Antithrombotic Agents in Cerebral Ischaemia
PM Dalal*, NK Mishra**, Madhumita Bhattacharjee**, Priya Bhat**

Abstract
The current evidence suggests that aspirin is treatment of choice when compared to anticoagulants for patients with non-cardioembolic stroke. The usefulness of combination therapy (aspirin vs. with or without warfarin) is still debated. Likewise the combination of Aspirin with clopidogrel has no added advantage (MATCH Trial). However anticoagulant therapy significantly benefits high-risk patients with atrial fibrillation in the elderly subjects whereas aspirin may still be the drug of choice in stroke prevention in low risk group in the younger age. There is dire need for well planned randomized double blind controlled studies to define the role of Antithrombotic agents in “cryptogenic stroke” (PFO/ASD related) antiphospholipid antibody syndrome, arterial dissections and intraluminal clot syndromes. Evaluation and treatment of associated risk factors in all categories needs greater emphasis. ©

Ischaemic Stroke Subtypes
- Atherothrombotic (Large artery disease)
- Lacunar State / Infarcts (Small Vessel Disease)
- Cardioembolism and Other Determined Etiology
  Hypercoaguable states; Hyperhomocysteinemia, Protein C or S deficiency, Vasculitis, Arterial dissections, etc.
- Undetermined Etiology
  Cryptogenic Strokes [e.g. in Patent Foramen Ovale (PFO), Atrial Septal Defect (ASD) etc.]
- Multiple Possible Etiologies

Recurrent Stroke
After an acute event, recurrence is another major problem. For example, in NINDS Stroke data bank, stroke due to large artery atherosclerosis revealed greater risk

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of worsening (30%) and recurrence (7.9%). In North American Symptomatic Carotid Endarterectomy Trial, patients with transient ischaemic attack or stroke and ipsilateral carotid stenosis (> 70%) who were treated medically had 26% risk of recurrence at two years. In Northern Manhattan Stroke Study, 30 days risk of recurrence was 8% for patients with extracranial atherosclerosis and 7.1% for those with intracranial atherosclerosis. Such risk being six times higher than in those with nonatherosclerotic etiology. It has been suggested that propagation or progression of thrombus or distal embolism may be responsible for worsening or recurrence of ischaemic events. Here, antithrombotic drugs have been advocated as a rational approach.

Likewise, Stroke in evolution or “progressive stroke” has been considered an indication for anticoagulation treatment. Studies reported in 1960’s suggested that IV heparin therapy may be beneficial for patients with unstable ischaemic stroke with almost 50% reduction in chance of further worsening. However, most of these studies were not randomized or blinded and had poorly defined inclusion / exclusion criteria and use of standardized protocols for outcome measures were not used. Furthermore, recurrent cerebral embolism, pale infarct turning into hemorrhagic one, increase in focal or global edema, bleeding within neoplasm or expanding subdural hematoma can all mimic progressive stroke. Therefore, CT confirmation of diagnosis is mandatory.

For cardioembolic strokes, earlier studies indicated a recurrence risk - of 1% per day in the first 14 days. Here, the underlying mechanism for recurrence is often attributed to dislodgement of another thrombus from an underlying cardiac lesion like myocardial infarction, valvular rheumatic heart disease or prosthetic valve etc. For prevention of recurrence, antithrombotic therapy is routinely prescribed.

Lacunar infarcts caused by small artery disease (e.g. lipohyalinosis, etc.) have low risk of recurrence and better chance of survival but may result in significant functional morbidity.

**Therapeutic Considerations**

The goal of therapy is to avoid development of brain ischaemia / infarction and, if already present, to prevent its progression or recurrence. The treatment of acute ischaemic stroke is divided into three phases: (I) Saving life and medical management; (II) Measures to prevent recurrence of stroke and (III) Rehabilitation to achieve physical, occupational and social adaptation for gainful employment.

**Antithrombotic Agents**

Platelet Antiaggregants:

Aspirin (Acetyl salicylic acid) prevents platelet adhesion/aggregation by blocking production of platelet derived thromboxane A2 and suppresses the release of prostacyclin from vascular endothelium. It is widely used in secondary prevention of strokes. In treatment of TIA/RIND and in secondary prevention of strokes, the optimal dose is still debated but results based on recent studies indicate that low dose therapy (100 mg/day or less) may be as effective as high dose (325 mg/day or more). In a combined analysis, of 40,000 randomised patients with acute stroke showed a significant reduction of 7 per 1000 in recurrent ischaemic events (1.6% for aspirin against 2.3% for controls, 2P < 0.000001); and haemorrhagic transformation of original infarct occurred in 1% of treated versus 0.8% in placebo group (2P = 0.07). The reviewers concluded: “early aspirin is of benefit for a wide range of patients, and its prompt use should be routinely considered for all patients with suspected acute ischaemic stroke, mainly to reduce the risk of early recurrence”. They also noted that among 9000 patients (22%) who were randomized without prior CT scan, aspirin appeared to show net benefit “with no unusual excess of haemorrhagic stroke; moreover, even among the 800 (2%) who had inadvertently been randomized after a haemorrhagic stroke, there was no evidence of net hazard (further stroke or death: 62 in aspirin group versus 67 in control”).

Other antiplatelet drugs like sulfinpyrazone or dipyridamole used alone do not offer any specific advantage. In the ESPS-II (European Stroke Prevention Study-II) study it was suggested that combination of aspirin (50 mg) with extended release dipyridamole (200mg bd) had additive benefit due to putative synergistic activity in reduction of recurrent strokes and vascular events.

**Thienopyridine Derivatives** (Ticlopidine, Clopidogrel etc.), inhibit platelet aggregation induced by adenosine diphosphate (ADP), collagen, arachidonic acid, thrombin and platelet aggregating factors (PAF). It also reduces plasma fibrinogen and increases red cell deformability. However, the drug is expensive and relatively toxic (i.e. reversible neutropenia and diarrhea are some of the side-effects); hence, routine hematological check up is necessary. In four randomized trials of 22,656 patients having TIA/ischemic stroke, thienopyridines reduced the odds ratio (OR) for vascular event by 9% (OR 0.91; CI 0.84 - 0.98; 2P = 0.01) preventing 11 events per 1000 patients treated for two years.

In a recent study on Management of Atheroembolic stroke with Clopidogrel in High-risk patients (MATCH), 7599 patients having ischaemic strokes or TIA received Clopidogrel (75 mg) alone or Clopidogrel (75 mg) plus Aspirin (75 mg). Here, no significant difference was reported in primary end point outcomes (i.e. ischaemic stroke, myocardial infarction, vascular death, or rehospitalisation for acute ischaemia) thereby showing no real benefit in the use of such a combination. However, result of other studies are awaited.
**Anticoagulant Drugs**

**HEPARIN** was discovered in 1916 by medical student Mc Leod. It is a nonuniform mixture of straight chain mucopolysaccharides (MW 10,000 to 20,000), comprising D-glucosamine D-glucuronic Acid and D-glucosamine L-iduronic Acid. It acts by activating Antithrombin III (ATIII) (a serine protease inhibitor) and other similar cofactors. The Heparin-ATIII complex then inactivates the clotting factors such as Xa, IIa, IXa, Xla, XIIa and XIIIa. At low concentrations, it selectively inhibits factor X and thereby prolongs Activated Partial Thromboplastin Time (aPTT) without much effect on Prothrombin Time (PT).24

**Monitoring**: During the stage of heparinisation, thromboplastin time (aPTT) is kept at 2.0 times the control value. In absence of automatic infusion pump, an IV bolus of 100 units per kg body weight followed by continuous infusion (1000 units per hour for 24 hours), under constant aPTT control, preferably in an acute care unit, is often practiced. If subject worsens under anticoagulant therapy diagnostic reevaluation should be done and a second CT or MRI scanning may have to be carried out to ascertain the accuracy of diagnosis and cause of worsening. *Heparin induced thrombocytopenia* is not an uncommon cause of bleeding and platelet counts at frequent intervals are mandatory. Active bleeding ulcers, haemorrhagic diathesis, malignant hypertension, hepatic failure, drug allergy and patient’s poor compliance are considered major contraindications to anticoagulant therapy.

**Low Molecular Weight Heparin (LMWH)**: Heparin (MW 10,000 to 20,000) through the process of fractionation is converted to LMWH (MW 3000 to 7000 Daltons). Though no two LMWH are alike, it is claimed to have better bioavailability (90%) with longer and consistent mono-exponential half life. It induces conformational changes in AT III and inactivates Factor Xa without significant interaction with factor IIa. Thrombocytopenia is not rare and periodic platelet counts are advisable.24

**Warfarin**, a hydroxycoumarin derivative, acts as a competitive antagonist of vitamin K and inhibits the carboxylation of factor II, VII, IX and X. Therapeutic effect occurs when inhibition of clotting factor is achieved by 40 to 50 percent. Its activity is monitored by estimating Prothrombin Time (PT) and by maintaining International Normalised Ratio (INR) between 1.4 to 2.8 range with a view to prevent bleeding complications.

**Anticoagulation Therapy**

Anticoagulation is controlled therapeutic inhibition of blood coagulation factors by specific drugs (e.g. heparin, heparin analogues and warfarin group of drugs). They are administered on theoretical grounds that it halts formation or extension of a thrombus, maintains collateral flow, and thereby possibly prevents recurrent stroke. Parenteral heparin and long-term oral anticoagulants have been extensively tried in acute ischaemic strokes. Though such treatment can prevent extension of thrombus, its value in completed stroke is doubtful and its use is often fraught with dangers. On the other hand, in recurrent TIAs, thrombosis in-evolution, cardio-embolic strokes in acute coronary syndrome and in those with valvular or nonvalvular atrial fibrillation, in subjects not responding to platelet antiagregant, and in pulmonary embolism, the judicious use of anticoagulants is considered beneficial.

However possible hemorrhagic complications despite monitoring of International Normalised Ratio (INR) continues to pose a problem about its safety. To minimise the risk of hemorrhagic complications ischaemic infarction should be confirmed by CT or MRI scan and possibly by CSF test and not based on clinical acumen alone!

Table 1 shows comparative evaluation of Heparin/LMWH/Aspirin treatment in prevention of recurrent strokes in various clinical trials.

In Stroke Prevention with the Oral direct Thrombin Inhibitor in atrial Fibrillation (SPORTIF) III Trial, Ximelagatran, an oral direct thrombin inhibitor was compared with warfarin (INR 2 - 3) in a cohort of atrial fibrillation with high risk factors for stroke similar to SPAFIII. There was no significant difference in ischaemic stroke outcomes, RRR for Ximelagatran was 14% and P 0.0065. US-FDA approval has been with held on account of hepatic dysfunction.

The author summarised that “though these trials have inherent limitations, they demonstrate that emergent use of an anticoagulant is associated with modest but significant risk of hemorrhagic transformation of the ischaemic stroke or serious non-neurological bleeding.

These trials do not demonstrate benefit from emergent anticoagulation in improving outcome, reducing mortality, and preventing early recurrent stroke. These results suggest that most patients with acute stroke should not be treated with unfractionated heparin or other rapidly acting anticoagulants after stroke. Prevention of deep vein thrombosis and pulmonary embolism among bedridden patients is the only established indication for early anticoagulation after acute ischaemic stroke”.26
Similarly International Stroke Trial (IST)\textsuperscript{15}, examined the value of heparin versus aspirin in ICVD. Here, 19,435 patients within 48 hours of acute ischaemic stroke received 14-day treatment with 5000 units (U) heparin twice daily, or 12500 U heparin twice daily and NO heparin, and each of these three groups received NO aspirin or 30 mg of aspirin per day. In the final analysis of death or non-fatal recurrent stroke, there was no added advantage in the group who received heparin treatment.\textsuperscript{15}

It should be noted that IST was not a blinded study and nearly in one-third patients CT Scanning to exclude hemorrhage was not done.\textsuperscript{28} To minimize the risk of hemorrhagic complications, it is mandatory that the ischaemic infarction is confirmed by investigations like CT scan. The value of Diffusion Weighted Imaging (DWI) and Magnetic Resonance Angiography (MRA) in acute ischaemic stroke substantially improves the accuracy of diagnosis of stroke subtypes.

Likewise, Gubitz G et al\textsuperscript{33} in a COCHRANE review (2004) based on six trials (21,966 patients) in acute ischaemic stroke noted that “there was no evidence that anticoagulants reduced the odds of being dead or dependent at the end of follow-up (OR = 0.99; 95% CI 0.93 to 1.04). Although anticoagulant therapy was associated with about 9 fewer recurrent ischaemic strokes per 1000 patients treated (OR = 0.76; 95% CI 0.65 to 0.88), it was also associated with a similar sized 9 per 1000 increase in symptomatic intracranial haemorrhages (OR = 2.52; 95% CI 1.92 to 3.30). Similarly, anticoagulants avoided about 4 pulmonary emboli per 1000 (OR = 0.60, 95% CI 0.44 to 0.81), but this benefit was offset by an extra 9 major extracranial haemorrhages per 1000 (OR = 2.99; 95% CI 2.24 to 3.99). Sensitivity analyses did not identify a particular type of anticoagulant regimen or patient characteristic associated with net benefit.”\textsuperscript{33}

From above studies, it is evident that there is no strong evidence to support anticoagulant therapy in acute ICVD in prevention of recurrent stroke nor improvement in worsening or outcome status or reduction in mortality. Bleeding complication in ischaemic infarct remains a serious concern.

**ANTICOAGULATION IN STROKE PREVENTION: CARDIOEMBOLIC STROKES**

Cardioembolic strokes are common in subjects having non valvular atrial fibrillation, post acute coronary syndrome (e.g. mural thrombi, ruptured chordae tendineae, ventricular aneurysm, etc.), valvular rheumatic heart disease, cardiomyopathy, septal defects and patent foramen ovale (PFO). In atrial fibrillation, the stroke recurrence risk is as high as 12 percent per year.\textsuperscript{34} Though aspirin, anticoagulation or both are essential drugs the question remains as to which drug is superior in stroke prevention. Clinical trials are summarised in Table 2.

**Table 1: Antithrombotic therapy – comparative evaluation in acute cerebral ischaemia**

<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>Antithrombotic Agents</th>
<th>Sample Size</th>
<th>Recurrent Strokes</th>
<th>Side Effects - Intracerebral Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of patients (N)</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>FISS\textsuperscript{27}</td>
<td>HD nadroparin</td>
<td>102</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4100 U bd x 10 day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LD nadroparin</td>
<td>101</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>(4100 U bd x 10 day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>105</td>
<td>5</td>
<td>4.7</td>
</tr>
<tr>
<td>IST\textsuperscript{15}</td>
<td>HD Heparin</td>
<td>2426</td>
<td>86</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>12500 U bd x 14 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LD Heparin</td>
<td>2429</td>
<td>78</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>5000 IU bd x 14 Days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>4859</td>
<td>214</td>
<td>2.2</td>
</tr>
<tr>
<td>TOAST\textsuperscript{29}</td>
<td>Danaparoid (Dose adjusted by antifactor Xa activity)</td>
<td>638</td>
<td>7</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>628</td>
<td>7</td>
<td>1.1</td>
</tr>
<tr>
<td>HAEST\textsuperscript{30}</td>
<td>Dalteparin (100 U/kg bd)</td>
<td>224</td>
<td>19</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>Aspirin (160 mg od)</td>
<td>225</td>
<td>17</td>
<td>7.5</td>
</tr>
<tr>
<td>TOPAS\textsuperscript{31}</td>
<td>Certoparin 3000 OD</td>
<td>99</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Certoparin 3000 BD</td>
<td>102</td>
<td>3</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>Certoparin 5000 BD</td>
<td>103</td>
<td>4</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>Certoparin 8000 BD</td>
<td>100</td>
<td>3</td>
<td>3.0</td>
</tr>
<tr>
<td>TAIST\textsuperscript{32}</td>
<td>HD Tinzaparin</td>
<td>486</td>
<td>16</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>175 anti Xa U/kg x 10 d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LD Tinzaparin</td>
<td>507</td>
<td>24</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>10 U anti Xa U/kg x10 d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspirin 300 mg od</td>
<td>491</td>
<td>15</td>
<td>3.1</td>
</tr>
</tbody>
</table>


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of recurrence) risk in patients with atrial fibrillation at INR 2 to 3.9 but at INR greater than 3.0 the chances of bleeding in high-risk group were high. “Choice of antithrombotic therapy depends upon the etiology of stroke. Oral anticoagulation treatment is the preferred choice for inferred cardioembolism in setting of atrial fibrillation, while the varying rates of hemorrhage with oral anticoagulants continue to favor antiplatelet therapy in other setting of inferred etiology. Combinations of antithrombotic therapy vary in their lowering of stroke rate and some raise the risk of hemorrhage. Insufficient data exist to determine whether antithrombotic therapy combined with antihypertensives, statins or other agents will further reduce the risk of stroke in synergistic or supplemental fashion or give no additional benefit”.

**Anticoagulation in Non-cardioembolic Stroke**

WARSS – a large randomised double blind study, using warfarin (INR 1.4-2.8) versus aspirin (325 mg), was planned to compare prevention of recurrence in non-cardioembolic strokes between the two groups. They enrolled 2206 patients with 59% were males over 60 years of age. Over a two year period, the combined death and/or recurrent stroke rate was 16.9%. In this study, in the two treatment arms there was no statistically significant difference in the rate of recurrent stroke but the warfarin group had significantly more minor hemorrhages. It was suggested that warfarin can be used as a “Fall Back therapy” in the event of aspirin failure.

In the WASID (Warfarin Aspirin Symptomatic Intracranial Disease Study) patients with angiographically proven intracranial large artery disease were analysed retrospectively. In this subgroup analysis, recurrent stroke rate for patients on aspirin for stroke prevention was 10.4/100 patient-years whereas patients on warfarin had stroke rate of 3.6/100 patient-years suggesting the superiority of warfarin arm.

In a subsequent prospective randomised trial similar to WARSS with higher INR (2.3) for warfarin as well as higher dose (1300mg) for the aspirin group, the final analysis showed no difference in stroke or vascular death rate between the two groups. “In the aspirin arm, there was a decreased death rate (RR 0.46, CI 0.24-1.79) and a non significant increase in stroke (RR 1.23, CI 0.84-1.79).” On account of higher rate of hemorrhage into warfarin group as compared to aspirin arm the study was possibly terminated.

In a COCHRANE review (2004) in 4000 patients having TIA or minor stroke in retrospective analysis found no difference in the outcome of vascular death and stroke, even at different INR intensities, between anticoagulation versus antiplatelet therapy. On the other hand, at high INR (3-4.5) the anticoagulation group had increased risk of bleeding (RR 9.02 CI 3.9-20).

**Concluding Remarks**

The current evidence suggests that aspirin is treatment of choice when compared to anticoagulants for patients with non-cardioembolic stroke. The usefulness of combination therapy (aspirin vs with or without warfarin) is still debated. Likewise the combination of Aspirin with clopidogrel has no added advantage (MATCH Trial). However anticoagulant therapy significantly benefits high risk patients with atrial fibrillation in the elderly subjects whereas aspirin may still be the drug of choice in stroke prevention in low risk group in the younger age. There is dire need for well planned randomized double blind controlled studies to define the role of Antithrombotic agents in “cryptogenic stroke” (PFO/ASD related) antiphospholipid antibody syndrome, arterial dissections and intraluminal clot syndromes. Evaluation and treatment of associated risk-factors in all categories

### Table 2: Anticoagulation in cardioembolic stroke: review of trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Agents</th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>Placebo</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPAF-I</td>
<td>@ INR 2-4.5</td>
<td>RR 67%</td>
<td>RR 42 %</td>
<td>6%</td>
<td>Significant reduction of stroke recurrence in warfarin arm – STUDY STOPPED</td>
</tr>
<tr>
<td>SPAF II</td>
<td>@ INR 2-4.5</td>
<td>325 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPAF III</td>
<td>@ INR 2-3</td>
<td>Aspirin (325 mg) + fixed dose Warfarin INR &lt; 1.5</td>
<td>SR - 2%</td>
<td>SR 8%</td>
<td></td>
</tr>
<tr>
<td>European Atrial Fibrillation Trial</td>
<td>@INR 2.5-3.9</td>
<td>SR - 4%</td>
<td></td>
<td>SR – 12%</td>
<td>Optimal level of anticoagulation to maximize stroke risk reduction and minimize haemorrhagic complications is INR 2-3.9</td>
</tr>
</tbody>
</table>

RR – Risk Reduction; SR – Stroke Risk; INR – International Normalized Ratio
needs greater emphasis.40

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