# Aggrenox

## An Aspirin and Extended-Release Dipyridamole Combination

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Stroke is one of the leading causes of death in the United States. The risk of experiencing a recurrent stroke remains elevated for several years after an initial stroke or a transient ischemic attack (TIA), therefore secondary prevention is crucial in reducing the risk of stroke and the complications and costs associated with stroke. Aggrenox, a combination of low-dose aspirin and extended-release dipyridamole, is a new agent that is effective in the secondary prevention of stroke and transient ischemia of the brain. The clinical effect of its two antiplatelet agents are additive and significantly better than either aspirin or dipyridamole alone, although it has not been shown to be more effective than aspirin alone in preventing death. Aggrenox is much more expensive than aspirin alone but has been shown to be more cost-effective. At this point, much of the pharmacologic information concerning this combination agent is based on previous data about aspirin and immediate-release dipyridamole. This combination of aspirin and extended-release dipyridamole may play a significant role in secondary stroke and TIA prevention. **Key words:** Aspirin—Dipyridamole—Stroke.

When considered apart from other cardiovascular diseases, stroke ranks as the third leading cause of death in the United States.[1] In both men and women, the risk for developing a stroke increases with the presence of cardiovascular risk factors such as hypertension, atrial fibrillation, and prior cardiovascular disease.[2] Eight percent of men and 11% of women will have a stroke within 6 years after a myocardial infarction.[1] Half of the men and women under age 65 who have a stroke die within 8 years. From 1988 to 1998, the stroke death rate fell approximately 15%, but the actual number of stroke deaths rose 5.3%. In 1998, stroke accounted for about 1 in every 14.8 deaths in the United States, with about 47% of those deaths occurring out of the hospital. Morbidity is approximately equal between men and women, but at all ages, mortality is higher in women. Mortality is also high among non-Hispanic blacks, whites, and those of Asian/Pacific Island descent.[1]

Approximately 80% of strokes are caused by a blood clot that blocks or reduces blood flow to the brain.[3] The most common type of complete stroke is an atherothrombotic brain infarction, which accounts for 61% of all strokes, excluding transient ischemic attacks (TIAs). Cerebral embolus, accounting for 24%, is the next most common. Of the definite or probable strokes reported in a 1987 to 1995 study, 83% were thromboembolic, or ischemic. Of the definite thrombotic brain infarctions, 38% were classified as lacunar strokes.[4]

Fourteen percent of persons who survive a first stroke or TIA will experience a recurrence within 1 year.[1] The risk of having a recurrent stroke is highest early after the first stroke—15 times the risk in the general population in the first year. By the fifth year, the risk is about nine times the risk of stroke in the general population. The risk of stroke recurrence did not appear to be related to age or pathologic type of stroke.[5] In the United States, stroke is a leading cause of serious, long-term disability, with a large proportion of stroke patients remaining handicapped and dependent.[1,6] These statistics together with a projected increase in the population at risk for stroke development suggest a major burden on the community with respect to the care of patients who have experienced strokes.[6]

The absolute and relative risks of recurrent strokes remain elevated for several years after an initial stroke, so efforts at secondary prevention should be initiated as soon as possible and continued for several years to gain the greatest benefit.[5] Various antiplatelet agents, as monotherapy and in combination, have been studied for use in secondary prevention of stroke and TIA.[7] The efficacy of aspirin, or acetylsalicylic acid (ASA), is well accepted.[7–10] However, its

Heart Disease 2001;3:340–346

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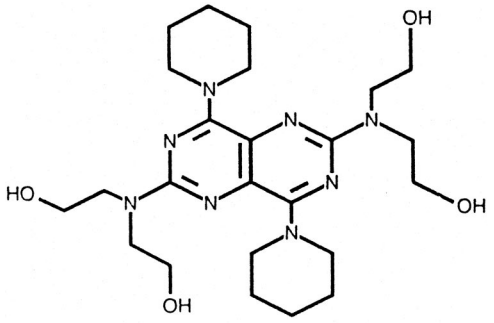
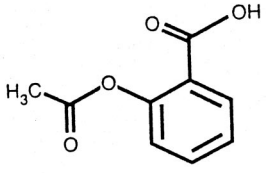



DIPYRIDAMOLE




ASPIRIN

**Figure 1.** Chemical structures of dipyridamole and aspirin, the components of Aggrenox (Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT).

overall efficacy in preventing vascular events, whether in low (<100 mg/day), medium (300 to 325 mg/day), and high (>900 mg/day) doses, is only about 9 to 14% relative to placebo.[11,12] Data on other agents, such as clopidogrel (75 mg once daily) and ticlopidine (250 mg twice daily), are less definitive and expert opinions vary regarding the merits of individual agents.[7,12,13]

The combination of ASA and dipyridamole (DP) is also an acceptable option for initial therapy.[12] Combining ASA with DP, another antiplatelet agent that inhibits platelet function by another mechanism, has the potential for greater efficacy. An ASA and extended-release dipyridamole (ER-DP) combination (Aggrenox, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT) (Fig. 1) has been approved and indicated to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis.[14]

## PHARMACOLOGY

The pharmacodynamic effects of ASA monotherapy and DP monotherapy and the pharmacokinetic profile of ASA are well established, but there is limited pharmacokinetic data available for ER-DP and for the ASA/ER-DP combination.[8–10] ASA and ER-DP pharmacology is summarized in Table 1.

## MECHANISM OF ACTION

The antithrombotic effect of ASA/ER-DP is the result of the additive antiplatelet effects of each agent. ASA irreversibly inhibits platelet cyclooxygenase and blocks prostaglandin synthetase, preventing formation of the platelet aggregating substance thromboxane $A_2$. DP inhibits adenosine deaminase and phosphodiesterase, resulting in an accumulation of adenosine, adenine nucleotides, and cyclic-3', 5'-adenosine monophosphate (cAMP). These mediators inhibit platelet aggregation, may stimulate release or synthesis of prostacyclin, which also has antiplatelet effects, and may cause vasodilation.[8–10] The combination of ASA and DP also significantly increase the antiplatelet effect of leukocytes *in vitro* through an increase in nitric oxide.[15,16]

## PHARMACOKINETICS

There are no significant interactions between ASA and DP, so the pharmacokinetics of each agent remain unchanged by their coadministration.[9,14,17]

After the administration of a 25-mg dose, plasma concentrations of ASA peak in 0.63 hours (0.5 to 1 hour) and are essentially undetectable in 2 to 2.5 hours. At steady state, the peak plasma concentration is 319 ng/mL (175 to 463 ng/mL).[14] It is poorly protein bound, has a volume of distribution of 0.15 to 0.2 L/kg, is eliminated via first-order kinetics, and has a half-life of 15 to 20 minutes.[9] About 1% of a dose of ASA is excreted as ASA in the urine.[8,9] ASA is rapidly hydrolyzed to salicylic acid in the liver and gastrointestinal wall, with 50 to 75% of the dose reaching the systemic circulation as intact ASA.[8,14] Peak concentrations of salicylic acid are achieved 1 hour after administration. It is highly plasma protein bound and distributes into all tissues and fluids, including the central nervous system. Salicylic acid exhibits concentration dependent (nonlinear) protein binding, with 90% bound to albumin at low concentrations (<100 $\mu$g/mL). The elimination of salicylic acid follows zero-order kinetics, with a half-life of 2 to 3 hours at low dosages. As urine pH rises above 6.5, the renal clearance of free salicylic acid increases from <5 to >80%. Salicylic acid is conjugated by the liver into various metabolites, which are excreted in urine.[14]

The DP component in Aggrenox is an extended-release formulation. Absorption is incomplete and variable; oral bioavailability is 37 to 66%.[8,18] Peak plasma concentrations occur about 2 hours (1 to 6 hours) after administration.[8,14] In a study evaluating ER-DP and food, peak plasma concentrations occurred 2.4 hours after administration without food, and at 3.3 hours after administration with food. At 45 minutes after administration, 30% of the maximum concentration was detected when DP was taken without food, and 10% of the maximum concentration detected when taken with food.[19] At steady state, peak plasma concentrations are 1.98 $\mu$g/mL (1.01 to 3.99 $\mu$g/mL) and trough concentrations are 0.53 $\mu$g/mL (0.18 to 1.01 $\mu$g/mL). DP is highly lipophilic, but animal studies have shown that it does not significantly cross the blood–brain barrier. Approximately 99% of the drug is bound to plasma proteins, predominantly $\alpha$1 acid glycoprotein and albumin.[14] The steady-state volume of distribution is about 2 to 3 L/kg.[10] DP exhibits triphasic elimination, with an initial phase half-life ($t_{1/2\alpha}$) of approximately 3.4 minutes, a sec-

**TABLE 1**
Properties of aspirin and extended-release dipyridamole

| | ASA | ER-DP |
|---|---|---|
| Mechanism of action | Inhibits cyclooxygenase and synthesis of thromboxane $A_2$ | Inhibits adenosine deaminase and uptake of adenosine |
| Dosage | 25 mg twice daily | 200 mg twice daily |
| Time to peak, h | 0.63 | 2 |
| Volume of distribution, L/kg | 0.15–0.2 | 2–3 |
| Protein binding | Poor | High |
| Metabolism | Liver | Liver |
| Metabolite | Salicylic acid | None active |
| Half-life, h | 2–3 | 13.6 |
| Drug interactions | ACE inhibitors, acetazolamide, anticoagulants, anticonvulsants, $\beta$-blockers, diuretics, methotrexate, NSAIDs, oral hypoglycemics, uricosuric agents | Adenosine, cholinesterase inhibitors |

ASA = acetylsalicylic acid (aspirin); ER-DP = extended-release dipyridamole; ACE = angiotensin-converting enzyme; NSAIDs = nonsteroidal antiinflammatory drugs.

ond phase half-life ($t_{1/2\beta}$) of 39 minutes, and a terminal phase half-life of 13.6 hours.[9,14,18] Only the terminal phase half-life is apparent following oral administration of the ER-DP formulation.[14] DP is metabolized by the liver. In plasma, about 80% of the drug is present as the parent compound and 20% as the pharmacologically inactive metabolite, monoglucuronide. Most of the metabolite is excreted via bile into the feces. Renal excretion is negligible.[14]

In 24 healthy volunteers who were given DP or ASA in combination or as monotherapy for 4 days, the 2-hour plasma concentrations were similar. Plasma DP concentrations were 1.77 and 1.79 mg/L in the DP monotherapy and the ASA/ER-DP groups, respectively. Plasma salicylate concentrations were 1.07 and 1.22 mg/L in the ASA monotherapy and ASA/ER-DP groups, respectively.[20]

In healthy subjects older than 65 years who received ASA/ER-DP, DP plasma concentrations were about 40% higher than in subjects younger than 55 years.[21] No studies have been done with ASA/ER-DP in patients with renal or hepatic dysfunction. DP can be dosed without adjustment in patients with hepatic failure. ASA is to be avoided in patients with severe hepatic insufficiency or with severe renal failure. The effect of food on ASA/ER-DP also has not been studied.[14]

## CLINICAL EFFICACY

Two studies using high-dose ASA and short-acting DP (Persantine, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; various others) together in patients who had experienced a transient or completed ischemic stroke failed to demonstrate any advantage over aspirin alone.[18,22] These studies had high withdrawal rates and were possibly underpowered. A third study, also using high-dose ASA and short-acting DP, showed that the ASA and DP combination was more effective than placebo; however, this study did not add any new information because it was already known that ASA was superior to placebo in stroke prevention.[18] The comparison of an ASA and DP combination to the established ASA monotherapy for stroke prevention still had to be investigated. Information regarding these studies is summarized in Table 2.

The safety and efficacy of low-dose ASA (25 mg twice daily) and ER-DP (200 mg twice daily) as monotherapy and in combination for the secondary prevention of ischemic stroke was investigated in the second European Stroke Prevention Study (ESPS-2).[21,23,24] In this randomized, double-blind, multicenter, placebo-controlled trial, 5,038 patients with prior stroke and 1,562 patients with prior TIA were followed for 2 years. Primary end points were stroke, stroke or death or both, and death from all causes. Figure 2 summarizes the results of the study.

In pairwise comparisons with placebo, low-dose ASA produced a significant risk reduction of 18.1% for stroke ($P = 0.013$), 13.2% for stroke or death or both ($P = 0.016$), and 10.9% for all-cause mortality (not significant). ER-DP produced a significant risk reduction of 16.3% for stroke ($P = 0.039$), 15.4% for stroke or death or both ($P = 0.015$), and no significant reduction (7.3%) in mortality when compared with placebo. The ASA/ER-DP combination, when compared with placebo, produced a risk reduction of 37.0% in stroke ($P < 0.001$), 24.4% reduction in stroke or death or both ($P < 0.001$), and no significant reduction (8.5%) in mortality. The ASA/ER-DP combination resulted in a 23.1% and 24.7% reduction in stroke when compared with ASA alone and ER-DP alone, respectively ($P < 0.01$ for both). Nonfatal strokes occurred in 228 patients taking placebo, 186 taking ASA, 183 taking ER-DP, and 137 taking ASA/ER-DP. Fatal strokes occurred in 22 patients taking placebo, 20 taking ASA, 28 taking ER-DP, and 20 taking ASA/ER-DP. Death from any cause occurred in 202 placebo patients, 182 ASA patients, 188 ER-DP patients, and 185 ASA/ER-DP patients. The differences for death were not significant.[8,21,24]

The calculated risk reductions, in terms of number of events avoided per thousand patients treated over 2 years, illustrates the clinical effects of these treatment regimens. It is calculated that, when compared with placebo, ASA alone can prevent 29 strokes, 30 strokes or deaths or both, and 13 deaths. ER-DP can prevent 26 strokes, 35 strokes or deaths or both, and 9 deaths. ASA/ER-DP can prevent 58 strokes, 56 strokes or deaths or both, and 10 deaths.[21] None of the treatment groups decreased the severity of

**TABLE 2**
Summary of aspirin and immediate release dipyridamole studies

| | AICLA[36] | ACCSG[37–38] | ESPS-1[39] |
|---|---|---|---|
| Study type | Randomized, double-blind, placebo-controlled, 3 year | Randomized, double-blind, multicenter, 1 year (many followed for 4 to 5 years) | Randomized, double-blind, placebo-controlled, 2 year |
| Outcome measure(s) | Reduction in fatal and nonfatal cerebral infarction in patients who had at least one atherothrombotic ischemic event in the preceding year | Lower risk of cerebral or retinal infarction or death in persons with a recent history of carotid territory TIAs | Prevention of recurrent stroke in patients who previously had TIA, reversible ischemic neurologic deficits, or completed strokes |
| Total no. of patients | 604 | 890 | 2,500 |
| ASA dosage | 1 g/d | 325 mg qid | None |
| ASA/DP dosage | 1 g/d ASA, 225 mg/d DP | 325 mg ASA qid, 75 mg DP qid | 330 mg ASA tid, 75 mg DP tid |
| Results | ASA significantly better than placebo, $P < 0.05$; ASA/DP better than placebo, $P < 0.06$ (not significant); no significant difference between ASA and ASA/DP; no difference in mortality between the three groups | No significant difference between groups for all end points; no significant difference in adverse effects between groups | ASA/DP better than placebo, $P < 0.001$, for all end points; no significant difference due to age, sex, or nature or site of qualifying event |
| Study limitations | 41 subjects withdrawn because of adverse effects | 382 subjects (43%) withdrawn | Did not include ASA monotherapy group |

AICLA = Accidents Ischemiques Cerebraux Lies a l'Atherosclerose; ACCSG = American–Canadian Cooperative Study Group; ESPS = European Stroke Prevention Study; ASA = acetylsalicylic acid (aspirin); DP = dipyridamole; TIA = transient ischemic attack; qid = four times daily; tid = three times daily.

recurrent strokes, but ASA/ER-DP may lengthen the time to recurrent stroke.[18,21]

TIAs and other vascular events were secondary end points. Factorial analysis also demonstrated a highly significant effect of ASA ($P < 0.001$) and DP ($P < 0.01$) for preventing TIA. The risk reduction for ASA/ER-DP was 36% ($P < 0.001$) in comparison with placebo. Low-dose ASA alone or DP alone is equally effective for the secondary prevention of ischemic stroke or TIA. When used in combination, their protective effects were additive and significantly more effective than those of the single agents.[21,23,24]

*Ex vivo* inhibition of the platelet and blood vessel wall interaction in whole blood was studied in a randomized, double-blinded, placebo-controlled trial in healthy volunteers.[17] Subjects were given one of the following: 200 mg ER-DP, 25 mg ASA, the ASA/ER-DP combination, or placebo twice daily for 3.5 days. The mean area of all platelet aggregates was reduced by 6.2 ± 4.2% (mean ± standard error [SE]) with placebo, 19.8 ± 6.7% with ER-DP, 53.7 ± 4.9% with ASA, and 71.4 ± 3.7% with the ASA/ER-DP combination. Low-dose ASA significantly inhibited platelet aggregation ($P < 0.001$), and ER-DP significantly reduced the size of platelet aggregates by reducing adhesion to blood vessel wall ($P < 0.01$). The ASA/ER-DP combination significantly inhibited *ex vivo* platelet aggregation/thrombus formation to a greater extent than either agent alone. The combination also significantly reduced the size of platelet aggregates to a greater extent than the added effect of ASA alone and ER-DP alone.[17]

The relative efficacy of ASA/ER-DP compared with clopidogrel, ticlopidine, ASA/clopidogrel, or ASA/ticlopidine for secondary stroke prevention has yet to be determined.[18] One study indicated that ASA/ER-DP or a low-dose ASA and ticlopidine (200 mg/day) combination were both significantly effective in preventing cardiac events such as myocardial infarction, death by congestive heart failure, and sudden death in patients who have had prior myocardial infarctions.[25] Various trials are either underway or are necessary to better evaluate the different antiplatelet combinations for secondary prevention of stroke or TIA.[26]

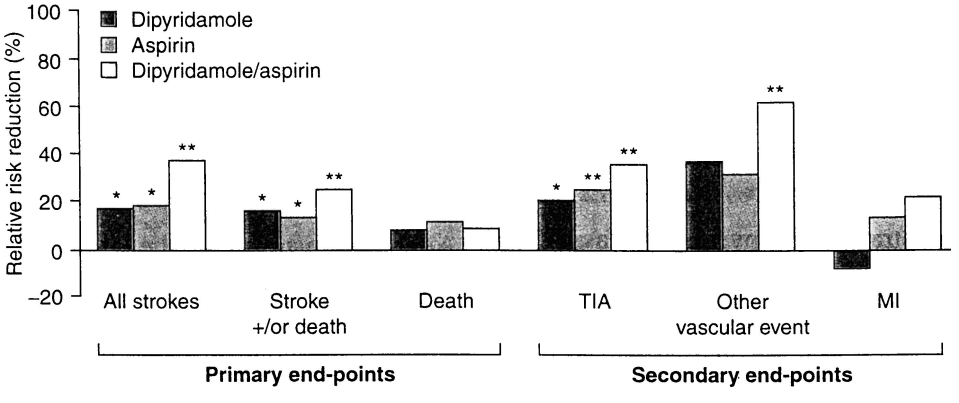



**Figure 2.** Risk reduction relative to placebo for primary and secondary end points at 24 months as reported in the second European Stroke Prevention Study. Patients with prior stroke or transient ischemic attacks (TIA) received extended-release dipyridamole/aspirin 400/50 mg/day ($n$ = 1,650), aspirin 50 mg/day ($n$ = 1,649), extended-release dipyridamole 400 mg day ($n$ = 1,654), or placebo ($n$ = 1649). MI = myocardial infarction. * $P < 0.05$, ** $P < 0.001$ versus placebo. Reprinted from Hervey and Goa[8] with permission.

**TABLE 3**
Incidence of adverse events that occurred in ≥1% of the treatment groups and led to the discontinuation of treatment in ESPS-2

| | Treatment groups | | | |
|---|---|---|---|---|
| | ASA/ER-DP ($n$ = 1,650) | ER-DP ($n$ = 1,654) | ASA ($n$ = 1,649) | Placebo ($n$ = 1,649) |
| Patients with at least one adverse event that led to treatment discontinuation | 417 (25) | 419 (25) | 318 (19) | 352 (21) |
| Headache | 165 (10) | 166 (10) | 57 (3) | 69 (4) |
| Dizziness | 85 (5) | 97 (6) | 69 (4) | 68 (4) |
| Nausea | 91 (6) | 95 (6) | 51 (3) | 53 (3) |
| Abdominal pain | 74 (4) | 64 (4) | 56 (3) | 52 (3) |
| Dyspepsia | 59 (4) | 61 (4) | 49 (3) | 46 (3) |
| Vomiting | 53 (3) | 52 (3) | 28 (2) | 24 (1) |
| Diarrhea | 35 (2) | 41 (2) | 9 (<1) | 16 (<1) |
| Stroke | 39 (2) | 48 (3) | 57 (3) | 73 (4) |
| Transient ischemic attack | 35 (2) | 40 (2) | 26 (2) | 48 (3) |
| Angina pectoris | 23 (1) | 20 (1) | 16 (<1) | 26 (2) |

Values are expressed as $n$ (%).
ASA = acetylsalicylic acid (aspirin); ER-DP = extended-release dipyridamole.
Reproduced from the Aggrenox package insert.[14]

ASA (50 to 325 mg daily), clopidogrel (75 mg daily), ticlopidine (250 mg twice daily), and ASA/ER-DP are all acceptable options for initial therapy in secondary stroke prevention.[12,27]

## ADVERSE EFFECTS

The adverse effects of ASA/ER-DP are similar to those of the two individual agents.[8] The most common adverse effects in patients treated with ASA/ER-DP, where the incidence was greater than those treated with placebo, include headache, bleeding, dyspepsia, abdominal pain, nausea, and diarrhea. Less common side effects include vomiting, body or muscle pain, and fatigue.[14]

The incidence of adverse events reported from ESPS-2 with ASA/ER-DP was greater than with placebo but only slightly greater than with either ASA or DP alone.[21] In the ASA/ER-DP group, 64% of patients reported an adverse event compared with 56.6% taking placebo, 60.0% taking ASA, and 62.5% taking ER-DP. Most adverse effects were reported to be mild, not specifically treatment related, and diminished over time. Twenty-one percent of patients discontinued treatment in the placebo group, 19% in the ASA group, 25% in the ER-DP group, and 25% in the ASA/ER-DP group. Headache and gastrointestinal events predominated as reasons for early discontinuation of treatment and occurred more often in patients receiving ER-DP or ASA/ER-DP. Adverse events associated with ER-DP were generally reported early in treatment, but risks of developing adverse events related to ASA persisted throughout treatment exposure. The ASA/ER-DP combination has no clear benefit over ASA with respect to safety.[21,23] The adverse events that led to discontinuation of treatment from ESPS-2 are listed in Table 3.[14,21]

Although low dose ASA does not eliminate the propensity for induced bleeding, the incidence of possible gastrointestinal and bleeding adverse events may be lower.[12,21,22] Many studies have shown that the increase in the incidence of hemorrhagic stroke observed with ASA is less than the reduction in the incidence of ischemic stroke.[22] In ESPS-2, the incidence of bleeding remained stable over time. All-site bleeding and gastrointestinal bleeding were significantly more frequent and more often moderate or severe/fatal in patients taking ASA and ASA/ER-DP.[8,21] The incidence was significantly higher in the combination and the ASA groups, 8.7% and 8.2%, respectively, than in the ER-DP and placebo groups, 4.7% and 4.5%, respectively, $P < 0.001$ for both groups. The incidence of severe or fatal bleeding was 1.6% with ASA/ER-DP, 1.2% with ASA, and 0.4% in the ER-DP and placebo groups.[23,24]

Headache was the most common adverse effect, occurring more frequently in ER-DP–treated patients. It was most marked early in treatment and diminished over time. After the first month of treatment, the event rate was 38.2% in the ASA/ER-DP group, similar to the 37.2% incidence in the ER-DP group, but significantly higher than 33.1% in the ASA and 32.4% in the placebo group ($P < 0.001$).[21] The ER-DP formulation was used in an attempt to reduce the peaks of serum levels that are associated with headache.[24] Headache was more common with the combination than with ASA alone.[8]

In one report, a patient who used ASA 100 mg daily for many years received two doses of ASA/ER-DP and subsequently developed transient cerebellar deficits that were attributed to TIAs, along with adverse effects that may be attributed to ER-DP. Although a coincidence between ASA/ER-DP use and atherothrombotic TIAs can not be excluded, the authors concluded that ER-DP induced cerebral vasodilation and a steal phenomenon that led to a hemodynamic TIA. The authors suggest that DP should be used carefully in stroke patients with impaired cerebral autoregulation due to occlusive cerebrovascular disease.[19]

Diarrhea was also more common in the ASA/ER-DP (12.1%) and ER-DP groups (15.4%) than in the ASA or placebo groups (6.6% and 9.3%, respectively), $P < 0.001$ versus ER-DP regimens.[21]

According to ESPS-2, patients treated with ASA/ER-DP had a mean change from baseline in hemoglobin of

−0.25 g/dL, hematocrit of −0.75%, and erythrocyte count of $-0.13 \times 10^6/mm^3$. The incidence of those developing lower erythrocyte counts was 0.8% and of those with lower hematocrit and hemoglobin values was about 2%. This occurred mainly in the first year of therapy.[21] ASA has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time. DP has been associated with elevated hepatic enzymes.[14]

## DRUG INTERACTIONS

No drug–drug interaction studies have been conducted with the commercially available ASA/ER-DP combination.[14] Current information, summarized in Table 1, is based on previously reported drug interactions for ASA monotherapy and immediate-release DP monotherapy.

ASA may decrease the effectiveness of angiotensin-converting enzyme inhibitors, β-blockers, and diuretics. Acetazolamide toxicity is possible with concurrent ASA use owing to competition at the renal tubule for secretion. Increased risk of bleeding is possible when ASA is used with anticoagulants such as heparin and warfarin, and with nonsteroidal antiinflammatory drugs (NSAIDs). Chronic or heavy alcohol consumption (three or more alcoholic drinks a day) may also increase the risk of bleeding. Moderate doses of ASA may increase the hypoglycemic effects of oral hypoglycemic agents. Salicylic acid can displace protein-bound phenytoin and valproic acid, inhibit renal clearance of methotrexate, and antagonize the uricosuric action of agents such as probenecid and sulfinpyrazone.[14,18]

DP has been reported to increase the plasma levels and cardiovascular effects of adenosine.[14] Because induction of hypotension and atrioventricular block may occur, patients using ASA/ER-DP who are referred for adenosine pharmacologic stress testing should receive DP for perfusion imaging instead.[28,29] DP may also counteract the anticholinesterase effects of cholinesterase inhibitors, such as tacrine and donepezil, potentially aggravating myasthenia gravis.[14]

## CONTRAINDICATIONS, PRECAUTIONS, AND SPECIAL POPULATIONS

ASA/ER-DP is contraindicated in patients with hypersensitivity to any of its components.[14]

There have been no adequate and well-controlled studies with ASA/ER-DP in pregnant or nursing women. ASA is a pregnancy category C/D agent and DP is a pregnancy category B agent. ASA/ER-DP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Due to the ASA component, ASA/ER-DP is contraindicated in the third trimester of pregnancy. Both agents are excreted in breast milk in low concentrations, so caution should be used when administering the drug to a nursing woman.

Because of the ASA component, ASA/ER-DP is contraindicated in patients with a known allergy to NSAIDs and in patients with asthma, rhinitis, and nasal polyps. ASA should also not be used in children or adolescents for viral infections because of the risk of developing Reye syndrome. Patients with a history of peptic ulcer disease should avoid using ASA because it can cause gastric mucosal irritation and bleeding. Patients with inherited or acquired bleeding disorders, such as severe liver disease or vitamin K deficiency, may have an increase in bleeding time. Patient with severe renal failure should also avoid ASA use.[14]

DP should be used with caution in patients with severe coronary artery disease. Chest pain may be aggravated in patients with underlying coronary artery disease. Patients with hypotension should also use DP with caution because it can produce peripheral vasodilation.[14] DP frequently causes orthostatic hypotension in the elderly and whenever possible its use in the elderly should be avoided.[30] DP has also been associated with hepatic failure.[14]

## DOSAGE AND ADMINISTRATIONS

ASA/ER-DP is available as a red and ivory, hard, gelatin capsule, imprinted with "01A." Each capsule contains 200 mg DP as yellow extended-release pellets and a round, white, sugar-coated, immediate-release ASA 25 mg tablet. The recommended dosage of ASA/ER-DP is one capsule twice daily. Capsules should be swallowed whole. No studies have been done with ASA/ER-DP in patients with renal or hepatic dysfunction.[14]

## COST AND COST-EFFECTIVENESS

The average wholesale price (AWP) of a 30-day supply of Aggrenox is $95.71. The AWP of a 30-day supply of ASA 81 mg/day is less than $1.50. The AWP of a 30-day supply of DP 400 mg/day, Persantine and various other brands, is $180.30 and less than $50.00, respectively. Aggrenox capsules are not equivalent to the combination of an ASA tablet (various manufacturers) and a DP tablet (various manufacturers).

In 1999, $51 billion was the estimated economic burden resulting from stroke.[31] Limited pharmacoeconomic analyses suggest that treatment with the ASA/ER-DP combination was more cost effective compared with ASA monotherapy for secondary prevention of stroke.[8] Based on data from ESPS-2,[21] one study evaluated the cost-effectiveness of ASA, ER-DP, ASA/ER-DP, and placebo for the prevention of recurrent stroke in 30-day survivors of ischemic stroke.[32] The decision-analytical model predicted that over 5 years, the ASA/ER-DP combination would prevent 2.9% more strokes than ASA alone. Each antiplatelet therapy was more cost-effective than placebo. The ASA/ER-DP combination is likely to generate significant health benefits at modest extra costs. These extra costs are balanced by savings in future costs.[32] Another cost-effectiveness analysis that also utilized data from ESPS-2[21] compared ASA/ER-DP with clopidogrel or ASA alone. The analysis concluded that ASA/ER-DP was cost-effective compared with ASA monotherapy for the secondary prevention of stroke,

whereas clopidogrel was not.[33] These results have been confirmed by another cost-effectiveness analysis, which compared ASA/ER-DP with ASA alone or with clopidogrel for secondary prevention of stroke and TIA in high-risk patients.[34] Ticlopidine has been shown to be more cost effective than high-dose ASA alone, but no cost analyses have been performed comparing ticlopidine with ASA/ER-DP.[35]

## CONCLUSION

The combination of low-dose ASA and ER-DP has demonstrated clinical efficacy in the prevention of secondary stroke and TIA in patients who have had a stroke or TIA. The clinical effects of its two antiplatelet agents are additive and significantly better than either ASA or ER-DP alone in preventing recurrent strokes and TIA. The ASA/ER-DP combination has not been shown to be more effective than ASA alone in preventing death. Although it is much more expensive than ASA alone, it may be pharmacoeconomically advantageous in preventing hospitalizations and other complications that accompany a stroke. These properties may give ASA/ER-DP a significant role in secondary stroke prevention.

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