำเนื่องจากมีผลข้างเคียงน้อย ยาในกลุ่มยาค้านตัวรับอะดีโนซีนไดฟอสเฟต เช่น ทิโคลปีดีน หรือโคลพิโดเกรล มีประสิทธิภาพดีกว่าแอสไพรินเล็กน้อยในผู้ป่วยกลุ่มเสี่ยงสูง อย่างไรก็ตามยากลุ่มนี้มีผลข้างเคียงต่างกันไปและมีราคาสูงกว่ายาอื่น ๆ เช่น ไคโปรคาโมล หรือ ยาค้านตัวรับจีพีทูบี/ทรีเอ ยังไม่มีบทบาทยืนยันในการใช้เป็นยาเดี่ยว ดังนั้นการเลือกยาในกลุ่มนี้จะต้องคำนึงถึงปัจจัยต่าง ๆ ในผู้ป่วยแต่ละราย เช่น ประสิทธิภาพ ผลข้างเคียง การมีไว้ใช้และราคา