Anticoagulation After Cardioembolic Stroke

To Bridge or Not to Bridge?

Hen Hallevi, MD; Karen C. Albright, DO, MPH; Sheryl Martin-Schild, MD, PhD; Andrew D. Barreto, MD; Sean I. Savitz, MD; Miguel A. Escobar, MD; Nicole R. Gonzales, MD; Elizabeth A. Noser, MD; Kachi Illoh, MD; James C. Grotta, MD

Background: Most patients with cardioembolic stroke require long-term anticoagulation. Still, uncertainty exists regarding the best mode of starting long-term anticoagulation.

Design, Setting, and Patients: We conducted a retrospective review of all patients with cardioembolic stroke admitted to our center from April 1, 2004, to June 30, 2006, and not treated with tissue plasminogen activator. Patients were grouped by treatment: no treatment, aspirin only, aspirin followed by warfarin sodium, intravenous heparin sodium in the acute phase followed by warfarin (heparin bridging), and full-dose enoxaparin sodium combined with warfarin (enoxaparin bridging). Outcome measures and adverse events were collected prospectively. Laboratory values were captured from the records.

Main Outcome Measures: Symptomatic hemorrhagic transformation, stroke progression, and discharge modified Rankin Scale score.

Results: Two hundred four patients were analyzed. Recurrent stroke occurred in 2 patients (1%). Progressive stroke was the most frequent serious adverse event, seen in 11 patients (5%). Hemorrhagic transformation occurred in a bimodal distribution—an early benign hemorrhagic transformation and a late symptomatic hemorrhagic transformation. All of the symptomatic hemorrhagic transformation cases were in the enoxaparin bridging group (10%) (P = .003). Systemic bleeding occurred in 2 patients (1%) and was associated with heparin bridging (P = .04).

Conclusions: Anticoagulation of patients with cardioembolic stroke can be safely started with warfarin shortly after stroke. Heparin bridging and enoxaparin bridging increase the risk for serious bleeding.

 Arch Neurol. 2008;65(9):1169-1173

CARDIOEMBOLISM ACCOUNTS for 20% of ischemic strokes. The infarct is typically larger than that in atherothrombotic stroke and the outcome is poorer.1 In addition, cardioembolic stroke (CES) carries increased risk of hemorrhagic transformation (HT).2 Current guidelines do not support the routine anticoagulation (AC) of patients with CES in the acute phase.3,4 Nevertheless, most patients with CES ultimately need AC. There is no consensus on the best way to initiate AC after CES.

CME available online at www.jamaarchivescme.com and questions on page 1151

Our aim was to compare these AC strategies, focusing on efficacy in preventing early stroke recurrence, risk of serious bleeding, functional outcome, and mortality.

METHODS

We conducted a retrospective review of all patients admitted to our stroke center who were diagnosed with CES from April 1, 2004, to June 30, 2006, and not treated with tissue plasminogen activator. A cardioembolic cause was diagnosed when the patient had 1 of the following: atrial fibrillation (by history or electrocardiography), mechanical heart valve, signifi-
cant rheumatic valvular disease, severe focal cardiac wall motion abnormalities (in the absence of significant ipsilateral carotid atherosclerosis) or a cardiac clot visualized on an echocardiogram, and patent foramen ovale in the presence of venous thrombosis and in the absence of significant atherosclerosis. Patients receiving thrombolytic therapy were excluded. All of the patients were cared for by the same stroke team. As a general rule, in patients with large infarcts who were debilitated, there is an inclination to defer the decision of AC until the patient is stabilized. In patients deemed candidates for AC, warfarin treatment is started in the hospital. The decisions of whether to bridge and whether to use heparin or low-molecular-weight heparin were made based on clinical judgment and personal preference of the treating physician. Outcome measures and adverse events were captured prospectively. Severe systemic bleeding was defined as any gastrointestinal tract, intra-abdominal, or external bleeding necessitating transfusion. Computed tomographic scans were done for all of the patients on admission and before initiation of AC. Additional imaging was done if a patient’s condition worsened. All of the scans were reviewed for the presence of HT by one of us (H.H.) blinded to treatment strategy. The HT was categorized as either benign HT (small petechial hemorrhage occupying <30% of the infarct volume without mass effect) or parenchymal hematoma, grade 2 (PH2) (dense hematoma, >30% of the infarct, and causing mass effect). Progressive stroke was defined as a worsening of the original deficit (≥1 point increase on the motor examination) in the absence of a new infarct in an adjacent territory, HT, infection, or metabolic abnormality that could account for it, occurring within the first week after the stroke. Recurrent stroke was defined as the appearance of a new infarct or the development of new symptoms referable to a territory different from that of the index infarct.

We identified 204 eligible patients. Eight patients were assigned to the NT group, 88 to the ASA group, 35 to the WAR group, 44 to the HB group, and 29 to the EB group. Patients’ baseline characteristics, stroke severity, interval to treatment, and cardiac causes are shown in Table 1. The median (range) time from stroke onset to therapeutic AC (INR > 2.0 or partial thromboplastin time > 50 seconds) was 2.5 (1-6) days for HB and 7 (1-14) days for patients receiving warfarin (INR > 2.0) regardless of bridging. For the HB group, the average partial thromboplastin time during the infusion was 60 seconds (therapeutic range, 50-80 seconds).

The adverse events distribution is shown in Table 2. Both cases of recurrent stroke were associated with atrial fibrillation. Stroke progression was the most common serious adverse event. All cases of stroke progression except one occurred in the ASA group. Patients in the ASA group were 12.5 times more likely to experience stroke progression compared with the AC group (χ² odds ratio = 12.5; 95% confidence interval, 1.6-100.0; P = .003). Patients who experienced stroke progression were 18 times more likely to have a poor outcome (P < .001).

Hemorrhagic transformation was observed in 23 cases (11%); however, only 3 cases (1%) experienced PH2. A bimodal distribution was observed for HT, with 19 of 20
Late, 9-12 d

cases (95%) of benign HT occurring 0 to 3 days from stroke onset and 3 of 3 cases (100%) of PH2 occurring 9 to 12 days from stroke onset (Figure 1). All of the PH2 cases were bridged with enoxaparin sodium, 1 mg/kg twice daily, composing 10% of the EB group. One patient was aged 40 years and had a patent foramen ovale and a posterior inferior cerebellar artery infarct. His INR at the time of intracerebral hemorrhage (ICH) was 2.2 (Figure 2). The second was aged 78 years and had a partial (M2) middle cerebral artery infarct; his INR at the time of ICH was 3.4. The third patient was aged 82 years and had a complete middle cerebral artery infarct; his INR at the time of ICH was 1.4. In the 3 PH2 cases, EB was started 1 to 4 days from stroke onset and none had renal insufficiency. When compared with patients who did not receive bridging with enoxaparin, EB was significantly associated with PH2 (Fisher exact test P = .003).

Systemic bleeding was observed in 2 cases (1%) (1 gastrointestinal tract and 1 retroperitoneal bleed), both in the HB group. Compared with other forms of treatment, heparin was statistically associated with systemic bleeding (Fisher exact test P = .046, HB vs non-HB treatment).

The outcome distribution is shown in Table 3. Patients with AC were 2.4 times more likely than their counterparts without AC to experience a favorable outcome (71 of 108 patients with AC vs 43 of 96 patients without AC; χ² odds ratio = 2.4; 95% confidence interval, 1.3-4.2; P = .003). Although the NT and ASA groups had more severe strokes, these associations remained significant after controlling for baseline National Institutes of Health Stroke Scale scores and age using logistic regression (Wald statistic = 4.4; P = .04).

Our study attempted to address a common clinical dilemma in patients with CES: when and how to institute long-term AC for secondary stroke prevention. Currently, short-term AC of patients with CES for preventing early stroke recurrence is not endorsed by published guidelines. However, the common practice of bridging patients with heparin or enoxaparin often leads to very early full AC. Our data showing a very low rate of recurrent stroke regardless of treatment are in agreement with the repeated observation that the rate of early stroke recurrence is quite low and unaffected by AC. The decision to institute long-term AC with warfarin is often made while the patient is in the hospital. Typically in patients with an extensive and disabling infarct, the decision may be deferred fearing ICH. Many physicians are reluctant to start warfarin treatment without bridging with either heparin or enoxaparin, aiming at prevention of a warfarin-related hypercoagulable state. Indeed, a transient hypercoagulable state may occur when warfarin is initiated without heparin and may lead to abnormal clotting and skin necrosis. This is in fact uncommon in routine clinical practice, with most cases associated with protein C deficiency. Our data showing no episodes of skin necrosis in the WAR group further support this. Currently, bridging patients to prevent skin necrosis when initiating warfarin in a maintenance dosage is not recommended by hematological guidelines unless the patient is known to have protein C deficiency. Another feared complication of CES is HT. A novel observation from our data suggests that following CES, HT behaves in a bimodal fashion. The first peak occurs within the first 3 days and may be identified on the admission computed tomographic scan. This presentation is fairly common and typically asymptomatic. This benign HT is likely the result of reperfusion injury to microcirculation. Our data reflect the self-limiting benign nature of this condition, as no patients with early HT experienced hemorrhage growth. The second peak
occurs after 9 days. Unlike the benign HT it is symptomatic, with development of a parenchymal hematoma in the infarcted territory. This finding, which to our knowledge has not been reported before, suggests a different pathophysiology of the late HT. We hypothesize that the vessels in the ischemic territory were rendered fragile by the ischemic insult to the vasa vasorum, thus promoting microhemorrhage. It is thus understandable that AC may increase the risk of late HT. In our cohort, all cases of symptomatic late HT were bridged with the combination of full-dose enoxaparin and warfarin, composing an alarming 10% of the EB group. Although our numbers are small and a chance occurrence cannot be ruled out, the congregation of cases in the EB group with none in the HB and WAR groups suggests a pathophysiological link. Intravenous heparin usually produces variable levels of AC. Our observed median partial thromboplastin time of 60 seconds in the HB group is in the lower end of the therapeutic range and may suggest a lower level of AC. Warfarin alone rarely produces extreme INR elevations in the first few weeks—especially when proper follow-up is done. On the other hand, full-dose enoxaparin provides complete and constant AC. It is possible that this level of AC when combined with warfarin may increase the risk of late HT. The Heparin in Acute Embolic Stroke Trial of low-molecular-weight heparin in patients with CES did not show an increased rate of ICH when treated with low-molecular-weight heparin as compared with aspirin. These data are in agreement with our observations as no patients in the Heparin in Acute Embolic Stroke Trial were bridged (warfarin was started after 14 days when the study medication was discontinued). The International Stroke Trial that tested heparin vs aspirin in acute stroke did show an increased risk of HT with heparin. The rate, however, was low (1.2%) and is consistent with our observation of a 0% rate of HT in the HB group.

Cardioembolic stroke is associated with a poorer outcome compared with other types of ischemic stroke. 

Table 3. Outcome Events

<table>
<thead>
<tr>
<th>Event</th>
<th>NT (n=8)</th>
<th>ASA (n=88)</th>
<th>HB (n=44)</th>
<th>WAR (n=35)</th>
<th>EB (n=29)</th>
<th>Total (N=204)</th>
<th>P Value by χ² Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome</td>
<td>4 (50)</td>
<td>39 (44)</td>
<td>32 (73)</td>
<td>19 (54)</td>
<td>20 (69)</td>
<td>114 (56)</td>
<td>.02</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 (38)</td>
<td>4 (5)</td>
<td>0</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>9 (4)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: ASA, acetylsalicylic acid (aspirin) only; EB, enoxaparin bridging (full-dose enoxaparin sodium combined with warfarin sodium); HB, heparin bridging (intravenous heparin sodium in the acute phase followed by warfarin); NT, no treatment; WAR, aspirin followed by warfarin.

Figure 2. Late hemorrhagic transformation. A. A head computed tomographic scan of late hemorrhagic transformation showing the cerebellar infarct 4 days from stroke onset. B. A repeated computed tomographic scan 7 days later, when the patient developed severe headache and a decrease in consciousness, shows parenchymal hematoma in the infarcted cerebellum.
come. Stroke progression was the most common serious adverse event in our cohort and was significantly associated with a poor outcome. Stroke progression is likely multifactorial, with brain edema, clot propagation, reocclusion of the parent vessel, recurrent emboli to the same territory, and hemodynamic fluctuations accounting for most cases. In our cohort, there was an excess of stroke progression in the ASA and NT groups, and patients treated with warfarin alone or bridged with heparin or low-molecular-weight heparin were nearly 13 times less likely to experience stroke progression compared with ASA treatment. This may suggest a role of AC in preventing stroke progression, which is supported by 2 studies recently demonstrated a better outcome with early AC treatment of patients with CES. Stroke progression may be difficult to distinguish from recurrent embolization to the same arterial territory. This may also account for some of the observed reduction in stroke progression in our study. Finally, our ASA group had more severe strokes at baseline, so the excess of progression in this group may simply reflect the extent of their infarct and not treatment effect.

Our work has several limitations. First, this is a retrospective study comparing various treatments assigned in a nonrandomized manner. Therefore, differences are present between the treatment groups that might not be completely accounted for by our multivariate analysis. The results should be viewed as hypothesis generating, and further prospective validation may be required. Until such validation occurs, our conclusions should be interpreted with caution. Second, our series lacks long-term follow-up. It is possible that patients may improve at 30 to 90 days. This was not addressed because our primary end point was adverse events. The stroke severity was not equally distributed among the treatment groups. This probably reflects selection bias of the treating physician and makes any comparison of treatment effects difficult. We did not routinely obtain a head computed tomographic scan on AC-treated patients; thus, it is possible that some asymptomatic HTs were missed. Our study was not designed to specifically address patients who may be at high risk for early thrombotic complications (ie, mechanical heart valves) or patients who have protein C deficiency or another hypercoagulable state that may be aggravated by warfarin initiation. In these patients, the benefit of bridging may outweigh the additional risk of bleeding.

Our data may provide guidance as to the mode of starting long-term AC in patients with CES. Warfarin treatment appears to be safe and can be started at any point during the hospital stay along with deep vein thrombosis prophylaxis. Bridging with a full dose of enoxaparin or heparin may carry a high risk of intracranial and systemic bleeding. However, it may be considered in special circumstances.

Accepted for Publication: November 12, 2007.

Published Online: July 14, 2008 (doi:10.1001/archneur.65.9.noc70105).

Correspondence: Hen Hallevi, MD, Department of Neurology, University of Texas Health Science Center at Houston, 6431 Fannin St, MSB 7.044, Houston, TX 77030 (hen.hallevi@uth.tmc.edu).

Author Contributions: Study concept and design: Hallevi, Albright, Martin-Schild, Savitz, Gonzales, Noser, and Grotta. Acquisition of data: Hallevi and Barreto. Analysis and interpretation of data: Hallevi, Albright, Savitz, Escobar, Illoh, and Grotta. Drafting of the manuscript: Hallevi, Barreto, Savitz, Escobar, Gonzales, and Grotta. Critical revision of the manuscript for important intellectual content: Hallevi, Albright, Martin-Schild, Savitz, Noser, Illoh, and Grotta. Statistical analysis: Hallevi and Albright. Study supervision: Savitz and Grotta.

Financial Disclosure: None reported.

REFERENCES