



# THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

## Antiplatelet Chemoprevention of Occlusive Vascular Events and Death

**A**ntiplatelet drugs are taken to prevent future adverse cardiovascular events. In this review, we summarize the benefit and harm from taking four common antiplatelet drugs: acetylsalicylic acid, (Aspirin<sup>®</sup>, etc.), ticlopidine (Ticlid<sup>®</sup>), clopidogrel (Plavix<sup>®</sup>) and dipyridamole (Aggrenox<sup>®</sup>). **The Antiplatelet Trialists Collaboration (ATC) systematic review published in 1994<sup>1</sup> provides the basic evidence.**

### What are the clinical implications of the ATC systematic review?<sup>1</sup>

#### SECONDARY PREVENTION:

Patients with proven vascular occlusive disease (increased risk for subsequent event).

- Antiplatelet therapy, mostly acetylsalicylic acid (ASA) provides a clear benefit (ARR in vascular events = 3.3%, NNT = 30 for 2.5 years) for secondary prevention for a wide range of patients.
- Antiplatelet therapy benefits patients with suspected acute myocardial infarction, prior myocardial infarction, unstable or stable angina, stroke, transient ischemic attack (TIA), arterial bypass surgery, angioplasty or peripheral vascular disease. *Acute ischemic stroke can be added to this list. ASA 160 to 300 mg started within 48 hrs of a proven ischemic stroke was found to significantly reduce death or dependency (ARR = 1.3%, NNT = 77 for 3 months) and recurrent stroke (ARR = 0.5%, NNT = 200 for 3 months).*<sup>2</sup>



- Medium dose ASA (75 - 325 mg/day) is the most widely tested regimen. No other drug or regimen is better at preventing death, myocardial infarction, or stroke. There is a trend towards superior effectiveness of medium dose ASA versus higher doses in the ATC analysis. *Similarly, a recent study showed a reduction in the combined outcome: stroke, myocardial infarction and death within 3 months of carotid endarterectomy for patients taking 81 or 325 mg ASA compared to those taking 650 or 1300 mg ASA.*<sup>3</sup>

#### PRIMARY PREVENTION:

Patients without proven occlusive vascular disease (decreased risk for adverse cardiovascular event).

- In the ATC review, benefit was not found to exceed harm for primary prevention. *More recently the HOT trial tested ASA 75 mg versus placebo for primary prevention in hypertensive patients. It corroborated the ATC review, showing no effect on mortality or stroke and a small reduction in myocardial infarction. This benefit was outweighed by an increased incidence of bleeding*<sup>4,5</sup> (see Letter # 27).



**What is the role for other antiplatelet drugs?**

**The CAPRIE Trial**

CAPRIE compared 75 mg of clopidogrel with 325 mg of ASA daily in 3 subgroups of patients: prior MI, prior TIA or stroke, and peripheral vascular disease.<sup>6</sup> The primary outcome, a cluster of ischemic stroke, myocardial infarction, or vascular death as first events, was lower in the clopidogrel group, 9.8%, than in the ASA group, 10.7% (RR = 0.92, ARR = 0.9%, NNT = 115 for 1.9 yrs). The only subgroup showing a clinically significant benefit were

patients with peripheral vascular disease at entry (90% current or ex- smokers).

A Cochrane review<sup>7</sup> which included the CAPRIE Trial findings presented data as single, as opposed to a cluster of clinical outcomes. The results are shown in Table 1. The small absolute benefit of a reduction in total MI, 0.7%, and GI hemorrhage, 0.4% for clopidogrel is partially offset by an increased incidence of rash, leading to withdrawal, ARI = 0.5%.

**Table 1. Results of the CAPRIE trial <sup>7</sup>**

| Outcome                       | Clopidogrel Events % | ASA Events % | RR (95% CI)    | ARR<br>ARI % | NNT<br>NNH |
|-------------------------------|----------------------|--------------|----------------|--------------|------------|
| Total death                   | 5.8                  | 6.0          | NS             |              |            |
| Total MI                      | 2.9                  | 3.6          | 0.8 (0.7, 0.9) | 0.7          | 143        |
| Total stroke                  | 4.8                  | 5.3          | NS             |              |            |
| Any hemorrhage*               | 8.9                  | 8.8          | NS             |              |            |
| GI hemorrhage#                | 0.5                  | 0.9          | 0.6 (0.4, 0.8) | 0.4          | 250        |
| Neutropenia <sup>^</sup>      | 0.05                 | 0.04         | NS             |              |            |
| Thrombocytopenia <sup>^</sup> | 0.2                  | 0.1          | NS             |              |            |
| Rash#                         | 0.9                  | 0.4          | 2.2 (1.5, 3.2) | <b>0.5</b>   | <b>200</b> |
| Diarrhoea#                    | 0.4                  | 0.3          | NS             |              |            |

\* excluding intracranial hemorrhage

# adverse effect leading to withdrawal

<sup>^</sup> severe < 0.45 x 10<sup>9</sup> / L for N, and < 80 x 10<sup>9</sup> / L for P

**The TASS Trial**

TASS compared 500 mg of ticlopidine with 1300 mg of ASA, for patients with TIA, reversible ischemic neurological deficit (RIND) or mild stroke within the previous 3 months<sup>8</sup>. The primary outcome, stroke or death, was not significantly different, 20.0% for

ticlopidine and 22.7% for ASA (RR = 0.88 [0.77,1.01]). Other results taken from a Cochrane review are shown in Table 2.<sup>7</sup> The benefit of ticlopidine seen as a reduced incidence of stroke, 2.6%, and GI hemorrhage, 0.9%, are offset by increased harm leading to withdrawal: severe neutropenia, 0.9%, rash, 2%, and diarrhea, 4%.

**Table 2. Results of the TASS trial <sup>7</sup>**

| Outcome                  | Ticlopidine Events % | ASA Events % | RR (95% CI)     | ARR<br>ARI % | NNT<br>NNH |
|--------------------------|----------------------|--------------|-----------------|--------------|------------|
| Total death              | 11.4                 | 12.7         | NS              |              |            |
| Total MI                 | 6.8                  | 5.8          | NS              |              |            |
| Total stroke             | 11.2                 | 13.8         | 0.8 (0.7, 0.99) | 2.6          | 39         |
| Any hemorrhage*          | 8.5                  | 9.4          | NS              |              |            |
| GI hemorrhage#           | 0.5                  | 1.4          | 0.3 (0.1, 0.8)  | 0.9          | 111        |
| Neutropenia <sup>^</sup> | 0.9                  | 0            | 7.5 (2.5,22.3)  | <b>0.9</b>   | <b>111</b> |
| Rash#                    | 3                    | 1            | 3.1 (1.7, 5.5)  | <b>2</b>     | <b>50</b>  |
| Diarrhoea#               | 6                    | 2            | 2.8 (2.0, 4.1)  | <b>4</b>     | <b>25</b>  |

\* excluding intracranial hemorrhage

# adverse effect leading to withdrawal

<sup>^</sup> severe < 0.45 x 10<sup>9</sup> / L for N, and < 80 x 10<sup>9</sup> / L for P

**RR** - Relative Risk

**CI** - Confidence interval NS - Not Statistically Significant

**ARR** - Absolute Risk Reduction

**NNT** - Number Needed to prevent one event

**ARI** - Absolute Risk Increase

**NNH** - Number Needed to treat to cause one Harmful event

## Adding other antiplatelet drugs to ASA?

### The ESPS-2 Trial

The ESPS-2 trial compared placebo to 4 active treatment groups: an extended release form of dipyridamole (DP), 400 mg/day, ASA, 50 mg/day and ASA-DP.<sup>9</sup> This trial reported a reduction in non-fatal stroke as a first event in all 4 active treatment groups. The results are consistent with an additive benefit of ASA-DP on first event non-fatal stroke, 8.3% as compared to ASA alone, 11.3% (RR = 0.7 [0.6,0.9], ARR = 3%, NNT = 33 for 2 yrs). However, the proper analysis of the data using the factorial design separates the ASA effect and the DP effect. This is shown in Table 3.

Any benefit of the combination of DP and ASA has to be weighed against a 7.4% increase in withdrawals due to adverse events with DP (primarily headache and GI events). There was no increase in these adverse events associated with ASA. It is also of concern that, while DP shows a trend toward increased incidence of fatal stroke, RR = 1.14 [0.9, 1.5] ASA shows the opposite, a trend towards a reduction in fatal stroke, RR = 0.78 [0.6, 1.04] (see Table 3).

Table 3. Results of the ESPS-2 trial <sup>9</sup>

| Outcome                            | Dipyridamole effect |                  |                 |              |            | ASA effect     |                   |                 |              |            |
|------------------------------------|---------------------|------------------|-----------------|--------------|------------|----------------|-------------------|-----------------|--------------|------------|
|                                    | DP<br>Event %       | no DP<br>Event % | RR<br>(95% CI)  | ARR<br>ARI % | NNT<br>NNH | ASA<br>Event % | no ASA<br>Event % | RR<br>(95% CI)  | ARR<br>ARI % | NNT<br>NNH |
| Total death                        | 11.3                | 11.6             | NS              |              |            | 11.1           | 11.8              | NS              |              |            |
| Total MI                           | 4.0                 | 4.3              | NS              |              |            | 3.8            | 4.5               | NS              |              |            |
| Fatal stroke                       | 2.8                 | 2.5              | NS              |              |            | 2.3            | 3.0               | NS              |              |            |
| Non-fatal stroke                   | 9.7                 | 12.6             | 0.77 (0.7, 0.9) | 2.9          | 34         | 9.8            | 12.4              | 0.79 (0.7, 0.9) | 2.6          | 38         |
| Withdrawals due to adverse effects | 15.5                | 8.1              | 2.0 (1.7, 2.4)  | 7.4          | 14         | 12.2           | 11.4              | NS              |              |            |
| Withdrawal due to GI hemorrhage    | 0.7                 | 0.8              | NS              |              |            | 1.2            | 0.2               | 3.9 (2.2, 6.8)  | 1.0          | 100        |

RR - Relative Risk  
 CI - Confidence interval NS - Not Statistically Significant  
 ARR - Absolute Risk Reduction  
 NNT - Number Needed to Treat to prevent one event  
 ARI - Absolute Risk Increase  
 NNH - Number Needed to treat to cause one Harmful event

## Do all antiplatelet drugs act by the same mechanism of action?

No. The mechanism of action and kinetics of platelet-active drugs has been recently reviewed.<sup>10</sup> **ASA uniquely acts to acetylate (PG)H-synthase and to irreversibly inhibit the cyclooxygenase activity in platelets and vascular endothelium.** This action occurs with doses of ASA as low as 50 mg.

Ticlopidine and clopidogrel are thienopyridines which act by selectively inhibiting adenosine phosphate induced platelet aggregation. Platelet function only recovers slowly upon drug withdrawal. Dipyridamole inhibits platelet cyclic nucleotide phosphodiesterase and uptake of adenosine. The antiplatelet effects of these actions is unknown.

## How are these drugs handled by the body?

ASA has a very short half life (15-20 min). However, because its effect on platelets is irreversible, the duration is dependent on the life span of the platelet. This results in a pharmacologic half-life of about 6 days. Ticlopidine and clopidogrel are extensively metabolized by the liver. Ticlopidine has a 4 day half-life with chronic dosing. Clopidogrel has an 8 hour elimination half-life, but the pharmacologic half-life is relatively long and it takes 4 to 7 days of administration to reach a steady state effect on platelets. Dipyridamole is metabolized in the liver and has a terminal half-life of 10 hours. The recommended dose and the cost of these drugs are shown in Table 4.

## Conclusions

### SECONDARY PREVENTION:

1. ASA, 80 - 325 mg/day, is proven effective for the prevention of vascular occlusive events for patients with established disease. There is little evidence of benefit beyond a maximum dose of ASA of 325 mg/day.
2. Other antiplatelet drugs should be used in patients allergic to or intolerant of ASA.
3. Patient characteristics, benefits, harm and cost should be considered when selecting an agent other than ASA.
4. Combination of ASA with other antiplatelet agents requires further study.

### PRIMARY PREVENTION:

**Benefit of platelet prevention has not been shown to exceed harm in patients without proven vascular occlusive disease.**

**Table 4. Dose and cost of antiplatelet drugs**

| Chemical name    | Trade name                    | Daily dose    | Daily cost      |
|------------------|-------------------------------|---------------|-----------------|
| ASA              | Aspirin <sup>®</sup> , etc.   | 80 - 325 mg   | \$0.01 - \$0.16 |
| Clopidogrel      | Plavix <sup>®</sup>           | 75 mg         | \$2.56          |
| Ticlopidine      | Ticlid <sup>®</sup> , generic | 250 mg BID    | \$1.56          |
| Dipyridamole/ASA | Aggrenox <sup>®</sup>         | 200/25 mg BID | \$1.69          |

## References

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This Letter contains an assessment and synthesis of published (and whenever possible peer-reviewed) publications to October 1, 2000. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 81 experts and primary care physicians in order to correct any identified shortcomings or inaccuracies and to ensure that the information is concise and relevant to clinicians.