Expert Opinion

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Aggrenox® versus other pharmacotherapy in preventing recurrent stroke

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Stroke is the third leading cause of death in the US with recurrent events a high likelihood in those who survive an initial event. The long-term goal of therapy is to prevent the recurrence of stroke and other atherosclerotic events. Aspirin has been the first-line agent for stroke prevention for a long time. As new antiplatelet agents have been introduced, their role in the secondary prevention of stroke remains to be defined. In particular, the role of the combination of aspirin and modified-release dipyridamole (Aggrenox®, Boehringer Ingelheim Corp.), the newest product, in the secondary prevention of stroke, remains unknown. The purpose of this manuscript is to review the evidence of these antiplatelet agents in the secondary prevention of stroke and arrive at a conclusion specifically regarding the role of Aggrenox®. Clinical studies which examined stroke as a single primary outcome or as one event in a combined primary outcome will be reviewed.

Keywords: aspirin, cerebrovascular disorders, clopidogrel, dipyridamole, ischaemic stroke, ticlopidine

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1. Statistics

In the US, someone has a stroke every 45 s and someone dies of a stroke every 3.1 min [1]. Each year, 500,000 patients in the US experience a first time stroke whereas 200,000 patients experience a recurrent event [1]. When considered separately from other cardiovascular diseases, stroke is the third leading cause of death in the US, after heart disease, specifically, and cancer [1]. Among patients who survive a first stroke or transient ischaemic attack (TIA), 14% will have a second event within 1 year [1].

2. Definitions

A stroke is defined as a focal neurological deficit lasting for ≥ 24 h [2], whereas a TIA is defined as a focal neurological deficit lasting < 24 h [2-4]. A revised definition of TIA has been proposed based on the presence of cerebral ischaemia and the absence of cerebral infarction [3].

3. Risk factors

Data pooled from the Framingham [5] and Busselton [6] studies indicate the following consistent risk factors for stroke: history of prior stroke or TIA; age; hypertension; diabetes mellitus; cigarette smoking; atrial fibrillation; coronary artery disease; and left ventricular hypertrophy. Elevated haematocrit and hypercholesteroleamia are additional risk factors for stroke [4]. The control of modifiable risk factors, such as hypertension and hypercholesterolaemia and cessation of smoking, are imperative to the overall management of stroke [4].

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4. Pathophysiology

Approximately 15% of strokes are classified as haemorrhagic strokes, whereas 85% are classified as ischaemic strokes [7]. Of ischaemic strokes, 20% are due to atherosclerotic disease. The atherosclerotic process begins as a deposition of lipids in the endothelium of the blood vessel wall. As this process continues, yellow fibrous plaques develop that enhance platelet aggregation. Over time, narrowing of the blood vessel continues until the vessel ultimately becomes occluded [4], resulting in either hypoperfusion or arteriogenic emboli [7]. These types of strokes are termed noncardioembolic or atherothrombotic. Another 20% of ischaemic strokes are due to cardiogenic embolism. These occur when a blood clot originating in the heart becomes lodged in a cerebral artery [4]. Underlying causes of cardiogenic embolism include atrial fibrillation, valvular disease and ventricular thrombi [7]. Approximately 25% of ischaemic strokes are due to occlusion of small penetrating cerebral arteries. These lacunar infarcts result from microatheroma, lipohyalinosis and other occlusive processes of these small cerebellar arteries [4,7]. Despite rigorous assessments, the cause of 30% of ischaemic strokes remains cryptogenic [7]. The remaining 5% of ischaemic strokes are due to unusual causes such as vasospasm, migraine headache and drug abuse.

5. Goals of therapy

The long-term goal of therapy in a patient who has experienced a stroke is to prevent stroke and other atherosclerotic events in the most cost-effective and least toxic manner.

5.1 Available compounds

Antiplatelet medications are the treatment of choice in the secondary prevention of recurrent noncardioembolic stroke. Currently available options include aspirin, ticlopidine, clopidogrel and the combination of aspirin and modified-release dipyridamole.

5.2 Guideline recommendations

For the secondary prevention of noncardioembolic stroke, The American Heart Association (AHA) [8] recommends one of the following regimens of antiplatelet agents: aspirin 50 – 325 mg/day, ticlopidine (Ticlid®, Syntex) 250 mg b.i.d., clopidogrel (Plavix®, Sanofi-Synthelabo) 75 mg/day or aspirin 25 mg and modified-release dipyridamole (Aggrenox®, Boehringer Ingelheim Corp.) 200 mg b.i.d. According to the AHA, aspirin is the most economical and frequently used agent. Although this is not an evidence based practice, the AHA has stated that ticlopidine or clopidogrel are typically substituted for aspirin in patients who cannot tolerate aspirin or who have had a stroke or TIA despite aspirin therapy. The AHA states the combination of aspirin and modified-release dipyridamole provides another useful alternative to aspirin [8].

The American College of Chest Physicians (ACCP) [7] recommendations concur with the AHA guidelines in terms of aspirin, clopidogrel or the combination of aspirin and modified-release dipyridamole as appropriate initial treatment options for the secondary prevention of noncardioembolic stroke. For patients intolerant to aspirin, the ACCP recommends clopidogrel instead of ticlopidine due to differences in the adverse effect profile.

6. Individual treatment options

6.1 Aspirin

Aspirin irreversibly inhibits platelet aggregation by inhibiting the activity of COX and the subsequent formation of thromboxane A_2, a platelet proaggregant and potent vasoconstrictor [9].

The Antiplatelet Trialists' Collaboration [10] provides an overview of antiplatelet therapy in patients at risk of occlusive vascular disease. Compared to adjusted controls, a pooled analysis of aspirin studies was associated with a 25% ($2p < 0.00001$) reduction in the risk of stroke, myocardial infarction (MI) or vascular death. This analysis indicates that compared to placebo, aspirin provides an absolute risk reduction (ARR) of ~ 3.3% for stroke, MI or vascular death (number needed to treat [NNT]: 30) (Table 1). This effect remained significant when analysed across doses ranging from 75 to 1500 mg/day.

In 1991, evidence became available that low doses of aspirin are superior to placebo and that the effectiveness of various aspirin doses is comparable. In the Swedish Aspirin Low-Dose Trial (SALT) [11], a randomised, placebo-controlled, double-blind, multi-centre trial, 1360 patients with minor ischaemic stroke, TIA or retinal artery occlusion within the previous 3 months received either aspirin 75 mg/day or placebo. An 18% reduction in the relative risk of stroke and non-stroke deaths was found in the aspirin group ($p = 0.02$; ARR: 4.6%; NNT: 22). It was concluded that low-dose aspirin was superior to placebo.

In the UK-TIA study [12], a randomised, placebo-controlled, double-blind, multi-centre trial, 2435 patients with a history of transient ischaemic attack or minor ischaemic stroke within the previous 3 months received either aspirin 300 or 1200 mg/day. The odds ratio for all strokes was 1.03 (95% CI = 0.78 – 1.36). It was concluded that there was no difference in effectiveness between high-dose aspirin and aspirin 300 mg/day.

Finally, in the Dutch TIA Trial [13], a randomised, double-blind study, 3131 patients with a history of transient ischaemic attack or minor ischaemic stroke within the previous 3 months were randomised to receive either aspirin 30 or 566 mg/day. The adjusted hazard ratio for the primary outcome of death from vascular causes, non-fatal stroke or non-fatal MI was 0.91 (95% CI = 0.76 – 1.09). This study suggested that there was no significant difference in effectiveness between aspirin 566 or 30 mg/day.

6.2 Ticlopidine

Ticlopidine is a thienopyridine derivative that irreversibly inhibits the binding of ADP to platelets [7,14]. This inhibits

Table 1. Comparison of outcome results of major clinical studies*.

Clinical trial	Outcome	Comparison	Relative risk reduction	Absolute risk reduction‡ (%)	Number needed to treat§
Antiplatelet Trialists' Collaboration [10]	Stroke, myocardial infarction or vascular death	Aspirin 75 – 1500 mg/day versus placebo	25% (2p < 0.00001)	3.3	30
Swedish Aspirin Low-Dose Trial (SALT) [11]	Stroke and non-stroke deaths	Aspirin 75 mg/day versus placebo	18% (p = 0.02)	4.6	22
Ticlopidine Aspirin Stroke Study (TASS) [16]	Combined outcome of non-fatal stroke or death	Ticlopidine versus aspirin	12% (p = 0.048)	2	50
	Combined outcome of fatal or non-fatal stroke	Ticlopidine versus aspirin	21% (p = 0.024)	3	33
American Antiplatelet Stroke Prevention Study (AAASPS) [17]	Recurrent stroke	Ticlopidine versus aspirin	-23% (p = 0.10)	2.2	45
Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) [18]	Combined outcome of ischaemic stroke, myocardial infarction or vascular death	Clopidogrel versus aspirin	8.7% (p = 0.043)	0.51	196
The second European Stroke Prevention Study (ESPS2) [25]	Recurrent stroke	Aspirin versus placebo	18.1% (p = 0.013)	2.9	34
	Recurrent stroke	Dipyridamole versus placebo	16.3% (p = 0.039)	2.6	38
	Recurrent stroke	Aspirin and dipyridamole versus placebo	37% (p < 0.001)	5.9	17
	Recurrent stroke	Aspirin and dipyridamole versus aspirin	23.1% (p = 0.006)	3	33

*The table is intended to be a summary of trial results. Direct comparisons cannot be made across all trials due to differences in the study design, patient populations and interventions. ‡Calculated as: control group event rate – experimental group event rate. Number needed to treat calculated as follows: 1/(control group event rate – experimental group event rate) [33].

the expression of the glycoprotein (GP) IIb/IIIa receptor on platelet membranes. Fibrinogen is then unable to form an interplatelet bridge between platelet GP IIb/IIIa receptors and platelet aggregation is inhibited [15]. Ticlopidine has no effect on prostaglandin metabolism [14].

The efficacy of ticlopidine and aspirin in the secondary prevention of strokes was compared in the Ticlopidine Aspirin Stroke Study (TASS) [16]. In this randomised, double-blind, multi-centre trial, 3069 subjects with documentation of TIA, amaurosis fugax, reversible ischaemic neurological deficit or minor stroke within the preceding 3 months were randomised to ticlopidine 500 mg/day or aspirin 1300 mg/day. Subjects were evaluated every 4 months over the 3-year study period.

Ticlopidine reduced the primary end point, the combined outcome of non-fatal stroke or death, by 12% (p = 0.048). The combined risk of fatal or non-fatal stroke (the secondary outcome) was reduced by 21% (p = 0.024). The ARR for the primary end point was 2% (NNT: 50) whereas the ARR for the secondary end point was 3% (NNT: 33) (Table 1). An absolute neutrophil count (ANC) of < 450/mm^3 developed in 0.8% of subjects taking ticlopidine compared to no subjects taking aspirin. Ticlopidine had a higher risk of severe neutropenia, diarrhoea, rash and urticaria than aspirin but bleeding risk was comparable between groups. The investigators concluded that ticlopidine was somewhat more effective than aspirin although the risk of ticlopidine-related side effects was greater.

Between 1992 – 1997, postmarketing surveillance revealed 100 cases of ticlopidine-associated thrombotic thrombocytopenia purpura (TTP) in the US. TTP is a multi-organ disease characterised by thrombocytopenia, microangiopathic haemolytic anaemia, neurological changes such as disorientation and speech changes, fever and renal abnormalities. Of the reported cases, 80% occurred in the first 30 days of treatment [101].

A more recent study evaluating ticlopidine in a specific patient population is the African-American Antiplatelet Stroke Prevention Study (AAASPS) [17]. This was a double-blind, randomised, multi-centre, placebo-controlled trial which lasted 6.5 years (n = 1809). Ticlopidine 500 mg/day was compared to aspirin 650 mg/day in African-American patients with a recent history of noncardioembolic ischaemic stroke. The primary outcome studied was the combined risk of recurrent stroke, MI or vascular death. The secondary

outcome studied was fatal or non-fatal stroke. The rate of any recurrent stroke was 11.7% in the ticlopidine-treated group and 9.5% in the aspirin-treated group (p = 0.10; ARR: 2.2%; NNT: 45). The rate of serious adverse events was similar in each group (p > 0.1). Thrombocytopenia was rare and affected 0.3 and 0.2% of the ticlopidine and the aspirin treated patients, respectively (p = 0.69).

6.3 Clopidogrel

Clopidogrel is another thienopyridine derivative that inhibits platelet aggregation through the same pharmacological mechanism as ticlopidine [4,7,14].

The only published clinical trial to evaluate the efficacy of clopidogrel in the secondary prevention of stroke included patients who had a history of one of three different types of atherosclerotic processes: ischaemic stroke, MI or symptomatic peripheral arterial disease (PAD). The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) Study [18] compared the efficacy of clopidogrel 75 mg/day or aspirin 325 mg/day in reducing the risk of ischaemic stroke, MI or vascular death. In this double-blind, multi-centre trial, 19,185 subjects were evaluated monthly for the first 4 months and then every 4 months for the study duration of 3 years.

Clopidogrel reduced the primary end point, the combined outcome of ischaemic stroke, MI or vascular death, by 8.7% (p = 0.043). The ARR for this primary end point was small (0.51%, NNT: 196) (Table 1). Within the clinical subgroups, clopidogrel reduced the primary outcome rate by 7.3% (p = 0.26) in patients with stroke (ARR: 0.56%; NNT: 179). An ANC of < 450/mm^3 developed in 0.05 and 0.04% of clopidogrel and aspirin subjects, respectively. Clopidogrel caused higher rates of diarrhoea (p = 0.08) and severe rash than aspirin (p = 0.017) whereas the gastrointestinal haemorrhage rate was higher (p = 0.05) with aspirin therapy. Intracranial haemorrhage did not differ between the two groups (p = 0.23). The investigators concluded that clopidogrel was more effective than aspirin in reducing the combined risk of ischaemic stroke, MI or vascular death and that the safety profile of clopidogrel is comparable to aspirin.

Similar to ticlopidine, cases of clopidogrel-associated TTP surfaced once the drug was marketed. Between March 1998 and March 2000, 11 cases were reported [19]. A total of 91% of cases occurred within 14 days of clopidogrel initiation.

6.4 Aspirin and dipyridamole combination

As described above, aspirin inhibits platelet aggregation by COX inhibition. Dipyridamole, a phosphodiesterase inhibitor, decreases platelet adhesion to damaged endothelium by increasing platelet concentrations of cAMP [9,20].

As mentioned earlier, the combination of aspirin 25 mg and modified-release dipyridamole 200 mg is available commercially as Aggrenox®. Various combinations of aspirin and dipyridamole have been studied in the secondary prevention of stroke for 20 years. An early trial did show that the combination was more effective than placebo [21]. However, the results from several early trials suggest that there is no benefit to adding dipyridamole to aspirin [22-24]. The most recent study evaluating this combination, the second European Stroke Prevention Study (ESPS-2), assessed the individual and combined efficacy of aspirin and dipyridamole [25]. In this double-blind, placebo-controlled, multi-centre trial, 6602 patients with documentation of TIA or ischaemic stroke within the preceding 3 months were randomised to one of four groups: aspirin 50 mg/day, modified-release dipyridamole 400 mg/day, aspirin 50 mg/day plus modified-release dipyridamole 400 mg/day and placebo. Subjects were evaluated every 3 months throughout the 2-year study.

The primary end points of this study were recurrent stroke, death and the combined end point of stroke or death. Compared to placebo, aspirin reduced the relative risk for secondary stroke by 18.1% (p = 0.013), dipyridamole by 16.3% (p = 0.039) and the combination of aspirin and dipyridamole by 37% (p < 0.001). Compared to placebo, the ARR and NNT for the secondary prevention of stroke are as follows: aspirin (ARR: 2.9%; NNT: 34); dipyridamole (ARR: 2.6%; NNT: 38) and the combination of aspirin and dipyridamole (ARR: 5.9%; NNT: 17). The combination of aspirin and dipyridamole reduced the risk for recurrent stroke by 23.1% (p = 0.006; ARR: 3%; NNT: 33) compared with aspirin alone and by 24.7% (p = 0.002; ARR: 3.3%; NNT: 30) compared with dipyridamole alone (Table 1). There was no significant difference in the combined end point of stroke or death when the combination of aspirin and dipyridamole is compared to either medication alone. Of patients who withdrew from the study due to adverse effects, subjects taking a dipyridamole combination had more headaches (p < 0.001) and gastrointestinal upset (p < 0.001) whereas those taking an aspirin combination had more bleeding episodes (p < 0.001). The investigators concluded that aspirin and dipyidamole alone were superior to placebo and that the combination had an additive effect in the prevention of recurrent strokes.

Although there are several precautions to the use of Aggrenox®, it is particularly important to note that it should be used with caution in patients with severe coronary artery disease (CAD) such as unstable angina or recent MI [101]. Dipyridamole can increase the risk of MI or exacerbate angina secondary to coronary steal. As patients with stroke are at risk for other atherosclerotic events, a history of these or development of these would preclude the use of Aggrenox®.

7. Issues

Aspirin has long been considered a first-line agent in the secondary prevention of noncardioembolic stroke. With the advent of new antiplatelet agents and the addition of agents such as dipyridamole to aspirin therapy, its role as a single, first-line agent is now being challenged. Although well-designed clinical studies have evaluated these newer antiplatelet agents, inherent differences among the studies make across the board comparisons of their results difficult.

Of the available trials, some report a combined outcome such as stroke, MI or vascular death as the primary outcome [10,18] whereas others report a stroke-related outcome as the primary outcome [11,16,25]. Some trials included patients with a history of atherosclerotic processes in addition to stroke [10,18] whereas some included only patients with a history of stroke-related events [11,16,17,25]. Some trials compared an active treatment to placebo [10,11] rather than to another active treatment [16,17,18,25]. Finally, in all the studies, other medications used by study participants such as hypertension therapy were not discussed.

8. Future directions

There are currently several ongoing trials evaluating various combinations of agents in the secondary prevention of recurrent stroke. The European/Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) [26,102] is a prospective, open, randomised, multi-centre trial in which subjects with a history of stroke or TIA within the preceding 6 months are being randomised to one of three groups: anticoagulation to maintain an International Normalised Ratio between 2.0 – 3.0, the combination of dipyridamole 400 mg/day and aspirin 30 – 325 mg/day and aspirin 30 – 325 mg/day alone. Subjects will be assessed over an average of 3 years for the primary end point of the combined outcome of non-fatal stroke, non-fatal MI, vascular death and major bleeding complications. As of July 2003, the study has enrolled 2387 of the projected 4500 subjects needed.

The Management of ATherothrombosis with Clopidogrel in High-risk patients with recent TIA or ischaemic stroke (MATCH) Study [103] is a randomised, double-blind, prospective, parallel-group trial in which subjects with a history of stroke or TIA within the previous 3 months and at least one additional atherosclerotic risk factor will be randomised to clopidogrel 75 mg/day or clopidogrel 75 mg/day plus aspirin 75 mg/day. Subjects will be evaluated over 18 months for the primary end point of the combined outcome of ischaemic stroke, MI, vascular death or rehospitalisation for an acute ischaemic event. Enrollment for MATCH Study was complete in April 2002 with a sample size of 7601 patients.

The Prevention Regimen for Effectively avoiding Second Strokes (PRoFESS) trial [103] is a randomised, parallel group, double-blind, double-dummy, placebo-controlled, multinational trial in which subjects with a history of stroke within the preceding 3 months are eligible for enrollment. The efficacy of two different antiplatelet combinations is being compared with and without the addition of an angiotensin II receptor antagonist. Subjects are being randomised to one of four groups, two active groups and two placebo groups. The active groups will receive either aspirin 25 mg and modified-release dipyridamole 200 mg (Aggrenox®) and telmisartan (Micardis®, Boehringer Ingelheim Corp.) or clopidogrel, aspirin and telmisartan. The placebo groups will receive either Aggrenox® and placebo or clopidogrel, aspirin and placebo. The primary outcome is the time to first recurrent stroke whereas the secondary outcome is the combined outcome of non-fatal stroke, non-fatal MI and vascular death. Enrollment started in September 2003 and the projected sample size is 15,500 subjects.

The Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management and Avoidance (CHARISMA) trial [104] is a double-blind, placebo-controlled, parallel group trial in which subjects with a major or minor atherothrombotic risk factor and/or documented cerebrovascular disease, documented CAD or documented peripheral arterial disease are being enrolled. All patients in the trial will take low-dose aspirin (75 – 162 mg/day) and in addition, will be randomised to one of two treatment groups: clopidogrel 75 mg/day or placebo. Subjects will be assessed over a maximum of 3.5 years for the primary end point of the combined outcome of cardiovascular mortality, stroke and acute MI. Enrollment started in October 2002 and the projected sample size is 15,200 subjects.

In the Secondary Prevention of Small Subcortical Strokes (SPS3) trial [104], subjects with a history of lacunar or small subcortical stroke will be randomised to one of two treatment groups: aspirin alone or the combination of aspirin and clopidogrel. In addition, patients with hypertension will be assigned to one of two groups differing in the level of systolic blood pressure control: either 130 – 149 mmHg or < 130 mmHg. Goals of the trial are to determine if the combination of aspirin and clopidogrel is more effective than aspirin alone and if lowering a patient's blood pressure below the usual limits will prevent recurrent stroke and maintain thinking ability. The projected enrollment for this study in which recruitment has not yet started is 2500 subjects.

9. Cost-effectiveness data

The combination of aspirin and dipyridamole for the secondary prevention of stroke has been evaluated in three pharmacoeconomic analyses [27-29]. All three studies concluded that the combination of aspirin and modified-release dipyridamole (Aggrenox®) was more cost-effective than aspirin monotherapy for the prevention of recurrent stroke. Two of the studies [27,28] were not conducted in the US, hence the results are based on non-US costs and cannot be extrapolated to the US healthcare system due to differences in healthcare costs [30,31].

The analysis conducted by Shah *et al.* [28] was based on US costs; however, relative risk reductions from different studies were compared. The relative risk reduction of aspirin versus placebo was from a meta-regression analysis [32] whereas the relative risk reduction of aspirin versus the combination of aspirin and modified-release dipyridamole (Aggrenox®) was from the ESPS-2 trial [25]. This may skew the results of the pharmacoeconomic analysis as the relative risk reduction of aspirin versus placebo was 15% in the meta-regression analysis versus 18.1% in ESPS-2. The analysis should have included both relative risk reductions from ESPS-2. In addition, the

Shah *et al.* [28] analysis used an 8% relative risk reduction of stroke for clopidogrel versus aspirin which they state is derived from the CAPRIE Study [18]. Based on this, they concluded that clopidogrel was not cost-effective when compared to aspirin. However, the actual primary outcome in the CAPRIE Study was a combined end point of stroke, MI or vascular death. Compared to aspirin, clopidogrel reduced the risk of this end point by 8.7% [18]. In contrast, the three separate primary end points of ESPS-2 were stroke, death and stroke and/or death. As there was a broader range of end points in CAPRIE Study than in ESPS-2, the comparison of these results is not valid. The ideal pharmacoeconomic analysis would compare aspirin monotherapy, the combination of aspirin and modified-release dipyridamole, clopidogrel and placebo across identical end points.

10. Expert opinion

The clinical studies have established that aspirin [10], ticlopidine [16], clopidogrel [18] and the combination of aspirin and modified-release dipyridamole (Aggrenox®) [25] are all effective in the secondary prevention of stroke. As mentioned earlier, differences in the number of outcomes evaluated in these studies make direct comparisons difficult. The two studies assessing either the dipyridamole and aspirin combination or ticlopidine only, evaluated the outcome of recurrent stroke [16,25] whereas studies assessing clopidogrel and aspirin have evaluated the combined outcome of MI, stroke and vascular death [10,18]. As the long-term goal of stroke therapy is to prevent stroke and other atherosclerotic events, it would seem prudent to recommend pharmacotherapy effective at preventing stroke and these related events. Based on this premise and the currently available evidence, the combination of aspirin and modified-release dipyridamole (Aggrenox®) is not recommended as first-line therapy. As results of other studies evaluating this combination in the prevention of atherosclerotic events [102] become available, its role as first-line therapy should be re-evaluated.

A combination of antiplatelet agents may, in fact, be the best way of preventing strokes and other recurrent events. Despite a lack of currently available evidence, there is already a trend towards the use of agents, such as aspirin and clopidogrel together. Ongoing trials such as [103,104] have been designed to answer this important question.

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