COMMENTARY

Anticoagulation for atrial fibrillation: should warfarin be temporarily stopped or continued after acute cardioembolic stroke?

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Abstract

Despite anticoagulation for atrial fibrillation, some patients still suffer an ischaemic stroke. The issue of whether to stop or continue warfarin, or possibly to reverse the anticoagulation is an area of uncertainty. Continued anticoagulation may, however, increase haemorrhagic transformation of the infarct. In this article we review the published evidence in an attempt to quantify the risks and benefits of each treatment strategy and identify areas for further research.

Keywords: stroke, atrial fibrillation, warfarin, haemorrhage, elderly

Example case

A 75-year-old man with hypertension, diabetes mellitus and atrial fibrillation (AF) is taking warfarin for the primary prevention of stroke. He developed aphasia and right hemiparesis 6 hours ago. An urgent CT brain scan suggests early infarction in the left middle cerebral artery territory. His international normalised ratio (INR) is 2.0. What action, if any, should be taken regarding his warfarin treatment?

The above scenario (involving a hypothetical patient) may affect 1–4% of AF patients per year despite anticoagulation [1].

Treatment options include the following:

(1) Continue his warfarin, aiming for an INR above the conventional target of 2.5 (range 2.0–3.0) as warfarin has ‘failed’ to prevent a stroke. Review his INR records to look for recent readings below 2.0.

(2) Stop his warfarin and allow the INR to fall slowly. Consider giving aspirin or heparin as temporary ‘bridging therapy’ until warfarin is re-started later.

(3) Stop his warfarin and normalise the INR immediately given the risks of haemorrhagic transformation of the infarct and potential neurological worsening.

Long-term treatment with warfarin gives a 60% relative risk reduction for cardioembolic stroke, but if the INR falls below 2.0 the risk of embolism increases, and at INRs over 3.9, the risk of haemorrhage outweighs any benefit [1]. Strokes occurring despite adequate anticoagulation should prompt a search for other causes, such as small artery occlusion or carotid thromboembolism. Increasing numbers of patients are being anticoagulated for the primary and secondary prevention of stroke related to AF, but there is still uncertainty regarding the timing and method of anticoagulation after an acute stroke. Many clinicians withhold anticoagulants for 10–14 days in the belief that this limits haemorrhagic transformation of infarction (HTI) but some still give unfractionated or low molecular weight heparin in selected patients at an earlier stage [2]. In general, however, national guidelines do not recommend early anticoagulation (Table 1).

The fundamental question is, therefore, ‘How do we balance the risk of recurrent cardioembolism against the risk of haemorrhagic transformation in a large infarct?’ We reviewed the evidence by posing a series of four questions...
Heparin treatment for 5 days was associated with a significant reduction in disability, but rates of symptomatic brain hemorrhage increased significantly. Some of the studies that reported no increase in HTI were small, so no conclusions could be drawn about recurrence rates in this group.

In the International Stroke Trial (IST), 16% of patients had AF, and in the group randomised to placebo treatments, ischaemic stroke occurred in 4.9% of AF patients within 14 days [7, 8]. Early anticoagulation with subcutaneous heparin was associated with a 2.1% absolute reduction in recurrent ischaemic stroke, but this benefit was negated by a similar increase in cerebral haemorrhage.

A trial of low molecular weight heparin in acute ischaemic stroke and AF (HAEST) compared dalteparin with aspirin and had no placebo arm to inform on the course of this condition when left untreated [9]. The incidence of recurrent ischaemic stroke in the first 14 days was approximately 8% in both treatment groups.

These large, randomised trials provide the best evidence about recurrence of cardioembolic stroke, but some smaller studies have provided useful insights.

Camerlingo et al. [10] investigated the use of intravenous heparin within 3 h of the onset of non-lacunar stroke. Heparin treatment for 5 days was associated with a significant reduction in disability, but rates of symptomatic brain haemorrhage increased significantly.

In a retrospective study of anti-thrombotic treatments after cardioembolic stroke, just 2 out of 204 patients (1%) had a further stroke during their inpatient stay (the length of time not stated) [2]. The number of patients on ‘no treatment’ was small, so no conclusions could be drawn about recurrence rates in this group.

A post hoc analysis of data from the HAEST trial found no clinical, haemostatic or inflammatory variables that were associated with benefit from early heparin treatment [11]. No study has found reliable echocardiographic predictors of early stroke recurrence.

Answer: Most large, well-designed studies suggest that cardioembolic stroke in patients with AF recurs in 5–8% within 14 days. Anticoagulation appears to reduce early recurrence, but at the expense of increased intracerebral haemorrhage.

How common is haemorrhagic transformation and does anticoagulation increase the risk?

Some degree of HTI occurs in 15–45% of cerebral infarcts at 1–4 days (published incidence rates vary depending on the imaging modality and study methodology). The majority of haemorrhagic transformations are early petechial haemorrhages with no mass effect and appear to be of little clinical significance. The other subgroup of HTI, parenchymal haematomas (PHs), tends to be larger, and the more severe type 2 PH with mass effect is associated with significant symptoms and adverse prognosis [2, 12].

A study involving CT scanning 5 days after an ischaemic stroke found HTI in 9%, of which one-third were PHs [13]. PHs showed a significant association with large infarcts, strokes of presumed cardioembolic origin and increased mortality.

In the IST, medium-dose heparin (12,500 units twice daily) given within 48 h of stroke onset increased haemorrhagic transformation in patients with and without AF [8]. Intravenous heparin also increased symptomatic brain haemorrhage from 1.4 to 6.2% in the study by Camerlingo et al. [10].

Many of the studies that reported no increase in HTI with anticoagulation were small and non-randomised, but overall, reviews of heparin use in acute ischaemic stroke have concluded that it increases haemorrhagic transformation [14, 15]. Some clinicians repeat brain imaging several days after a stroke to look for HTI and therefore guide the

### Table 1. Summary of national guideline recommendations regarding anticoagulation in acute ischaemic stroke.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Early anticoagulation in acute ischaemic stroke</th>
<th>Management of patients already warfarinised at the time of ischaemic stroke</th>
<th>When to start warfarin after stroke due to AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Clinical Guideline for Stroke, Royal College of Physicians 2008 [3]</td>
<td>Not recommended</td>
<td>No guidance</td>
<td>Usually not within 14 days</td>
</tr>
<tr>
<td>European Stroke Organisation 2008 [4]</td>
<td>Could start warfarin immediately after minor stroke. Early heparin not recommended</td>
<td>No guidance</td>
<td>Wait for some (e.g. 4) weeks</td>
</tr>
<tr>
<td>American Heart Association/American Stroke Association 2007 [5]</td>
<td>Not recommended</td>
<td>No guidance</td>
<td>Within 2 weeks (or longer if large infarct or uncontrolled hypertension)</td>
</tr>
</tbody>
</table>

*Except in selected patients with a high risk of venous thromboembolism.*
timing of anticoagulation, although evidence to support this practice is lacking [16].

Other clinical scenarios requiring anticoagulation after acute stroke can provide useful information. Current guidelines suggest that in stroke patients with proximal deep vein thrombosis, the risk of HTI is low enough to recommend acute anticoagulation to prevent pulmonary embolism [3].

Patients who are anticoagulated for prosthetic heart valves who suffer an ischaemic stroke are recommended to switch to aspirin 300 mg daily temporarily and restart anticoagulation after 1 week but this is based on expert consensus rather than trial evidence [3].

**Answer**: HTI is common, but only large PHs are clinically significant. Anticoagulation is associated with a small increase in parenchymal brain haemorrhage.

**Is there evidence that HTI increases with the level of anticoagulation and is reversal of anticoagulation, therefore, beneficial?**

In the IST, medium-dose heparin caused more haemorrhagic strokes than low-dose heparin but the level of anticoagulation was not monitored or adjusted [8]. Chamorro et al. [17] analysed a case series of 231 stroke patients with AF treated acutely with heparin and found that symptomatic haemorrhagic transformation occurred in five patients and was associated with higher levels of anticoagulation. It is possible that rapid reversal of anticoagulation reduces the risk of early haemorrhagic transformation compared with a practice of stopping warfarin and allowing the INR to fall slowly, but no clinical trials of this question were found.

**What is the role of aspirin as a bridging therapy in cardioembolic stroke?**

The absolute reduction of 1% in early stroke recurrence for AF patients in the IST and CAST is similar to that for patients in sinus rhythm, raising the possibility that aspirin does not prevent cardioembolism, but prevents vascular complications in general [6, 8]. Aspirin was not associated with a significant increase in haemorrhagic transformation in the AF subgroups.

**Meta-analysis and expert consensus**

A Cochrane review found that ischaemic strokes in general did not benefit from early anticoagulation, but did not specifically address cardioembolic stroke [14]. A meta-analysis of seven trials concluded that ‘early anticoagulation is associated with a non-significant reduction in recurrence of ischaemic stroke, no substantial reduction in death and disability, and an increase in intracranial bleeding’ [15]. Hart et al. [16] performed a meta-analysis of 3 acute trials involving AF patients (IST, CAST and HAEST) and found a small benefit from aspirin but no net benefit with heparin. No guidance is given for patients already taking warfarin at the time of their stroke.

**Questions for future research**

In order to clarify the best management of our example patient, more evidence is needed to answer the following questions.

1. Is there an INR level above which emergency reversal is advisable to minimise the risk of HTI in acute cardioembolic stroke?
2. Are there methods to predict the risk of HTI in acute stroke, to guide the risk–benefit decision regarding the timing of future anticoagulation?
3. How does the risk of HTI relate to hypertension in acute stroke or to the presence of leukoaraiosis or previous microbleeds on brain imaging?

**Key points**

- Cardioembolic stroke due to AF recurs in about 5–8% of patients in the first 2 weeks.
- The risk of the PH type of HTI is increased by anticoagulation, so it seems reasonable to stop warfarin in anticoagulated patients who suffer ischaemic stroke and allow the INR to fall slowly to normal.
- Current guidelines recommend starting warfarin at least 2 weeks after a major cardioembolic stroke, but robust studies are lacking and earlier anticoagulation of specific patient subgroups cannot be discounted. By the same token, some anticoagulated patients may benefit from continued anticoagulation (with warfarin or heparin) after a cardioembolic stroke.

**Conflicts of interest**

None declared.

**References**


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