

## Anticoagulation for Stroke Prevention

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Anticoagulation therapy has been common practice for a long time, based on the assumption that anticoagulation medication is more effective than anti-aggregation therapy even though it was known to be more dangerous. This trend among most treating physicians was reinforced by the many cases of failure of anti-aggregation therapy. The increasing number of studies with better designs and larger groups led to the knowledge that anticoagulation could be crucial in the treatment of some types of stroke but is unnecessary or even dangerous in others. This review presents the latest data on the efficacy and safety of anticoagulant therapy for various types of stroke. However, it should be borne in mind that in some stroke types the data are still limited and further study is necessary to make decisions regarding treatment.

### Anticoagulants as secondary prevention of non-cardioembolic stroke

The common recommendation by physicians for anticoagulants as secondary prevention in non-cardioembolic stroke was based on the assumption that anticoagulation is more effective than anti-aggregation since the relative risk of aspirin is low, 19% [1]. Thus, it seemed rational to use anticoagulants, especially in cases of aspirin failure. However, the findings of recent well-designed studies have led to the opposite conclusion. The SPIRIT study (Stroke Prevention In Reversible Ischemia Trial) [2,3] was designed as an efficacious study comparing an oral anticoagulant (international normalized ratio 3.0–4.5) with 30 mg aspirin daily. The target patients had transient ischemic attack or minor stroke handicapped with modified Rankin scale  $\leq 3$ . The primary outcome was vascular death, stroke, myocardial infarction, and major bleeding. After enrolling 1316 patients, the study was discontinued for safety reasons. Patients taking anticoagulants demonstrated a significant higher hazard ratio of 2.3 (95% confidence interval 1.6–3.5) for major bleeding compared to the aspirin group. Patients with older age (above 65 years) and radiologic findings of leukoaraiosis constituted the highest risk group. The ESPRIT study (European Stroke Prevention in Reversible Ischemic Trial) [4] comprised a similar target patient group but excluded patients with cardiac stents, leukoaraiosis demonstrated on CT scan or MRI imaging, or known cardioembolic source for stroke. The overall rate of intracerebral bleeding

was 0.31/100 patients per year. The intracerebral bleeding rate among the warfarin group was 1.21/100 patients per year.

The WARSS (Warfarin-Aspirin Recurrent Stroke Study) [5] was a randomized double-control clinical trial that compared warfarin INR 1.2–2.8 to aspirin 325 mg for prevention of secondary stroke with a follow-up of 2 years. The results in 2206 patients with non-embolic stroke showed no statistical difference in recurrent stroke and death (17.8 vs. 16/100 patients per year) and there was a higher rate of minor bleeding among the warfarin group (2.2 vs. 1.5/100 patients per year).

The WASID study (Warfarin Aspirin Symptomatic Intracranial Disease) [6] compared warfarin (INR 2–3) to aspirin 1300 mg daily in patients with transient ischemic attack or minor stroke attributed to intracranial stenosis higher than 50% of major cerebral artery. The study was discontinued for safety reasons because of the very high percentage of myocardial infarction, major bleeding and death in both groups. During 1.8 years of follow-up, adverse events, including death, occurred in 4.4% in the aspirin group and 9.7% in the warfarin group (hazard ratio for aspirin compared to warfarin 0.46, 95% CI 0.23–0.90,  $P = 0.02$ ).

An analysis of all the data by the Cochrane Review [7], which included five trials and 4000 patients, concluded that for an outcome of vascular death and stroke, no difference was found between antiplatelets and warfarin with INR 2.1–3.6. Recurrent stroke risk was equal between groups. The rate of major bleeding among patients on warfarin treatment and INR 3–4.5 was highly significant (RR 9.02, 95% CI 3.9–20).

### Antiphospholipid antibody syndrome

The association between antiphospholipid antibodies and cerebral infarction is clear, especially in young adults [8]. Among patients with APLA, the absolute risk of developing any kind of new thrombosis, including cerebral thrombosis, is lower than 1% in otherwise healthy patients and less than 10% in patients with evidence of venous thrombosis who discontinued anticoagulant treatment within 6 months after the last event [9].

INR = international normalized ratio

CI = confidence interval

RR = relative risk

APLA = antiphospholipid antibodies

The APASS (Antiphospholipid Antibodies and Stroke Study) [10] evaluated 1770 patients within the WARSS clinical trial [5]. There was no increased risk of thrombo-occlusive events associated with baseline APLA levels in patients treated with aspirin or warfarin. No difference between groups for stroke, transient ischemic attack, myocardial infarction, deep vein thrombosis or pulmonary embolism was found (RR 0.99,  $P = 0.94$  for aspirin and RR 0.94,  $P = 0.71$  for warfarin).

In conclusion, aspirin appears to be as effective as warfarin for preventing recurrent strokes in patients post-stroke with positive APLA. This conclusion is based on the results of three prospective trials – two controlled and one uncontrolled. However, these results do not concur with earlier retrospective studies. In order to substantiate the conclusion that aspirin is not less effective for stroke prophylaxis than an anticoagulant, further prospective larger studies are necessary, especially comparing various INR values.

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*The efficacy of anticoagulation to treat non-cardiogenic ischemia stroke is unproven and therefore not recommended*

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### Anticoagulation treatment in thrombophilias

Inherited thrombophilias such as protein C, protein S, or anti-thrombin III deficiency; factor V Leiden; or the prothrombin G20210A mutation rarely contribute to adult stroke but may play a larger role in pediatric stroke [11]. FVL, a mutation causing activated protein C resistance, and the G20210A polymorphism in the prothrombin gene have similarly been linked to venous thrombosis, but their role in ischemic stroke specially in an older population with vascular risk factors remains controversial. [12,13].

The recommendation for anticoagulant treatment in stroke patients with thrombophilia is based upon the extrapolation of a large amount of data on thrombophilia and vein thromboembolism in general. Whereas the guidelines of anticoagulation treatment after stroke with evidence of cerebral vein thrombosis is clear and advised [14], the recommendation of unproven cerebral venous involvement is uncertain [15].

### Anticoagulants as secondary prevention of cardioembolic stroke

#### Non-valvular atrial fibrillation

The prevalence of atrial fibrillation rises rapidly after age 60 years to reach nearly 10% in persons aged 80 years and older. AF increases the risk of stroke four- to sixfold across all age groups. The risk for recurrent stroke due to atrial fibrillation has been reported as 12% per year and approximately 5% within 2 weeks of onset of an AF-associated ischemic stroke [16]. The

details of many randomized clinical trials comparing oral anti-coagulants with placebo and aspirin/triflusal (non-aspirin salicylate) in varying doses for primary or secondary stroke prevention were recently reviewed [17,18]. The intention-to-treat analysis of pooled data from the primary prevention trials revealed an annual stroke rate of 4.5% in the control group and 1.4% in the adjusted-dose warfarin group, for a relative risk reduction of 68% (95% CI 50–79%). The effect was more significant in women (RRR = 84%, 95% CI 55–95%) than men (RRR = 60%, 95% CI 35–76%). In addition, anticoagulant therapy was associated with a 33% RRR (95% CI 9–51%) in all-cause mortality and a 48% RRR (95% CI 34–90%) in the composite outcome of stroke, systemic embolism, and death. Aspirin therapy was associated with an RRR of 21% (95% CI 0–38%) and appears to be more effective in preventing non-cardioembolic than cardioembolic strokes. Among patients who received aspirin in the SPAF trials (Stroke Prevention in Atrial Fibrillation) [19], the risk of stroke was similar in patients with persistent and paroxysmal AF [20]. In a pooled analysis, the annual rate of major hemorrhage was 1.0% in control patients and 1.3% in warfarin-treated patients, while the annual rate of intracranial hemorrhage was 0.1% in control patients and 0.3% in warfarin-treated patients. The risk of intracranial hemorrhage seems highest in patients 75 years and older. In a meta-analysis [21] of trials comparing aspirin with oral anticoagulants in patients with chronic or paroxysmal AF, patients receiving oral anticoagulants were less likely to experience any stroke (hazard ratio 0.55, 95% CI 0.43–0.71), ischemic stroke (HR 0.48, 95% CI 0.37–0.63), or cardiovascular events (HR 0.71, 95% CI 0.59–0.85). The Atrial Fibrillation Follow-up Investigation of Rhythm Management trial (AFFIRM) [22] showed that there was no difference in mortality between the rate- and rhythm-management groups. The use of warfarin reduced stroke risk regardless of assigned treatment strategy. In the secondary prevention trial, EAFT (European Atrial Fibrillation Trial) [23], the annual stroke rate was 12% in the aspirin group and 4% in the warfarin group (INR 2.5–3.9). A subsequent analysis of the EAFT data suggested that the optimal level of anticoagulation to maximize stroke risk reduction and minimize hemorrhagic complications was an INR of 2–3.9. Despite this wide range of INR the total rate of major bleeding complications was 2.8 per 100 patient-years.

Secondary analyses of the clinical trials indicated that there are risk factors for stroke prediction in patients with non-valvular AF. These factors include increasing age, hypertension, moderate-to-severe reduced left ventricular function, congestive heart failure, diabetes mellitus, previous stroke, transient ischemic attack, or systemic embolism. Risk scores for predicting stroke have been developed and may be used to guide the choice of antithrombotic therapy in patients with atrial fibrillation [24].

These studies showed that anticoagulation that results in an INR of 2–3 significantly reduced stroke risk in AF-related stroke and can be used safely. It was also demonstrated that those patients younger than 65 who have no stroke risk factors or

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RRR = relative risk reduction

HR = hazard ratio

those with only AF have a low stroke risk, and aspirin therapy seems to be adequate [25].

### Patent foramen ovale with or without atrial septal aneurysm

Patent foramen ovale was described by Botallo in 1564. PFO is a persistent, usually flap-like opening between two overlapping embryologic structures – the atrial septum primum, which allows a potential shunt between the right and left atria of the heart [26]. This finding is highly prevalent incidentally, from 17% to 27% in autopsy series and 25.6% in transesophageal echocardiography studies [27]. An atrial septal aneurysm refers to the presence of redundant atrial septal tissue in the region of the fossa ovalis, resulting in excessive septal wall motion during respiration. It is usually defined as > 10–15 mm excursion. One meta-analysis of case-control studies of patients younger than 55 with stroke showed increased findings of a PFO (odds ratio 3.1, 95% CI 2.3–4.2) or an ASA (OR 6.1, 95% CI 2.5–15.2) [28]. Potential mechanisms of stroke in PFO include paradoxical embolism, *in situ* thrombus formation at the site of the PFO or associated ASA, and atrial arrhythmias [29]. A prospective study of young patients, less than 55 years old, with cryptogenic stroke treated with 300 mg aspirin for secondary prevention reported a recurrent event rate of 5.6% for a PFO versus 19.2% with PFO and ASA, versus 6.2% for those with no septal defect versus 0% for ASA alone [30]. From this observational study, it would appear that among young patients with prior stroke and both PFO and ASA, aspirin alone is not an effective preventive treatment.

agulant therapy. If there is evidence for paradoxical embolization with concomitant deep vein thrombosis or presence of hypercoagulable genetic variables, the use of long-term anticoagulation appears appropriate [29]. Clinical trials comparing either surgical or percutaneous closure of PFO with medical management are currently underway.

### Acute myocardial infarction

In the thrombolytic era, stroke occurs at a rate of 1–2% per year in survivors of acute myocardial infarction, particularly in the first 3 months – with the greatest risk being the first week. The distribution of stroke subtypes now also includes various forms of intracranial hemorrhage. Mortality ranges from 17% to 57% for ischemic stroke and up to 60% for intracranial hemorrhage. Risk factors for ischemic stroke after acute myocardial infarction include older age, anterior or apical infarction, atrial arrhythmias (such as AF), thrombus mobility, thrombus protrusion, proximity of thrombus to a hypokinetic segment, cardiac pump failure, history of previous myocardial infarction and history of previous stroke [29,32]. Anticoagulation for 6 months leads to endothelialization and attachment of the thrombus to the ventricular wall, with a 60% lower incidence of embolization. Chronic thrombi, more than 6 months old, have less emboligenic potential, although anticoagulation should be considered if the thrombus is protruding or mobile [33].

### Cardiomyopathy and reduced ejection fraction

Cardiomyopathy is the second most common cause of cardioembolic stroke [29], with a threefold increase in relative risk. Ventricular thrombus formation occurs in 30–50% of patients with dilated cardiomyopathy, and the annual risk of systemic embolism is 3–4%. Reduced ejection fraction is inversely related to stroke occurrence [34].

In the absence of completed prospective clinical trials assessing the roles of antithrombotic agents in preventing stroke associated with reduced ejection fraction, long-term anticoagulation (INR 2.0–3.0) is recommended for ischemic stroke patients with ejection fraction less than 35%, irrespective of cause. The ongoing WARCEF trial (Warfarin Aspirin Reduced Cardiac Ejection Fraction) will determine whether adjusted warfarin (INR 2.0–3.0) is superior to aspirin 325 mg for stroke prevention in this setting.

### Valvular heart disease: native and prosthetic

Cerebral embolism is an important complication of valvular heart disease [35,36]. For rheumatic mitral valvular disease, the incidence of emboli ranges from 1.5% to 4.7% per year and is increased in older patients or in those with lower cardiac indices, in the presence of left atrial clot, and in cases with significant aortic regurgitation. AF increases the risk by approximately sevenfold. Mitral stenosis is associated with recurrent emboli that occur in 30–65% of cases. Maintenance of normal sinus rhythm with an enlarged left atrium and mitral valvuloplasty do not appear to reduce the risk of thromboembolism. Observational studies reported a reduction in annual stroke risk from 10% to 3% with oral anticoagulation therapy.

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## *Anticoagulants are highly recommended for treatment of cardioembolic stroke as well as for cerebral vein thrombosis*

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The PFO Cryptogenic Stroke Study (PICSS) [31] evaluated TEE findings in 630 enrolled patients to the WARSS clinical trial [5]. PFO was found in 39% of patients with cryptogenic stroke versus 30% with a known cause ( $P < 0.02$ ). This confirms earlier studies that showed PFO to be an independent risk factor for ischemic stroke. Large PFOs were much more common in patients with cryptogenic stroke (20% versus 9.7%,  $P < 0.001$ ). When the groups with or without PFO were analyzed in relation to the efficiency of aspirin or warfarin, no significant differences were found in stroke recurrence or death. However, minor bleeding rates were higher in warfarin-treated patients (22.9/100 versus 8.66/100 patient-years, rate ratio = 2.64,  $P < 0.001$ ) [27,31]. Although the management of patients with PFO and stroke remains uncertain, the currently accepted medical treatment options include antiplatelet or antico-

PFO = patent foramen ovale

ASA = atrial septal aneurysm

TEE = transesophageal echocardiography

Mitral annular calcification is associated with a 2.1-fold increase in stroke risk and can be associated with atrial fibrillation at a 12-fold increase. In the absence of associated mitral valve disease or AF, systemic embolism in patients with aortic valve disease is uncommon [35].

Thromboembolic complications of the various types of prosthetic valves are common and were recently reviewed [35,36]. The rate of embolism in patients with mechanical prosthetic valves is estimated to be 2–4% per year, even with proper anticoagulant therapy. In patients who experience additional thromboembolic events despite adequate anticoagulation, TEE should be performed to seek for atrial, ventricular, or valve thrombi and infective vegetations. Some studies showed that a combination treatment of warfarin and aspirin reduced the risk of thromboembolism, but this combined treatment increased the risk of major hemorrhage from 1.3% to 24.7% [35]. An exact control of INR is necessary to avoid hemorrhage.

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*The benefit of anticoagulation management in stroke patients with patent foramen ovale is not yet established*

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### Aortic arch atheroma

Complex atherosclerotic aortic plaques are an independent risk factor for incidental and recurrent ischemic stroke. Plaques > 4–5 mm in thickness, ulcerated plaques, and those with mobile components on TEE are more likely to be associated with stroke [37,38]. Studies have shown an annual stroke risk of 11.9–33% with plaques > 4–5 mm, 3.5–7% with plaques < 4–5 mm, and 2.8% with no significant aortic plaque. Two retrospective and non-randomized studies [39,40] have suggested a benefit of oral anticoagulants over aspirin in patients with mobile thrombi in the aortic arch, but this benefit was possibly outweighed by hemorrhagic complications.

### Conclusions

There is a large body of literature addressing medical therapy for stroke prevention. Several large trials have recently provided evidence to support specific preventive strategies. In the absence of contraindications, anticoagulation in stroke prevention should be planned for those at high risk for cardioembolic stroke.

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