NEUROLOGY OF BODY SYSTEMS

Antithrombotic and interventional treatment options in cardioembolic transient ischaemic attack and ischaemic stroke

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Peer-reviewed data pertaining to anti-thrombotic and interventional therapy for transient ischaemic attack (TIA) or ischaemic stroke patients with non-valvular atrial fibrillation, atrial flutter, interatrial septal abnormalities, or left ventricular thrombus were reviewed. Long-term oral anticoagulant therapy with warfarin is the treatment of choice for secondary stroke prevention following TIA or minor ischaemic stroke in association with persistent or paroxysmal non-valvular atrial fibrillation or atrial flutter. If warfarin is contraindicated, long-term aspirin is a safe, but much less effective alternative treatment option in this subgroup of patients with cerebrovascular disease. Management of young patients with TIA or stroke in association with an interatrial septal defect is controversial. Various treatment options are outlined, but readers are encouraged to include these patients in one of the ongoing randomised clinical trials in this area. It is reasonable to consider empirical anticoagulation in patients with TIA or ischaemic stroke in association with left ventricular thrombus formation following myocardial infarction or in association with idiopathic dilated cardiomyopathy. If warfarin is prescribed, one should aim for a target international normalised ratio of 2.5 (range 2–3) to achieve the best balance between adequate secondary prevention of cardioembolic events and the risk of major haemorrhagic complications.

ATRIAL FIBRILLATION

Six percent of the population >65 years of age has atrial fibrillation.¹⁷ Approximately 70% of patients with atrial fibrillation have non-valvular atrial fibrillation (NVAf) associated with underlying non-rheumatic heart disease, 20% have underlying rheumatic heart disease and 10% have lone atrial fibrillation without obvious structural heart disease.¹⁸ Atrial fibrillation is the most common source of cardiogenic brain embolism,² and patients with NVAf who present with TIA or stroke have an overall risk of recurrent stroke of 12% in the first year and 5% per annum thereafter.¹⁹ If we strongly suspect that a patient has had a cardiogenic TIA or ischaemic stroke in association with paroxysmal atrial fibrillation (eg, simultaneous anterior and posterior circulation infarction), but the initial electrocardiogram, 24-h Holter monitor or echocardiogram are normal, a repeat 24-h or more prolonged Holter recording may identify the arrhythmia in some cases.

Data pertaining to the use of different anticoagulant drugs for early and long-term secondary prevention of vascular events in patients with cardioembolic TIA or ischaemic stroke in association with NVAf are discussed. Evidence for the use of aspirin in these patients is also alluded to.

Unfractionated heparin

The Cerebral Embolism Study Group²⁰ reported that intravenous heparin, given within 48 h of onset, and continued for 10 days after a cardioembolic stroke (target activated partial thromboplastin time (APTT) of 1.5–2.5 times the pretreatment level, $n = 24$), reduced the rate of early recurrent embolism to 0% compared with 10% in patients randomised to avoid anticoagulation ($n = 21$). No major bleeding complications were associated with anticoagulation, but the numbers were too limited to make any firm conclusions or reliable statistical comparisons between groups. In all, 56% of patients had NVAf as the presumed cardioembolic source.

In a subsequent, mainly retrospective analysis, the Cerebral Embolism Study Group²¹ reported that the risk of recurrent cardioembolic stroke could be

One can classify a patient as having had a cardioembolic transient ischaemic attack (TIA) or ischaemic stroke if appropriate investigations show a potential cardiac or transcardiac (paradoxical) source of embolism, without another obvious cause for the symptoms.¹ Cardiogenic brain embolism accounts for 18–19% of ischaemic strokes overall,^{2,3} and optimal secondary preventive measures are essential to minimise the risk of recurrent vascular events.

This article reviews the available evidence regarding antithrombotic and interventional treatment for secondary prevention of vascular events after cardioembolic TIA or stroke in patients with non-valvular atrial fibrillation, atrial flutter, interatrial septal abnormalities or left ventricular thrombus. The management of patients with TIA or stroke in association with valvular heart disease, infective endocarditis or intracardiac tumours is beyond the scope of this review, but readers are referred to relevant articles on these topics.^{4–16} The term cerebrovascular disease (CVD) will be used intermittently throughout the article to encompass both TIAs and ischaemic stroke.

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reduced from 15% to 5% with early anticoagulation, but that immediate anticoagulation could lead to intracerebral haemorrhage in 5–20% of patients, depending on the infarct size. The risk:benefit ratios derived from these small prospective²⁰ and retrospective²¹ series did not provide any robust evidence to support the use of early anticoagulation in acute cardioembolic ischaemic stroke. Other reports suggested that early heparin treatment in cardioembolic stroke may be safe,^{22–23} but perhaps of no clear benefit.²²

In the International Stroke Trial,²⁴ 19 345 patients with suspected acute ischaemic stroke were randomised to receive one of six different treatment regimens:

- aspirin 300 mg daily;
- low-dose subcutaneous unfractionated heparin 5000 IU twice daily;
- medium-dose subcutaneous unfractionated heparin 12 500 IU twice daily;
- aspirin and low-dose heparin;
- aspirin and medium-dose heparin;
- no aspirin and no heparin (control group).

Treatment was given within 48 h of acute stroke onset and continued for 14 days or until death or discharge. During the International Stroke Trial, 3169 patients with acute ischaemic stroke associated with atrial fibrillation were randomised to receive subcutaneous unfractionated heparin (5000 IU twice daily or 12 500 IU twice daily) or no heparin. This is the largest group of patients with acute ischaemic stroke in association with atrial fibrillation to be randomised to receive unfractionated heparin or no heparin. Patients allocated to receive heparin did not have obligatory monitoring of their APTT ratios. Furthermore, concomitant use of non-steroidal anti-inflammatory drugs, which theoretically could increase the risk of haemorrhagic complications associated with heparin, was not prohibited by the study protocol. Although heparin treatment considerably reduced the rate of recurrent ischaemic stroke by 2.1% (the exact proportion of recurrent cardioembolic strokes was not specified), this beneficial effect was negated by a marked increase in the risk of haemorrhagic stroke associated with its use (1.7%).

Chamorro *et al*²⁵ subsequently published a non-randomised case series in which patients with confirmed acute ischaemic stroke and NVAF were treated with either intravenous unfractionated heparin (target APTT ratio 1.5–2, *n* = 171) or 12 500 IU of subcutaneous heparin twice daily (*n* = 60) for 5–10 days.²⁵ In all, 32% of patients received anticoagulation within 6 h, and 68% between 6 and 48 h after symptom onset. Therapeutic APTT ratios were achieved 24 h after starting treatment in 49% of patients receiving intravenous heparin and 43% of patients receiving subcutaneous heparin, but excessively high APTT ratios were more common with intravenous heparin treatment (33% *v* 14%). The low rate of early stroke recurrence in this study (2.2% overall) precluded any firm conclusions on the relative effectiveness of intravenous or unfractionated heparin for early secondary prevention in patients with ischaemic stroke associated with NVAF. This study had several limitations in that the number of patients included was relatively small, they were not randomised to early or delayed anticoagulation or to the route of administration of heparin, and no placebo group was included. Although patients receiving subcutaneous heparin did have APTT monitoring in this study, it was not clearly specified how often this was performed or how treatment was subsequently modified.

Low-molecular-weight heparins

Most randomised, double-blind, placebo-controlled,^{26–27} aspirin-controlled²⁸ and heparin-controlled trials,²⁹ and dose escalation

studies of low-molecular-weight heparins (LMWHs) in acute ischaemic stroke³⁰ were not designed to specifically deal with the effect of these agents on the risk of recurrent TIA or ischaemic stroke in patients with cardiogenic brain embolism.

The Heparin in Acute Embolic Stroke Trial was the first trial to specifically examine the effects of treatment with a LMWH (dalteparin) in acute cardioembolic ischaemic stroke.³¹ Patients were randomised within 30 h of onset of a confirmed acute ischaemic stroke in association with atrial fibrillation to receive either

- 100 IU/kg of subcutaneous dalteparin twice daily and a placebo tablet every day (*n* = 224) or
- 160 mg of aspirin daily and placebo ampoules subcutaneously twice daily (*n* = 225).

In each treatment group, 89% of patients were in atrial fibrillation at the time of assessment, and almost all remaining patients had documented atrial fibrillation within 2 years of presentation. The exact percentage of patients with NVAF was not specified. The median duration of treatment was 13 days and adherence with treatment was >98%.³¹ The rates of recurrent ischaemic stroke (8.5% *v* 7.5%) and intracerebral haemorrhage (11.6% *v* 14.2%) were not markedly different in patients treated with dalteparin and aspirin, respectively. However, extracranial haemorrhage was more common (5.8% *v* 1.8%; *p* = 0.03), and intracerebral haemorrhage tended to be more severe with dalteparin than aspirin. Therefore, this trial failed to show that dalteparin was superior to aspirin at preventing early ischaemic stroke recurrence in this group of patients.

Heparinoids

As for LMWHs, early trials comparing the outcome of treatment with heparinoids in patients with acute ischaemic stroke were not designed to examine the effect of these agents on reducing the risk of recurrent ischaemic stroke in patients with cardioembolic CVD.³² In the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) study, 1281 patients aged between 18 and 85 years were randomised to receive intravenous danaparoid sodium or placebo within 24 h of onset of an acute or progressing ischaemic stroke.³³ However, there were too few recurrent ischaemic strokes within the first 7 days in the cardioembolic stroke subgroup in the TOAST study (0% in the danaparoid group (*n* = 143) *v* 1.6% in the placebo group (*n* = 123)) to make any firm conclusions about the efficacy of danaparoid for early secondary prevention in these patients.³³

Therefore, the limited available evidence does not support the routine use of unfractionated heparin, LMWH or heparinoids for the secondary prevention of recurrent vascular events in patients with recent cardioembolic CVD in association with atrial fibrillation.

Long-term oral anticoagulant treatment in cardioembolic TIA or ischaemic stroke in association with non-valvular atrial fibrillation

Warfarin

The European Atrial Fibrillation Trial compared the outcome of treatment with oral anticoagulants, aspirin or placebo in patients with persistent or paroxysmal NVAF who had experienced a cardioembolic TIA or minor ischaemic stroke in the preceding 3 months.¹⁹ Patients eligible for anticoagulation were randomised to receive oral anticoagulant treatment (including warfarin), aspirin or placebo; those ineligible for anticoagulation were randomised to receive aspirin or placebo. Overall, 1007 patients were randomised to receive treatment with oral anticoagulants (target international normalised ratio (INR) 3.0, *n* = 225), aspirin (300 mg daily, *n* = 404) or placebo

($n = 378$). In total, 43% were randomised within 2 weeks of onset of their neurological symptoms and the mean duration of follow-up was 2.3 years. The annual risk of recurrent stroke alone was markedly reduced from 12% with placebo ($n = 214$) to 4% with oral anticoagulants ($n = 225$, $p < 0.001$), and oral anticoagulants were more effective than aspirin at preventing recurrent stroke ($p < 0.001$). Although there was a trend towards benefit, the reduction in the annual risk of recurrent stroke with aspirin (10%, $n = 404$) compared with placebo (12%, $n = 378$) did not reach significance ($p = 0.31$). Anticoagulation was more hazardous than antiplatelet treatment, with an annual incidence of major bleeding complications of 2.8% with anticoagulants and 0.9% with aspirin.

Slightly more than one third of participants in the Stroke Prevention in Atrial Fibrillation III study³⁴ had experienced a previous thromboembolic event in association with NVAF >30 days earlier (TIA or non-disabling ischaemic stroke in 96%, and systemic thromboembolism in 4%). As the exact reduction in the risk of recurrent vascular events in the TIA and stroke subgroup alone was not reported, these data will not be discussed further.

The optimal time to start oral anticoagulant treatment in patients with cardioembolic TIA or ischaemic stroke in association with NVAF is uncertain. There are several reasons why we cannot extrapolate the results of the European Atrial Fibrillation Study to conclude that oral anticoagulation should be started immediately in this subgroup of patients with CVD. Most patients received delayed anticoagulation treatment, and depending on the dose, the optimal anticoagulant effect of warfarin may be delayed for 1–7 days after starting treatment.³⁵ Because previous meta-analyses have suggested that treatment with 160–300 mg of aspirin daily within 48 h of symptom onset leads to a non-significant reduction in the relative risk of recurrent ischaemic stroke in patients with acute cardioembolic ischaemic stroke by 30% (95% confidence interval –4 to 53%),^{36, 37} immediate warfarin treatment in this subgroup may lead to the withholding of aspirin during this important therapeutic period. If heparin is started concurrently with warfarin in the acute phase after cardioembolic ischaemic stroke, the increased risk of bleeding associated with both these treatment regimens^{19–24} could theoretically increase the risk of intracerebral haemorrhage or haemorrhagic transformation of the infarct. As approximately one third of patients with stroke in association with NVAF may have another underlying cause for their stroke (see later),³⁸ early anticoagulation in these patients may also be inappropriate.

Ximelagatran

The clinical efficacy of warfarin is limited by its delayed onset of action, its unpredictable anticoagulant effect, the need for regular monitoring to ensure that the INR remains within its narrow therapeutic window, and the potential for interaction with other drugs and with foodstuffs.³⁹ Owing to these limitations, many patients who might benefit from long-term anticoagulant treatment for secondary stroke prevention are not treated with warfarin. This has generated much interest in a new class of anticoagulant drugs, the direct thrombin inhibitors.

Thrombin is an enzyme generated by the coagulation cascade, which stimulates further activation of the coagulation cascade and platelet activation. Ximelagatran is a prodrug that is converted into its active metabolite, melagatran, after absorption from the small intestine.³⁹ Melagatran is a direct thrombin inhibitor, with immediate anticoagulant effects, which reversibly binds to and inhibits the active site of thrombin. It is completely cleared from the circulation within 12 h by renal excretion.³⁹ The potential advantages of ximelagatran over warfarin are that it prolongs the prothrombin time

and the APTT, and because its anticoagulant effects are predictable with fixed doses, routine anticoagulant monitoring is not required.³⁹

Subsequent to the encouraging results of an initial randomised open-labelled trial,⁴⁰ the Stroke Prevention by ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) investigators published the results of the SPORTIF V trial.⁴¹ This was a multicentre double-blind trial in which patients with persistent or paroxysmal NVAF, and at least one additional risk factor for stroke, were randomised to receive either dose-adjusted warfarin (INR 2–3, $n = 1962$) or 36 mg of ximelagatran twice daily ($n = 1960$). The primary end point was the combined rate of recurrent stroke (ischaemic or haemorrhagic) and systemic embolic events, and patients were followed up for a mean duration of 20 months. The annual incidence of the primary end point was similar in the warfarin (1.2%) and ximelagatran groups (1.6%; $p = 0.13$), and the rates of major extracerebral bleeding were 3.1% per year with warfarin versus 2.4% per year with ximelagatran ($p = 0.15$). Patients who took concomitant aspirin treatment had an increased risk of bleeding with each drug. One of the most important adverse effects of ximelagatran was a 6% risk of severe hepatic transaminitis, usually between 2 and 6 months after starting treatment, although this usually settled either spontaneously or after discontinuing treatment.⁴¹

We must emphasise that this trial predominantly focused on primary stroke prevention in patients with atrial fibrillation; only 18% of the patients allocated to treatment with warfarin and 19% of the patients allocated to treatment with ximelagatran had experienced a prior stroke or TIA at entry into the study. Because the investigators did not specifically report the outcome in this ischaemic CVD subgroup, we cannot extrapolate the results of this study to make any firm conclusions about the safety or efficacy of ximelagatran for secondary stroke prevention in patients presenting with cardioembolic CVD. In addition, as ximelagatran is more expensive than warfarin,⁴² and requires regular monitoring of the liver function tests, the cost effectiveness of this agent for secondary stroke prevention in these patients is yet to be determined.

ROLE OF LEFT ATRIAL APPENDAGE IN THROMBOEMBOLISM AND POTENTIAL INTERVENTIONAL TREATMENT OPTIONS

The left atrial appendage (LAA) is an embryonic remnant of the original left atrium that develops in the third week of gestation.⁴³ It is a long, tubular, trabeculated structure, which is in continuity with the left atrial cavity⁴³; the orifice of the LAA has a diameter of between 5 and 40 mm.⁴⁴ The LAA decompresses the left atrium during left ventricular systole, contributes to cardiac output, and may serve an important role in volume regulation in response to stretch by releasing atrial natriuretic peptides and possibly brain natriuretic peptides.⁴³ The unique anatomy of the LAA predisposes to *in situ* thrombus formation, and >90% of atrial thrombi in patients with NVAF are believed to originate in the LAA.⁴³ Factors that may predispose to thrombus formation include LAA enlargement, decreased LAA contractility and stasis of blood flow in the LAA, which may manifest as spontaneous echocardiographic contrast.⁴³ LAA enlargement and reduced contractility may be secondary to an underlying LAA myopathy or may occur as a consequence of atrial fibrillation itself (atrial fibrillation-induced myopathy).⁴⁴ Structural changes in the LAA may further increase the risk of atrial fibrillation because of electric remodelling of the heart chamber.⁴³ However, indicators of LAA dysfunction have not been definitively proved to be independent predictors of recurrent stroke or TIA in prospective studies of patients with cardioembolic stroke associated with NVAF.⁴³

Although warfarin is the most effective antithrombotic agent available to reduce subsequent thromboembolic risk in patients with cardioembolic stroke and NVAF, up to 20% of patients have relative or absolute contraindications to treatment.⁴⁴ Furthermore, some patients taking warfarin have recurrent vascular events when the INR is subtherapeutic. Therefore, obliteration of the LAA might facilitate secondary stroke prevention in patients who are deemed unsuitable for treatment with warfarin. Methods for LAA obliteration include (a) open surgical resection, ligation or stapling,^{45–46} or (b) percutaneous transvenous catheter-based obliteration techniques, which require atrial septal puncture.^{47–48} Ongoing trials are comparing the outcome of surgical obliteration versus no obliteration of the LAA in patients undergoing coronary artery bypass surgery who are at increased risk of subsequent stroke or atrial fibrillation.⁴⁶ However, it is important to note that this procedure may be complicated by atrial arrhythmias, atrial rupture or subsequent fluid retention, and complete occlusion of the LAA may not be achieved.⁴⁶ Randomised clinical trials are required to compare the safety and efficacy of treatment using percutaneous LAA device closure with best medical treatment in patients with NVAF. Percutaneous device deployment will inevitably be associated with complications such as haemopericardium, device embolisation or cardiac arrhythmias,^{47–48} and may open up a right–left interatrial shunt with the risk of subsequent paradoxical embolism (see below). Furthermore, long-term antiplatelet treatment will be required even after successful surgical or percutaneous LAA obliteration, because the LAA is not the only potential source of emboli in these patients.

What therapeutic advice can a neurologist currently offer a patient with an acute cardioembolic TIA or ischaemic stroke in association with NVAF?

Some experienced vascular neurologists consider starting warfarin treatment 2–3 days after the onset of an acute cardioembolic ischaemic stroke once the patient has been medically and neurologically stable, on the basis that it may take up to a week to achieve anticoagulation targets, and because secondary haemorrhagic transformation of an infarct usually occurs between 12 h and 4 days after symptom onset.³⁷ Repeat computed tomography imaging of the brain is performed before starting warfarin treatment if the infarct is large, if the patient deteriorates or “has undue headache”.³⁷

We are somewhat more cautious in our approach, because some patients rapidly reach therapeutic anticoagulation targets after starting warfarin treatment, and if secondary delayed haemorrhagic transformation occurs, reversal of anticoagulation becomes problematic and may actually increase the risk of subsequent thromboembolism. Our current practice is to treat eligible patients with acute cardioembolic ischaemic stroke in association with NVAF with aspirin monotherapy (300 mg daily) for 7 days, and then we start warfarin treatment once the patient has been clinically stable and there is no clinical suspicion of haemorrhagic transformation of the infarct. When the INR increases to ≥ 2.5 , aspirin is discontinued and warfarin monotherapy is continued, aiming for a target INR of 2.5 (range 2.0–3.0). We start aspirin and warfarin treatment concurrently in suitable patients who present with an acute cardioembolic TIA in association with NVAF, and who have no evidence of acute cerebral infarction on computed tomography of the brain. When the INR increases to ≥ 2.5 , aspirin is discontinued and warfarin monotherapy is continued, as outlined earlier.

As stated above, there is no evidence to support the routine use of unfractionated heparin, LMWH or heparinoids in acute cardioembolic ischaemic stroke, but sufficient data from randomised controlled clinical trials in patients with cardioembolic TIAs are lacking. We empirically consider immediate

anticoagulation, initially with LMWH or dose-adjusted intravenous unfractionated heparin alone, in selected patients with NVAF who are judged to be at high risk of subsequent thromboembolism—for example, patients who have had multiple cardioembolic TIAs on antiplatelet treatment. When the patient has stabilised and the hyperacute phase has passed, long-term warfarin treatment is started.

Although the evidence is less robust, we also consider it reasonable to treat patients with paroxysmal atrial fibrillation in a similar manner to those with persistent NVAF, because of the theoretical increased risk of stroke during periods of intermittent atrial fibrillation, and at the time of transition from NVAF to normal sinus rhythm.⁴⁹

We must emphasise that our current practice regarding the vexing issue of when to start oral anticoagulation treatment is based on extrapolating the evidence from clinical trials, appreciating the time taken to anticoagulate a patient with warfarin and weighing the risks and benefits of anticoagulant treatment versus antiplatelet treatment in individual patients, rather than being based on direct evidence from randomised clinical trials. Individual clinicians must make their own decision about when to start oral anticoagulant treatment. Future randomised trials are warranted to investigate the safety and efficacy of dose-adjusted intravenous unfractionated heparin treatment versus immediate aspirin treatment in the acute phase after a cardioembolic TIA or ischaemic stroke.

If warfarin is contraindicated—for example, patients at high risk of falling, or those who are unable or unwilling to comply with regular INR monitoring—data from the European Atrial Fibrillation Trial suggest that aspirin (300 mg daily) is a safe, although considerably less effective, alternative treatment option. Whether treatment with combination antiplatelet therapy (such as aspirin and dipyridamole or clopidogrel and dipyridamole) or newer anticoagulants is more effective than aspirin monotherapy in these patients remains to be established.

As approximately one third of patients with stroke in association with NVAF also have another potential underlying cause for their stroke,³⁸ patients presenting with a presumed cardioembolic anterior circulation TIA or stroke secondary to occlusion of a large intracranial artery should also be screened for extracranial carotid stenosis with colour Doppler ultrasound, magnetic resonance angiography or computed tomography angiography. These patients may also require surgical or endovascular treatment for carotid stenosis.

ATRIAL FLUTTER

To our knowledge, the management of patients with cardioembolic TIA or ischaemic stroke in association with isolated atrial flutter has not been the subject of randomised controlled clinical trials. We might expect the stroke risk in association with atrial flutter to be lower than that in patients with NVAF because of more organised mechanical contraction of the left atrium in those with flutter. However, data from recently published prospective case series have suggested that the risk of stroke in patients with atrial flutter is higher than that in controls,⁵⁰ and similar to the risk associated with atrial fibrillation.^{50–51} Although these case series have their methodological limitations, the higher-than-predicted stroke risk with atrial flutter may be partly due to fact that some of these patients subsequently develop atrial fibrillation,^{49–51} they may have alternating periods of atrial flutter and fibrillation,^{49–51–52} and they may intermittently revert to sinus rhythm,⁴⁹ with the subsequent risk of left atrial “stunning” and stasis of blood flow. All these factors could predispose to left atrial thrombus formation and increase the risk of cardiogenic brain embolism. For these reasons, recent evidence-based guidelines

recommend treatment of patients with atrial flutter in a similar manner to those with atrial fibrillation.⁴⁹ Therefore, it is reasonable to aim to treat all suitable cardioembolic CVD patients who have atrial flutter with anticoagulant therapy, as outlined above.

PATENT FORAMEN OVALE, ATRIAL SEPTAL ANEURYSM AND ISCHAEMIC STROKE: DIAGNOSTIC AND TREATMENT OPTIONS

A patent foramen ovale (PFO) represents the failure of fusion of the valve of the foramen ovale (septum primum) with the atrial septum (septum secundum),⁵³ leaving a potential interatrial channel through which blood may shunt if the pressure in the right atrium exceeds that in the left.⁵⁴ Autopsy series have identified a PFO in up to 35% of the general population,⁵⁵ with the incidence decreasing with advancing years.⁵⁴ Paradoxical embolism occurs when thrombus, air or fat passes across the interatrial defect from the right to left atrium, with resultant cerebral or peripheral systemic embolisation. In theory, the presence of a PFO may also predispose to the occurrence of emboligenic atrial arrhythmias,⁵⁶ although these are not usually identified on 24-h Holter monitoring,⁵⁷ and in situ thrombus formation within the PFO channel itself could directly lead to cerebral embolisation.⁵⁵

Case-control studies have established that a PFO is more commonly identified by contrast echocardiography in young adults with ischaemic stroke of undetermined aetiology (54–56%) than in those without stroke (controls; 10–18%).^{58–60} Preliminary data have suggested that a PFO may be more commonly seen on echocardiography in patients <55 years of age with ischaemic stroke of indeterminate or undetermined aetiology (49%) than in young patients with an identifiable cause for their stroke (21%).⁵⁸ The PFO in Cryptogenic Stroke Study investigators also showed that a PFO was more commonly identified in patients with ischaemic stroke of undetermined aetiology than in those with an identifiable cause for stroke who were aged between 30 and 85 years (39% *v* 30%, *p* < 0.02).⁶¹ However, the relationship between PFO and stroke has not been definitely established in patients >55 years of age in whom many other causes for cerebral ischaemia may be identified.⁵⁵

An atrial septal aneurysm may be defined as an interatrial septal excursion that protrudes by ≥ 10 mm beyond the plane of the septum into either the left or right atrium on echocardiography⁵⁵; some studies also require the base of the atrial septal aneurysm to be ≥ 15 mm.⁵³ An atrial septal aneurysm may be identified on transoesophageal echocardiography (TOE) in up to 4.6% of the general population,⁵⁵ but the incidence increases to as much as 10.5% in young patients with ischaemic stroke of undetermined aetiology.⁵⁷ A PFO and an atrial septal aneurysm may coexist, and the risk of recurrent stroke associated with these atrial septal abnormalities has been investigated (see below).

Diagnosis of PFO and atrial septal aneurysm

A potentially clinically relevant PFO in a patient with cryptogenic CVD may be diagnosed by echocardiography, ideally disclosing evidence of right to left shunting across the interatrial septum. One typically injects a contrast agent (agitated colloid or saline) into a peripheral vein as part of a “bubble study”. If normal, the patient is then asked to perform a Valsalva manoeuvre and to cough during the contrast injection to increase right-sided heart pressure and to reveal any passage of microbubbles across the septum. The appearance of microbubbles in the left-sided cardiac chambers within three cardiac cycles of maximal right atrial contrast opacification confirms right to left atrial shunting⁵⁵ and supports the theory that the symptoms may have been caused by paradoxical

embolism. Depending on the number of microbubbles crossing the interatrial septum, the degree of shunting via a PFO can be graded as small (3–9 microbubbles), moderate (10–30 microbubbles) or large (>30 microbubbles),⁶² although grading systems vary between series.⁶³ However, the usefulness of this classification is probably limited because the number of microbubbles detected will vary depending on the number of microbubbles injected, the speed of injection, and variability in cardiac anatomy between subjects.⁵⁵ The sensitivity of echocardiography in detecting a PFO may be increased by injecting a colloid rather than a crystalloid contrast agent.⁶⁴ Diagnostic sensitivity may also be improved by contrast injection into the femoral rather than an antecubital vein, because blood flow from the inferior vena cava tends to flow directly towards a PFO, whereas blood flow from the superior vena cava tends to be directed away from the interatrial septum.⁵³

TOE is the reference standard for diagnosis, and although it is more difficult to perform a Valsalva manoeuvre during TOE than during transthoracic echocardiography (TTE), the images obtained during a TTE study may be degraded by performing a Valsalva manoeuvre and the acoustic window may be lost.⁵³ Other relatively non-invasive diagnostic techniques that have been used include TOE and TTE with colour Doppler ultrasound, transmitral Doppler ultrasound and transcranial Doppler (TCD) ultrasound after injection of a contrast agent, before and after a Valsalva manoeuvre and coughing. The detection of air microemboli in the middle cerebral artery on TCD after intravenous injection of agitated saline into a peripheral vein is supportive of a route of paradoxical embolism, but does not inform us of the exact site of paradoxical embolisation and cannot exclude shunting across a pulmonary arteriovenous fistula or a ventricular septal defect.⁵³ Therefore, the combination of TOE and TCD in suspicious cases may be informative. Using TOE with contrast injection as the gold standard for diagnosis (fig 1⁶⁵), the respective sensitivity and specificity of the other diagnostic techniques are as follows: TOE with colour Doppler ultrasound (79% and 75%); TTE with contrast (50% and 92%); TTE with colour Doppler (7% and 100%)⁶⁶ and TCD with contrast (91% and 94%).⁶⁷

Owing to superior visualisation of the interatrial septum with TOE, this is also the diagnostic test of choice to exclude an atrial septal aneurysm that may be associated with a PFO.⁵³

It is difficult to definitively prove that a PFO (with or without an atrial septal aneurysm) is involved in the aetiology of a TIA or an ischaemic stroke in a patient unless we see a thrombus straddling the interatrial septum on echocardiography,⁶⁸ with typical cardioembolic cerebral ischaemia or infarction on neuroimaging. However, a history of performing a Valsalva manoeuvre just before stroke onset (straining at defecation, having sexual intercourse, lifting or coughing), the finding of an occult deep venous thrombosis on venous imaging, the demonstration of a right to left interatrial shunt or the presence of an underlying hypercoagulable state in such a patient all increase the likelihood that the PFO is relevant. Unfortunately, these supportive clinical features are often not identified.⁵⁷

Risk of recurrent vascular events in patients with cryptogenic ischaemic stroke with a PFO or ASA

Mas *et al*⁶² prospectively studied 581 adults <55 years of age who presented with cryptogenic ischaemic stroke; 52% of patients had no atrial septal abnormality, 2% had an atrial septal aneurysm alone, 37% had an isolated PFO and 9% had an atrial septal aneurysm in combination with a PFO. All patients received aspirin monotherapy (300 mg daily) unless the treating doctor altered their antiplatelet regimen or temporarily prescribed anticoagulants—for example, for deep venous

Figure 1 (A) Transoesophageal echocardiogram (TOE) showing a patent foramen ovale (arrow); (B) TOE after injection of agitated saline into an antecubital vein in association with the Valsalva manoeuvre showing complete opacification of the right atrium and the passage of microbubbles (arrow) (adapted with permission from Kizer JR *et al*⁶⁵).

thrombosis. There was no significant difference in the combined risk of recurrent stroke and TIA over 4 years between patients without an atrial septal abnormality (6.2%) and those with an isolated ASA (0%) or those with a PFO alone (5.6%). However, the recurrence risk was significantly higher in patients with both a PFO and an ASA (19.2%) compared with those without an atrial septal abnormality ($p = 0.04$; fig 2). The degree of right to left interatrial shunting was not a major predictor of the risk of recurrent neurological events. This study suggests that the presence of both interatrial septal abnormalities, rather than the presence of an isolated septal abnormality alone, increases the risk of recurrent stroke or TIA with aspirin treatment. However, we must be cautious in interpreting the data in patients with an isolated ASA because of the limited number of patients with this finding alone.

It is plausible that the presence of a PFO and an ASA do interact to increase the risk of stroke in patients with atrial

septal disease. Increased interatrial septal mobility in a patient with an interatrial septal aneurysm could promote blood flow across the interatrial septum, with subsequent paradoxical embolism in a patient with a PFO.⁶⁹ Furthermore, some patients with an interatrial septal aneurysm have a larger PFO that could also facilitate paradoxical embolism from the right to left atrium.⁶⁹ The presence of two atrial septal abnormalities could also, in theory, increase the likelihood of atrial arrhythmias and atrial thrombus formation, and hence increase the risk of cardiogenic brain embolism.

As part of the PFO in Cryptogenic Stroke Study, the 2-year risk of recurrent ischaemic stroke, TIA or death was assessed in an older population of patients with cryptogenic ischaemic stroke who did or did not have a PFO on TOE ($n = 250$; age range 30–85 years).⁶¹ The 2-year event rates were similar in cryptogenic patients with and without a PFO (20.4% *v* 16.6%). However, the risk of recurrent vascular events in patients with cryptogenic stroke who had both a PFO and an ASA was not specifically reported. Neither of these studies specified the subtype of the recurrent TIA or ischaemic stroke, although we assume that recurrent events were also deemed to be of undetermined aetiology after adequate investigation.

Management

The optimal management of cryptogenic ischaemic stroke patients with PFO with or without an ASA remains to be determined. Treatment options include (a) antithrombotic treatment with antiplatelet treatment or warfarin, (b) percutaneous device closure or (c) surgical closure. There are no published large, double-blind, randomised controlled clinical trials comparing the efficacy and safety of best medical management with percutaneous device closure or surgical treatment in these patients. Data from some case series that examined the outcome after these treatment modalities is discussed, followed by a practical guide to management.

Antiplatelet versus anticoagulant treatment

Homma *et al*⁶¹ reported that the 2-year risk of recurrent ischaemic stroke, TIA or death was similar in patients with cryptogenic ischaemic stroke with PFO who were treated with 325 mg of aspirin daily or anticoagulated with warfarin aiming for an INR of 1.4–2.8 (23% *v* 17%, $p = \text{NS}$). The authors did not report the outcome of treatment with aspirin versus warfarin in the subgroup of patients with cryptogenic ischaemic stroke who had both a PFO and an ASA.

Percutaneous device closure

Recent advances in catheter technology have led to the use of percutaneous devices to close either a PFO or an atrial septal defect (ASD). Percutaneous device closure is a potentially attractive treatment for patients with cryptogenic ischaemic

Number at risk					
No PFO or ASA	304	291	267	158	48
PFO alone	216	207	198	122	43
ASA alone	10	10	9	4	1
PFO and ASA	51	46	44	25	10

Figure 2 Four-year survival free from recurrent stroke or TIA in the presence of an atrial septal aneurysm (ASA) alone, no interatrial septal abnormality (no patent foramen ovale (PFO) or ASA), a PFO alone, and the combination of both a PFO and an ASA (PFO and ASA). The p Value refers to the comparison between the patients with both a PFO and an ASA (PFO and ASA) versus those without an atrial septal abnormality (no PFO or ASA). Reproduced with permission from Mas *et al*.⁶²

stroke who have a PFO or an ASD. The patient does not require open-heart surgery, and if successful, closure of the interatrial defect should be permanent, thus avoiding the need for long-term anticoagulation. Several devices have been used, including the Clamshell device, Amplatzer PFO and Amplatzer atrial septal defect occluders, PFO STAR, StarFlex occluder, Sideris buttoned device, Angel Wing device, CardioSEAL and Helex Septal occluder devices.^{63 70 71}

Windecker *et al*⁶³ recently published a non-randomised case series of patients with cryptogenic ischaemic stroke or TIA in association with a PFO with or without an ASA who were treated with either antithrombotic agents ($n = 158$) or percutaneous device closure ($n = 150$).⁶³ The medically treated patients received unblinded treatment with aspirin ($n = 77$), clopidogrel ($n = 2$) or initial warfarin ($n = 79$, INR range 2–3); those in the percutaneous closure group were treated with a variety of different devices, and aspirin was prescribed for at least 6 months after the procedure to allow for device endothelialisation.⁶³ A non-significant trend was observed towards a lower incidence of the combined end point of TIA, stroke or death over 4 years with percutaneous device closure compared with antithrombotic treatment overall (8.5 v 24% ; $p = 0.05$). Although there were no significant differences in outcome between the percutaneous closure group and patients treated with warfarin (8.5 v 13% ; $p = \text{NS}$), the combined end point was less commonly reached in the percutaneous closure group compared with the subgroup of medically treated patients who received antiplatelet treatment (8.5 v 28% ; $p = 0.03$). It is important to emphasise that there was no significant difference in outcome between the medically treated patients who received anticoagulant agents compared with those who received antiplatelet agents. Periprocedural complications occurred in 6% of patients after percutaneous PFO closure, including device embolisation, air embolism, and vascular access site complications; 17% of patients required long-term antiplatelet treatment because of incomplete PFO closure, the long-term consequences of which are unknown.⁶³ Other case series have also shown that percutaneous PFO closure is certainly feasible, but is occasionally associated with periprocedural complications including pericardial effusion and tamponade,^{72 73} atrial arrhythmias,⁷² device embolisation,^{72 73} femoral artery laceration and retroperitoneal haematoma formation,⁷³ pulmonary emboli,⁵⁵ device thrombosis,⁵⁵ and death.⁵⁵ A recent review of several case series of percutaneous PFO closure, which did not include the data from Windecker's study,⁶³ estimated a periprocedural major complication rate of approximately 1.5% and a minor complication rate of 7.9%.⁵⁵

Surgical closure

Case series have suggested that open cardiac surgery with primary PFO closure,⁷⁴ autologous pericardial patching,⁷⁴ or primary PFO closure with obliteration of an associated ASA⁷⁵ in patients with cryptogenic ischaemic stroke or TIA are feasible treatment options. However, in one retrospective series of 91 patients, the overall risk of perioperative complications including atrial fibrillation, pericardial effusion, re-exploration for post-operative bleeding, wound infection or sternal non-union was 24%.⁷⁴ Furthermore, TIAs of unexplained aetiology occurred in 8% of patients during a mean follow-up period of 1.9 years despite successful surgical closure of the PFO, raising the possibility that at least some of the original ischaemic cerebrovascular symptoms may not have been related to the PFO at all.⁷⁴ In another series of 10 patients with a PFO and an ASA who were treated surgically, some postoperative complication was observed in 40–50%, but no patient had a recurrent cerebrovascular event during a mean follow-up period of 4.3 years.⁷⁵ A recent review of published case series of surgical

PFO closure showed an annual rate of stroke, death or TIA postoperatively of up to 5.6%.⁵⁵

Several ongoing randomised trials are comparing antithrombotic treatment with percutaneous device closure in patients with cryptogenic stroke and presumed paradoxical embolism: The Patent foramen ovale and Cryptogenic embolism (PC) trial; the Randomized Evaluation of recurrent Stroke comparing PFO closure to Established Current standard of care Treatment (RESPECT) trial; the Evaluation of the STARflex Septal Closure System in Patients with a Stroke or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a PFO (CLOSURE 1) trial; (<http://www.strokecenter.org/trials>); and the Cardia PFO trial.⁵⁵ Data from these studies are required to assess the long-term efficacy and safety of percutaneous device closure compared with best medical treatment to guide future clinical decision making in this patient cohort. Because of increasing interest and developments in the field of percutaneous PFO closure, a randomised trial comparing surgical treatment with best medical management or percutaneous closure in patients with cryptogenic stroke who have a PFO or an ASA is unlikely to be performed.

Treatment options for patients with cryptogenic TIA or ischaemic stroke who have an associated PFO or atrial septal aneurysm

Figure 3 shows the treatment options for patients with cryptogenic TIA or ischaemic stroke who have an associated PFO or atrial septal aneurysm.

Recent consensus guidelines state that there is insufficient evidence to assess the relative efficacy of antiplatelet treatment versus warfarin, or best medical treatment versus percutaneous or surgical PFO closure for the secondary prevention of stroke or death in this setting.⁷⁶ However, for the neurologist faced with such a patient, treatment decisions need to be made.

In view of the higher risk of bleeding with warfarin⁶¹ and the need for regular monitoring, aspirin is a reasonable first-line treatment to use for secondary prevention in patients with cryptogenic ischaemic stroke who have an isolated PFO or isolated ASA. In patients with an underlying thrombophilia or evidence of a deep venous thrombosis, anticoagulation with warfarin (target INR 2.5 (range 2–3)) is advised. In patients who experience a recurrent stroke or TIA despite aspirin treatment that is believed to be secondary to the cardiac abnormality, one should seriously consider randomising the patient into one of the ongoing treatment trials of percutaneous device closure versus anticoagulant treatment. If this is not feasible, we have to decide whether to empirically treat with warfarin monotherapy, to alter the antiplatelet regimen, or to advise the patient to undergo percutaneous device closure. It is important to emphasise that we have no evidence that clopidogrel monotherapy, or combination antiplatelet treatment with either aspirin and dipyridamole or aspirin and clopidogrel are superior to aspirin monotherapy in these patients. If the patient opts for and undergoes successful percutaneous PFO closure, we empirically advise continuing long-term antiplatelet therapy—for example, aspirin—because of the potential risk of further TIA or stroke despite successful device closure.⁷³

Ideally, one should randomise patients who have both a PFO and an ASA into one of the ongoing trials. If this is not possible, the clinician must empirically decide on an individualised treatment regimen for the patient, having taken into account the potential high risk of recurrent events on aspirin alone.⁶² If long-term warfarin is prescribed, treatment should be reviewed when the results of ongoing trials become available. One may consider surgical intervention in patients who experience recurrent cryptogenic TIAs or stroke in association with a PFO and an ASA despite maximal medical treatment, and in whom

Figure 3 Management algorithm for patients <55 years old with cryptogenic transient ischaemic attack (TIA) or ischaemic stroke in association with a patent foramen ovale (PFO). DVT, deep venous thrombosis; PDC, percutaneous device closure; Rx, treatment.

intensive investigations fail to show an alternative cause for the symptoms and where percutaneous device closure or long-term anticoagulation is not possible. For example, one of us dealt with a patient who had multiterritory cerebral infarction in association with a large mobile ASA and multiple inter-ASDs that were not amenable to successful percutaneous closure; this patient underwent successful open surgical repair of the cardiac defects.

CEREBRAL EMBOLISM SECONDARY TO LEFT VENTRICULAR THROMBUS

Mural thrombus formation on the left ventricular free wall may occur in the acute or convalescent phase after myocardial infarction, and may cause cardioembolic CVD. The risk of thrombus formation is related to the site and extent of the myocardial injury⁷⁷ and is more common in the acute than convalescent phase after symptom onset⁷⁸; 1 in 3 anterior Q wave myocardial infarcts, but <1 in 20 inferior Q wave infarcts or non-Q wave infarcts are associated with left ventricular thrombus formation.⁷⁷ Chronic mural thrombi are also commonly identified in patients with chronic left ventricular aneurysm after myocardial infarction, but most of these patients do not subsequently develop cardioembolic TIA or stroke.⁷⁹ High-risk factors for embolisation include a fresh mobile thrombus protruding into the ventricular cavity and

acute anterior infarction associated with apical dyskinesia or akinesia.⁷⁸

Left ventricular thrombus formation also occurs in idiopathic dilated cardiomyopathy (ie, in the absence of coronary artery disease), and is usually confined to the left ventricular apex because of relative stasis of blood in this region.⁷⁹ Patients with idiopathic dilated cardiomyopathy seem to have a higher risk of cardiogenic embolism than patients with a left ventricular aneurysm after a myocardial infarction.⁷⁸ This may in part be secondary to the fact that a left ventricular thrombus in patients with cardiomyopathy is more likely to protrude into the lumen of the ventricle and embolise,⁷⁸ rather than undergo organisation in a left ventricular aneurysmal cavity.

Two-dimensional TTE has a sensitivity of up to 95% and a specificity of up to 86% for diagnosing left ventricular thrombus in suitably “echogenic” patients,⁸⁰ and usually visualises the left ventricular apex better than TOE.¹⁸ Alternative imaging techniques include left ventricular contrast angiography, which is more invasive and less sensitive and specific than TTE, and more recently, contrast-enhanced magnetic resonance imaging, which may be more sensitive than TTE at identifying left ventricular thrombus.⁸¹

There are no randomised controlled trials comparing anticoagulation with combination antiplatelet treatment in patients taking aspirin who experience a TIA or stroke associated with left ventricular thrombus formation after myocardial infarction, with or without a left ventricular aneurysm. Therefore, therapeutic recommendations for such patients are entirely empirical. Acute treatment options include immediate anticoagulation with full-dose LMWH, dose-adjusted intravenous unfractionated heparin or combination antiplatelet treatment. Warfarin should be started once the hyperacute phase has passed (target INR 2.5, range 2–3). If acute anticoagulation is recommended, patients and their relatives should be clearly advised of the risks of major intracerebral and extracerebral bleeding in the acute stroke setting, especially if the infarct is moderate–large in size. It is unknown whether long-term antiplatelet treatment might subsequently be sufficient for secondary prevention of vascular events—for example, if a repeat echocardiogram at 3 months does not show a residual left ventricular thrombus or a left ventricular aneurysm. Obviously, if there are additional risk factors for subsequent cardiogenic brain embolism, such as atrial fibrillation, anticoagulation should be continued for life.

Patients with TIA or stroke in association with idiopathic dilated cardiomyopathy should probably be treated with warfarin for life (target INR 2.5, range 2–3) once the hyperacute phase has passed, because of the high risk of embolisation without anticoagulant treatment.⁸² However, to our knowledge, randomised controlled trials comparing the outcome with warfarin treatment versus antiplatelet treatment for secondary stroke prevention in this patient population have not been performed either.

In conclusion, long-term oral anticoagulant treatment with warfarin is the treatment of choice for secondary stroke prevention in patients who have had a recent TIA or minor ischaemic stroke in association with persistent or paroxysmal NVAF or atrial flutter. If warfarin is contraindicated, long-term antiplatelet treatment with aspirin is a safe, but much less effective, alternative treatment option that should be considered pending future data on the efficacy of, and potential licensing of, direct thrombin inhibitors in this subgroup of patients with CVD. Future studies may also provide information about the efficacy and safety of combination antiplatelet treatment, or percutaneous or surgical LAA ablation, in patients with cardioembolic CVD who are deemed unsuitable for long-term warfarin. The management of young patients with TIA or

Table 1 Summary of the antithrombotic and interventional treatment options in patients with cardioembolic transient ischaemic attack and ischaemic stroke

Cardiac condition associated with TIA or stroke	Treatment	References
NVAF	Acute stroke: aspirin 300 mg daily for 7 days; then warfarin if clinically stable (target INR 2.5); stop aspirin when INR ≥ 2.5 TIA with normal CT/MRI: aspirin 300 mg daily and warfarin; stop aspirin when INR ≥ 2.5 Multiple TIAs on aspirin: empirical LMWH or intravenous heparin (target APTT ratio 2.3, range 2–2.5), then warfarin when clinically stable (target INR 2.5) Long-term secondary prevention: warfarin (target INR 2.5)	19, 24, 31
Atrial flutter	As per NVAF	(http://www.chestjournal.org/cgi/content/full/126/3_suppl/429S) ⁴⁹
PFO alone in cryptogenic stroke	Aspirin	(http://circ.ahajournals.org/cgi/content/full/105/22/2625) ⁶¹ (http://content.nejm.org/cgi/content/full/345/24/1740) ⁶²
ASA alone in young cryptogenic stroke	Aspirin	(http://content.nejm.org/cgi/content/full/345/24/1740) ⁶²
PFO and ASA in young patients with cryptogenic stroke	See fig 3	(http://content.nejm.org/cgi/content/full/345/24/1740) ⁶² (http://www.strokecenter.org/trials)
LV thrombus post-MI	Acute stroke/TIA: empirical LMWH, i/v heparin, or combination antiplatelet treatment; then warfarin when clinically stable (target INR 2.5) Long-term secondary prevention: initially warfarin (target INR 2.5); Consider antiplatelet treatment later (see text)	N/A
LV thrombus with IDC	Empirical long-term warfarin (target INR 2.5)	81

APTT, activated partial thromboplastin time; ASA, atrial septal aneurysm; CT, computed tomography; IDC, idiopathic dilated cardiomyopathy; INR, international normalised ratio; i/v, intravenous; LMWH, low-molecular-weight heparin; LV, Left ventricular; MI, myocardial infarction; MRI, magnetic resonance imaging; NVAF, non-valvular atrial fibrillation; PFO, patent foramen ovale; TIA, transient ischaemic attack.

stroke in association with an interatrial septal defect is controversial. Various treatment options have been outlined, but readers are encouraged to consider including these patients in one of the ongoing randomised clinical trials in this area. It is reasonable to consider empirical anticoagulation in patients with TIA or ischaemic stroke in association with left ventricular thrombus formation after myocardial infarction or in patients with idiopathic dilated cardiomyopathy. If warfarin is prescribed for any of these patients, one should aim for a target INR of 2.5 (range 2–3) to achieve the best balance between adequate secondary prevention of cardioembolic events and the risk of major haemorrhagic complications.

Table 1 summarises the antithrombotic and interventional treatment options in patients with cardioembolic transient ischaemic attack and ischaemic stroke.

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