Evidence-Based Review of Stroke Rehabilitation

Appendix: Anticoagulant Therapy

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Secondary Prevention of Stroke: Anticoagulant Therapy

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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

Various cardiac conditions have been clearly associated with an increased risk of ischaemic stroke (Sacco et al. 2001) (see Table 2). Sacco et al. (2001) noted, *"because certain stroke risk factors, like hypertension, may also be determinants of cardiac disease, some cardiac conditions may be viewed as intervening events in the causal chain for stroke".*

Table 2. Cardiac Risk Factors for Ischaemic Stroke

Definite Risk Factor	Possible Risk Factor
Atrial Fibrillation	
Myocardial Disease: *Coronary artery disease* *Cardiac failure* *Left ventricular failure* *Intracardiac thrombus*	*Patent foramen ovale* *Atrial septic aneurysm* *Spontaneous echo contrast*
Cardiac Valve Abnormalities: *Mitral stenosis* *Mitral valvular calcifications* *Prosthetic valves* *Endocarditis*	*Valve strands*

Atrial Fibrillation

Atrial fibrillation (AF) is a common, pathological tachycardia the prevalence of which increases with age. Under the age of 30, prevalence has been estimated at approximately 0.2% (Thrombosis Interest Group 2002) whereas estimates vary from 5 – 12% over the age of 70 (Hart & Halperin 2001; Khairy & Nattel 2002; Thrombosis Interest Group 2002; Snow et al. 2003). During the acute

phase following first ischemic stroke, the prevalence of AF may be as high as 24% (Marini et al. (2005). Marini et al. (2005) reported that patients with AF were more likely to be women, over the age of 80 and have coronary heart disease and peripheral artery disease.

Atrial fibrillation has been identified as a powerful, independent risk factor for ischaemic stroke (SPAF III writing committee 1998) increasing the risk of stroke as much as 5-fold for individuals over the age of 70. Sixteen percent (16%) of all ischaemic strokes within this age group are associated with non-valvular AF (Hart & Halperin 2001; Devuyst & Bogousslavsky 2001).   Approximately two thirds of those can be attributed to left atrial thrombi (Hart & Halperin 2001). The formation of left atrial thrombi in AF patients is linked to stasis within the fibrillating atrium, although the factors that serve to promote stasis have not been well defined (Khairy & Nattel 2002; Hart & Halperin 2001).

Following a primary ischaemic event, patients with AF are at a high risk for recurrent stroke. Within the first 2 weeks following a stroke event, risk has been estimated to be 0.1% - 1.3% per day, while subsequent to this the risk for AF patients with a history of prior stroke or TIA has been estimated to be 12% per annum (Devuyst & Bogousslavsky 2001). A recent review of the literature reported that ischaemic stroke associated with AF is more likely to be fatal both in the short-term (within one month of the stroke event) and in the longer term (one year post stroke) (Miller et al. 2005). Among stroke survivors with AF, recurrence rates are at least twice those for non-AF stroke survivors. Strokes in individuals with AF tend to be more severe, require longer periods of hospitalization and are associated with greater levels of disability and dependency (Miller et al. 2005). Marini et al. (2005) reported that the presence of AF in individuals following first ischaemic stroke was associated with higher 30-day (32.5%) and one-year (49.5%) fatality rates as well as with a higher rate of stroke recurrence (6.9% vs. 4.7% in individuals without AF, p=0.04).

One approach to treatment of atrial fibrillation focuses on control of the ventricular heart rate and the use of anti-coagulant therapy to reduce the risk of thromboembolic complications resulting in stroke (Khairy & Nattel 2002). Our discussion will focus on the use of anti-coagulant therapy in stroke prevention.

Anticoagulant Therapy

The study of pharmacologic management of AF through anti-coagulation therapy has been focused primarily on the use of oral vitamin K antagonists (which inhibit vitamin-K dependent clotting factors) and aspirin either alone or in combination with each other. Various other agents have also been assessed for use when a vitamin K antagonist might be contraindicated.

Warfarin (Coumadin)

The most thoroughly studied anticoagulant therapy is the vitamin K antagonist, warfarin. Warfarin inhibits the synthesis of vitamin K-dependent clotting factors (ie. Factors II, VII, IX or X) leading to the synthesis of inactive clotting proteins. Therapeutic anticoagulation requires inactivation of factor II, which has a half-life of 60 hours, the longest of the clotting proteins. The activity of warfarin is monitored by the measurement of the prothrombin time (PT). Therapeutic anticoagulation has generally had as its goal an increase of the prothrombin time (PT) of 2 to 2.5 times control. Because of the prolonged onset of action of Warfarin, the results of dosage adjustments may not be seen until 3 to 5 days later.

Warfarin's greatest advantage is that it is well absorbed by the gastrointestinal system. Side effects of warfarin include bleeding and, uncommonly, skin necrosis, dermatitis and a syndrome of painful blue toes. During pregnancy, Warfarin crosses the placenta and must be avoided.   Warfarin is highly bound to plasma proteins and medications like salicylates, sulfonamides, tolbutamide and phenytoin may increase the anticoagulant effect by displacing warfarin from these plasma proteins. Drugs such as barbituates, rifampin and spironolactone may decrease the anticoagulant effect by inducing hepatic microsomal enzymes. Patients with dietary deficiencies of vitamin K are more susceptible to bleeding complications. Vitamin K is an antagonist of Warfarin's anticoagulant effect; however, because of the time taken to make clotting proteins there is a delay before it reverses the anticoagulation effect. Vitamin K must be given carefully and patients have developed a stroke as a result of too aggressive administration of vitamin K. With significant bleeding, the depleted clotting factors can be replaced with whole blood or fresh frozen plasma.

Anticoagulation therapy using warfarin has been assessed in various adjusted-dose treatment plans alone and in combination with ASA as well as in low intensity and fixed mini-dose regimens. Clinical trials assessing the effectiveness of warfarin and ASA in reducing the risk of cardioembolic stroke among individuals with atrial fibrillation are summarized in Table 3.

Table 3.   Warfarin and ASA Therapy In Atrial Fibrillation

Author, Year Country Pedro Score	Methods	Outcomes
AFASAK I Petersen et al. 1989 Denmark 6 (RCT)	A total of 1,007 patients with chronic, non-rheumatic AF were randomly allocated to receive adjusted dose warfarin (INR target range = 2.8 – 4.2), 75 mg ASA once daily, or a placebo (matched to ASA). Follow-up was over a period of 2 years. Thromboembolic complications were defined as (TIA, minor stroke, nondisabling stroke,	Annual incidence of thromboembolic complications was 2.0% on warfarin and 5.5% on aspirin and placebo (p<0.05). 21 patients who withdrew due to side effects of warfarin treatment experienced bleeding complications. Two bleeding events were noted with ASA treatment and none in the placebo group.

Author, Year Country Pedro Score	Methods	Outcomes
	disabling stroke, fatal stroke, embolism to viscera or extremities).	
BAATAF Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators 1990 USA 7 (RCT)	420 adults with chronic atrial fibrillation with no evidence of mitral stenosis were randomly assigned to receive either adjusted dose warfarin (INR 1.5 – 2.7) or nothing. Patients were advised regarding therapy they received. Patients who received no warfarin therapy were allowed to take ASA – doses and frequencies were recorded.	The risk of stroke was reduced in the warfarin therapy group compared to the no therapy group by 86% (p=0.0022). Mortality was also significantly lower in the treatment group (p=0.005). The frequency of major haemorrhage was similar in both groups. Minor haemorrhages were higher within the warfarin group.
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).
CAFA Connolly et al. 1991 Canada 8 (RCT)	187 patients with non-rheumatic AF were randomized to receive adjusted dose warfarin, 191 to receive a matching placebo. The study was stopped early (prior to completing projected recruitment of 630 patients) subsequent to publication of results of SPAF. Targeted INR was 2 – 3. INR was within range for 43.7% of study days.	Combined primary outcome event cluster was comprised of non-lacunar stroke, non-central nervous system embolism and fatal or intracranial haemorrhage. Annual rate of the combined outcome was 3.5% in patients receiving warfarin vs. 5.2% in the placebo group. Relative risk reduction with warfarin was 37% (p=0.17). The annual rate for fatal or major bleeding was increased in the warfarin group (2.5% vs. 0.5%), as was minor bleeding (16% vs. 9%).
Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators Ezekowitz et al. 1992 USA 8 (RCT)	571 men with chronic nonrheumatic atrial fibrillation were randomly allocated to a treatment condition receiving adjusted dose, low intensity warfarin (INR 1.5 – 2.7) or to a matching placebo condition. Mean follow-up was 1.7 years.	Among patients with no history of stroke, the reduction in risk for stroke associated with warfarin therapy was 0.79 (p=0.001). The annual event rate in patients over age 70 was 4.8%/annum in the placebo group and 0.9%/annum in the warfarin therapy group. Stroke was more common among patients with a history of previous cerebral infarction (9.3%/annum in the placebo group vs. 6.1%/annum in the warfarin group). Major haemorrhages occurred at the rate of 1.3% per annum with warfarin therapy.

Author, Year Country Pedro Score	Methods	Outcomes
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.
SPAF II Stroke Prevention in Atrial Fibrillation Investigators 1994 USA 6 (RCT)	715 patients $\leq$ 75 years of age and 385 patients over the age of 75 were randomly allocated to receive adjusted dose warfarin (INR 2.0 – 4.5) or enteric-coated ASA 325 mg/day. Primary events were ischaemic stroke and systemic embolism.	In younger patients, rate of primary events was reduced by 0.7% per year among those receiving warfarin therapy vs. ASA therapy (RR= 0.67; p=0.24). By comparison, rate of primary events was reduced by 1.2% per year with warfarin therapy vs. ASA (RR=0.73; p=0.39). In the older group the rate of all stroke (ischaemic & haemorrhagic, with & without residual deficits) was 4.3% in the ASA group vs. 4.6% in the warfarin group. Among older patients, there was a significantly greater risk of major haemorrhage with warfarin than with ASA therapy (4.2% vs. 1.6%; p=0.04).
SPAFIII Stroke Prevention in Atrial Fibrillation Investigators 1996 USA 7 (RCT)	1044 patients with atrial fibrillation and one other risk factor for thromboembolism were randomly assigned to receive either adjusted dose warfarin (INR 2.0 – 3.0) or low-intensity, fixed dose warfarin (initial dose adjusted to INR 1.2 – 1.5) and ASA (325 mg/day). Mean follow-up = 1.1 years.	Rate of ischaemic stroke and systemic embolism was significantly higher among patients receiving combination therapy than those given adjusted-dose warfarin (7.9% per year vs. 1.9% per year; p<0.0001). Annual rates of disabling stroke and of primary event/vascular death were also significantly higher in the lower intensity group.
Second Copenhagen Atrial Fibrillation, Aspirin & Anticoagulation Study Gullov et al. 1998 Denmark 6 (RCT)	677 patients with atrial fibrillation (mean age= 74) were randomized to received either; 1) warfarin 1.25 mg/day or 2) warfarin 1.25 mg/day and ASA 300 mg/day or 3) ASA 300 mg/day. These were compared with 4) a group receiving adjusted dose warfarin therapy (INR 2.0 – 3.0).	Cumulative primary event rate (stroke or systemic embolic event) after one year was 5.8% in low-dose warfarin group, 7.2% in the warfarin + ASA group, 3.6% in the ASA group and 2.8% in the group receiving adjusted dose warfarin. Major bleeding events were rare. Though difference between groups was not significant (p=0.67), results favour adjusted dose warfarin over minidose or minidose + aspirin.
Japanese Nonvalvular Atrial Fibrillation-Embolism Prevention	115 patients with non-valvular atrial fibrillation less than 80 years of age with a history of previous ischaemic stroke or TIA were randomly allocated to receive either conventional intensity	Frequency of major haemorrhage was 6.6% per annum in the conventional therapy group compared with 0% in the low intensity group (p=0.01). The mean INR in patients experiencing major haemorrhage

Author, Year Country Pedro Score	Methods	Outcomes
Cooperative Study Group 2000 Japan 5 (RCT)	warfarin therapy (INR 2.2 – 3.5) or low-intensity warfarin therapy (INR 1.5 – 2.1). The trial was stopped following major haemorrhage in 6 patients.	was 2.8 and their mean age was 74 years. The annual rate of stroke was not significantly different between groups (1.1% with conventional therapy vs. 1.7% with low intensity therapy).
Li-Saw-Hee et al. 2000 UK 5 (RCT)	61 patients with non-valvular AF were randomized to one of three treatment groups: warfarin 2mg (n=23), 1 mg warfarin + 300 mg ASA or 2 mg warfarin + 300 mg ASA. Blood samples were taken at 2 weeks and 8 weeks (phase 1). Subsequent to this (phase 2), all patients were offered adjusted-dose warfarin therapy (INR 2.0 – 3.0). An additional blood sample was taken 6 weeks after the start of phase 2. Blood samples were analysed for the normalization of haemostatic markers in individuals with AF.	At baseline, AF patients had significantly elevated levels of fibrinogen (p=0.025), von Willebrand factor (p<0.0001) and fibrin D-dimer (p<0.0001) compared to a group of healthy, age, BP and sex-matched controls. At 2 and 8 weeks (phase 1), there were no significant changes in levels in all three groups, except for an increase in PAI-1 level in the 2mg warfarin+300 mg ASA group (p=0.024). At the end of phase 2 (treatment with adjusted-dose warfarin), there were significant reductions in plasma fibrinogen (p=0.023) and fibrin D-dimer (p=0.0067).

Discussion

A significant amount of research has been conducted to examine the relative efficacy and safety of anticoagulation with warfarin in patients with nonrheumatic atrial fibrillation. The conclusion that adjusted dose warfarin therapy is substantially more effective than ASA in reducing risk of cardioembolic stroke in individuals with atrial fibrillation is well supported in meta-analyses (Segal et al. 2000; Albers et al. 2001; Hart et al. 1999; Perret-Guillaume & Wahl 2004) and in the results of individual clinical trials. Hart et al. (2002) reported that, when compared to a placebo group, the occurrence of all stroke is reduced by approximately 60% with adjusted dose warfarin therapy and by approximately 20% with ASA. It is estimated that anticoagulation of 1000 patients with warfarin rather than treatment with ASA would prevent 48 strokes per year at the cost of 2 major extracranial haemorrhages (Hart et al. 1999). A summary of the effects of anticoagulation with warfarin on stroke prevention is provided in Table 4.

Table 4 Summary of Anticoagulation with adjusted-dose Warfarin in Atrial Fibrillation

Study	INR Range	Reduced Stroke Risk
AFASAK 1	2.8 – 4.2	+
BAATAF	1.5 – 2.7	+
SPAF 1	2.0 – 4.5	+
CAFA	2.0 – 3.0	+ (ns)
VA-Stroke Prevention	1.5 – 2.7	+
EAFT	2.5 – 4.0	+
SPAFII	2.0 – 4.5	+
SPAFIII	2.0 – 3.0	+
Second Copenhagen Study AF	2.0 – 3.0	+
Japanese AF study	2.2 – 3.5 vs. 1.5 – 2.1	+ (both groups)
ns = reduction in stroke risk was non-significant		

Few trials have focussed specifically on secondary prevention in atrial fibrillation. Hart et al. (2004) examined the question of secondary prevention by pooling data from the 2 large clinical trials (SPAF III 1996 & EAFT 1993) whose subject populations had a history of stroke or TIA. In pooling the data from these 2 trials, the annualized rate of stroke events while on ASA therapy was 7% for patients with a previous history of TIA versus 11% for those participants with prior stroke. Anticoagulation therapy reduced the rate of stroke in patients with previous TIA by 56% (p=0.09) and by 63% (p<0.001) in patients with a history of stroke (Hart et al. 2004). A recent Cochrane review (Saxena and Koudstaal, 2004) reported a reduction in the odds of recurrent stroke of approximately two-thirds (OR = 0.36) based on data from the VA study (1992) and EAFT (1993).

Among individuals over the age of 75, in whom AF is most prevalent, oral anticoagulation is effective in reducing mortality and stroke recurrence. A recent prospective case series analysis of 207 individuals with AF and first-ever stroke over the age of 75 demonstrated a reduced risk of mortality (HR=0.47) and stroke recurrence (HR=0.31) after adjusting for known stroke risk factors (Tsivgoulis et al. 2005). A randomized controlled trial examining the use of warfarin for stroke prevention in the elderly is currently underway (BAFTA: Birmingham Atrial Fibrillation Treatment of the Aged Study).

Anti-coagulation therapy is associated with a risk for both major and minor haemorrhagic events. The risk for bleeding is related to a number of factors including intensity of treatment, patient age, and fluctuation of the INR (International Normalized Ratio) (Devuyst & Bogousslavsky 2001; MacWalter & Shirley 2002). The INR must be carefully monitored during warfarin therapy. The most effective range has been identified as between 2.0 and 3.0. INR's below 2.0 have been associated with increasing risk for thromboembolic stroke while INR values of >4.0 are associated with increasing risk for intracerebral haemorrhage (Albers et al. 2001; Khairy & Nattel 2002; Hart & Halperin 2001, Oden et al. 2006). In a recent analysis of 6 clinical trials, Hart & Halperin (2001) reported the rate of intracerebral haemorrhage while on an appropriately adjusted dose to be 0.5% per year. However, the risks of long-term anticoagulation are dependent upon the intensity and duration of therapy as well as the patient's age, compliance and medical condition (Anderson 1987). Contraindications to the use of anticoagulants include GI bleed, active peptic ulcer disorders,

Table 5 Contraindications to Anticoagulant Therapy

Absolute Contraindications
- Subarachnoid or cerebral haemorrhage
- Malignant hypertension
- Serious active bleeding
- Recent brain, eye and spinal cord surgery
- Lack of patient compliance ie. monitoring the PT, PTT.

Relative Contraindications
- Severe hypertension
- Major recent surgical operation
- Recent major trauma
- Active GI bleeding
- Bacterial endocarditis
- Severe renal failure
- Severe hepatic failure
- Haemorrhagic diathesis

frequent falls, alcohol misuse and a history of intracranial hemorrhage (Table 5).

In an attempt to determine the best therapeutic levels with minimum risk, minidose and low-dose warfarin therapies have been assessed. A recent meta-analysis concluded that while mini or low dose warfarin therapy tended to reduce major bleeding events when compared to adjusted dose therapy, it was significantly less effective in reducing the risk of thrombosis (OR for adjusted-dose versus low or minidose therapy = 0.50) (Perret-Guillaume & Wahl 2004).

In general, it is recommended that oral anticoagulation begin between 1 and 2 weeks following a stroke event (Saxena and Koudstaal 2004). However, Hart et al. (2002) suggest that ASA followed by early initiation of adjusted dose warfarin therapy for secondary prevention is reasonable for AF patients following a primary stroke event. The authors suggest that anticoagulation could be undertaken as soon as the patient is both medically & neurologically stable. Prior to initiation, it is recommended that a repeat CT scan be undertaken "*if there is clinical worsening, the infarct is large or in the presence of undue headache*" (Hart et al. 2002).

The use of combined therapy, most often ASA and warfarin, is not uncommon among patients with atrial fibrillation. A recent study reported that 20% of patients admitted to hospital with atrial fibrillation were discharged on warfarin plus one antiplatelet medication (Shireman et al. 2004). In 89.5% of the cases, the antiplatelet agent used in combination with warfarin was aspirin, given most frequently in association with the presence of coronary heart disease. However, an increased risk for bleeding events associated with combined warfarin-antiplatelet therapy was also demonstrated. Individuals using combined therapy were found to be 1.53 times more likely to experience a bleeding event and had a 3-fold risk of intracranial haemorrhage than individuals using warfarin alone (Shireman et al. 2004).

Conclusions Regarding Warfarin Therapy

Atrial Fibrillation has been associated with an increased risk of cardioembolic stroke. There is strong (Level 1a) evidence that the use of anti-coagulation therapy, particularly with adjusted dose warfarin, substantially reduces the risk of primary and secondary stroke in individuals with atrial fibrillation.

> *Atrial fibrillation increases the risk of cardioembolic stroke; stroke patients with atrial fibrillation are at high risk for recurrent stroke and should receive anti-coagulation therapy.*

Use of Warfarin Therapy

Despite the evidence indicating that treatment with warfarin is clearly associated with a reduced risk of stroke in patients with atrial fibrillation, studies have shown that relatively few patients for whom warfarin therapy is appropriate receive warfarin (Sudlow et al. 1998; Elkind and Sacco, 2004; Blich and Gross 2004, Tapson et al. 2005, Deplanque et al. 2006, Birman-Deych et al. 2006). In a large community sample of individuals ≥65 years of age (n=4843), 4.7% of participants were identified as having atrial fibrillation (Sudlow et al. 1998). Of these, 61% were identified as being suitable for anticoagulation therapy but only 23% actually used anticoagulant medication. A recent study based on review of 3778 medical records (Tapson et al. 2005) reported that only 54.7% of patients with atrial fibrillation and at high risk for stroke received warfarin therapy. More alarmingly, 20.6% of the identified high-risk AF patients received no anti-coagulation therapy despite no obvious contraindications (Tapson et al. 2005). Similarly, Deplanque et al. (2006) reported 58.1% of stroke patients with AF in their study were treated with oral anticoagulants at discharge from hospital although more than 81% were eligible to receive them according to current guidelines. Previous use of oral anticoagulants, being under the age of 75, being married and having a history of angina pectoris were identified as significant predictors of treatment with oral anticoagulants after stroke (Deplanque et al. 2006).

Indredavik et al. (2005) recorded data on 394 patients over the age of 60 with known atrial fibrillation admitted to a stroke unit for acute treatment. Most patients had one or more additional risk factors for stroke and were classified as high-risk patients. At the time of admission, 29% were being treated with warfarin; however, only 16% of these had an INR ≥ 2.0. The proportion of patients treated with warfarin increased to 68% by discharge. Patients receiving no anticoagulation therapy (OR = 2.5), ASA (OR=2.4) or warfarin with an INR less than 2.0 (OR=3.7) were more likely than patients receiving warfarin therapy (INR ≥ 2.0) to experience poor functional outcome at 7 days post stroke. Similarly, optimal anticoagulation was associated with less risk of the combined outcome of death or discharge to a nursing home facility. For the study outcomes of death (alone) or stroke severity, no significant difference was noted between treatment groups (Indredavik et al. 2005).

Potential causes for underutilization of warfarin therapy have been identified as physician concerns with regard to potential bleeding events, unpredictable dose-response, slow onset of action, potential food and drug interactions and the need to closely monitor INR via blood testing (Elkind and Sacco, 2004; Blich and Gross 2004; Donnan et al. 2004). A recent study by Choudhry et al. (2006) examined patterns of prescribing for patients with AF before and after physician exposure to an adverse bleeding event in one of their patients receiving warfarin and to thromboembolic stroke in one of their patients with AF not receiving warfarin. Exposure to a serious bleeding event was associated with significantly

reduced odds of prescribing warfarin in the 90 days following the event (OR = 0.77, 95% CI 0.61 – 098), whereas exposure to stroke did not change the likelihood that the physician would prescribe warfarin (Choudhry et al. 2006).

Patients, however, may be more willing to accept increased levels of risk for bleeding than physicians, if it means a reduced risk of stroke (Devereaux et al. 2001). In an attempt to examine the issue of underutilization, a recent qualitative study examined the effects of warfarin therapy from the perspective of the patient (Dantas et al. 2004). Patients in a family practice clinic who participated in the study were generally satisfied with therapy. A lack of knowledge about the risks and benefits of warfarin therapy was discovered; however, the majority of patients reported no complications and identified only minimal impact on daily life (regular visits to the clinic, restrictions on diet and alcohol intake and anxiety regarding potential adverse effects).

Randomized controlled trials examining the use of decision aids in implementing anti-thrombotic therapy are summarized in Table 6.

Table 6. Patient Decision Aids and Anti-thrombotic Therapy

Author, Year Country Pedro Score	Methods	Outcomes
Man-Song-Hing et al. 1999 International (RCT)	Centres participating in the SPAF III aspirin cohort study were eligible for participation. Patients at high risk were excluded. In addition to usual study end counselling, 280 non high risk patients from 14 centers were randomized to receive the audiobooklet decision aid (n=139) or not (n=148). The decision aid was designed to help patients with the initial post-study decision of appropriate antithrombotic therapy.	More patients in the decision aid group were able to make decisions regarding anti-thrombotic therapy than patients in the usual care group (p=0.02). Most patients in the decision aid group were inclined to take ASA (91%). Following a meeting with their primary care physician, most took the medication for which they expressed a preference. Patients in the decision aid group were more knowledgeable about the use of aspirin (p<0.001) and the use of warfarin (p<0.001). There were no between group differences in patients satisfaction or decisional conflict.
McAlister et al. 2005 Canada 8 (RCT)	446 community dwelling patients with atrial fibrillation seen in 102 primary care practices were randomly allocated to receive either usual care or a self-administered booklet and audiotape decision aid tailored to their own risk profile for stroke. The aid contained information regarding the consequences of stroke or TIA, personalized estimates of stroke risk, recommendations for anti-thrombotic therapy and the potential for benefit and risks associated with warfarin & ASA therapy (based on the patient's personal risk profile). Primary study outcome was change in the	At baseline, 31.5% and 39.5% of patients allocated to the decision aid and to the usual care group were receiving antithrombotic therapy appropriate to their stroke risk according to the American College of Chest Physicians (ACCP) Guidelines. Two weeks following the initiation of the intervention, patients in the decision aid group were better informed and reported less conflict in decision-making. At 3 months, there was a 9% increase in patients receiving appropriate therapy in the decision aid group compared to a 3% decline in number of patients receiving appropriate therapy in the usual care group (12% absolute difference, 34% relative improvement, p=0.03). However, by 12 months, care regressed toward

Author, Year Country Pedro Score	Methods	Outcomes
	proportion of patients taking appropriate antithrombotic therapy at 3 months.	baseline levels in both groups. At 12 months, the strongest predictor of appropriate anti-thrombotic therapy was being on that therapy at baseline.

Discussion

The use of patient decision aids appears, in both studies, to be associated with improved patient knowledge and expectations associated with treatment. In the McAlister et al. (2005) study, patients with non-valvular atrial fibrillation at high risk for stroke were more likely to receive appropriate warfarin-based therapy following the use of a patient decision aid. Unfortunately, this effect was not sustained and rates of appropriate therapy reverted to baseline levels by one year post intervention.

Conclusions Regarding Patient Decision Aids and Use of Warfarin Therapy.

There is strong (Level 1a) evidence that the use of patient decision aids is associated with an increase in patient knowledge. There is moderate (Level 1b) evidence that, among high risk patients with atrial fibrillation, this is associated with a temporary increase in the use of appropriate warfarin-based therapy.

> ***Patient decision aids increase patient knowledge and result in more realistic expectations regarding therapy. While their use is also associated with improved rates of warfarin therapy, this effect is not sustained.***

Treatment Recommendations in Atrial Fibrillation

The magnitude of benefit achieved with warfarin therapy is dependent upon the individual patient's stroke risk (Hart & Halperin 2001). Patients with atrial fibrillation who are at lower risk have fewer cardioembolic strokes than those at a higher risk (e.g. patients who have had a previous stroke or TIA). ASA, which is more effective in the treatment of noncardioembolic stroke than cardioembolic stroke in AF, may be an appropriate treatment for those patients in low risk categories (Devuyst & Bogousslavsky 2001; Hart & Halperin 2001). Warfarin therapy, on the other hand, is approximately twice as effective as aspirin in reducing the risk of cardioembolic stroke among high-risk patients and would, therefore, be a more appropriate choice in secondary prevention (Khairy & Nattel 2002; Hart & Halperin 2001). Therefore, identification of risk is an important component in determining the appropriate prophylactic treatment.

Factors associated with high risk for cardioembolic stroke in AF include prior stroke or TIA, hypertension, poor left ventricular function, age $\geq$ 75, rheumatic mitral valve disease, prosthetic heart valve, diabetes mellitus and recent congestive heart failure (Albers et al. 2001; Snow et al. 2003). Table 7 outlines one risk stratification scheme for use in determining appropriate anti-coagulation treatment. The principles of this stratification framework are similar in nature to the recommendations of the SPAF III Investigators (1998) and the American College of Chest Physicians (Albers et al. 2001a).

Table 7. Risk Stratification with Atrial Fibrillation and Treatment Recommendations (Based on Quality Standards Subcommittee of the American Academy of Neurology, 1998)

Risk	Characteristic	Stroke Risk	Treatment
Low	Less than 65 years old with no risk factors.	1% per year	ASA 325 mg/day
Medium	65-75 years old with no high risk factors or any age with history of hypertension and no high risk factors.	2-3.5% per year	ASA or anticoagulation; consider patient preference and risk of haemorrhage.
High	Previous TIA/stroke/systemic embolism, greater than 75 years of age, diabetes mellitus, hypertensive (systolic blood pressure over 160 mmHg, poor LVF (less than 25% or CHF in the last 3 months), prosthetic heart valve, rheumatic mitral valve disease.	6-8% per year and may be even higher depending on the risk factors.	Anticoagulation aiming for an INR of 2.5 (range 2-3). In elderly patients a target dose of 2.0 may be considered.

The Heart and Stroke Ontario Clinical Guidelines (2003) state that, *"level 1 evidence supports anticoagulation in individuals with atrial fibrillation or previous MI".* In its 2003 clinical guidelines for the management of newly detected atrial fibrillation, the American Academy of Family Physicians and American College of Physicians recommend "patients with atrial fibrillation should receive anticoagulation with adjusted-dose warfarin, unless they are at low risk of stroke or have a specific contraindication to the use of warfarin (thrombocytopenia, recent trauma or surgery, alcoholism)" (Snow et al. 2003). This recommendation is considered to be Level 1a, that is, with clear

Table 8 Treatment Recommendations for New Onset Atrial Fibrillation

- Reversible causes of atrial fibrillation be ruled out. e.g. hyperthyroid, fever, mitral valve disease, pulmonary causes (pneumonia, pulmonary embolus).
- Control heart rate with digoxin and a beta-blocker if necessary.
- If not in sinus rhythm in 48 hours, consider cardioversion after 3 weeks of anticoagulation with INR 2-3 and following echocardiogram to ensure no intracardiac thrombus.
- If unstable, consider immediate cardioversion by chemical (procainamide, quinidine, amiodarone) or electrical means.

evidence to support it and one that should be applied to most AF patients in most circumstances without reservation. Recent guidelines for the secondary prevention of stroke from the AHA/American Stroke Association (Sacco et al. 2006), recommend that patients with ischemic stroke or TIA with AF (either proxysmal or persistent) receive anticoagulation therapy with adjusted dose warfarin (INR 2.0 to 3.0, target 2.5). In addition, for those patients who are unable to take oral anticoagulants, ASA 325 mg/day is recommended. Table 8 presents Best Practice Guidelines for Stroke Care from the Heart and Stroke Foundation of Ontario (2003) for new onset atrial fibrillation.

Other Cardiac Disease

The types of cardiac disease that contribute to the risk of cardioembolic stroke include: valvular heart disease (including endocarditis, mitral valve prolapse and prosthetic heart valves), recent myocardial infarction, intracardiac thrombus, dilated cardiomyopathy, sick sinus syndrome, patent foramen ovale, hypokinetic/akinetic left ventricular segment, and calcification of the mitral valve.

Overall, approximately 20% of strokes are cardioembolic. Acute myocardial infarction is infrequently associated with stroke, occurring in only 0.8% of patients. There is a 1-2% per year risk of ischaemic stroke after myocardial infarction with the risk being greatest in the first month after the MI. Perioperative stroke occurs in 1-7% of patients undergoing cardiac surgical procedures. Risk factors include: previous neurological events, atrial fibrillation, diabetes mellitus, increasing age, aortic atherosclerosis and duration of bypass.

The Aspirin & Coumadin after Acute Coronary Syndromes (ASPECT-2) study examined and compared the effectiveness of ASA and moderate intensity anti-coagulation therapy in preventing the occurrence of ischaemic events following myocardial infarction. Details of the ASPECT-2 study are summarized in Table 9.

Table 9. Details of the ASPECT-2 Trial

Author, Year Country Pedro Score	Methods	Outcomes
ASPECT-2 Research Group 2002 Netherlands 7 (RCT)	999 patients with previous MI were randomly allocated to treatment with low-dose ASA, high intensity anti-coagulation therapy or low-dose ASA in addition to moderate intensity oral anti-coagulation therapy. Maximum follow-up was 26 months.	Treatment with high intensity anti-coagulant therapy (HR=0.55) or combination therapy (HR=0.50) was more effective than ASA alone in reducing the risk of ischaemic events following myocardial infarction. Frequency of minor bleeding was 5% in the ASA group, 8% in the anti-coagulant group and 15% in the combination therapy group. Rate of major bleeding was 1% in each of the ASA and anti-coagulant groups and 2% in the group receiving combination therapy.

Conclusions Regarding Cardiac Abnormalities

A variety of cardiac abnormalities increase the risk of cardioembolic strokes. As demonstrated in the previous discussion of atrial fibrillation, there is strong (Level 1a) evidence that this risk is decreased with anticoagulation therapy, primarily adjusted-dose warfarin. There is additional moderate (Level 1b) evidence to support the effectiveness of anti-coagulant therapy in reducing the risk of stroke subsequent to myocardial infarction.

Cardiac abnormalities increase the risk of cardioembolic strokes; that risk is decreased with anticoagulation.

Anticoagulants for The Prevention of Noncardioembolic Stroke

Anticoagulation therapy has been found to be effective in the primary and secondary prevention of cardioembolic stroke. Anticoagulants have also been assessed, alone and in combination with antiplatelet therapy, for effectiveness in the secondary prevention of noncardioembolic stroke. Details of recent studies assessing anticoagulation in noncardioembolic stroke are summarized in Table 10.

Table 10. Anticoagulants in the Prevention of Noncardioembolic Stroke

Author, Year Country Pedro Score	Methods	Outcomes
SPIRIT Stroke Prevention in Reversible Ischemia Trial Study Group 1997 7 (RCT)	1,316 patients with previous ischaemic stroke of noncardiac origin were randomly allocated to receive either 30 mg ASA daily or dose-adjusted oral anticoagulation (INR = 3.0 – 4.5). Mean follow-up = 14 months.	The primary combined outcome was death from all vascular causes, nonfatal stroke, nonfatal MI or nonfatal bleeding complication. Patients in the anti-coagulant groups were more likely to experience a primary outcome (HR = 2.3) than patients in the ASA group. This could be attributed to the excess of bleeding complications experienced by patients in the anticoagulant condition (53 vs. 6 on ASA therapy). Bleeding incidence increased by a factor of 1.43 for every 0.5 unit increase in INR above 3.0.
WARSS Warfarin-Aspirin Recurrent Study Stroke Group 2001	Patients with prior noncardioembolic stroke were randomized to receive either ASA 325 mg/day (n=1103) or adjusted dose warfarin to INR = 1.4 to 2.8 (n=1103). Follow-up = 2 years.	No significant differences were found between treatment conditions with regard to primary study outcomes (recurrent ischaemic stroke or death from any cause). HR comparing warfarin to ASA = 1.13. Rates of major haemorrhage were 2.22/100 patient years in the warfarin

Author, Year Country Pedro Score	Methods	Outcomes
USA 8 (RCT)		group vs. 1.49/100 patient years in the ASA group.
WASID Trial Chimowitz et al. 2005 USA/Canada 9 (RCT)	569 patients with history of TIA or non-disabling stroke (within 90 days of enrolment) associated with major cranial artery stenosis of 50 – 99% were randomized to receive either warfarin (5 mg daily) or ASA (650 mg twice daily). If side effects developed from high dose ASA, the dosage could be lowered to 325 mg twice daily. Mean follow-up = 1.8 years.	The study was stopped early due to concerns about the safety of patients assigned to the warfarin condition. During the follow-up period, study medication was discontinued in 22.5% of patients – significantly more of these had been allocated to the warfarin treatment (p<0.001). There was no significant difference in the primary endpoint (ischaemic stroke, brain haemorrhage or death from vascular causes other than stroke) between treatment conditions (HR=1.04; ns). There were no differences between groups on any secondary endpoint. There were fewer major cardiac events among patients allocated to the ASA group than in the warfarin group (HR = 0.40, p=0.02) although this was not initially specified as a study endpoint. The rate of death was significantly lower in the ASA group (HR= 0.46, p=0.02) and fewer major haemorrhages were reported in this group (HR=0.39, p=0.01). In the warfarin treatment condition, INR's <2.0 were associated with greater risk of ischaemic stroke (p<0.001) and with major cardiac events (p<0.001). Higher risk of haemorrhage was associated with INRs of >3.0.

Discussion

Ariesen et al. (2004) note that patients who receive anticoagulant therapy following an ischaemic stroke of arterial origin are 19 times more likely to experience an intracerebral haemorrhage (ICH) than patients whose stroke was from a cardiac source. In their recent meta-analysis of data from 9 clinical trials examining the use of ASA therapy, however, they found that ASA treated patients with a history of arterial origin stroke had a 3.7% incidence per year of ICH while ASA treated patients with a history stroke from a cardiac source had a 0.39% risk (Ariesen et al. 2004). The authors propose that cerebral ischemia of arterial origin is not in itself associated with an increased risk of ICH but rather that elevated risk exists only in the presence of high-intensity anti-coagulation therapies (INR 3.0 – 4.5). Certainly, the results of the recent WARSS study suggest that adjusted-dose therapy at a lower intensity (INR 1.4 – 2.8) is as effective as ASA in preventing recurrent stroke events while carrying with it a slightly increased, though non-significant, risk for bleeding events. However, results of the more recently published WASID study demonstrated no benefit associated with warfarin therapy in a population of patients with a history of TIA or stroke attributable to confirmed stenosis of a major intracranial artery. In

addition, treatment with warfarin therapy was associated with a higher rate of adverse events such as death and major haemorrhage (Chimowitz et al. 2005).

Given the increased risk profile and cost associated with warfarin therapy, ASA remains the preferred choice (Diener & Ringleb 2002). An ongoing clinical trial, ESPRIT (European/Australian Stroke Prevention in Reversible Ischaemia Trial) is examining the safety and efficacy of ASA, dipyridamole in addition to ASA and adjusted-dose oral anticoagulants (INR 2.0 – 3.0) in preventing future vascular events in patients with atherosclerotic cerebral ischemia.

Conclusions Regarding Anticoagulant Therapy in Noncardioembolic Stroke

There is conflicting evidence (Level 4) with regard to the use of oral anticoagulant therapy in noncardioembolic stroke. Of three studies, one favoured treatment with ASA over high intensity warfarin therapy (INR 3.0 – 4.5), one favoured treatment with moderate intensity warfarin (INR 1.4 – 2.8) and one found no benefit associated with either ASA or warfarin (INR 2.0 – 3.0).

There is strong evidence (Level 1a) that treatment with oral anticoagulant therapy is associated with higher risk for adverse events. High intensity therapy is associated with significant risk of major bleeding events and intracerebral haemorrhage.

Anti-coagulant therapy with warfarin may be no more effective than ASA in preventing secondary events in patients with a history of noncardioembolic stroke. Given that warfarin is associated with increased risk and cost, ASA remains the preferred treatment choice.

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