Is acetylsalicylic acid plus dipyridamole superior to ASA alone for secondary prevention of stroke?

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Research question
Should a fixed combination of 25 mg of acetylsalicylic acid and 200 mg of dipyridamole (DP) be the drug of choice for secondary prevention of stroke?

Type of article and design
Prospective, multicentre, randomized placebo-controlled 2-year trial.

Relevance to family physicians
Stroke causes considerable morbidity and mortality in Canada. Previous strokes or transient ischemic attacks (TIAs) are powerful predictors of subsequent ischemic strokes. Pooled analysis of antiplatelet drug (mostly ASA) studies indicates an absolute risk reduction (ARR) of approximately 3.3% of subsequent strokes (number needed to treat [NNT] 30) among people who have had strokes or TIAs in the past 2.5 years.1

Newer agents such as ticlopidine and clopidogrel have shown efficacy in stroke prevention, but they are typically reserved for second-line therapy for patients who cannot tolerate ASA.2-4 One large, well conducted study5 showed ticlopidine to be more effective than ASA, but ticlopidine carries considerable risk of serious toxicity, such as agranulocytosis and thrombotic thrombocytopenia purpura. Clopidogrel was shown in the CAPRIE study6 to have greater efficacy than ASA in reducing the combined end points of vascular death, myocardial infarction, or stroke in patients with recent previous vascular events. The magnitude of the ARR compared with ASA was small (0.5% NNT 200), so the greater efficacy was of questionable clinical relevance.

Studies of DP’s role in thrombosis have had conflicting results. For secondary prevention of stroke among those who had had previous strokes or TIAs, several trials were unable to show any benefit from combining DP with ASA.7,8 In contrast, the first European Stroke Prevention Study (ESPS) comparing ASA combined with DP (ASA/DP) (75/325 mg three times daily) with placebo9 demonstrated a 7.4% ARR (NNT 13.5) of stroke recurrence over a 2-year period. The authors attributed the difference in results to the larger sample size and statistical power of their study, but there were also differences in how patients were chosen for the studies. The magnitude of the difference suggested that comparing combination therapy with ASA alone was warranted. Such a trial needed to have sufficient power to determine whether combining DP with ASA was advantageous in secondary prevention of stroke.

As a result, the second ESPS trial compared the effectiveness of ASA/DP with ASA alone and with DP alone. Dipyridamole is thought to inhibit adenosine 5-diphosphate, collagen, and platelet activating factor–induced platelet aggregation.10 Its activity, however, is dependent on achieving high levels in circulating blood.10,11 The bioavailability of previous formulations of DP was reported to be variable (27% to 88%),11 which might explain DP’s inconsistent performance in previous studies. A new formulation of ASA and modified-release DP, designed to improve bioavailability, was tested in the second ESPS trial in an effort to address this inconsistency.12,13

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Overview of study and outcomes
The ESPS 2, a randomized, double-blind, placebo-controlled trial, enrolled 7054 patients who had had strokes or TIA s within the previous 3 months. Exclusion criteria were requirement of ASA (for reasons other than stroke prevention), anticoagulation, intolerance of ASA or DP, previous or current bleeding disorders, and life-threatening diseases. Patients were randomized to one of four groups: ASA with modified-release DP (25/200 mg twice daily), ASA (25 mg twice daily), modified-release DP (200 mg twice daily) or placebo in a 2x2 factorial design. Follow-up visits were scheduled at 1 month and then every 3 months for the duration of the 2-year study period.

Primary end points were stroke, death, and combined stroke and death; TIA s, MIs, and other vascular events and safety end points were also analyzed. A sample size of 5000 was originally calculated to detect a 25% difference in rates of stroke recurrence with 80% accuracy at a significance level of .05. After interim analysis, researchers decided to increase the sample size to 7000 to detect smaller (<25%) differences between treatment arms.

Results
Data for 438 of the 7054 patients initially recruited were deemed unreliable; intention to treat (ITT) analyses included 6602 patients. Also, 42 patients were lost to follow-up. More patients withdrew prematurely from the treatment groups (26.8%) than the placebo group (21.2% P < .001); most withdrawals were from the ASA/DP and DP alone groups.

Baseline characteristics of patients in the three treatment groups were similar. Average age was 66.7 years. Male-to-female ratio was 58:42. Most (76%) patients had had strokes rather than TIA s as the baseline event. Most patients had little or no dysfunction resulting from baseline events.

Over the 2-year study period, stroke rates were 9.5% in the ASA/DP group, 12.9% in the ASA alone group (P = .006), 12.7% in the DP alone group (P = .002), and 15.2% with placebo (P < .001). This resulted in a reduced relative risk of 37% with ASA/DP, 18.1% with ASA alone, and 16.3% with DP alone when compared with placebo. Death rates were not significantly reduced in any treatment group as compared with placebo, but the combined end point of stroke or death was significantly lower in all treatment groups compared with placebo. No difference in combined stroke or death end points was found among treatment groups.

Rates of MI were not significantly different among study groups. Rates of other vascular events (pulmonary embolism, deep vein thrombosis, and peripheral or retinal arterial occlusion) were significantly lower in the treatment groups than in the placebo group, but were similar in the three treatment groups.

Adverse events were more common in the treatment groups, but side effects were frequent (>50%) in all groups, including placebo. Episodes of severe or fatal bleeding were more common in the ASA/DP (1.6%) and ASA alone (1.2%) groups than in the placebo group (0.36%); statistical analysis was not reported. Withdrawal due to headache or nausea was greater in the ASA/DP and DP alone groups (8, 6.5%) than in the placebo group (2.3, 3.6% P = .001). Withdrawal for any adverse event was more frequent in the ASA/DP (15.9%) and DP alone (15.1%) groups than in the ASA alone (8.6%) or placebo (7.7%) groups.

Analysis of methodology
This well-conducted trial accounted for meaningful baseline characteristics (eg, hypertension, stroke history, diabetes mellitus, coronary artery disease) and end points (stroke, death, stroke and death), and had an appropriate sample size and a reasonable number of participant withdrawals. This study has come under scrutiny owing to two issues, however: exclusion of study data and the dose of ASA used.

Data on 438 patients at one centre were excluded from the analysis because their integrity could not be assured. The authors reported that the excluded data would not affect the findings. No evidence indicates whether corruption was isolated or widespread among study centres. Because we know the steering committee chose to reveal the fact that data were perhaps tainted, our instinct is to trust these results as much as we would those of other large multicentre randomized controlled trials.

Despite extensive, long-standing use of ASA for secondary prevention of stroke, debate about the most effective dose continues. The American Association of Chest Physicians and the Stroke Council of the American Heart Association recommend from 50 to 325 mg of ASA daily. The Thrombosis Interest Group of Canada (TIGC) guidelines recognize that the most effective dose is uncertain but the most commonly prescribed dose is 325 mg/d. Only one large randomized controlled trial has compared low-dose ASA (300 mg) with high-dose ASA (1200 mg), and it concluded there was no important difference in efficacy, but that the lower dose was associated with nearly twice the risk of gastrointestinal bleeding (odds ratio 3.3:6.4).

The 50-mg dose of ASA had not been tested in placebo-controlled double-blind conditions until the ESPS 2; results of that trial prompted revision of ASA dosing
recommendations. Other evidence for the efficacy of the 50-mg dose comes from the Dutch TIA trial and the Swedish Aspirin Low-dose Trial (SALT). The Dutch trial compared 30 mg of ASA with 283 mg daily and found no difference in efficacy. The SALT trial found 75 mg of ASA daily significantly more effective than placebo.

Several editorials in recent years have supported use of high-dose (650 to 1300 mg/d) ASA for stroke prevention. Claims of increased efficacy are based on placebo-controlled trials that have shown relatively greater risk reduction with high-dose ASA compared with placebo than trials where medium- or low-dose ASA was compared with placebo. Comparing the relative benefit of a dose in one trial with another dose in another trial is unacceptable evidence for superiority in the absence of direct comparative data.

**Application to clinical practice**

The TIGC guidelines recommend ASA as first-line therapy for secondary prevention of stroke because its safety, efficacy, and cost-effectiveness are well established. They recommend ASA or other agents be reserved for patients who have recurrent strokes while taking ASA. The ESPS 2 supports use of ASA for patients who have had strokes or TIAs because the combination proved superior to ASA alone for preventing strokes. The 3.4% ARR of ASA in comparison with ASA alone suggests a NNT of 29 for 2 years. This is a clinically relevant risk reduction based on the morbidity and mortality of stroke. The American Association of Chest Physicians and TIGC recommendations suggest that ASA is superior to ASA alone (grade 1A recommendation) and to clopidogrel (Grade 2C recommendation). This indicates that, if cost (coverage by provincial plans) or tolerability (headache, nausea with DP) are not issues, use of ASA/DP should be considered the first-line approach.

Although ASA/DP can be considered appropriate therapy for people who have had strokes while taking ASA, no large-scale study evaluating any of the antiplatelet agents in ASA failure in stroke patients has been conducted. Therefore, we need to assess each patient individually and consider referral to stroke specialists when appropriate.

Since the success of ASA combined with modified-release DP (25/200 mg) (Aggrenox) has been demonstrated for twice-daily dosing only, this regimen should be followed. Use of immediate-release DP or ASA alone should not replace the specific Aggrenox product at this time.

**Points saillants**

- La combinaison d’AAS et de dipyridamole (DP) était d’efficacité supérieure à l’administration d’un seul agent pour prévenir les accidents vasculaires cérébraux chez les personnes qui avaient déjà souffert d’AVC ou d’accidents ischémiques transitoires. La réduction du risque absolu était de 3,4% (NNT =29 pendant deux ans).
- Il s’agissait d’un essai bien administré, exception intéressante faite d’un centre qui a été exclu de l’étude en raison de « l’intégrité douteuse » de ses données. Nous considérons cet élément d’unceil favorable (au moins, le comité directeur exerçait un suivi), mais d’autres pourraient ne pas être d’accord.
- La dose d’AAS était faible (50 mg), mais efficace.
- En raison des différences sur le plan théorique entre les effets pharmacodynamiques à action immédiate et contrôlée, les médecins ne devraient pas substituer le DP ou l’AAS en administration exclusive à l’Aggrenox.

**Bottom line**

- The combination of ASA and DP was superior to either drug alone in prevention of stroke in people who had already had strokes or TIAs. Absolute risk reduction was 3.4%(NNT 29 for 2 years).
- This was a well-run trial with the interesting exception of one reporting centre being dropped from the study because of the questionable “integrity” of their data. We view this as positive (at least the steering committee was tracking it), but others might see it differently.
- The dose of ASA was low (50 mg) but effective.
- Because of theoretical differences between the pharmacodynamic effects of immediate- and controlled-release products, physicians should not substitute DP or ASA alone for Aggrenox.

**References**


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