Evidence-Based Review of Stroke Rehabilitation

Appendix: Antiplatelet Therapy

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Secondary Prevention of Stroke: Antiplatelet Therapy

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TABLE OF CONTENTS

Specific Stroke Preventative Therapy

In addition to treatment of identified, modifiable risk factors, secondary prevention should include treatment or prophylaxis based on the underlying etiology of the primary event. Specific mechanisms of ischemia are associated with corresponding treatments or prophylaxes as illustrated in Table 1 (Diener & Ringleb 2002). A recent analysis of data from 9 clinical trials examining the effects of ASA post stroke, revealed that patients with stroke from an arterial rather than cardiac origin tend to be younger, more likely to be a current smoker and less likely to have a history of hypertension (Ariesen et al. 2004).

Table 1 Mechanisms of Stroke and Secondary Prevention

Underlying Etiology	Treatment/Prophylaxis
Atherosclerotic plaque/atherothrombosis	Antiplatelet therapy
Cardiac abnormalities (cardiogenic emboli)	Anticoagulation therapy
Internal Carotid Artery (ICA) stenosis (severe occlusion)	Reperfusion techniques

The vast majority of all strokes are ischaemic in nature and are caused by atherothrombotic or thromboembolic occlusion. Common sites for thrombus formation include the extracranial cerebral arteries, the heart, the small penetrating arteries of the brain (as in the case of lacunar infarcts), and aortic arch plaque (Goldszmidt & Caplan 2003; Easton 2001). Blood factors (clotting agents), primarily platelets and fibrin, aggregate on diseased or damaged arteries and promote the formation of thrombi which can occlude the artery at the site of formation or embolise and cause an occlusion at a different location. As such, platelets and the mechanisms of adhesion, activation and aggregation occurring at the site of arterial damage play an important role in thrombus development and progression of atherothrombosis (Serebruany et al. 2004; Goldszmidt & Caplan 2003; Easton 2001). Antiplatelet therapy is used to disrupt platelet mechanisms particularly with regard to non-cardiac thrombosis.

Antiplatelet Therapy

The recent Antithrombotic Trialists' Collaboration meta-analysis of randomized trials of preventive antiplatelet therapy in high-risk patients reviewed 287 studies available by September 1997 (Antithrombotic Trialists' Collaboration 2002). More than 77,000 patients were included in trials comparing antiplatelet regimens, and 135,000 patients were included in trials comparing active therapy with control. In high-risk patients, antiplatelet therapy reduced nonfatal MI by one-third, nonfatal stroke by one-quarter, and vascular death by one-sixth. In high-risk individuals with a history of previous stroke or TIA, antiplatelet therapy was associated with a decrease in risk of ischaemic stroke (OR=0.75) and a corresponding increase in risk for haemorrhagic stroke (OR=1.2) (Antithrombotic Trialists' Collaboration 2002).

Antiplatelet therapy is associated with an increased risk for bleeding, however, the benefits of antiplatelet therapy seem to far outweigh the risks for the most part. A 25% reduction in risk of stroke carries with it the risk of approximately 1 – 2 additional major extracranial bleeds per 1000 patients per year (Antithrombotic Trialists' Collaboration 2002). Given the magnitude of benefit and relatively few risks, antiplatelet therapy has become central to the secondary prevention of stroke (Diener & Ringleb 2002). Unless there is a definite contraindication, antiplatelet therapy should be considered for anyone who is considered to be at an increased risk for the development of occlusive vascular disease (Antithrombotic Trialists' Collaboration 2002). Unfortunately, results of the recent GIFA study demonstrated that a large proportion of patients with TIA and/or stroke are still discharged from hospital without either antiplatelet or anticoagulant therapy (Volpato et al. 2004). Treatment with antithrombotic therapy was inversely associated with functional disability and cognitive impairment such that patients with increasing levels of cognitive impairment or severe disability were the least likely to receive antithrombotic medication (OR= 0.26 & OR= 0.27, respectively).

There are several different types of antiplatelet therapy, each using different mechanisms to disrupt platelet processes. These include ASA monotherapy, thienopyridines (which include clopidogrel and ticlopidine), combination therapy (more than one antiplatelet agent) and anticoagulants. The most commonly used agent in antiplatelet therapy is aspirin.

ASA Monotherapy

Aspirin is the least expensive, most widely studied and most commonly used antiplatelet agent (Goldszmidt & Caplan 2003; MacWalter & Shirley 2002; Easton 2001). ASA is a cyclo-oxygenase inhibitor. It blocks the formation of thromboxane A_2 (a platelet aggregating prostaglandin) by acetylation of the enzyme cyclo-oxygenase, which reduces the likelihood for thrombus formation by interfering with platelet aggregation. However, for the duration of its presence in the cells, ASA also inhibits the production of prostacyclin, an antiaggregating prostaglandin produced in endothelial cells. Low dose ASA may effectively block thromboxane A_2 formation while not substantially inhibiting the production of prostacyclin (Easton 2001).

In an extensive 2002 meta-analysis, the Antithrombotic Trialists' collaborative (ATC) found that treatment with aspirin reduced the risk of vascular events in high-risk patients (including recurrent stroke) by 23%. Algra and van Gijn (1999) performed a mini-meta-analysis of 10 trials evaluating the benefit of ASA monotherapy in patients with prior stroke or TIA and found that aspirin reduced the odds of stroke, myocardial infarction or vascular death by 16% and the relative risk reduction when compared to placebo was 13%.

Given the established effectiveness of ASA as an antiplatelet therapy, recent trials have focused on the issue of optimal dosage and timing for the initiation of treatment. Recent studies examining these issues are summarized in Table 2.

Table 2. Details of ASA Monotherapy Post-stroke Trials

Author, Year Country Pedro Score	Methods	Outcomes
UK-TIA Farrell et al. 1991 UK 8 (RCT)	2435 patients with TIA or minor stroke were randomly assigned to receive long-term treatment in 1 of 3 groups; 1) 600 mg ASA twice daily 2) 300 mg once daily 3) placebo.	OR of major stroke, MI or vascular death was reduced by 15% in the combined ASA treatment groups. There was no significant difference in the efficacy of treatment with 1200 mg vs 300 mg/day ASA. However, the lower dose was less gastro-toxic.
Dutch TIA Trial Study Group 1991 Netherlands 7 RCT)	3131 patients with previous TIA or minior stroke were randomly allocated to treatment with 30 mg of water-soluble ASA vs. 283 mg water-soluble ASA. Mean follow-up was 2.6 years.	Age & sex adjusted hazard ratio for the group receiving the lower dose ASA treatment was 0.91. There was a trend toward fewer major bleeding events in the low-dose group and significantly fewer minor bleeding reports (49 vs. 84). In addition, patients receiving low-dose ASA reported fewer gastrointestinal symptoms.
SALT Swedish Aspirin Low-dose Trial 1991 Sweden 8 (RCT)	1360 patients with prior TIA or minor stroke were randomly assigned to receive treatment with aspirin (75mg/day) or a placebo. Mean duration of follow-up was 32 months.	Compared to placebo, treatment with ASA was associated with a 18% reduction in the risk for stroke or death (p=0.02). Adverse reactions were more common in the ASA group and patients treated with ASA reported a significantly greater number of "bleeding episodes" (p=0.04).
IST International Stroke Trial Collaborative Group 1997 International 5 (RCT)	19,435 patients with acute stroke were assigned to receive 14 days therapy with either subcutaneous heparin or ASA as soon as was possible after stroke onset. In a factorial design, patients were further randomised to "receive heparin" (5000 or 12500 IU bd) or "avoid heparin" and to "receive ASA" (300 mg/day) or "avoid ASA"	At 6 months post-stroke, neither heparin condition resulted in any benefit. Heparin treatment was associated with a significant increase in major extracranial bleeds (requiring transfusion or causing death) – especially in the case of 12500 IU doses. In the first 14 days post-stroke, patients allocated to receive heparin had fewer nonfatal ischaemic strokes than "avoid heparin" patients, however, this was offset by an increase in haemorrhagic stroke. At 6 months, there was a trend toward fewer deaths and less dependency in the group who had received ASA versus "avoid ASA". Within the first 14 days, there were significantly fewer ischaemic strokes and no significant increase in haemorrhagic stroke.
CAST Chinese Acute Stroke Trial	21,106 patients with acute ischaemic stroke were assigned to receive either aspirin 160 mg/day	At the end of 4 weeks, there was a 12% reduction for risk of non-fatal stroke or death among patient assigned to receive

Author, Year Country Pedro Score	Methods	Outcomes
Collaborative Group 1997 China 8 (RCT)	(within 48 hours of onset and for up to 4 weeks during hospital admission) or placebo.	ASA vs. placebo (p=0.03). There were significantly fewer ischaemic strokes among patients receiving ASA, but only slightly more haemorrhagic strokes.

Discussion

The optimal dose of ASA has still not been established formally and is currently the subject of an ongoing clinical investigation (ADONIS, Aspirin Dose Optimized in Non-Cardioembolic Ischaemic Stroke). However, it is generally agreed that high doses are not necessary and in fact may be counterproductive. In their 2002 meta-analysis, the Antithrombotic Trialists' Collaboration reported that doses of 75 – 150 mg/day appeared to have the greatest effect reducing the risk for ischaemic stroke by 32% (see Table 3). It has been reported that risk for major bleeding associated with ASA therapy has not been found to be dose dependent and is similar with all levels of daily dosages under 325 mg (Diener & Ringleb 2002; Antithrombotic Trialists' Collaboration 2002). A recent meta-analysis of bleeding complications in antiplatelet therapy reported low-dose ASA (<100 mg/day) to be associated with the lowest risk (3.6%) for haemorrhagic events (including both major and minor events) while doses in excess of 100 mg/day were associated with a relatively high risk (9.1%) (Serebruany et al. 2004). A dose of less than 325 mg/day is commonly prescribed for the prevention of atherosclerosis (Easton 2001). Enteric-coated preparations are recommended to reduce the incidence of gastrointestinal side effects (Diener & Ringleb 2002).

Table 3. ASA Dose Regimens, Associated Risk Reduction and Proportional Increase in Risk for Major Extracranial Bleed

ASA Dose/Day	Risk Reduction	Risk of Major Extracranial Bleed *(Odds ratio of ASA compared to control; 95% CI)*
<75 mg	13%	1.7 (0.8 – 3.3)
75 – 150 mg	32%	1.5 (1.0 – 2.3)
160 – 325 mg	26%	1.4 (1.0 – 2.0)
500 – 1500 mg	19%	N/a
**Antithrombotic Trialists' Collaboration, 2002*		

The IST and CAST trials examined the effects of introducing ASA therapy in the acute phase post-stroke. Meta-analyses of the data from these studies revealed a 13% reduction in the risk for recurrent stroke and mortality (Diener & Ringleb 2002; Algra & van Gijn 1999). The Antithrombotic Trialists' Collaboration reported that antiplatelet therapy in acute stroke patients results in 9 fewer strokes for every 1000 patients treated. With prolonged therapy (mean=29 months), this number increases to 36 per 1000 (Antithrombotic Trialists' Collaboration 2002). Aspirin therapy, therefore, should be initiated acutely post-stroke and continued over the long-term for maximum benefit.

Conclusions Regarding ASA Monotherapy

There is strong evidence (Level 1a) that ASA therapy effectively reduces the risk for recurrent stroke. In patients with acute stroke, aspirin therapy reduces the risk for recurrent ischaemic stroke or death by 13%. Aspirin reduces the risk for serious vascular events in patients with a history of previous TIA or minor stroke by 22% with long-term therapy. Doses of 75 – 150 mg/day are sufficient to produce the most effect with least risk. Therapy should be initiated as soon as is safe following the onset of the stroke event and maintained over the long-term.

Aspirin reduces the risk of a second ischaemic stroke.

Thienopyridines (Ticlopidine and Clopidogrel)

For patients in whom ASA therapy is contraindicated or who experience stroke while on ASA therapy, thienopyridines have been investigated as an alternative. Thienopyridines are adenosine diphosphate (ADP) receptor blockers that inhibit platelet activation and aggregation induced by ADP (Easton 2001; MacWalter & Shirley 2002; Goldszmidt & Caplan 2003).

A recent review of studies examining the effectiveness of therapy with thienopyridines (ticlopidine and clopidogrel) reported that, among patients with previous TIA or stroke, thienopyridine therapy reduced the risk of vascular events and further stroke events more than aspirin therapy (OR=0.90 and OR=0.86, respectively). This reduction in stroke risk is equivalent to an absolute reduction in stroke events of 16 strokes per 1000 patients (Hankey et al. 2000). An examination of adverse effects associated with the thienopyridines compared with those associated with ASA, demonstrated no significant difference between the two therapies in terms of risk of intracranial or extracranial haemorrhage. Overall, treatment with thienopyridines was associated with a reduced risk for gastrointestinal haemorrhage (OR=0.71), indigestion/nausea/vomiting (OR=0.84) and an increased risk for diarrhea (OR= 1.34 to 2.27) and skin rashes (OR= 1.32 to 2.23). However, the risk profile of ticlopidine differed significantly from clopidogrel especially with regard to diarrhea, skin rashes and adverse haematological effects (Hankey et al. 2000).

Ticlopidine

Ticlopidine is an ADP receptor antagonist that inhibits platelet aggregation by directly altering platelet membranes (Diener & Ringleb 2002). It has been shown to be effective in reducing risk of stroke, but use of ticlopidine has been associated with a high rate of adverse effects. An analysis of 2 trials revealed

that the incidence of adverse effects was 62.3% overall in patients treated with ticlopidine versus 53.2% for ASA and severe neutropenia was reported in 0.9% of the patients studied (Diener & Ringleb 2002). Studies assessing the use of ticlopidine in antiplatelet therapy are summarized in Table 4.

Table 4. Details of Studies Assessing Antiplatelet Therapy Using Ticlopidine

Author, Year Country Pedro Score	Methods	Outcomes
CATS Gent et al. 1989 Canada/USA 8 (RCT)	1072 patients with previous history of stroke (1-4 months prior to study) were randomly allocated to receive either ticlopidine (250 mg twice per day) or placebo. Treatment and follow-up continued for up to 3 years.	Intention-to-treat analysis revealed a risk reduction for stroke, MI or vascular death of 23.3% (p=0.020). Adverse events included severe neutropenia (1%), severe skin rash and diarrhea (2%). All severe adverse events were reversible with termination of treatment.
TASS Study Hass et al. 1989 USA 8 (RCT)	3069 patients with recent TIA or mild, persistent focal retinal or cerebral ischemia were randomized to receive either ticlopidine hydrochloride (500 mg/day) or ASA (1300 mg/day). Follow-up lasted 2 – 6 years.	Three-year event rate for nonfatal or fatal stroke was 10% in the ticlopidine group and 13 % in the ASA group. This represented a risk reduction of 21% (p=0.24) with ticlopidine treatment. Risk of side effects with ticlopidine included severe but reversible neutropenia (<1%), diarrhea (20%) and skin rash (14%). ASA side effects included diarrhea (10%), rash (5.5%), peptic ulceration (3%), gastritis (2%) and gastrointestinal bleeding (1%).
TISS Bergamasco et al. 1997 Italy 6 (RCT)	1632 patients (aged 32-80) with history of TIA, amaurosis fugax or minor stroke within one month of trial entry, were randomly allocated to receive 250 mg/day ticlopidine or 200 mg indobufen (once or twice per day). Median duration of treatment = 1 year.	Ticlopidine therapy was significantly better than indobufen in preventing fatal and non-fatal stroke (49.6% relative risk reduction). The two groups had similar rates of adverse events (5.5% vs. 6.4%). Gastrointestinal disorders were more frequent with indobufen treatment. Skin rashes and abnormal liver function were more frequent among patients treated with ticlopidine.
AAASPS Gorelick et al. 2003 USA 9 (RCT)	1809 black men and women with a recent history of noncardioembolic, ischaemic stroke were randomized to receive either 500 mg/day ticlopidine or 650 mg/day ASA. Duration of follow-up = 2 years	Study was halted prematurely when futility analysis showed <1% likelihood that ticlopidine would be superior to ASA in prevention of recurrent stroke, MI or vascular death. Kaplan-Meier curves for time to fatal or nonfatal stroke approached a statistically significant reduction in favour of ASA over ticlopidine (p=0.08). Frequency of serious neutropenia among patients receiving ticlopidine was 3.4% vs. 2.2% for ASA treatment.

Discussion

While producing, at most, moderate risk reductions beyond those achievable with ASA therapy (Antiplatelet Trialists' Collaboration 1994 & 2002; Hankey et al. 2000; Easton 2001), the risk for adverse events associated with the use of ticlopidine is substantial. A recent review (Hankey et al. 2000) reported that ticlopidine is associated with a 2-fold increase in the odds of developing a skin rash and/or diarrhea, when compared to treatment with ASA. In addition, ticlopidine use is associated with neutropenia more often than ASA (OR=2.7; Hankey et al. 2000) and has been linked to thrombotic thrombocytopenic purpura (MacWalter & Shirley 2002; Diener & Ringleb 2002).

Given the risk for adverse haematologic consequences, it is important to perform blood counts at 2-week intervals for the first 3 months of therapy and to continue this screening indefinitely, though on a less frequent basis (Easton 2001; Diener & Ringleb 2002; MacWalter & Shirley 2002). Ticlopidine is an expensive drug, not available in a generic preparation whose cost is increased by the requirements of frequent and ongoing blood testing. Contraindications to treatment with ticlopidine include "*the presence of haematopoietic disorders, active haemostatic disorders or active pathologic bleeding and severe liver impairment*" (Diener & Ringleb 2002).

The recent AAASPS trial provided evidence to support the use of ASA over ticlopidine particularly among black patients (Gorelick et al. 2003). Data from this most recent trial suggest that ticlopidine should no longer be considered an effective and acceptable alternative to aspirin for the secondary prevention of stroke (Sacco 2003). Despite the potential for adverse effects associated with ticlopidine, it remains the third most commonly prescribed non-aspirin antiplatelet therapy in the United States (Sacco 2003).

The Heart and Stroke Ontario Clinical Guidelines (2003) state that "*Ticlopidine, an inhibitor of platelet aggregation that is related to clopidogrel, is associated with significant side-effects, including neutropenia and thrombocytopenic purpura, and guidelines now recommend that individuals not be started on this agent. These idiosyncratic adverse events occur early in therapy, so individuals already on ticlopidine may safely be continued on this antiplatelet agent".*

Conclusions Regarding the Use of Ticlopidine

There is strong evidence (Level 1a) that ticlopidine is moderately more effective than ASA in reducing the risk of vascular complications, particularly among patients with a history of prior TIA or stroke. However, ticlopidine is associated with a poor safety profile in terms of associated adverse events.

Although moderately more effective than ASA, the use of ticlopidine is associated with a substantial risk for adverse events.

Clopidogrel

Clopidogrel is a newer thienopyridine derivative that is chemically related to ticlopidine (Easton 2001; Diener & Ringleb 2002; Goldszmidt & Caplan 2003). It is faster acting than ticlopidine and has a longer duration of effectiveness (Goldszmidt & Caplan 2003). The benefits of clopidogrel are similar to those of ticlopidine, while its side effects are similar to those seen with ASA therapy (Easton 2001; Diener & Ringleb 2002).

There is a single, pivotal, large-scale trial assessing the efficacy of clopidogrel in comparison to ASA for patients with a history of recent cardiovascular events. The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Stroke (CAPRIE 1996) study was a randomized multicentred trial comparing the efficacy of clopidogrel to aspirin (325 mg/day) in reducing the combined risk of ischaemic stroke, myocardial infarction or vascular death. Details of the CAPRIE trial are summarized in Table 5.

Table 5. Details of the CAPRIE Trial

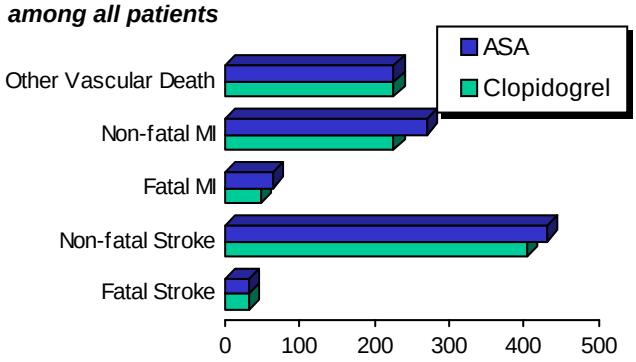
Author, Year Country Pedro Score	Methods	Outcomes
CAPRIE Steering Committee Gent et al. 1996 Canada/ International 8 (RCT)	Patients with a history of recent cardiovascular events were randomized to receive 75 mg clopidogrel + aspirin placebo (n=9553) or 325 mg aspirin + clopidogrel placebo (n=9546) for 1-3 years.	Patients treated with clopidogrel had a 5.32% annual risk of ischaemic stroke, MI or vascular death compared with 5.83% with aspirin. The difference in rates was statistically significant and reflects a relative risk reduction of 8.7% in favour of clopidogrel. There were no differences in terms of safety.

Discussion

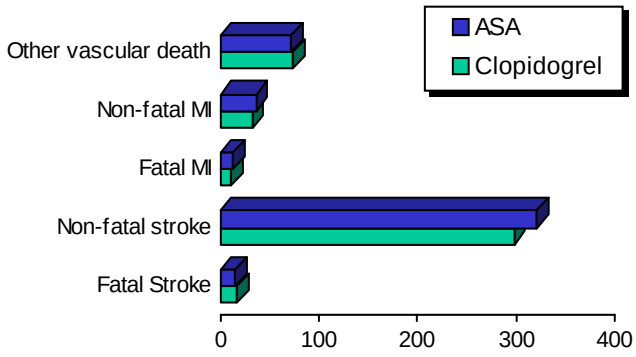
Clopidogrel vs. ASA in Patients at Risk for Ischaemic Events (CAPRIE): CAPRIE Steering Committee (1996).

To assess the relative efficacy of clopidogrel and aspirin in reducing the risk of ischaemic stroke, MI or vascular death, 19,185 patients with atherosclerotic vascular disease (recent history of myocardial infarction, ischaemic stroke or symptomatic peripheral artery disease) were divided into subgroups based upon their history at baseline and assigned to receive either clopidogrel 325 mg/day or ASA 75 mg/day: (1) previous stroke patients – clopidogrel n=3,233, ASA n= 3,198, (2) previous MI patients – clopidogrel n=3,143, ASA n=3,159 and (3) peripheral artery disease (PAD) clopidogrel n=3,223, ASA n=3,229. Mean follow-up time was 1.91 years.

Clopidogrel vs. ASA -- Individual first-outcome events among all patients



Clopidogrel vs. ASA -- Individual first-outcome events among previous stroke subgroup



Long-term administration of clopidogrel in patients with atherosclerotic vascular disease is more effective than ASA in reducing risk of ischaemic stroke, MI or vascular death.

The CAPRIE study demonstrated that clopidogrel was approximately as effective in reducing the risk of stroke as ticlopidine (8.7% vs. approximately 10%) when compared to ASA therapy. Post hoc analysis demonstrated that CAPRIE patients with pre-existing, symptomatic, atherosclerotic disease had elevated 3-year rates of ischaemic stroke, myocardial infarction or vascular death; 20.4% among patients receiving clopidogrel and 23.8% among patients receiving ASA (Ringleb et al. 2004a). This represented an absolute risk reduction of 3.4% (relative risk reduction = 14.9%, p=0.045) associated with the use of clopidogrel. According to the analysis presented by Ringleb et al. (2004a), one would need to treat 29 patients for 3 years with clopidogrel instead of ASA to prevent one ischaemic event.

The clear advantage of clopidogrel over ticlopidine lies in its improved adverse event profile. Contraindications to clopidogrel therapy include "*severe liver impairment and haemostatic disorders or pathological bleeding*" (Diener & Ringleb 2002). A recent meta-analysis of bleeding complications associated with antiplatelet therapy found clopidogrel to be associated with an 8.5% rate of bleeding complications, which is slightly less than that associated with a treatment regimen of 100 – 325 mg

ASA/day (Serebruany et al. 2004). Clopidogrel therapy was associated with an increase of approximately 1/3 in the odds for developing a skin rash and/or diarrhea when compared to ASA (Hankey et al. 2000). This is substantially less than the reported risks associated with ticlopidine in the same analysis (p=0.0002 & p=0.00003, respectively). Neutropenia has been reported as occurring in 0.1% of patients treated with clopidogrel. This is significantly less than reported for ticlopidine (p=0.003) (Hankey et al. 2000).

Clopidogrel is not available in generic form and is an expensive alternative to ASA (Diener & Ringleb 2002). However, recent cost effectiveness analyses have proposed that, while expensive, clopidogrel is within accepted limits for cost-effectiveness (Scheinitz et al. 2004; Sarasin et al. 2000).

Conclusions Regarding Clopidogrel

There is moderate (Level 1b) evidence that Clopidogrel is similar to aspirin with regard to safety, but as effective as ticlopidine in reducing the risk of recurrent stroke.

Clopidogrel is an appropriate substitute for those patients who are intolerant of ASA.

Combination Therapies

Since various antiplatelet drugs work through different mechanisms, it has been theorized that the effects of different drugs may be cumulative. In examining the potential effectiveness of combination or dual-platelet therapy, ASA has been added to thienopyridines as well as to dipyridamole (Antithrombotic Trialists' Collaboration 2002; Ringleb et al. 2004).

Clopidogrel plus ASA

The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study compared the effects of treatment with a combination of clopidrigel and ASA with ASA monotherapy in patients with unstable angina and non-Q-wave MI (Yusuf et al. 2001). To examine the potential effectiveness in secondary prevention of stroke, the Management of Atherosclerosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke (MATCH) study, compared treatment with clopidogrel plus ASA to clopidogrel monotherapy in high-risk patients with recent ischaemic stroke or TIA. Details of both studies are summarized in Table 6.

Table 6. Details of Trials Assessing ASA in Combination with Clopidogrel

Author, Year Country Pedro Score	Methods	Outcomes
CURE Collaborative Group Yusuf et al. 2001 Canada/ International 8 (RCT)	Patients with unstable angina hospitalized within 24 hours of onset of symptoms were randomized to receive clopidogrel 75 mg/day (n=6259) or placebo, in addition to aspirin (n=6303) for 3-12 months.	Significant reduction in primary outcome (composite of death from cardiovascular disease, nonfatal MI or stroke) among patients in the treatment group. Relative risk reduction of 0.08. However, there were significantly more major bleeding episodes in the clopidogrel group.
MATCH Investigators Diener et al. 2004 International 8 (RCT)	7599 patients who had an ischaemic stroke or TIA within 3 months. Patients also had at least one of previous ischaemic stroke, previous myocardial infarction, angina pectoris, diabetes mellitus or symptomatic peripheral artery disease (PAD). Participants were randomly assigned to the ASA treatment group (clopidogrel 75 mg/day plus aspirin 75 mg/day; n=3797) or the placebo condition (75 mg/day clopidogrel plus matching placebo). Treatment continued for 18 months. Follow-up occurred at 1,3,6,12 and 18 months after randomization.	With regard to the primary outcome (composite of ischaemic stroke, myocardial infarction, vascular death or re-hospitalization for any acute ischaemic event), there was a small, nonsignificant trend favouring the combination of clopidogrel and ASA vs. clopidogrel alone (relative risk reduction = 6.4%; p=0.244). With regard to the secondary endpoint of ischaemic stroke, either fatal or non-fatal, there was a relative risk reduction of 7.1% in favour of combined therapy. However, this trend was not significant (p=0.353). In the combined therapy group, there were significantly more incidents of life-threatening bleeding (p<0.0001) as well as more incidents of major bleeding (p<0.0001) and minor bleeding (p<0.0001). Gastrointestinal bleeding was the most common cause of both life-threatening and major bleeding events in the clopidogrel plus aspirin treatment group.
Markus et al. 2005 UK 8 (RCT)	107 patients with recently symptomatic carotid stenosis of ≥50% and recent ipsilateral TIA or stroke were randomly assigned to treatment with either clopidogrel (300 mg on day one followed by 75 mg. o.d. for 7 days) and 75 mg. ASA o.d. OR 75 mg ASA & matching placebo o.d. Asymptomatic microembolic signals (MES), markers of risk for stroke or TIA, were used to evaluate antiplatelet efficacy. Primary study endpoint was proportion of patients who were MES positive on day 7.	43.8% of patients in the dual therapy condition were MES positive compared with 72.7% of patients receiving ASA monotherapy. MES frequency was reduced by 61.6%in the combination therapy group at day 7 compared to baseline (p=0.013) while in the ASA group, MES frequency was reduced by 61.4% by day 2 (p=0.0005). Among patients in the ASA group, there were 4 recurrent strokes and 7 TIAs, while there were no strokes and 4 TIA's in the treatment group. 2 TIA's occurred prior to the initiation of treatment protocols.
Serebruany et al. 2005 USA 5(RCT)	70 patients with recent ischemic stroke were randomly assigned to receive either 81 mg ASA or 81 mg ASA plus 75 mg clopidogrel per day. All patients were treated with 81 mg ASA for at least one month prior to trial commencement. Platelet function was assessed at	With ASA monotherapy, collagen-induced platelet aggregation was reduced at 30 days (p=0.001). Addition of clopidogrel resulted in reductions of platelet activity assessed by ADP- (p=0.00001), reduction of PAU (p=0.001), decreased expression of PECAM-1(p=0.005) and GPIIb/IIIa activity with PAC-1(p=0.27). Collagen-induced aggregation was also reduced

Author, Year Country Pedro Score	Methods	Outcomes
	baseline and then at 30 days post-randomization.	(p=0.012). Reduced formation of platelet-leukocyte microparticles (p=0.01) was demonstrated in patients assigned to combination therapy.
CHARISMA Investigators Bhatt et al. 2006 International 9 (RCT)	15,603 patients with either established cardiovascular disease or multiple risk factors were randomly assigned to receive either 75 mg/day clopidogrel + 75 – 162 mg/day ASA (n=7802) or matching placebo + 75 – 162 mg/day ASA (n=7801). Primary study outcome was a composite of MI, stroke or death from cardiovascular causes. Median length of follow-up was 28 months.	For the primary study endpoint, there was no significant between-group difference reported (RR = 0.93, p=0.22), although fewer events were recorded in the treatment condition. For nonfatal stroke, there were significantly fewer events reported in the clopidogrel/ASA group than in the ASA alone control condition (150 vs. 189; RR = 0.79; p=0.03). On subgroup analysis, for patients with symptomatic cardiovascular disease, treatment with clopidogrel/ASA was associated with a reduction in risk for the primary study outcome when compared to the placebo/ASA condition (RR = 0.88, p=0.046). However, there was a trend toward increased rates of severe bleeding associated with clopidogrel/ASA treatment for both symptomatic and asymptomatic patients. Moderate bleeding was also more frequent in the treatment condition for both asymptomatic (p=0.08) and symptomatic patients (p<0.001).

Discussion

In patients with unstable angina, the CURE trial demonstrated a relative risk reduction of 14% for cardiovascular death, nonfatal MI, nonfatal stroke or refractory ischemia (p<0.001). The use of clopidogrel plus ASA demonstrated both early and sustained benefit in the CURE subject population. While these results seemed promising, there was no evidence available specific to the secondary prevention of stroke. Recently, results from the MATCH trial demonstrated little benefit associated with the use of clopidogrel in combination with ASA in a population of high-risk stroke patients. Furthermore, any beneficial effect attributable to the use of combined therapy in the MATCH study was offset by the significantly higher rates of life-threatening, major and minor bleeding events associated with the use of clopidogrel in combination with ASA (Diener et al. 2004).

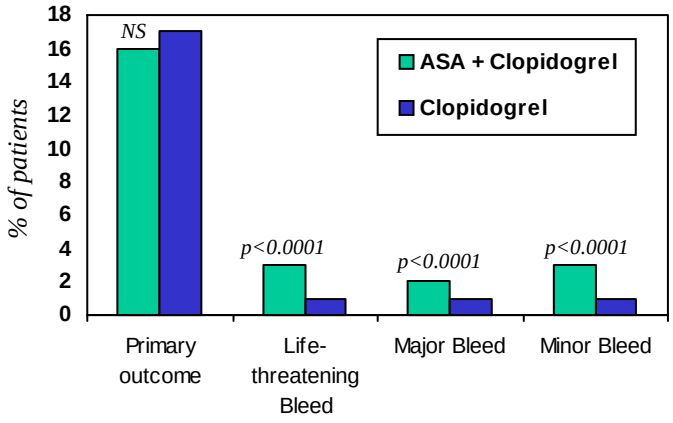
A number of commentaries published subsequent to the MATCH study highlight several issues to consider with regard to the interpretation of the reported results. The MATCH study population contained a disproportionately large number of patients with diabetes (68%) and with small vessel or lacunar strokes (54%) (Caplan 2004; Amarenco & Donnan 2004; Rothwell 2004). Only 34% of patients had large artery disease and of these, an unexpectedly small proportion (5%) reported previous MI (Amarenco & Donnan 2004). In addition to creating an

unrepresentative population sample and reducing generalizability of results, this may have affected specific study outcomes. For instance, antiplatelet therapies may not be particularly efficacious in the prevention of secondary events in diabetic patients (Antithrombotic Trialists' Collaboration 2002; Caplan 2004) and patients with diabetic microangiopathy are more prone to bleeding complications (Amarenco & Donnan 2004). Small vessel or lacunar stroke patients have a much lower risk for recurrent stroke than patients with large artery disease (Rothwell 2004; Amarenco & Donnan 2004; Caplan 2004). In addition to problems with the composition of the study population, it has been noted that the MATCH study did not include an ASA only treatment group for comparison (Caplan 2004; Amarenco and Donnan 2004). The comparison between ASA and the combined therapy may have yielded additional information and provided a different perspective with regard to bleeding complications (Amarenco and Donnan 2004).

Management of Atherosclerosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke Study (MATCH): Diener et al. 2004.

7,599 patients with previous ischaemic stroke and at least one additional vascular risk factor were assigned at random to receive either ASA (75 mg/day; n=3797) or matching placebo (n=3802). All patients received 75 mg clopidogrel once per day. Treatment continued for 18 months. Primary outcome was the composite of ischaemic stroke, myocardial infarction, vascular death and rehospitalization for an acute ischaemic event.

At the end of 18 months, there were fewer primary outcomes among patients receiving combination therapy than those receiving clopidogrel alone. However, this difference was not significant. In addition, there were significantly more bleeding events associated with the use of combined therapy.



The addition of aspirin to clopidogrel had little benefit in the prevention of the primary study outcome. The small demonstrated benefit was outweighed by the higher rate of bleeding events associated with combined therapy.

The CHARISMA trial (Bhatt et al. 2006) provided an opportunity to examine the effectiveness of clopidogrel + ASA combination therapy compared to ASA monotherapy in a broad population of patients with either cardiovascular disease or multiple risk factors. Approximately 12% of patients assigned to each condition reported a previous history of stroke and 42% had diabetes. Results of CHARISMA demonstrated no significant benefit associated with combination therapy when compared to ASA monotherapy, in terms of the composite study endpoint of myocardial infarction, stroke or death from cardiovascular causes. However, for the outcome of non-fatal stroke alone, there was a significant protective effect associated with combination therapy. Unfortunately, treatment with clopidogrel plus ASA was associated with increased episodes of moderate

to severe bleeding, particularly among individuals with symptomatic cardiovascular disease (Bhatt et al. 2006). The authors note that while 94 ischemic endpoints were prevented by treatment with combination therapy, it was at the expense of 93 moderate or severe bleeding events.

Additional research is needed. A study is currently underway to assess the effectiveness of clopidogrel in populations of stroke survivors when treatment is initiated acutely (FASTER or the Fast Assessment of Stroke and Transient ischaemic attack to prevent Early Recurrence trial). Like the CHARISMA trial, FASTER is designed so that clopidogrel or a placebo is added to ASA therapy (Hankey 2004) allowing for the comparison of clopidogrel combination therapy directly with ASA monotherapy. A second, ongoing trial, SPS3 (Secondary Prevention of Small Subcortical Strokes) will assess the efficacy of ASA monotherapy versus clopidogrel plus ASA dual therapy in the prevention of secondary stroke specific to patients with previous lacunar or small subcortical strokes (Hankey 2004).

Results from the MATCH study demonstrated that the benefits associated with the use of combined clopidogrel/ASA therapy are outweighed by the risks for serious bleeding complications. These findings are supported by the results of the CHARISMA trial, although the authors suggest that, among symptomatic patients with cardiovascular disease, there may be a potential benefit requiring further examination (Bhatt et al. 2006). Ongoing trials will provide additional information with regard to the safety and efficacy of clopidogrel plus ASA therapy.

Conclusions Regarding Clopidogrel plus ASA

There is moderate (Level 1b) evidence that clopidogrel in combination with ASA is more effective than ASA alone in preventing stroke among patients with <u>unstable angina and non-Q-wave MI only</u>.

There is moderate (Level 1b) evidence that combination therapy with clopidogrel and low-dose ASA is not more effective than ASA alone in reducing the risk for myocardial infarction, stroke or death from cardiovascular causes in individuals with cardiovascular disease or multiple risk factors. In addition, combination therapy may be associated with an increased risk for moderate-to-severe bleeding particularly in individuals with symptomatic cardiovascular disease.

There is moderate (Level 1b) evidence that, in patients with previous stroke or TIA, clopidogrel combined with ASA is not more effective than clopidogrel alone in preventing recurrent stroke, myocardial infarction, vascular death or rehospitalization for acute ischaemic events and is associated with increased bleeding events.

There is strong (Level 1a) evidence that clopidogrel used in combination with ASA is more effective in modifying platelet activity than ASA alone.

The combination of clopidogrel and ASA is not more effective than either clopidogrel or ASA alone and is associated with an increased incidence of bleeding events.

Dipyridamole plus ASA

Dipyridamole is an antiplatelet agent working through inhibition of "*cyclic nucleotide phosphodiesterase and blockade of the uptake of adenosine*" (Diener & Ringleb 2002).

A recent metanalysis of individual patient data from 6 randomized controlled trials assessing the effectiveness of the combination therapy (dipyridamole plus ASA) reported that patients randomized to treatment with combination therapy had 22%, 26% and 39% less risk for stroke than patients who had been treated with aspirin alone, dipyridamole along or placebo, respectively (Leonardi-Bee et al. 2005). Of all the trials included in this analysis, however, only the ESPS-II used the now standard dosage of ASA and dipyridamole (25 mg ASA and 200 mg dipyridamole twice daily).

The first European Stroke Prevention Study (ESPS Group 1987) examined the effects of a high dose of ASA plus dipyridamole on the risk for fatal and nonfatal stroke in a subject population that included 2500 patients with previous stroke or TIA. Fatal and nonfatal stroke were reported as reduced by 38.1% when compared to a placebo condition. The second European Stroke Prevention Study (ESPS-2) was undertaken to assess the relative effectiveness of the combination therapy versus ASA monotherapy. The details of the ESPS-2 are summarized in Table 7.

Table 7. Details of Trials Assessing ASA in Combination with Dipyridamole.

Author, Year Country Pedro Score	Methods	Outcomes
ESPS Group 1990 Belgium 8 (RCT)	2500 patients with a recent history of cerebrovascular disorders of atherthrombotic origin (TIA, RINDs or complete stroke). Patients were randomly allocated to receive either 75 mg dipyridamole + 330 mg ASA or matching placebo. Patients were followed for 2 years with assessments occurring every 3 months.	There was a 33.5% reduction ($p<0.001$) the combined endpoint of all-cause death and stroke and a 38.1% reduction ($p<0.001$) in all strokes associated with treatment. The reduction death and stroke did not differ by gender, age, nature of cerebrovascular event used to qualify for study participation, site of lesion or diastolic blood pressure.

Author, Year Country Pedro Score	Methods	Outcomes
ESPS-2 Diener et al. 1996 Belgium 8 (RCT)	6602 patients with prior TIA or stroke were randomized to receive 50 mg ASA daily, dipyridamole, the 2 agents in combination or placebo. The primary end points were stroke death or the combined stroke/death.	After 24 months of follow-up, the risk of stroke or death was reduced by 18% with ASA alone;16% with dipyridamole alone and 24% with combination therapy when compared to placebo. In the group receiving combination therapy, the risk for stroke was reduced by 36% vs. placebo. There was no statistically significant effect on the overall death rate.
AGATE Serebruany et al. 2004 International 6 (RCT)	40 patients who had suffered an ischaemic stroke in the previous 2 – 6 months and had not taken ASA for at least one month were randomized to receive either 81 mg ASA/day or Aggrenox twice daily. Treatment continued for 30 days. Blood samples & testing were conducted at baseline, day 1,3,7,15 and day 30. Platelet characteristics were assessed via conventional aggregometry, rapid cartridge-based platelet function analyzers and whole blood flow cytometry.	Both treatments were associated with rapid and sustained platelet inhibition. At individual time points, Aggrenox was superior to aspirin on 25/90 measures (including inhibition of protease activated receptors) while aspirin was superior to Aggrenox on only 4/90 comparisons. In 61/90 comparisons, ASA and Aggrenox were equivalent. The stronger antiplatelet properties of Aggrenox were apparent later in the trial and differences favouring Aggrenox were clear only after 2 weeks of therapy.

Discussion

Results from the first ESPS trial demonstrated the effectiveness of combined therapy in reducing recurrent cerebrovascular events and death in patients with a history of TIA, RINDs or stroke (ESPS Group 1990). The reported results from the ESPS-2 trial suggest that the benefits of dipyridamole and ASA have an additive effect in the secondary prevention of stroke by including an ASA-only treatment condition. In ESPS-2, the use of the combination therapy was associated with an absolute risk reduction of 5.9% for stroke when compared to placebo while in the aspirin-only condition this reduction was 2.9% (Redman & Ryan 2004). In addition, the AGATE study (2004) has demonstrated that, after approximately 2 weeks of treatment, the combination of dypridamole and ASA in the form of Aggrenox©, exhibits antiplatelet properties superior to ASA alone.

The standard dosage used in combination therapy is ASA 25mg plus extended-release dipyridamole 200 mg twice daily (Diener & Ringleb, 2002). Dipyridamole is available in a generic preparation and is considerably less expensive than other aspirin alternatives. It is also available in a combination drug (Aggrenox©) containing 25 mg ASA and 200 mg dipyridamole; however, the combination form is not available generically.

A recent meta-analysis reported the rate of bleeding events with combination dipyridamole therapy to be 6.7% (Serebruany et al. 2004). Rate of bleeding

complications is less with dipyridamole combination therapy than in clopidogrel combination therapy. In the recent MATCH trial, life-threatening, major and minor bleeding events were reported by a total of 8% of patients receiving combined therapy with clopidogrel and ASA (Diener et al. 2004). In the ESPS-2 trial, approximately 1/3 of patients treated with dipyridamole experienced some mild recurring events such as diarrhea or headache. In a recent meta-analysis it was reported that patients receiving dipyridamole alone or in combination with aspirin were more likely to drop out of trials or report significant headache associated with treatment (Leonardi-Bee et al. 2005).

Contraindications to combination therapy with dipyridamole include "*active haemostatic disorder or active pathologic bleeding*" with a caution regarding patients with hypotension as it has the potential to cause peripheral vasodilation (Diener & Ringleb 2002). Aggrenox© should be used with caution in patients with severe coronary artery disease as dipyridamole can increase the risk of MI or exacerbate angina (www.cp.gsm.com cited in Redman & Ryan 2004). There is also a potential for a hazardous interaction between Aggrenox© and adenosine (eg. used during stress tests, nuclear perfusion heart scans or in the termination of supraventricular tachycardia). Dipyridamole increases local adenosine levels and may cause an exaggerated reaction to adenosine, which could result in hypotension and AV block (Littmann et al. 2002; Bergmann 2001).

Conclusions regarding Dipyridamole plus ASA

There is moderate (Level 1b) evidence that dipyridamole in combination with ASA is more effective than either agent used on its own in the prevention of recurrent stroke.

ASA in combination with dipyridamole is more effective than ASA alone in reducing the risk for recurrent stroke.

Clopidogrel vs. Dipyridamole-based Combination Therapies

An indirect comparison between ASA, Aggrenox© (dipyridamole plus ASA) and Plavix© (clopidogrel) is available, which suggests that Aggrenox© is the more effective medication for this population (Albers et al. 2001). However, the authors of a recent review (Redman and Ryan 2004) do not consider Aggrenox© an appropriate first-line therapy citing a lack of evidence for the prevention of other, related atherosclerotic events for which stroke patients are at risk.

A single randomised controlled trial has made a direct comparison of the antiplatelet effects associated with clopidogrel plus ASA and extended release dipyradamole in combination with ASA (Table 8).

Table 8. Details of Trials Assessing Clopidogrel vs. Dipyridamole-based Combination Therapies

Author, Year Country Pedro Score	Methods	Outcomes
Caplain 2005 France 5 (RCT)	In a randomized, 3X2 crossover design, health men aged 18 – 45 (n=26) were allocated to one of six possible sequences of treatment with ASA, clopidogrel + ASA (75 mg ASA, 75 mg clopidogrel) and dipyridamole + ASA (25 mg ASA, 200 mg dipyridamole). Each treatment period lasted 10 days with a 14-day washout period between treatments.	ASA treatment reduced collagen-induced platelet aggregation in whole blood by a mean of 26.8%, whereas clopidogrel+ASA reduced collagen-induced platelet aggregation by a mean of 44.9% and dipyridamole+ASA by a mean of 16.5%. The difference between clopidogrel and dipyraimole based treatments was significant (p=0.0009). Clopidogrel + ASA was more effective than the other treatments in inhibiting collagen-induced platelet aggregation in platelet rich plasma (PRP) ($p \leq 0.0001$). Clopidogrel+ASA treatment was also significantly more effective than either of the other treatments in inhibiting ADP-induced aggregation in whole blood and PRP ($p \leq 0.0001$). Both ASA and clopidogrel + ASA were more effective than dipyridamole in the inhibition of arachidonic acid-induced platelet aggregation ($p \leq 0.0001$) in whole blood. In PRP, all three treatments produced 100% arachidonic acid-induced platelet aggregation.

Discussion

Clopidogrel+ASA appears to provide superior platelet inhibition, based on a single, small RCT reporting results of *ex vivo* platelet aggregometry (Caplein, 2005). However, there is no information available at the present time to confirm or refute the apparent superiority of Clopidogrel+ASA in a clinical setting.

At present, there is a clinical trial underway designed to enable the assessment of the effectiveness and safety of Aggrenox© (25 mg ASA/200 mg extended release dipyridamole) in reducing risk for recurrent stroke when compared to clopidogrel plus aspirin (PRoFESS – Prevention Regimen for Effectively Avoiding Second Strokes).

Conclusions Regarding Clopidogrel vs. Dipyridamole-based Combination Therapies

There is moderate (Level 1b) evidence that clopidogrel in combination with ASA provides more effective platelet inhibition than either ASA alone or ASA in combination with dipyridamole.

Miscellaneous Antiplatelet Therapies

Triflusal

Triflusal is an anti-platelet agent that is structurally similar to aspirin. It works by acting on platelet aggregation and in addition, has anti-inflammatory and vasodilatory properties. Treatment with triflusal has been shown to yield effects similar to ASA although reports of major and minor bleeding incidents were fewer when patients were treated with triflusal. The TACIP study and the TAPIRSS pilot study examining the safety and efficacy of triflusal in preventing vascular events in patients with previous TIA or stroke are summarized in Table 9.

Table 9. Trifusal Safety and Efficacy Studies

Author, Year Country Pedro Score	Methods	Outcomes
TACIP Study Investigators 2003 Spain 8 (RCT)	2113 patients with previous stroke of TIA were randomly assigned to receive either 600 mg/day triflusal or 325 mg/day aspirin. Mean follow-up period = 30.1 months.	There was no significant difference found between treatment groups for the combined study endpoint of nonfatal ischaemic stroke, nonfatal MI or vascular death or for any of these outcomes individually. A significantly lower number of bleeding incidents (both major and minor) were recorded in the group receiving triflusal compared to ASA (OR=0.76; p=<0.001).
TAPIRSS Culebras et al. 2004 Argentina 9 (RCT)	431 patients with a history of stroke or TIA within 6 months of enrollment were randomized to receive either 325 mg. ASA daily or 600mg trifusal daily. Treatment duration was for a mean 586 days.	There was no significant difference in the incidence of vascular death, cerebral ischaemic infarction, nonfatal MI, or major haemorrhage between treatment conditions. Post hoc analysis revealed significantly fewer bleeding events among patients receiving triflusal.

Discussion

While Triflusal has been demonstrated to be as effective as ASA with fewer reported bleeding events, it has been approved for use only in Italy, Portugal, Greece, parts of Asia and most of Latin America, including Mexico and Argentina (American Heart Association 2001).

Conclusions Regarding the Use of Triflusal

There is strong (Level 1a) evidence that Triflusal is not inferior to ASA in the prevention of stroke and is associated with fewer bleeding incidents.

Trifusal is not inferior to ASA in the prevention of stroke.

Glycoprotein IIb/IIIa Inhibitor (Lotrafiban)

Glycoprotein (GP) IIb/IIIa inhibitors function through a different mechanism involved in platelet aggregation. They block what is termed the "*final common pathway of platelet aggregation*" by preventing fibrinogen binding to the GP IIb/IIIa receptors (Antithrombotic Trialists' Collaboration 2002; Harrington et al. 2000). According to a recent meta-analysis, which includes fifteen studies up to 1997 (Antithrombotic Trialists' Collaboration 2002), short-term treatment with an intravenous GP IIb/IIIa receptor antagonist produced a highly significant reduction in serious vascular events when compared to treatment with ASA alone (19%). However, the benefits associated with this treatment must be considered along with an increased risk for bleeding events. The Antithrombotic Trialists' Collaboration (2002) reported an absolute excess of 23 major extracranial bleeds per 1000 patients while fatal bleeding was rare. In a 2004 analysis of reported bleeding events associated with antiplatelet therapies, Serebruany et al. (2004) reported that the highest rate of bleeding complications were associated with IV GPIIb/IIIa blocker therapy (49%). The rate of bleeding events was reported to be slightly less for oral therapy (44.6%).

A single, recent clinical trial has examined the effectiveness of an oral GP IIb/IIIa inhibitor in addition to ASA in secondary prevention of stroke. Details of the APLAUD (Anti-platelet Useful Dose) study are summarized in Table 10.

Table 10. Details of the APLAUD Study.

Author, Year Country Pedro Score	Methods	Outcomes
APLAUD Study Investigators Harrington et al. 2000 USA 7 (RCT)	451 patients with recent cardiovascular or cerebrovascular acute ischaemic events were randomized to 1 of 5 dosing regimens for 12 weeks: 1) placebo; 2) 5 mg lotrafiban 3) 20 lotrafiban 4) 50 mg lotrafiban 5) 100 mg lotrafiban – all given twice daily with 300 – 325 mg ASA.	The 5 mg treatment group had a rate of bleeding complications similar to the placebo group. The 100 mg group was terminated early due to excessive major bleeding events. Thrombocytopenia (<100 000 platelets/μL) occurred in 5 patients treated with lotrafibran. Lotrafiban produced dose-dependent inhibition of platelet aggregation – 5 mg did not differ from placebo, whereas 100 mg produced nearly 100% inhibition of platelet aggregation.

Discussion

While GP IIb/IIIc inhibitors are capable of blocking platelet aggregation in a dose-dependent fashion, they also produce major bleeding events in a similar, dose-dependent fashion. Lotrafiban, at its safest dosage, does not inhibit platelet aggregation any more effectively than ASA alone. Given the strong correlation between increased platelet inhibition and increased bleeding, it would not be

appropriate to use GP IIb/IIIa inhibitors for long-term secondary prevention of stroke (Diener & Ringleb 2002).

BRAVO was a clinical trial specifically designed to test the effectiveness of Lotrafiban in preventing stroke in patients with a history of recent MI, TIA, stroke or any peripheral vascular disease. The drug's manufacturer stopped the trial in December 2000 when serious safety and efficacy concerns became apparent.

Conclusions Regarding the Use of Glycoprotein IIb/IIIa Inhibitor (Lotrafiban)

There is moderate (Level 1b) evidence that the use of Glycoprotein IIb/IIIa inhibitors (Lotrafiban) in the secondary prevention of stroke is associated with excessive bleeding incidents.

The use of Glycoprotein IIb/IIIa inhibitors (Lotrafiban) is associated with excessive bleeding incidents.

Treatment Recommendations

Goldszmidt & Caplan (2003) recommend that all patients with previous TIA or stroke due to large artery atherothrombosis should be treated with antiplatelet therapy unless there is a specific contraindication.

The UK National Clinical Guidelines for Stroke note that, *"All patients with ischaemic stroke who are not on anticoagulation, should be taking an antiplatelet agent, i.e. aspirin (75-325 mg) daily, or clopidogrel, or a combination of low-dose aspirin and dipyridamole modified release (MR). Where patients are aspirin intolerant an alternative antiplatelet agent (clopidogrel 75 mg daily or dipyridamole MR 200 mg twice daily) should be used."*

The Canadian Heart and Stroke Foundation recommendations are provided in Table 12, while the more recent recommendations for the secondary prevention of stroke provided by the American Heart Association/American Stroke Association Council on stroke appear in Table 13.

Table 12. Recommendations for Antiplatelet Drug Use (Heart and Stroke Foundation)

- Use antiplatelet agents in secondary prevention of stroke when the origin is not cardioembolic.
- Current choices include ASA, Plavix and Aggrenox (strong evidence).
- Ticlid (ticlopidine) is no longer recommended for stroke prevention due to its side effect profile
- Dose of 81-325 mg ASA/day should be initiated within 48 hours after the first stroke.
- Aggrenox and Plavix are indicated in Canada only if there is an ASA failure, i.e. TIA/stroke on ASA.
- ASA use results in an 18% risk reduction of stroke vs. placebo.
- High doses of ASA are not required to achieve therapeutic effect, i.e. 81-325 mg daily is effective.
- Plavix is at least as effective as ASA and may be slightly more effective.
- Combo ASA and dipyridamole results in up to a 37% risk reduction of stroke vs. placebo and is up to 23% more effective than either alone.
- Combination of Plavix/ASA is currently under investigation.

Table 13. AHA/ASA Recommendations for Antithrombotic Therapy for Noncardioembolic Stroke or TIA (Sacco et al. 2006).

For patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events.

- Aspirin (50 mg – 325 mg/day), the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy.
- Compared with aspirin along, both the combination of aspirin and extended-release dipyridamole and clopidogrel are safe. The combination of aspirin and extended-release dipyridamole is suggested over aspirin alone.
- Clopidogrel may be considered over aspirin alone on the basis of direct-comparison trials. Insufficient data are available to make evidence-based recommendations with regard to choices between antiplatelet options other than aspirin. Selection of an antiplatelet agent should be individualized based on patient risk factor profiles, tolerance and other clinical characteristics.
- Addition of aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended for ischemic stroke or TIA patients.
- For patients allergic to aspirin, clopidogrel is reasonable.
- For patients who have an ischemic cerebrovascular event while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered for noncardioembolic patients, no single agent or combination has been well studied in patients who have had an event while receiving aspirin.

Antiplatelet Therapy in Atrial Fibrillation

ASA Monotherapy

Aspirin has been used in the prevention of stroke for individuals with non-valvular atrial fibrillation both alone and in combination with Warfarin. Several studies

provide the opportunity to evaluate the effectiveness of ASA monotherapy when compared to a placebo condition.

Table 14. ASA Monotherapy in Patients with AF

Author, Year Country Pedro Score	Methods	Outcomes
SPAF I Stroke Prevention in Atrial Fibrillation Investigators 1991 USA 7 (RCT)	1,330 patients with constant or intermittent, non-valvular atrial fibrillation were separated into two groups based on their eligibility to receive warfarin. Warfarin eligible patients were randomized to receive either dose-adjusted warfarin - INR target range 2.0 – 4.5 - (n=210), enteric-coated aspirin 325 mg/day (n=206) or placebo (n=211). Patients not eligible to receive warfarin were randomized to receive either ASA (n=346) or placebo (n=357). Mean follow-up time was 1.3 years.	Rate of primary events (ischaemic stroke and systemic embolism) was 6.3% per annum in patients assigned to placebo. This rate was reduced by 42% in patients receiving ASA and by 67% in warfarin-eligible patients assigned to receive adjusted dose warfarin. Primary events & death were reduced by 58% with warfarin (p=0.01) and 32% by ASA (p=0.02).
EAFT European Atrial Fibrillation Study Group 1993 Netherlands 7 (RCT)	1,007 non-rheumatic atrial fibrillation patients with a recent TIA or minor ischaemic stroke were grouped by eligibility to receive anti-coagulation therapy. Anti-coagulation eligible patients (group 1) were randomized to receive adjusted dose anticoagulation (INR 2.5 – 4.0), aspirin (300 mg/day) or placebo. Those not eligible for anti-coagulation therapy (group 2) were randomized to receive either ASA or placebo. Mean duration of follow-up was 2.3 years.	Among group 1 patients, risk of stroke was reduced from 12% per year to 4% per year when anti-coagulation therapy was compared to placebo (HR = 0.34). Among all patients receiving ASA, the rate of events was 15% compared to 19% for those patients receiving placebo (HR=0.83). Anticoagulation therapy was significantly more effective in preventing stroke than ASA (HR=0.60). The rate of major bleeding events while on anti-coagulation therapy was 2.8% and 0.9% while taking ASA.
JAST Japan Atrial Fibrillation Stroke Trial Group 2006 Japan 7 (RCT)	In this open-label study, 871 patients with non-valvular atrial fibrillation were randomly allocated to treatment (n=426) or control (n=445) groups. Treatment consisted of daily ASA therapy (150 – 200 mg) or no treatment. Primary study outcomes were cardiovascular death, symptomatic brain infarction or TIA.	The trial was stopped early due to higher risk of major bleeding associated with ASA therapy. It was also determined that ASA was unlikely to be associated with superior prevention of study endpoints. Data collected revealed no difference between groups on any of the primary end points including stroke (p=0.967). 7 patients in the treatment group and 2 patients in the control group experienced major bleeding (p=0.1).

Discussion

ASA therapy (300 – 325 mg/day) was associated with reduction of stroke risk in individuals with AF when compared to no treatment. However, doses of 150 – 200 mg/day do not appear to be either safe or effective. Based on the results of

the EAFT trial and several meta-analyses (Segal et al. 2000; Albers et al. 2001; Hart et al. 1999; Perret-Guillaume & Wahl 2004), it is clear that anticoagulant therapy (dose-adjusted warfarin) is more effective in preventing strokes among individuals with atrial fibrillation than antiplatelet therapy (ASA).

Conclusions Regarding ASA Monotherapy

There is strong (Level 1a) evidence that treatment with ASA 300 – 325 mg/day is associated with reduced risk of stroke when compared to no treatment in individuals with atrial fibrillation. However, anticoagulant therapy (dose-adjusted warfarin) is more effective in preventing strokes among individuals with atrial fibrillation than antiplatelet therapy (ASA).

Treatment with ASA (300 – 325 mg/day) reduces the risk of stroke in individuals with atrial fibrillation. However, it is not as effective as therapy with dose-adjusted warfarin.

Indobufen

Given the potential for bleeding complications associated with the use of oral anticoagulation therapy, the use of antiplatelet therapy has been explored as a safer alternative. Aside from ASA, which has been identified as a less effective alternative to warfarin in terms of reducing the risk of cardioembolic stroke among individuals with AF (Segal et al. 2000; Albers et al. 2001; Hart et al. 1999; Perret-Guillaume & Wahl 2004), indobufen has been investigated as an alternative therapy. Indobufen is a reversible inhibitor of platelet cyclo-oxygenase activity shown to be effective in preventing thromboembolic events in several patient populations (Saxena and Koudstaal 2003, Morocutti et al. 1997, Fornaro et al. 1993). Trials assessing the effectiveness of indobufen in the prevention of stroke are summarized in Table 15.

Table 15. Indobufen Therapy in Patients with AF

Author, Year Country Pedro Score	Methods	Outcomes
Fornaro et al. 1993 Italy 7 (RCT)	196 patients with history of heart disease and at risk for cardioembolism (90 patients with AF, 106 patients in sinus rhythm with one additional risk factor for cardioembolism) were randomized to treatment with indobufen (100 mg twice daily, n=98) or placebo groups (n=98). Study duration = 3 years. Patients were examined every 3	Age, sex and risk factor adjusted relative risk reduction for primary study endpoints (TIA & fatal or non-fatal stroke) was reported for the group treated with indobufen (RR=0.35, $p<0.05$, 95% CI = 0.14 – 0.89). Overall, 6 primary events (2 fatal) were reported in the treatment group while there were 17 events reported in the placebo group (7 fatal).

Author, Year Country Pedro Score	Methods	Outcomes
	months.	
SIFA Investigators Morocutti et al. 1997 Italy 7 (RCT)	916 patients with nonrheumatic AF were randomly assigned to receive either indobufen (100 or 200 mg p.o. o.d.) or adjusted dose warfarin (INR 2.0 – 3.5) for 12 months.	Incidence of primary outcome events (nonfatal stroke, systemic embolism, nonfatal MI and vascular death) was not significantly different between groups (10.6% in the indobufen group vs. 9.0% in the warfarin treatment group). A low frequency of noncerebral bleeding events was observed – there were 4 GI bleed events recorded; all within the warfarin treatment group.

Discussion

While results of the EAFT trial and several meta-analyses (Segal et al. 2000; Albers et al. 2001; Hart et al. 1999; Perret-Guillaume & Wahl 2004), clearly suggested that anticoagulant therapy (dose-adjusted warfarin) is more effective in preventing strokes among individuals with atrial fibrillation than antiplatelet therapy (ASA), results of clinical trials examining the use of indobufen suggest that it might be an effective alternative antiplatelet therapy.

In patients with AF who were treated with ASA, the risk of recurrent stroke was reported to be 10% per year in the EAFT trial (EAFT study group, 1993), while in the SIFA trial, the rate of recurrent stroke was reported to be 5% per year in patients treated with indobufen (Morocutti et al. 1997). However, considerable heterogeneity was identified between trials (e.g. clinical heterogeneity of patients, differing degrees of anti-coagulation used) and follow-up was much shorter for the SIFA trial than for EAFT (Saxena and Koudstaal, 2003). A single, earlier systematic review and analysis demonstrated no significant difference between anticoagulation and antiplatelet therapies (Taylor et al. 2001). This review included data from 5 trials comparing the effects of long-term anticoagulation directly with long-term antiplatelet therapy; 4 trials used ASA as the antiplatelet therapy of interest, while only one (SIFA) examined the effectiveness of indobufen. Similar to the review undertaken by Saxena and Koudstaal (2003), significant heterogeneity was identified between trials. Side effects associated with indobufen therapy include stomach pain, nausea and vomiting (Morocutti et al. 1997).

Conclusions Regarding Indobufen

There is moderate (Level 1b) evidence that the antiplatelet Indobufen may be as effective as warfarin, but is associated with a reduced risk of bleeding events.

Ximelagatran

Ximelagatran is a prodrug to be administered orally. When taken, it converts rapidly *in vivo* to Melagatran, a reversible, direct thrombin inhibitor (Brighton 2004, Mohapatra et al. 2005). Melagatran functions to prevent clotting by inhibiting both soluble and clot-bound thrombin, a key enzyme in converting fibrinogen into fibrin (Brighton 2004, Nutescu et al. 2004).

Melagatran acts rapidly and has a relatively short half-life ranging from 1.5 – 2 hours in young, healthy individuals to approximately 4 hours in the elderly. Unlike warfarin, there are no known significant interactions with food or other drugs (Brighton 2004, Nutescu et al. 2004) and bioavailability of the drug is not affected by food (Mohapatra et al. (2005). Its short half-life necessitates twice daily administration, however, administration is by fixed dose. The drug is not well metabolised and approximately 80% is excreted renally (Brighton 2004, Nutescu et al. 2004). The effect of renal impairment on the use of Ximelagatran is not known (Brighton, 2004). Clinical studies have been undertaken to examine the effectiveness of Ximelagatran/Melagatran as therapy for vein thrombosis, prophylaxis for venous thromboembolism after orthopaedic surgery, in the prevention of recurrent vascular events in patients with acute coronary syndromes and in patients with atrial fibrillation. Studies focusing on the use of Ximelagatran for the prevention of stroke in individuals with AF are summarized in Table 16.

Table 16. Alternate Anticoagulation Therapy with Ximelagatran

Author, Year Country Pedro Score	Methods	Outcomes
SPORTIF II Petersen et al. 2003 International 6 (RCT)	A 12-week phase II study in which 254 patients were randomized to one of 4 groups: ximelagatran 20 mg bid (n=66), ximelagatran 40 mg bid (n=62), ximelagatran 60 mg bid (n=59) or open-label dose-adjusted warfarin (INR 2.0 – 3.0) (n=67).	One TIA and one stroke occurred in patients receiving ximelagatran. 2 TIAs were reported among patients treated with warfarin. No major bleeding events were reported among patients receiving ximelagatran. One major bleeding event was reported in the warfarin condition. Minor bleeding was reported in 4, 5 & 7 patients in the 20, 40 & 60 mg ximelagatran groups respectively. Minor bleeding was reported for 6 patients in the warfarin group. 4.3% (8) of patients treated with ximelagatran experienced elevations of the liver enzyme S-alanine aminotransferase greater than 3X the upper limit of normal. These resolved with either continued treatment (5 patients) or discontinuation of ximelagatran therapy (3 patients).

Author, Year Country Pedro Score	Methods	Outcomes
SPORTIF III 2003 Europe 7 (RCT)	3410 patients with atrial fibrillation and at least one risk factor for stroke, including previous stroke or TIA, were randomly allocated to receive open-label treatment with either ximelagatran (36 mg/day) or adjusted-dose warfarin (INR 2.0 – 3.0). Mean follow-up = 17.4 months.	The rate of stroke or systemic embolism was 2.3% per year in the warfarin group vs. 1.6% per year in the ximelagatran group (relative risk reduction associated with ximelagatran = 29%; p=0.1). Major and minor bleeding events were fewer in the group receiving ximelagatran (relative risk reduction = 14% for major or minor bleeds, p=0.007). Treatment with ximelagatran was associated with more cases of elevated alanine aminotransferase (6.1% of patients).
SPORTIF V 2005 USA/Canada 9 (RCT)	3922 patients with nonvalvular AF and at least one risk factor for stroke were randomized to receive therapy with either dose-adjusted warfarin (INR 2.0 – 3.0) or ximelagatran 36 mg bid. Mean length of follow-up = 20 months in both treatment groups.	For the primary study endpoint of all strokes and systemic embolic events, the incidence was 1.16% in the warfarin treatment group and 1.61% in the ximelagatran group (p=0.13). By intention to treat analysis, no significant differences were reported for nonfatal or fatal stroke of any type or for all cause mortality. While there were fewer major extracerebral bleeds reported in the ximelagatran group than in the warfarin group, this difference was not significant. When considering major and minor bleeding episodes combined, treatment with ximelagatran represented a relative reduction in bleeding risk of 21% (p<0.001). 6.0% of patients experienced elevated serum ALT levels > 3 times the upper limit of normal. For most, this resolved either spontaneously or following treatment cessation.

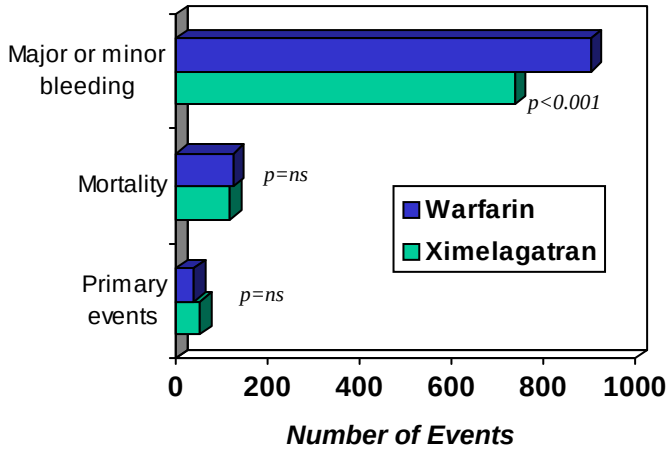
Discussion

The results of both the SPORTIF III and SPORTIF V trials have demonstrated the noninferiority of ximelagatran when compared to well-controlled warfarin therapy. In addition, 40% of SPORTIF participants were aged 75 years or older, suggesting that ximelagatran is effective in this high-risk age group in which AF is most prevalent. Ximelagatran may offer a less complicated treatment alternative to warfarin. It is administered by a fixed dose twice daily, requires no routine INR monitoring, has a quick onset and short half-life and has no known food or drug interactions. In clinical practice, it is conceivable that ximelagatran could produce superior risk reduction for stroke since it overcomes many of the perceived treatment barriers associated with warfarin therapy (Albers 2004).

Pooled analysis of data, on an intention-to-treat basis, from SPORTIF III and SPORTIF V (Albers 2004) demonstrated no significant difference between treatment with ximelagatran and well-controlled warfarin in the prevention of all stroke or systemic embolic events. Among the 20% of SPORTIF participants who had experienced previous stroke or TIA, there was also no difference in

Ximelagatran vs. Warfarin for stroke prevention in in patients with Nonvalvular Atrial Fibrillation: SPORTIF V (2005)

3922 patients with atrial fibrillation and one or more stroke risk factors were randomly assigned to receive either adjusted dose warfarin therapy (INR 2.0 – 3.0) or ximelagatran (36 mg twice daily). Primary events were stroke and systemic embolism. Mean follow-up time was 20 months.



Primary study events were stroke (ischaemic or haemorrhagic) or systemic embolic events. The primary event rate per year was 1.2% with warfarin therapy and 1.6% with ximelagatran (relative risk reduction in favour of warfarin = 0.45; 95% CI –0.13 to 1.0; p=0.13). Rates of major bleeding were similar between treatment conditions (p=0.15), however, combined major and minor bleeding events were significantly fewer in the group receiving ximelagatran.

treatment effect with regard to the primary study outcomes. The risk of intracranial haemorrhage was reported to be 0.11% per year in the ximelagatran group and 0.19% in the warfarin group. Risk of ischaemic stroke was reported to be 1.37% and 1.46% in the ximelagatran and warfarin groups respectively (Albers 2004). Pooled on-treatment analysis revealed a 1% absolute risk reduction and 16% relative risk reduction in favour of treatment with ximelagatran (p<0.038, Albers 2004).

Rates of major bleeding events appear to be similar between SPORTIF treatment groups (Albers 2004). However, when combined minor and major bleeding episodes are considered, there is significantly less bleeding associated with ximelagatran therapy (31.7% per year for ximelagatran vs. 38.7% for warfarin, p<0.0001). A recent pooled analysis of SPORTIF III and V (Douketis et al. 2006), reported an 18.2% reduction in risk for any bleeding events associated with ximelagatran when compared to warfarin therapy (p<0.001). For major bleeding events, relative risk reduction was 25.1%. Ximegalatran therapy was associated with a 0.67% (NNT = 149) and 7% (NNT = 14) annual absolute risk reduction for major and any bleeding events, respectively. Risk factors for bleeding events when treated with ximelagatran included diabetes mellitus (HR = 1.81 p=0.006), previous stroke or TIA (HR = 1.78 p=0.008), age ≥ 75 years (HR = 1.70 p<0.001) and aspirin use (HR = 1.68 p=0.02) (Douketis et al. 2006).

Albers (2004) reported that 6.1% of patients in the ximelagatran treatment groups experienced asymptomatic elevations of the liver enzyme alanine aminotransferase (ALT) to more than 3 times above the upper limit of normal. In most patients, this resolves either spontaneously or once therapy is withdrawn. In approximately 1% of patients, abnormal liver function has been reported

(Brighton 2004). Reported increases in liver enzyme levels have made it necessary to monitor liver function closely. It is recommended that patients undergo monthly liver function tests for the first 6 months of treatment. Elevated enzymes rarely develop after 6 months. Therapy should be withdrawn if levels exceed 5 times the upper limit of normal at any time (Brighton, 2004). It should be noted that ximelagatran is not currently approved for use in North America.

Conclusions Regarding Ximelagatran

There is strong (Level 1a) evidence that treatment with the direct thrombin inhibitor ximelagatran/melagatran is not inferior to treatment with warfarin. While associated with fewer bleeding events, ximelagatran treatment requires monitoring of liver function for the first six months of treatment.

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