Anticoagulation for cardioversion of atrial arrhythmias

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Introduction

Cardioversion of atrial arrhythmias may be accompanied by thromboembolic complications[1–6]. In order to avoid this, the American College of Chest Physicians have recommended that patients who have been in atrial fibrillation for more than 2 days should receive warfarin therapy for 3 weeks before elective cardioversion and that warfarin should be continued until sinus rhythm has been maintained for 4 weeks. The recommendations regarding atrial flutter are more guarded, but they suggest that consideration should be given to managing this arrhythmia in the same way as atrial fibrillation. They further suggest that no antithrombotic therapy for cardioversion of supraventricular tachycardia or for cardioversion of patients who have been in atrial fibrillation for less than 2 days is required unless other risk factors for systemic embolism are present[7]. In this paper we review the literature on which these recommendations are based; the aim of this work is to provide the necessary background information to allow clinicians to make informed decisions about the appropriate degree of anticoagulation in individual cases that may not fall neatly into a broad category.

Why anticoagulate at all?

Studies in the 1960s suggested that cardioversion is accompanied by thromboembolic complications in 1.5–6% of interventions[1–6]. These embolic events may occur at the time of cardioversion, but more often happen hours or days later. In 1969, Bjerkelund and Orning demonstrated that anticoagulation could reduce the rate of embolic events[6]. This was a key study. Two hundred and twenty-eight patients received warfarin, with a subsequent embolic rate of 1.1%, whilst in 209 patients who received no anticoagulants 6.8% had thromboembolic complications. Criticisms of the study include lack of randomization and that the exact atrial arrhythmias were not defined. However, patients considered to be at the highest risk of embolic complications were those who received anticoagulation and who subsequently had a comparatively low embolic event rate. The reason why even these patients had a relatively high embolic event rate of 1.1% may be because they were at high risk. There have been no blinded randomized studies, but reports of complications from further studies have chiefly been in patients either not receiving anticoagulation or in those who have not been adequately anticoagulated[8–11].

What is the mechanism of thromboembolism after cardioversion?

Initially it was thought that thrombus formed due to the relative stagnation of blood in the atria. The increase in some clotting factors[12,13] and elevated levels of atrial natriuretic peptide (which may cause an increase in haematocrit)[14] observed in atrial fibrillation may contribute to thrombus formation. Previously formed atrial thrombus may be dislodged by the return of mechanical atrial contraction after cardioversion. The delay in embolic complications can be explained by the observation that, although coordinated atrial electrical activity occurs immediately after cardioversion, normalization of mechanical atrial contraction often takes longer[15–20], maybe as long as a month[20]. Thrombus may be dislodged only later when atrial contraction is stronger. Thus, it was considered that only patients with pre-formed thrombus were at risk of thromboembolism. These theories, however, are inconsistent with the observation that patients with paroxysmal atrial fibrillation have a similar, if not lower, embolic complication rate than those in sustained atrial fibrillation[21–23]. In paroxysmal atrial fibrillation one might expect the increase in atrial mechanical contractile strength during each reversion to sinus rhythm to pose a threat of dislodging thrombus from the atria and thus for this type of arrhythmia to have a particularly high embolic event rate.

Recent studies have challenged the view that it is only pre-formed thrombus that poses a risk during cardioversion. These studies have viewed the atria using transoesophageal echocardiography during cardioversion. One study observed that up to 35% of patients

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either developed ‘smoke’ in the atria, or previously observed ‘smoke’ worsened; this finding has been replicated. ‘Smoke’ or spontaneous echo contrast in the atria is associated with the formation of atrial thrombus. Atrial thrombus has also been found to be present post-cardioversion, when none was present before. Additionally, left atrial appendage emptying velocities on average decrease, in spite of the development of coordinated electrical activity after cardioversion, presumably due to ‘stunning’ of mechanical function. This may produce an increased potential for thrombus to form in the left atrial appendage post-cardioversion.

Further evidence for the predisposition of the post-cardioversion atria to develop thrombus comes from studies that have used transoesophageal echocardiography to attempt to negate the need for anticoagulation, the premise being that if no thrombus was demonstrated by transoesophageal echocardiography, no anticoagulation was required for cardioversion. However, a number of thromboembolic complications have been reported from these studies. Although transoesophageal echocardiography is not perfect for excluding atrial thrombus, the number of embolic events exceeded those that would be expected if a small number of atrial thrombi were missed. This favours the assumption that thrombus develops in the atria after, and possibly as a consequence of, cardioversion.

**Chronic atrial fibrillation**

The above studies provide the background for the current American College of Chest Physicians’ proposals. For cardioversion of chronic atrial fibrillation the recommendation of 3 weeks of prior anticoagulation and 4 weeks of continued anticoagulation after the procedure would seem adequate. Although the time period for anticoagulation post-cardioversion can be justified by the finding that mechanical atrial contraction has recovered in most cases by this time (and thus the potential to develop further atrial thrombus is hopefully no longer present), the pre-procedure recommendation of duration of anticoagulation is anecdotal; it is thought to be sufficient time for thrombus that is performed to either resolve or to become adherent to the atrial wall so it will not dislodge when mechanical atrial contraction resumes. It is known that 3 weeks anticoagulation is not sufficiently long for all thrombus to resolve. Nevertheless, adequate anticoagulation for this period of time results in very few complications and thus the guidelines would seem to be sensible. If sinus rhythm is not restored, then the majority of patients will require long-term anticoagulation to prevent stroke. In the case of those who would not otherwise receive long-term anticoagulation it would seem reasonable to continue anticoagulants for 4 weeks after the procedure as one would if they had reverted to sinus rhythm; this is on the premise that the atria in these patients may also be ‘stunned’ and have a greater propensity to thrombus formation immediately after cardioversion.

Many further questions, however, arise: can acute atrial fibrillation be treated differently from chronic atrial fibrillation? Is chemical cardioversion safer than electrical cardioversion? What about atrial arrhythmias other than atrial fibrillation? There is incomplete information to date to answer these questions adequately, but while further studies are carried out patients need to be managed based on existing evidence.

**Acute atrial fibrillation**

Often the onset of atrial fibrillation can be timed from the presenting history. The American College of Chest Physicians give no recommendations for anticoagulation for patients developing atrial fibrillation within 48 h of cardioversion. They suggest that the usual practice is not to give anticoagulant therapy. It has been assumed in the past that 48 h is insufficient time for thrombus to form. However, more recent evidence suggests that this is not the case and thrombus has been found to form within a few hours of the development of atrial fibrillation in some patients. This study, using transoesophageal echocardiography, found left atrial appendage thrombus to be present in 14% of 143 patients with acute onset (<3 days) of atrial fibrillation, compared with 27% of 174 patients with chronic atrial fibrillation.

In addition there is the question of development of thrombus after cardioversion. It is possible that patients with recent onset of atrial fibrillation are less likely to develop post-cardioversion thrombus, since the return to normal mechanical atrial contraction is dependent on the length of time the patient has been in atrial fibrillation, those with recent onset of atrial fibrillation regaining normal mechanical atrial contraction within 24 h of cardioversion.

Until more information is available, it is the authors’ policy to anticoagulate with heparin all patients presenting acutely with atrial fibrillation. Such patients receive rate-limiting drug therapy and are observed for 24–36 h, during which time a large proportion of patients spontaneously revert to sinus rhythm. Those who require cardioversion receive warfarin, and heparin is continued until the international normalized ratio is 2, after which warfarin is continued for 4 weeks as an outpatient. If sinus rhythm is not restored after attempted cardioversion then all patients receive 4 weeks of warfarin therapy; this is continued indefinitely in the case of those patients who require long-term treatment for the prevention of stroke.

**Chemical cardioversion**

One of the cited studies reporting thromboembolic complications with cardioversion refers to 400 patients...
cardioverted using quinidine\textsuperscript{34}. The rate of embolism was 1.5\%, which is similar to the mean rate reported by studies observing electrical cardioversion without anticoagulation\textsuperscript{11–13}. There are other studies reporting embolic episodes following cardioversion with quinidine\textsuperscript{25–37} and a case report of embolic stroke following cardioversion of atrial fibrillation to sinus rhythm with oral amiodarone\textsuperscript{38}. In addition, it has been demonstrated that restoration of atrial mechanical function after pharmacological cardioversion is slow and gradual, as it is after electrical cardioversion\textsuperscript{39}. Therefore, we would advocate using anticoagulant therapy in chemical cardioversion in the same way as in electrical cardioversion.

Atrial arrhythmias other than atrial fibrillation

In the early studies of the complications of cardioversion no differentiation was made between different types of atrial arrhythmias. There are no adequate studies to offer guidance on the best anticoagulant regime for the cardioversion of atrial arrhythmias other than atrial fibrillation. It has been suggested that with atrial flutter there is coordinated atrial activity and therefore no anticoagulation is required\textsuperscript{9}. However, atrial thrombus has been reported in one of eight patients in atrial flutter in whom transeosophageal echocardiography was carried out pre-cardioversion; additionally, in a further two, spontaneous contrast was observed\textsuperscript{40}. In a further transeosophageal echocardiography study of seven patients with atrial flutter one patient had atrial thrombus and three had atrial spontaneous contrast\textsuperscript{28}. This would suggest that patients with atrial flutter are also prone to develop atrial thrombus. In addition there is the possibility that thrombus may form after cardioversion. Arnold and colleagues have reported on 122 patients with atrial flutter who were cardioverted\textsuperscript{9}. Thirty two received anticoagulation and 90 did not. There were no embolic events. The authors suggest that, based on these results, anticoagulation is not required for cardioversion of atrial flutter. However, if one assumes a similar embolic event rate for atrial flutter as fibrillation (about 2\% on average), one might expect two events in the 90 non-anticoagulated patients. The numbers in this study are too small to draw any conclusions. In view of the observations that atrial flutter seems to predispose to atrial thrombus formation\textsuperscript{27,40}, it is our practice to treat patients with atrial flutter identically to those with atrial fibrillation until further information becomes available.

Most other atrial arrhythmias, when not self-terminating, are chemically cardioverted in the accident and emergency department, after which patients are usually allowed home. These patients are often young and if thromboembolism was a real complication then this would be apparent by case reports.

Role of echocardiography

Transthoracic echocardiography is inadequate as a screening investigation for the detection of atrial thrombus owing to its low sensitivity\textsuperscript{41}. However, some groups of investigators have proposed transeosophageal echocardiography as a useful screening tool for pre-formed atrial thrombus in patients with atrial fibrillation. On average this has a 92\% sensitivity for detection of atrial thrombi (compared with surgical findings\textsuperscript{10}). It has been suggested that those patients in whom thrombus is not seen at transeosophageal echocardiography can be cardioverted without prior anticoagulation\textsuperscript{40,42–43}. However, there still seems to be the risk of thrombus forming post-cardioversion\textsuperscript{27} and a further study has reported on 17 patients who had embolic events after an atrial thrombus was excluded by transeosophageal echocardiography pre-cardioversion\textsuperscript{10}. A meta-analysis of patients who had atrial thrombus excluded by transeosophageal echocardiography pre-cardioversion and were inadequately anticoagulated showed an embolic event rate of 1.34\%, compared with 0.33\% in an anticoagulated control group (P = 0.04\textsuperscript{44}). A recent study has reported on 230 patients who underwent transeosophageal echocardiography before cardioversion\textsuperscript{45}. One hundred and ninety-six patients without atrial thrombi were cardioverted without prolonged previous anticoagulation. Those who were considered candidates for anticoagulation (i.e. those who were not at high risk of haemorrhage) received heparin prior to cardioversion and 3 weeks of warfarin thereafter. There were no embolic events in any patients using this protocol. These studies suggest that transeosophageal echocardiography may be used to reasonably exclude atrial thrombus and negate the requirement for prolonged pre-cardioversion anticoagulation; however, anticoagulation during cardioversion and for 3–4 weeks post-procedure is still required.

Degree of anticoagulation

Different studies have used different anticoagulant regimes so there are no clear guidelines; it seems reasonable to aim for an activated partial thromboplastin time of between 1.5 and 2.5 compared with control if using heparin and an international normalized ratio of between 2 and 3 if using warfarin. A recent study of patients with chronic atrial fibrillation indicated that among patients who were anticoagulated with warfarin the risk of stroke rose steeply when the international normalized ratio was maintained below 2\textsuperscript{46}. In addition, the risk of major haemorrhage with warfarin increases rapidly as the international normalized ratio exceeds 4–5, but is fairly stable at lower levels\textsuperscript{47–49}.

A further issue relates to the potential use of low molecular weight heparins. There are no studies reporting their use in this context but they are at least as effective as unfractionated heparin in treating and
Patients at high risk of haemorrhage

The above suggestions are based on patients with a low risk of haemorrhage. In those with a higher risk, individual decisions need to be made about whether to attempt cardioversion and if so, whether and for how long, the patient needs to be anticoagulated. Although the following percentages cannot be used as accurate assessments of the risks and benefits of anticoagulation in the setting of cardioversion, they help provide a framework to make informed decisions about individual cases: on average the embolic risk of cardioversion is approximately 2%. The degree of reduction of risk by using anticoagulants is unclear. The one study comparing a group of patients who received anticoagulants with a group who did not, had an embolic event rate of 1.1% in the anticoagulated group. However, this is almost certainly an overestimate of embolic risk with anticoagulation since the event rate in general was very high, with a rate of 6.8% in the untreated group. In addition, the study was not randomized, all of the high risk patients being given anticoagulants. Finally, the degree of anticoagulant control was not reported and some patients in the active limb may have been under-treated. Overall, the reduction in the risk of embolism with the use of anticoagulants would seem to be a least 1% (from 2% to 1%).

In the ‘stroke prevention in atrial fibrillation’ study, the rate of major bleeding in patients taking warfarin was 1.5% per year, half of which were cerebral bleeds. This rate, however, was similar in the placebo arm of the study. Estimates of the rate of anticoagulant-related intracranial haemorrhage are in the order of 0.3–0.6% per year (i.e. 0.05–0.10% for a 2 month period of anticoagulation). This rate may be about 2% per year in patients older than 75 years (i.e. 0.3% for a 2 month period). When compared with the degree of risk reduction with treatment the above evidence seems to favour the case for anticoagulation of all except those considered to be at very high risk of bleeding.

Summary

We would advocate 3 weeks of anticoagulation prior to, and 4 weeks post-cardioversion (either electrical or chemical) for patients in chronic atrial fibrillation or flutter. In selected cases it seems reasonable to use transoesophageal echocardiography to exclude preformed thrombus and negate the need for 3 weeks of prior anticoagulation. For patients presenting acutely with atrial fibrillation or flutter we suggest anticoagulating with heparin immediately on presentation and for those who do not spontaneously revert to sinus rhythm, using transoesophageal echocardiography to exclude atrial thrombi prior to cardioversion. Oral anticoagulation should be continued for 4 weeks post-procedure. If transoesophageal echocardiography is not readily available an alternative strategy would be to anticoagulate the patient for 3 weeks and thereafter readmit them for elective cardioversion, continuing the anticoagulation for a further 4 weeks after the procedure.

References


