Clinical review

Fortnightly review

Anticoagulation in heart disease

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Thromboembolism is a common complication of heart disease. The decision to prescribe an anticoagulant to prevent thromboemboli should be based on a particular patient's risk without treatment and the likely benefit and side effects of the proposed treatment. In this article we will discuss the use of warfarin and heparin in patients with heart disease.

Methods

This review article is based on our chapter in *Current Issues in Cardiology*, which was subject to formal peer review and published in 1997.¹ We undertook a full Medline search in each of the relevant subjects. We also sought references from recent papers, editorials, and review articles. When a choice was available we chose large well conducted double blind randomised trials, but we included observational series when they were the only available evidence.

Non-rheumatic atrial fibrillation

Atrial fibrillation is not benign and is the commonest cause of cardiogenic stroke (fig 1).² Within the general population the best available estimates suggest a

Fig 1 Computed tomogram of cerebral infarction, a well recognised complication of non-rheumatic atrial fibrillation

Summary points

Whether anticoagulant treatment should be started depends on the balance between the risk of thromboemboli without treatment and the likely benefits of treatment in each patient

Factors increasing the risk of bleeding include serious concomitant disease, previous gastrointestinal bleeding, uncontrolled hypertension, and immobility

Factors that cumulatively increase the risk of thromboembolism in non-rheumatic atrial fibrillation include age over 60, recent congestive heart failure, hypertension (treated or untreated), previous thromboembolism, and the presence of a large atrium or of global left ventricular dysfunction

Cardioversion of non-rheumatic atrial fibrillation (including fibrillation of new onset) is associated with an increased thromboembolic risk, which is reduced by anticoagulant treatment

Heparin and aspirin are both beneficial in unstable angina

Anticoagulants should be considered after myocardial infarction in patients with an increased risk of thromboemboli: patients in atrial fibrillation and those with persistent heart failure

prevalence of 0.5% for those aged 50-59, but this increases with age and dramatically after the age of 70 (fig 2).³ As many as 25% of patients presenting with an acute stroke will be in atrial fibrillation.⁴ Atrial fibrillation is more common in patients with heart failure, hypertension, and rheumatic heart disease, and the association with stroke is stronger. Although the association between atrial fibrillation and stroke can largely be explained by the propensity for thrombus to form within the fibrillating atria and subsequently embolise, a small but significant proportion of the strokes are not due to cardiogenic embolus: atrial

Fig 2 Prevalence of atrial fibrillation as function of age. Reproduced after Wheeldon with permission³

fibrillation may be a marker for coexistent cerebrovascular disease.

Not all patients with atrial fibrillation will benefit from anticoagulant treatment. The decision to treat an individual patient with warfarin should be based on convincing evidence that the risk of a thromboembolic event is greater than that of clinically significant bleeding. The age of the patient is an important determinant of events. For patients with atrial fibrillation but no evidence of any concurrent heart disease who are aged less than 60 the risk of serious bleeding is around 1.3%

Table 1 Risk stratification for thromboembolic events by clinical assessment in patients over 60 with non-rheumatic atrial fibrillation¹³

	Score*		
	0	1	≥2
No of patients	241	259	68
Prevalence of thromboembolic events (%)	2.5	7.2	17.6

*1 point each for history of hypertension (treated and untreated), congestive heart failure within previous three months, and previous embolism.

Table 2 Risk stratification for thromboembolic events by combined clinical and echocardiographic assessment in patients over 60 with non-rheumatic atrial fibrillation^{13 14}

	Score*		
	0	1-2	≥3
No of patients	147	336	78
Prevalence of thromboembolic events (%)	1.0	6.0	18.6

*1 point each for history of hypertension (treated and untreated), congestive heart failure within previous three months, previous embolism, global left ventricular dysfunction, and left atrial diameter >2.5 cm/m² body surface area. Addition of echocardiographic score permits reclassification of patients who seem to be at low risk clinically.

a year or more and greater than that of a thromboembolic event, which is around 0.6% a year.⁵ The recent trials of primary and secondary prevention in patients with non-rheumatic atrial fibrillation provide firm evidence of the benefit of anticoagulant treatment for some patients with atrial fibrillation.⁶⁻¹² However, these trials were based on highly selected patient populations, with only a few potentially eligible patients being randomised. To extrapolate data from such highly selected patients to a hospital based population is arguably hazardous—to the general community potentially more so.

An overview of the primary prevention trials suggests that the overall risk of stroke was 4.3% a year in the control group compared with 1.3% a year in those treated with warfarin (a 60% reduction in the incidence of stroke) (M S Leaning et al, unpublished data). This would mean treating 1000 patients with warfarin over 12 months to prevent 30 strokes. A similar reduction in relative risk for secondary prevention translates into the prevention of 80 strokes a year for every 1000 patients treated.¹² In these trials the overall incidence of haemorrhage was 1.3% a year for those receiving warfarin compared with 0.9% a year for the control group.

A history of recent congestive heart failure, hypertension, or thromboembolism and the presence of a large left atrium or global left ventricular dysfunction all increase the risk of thromboembolism. The more of these risk factors patients have the greater their risk of stroke (tables 1 and 2).^{13 14} Patients without any of these

Fig 3 Algorithm for anticoagulation in non-rheumatic atrial fibrillation

risk factors probably do not warrant anticoagulant treatment (because the risks of bleeding are likely to outweigh the potential benefits of anticoagulation). Although the potential benefits of warfarin generally increase in patients older than 60, clinical trials have either excluded or enrolled few patients aged 75-80 and above. Thus few data show benefit in this age group, but the risk of developing complications from anticoagulant treatment increases.¹¹ Although starting warfarin treatment may be hard to justify in patients aged 80 or over, those patients in whom anticoagulant treatment has been well tolerated should not be deprived of this treatment simply because they enter their ninth decade. However, anticoagulant treatment should be withdrawn if new clinically significant complications develop or become likely.

Trials of anticoagulation in atrial fibrillation have not compared different degrees of anticoagulation, but usual practice is to achieve an international normalised ratio in the range of 2-3, unless there is evidence of recurrent thromboemboli (fig 3). The idea that fixed dose low intensity warfarin treatment combined with aspirin might confer similar benefit to

conventional warfarin treatment but with fewer side effects was not proved when these treatment strategies were compared in patients with non-rheumatic atrial fibrillation at high risk of thromboemboli.¹⁵ Combined treatment was less effective in preventing systemic embolism and no safer than conventional warfarin treatment.

Aspirin treatment is often recommended for elderly patients with non-rheumatic atrial fibrillation. However, the benefits of aspirin are likely to be less than those of warfarin in the same way that the risks are less.¹² There is no evidence of the efficacy of aspirin in doses of less than 325 mg daily for primary prevention.^{6 11}

Paroxysmal atrial fibrillation

Paroxysmal atrial fibrillation covers a wide range of disease severity, with the duration and frequency of attacks varying markedly both between and within patients. As episodes become more frequent and of longer duration the risks may approach those of chronic atrial fibrillation, with factors such as associated heart disease and left ventricular function

Fig 4 Algorithm for anticoagulation and cardioversion of atrial fibrillation of recent onset (<3 days)

further modifying these risks. Patients should be given appropriate anticoagulant treatment.

Cardioversion of atrial fibrillation

An increased incidence of embolic events (0.8-5.6%) has consistently been reported in the weeks after cardioversion even when sinus rhythm is maintained.¹⁶ Transoesophageal echocardiography has improved the visualisation of clot within the left atrium and left atrial appendage and provided new insights into the mechanisms of thromboemboli complicating cardioversion, but it is not available in all centres. Persistent thrombus has been reported in some patients despite anticoagulation for the standard four weeks and with more prolonged anticoagulant treatment.¹⁷ Both new clot and spontaneous contrast (which is itself associated with clot formation) can develop after DC cardioversion and spontaneous reversion to sinus rhythm.¹⁸ Furthermore, patients who have undergone cardioversion without anticoagulation after the presence of left atrial and left atrial appendage clot had been excluded by transoesophageal echocardiography have subsequently developed thromboemboli.¹⁸ Cardioversion without anticoagulation has long been regarded as safe in atrial fibrillation of recent onset, but the basis for these recommendations is empirical, not without hazard, and increasingly questioned.¹⁹⁻²¹ Figures 4 and 5 show our suggested approach to anticoagulant treatment in patients with atrial fibrillation undergoing elective cardioversion.

Unstable coronary syndromes

Thrombosis on a substrate of plaque fissure (fig 6) in the coronary arteries is the usual precipitant of unstable angina and acute myocardial infarction. The high risk of infarction in patients with unstable angina is reduced by aspirin, and the combination of intravenous heparin and aspirin may reduce the acute risk further.²² Recent attention has focused on the use of low molecular weight heparin, which is easier to administer and seems to have fewer side effects than standard heparin. Low molecular weight heparin administered to patients already taking aspirin during the early high risk period of unstable angina has been reported to reduce death and infarction by 60%.²³ Other new anticoagulants including hirudin and its derivatives, argatroban, antithrombin III, and anicrod, are currently the subject of clinical trials. Whichever antithrombotic and anticoagulant agents are used in managing patients with unstable angina, urgent coronary angiography with a view to revascularisation is required if their condition does not settle.

Although evidence to support the use of thrombolytic agents in patients with unstable angina is lacking,²⁴ overwhelming evidence shows the benefit of aspirin and thrombolytic agents in patients with acute myocardial infarction.²⁴ Benefit is seen with either agent, but the combined effect is more powerful than the sum of both.²⁵ The earlier thrombolysis is given the greater the benefits.²⁶ Since the fissured plaque remains a potent stimulus for thrombosis even after thrombolysis, aspirin treatment should be continued indefinitely in patients who can tolerate it. Despite theoretical arguments that heparin should provide additional

Fig 5 Algorithm for anticoagulation and cardioversion of chronic atrial fibrillation (≥3 days)

Fig 6 Ruptured plaque in arterial vessel with thrombus occluding the lumen, which was fatal

Fig 7 Transthoracic echocardiographic images of thrombus in apex of left ventricle in patient presenting with cardiomyopathy and atrial fibrillation of recent onset. Top: Apical long axis view. Bottom: Parasternal short axis view

clinical benefit to thrombolysis and antiplatelet treatment, supporting evidence is little and such combination treatment increases the risk of major bleeding.²⁷ Even less evidence supports adding heparin to aspirin in patients with acute myocardial infarction who are not given thrombolytic agents, but this may change when the results of the first American study of infarct survival (ASIS) are reported.

After myocardial infarction

Long term anticoagulation after myocardial infarction has attracted considerable interest over the past 30 years. Most of the early trials were undertaken when patients were treated with prolonged strict bed rest for many weeks, which increases the risk of deep venous thrombosis and pulmonary embolism. An overview of several of the larger, more recent and better designed studies suggested a 22% reduction in mortality after myocardial infarction in patients taking warfarin compared with those who were not, but most of the trials included in this meta-analysis pre-dated the use of thrombolytic agents. A significant reduction in mortality was not shown in a recent study of oral anticoagulation after myocardial infarction.²⁸ For every 1000 patient years of anticoagulation there were 28 fewer first re-infarctions and five fewer cerebrovascular

events at the expense of 10 additional major haemorrhages. The efficacy and safety of warfarin or aspirin, or both, after myocardial infarction are being further examined in several trials. There is evidence that fixed, low dose warfarin combined with low dose aspirin (80 mg) does not confer any advantage over treatment with aspirin alone at 160 mg a day after acute myocardial infarction.²⁹

Most units in the United Kingdom do not use warfarin routinely after myocardial infarction, but long term anticoagulant treatment should be considered in selected patients at high risk of thromboembolism, including patients who are immobile, have severe heart failure, have left ventricular thrombus or aneurysm, or have a history of deep venous thrombosis or pulmonary embolism. Aspirin treatment is usually stopped when warfarin treatment is started.

Heart failure

Rates of thromboembolism in heart failure vary from 2.5% a year in patients with symptoms on mild to moderate exertion to 20% in hospital patients with dilated cardiomyopathy, although subclinical thromboemboli may be more common (fig 7).³⁰ Retrospective analyses of the role of anticoagulants (or antiplatelet agents) in reducing either mortality or thromboembolism rates in patients with heart failure have produced conflicting results. Several studies that may answer these questions are actively recruiting. Until the results from these trials are reported anticoagulant treatment should be considered in patients at high risk of embolism (including patients with atrial fibrillation, left ventricular thrombus, and previous thromboembolism). Patients whose condition is less stable and who have heart failure will require especially careful monitoring because varying hepatic congestion will alter their warfarin requirements and control of anticoagulation. There is no evidence to recommend routine anticoagulant treatment in patients in heart failure and sinus rhythm.

Rheumatic valve disease

Patients with atrial fibrillation and rheumatic valve disease have an increased risk of thromboembolism compared with patients in sinus rhythm and require long term anticoagulant treatment. This includes patients with rheumatic valve heart disease and both paroxysmal and chronic atrial fibrillation. In the presence of mitral (or tricuspid) stenosis and sinus rhythm indications for anticoagulation include an enlarged atrium, the presence of atrial clot, and evidence of previous thromboembolism. These patients should be referred for formal cardiological opinion because of the importance of ensuring optimal timing of intervention.

Anticoagulant control

In clinical practice the dose of warfarin is titrated against the induced coagulation defect assessed by a biological assay, the prothrombin time. The prothrombin ratio, of treated to untreated control, varies markedly depending on the source of thromboplastin. In the United Kingdom these inconsistencies have for

some years been minimised through national quality control: more recently there has been widespread acceptance of the international normalised ratio. However, much of the existing literature is based on estimated values, which are not equivalent to values derived using a reference source of thromboplastin.

In the United Kingdom anticoagulation is predominantly monitored by anticoagulant clinics, where decisions on the dose of warfarin may be entirely based on doctors' practice or computer programs,^{31 32} with resulting variations in achieved degrees of anticoagulation. A similar approach is found in other European countries.³³ Reported series suggest patients may be inadequately treated for large periods of time,^{34 35} and in some studies this correlates with increased rates of illness. Inadequate warfarin dosing occurs more often in the more intense target range (international normalised ratio 3.0-4.5) when determined by a doctor rather than with the help of a computer system.³¹

A potential advantage of the computer assisted dosing algorithms is that they can be designed to weight dosing recommendations towards the mid-point of a target range rather than assuming that either end of a range is acceptable. This would facilitate the practice of a target international normalised ratio within an accepted range, as recently advocated by the European Atrial Fibrillation Trial Study Group³⁶ and supported by others.³⁷ Historically the recommended degrees of anticoagulation have been broadly divided into low (international normalised ratio 2.0-3.0) and high (ratio 3.0-4.5) intensity ranges, now to be replaced by target ratios of 2.5 and 3.5 respectively.³⁷ International normalised ratios below 2.0 are associated with increased thromboembolic events and those above 5.0 with increased bleeding complications.^{33 36} For practical purposes anticoagulation will be achieved in most patients within the low intensity range (ratio 2.0-3.0 or target ratio 2.5). Exceptions to this include patients with certain prosthetic valves (see website at www.bmj.com) and patients who continue to experience thromboemboli despite anticoagulation in the range 2.0-3.0. In some of these patients who are also at increased risk of bleeding medium intensity anticoagulation (target ratio 3.0) may offer a compromise between the high intensity anticoagulation which their thromboembolic risks advocate and the lower degree of anticoagulation which their likelihood of bleeding advocates. For these patients this intermediate degree of anticoagulation should avoid the risks associated with international normalised ratios below 2.0 or above 5.0 which seem to be inevitable for at least some of the time with target ranges of 2.0 to 3.0 and 3.0 to 4.5 respectively.^{33 36}

Bleeding risks with warfarin

The risk of bleeding related to warfarin is highest at the start of treatment, the risk during the first month being 10 times the risk at 12 months.³⁸ Certain conditions are associated with an increased risk of bleeding (box). The commonest sites of such bleeding include the gastrointestinal tract, the urinary tract, the soft tissues, and the oropharynx. Intracranial bleeding is comparatively rare, accounting for about 2% of anticoagulant

Risk factors for bleeding with anticoagulants

Serious comorbid disease, including anaemia, renal, cerebrovascular, heart, and liver disease
Previous gastrointestinal bleeding
Erratic or excessive alcohol misuse
Immobility
Uncontrolled hypertension
Poor quality clinical and anticoagulant monitoring
Limited understanding of anticoagulation by patients

related bleeding, but it is the commonest cause of fatal bleeding (fig 8). Whether age itself is associated with an increased risk of bleeding remains unresolved, but the higher the international normalised ratio the greater the risk of bleeding.³⁸⁻⁴¹ The recent trials of anticoagulation in non-rheumatic atrial fibrillation emphasise another aspect of bleeding related to anticoagulants—namely, that the incidence can be reduced with diligent clinical follow up.⁶⁻¹²

Community and near patient testing

The principle of patients controlling their own treatment is well established for conditions such as asthma and diabetes, in which the benefits are considerable. For this approach to be safely adopted for anticoagulation an overall package of care needs to be developed. In recent years some of the necessary prerequisites have been met, including the widespread introduction of the international normalised ratio and the development and validation of sophisticated electronic advisory systems for warfarin dosage, follow up, and drug interactions.^{31 32 42} The improved consistency of advice on dosage that has accompanied the use of these systems has allowed other healthcare

Fig 8 Computed tomogram showing an intracerebral bleed (white area), a rare but devastating complication of anticoagulation

professionals (with appropriate medical support) to run anticoagulant clinics and to move from the hospital setting into the primary care environment.⁴³ Despite these advances, patients' participation in starting and controlling anticoagulation remains generally limited in the United Kingdom, although it is more widespread and actively promoted by the manufacturers of coagulometers in other European countries. There remains a paucity of literature on the role of patient education and participation in starting and controlling anticoagulation. Until these deficits have been adequately addressed the widespread introduction of self testing seems unwise.

Despite the limitations of the literature and resulting clinical uncertainties, the judicious use of anticoagulation is an important aspect of the management of patients with heart disease. The potential benefits of anticoagulation can be optimised by the careful assessment of the risks of thromboemboli and of haemorrhage in every person in whom this treatment is considered. Although this approach will be time consuming, the reward for patient and doctor can be profound.

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Endpieces

The country matters

There is a strategy of attacking established institutions. When this happens you release destructive power that those institutions had evolved to contain. You release bitterness and anger, not enlightenment and freedom.

Eric Bettelheim in *Labour Camp* by Stephen Bayley
(B T Batsford, 1998)