REVIEW ARTICLE

Drugs 2005; 65 (4): 461-471
0012-6667/05/0004-0461/$39.95/0

Adverse Effects and Drug Interactions of Antithrombotic Agents Used in Prevention of Ischaemic Stroke

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Abstract

Stroke is the third most common cause of death in the US. Primary prevention of stroke can be achieved by control of risk factors including hypertension, diabetes mellitus, elevated cholesterol levels and smoking. Approximately one-third of all ischaemic strokes occur in patients with a history of stroke or transient ischaemic attack (TIA). The mainstay of secondary prevention of ischaemic stroke is the addition of medical therapy with antithrombotic agents to control the risk factors for stroke. Antithrombotic therapy is associated with significant medical complications, particularly bleeding.

Low-dose aspirin (acetylsalicylic acid) has been shown to be as effective as high-dose aspirin in the prevention of stroke, with fewer adverse bleeding events. Aspirin has been shown to be as effective as warfarin in the prevention of noncardioembolic ischaemic stroke, with significantly fewer bleeding complications. Ticlopidine may be more effective in preventing stroke than aspirin, but is associated with unacceptable haematological complications. Clopidogrel may have some benefit over aspirin in preventing myocardial infarction, but has not been shown to be superior to aspirin in the prevention of stroke. The combination of clopidogrel and aspirin may be more effective than aspirin alone in acute coronary syndromes, but the incidence of adverse bleeding is significantly higher.

Furthermore, the combination of aspirin with clopidogrel has not been shown to be more effective for prevention of recurrent stroke than clopidogrel alone, while the rate of bleeding complications was significantly higher with combination therapy. The combination of aspirin and extended-release dipyridamole has been demonstrated to be more effective than aspirin alone, with the same rate of adverse bleeding complications as low-dose aspirin. When selecting the appropriate antithrombotic agent for secondary prevention of stroke, the adverse event profile of the drug must be taken into account when assessing the overall efficacy of the treatment plan.

Stroke is the third most common cause of death in the US. Stroke prevalence is increasing among Americans because of the aging general population, with 783 000 events occurring in 1996 compared with 750 000 in 1995.[1] Stroke occurs significantly more often among people of African heritage, with 288 events per 100 000 African Americans versus 179 per 100 000 Whites.[2] Furthermore, African Americans experience nearly twice the risk of stroke between the ages of 65 and 74 years than Whites.

Approximately one-third of all strokes occur in patients with a history of stroke or transient ischaemic attacks (TIAs).[3] Advanced age, congestive heart failure, persistent atrial fibrillation, recurrent stroke and ischaemic heart disease each pose significant independent risk factors for death after an initial stroke, with overall death rates of 7% at 7 days, 27% at 1 year, and 53% at 5 years.[4] Data drawn from 5184 participants in the Framingham Study further demonstrate that risk of death or stroke recurrence is substantial after an initial stroke and profoundly influenced by male gender, cardiac comorbidity and hypertension prior to the initial event.[5]

Ischemia accounts for as much as 85% of stroke events.[3] The three primary mechanisms for cerebral infarction are: (i) cardiac emboli causing obstruction of cerebral vessels; (ii) atherosclerotic disease of large vessels causing occlusion or artery to artery embolism; and (iii) microvascular disease in the arterioles of subcortical brain structures caused by diabetes mellitus and hypertension.

The effect on quality of life and the economic consequences associated with ischaemic strokes can be devastating, with the lifetime per-person cost of first ischaemic strokes estimated at $US90 981 (1990 values).[6] Patient history of TIA or stroke is a strong indicator of future ischaemic stroke risk,[7] therefore decisive steps must be taken to prevent ischaemic strokes in patients with documented TIA or stroke.

Prevention of stroke in patients with a cardioembolic source, particularly atrial fibrillation and valvular heart disease, is achieved primarily by anticoagulation with warfarin.[8] While the therapeutic effect of warfarin in preventing cardioembolic stroke in atrial fibrillation outweighs the risk, warfarin can be associated with a high rate of haemorrhagic complications. In fact, in the SPAF II (Stroke Prevention in Atrial Fibrillation II)[9] study, in which the average international normalised ratio (INR) was higher than in the other trials, the risk of haemorrhage in patients >75 years of age was 10.5%, reducing the benefit of prevention of ischaemic stroke.[9] For patients with mechanical heart valve replacement, INR in the higher therapeutic range >3.0 is required to prevent stroke, despite the higher rate of haemorrhage.[8] A randomised, open-label trial[10] and a randomised, double-blind trial[11] have determined that agents that inhibit factor X activity are as effective in preventing stroke as warfarin, with fewer haemorrhagic complications. In these trials, careful control of the level of anticoagulation reduced the bleeding rate in the warfarin group to a degree half of that of the SPAF II trial, showing that warfarin can be given safely in a controlled setting.

Prevention of stroke in patients with significant symptomatic atherosclerotic disease of >70% at the carotid artery bifurcation is achieved primarily by

carotid endarterectomy.[12] However, the risk of stroke or death with this procedure ranges from 2%[12] to 8%.[13] The value of endarterectomy in asymptomatic patients is still controversial, given the much lower incidence of initial strokes than the incidence of recurrent stroke in symptomatic patients.[14] A recent trial of carotid endarterectomy in asymptomatic patients confirmed a reduction in stroke risk over a 5-year period from 11.3% with medical therapy to 3.8% with surgical therapy.[15] Therefore, carotid endarterectomy is still often recommended for patients with >60% stenosis because there was a small but statistically significant difference in favour of surgery over medical therapy. Long-term benefit from carotid endarterectomy requires continued management of atherosclerotic disease with control of risk factors and platelet antiaggregant therapy.

The majority of patients with ischaemic stroke do not have a cardioembolic source or significant carotid artery stenosis. Primary prevention of stroke in these patients is focused on control of the main risk factors for stroke, that is, hypertension, diabetes and smoking. In patients with prior stroke or TIA, appropriate antithrombotic therapy has been clearly shown to decrease the incidence of subsequent strokes.[16]

1. Pharmacological Agents Used to Prevent Primary and Recurrent Thrombotic Stroke

The average risk of recurrent stroke following a first cerebral infarction is 12% at 1 year and 29% at 5 years, with advanced age and the presence of diabetes representing significant independent predictors of repeat stroke episodes.[4] Antithrombotic agents used alone or in combination to prevent primary and recurrent ischaemic stroke include warfarin, aspirin (acetylsalicylic acid), dipyridamole, ticlopidine and clopidogrel. Warfarin reduces clotting time by inhibiting vitamin K-dependent coagulation factors,[17] while aspirin decreases synthesis of endoperoxides and thromboxanes that mediate platelet aggregation.[18] Dipyridamole inhibits platelet phosphodiesterase, increasing levels of cyclic adenosine monophosphate to inhibit aggregation of platelets.[19] Dipyridamole may have other antithrombotic effects in addition to inhibiting platelet aggregation, including reduction of platelet-endothelial interactions through inhibition of adhesion molecule expression, inhibition of protease receptors and cleavage of thrombin receptors.[20] Ticlopidine[21] and clopidogrel[22] reduce platelet aggregation by inhibiting adenosine diphosphate-mediated activation of the glycoprotein (GP) IIb/IIIa complex.[23] Adverse effects reported in selected trials of these antithrombotic agents used alone or in combination to prevent primary and recurrent ischaemic stroke are summarised in table I.[24-33]

1.1 Warfarin

Warfarin remains the treatment of choice for preventing cardioembolic stroke, particularly in patients with atrial fibrillation. In this setting, the risk of thromboembolism is reduced by 51% with warfarin therapy, while the risk of intracranial haemorrhage is only moderately increased from 0.23 per 100 patient-years to 0.46 per 100 patient-years.[34] However, warfarin does not appear to have a role in the prevention of stroke in patients without a cardioembolic source.

Findings of a recent randomised, double-blind comparison of warfarin (dose-adjusted to produce an INR of 1.4–2.8) and aspirin 325 mg/day in 2206 patients with prior noncardioembolic ischaemic stroke demonstrated no benefit of warfarin over aspirin in prevention of recurrent ischaemic stroke or death in this population.[35]

The incidence of adverse events was higher among patients treated with warfarin, with a significantly elevated rate of minor haemorrhage noted in the warfarin group (20.8%) versus those treated with aspirin (12.9%) [$p < 0.001$].[35] Major bleeding was slightly higher in the warfarin group (2.2% per year) than in the aspirin-treated group (1.5% per year), but this difference was not statistically significant.[35]

The greatest risk of anticoagulation with warfarin occurs when the INR becomes elevated above 3.5. A trial comparing the use of aspirin 30 mg/day to warfarin (INR 3.0–4.5) was interrupted before com-

Table I. Adverse effects reported in selected trials of antithrombotic therapy

Trial/investigators	Antithrombotic agent(s) used	Population characteristics	Adverse effects
Single agents			
Dutch TIA Trial[24]	Low-dose ASA	Prior TIA or minor ischaemic stroke	No significant difference in major bleeding complications Significantly fewer episodes of minor bleeding and minor GI bleeding in patients taking 30mg od vs 283mg od
Farrell et al.[25]		Prior TIA or minor ischaemic stroke	Significantly less gastrotoxic; odds ratio for ASA 1200mg od compared with 300mg od was 1.54 (95% CI 1.25, 1.89)
Diener et al.[26]	DP	Increased risk for ischaemic stroke	All-site bleeding episodes were significantly greater in ASA group vs DP group (4.7% vs 8.7%, $p < 0.001$) Headache more common with DP vs ASA (37.2% vs 33.1%, $p < 0.001$)
Gent et al.[27]	Ticlopidine	Recent ischaemic stroke	Two patients in ticlopidine group had primary intracerebral haemorrhage, one of which was fatal; two patients in the placebo group had subarachnoid haemorrhage, both fatal Severe neutropenia in ≈1% of cases in ticlopidine group
Hass et al.[28]		Prior TIA, mild persistent focal cerebral or retinal ischaemia	Diarrhoea (ticlopidine group 20% vs ASA group 10%), severe neutropenia (<1%), skin rash (14%), increased total cholesterol (ticlopidine group 9% vs ASA group 2%, $p < 0.01$), bleeding (ticlopidine group 9% vs ASA group 10%)
CAPRIE Steering Committee[29]	Clopidogrel	Recent ischaemic strokes, other atherosclerotic diseases	Rash, diarrhoea, GI discomfort; no significant difference between groups in severe GI discomfort or intracranial haemorrhage Frequency of severe rash and severe diarrhoea significantly higher with clopidogrel than ASA Frequency of GI haemorrhage significantly higher with ASA than clopidogrel
Bennett et al.[30]		Review of all patients taking clopidogrel (3 million), March 1998 to March 2000	11 cases of TTP reported among patients receiving clopidogrel, ten within first 2 weeks
Fischer et al.[31]		Case report	Angioedema
Combination agents			
Yusuf et al.[32]	ASA + clopidogrel	Acute coronary syndromes without ST-segment elevation	Major bleeding significantly more common vs placebo ($p = 0.001$)
ESPS Group[30]	High-dose ASA + IR-DP	Prior TIA or stroke	GI disorders and bleeding more common vs placebo (p-values unstated)
Diener et al.[26]	Low-dose ASA + ER-DP	Increased risk for ischaemic stroke	Headache occurred more often in DP-treated patients All-site bleeding and GI bleeding were significantly more common in both ASA-containing regimens

ASA = aspirin (acetylsalicylic acid); **CAPRIE** = Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events; **DP** = dipyridamole; **ER** = extended-release; **ESPS** = European Stroke Prevention Study; **GI** = gastrointestinal; **IR** = immediate-release; **od** = once daily; **TIA** = transient ischaemic attacks; **TTP** = thrombotic thrombocytopenic purpura.

pletion because of an excessive rate of haemorrhage in the warfarin group. There were 53 major bleeding complications, including 27 intracranial haemorrhages and 17 fatal haemorrhages in the group treated with warfarin.[36] There were only six major bleeding complications in the group treated with aspirin, including three intracranial and only one fatal complication. The results of these trials indicate that warfarin should not be used to treat patients at risk for noncardioembolic ischaemic stroke be-

cause of the higher rate of significant haemorrhage, particularly when the INR rises above 3.0, without a demonstrable benefit in efficacy over aspirin for preventing ischaemic stroke.

A retrospective study of stroke patients with intracranial atherosclerotic occlusive disease demonstrated that patients treated with warfarin had a lower incidence of recurrent stroke than patients treated with aspirin.[37] However, a recent trial comparing aspirin and warfarin for prevention of stroke in patients with intracranial atherosclerotic disease (WASID [Warfarin-Aspirin Symptomatic Intracranial Disease]) was terminated prior to scheduled completion because the incidence of significant intracranial bleeding outweighed a small advantage of warfarin for prevention of ischaemic stroke that was not statistically significant.[38] While warfarin can be employed safely to prevent embolic stroke in patients with atrial fibrillation, it appears that patients with occlusive cerebrovascular disease are at a greater risk of haemorrhage, possibly because of the influence of hypertension.

1.2 Aspirin (Acetylsalicylic Acid)

Adverse effects of large aspirin doses are well known and include major and minor bleeding complications and gastrointestinal irritation.[24,39,40] Low-dose aspirin therapy is as effective as higher-dose regimens in prevention of initial and recurrent stroke and offers a more favourable adverse event profile,[24,25] but does not eliminate the possibility for induced bleeding in these patients.

In a large clinical trial of 3131 patients, aspirin 30 mg/day was no less effective than aspirin 283 mg/day in preventing stroke and other vascular events in patients with a history of TIA or minor stroke, but precipitated significantly fewer reports of major and minor bleeding complications (2.6% vs 3.36% and 3.2% vs 5.3%, respectively), gastrointestinal irritation (10.5% vs 11.4%) and other adverse effects (4.7% vs 5.7%).[24]

Similarly, in 2435 patients with prior TIA or minor ischaemic stroke, aspirin 600mg twice daily and 300mg once daily were equally preventive of serious vascular events and death, but the lower aspirin dose was significantly less gastrotoxic; the odds ratio for gastrotoxicity for the higher-dose group compared with the lower-dose group was 1.54 (95% CI 1.25, 1.89).[25] Initial loading doses of at least 120mg are recommended in patients treated with low-dose aspirin, as several days of treatment are otherwise required to achieve maximal platelet inhibition at lower aspirin dosages.[24]

1.3 Dipyridamole

Findings from a randomised, double-blind, placebo-controlled clinical trial of 6602 patients demonstrated a significant effect for extended-release dipyridamole monotherapy in reducing subsequent stroke by 16% versus placebo among patients at risk for ischaemic stroke ($p < 0.01$).[26] All-site bleeding was significantly less common among patients treated with dipyridamole (4.7%) versus aspirin (8.2%, $p < 0.001$, treatment groups overall comparison),[26] although headache, the most common adverse effect, occurred more often among patients treated with extended-release dipyridamole (37.2%) versus aspirin (33.1%) or placebo (32.4%, $p < 0.001$, treatment groups overall comparison).[26]

1.4 Ticlopidine

Results of a controlled clinical trial of 1072 patients showed that ticlopidine 250mg twice daily achieved a 30% relative risk reduction versus placebo in recurrence of stroke and other vascular events among patients with recent ischaemic stroke ($p < 0.01$).[27] Furthermore, ticlopidine 500 mg/day was more effective than aspirin 1300 mg/day in preventing subsequent strokes among 3069 patients with prior TIA or mild persistent focal cerebral or retinal ischaemia, with patients receiving ticlopidine demonstrating a 21% risk reduction versus those treated with aspirin ($p < 0.05$).[28] Adverse events associated with ticlopidine use include severe neutropenia (<2.4%), skin rash and diarrhoea (severe in 1–2% of patients), all of which were reversible in clinical trials.[27,28] Ticlopidine treatment has been associated with significantly higher rates of diarrhoea (20.4% vs 9.8%) and skin rash (11.9% vs 5.2%), but less gastrointestinal irritation (pain 7.2%

vs 10%; gastritis 0.9% vs 1.7%) and bleeding (0.5% vs 1.4%) versus aspirin treatment ($p < 0.05$ for all comparisons).[28] There is also a significant incidence of thrombotic thrombocytopenic purpura (TTP) associated with the use of ticlopidine; the estimated incidence of ticlopidine-associated TTP is 1 per 1600–5000 patients treated.[41-44]

1.5 Clopidogrel

Clopidogrel 75 mg/day proved more effective than aspirin 325 mg/day in reducing subsequent ischaemic strokes and other vascular events in a large clinical trial in 19 185 patients with recent ischaemic strokes or other atherosclerotic diseases.[29] Clopidogrel provided a 7.9% relative risk reduction compared with aspirin in the combined endpoint of vascular death, stroke and myocardial infarction. However, a significant reduction in recurrent stroke among stroke patients could not be demonstrated. There was a positive effect of clopidogrel in preventing recurrent hospitalisations for vascular ischaemic events and bleeding events compared with aspirin.[45] Patients with prior cardiac surgery derived a particular benefit, with a reduction in ischaemic events to 15.9% in the clopidogrel group compared with 22.3% in the aspirin group.[46] Severe adverse events included rash (0.3% with clopidogrel vs 0.1% with aspirin treatment), diarrhoea (0.2% vs 0.1%), upper gastrointestinal discomfort (1.0% vs 1.2%), and intracranial (0.3% vs 0.5%) and gastrointestinal haemorrhage (0.5% vs 0.7%) [$p < 0.05$ for all comparisons].[29] Clopidogrel has also been linked to development of angioedema in some patients.[31] No cases of TTP occurred in the clinical trial of 19 185 patients, but TTP was identified in 11 patients of 3 million treated with clopidogrel from March 1998 to March 2000.[30] Findings from another study compared clopidogrel-associated TTP with those reported previously for ticlopidine-associated TTP.[30,47] The study suggests that clopidogrel-associated TTP is 15 times more likely to occur within the first 2 weeks of drug use and more likely to require ≥20 therapeutic plasma exchanges before resolving. While the rate of TTP is reported in worldwide postmarketing surveillance at only 4 cases per million patients exposed,[48] calculations of the rate based on number of cases reported relative to number of patients estimated to be taking the drug ranges from 1.1 to 27.8 per million.[49] Clopidogrel, which is activated by cytochrome P450 (CYP) 3A4, may be inhibited by atorvastatin, another CYP34A substrate.[50] Use of an HMG-CoA reductase inhibitor (statin) not metabolised by CYP3A4 may, therefore, be warranted in patients treated with clopidogrel.

The use of ticlopidine and clopidogrel became more prevalent when secondary analysis of the clinical trials determined that ticlopidine may have been more effective than aspirin in preventing recurrent lacunar stroke, particularly in African American patients.[51] However, the recently completed African American Antiplatelet Stroke Study did not show a beneficial effect of ticlopidine in the prevention of recurrent stroke in African American patients, including patients with lacunar stroke.[52] In fact, there was a strong trend indicating that aspirin would be more effective than ticlopidine, but the study was interrupted before completion when it was determined that there was no statistical chance that ticlopidine would be superior to aspirin. Therefore, there is no compelling data that ticlopidine or clopidogrel are superior to aspirin in prevention of thrombotic stroke, and these agents should be reserved for patients with aspirin allergy or patients who cannot tolerate the gastrointestinal adverse effects of aspirin.

1.6 Triflusal

Triflusal is a fluorinated salicylate which may have neuroprotective properties in addition to inhibiting platelet aggregation. *In vitro* studies have demonstrated a decrease in proinflammatory molecules, particularly inducible nitric oxide synthase,[53] and inhibits glial nuclear factor-κB.[54]. Infarct volumes are reduced with triflusal in experimental models of cerebral ischaemia.[53,54] However, a trial of triflusal 600 mg/day compared with aspirin 325 mg/day did not show a significant difference in preventing recurrent stroke in 2113 patients with previous stroke or TIA.[55] The overall incidence of

haemorrhagic complications was lower in the triflusal group (16.7%) versus aspirin (25.2%), suggesting a possible role for triflusal in patients at risk for haemorrhagic complications with aspirin in circumstances where such a high dose of aspirin must be employed.

2. Combination Regimens

2.1 Aspirin Plus Clopidogrel

Inhibition of platelet aggregation and thrombus formation can be improved by dual antithrombotic regimens,[56] and those that inhibit multiple sites in the thrombotic pathway may enhance long-term patient outcomes. Antithrombotic regimens combining aspirin and clopidogrel have proven more effective in preventing myocardial infarction in patients with acute coronary syndromes than treatment with aspirin alone. In one large randomised, placebo-controlled clinical trial, clopidogrel plus aspirin proved more effective than aspirin alone in preventing cardiovascular events in 12 562 patients experiencing acute coronary syndromes without ST-segment elevation ($p < 0.01$) over a mean observation period of 9 months.[32] However, the risk of major and minor bleeding episodes was significantly increased among patients treated with both clopidogrel and aspirin (3.7%) than aspirin alone (2.7%) [$p < 0.01$].[29] The dose of aspirin varied from 75mg to 325mg in this study, with increasing rates of bleeding with higher doses of aspirin alone and in combination with clopidogrel.[57] With a dosage of aspirin <100mg, the bleeding rate was 2.0% with aspirin alone compared with 2.6% with clopidogrel. With doses of aspirin of 100–200mg, the bleeding rate with aspirin alone was 2.3% compared with 3.5% with clopidogrel. With doses of aspirin of >200mg, the bleeding rate of aspirin alone was 4.0% compared with 4.9% with clopidogrel.[57]

Because of the success of aspirin and clopidogrel combination therapy in the reduction of coronary events in patients with acute coronary syndromes, many patients with cerebrovascular disease are now being treated with this regimen. However, there were insufficient numbers of patients with an outcome of stroke to show a statistically significant benefit of the combination of aspirin and clopidogrel over clopidogrel alone in the prevention of stroke.[32]

The data for prevention of myocardial infarction cannot be extrapolated to conclude that the combination of aspirin and clopidogrel is more effective than aspirin in the prevention of stroke, because the aetiology of stroke is more variable than the aetiology of coronary artery disease. The risk of recurrent stroke following a first cerebral infarction is 12% at 1 year and 29% at 5 years, with advanced age and the presence of diabetes representing significant independent predictors of repeat stroke episodes.[4] Significantly, the prevalence of associated cardiovascular conditions is lower among stroke patients than is widely recognised, as those with a history of stroke or TIA are five to seven times more likely to have a subsequent stroke than a myocardial infarction.[58] Furthermore, findings of a large cohort of 8089 patients with previously diagnosed atherosclerotic vascular disease demonstrate that approximately three-quarters of subsequent cardiovascular events among patients with a history of stroke are secondary strokes.[58] Existing data also suggest that patients with previous stroke episodes are significantly more likely than those with prior myocardial infarctions to have adverse bleeding complications during antithrombotic therapy.[16,29]

Combination therapy with aspirin and clopidogrel has recently been compared with clopidogrel alone in the MATCH (Management of ATherothrombosis with Clopidogrel in High-risk patients) trial.[59] The MATCH trial was a randomised, double-blind, controlled trial comparing combination of aspirin 75mg and clopidogrel with placebo and clopidogrel for the prevention of recurrent stroke. The trial enrolled 7599 patients ≥40 years of age with a history of TIA (21.1%) or ischaemic stroke (78.9%) in the previous 3 months. All patients had comorbidities that would place them at high risk for recurrent stroke, including hypertension, previous myocardial infarction, symptomatic peripheral arterial disease, angina pectoris or diabetes. Follow-up lasted 18 months.

There was no significant reduction in the number of ischaemic events in patients taking combination therapy of aspirin and clopidogrel compared with placebo and clopidogrel. The endpoints of myocardial infarction, ischaemic stroke, vascular death or rehospitalisation for an acute ischaemic event occurred in 15.7% of patients treated with aspirin and clopidogrel and 16.73% of patients with placebo and clopidogrel (relative risk reduction 6.4%, $p = 0.244$). However, there was a significant increase in life-threatening haemorrhagic events in the patients taking aspirin and clopidogrel (2.6%) compared with patients taking placebo and clopidogrel (1.3%) [$p < 0.001$].[59] It appears that the risk of bleeding complications from the combination of aspirin and clopidogrel precludes the long-term use of this combination in the secondary prevention of ischaemic stroke.[60] There may be a role for combination therapy of aspirin and clopidogrel in the acute phase of cerebrovascular disease, but this has not as yet been studied.

2.2 Aspirin Plus Extended-Release Dipyridamole

Aspirin plus extended-release dipyridamole has been shown to be more effective than aspirin alone in the prevention of ischaemic stroke, with adverse event rates lower than those observed with ticlopidine and much lower than those noted with aspirin plus clopidogrel.[60] Extended-release dipyridamole has a good safety profile in patients with coexisting cardiovascular disease, as demonstrated by Diener et al.[26] Efficacy of high-dose aspirin (975mg) plus immediate-release dipyridamole was demonstrated in 2500 patients with prior TIA or stroke. In this study, patients receiving aspirin and dipyridamole achieved a 34% reduction in stroke or death compared with patients receiving placebo ($p < 0.001$).[33] Incidence of gastrointestinal disorders and bleeding was higher among patients receiving aspirin plus immediate-release dipyridamole. Other studies of aspirin and immediate-release dipyridamole have not demonstrated significant clinical efficacy.[61] However, adverse bleeding events associated with this higher aspirin dose remained of concern, particularly with regard to treatment of elderly stroke patients.[16]

A subsequent comparison in 6602 patients by the same investigators demonstrated that low-dose aspirin (50mg) and extended-release dipyridamole are equally effective in preventing secondary ischaemic stroke and death, and additive in effect when given in combination.[26] Subsequent stroke and risk of TIA were reduced by 18% with aspirin treatment, 16% with extended-release dipyridamole and 37% with combination therapy in comparison to placebo ($p < 0.05$ for all comparisons).[26] All-site bleeding and gastrointestinal bleeding were significantly more common among patients treated with aspirin alone versus placebo or extended-release dipyridamole alone.[26] There was no significant increase in bleeding complications with the combination of aspirin and extended-release dipyridamole compared with aspirin alone, although the rates were slightly higher.[26]

Headache was the most common adverse event with the aspirin/extended-release dipyridamole combination.[26] A recent study documented an incidence of headache in 39.7% of patients treated with aspirin/extended-release dipyridamole combination, with women having a higher incidence (49.6%) than men (28.6%).[62] The headaches were self limited, with 69% of patients treated with placebo headache-free 2 hours after onset compared with 75% treated with paracetamol (acetaminophen). There was no difference between placebo and paracetamol treatment when pre-emptive treatment was studied. Only 20% of patients who had a headache after the initial dose of aspirin/extended-release dipyridamole developed a subsequent headache when taking the second dose. Headaches are virtually eliminated by 4 days after the start of treatment.[62]

Taken together, available data suggest that aspirin/extended-release dipyridamole formulations may be more effective and safer than clopidogrel or ticlopidine combination compounds in prevention of ischaemic strokes.

A number of additional clinical trials are underway to further evaluate and compare the efficacy and safety of combination regimens in primary and

secondary prevention of ischaemic stroke. Of particular note is the PRoFESS (Prevention Regimen For Effectively avoiding Second Strokes) trial, which compares efficacy and safety of aspirin/extended-release dipyridamole with that of clopidogrel plus aspirin in preventing recurrent ischaemic stroke.[63] Results of this investigation will provide essential comparative adverse event information about these two combination regimens. In addition, the INTERACT (Interactions of Atorvastatin and Clopidogrel Therapy) trial is underway to explore in detail potential interactions between clopidogrel and the HMG-CoA reductase inhibitors.[64]

3. Conclusion

Low-dose aspirin is as effective as high-dose aspirin in preventing ischaemic stroke and offers a more favourable adverse effect profile. The combination of low-dose aspirin and extended-release dipyridamole is more effective than aspirin alone in preventing ischaemic stroke, with a similarly low adverse event profile, and can be safely used in patients with coexisting cardiovascular disease. The combination of aspirin and clopidogrel is more effective in preventing myocardial infarction than aspirin alone, but this has only been established in the short-term phase after acute coronary syndromes. A similar preventive relationship has not, as yet, been established for ischaemic stroke.

Adverse bleeding events are of particular concern with regard to antithrombotic regimens because patients with prior stroke episodes are more likely than those with previous myocardial infarctions to have adverse bleeding complications during antithrombotic therapy.[16,29] The incidence of adverse bleeding events associated with aspirin and clopidogrel has proved considerably higher than that observed with aspirin alone at both 75mg and 325mg doses.[32] Adverse events of antithrombotic therapy are often overlooked when selecting an agent for the prevention of recurrent stroke. The adverse event profile of each drug must be taken into consideration along with predisposing risk factors in individual patients, such as prior gastrointestinal bleeding, because the risks may reduce the ultimate benefit of the therapeutic intervention. This is particularly true in the elderly, who are more prone to haemorrhagic complications.

Acknowledgements

The author wishes to thank Nathalie Smith, MSN, RN, for her help in preparing this manuscript.

This work was supported by an unrestricted educational grant in aid to the author from Boehringer Ingelheim Pharmaceuticals, Inc.

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