Thrombosis prophylaxis in patients with ischaemic (cardioembolic) stroke

How long is long enough?

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Keywords
Ischaemic stroke

Summary
Cardioembolism accounts for approximately 20% of ischaemic strokes, and is associated with high mortality and propensity to recurrences. Approximately, 30% of ischaemic strokes remain cryptogenic despite improved imaging modalities and technological improvements to identify their cause. Of the long list of various cardiac conditions associated with an increased risk of cardioembolic strokes, non-valvular atrial fibrillation is the most common feature. Unsurprisingly, the stroke risk associated with these conditions is highly variable and non-homogenous, with many risk factors additive to the overall risk profile. Treatment with vitamin K-antagonists substantially reduces the risk of bleeding encountered with such therapy. Apart from atrial fibrillation, there is relatively limited evidence for the role of antithrombotic therapy for other cardiac conditions associated with cardioembolism and how long one should treat.

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Approximately 20% of strokes are ischaemic strokes due to a cardioembolic embolus (52). Strokes related to cardioembolism (22, 36) are

- sudden onset,
- maximal neurological deficit at presentation (8), with rapid recovery of symptoms (47), but often there is
- decreased consciousness (59),
- involvement of multiple territories (9),
- increased tendency to haemorrhagic transformation (33).

The diagnosis of cardioembolism is presumptive in many occasions given the absence of vascular pathology and the presence of cardiac co-morbid conditions during the initial presentation with ischaemic stroke, such as atrial fibrillation, rheumatic valve disease, or prosthetic valves or left ventricular (LV) thrombus (35). The stroke risk and recurrence embolic events associated with cardiac conditions are highly variable and Table 1 summarises the causes of cardioembolic strokes and their associated risk of cerebral embolism (3). The moderate risk category in Table 1 is a synthesis of the available data (4, 37, 45).

Of the possible causes of cardiogenic embolism, non-valvular atrial fibrillation (AF) is the commonest condition associated with increased risk of cardioembolic stroke. Nevertheless, other conditions like mitral stenosis, prosthetic valves, endocarditis, left ventricular mural thrombus, recent myocardial infarction, atrial myxoma and cardiomyopathies were also associated with a higher risk of stroke and thromboembolism. With the recent advances in the cardiac imaging modalities (for example, contrast and transoesophageal echocardiography, cardiac magnetic resonance imaging) there is improved detection of various cardiac sources of embolism.

Nonvalvular AF is the most common condition associated with increased risk of stroke and approximately half of all cardioembolic strokes are related to AF. The prevalence of AF increases with advancing age and the presence of this arrhythmia – which is the commonest sustained cardiac rhythm disorder – carries a substantial mortality and morbidity (12, 34).

There is a five-fold increased risk of stroke and thromboembolism with AF when compared to sinus rhythm (23) and the risk exponentially increases to eighteen-fold when AF is associated with mitral stenosis. The risk of stroke is also higher with advancing age, for example, patients aged <50 years has a stroke risk of 1.5% compared to a risk of 23.5% in subjects aged between 80–89 years (66). AF is commonly associated with conditions like hypertension, diabetes, coronary artery disease and heart failure, and these conditions are additive to stroke risk in AF.

The pathophysiology of thromboembolism in AF per se is highly complex and multifactorial. AF confers a prothrombotic or hypercoagulable state with fulfilment of Virchow’s triad of thrombogenesis, with “abnormalities in flow”, “abnormal blood constituents” (coagulation factors and activation of platelets), and “abnormal vessel wall” (that is, structural heart disease and/or endothelial, endocardial and structural changes in the left atrium) (16).
The role of stasis (blood flow abnormalities) is visualised on transoesophageal echocardiography by the presence of spontaneous echo contrast (SEC), and the latter is an independent predictor of stroke (58). Atrial structural abnormalities are also evident in AF, and related to stroke risk. In a study of 1655 older patients, for example, the enlargement of left atrium volume by 30% is associated with a 48% increase in the risk of AF and is predictive of subsequent ischaemic strokes (61). Many studies clearly have shown abnormal blood constituents associated with enhanced haemostasis and platelet activation, which in turn are associated with inflammatory cytokines, growth factors and indices of extracellular matrix turnover (17).

Prevention of stroke in AF

The risk of stroke associated with AF is non-homogenous. The Stroke risk in Atrial Fibrillation Working Group (56) reported that prior stroke or transient ischaemic event, advancing age (>75 years), hypertension and diabetes are independent risk factors for stroke in AF patients but no association found in patients with heart failure, coronary artery disease or female gender. In contrast, the systematic review as part of the United Kingdom National Institute for Health and Clinical Excellence (NICE) management guidelines for AF (30) identified as strong independent predictors of stroke in patients with AF:
- previous stroke or transient ischaemic attack (TIA),
- increased age (>75 years),
- hypertension,
- structural heart disease (left ventricular dysfunction or hypertrophy) and
- previous myocardial infarction (MI) but no association with gender or diabetes.

Anticoagulation is highly effective in both primary and secondary prevention of stroke in patients with AF. A recent meta-analysis of trials clearly demonstrated the superiority of warfarin in reducing the risk of stroke in high-risk patients, against placebo or acetylsalicylic acid, with relative risk reductions of 67% and 21%, respectively (28). Absolute risk reductions (ARR) annually, for primary and secondary prevention with warfarin were 2.7% and 8.4%, respectively – when compared to placebo or no treatment. In comparison, antiplatelet drugs showed ARRs of 0.8% for primary and 2.5% for secondary prevention of strokes in patients with AF, when compared to placebo or no treatment. The superiority with warfarin remained consistent even when compared to dual antiplatelet therapy (acetylsalicylic acid + clopidogrel) in patients with AF (1). Thus, high-risk patients in AF will require long-term anticoagulation with vitamin K-antagonists (target INR range 2–3) to minimise stroke and thromboembolic complications, in the absence of contraindications (38).

Current management guidelines also recommend that even when patients are cardioverted from AF to sinus rhythm anticoagulation should be continued long term, in the presence of stroke risk factors or where there is a risk of AF recurrence (11). Otherwise, given the risks of thromboembolism in the peri-cardioversion period anticoagulation therapy is recommended for a minimum of:
- three weeks pre-cardioversion, and
- four weeks post-cardioversion.

In paroxysmal AF, anticoagulation is recommended where stroke risk factors are present, since the available data suggests that such patients are at similar stroke risk to persistent or permanent AF (40).

Bleeding risk

The benefits of anticoagulation in high-risk patients do not come without risk. Bleeding is the most concerning complication associated with anticoagulation and therefore the selection of appropriate treatment needs to be very carefully assessed, weighing the potential benefits of thromboprophylaxis and risks of bleeding accordingly. There is an increased incidence of stroke with INR (international normalised ratio of < 2.0 and a risk of more bleeding with INR >3.0 (51).

Interestingly, recent guidelines advise a target INR > 3, if a patient with AF sustains a stroke whilst anticoagulated with lower INR (2–3) in AF (26). In a systematic review, patients with previous history of bleeding, ischaemic heart disease and co-administration of antiplatelets or non-steroidal anti-inflammatory drugs (NSAIDS) are prone to a much higher risk of bleeding with anticoagulation; also advocated advancing age, uncontrolled hypertension, cerebrovascular disease, anaemia and female gender to be considered as additional risk factors for bleeding (31).

The annual risk of major bleeding (a haemorrhage requiring ≥2 units of blood or requiring hospitalisation) ranges between 1.1–1.7% and 0.3–0.6% for intracranial haemorrhage, in anticoagulated patients (2, 27, 55). Also, during the early phase of stroke (that is, presentation <14 days), the risk of hemorrhagic stroke, death, intracranial and extracranial bleeding was substantially higher with unfractionated or low molecular weight heparin compared to acetylsalicylic acid alone (13, 49). Early treatment with acetylsalicylic acid in ischaemic stroke patients appears to be safe and effective with fewer deaths (at <14 days and at 6 months), recurrent stroke without excessive haemorrhagic strokes or bleeding complications (35). Whether these observations in “general” stroke populations apply to nonvalvular AF patients has been open to debate, although current guidelines suggest that anticoagulation with...
vitamin K antagonists can be started after 2 weeks in patients with AF presenting with acute stroke, due to the risk of haemorrhagic transformation in the early period.

**Other causes of stroke**

**Acute myocardial infarction, left ventricular thrombus and aneurysm**

The risk of stroke associated with acute myocardial infarction (MI) and left ventricular (LV) mural thrombus can be as high as 15% (63). Nearly half of all patients with LV aneurysm have LV thrombus, and in such patients the extent of MI, severity of LV dysfunction and age are independent predictors of stroke (43). There is a 68% risk reduction for stroke with LV thrombus when anticoagulated and recent recommendations advise anticoagulation for 3 months to minimise the stroke risk in these patients (6).

Anticoagulation trials post-MI has shown contrasting and inconclusive results. In the subgroup of patients in AF post-MI from the Efficacy and Safety of the oral direct Thrombin inhibitor ximelagatran in patients with recent Myocardial damage (ESTEEM) trial, the combination of ximelagatran and acetylsalicylic acid (6.9%) significantly reduce the risk of death, non-fatal MI and stroke compared to acetylsalicylic acid alone (20.6%) over a 6-month follow-up (57). The Coumadin acetylsalicylic acid Reinforcement study (CARS) (19) compared fixed low-dose warfarin (INR 1.3–1.8) to low dose acetylsalicylic acid (80 mg) and found no difference in the non-fatal re-infarction or non-fatal stroke or cardiovascular death (8.6% with acetylsalicylic acid, vs. 8.4% with warfarin) at a median of 14 months). Similar results were seen with the Combination Haemotherapy and Mortality Prevention (CHAMP) (25) trial which compared warfarin (mean INR 1.8) plus acetylsalicylic acid, versus acetylsalicylic acid monotherapy after acute MI, and found no differences in stroke (3.5% with acetylsalicylic acid and 3.1% with combination therapy) at a median 2.7 year follow-up.

In contrast, the Warfarin, Aspirin, Reinforcement (WARIS II) study (32) showed that anticoagulation with warfarin plus acetylsalicylic acid or warfarin (within 4 weeks of MI) reduced mortality, non-fatal reinfraction or stroke compared to acetylsalicylic acid alone (15% vs. 16.7% vs. 20% respectively) with an overall risk reduction of 29% with combination therapy and 19% with warfarin at a median follow-up of 2.7 years, but at the expense of more bleeding events in the warfarin groups compared to acetylsalicylic acid alone (0.62% vs. 0.17% per treatment year). The Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) study (64) showed similar benefits of anticoagulation compared to antiplatelet therapy with reduction in mortality, MI and strokes (9% acetylsalicylic acid vs. 5% warfarin vs. 5% warfarin and acetylsalicylic acid ) at a maximum 26 months follow-up, with a trend towards higher bleeding with warfarin.

Nonetheless, there is still still there is no clear consensus whether treatment with anticoagulation in all acute MI patients in sinus rhythm will be more effective in reducing adverse cardiac events, and if so, how long should treatment continue. This aspect raises a major concern in patients with coronary artery disease who require percutaneous intervention but are anticoagulated because of concomitant disorders such as AF, venous thromboembolism or prosthetic heart valves. Current recommendations suggest the use of bare metal stents in those patients and to consider triple therapy (acetylsalicylic acid + clopidogrel + warfarin) in the short-term to avoid recurrent cardiac ischaemia and/or stent thrombosis and thereafter, changing to warfarin plus clopidogrel to minimise bleeding risks, after carefully selecting the patients and stratifying their stroke risk (42).

**Heart failure**

Heart failure is an increasingly common condition, and is associated with increased thromboembolic risk (37). Some controversies remain with regard to the appropriate antithrombotic therapy to minimise stroke and thromboembolism in heart failure. In a Cochrane systematic review of antithrombotic drugs in patients with heart failure there was lack of evidence with acetylsalicylic acid compared to anticoagulation in reducing mortality and thromboembolism, although there was the suggestion from contemporary trials that heart failure hospitalisations were more common in acetylsalicylic acid users compared to warfarin (39). However, there was the suggestion that warfarin did reduce adverse outcomes in heart failure, although much of the evidence was based on trials performed >50 years ago, and more recent trials have not shown a significant benefit for anticoagulation on mortality, stroke and thromboembolism (41).

Of the contemporary trials of antithrombotic therapy in heart failure, a few studies merit brief mention. The Warfarin/Aspirin Study in Heart Failure (WASH) trial was a pilot study (18) that compared acetylsalicylic acid vs. warfarin vs. no treatment in heart failure subjects, but found no statistical differences in the primary end points of death, non-fatal MI or non-fatal stroke (26%, 32% and 26% respectively), after a mean followup of 27 months. Nonetheless, there was a significant increase in heart failure hospitalisations in the acetylsalicylic acid arm compared to warfarin or no treatment arms. Similar results were seen in the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial (46) where patients with ejection fraction <35% were randomised to blinded antiplatelet therapy (acetylsalicylic acid or clopidogrel) or warfarin to prevent thromboembolic events. WATCH found no difference in the primary endpoints of stroke, MI or death (20.5% vs. 21% vs. 19.8% respectively) at 18 months followup. Due to poor recruitment of patients the study was terminated earlier than expected, and therefore underpowered. The ongoing multicentered, double blind, randomised Warfarin versus Aspirin with Reduced Ejection Fraction (WARCEF) trial (65) is studying the benefits of warfarin or acetylsalicylic acid in heart failure subjects, and will provide evidence for the benefits of antithrombotic therapy in these patients.

**Aortic atheroma**

Atherosclerotic disease in aorta is an independent risk factor for ischaemic stroke (44). Specifically, aortic atheroma with protruding plaques of >4–5 mm is associated with a 4.3% relative risk of stroke recurrence in stroke patients (4, 10). Also the risk of recurrent stroke is higher with aortic plaques.
atheromatous plaques that are fissured and ulcerated, or non-calcified with mobile components (20). In patients with AF, the presence of complex aortic plaque (differentiated by thickness, surface abnormalities, calcifications and hyperchoic plaques) on the descending aorta is an independent predictor of stroke (14, 60). In one observational trans-oesophageal echocardiographic study (TOE) with stroke and transient ischaemic attack (TIA) patients the progression of aortic atheroma is associated with stroke recurrences (54). With respect to treatment, a few retrospective studies have shown conflicting results with antithrombotic therapy in high-risk mobile aortic atheromas to minimise stroke risk (21, 62).

The prospective randomised French Aortic Plaques in Stroke (FAPS) study (44) did not show any significant difference in primary outcomes with anticoagulation or acetylsalicylic acid amongst patients with ischaemic strokes. The ongoing Aortic Arch Related Cerebral Hazard (ARCH) trial (7) is a prospective, randomised, open label study, comparing warfarin vs. acetylsalicylic acid and clopidogrel in patients with aortic atheroma >4 mm with previous stroke, which will provide us with more guidance in the management of such patients.

For now, guidelines suggest the long-term use of antiplatelet drugs (either acetylsalicylic acid or clopidogrel) for secondary prevention, even with the presence of aortic atheroma (53). The superiority of warfarin over acetylsalicylic acid in preventing recurrent ischaemic strokes, in acute stroke has not been shown (48).

**Miscellaneous conditions**

Mitral valve prolapse (MVP) with myxomatous degeneration, redundancy and supraventricular arrhythmias are associated with increased risk of stroke (50). Both infective and marantic endocarditis carries higher risk of stroke, and persistent vegetation(s) of >10 mm despite treatment, or one or more embolic events in the first 2 weeks of treatment are the indications for acute surgical treatment of the affected valves (5). The benefits of antithrombotic drugs in these situations are lacking.

Patent foramen ovale (PFO) is identified in approximately one-third of patients with cryptogenic strokes. Isolated PFO or atrial septal aneurysm alone is not associated with high risk of recurrent strokes (24), but PFO with atrial septal aneurysm does carry a moderate risk (4%/year) for stroke recurrence (45). Various studies have demonstrated no major benefit with anticoagulation compared to acetylsalicylic acid in preventing stroke recurrence in these patients. For example, the Patent foramen ovale in Cryptogenic Stroke Study (PICSS) (29) found no difference with either warfarin (14.8%) or acetylsalicylic acid (15.4%) in preventing stroke recurrences in patients with PFO and prior cryptogenic strokes, at 2-year follow-up. There were also no significant differences in stroke event rates found between various sizes of PFO (small, medium and large) with or without atrial septal aneurysm. Recent interest has been directed towards endovascular percutaneous device closure of PFO, thereby minimising the morbidity associated with open surgical closures to reduce recurrence of strokes. However, there are still no convincing data to show the superiority of these procedures compared to medical therapy. For now, antiplatelet drugs remain the preferred long-term option of treatment in patients with PFO after stroke and closures may be reserved for further recurrences.

**Conclusion**

Cardioembolic strokes are common with varied presentations and are associated with higher mortality. Table 2 gives an overview of antithrombotic therapy for primary and secondary prevention in cardiac conditions to prevent ischaemic strokes.

For diagnosis of such conditions, one needs a higher index of clinical suspicion. Other than AF and left ventricular thrombus associated with acute MI, no large scale prospective randomised clinical trials of antithrombotic therapy are available to provide clear guidelines for the treatment of the wide variety of other cardioembolic causes, to minimise the stroke and thromboembolism risk. Limited evidence from cohort studies, retrospective posthoc analyses of trials and/or small prospective trials suggest the benefits of anticoagu-

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**Table 2**

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<thead>
<tr>
<th>Indication</th>
<th>Primary prevention</th>
<th>Secondary prevention</th>
<th>Duration</th>
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<tr>
<td>atrial fibrillation</td>
<td>high risk</td>
<td>vitamin K-antagonists</td>
<td>long-term</td>
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<td></td>
<td>moderate risk</td>
<td>vitamin K-antagonists or acetylsalicylic acid</td>
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<td></td>
<td>low risk</td>
<td>acetylsalicylic acid or none</td>
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<td>valves</td>
<td>mechanical prosthetic</td>
<td>vitamin K-antagonists</td>
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<td></td>
<td>bio-prosthetic</td>
<td>acetylsalicylic acid</td>
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<td>post-acute myocardial infarction</td>
<td>left ventricular thrombus</td>
<td>vitamin K-antagonists</td>
<td>3 months</td>
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<td></td>
<td>left ventricular aneurysm</td>
<td>acetylsalicylic acid</td>
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<td>antiocoagulation + surgery</td>
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<td>endocarditis</td>
<td>recurrent embolic phenomena</td>
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<td>persistent vegetations &gt;10 mm</td>
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<td>thrombus</td>
<td>vitamin K-antagonists</td>
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<td>myxoma</td>
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<td>vitamin K-antagonists or acetylsalicylic acid</td>
<td>long-term</td>
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<td>atheroma &gt;4 mm</td>
<td>acetylsalicylic acid and statins or vitamin K-antagonists</td>
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<td>protruding or mobile thrombus</td>
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<td>atrial septal aneurysm</td>
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<td>acetylsalicylic acid or vitamin K-antagonists</td>
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lation in some high-risk patients but the benefits and risks would need to be weighed. Many unanswered questions, remain, which would hopefully be answered by ongoing clinical trials. Given the uncertainties, many clinicians are reluctant to start warfarin, given the inconvenience of monitoring and wide intra/interpatient variability – however, this limitation may be overcome by the availability of new oral anticoagulant drugs, such as the direct thrombin inhibitors and oral factor Xa inhibitors.

References

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45. Omae T. Spectacular
47. Mas JL, Arquizan C, Lamy C et al. Patent Foramen
59. Correspondence to:
60. Correspondence to:
61. Correspondence to:
62. Correspondence to:
63. Correspondence to:
64. Correspondence to:
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