Acute Anticoagulation Following Cardioembolic Stroke

John F. Rothrock, MD, Howard C. Dittrich, MD, Steven McAllen, MD, Barbara J. Taft, RN, PA-C, and Patrick D. Lyden, MD

Whether acute anticoagulation after cardioembolic stroke affords substantial protection against early recurrent emboli or an unacceptable risk of hemorrhage remains controversial. To assess this further, we evaluated 121 consecutive patients with acute cardioembolic stroke. Forty-nine were therapeutically anticoagulated within 96 hours of stroke onset, and 41 received no anticoagulants within the first 2 weeks after stroke. These two groups did not differ significantly with regard to age, sex, severity of acute neurologic deficit, or spectrum of underlying cardiac disease. The incidences of clinically significant brain hemorrhage (2%) and early recurrent embolization (2%) were equally low in both groups. Our data suggest that acute anticoagulation may be employed safely in most patients with cardioembolic stroke but that such treatment does not clearly benefit this population as a whole. (Stroke 1989;20:730–734)

Although published guidelines exist for long-term, prophylactic antithrombotic therapy in various subgroups of patients at risk for cardiogenic emboli,1,2 consensus regarding the indications for acute anticoagulation after cardioembolic stroke has proven more elusive. Patients with cardioembolic stroke may suffer subsequent brain and systemic emboli, and the period of highest risk for recurrent embolization appears to be within the first few weeks after the initial stroke.3–5 In hopes of reducing the incidence of early recurrent embolization, some investigators have advocated using anticoagulant therapy acutely. Others employing this treatment have reported significant morbidity from brain hemorrhage.6–11 We further evaluated the safety and efficacy of anticoagulant therapy administered acutely after cardioembolic stroke.

Subjects and Methods

Between 1983 and 1988, staff of the University of California, San Diego Stroke Center evaluated 124 consecutive patients presenting acutely with presumed cardioembolic stroke. Criteria for the diagnosis of cardioembolic stroke included documented cardiac abnormality with significant embolic potential, involving one or more of the following: 1) valvular or nonvalvular atrial fibrillation, whether paroxysmal or sustained; 2) myocardial infarction (if >30 days, then echocardiographic evidence of left ventricular mural thrombus, left ventricular aneurysm, or significant left ventricular wall motion abnormality was required); 3) mechanical or bioprosthetic mitral or aortic valve; 4) mitral valve prolapse with echocardiographic evidence of two or more of the following: significant mitral regurgitation, pansystolic prolapse of both leaflets on multiple views, or mitral valve thrombus; 5) rheumatic disease of the aortic or mitral valves in the absence of atrial fibrillation as determined by clinical examination and echocardiography; or 6) dilated cardiomyopathy with diffuse left ventricular hypokinesis, with or without echocardiographically demonstrated mural thrombus. Other criteria for diagnosis of cardioembolic stroke included clinical presentation consistent with cardioembolic stroke, involving all of the following: 1) Sudden onset of focal neurologic deficit, with deficit maximal at onset; 2) either no antecedent transient ischemic attack (TIA), single TIA lasting at least 1 hour, or multiple antecedent TIs involving two or more vascular territories and occurring within 2 weeks before stroke onset; 3) absence of an anatomically significant (i.e., stenosis of ≥50%) intrinsic extracranial internal carotid stenotic/occlusive disease (as documented by carotid duplex testing or cerebral angiography; angiography was not required for patients with stroke in the posterior
TABLE 1. Underlying Cardiac Etiologies of Cardioembolic Stroke for 121 Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean age (yr)</th>
<th>% male</th>
<th>Nonvalvular</th>
<th>Valvular</th>
<th>Myocardial infarction</th>
<th>Prosthetic valve</th>
<th>Mitral valve prolapse</th>
<th>Rheumatic valve disease</th>
<th>Dilated cardiomyopathy</th>
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<tbody>
<tr>
<td>1</td>
<td>49</td>
<td>69.6</td>
<td>67</td>
<td>27</td>
<td>55</td>
<td>3</td>
<td>6</td>
<td>12</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>66.3</td>
<td>61</td>
<td>19</td>
<td>46</td>
<td>3</td>
<td>7</td>
<td>10</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>61.9</td>
<td>42</td>
<td>14</td>
<td>45</td>
<td>7</td>
<td>23</td>
<td>2</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
<td>66.5</td>
<td>59</td>
<td>60</td>
<td>50</td>
<td>13</td>
<td>11</td>
<td>24</td>
<td>20</td>
<td>11</td>
</tr>
</tbody>
</table>

*Three patients with mitral valve prolapse as well; one patient also status post aortic valve replacement.
†Eight patients (33%) with echocardiographic evidence of left ventricular mural thrombus.
‡Two patients (50%) with echocardiographic evidence of left ventricular mural thrombus.

Following are the results:

1) Brain computed tomography (CT) or magnetic resonance imaging (MRI) findings consistent with cardioembolic stroke (i.e., no evidence of tumor, infection, subdural hematoma, or other processes mimicking embolic stroke; primary intracerebral hemorrhage excluded; patients with lesions radiographically consistent with a diagnosis of lacunar stroke excluded). We excluded from our study patients with infectious or marantic endocarditis or intracardiac tumors.

After excluding three patients with bacterial endocarditis, 121 remained. Treatment was selective and varied according to the discretion of the patient’s primary physician. Patients were retrospectively assigned to one of three groups, depending on the use and timing of anticoagulant therapy. Group 1 comprised those patients not previously receiving anticoagulant therapy who were therapeutically anticoagulated (partial thromboplastin time [PTT] ≥1.5×control values) within 96 hours after stroke onset. Group 1 treatment was typically initiated with a 5,000- to 10,000-unit intravenous bolus of heparin followed by a constant infusion regulated to maintain the PTT between 1.5 and 2.5×control values. Oral warfarin was added either acutely or after several days, and therapeutic anticoagulation was continued for a minimum of 2 weeks. Group 2 included all patients not on anticoagulant therapy at the time of stroke who received no anticoagulants during the 2 weeks after stroke; the majority of the Group 2 patients received aspirin and/or dipyridamole in varying doses during that period. Group 3 consisted of the remaining patients and included those receiving anticoagulant therapy at the time of stroke, those with evidence of intracerebral hemorrhage (believed to preclude the use of anticoagulants) on CT or MRI scan, and those started on anticoagulant therapy >96 hours but <2 weeks after stroke onset.

All patients were examined acutely, and the degree of functional neurologic deficit was determined as follows: normal: no new neurologic deficit; mild: new stroke deficit, but individual can return to work or usual level of daily activity; moderate: individual cannot return to work or usual level of daily activity but does not require chronic institutionalization or assistance with dressing, feeding, or personal toilet; and severe: individual requires chronic institutionalization and/or assistance with dressing, feeding, or personal toilet. Surviving patients were examined again 1 month after initial stroke onset.

End points evaluated included mortality within the first week and first month following stroke, brain or systemic hemorrhage, recurrent cardiac emboli, and functional neurologic status.

Results

Underlying cardiac etiologies for the three groups are outlined in Table 1, with nonvalvular atrial fibrillation accounting for approximately one half of the embolic events overall and within each group. Mean age and sex distribution were similar in all three groups.

Incidences of hemorrhagic complications and recurrent embolization overall and for Groups 1 and 2 are presented in Table 2. Of all 121 patients, eight (7%) had CT or MRI evidence of brain hemorrhage (acute or delayed) and three (2.5%, one in each group) had brain hemorrhage with temporally associated clinical worsening. One Group 1 patient with clinically mild acute stroke deficit had evidence of a small hemorrhagic infarction on acute (8 hours) CT, received acute anticoagulant therapy despite this, and experienced no subsequent CT or clinical worsening. Brain hemorrhage occurred in four of 73 patients (5%) with moderate or severe acute stroke deficit and in four of 48 (8%) with no or mild acute stroke deficit. The time of first CT or MRI detection of brain hemorrhage ranged from 6 hours to 6 weeks after stroke onset, but in six of the eight cases (75%), hemorrhage was evident within the first week. Four patients (3%, three in Group 1 and one in Group 2) had other hemorrhagic complications, all of which were gastrointestinal. Within the 2-week study period, two patients (2%) had recurrent cardiac emboli, both manifested by recurrent stroke. One of these patients (in Group 1) had an acute myocardial infarction 3 days before the initial stroke, echocardiographic evidence of left ventricular mural thrombus, and stroke recurrence 1 day after the initial cardioembolic stroke; the other patient (in...
Group 2) had nonvalvular atrial fibrillation and recurrent stroke 11 days after the initial stroke.

Neurologic outcome and mortality data are also presented in Table 2. Seventy-three patients (60%) had a moderate or severe neurologic deficit at the time of initial evaluation, and of 107 survivors, 36 (34%) had moderate or severe neurologic deficit 1 month after stroke. The incidences of moderate to severe neurologic deficit were similar for Groups 1 and 2. Of the remaining 31 patients (Group 3), 18 were receiving oral warfarin at the time of stroke and remained on that medication for at least the subsequent 2 weeks; all but one of these 18 patients had a therapeutic prothrombin time (i.e., 1.5-2.5 x control value) at the time of stroke onset. Of the remaining 13 patients (Group 3), 18 were receiving oral warfarin at the time of stroke and remained on that medication for at least the subsequent 2 weeks; all but one of these 18 patients had a therapeutic prothrombin time (i.e., 1.5-2.5 x control value) at the time of stroke onset.

The incidences of clinically significant brain hemorrhage and recurrent embolization were identical for Groups 1 and 2. Acutely (69% and 63%, respectively) and at 1 month (44% and 32%, respectively). Six patients had evidence of intracerebral hemorrhage with acute anticoagulant therapy, without associated clinical worsening in five (18%). Previous experimental work using animal models of thrombolytic therapy promotes brain hemorrhage, 18-19 although one more recent study reported no increase in brain hemorrhage in animals acutely treated with therapeutic or excessive doses of heparin. 20

In the only randomized clinical trial of anticoagulant therapy for acute cardioembolic stroke to date, the Cerebral Embolism Study Group 16 reported no significant hemorrhagic complications and a trend toward reduction of recurrent embolization in their treated patients. Unfortunately, that study was terminated before statistically significant evidence of benefit from early anticoagulant therapy could be

**Table 2. Clinical Features and Outcome of 121 Patients With Cardioembolic Stroke**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=49)</th>
<th>Group 2 (n=41)</th>
<th>Total (N=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td><strong>Hemorrhagic complications/recurrent embolization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain hemorrhage</td>
<td>3</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>With clinical worsening</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other hemorrhagic</td>
<td>3</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent embolization</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Neurologic outcome/mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/severe deficit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At presentation</td>
<td>34</td>
<td>69</td>
<td>26</td>
</tr>
<tr>
<td>At 1 month</td>
<td>19</td>
<td>44</td>
<td>11</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mortality</td>
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</tr>
<tr>
<td>At 1 week</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>At 1 month</td>
<td>6</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

Group 1, patients receiving anticoagulants within 96 hours after stroke onset; Group 2, patients receiving no anticoagulants during 2 weeks after stroke; Total includes Groups 1 and 2 and Group 3 (patients receiving anticoagulants at time of stroke, patients with evidence of intracerebral hemorrhage [precluding use of anticoagulants], and patients receiving anticoagulants >96 hours but <2 weeks after stroke).

Discussion

Most previous studies of cardioembolic stroke have reported high incidences of early (first 2 weeks) recurrent embolization, ranging from 10% to 20%. Several investigators have reported a reduction in the incidence of recurrent embolization with acute anticoagulant therapy, without associated morbidity from brain hemorrhage. Numerous anecdotal reports of anticoagulant-related hemorrhagic transformation of cardioembolic ischemic stroke exist, however, and in their series of 28 patients receiving anticoagulant therapy after acute cardioembolic stroke, Shields et al found evidence of intracerebral hemorrhage with associated clinical worsening in five (18%). Previous experimental work using animal models of stroke has similarly suggested that anticoagulant therapy promotes brain hemorrhage, although one more recent study reported no increase in brain hemorrhage in animals acutely treated with therapeutic or excessive doses of heparin.
established. From this and subsequent work examining hemorrhagic transformation of cardioembolic stroke,21,22 these same investigators concluded that patients with extensive stroke are at greatest risk for spontaneous hemorrhagic transformation, typically occurring within the first 48-72 hours after the initial stroke. The Cerebral Embolism Study Group has consequently recommended delaying anticoagulant therapy in these patients until brain CT is performed at 7 days to exclude delayed hemorrhage. In patients with lesser degrees of neurologic deficit, immediate anticoagulant therapy is recommended if CT performed acutely demonstrates no evidence of hemorrhage. Despite a lack of incontrovertible supporting evidence, these recommendations have been widely adopted by practicing clinicians.

We found a 7% incidence of brain hemorrhage, acute or delayed, and a 2.5% incidence of brain hemorrhage with temporally associated clinical worsening in our series of 121 consecutive patients with cardioembolic stroke. The incidences of clinically significant brain hemorrhage in Groups 1 and 2 were equally low (2%), despite high prevalences of moderate or severe acute neurologic deficit in both groups. These low incidences suggest that clinically significant brain hemorrhage may be a relatively infrequent complication of cardioembolic stroke and that the occurrence of such hemorrhage is not clearly influenced by the decision to use anticoagulant therapy acutely. While spontaneous hemorrhagic transformation may be more common in patients with major strokes, as others have suggested, our data indicate that this complication may occur even in patients with little or no detectable acute neurologic deficit. Whether clinically stable patients with minor neurologic deficit from cardioembolic stroke may be safely anticoagulated despite CT or MRI evidence of brain hemorrhage is unknown.

The low incidence of early recurrent embolization in our patients overall and specifically in Group 1 suggests that the frequency of this complication of cardioembolic stroke may have been exaggerated in the past and that acute anticoagulant therapy may convey no significant benefit. Given the discrepancy between our findings and those of previous investigators, it is appropriate to seek confounding variables that may have artifactually lowered the incidence of early recurrent embolization in our Group 1.

First, treatment was nonrandomized, and patients at high risk for recurrent emboli may have been selectively treated, while those at lower risk for recurrent embolization were selectively untreated. Although our Groups 1 and 2 did not differ significantly in age, sex, etiologies of underlying cardiac disease, degree of acute stroke deficit, and CT/MRI findings, we cannot exclude the possibility of an additional, unidentified clinical variable that may significantly influence the risk of early recurrent embolization and may have varied between the two groups. Second, clinical diagnosis of cardioembolic stroke is imperfect, and our series may have contained some patients with stroke from noncardiac sources, thus inducing a bias toward lower rates of recurrent embolization. Our criteria for diagnosis of cardioembolic stroke, however, were relatively rigorous, were similar to those reported by others,16 and in fact we excluded a number of patients in whom the primary physician assumed a cardioembolic etiology and initiated management based on that assumption. Finally, our series may have been inadvertently biased toward patients with underlying cardiac pathology and a low potential for generation of early recurrent emboli. Sage and vanUitert23 reported that recurrent emboli tend to occur later in patients with nonvalvular atrial fibrillation (NVAF) than in those with rheumatic heart disease and atrial fibrillation. Other investigators, however, have examined cardioembolic stroke patients with a distribution of cardiac etiologies similar to ours (with NVAF consistently the embolic source most commonly identified3,14,16) and have concluded or implied that the potential for early recurrent embolization is largely independent of the specific underlying cardiac condition.4,13,16,24

In conclusion, our data indicate that anticoagulation acutely following cardioembolic stroke appears to be reasonably safe but of no clear benefit in preventing early recurrent emboli. The latter in particular appears to contradict existing clinical sentiment as to what constitutes optimal management of acute cardioembolic stroke. A well-designed, randomized study is needed to resolve this issue and to perhaps identify a subpopulation of cardioembolic stroke patients who are at relatively high risk for early recurrent emboli and who will benefit from early anticoagulant therapy.

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References


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