Anticoagulant Therapy and Central Nervous System Complications in Patients with Prosthetic Valve Endocarditis

WALTER R. WILSON, M.D., JOSEPH E. GERACI, M.D., GORDON K. DANIELSON, M.D., RODNEY L. THOMPSON, M.D., JOHN A. SPITTELL, JR., M.D., JOHN A. WASHINGTON II, M.D., and EMILIO R. GIULIANI, M.D.

SUMMARY Among 52 cases of prosthetic valve endocarditis, adequate anticoagulant therapy was administered in 38 and discontinued or given in subtherapeutic dosage in 14. Our data suggest that anticoagulant therapy does not appreciably increase morbidity or mortality in patients with prosthetic valve endocarditis. On the contrary, in our patients the incidence of major clinical CNS (central nervous system) complications was increased and the mortality was higher if anticoagulant therapy was discontinued. CNS complications occurred in 10 of the 14 patients without adequate anticoagulant therapy and in three of the 38 with adequate anticoagulant therapy. Mortality was 57% among those treated without adequate anticoagulation and 47% among those with adequate anticoagulation. At autopsy, CNS complications were thought to be the primary cause of five of the eight deaths in cases without adequate anticoagulation.

SINCE THE REPORT by Thill and Meyer, 1 published in 1947, many authorities have affirmed that anticoagulants are contraindicated by endocarditis of natural or prosthetic valves because of the potential risk of central nervous system (CNS) bleeding after thromboembolism. 2-4 Other investigators 5 have thought that anticoagulant therapy need not necessarily be discontinued in patients who have infective endocarditis.

With natural-valve endocarditis, the incidence of neurologic signs has ranged from 12.5 to 80%. 6,7 Few data are available concerning the frequency of CNS thromboembolism with prosthetic valve endocarditis. 8-10 Because of the increased risk of thromboembolism with discontinuance of anticoagulant therapy in patients with prosthetic valves, 11-18 it would be desirable to continue anticoagulant therapy in patients with prosthetic valve endocarditis, provided that such therapy did not increase morbidity and mortality, especially from CNS bleeding after thromboembolism.

Our experience with the use of anticoagulant therapy in patients with prosthetic valve endocarditis is the subject of this report.

Material and Methods

We reviewed the Mayo Clinic records of 52 patients who developed prosthetic-valve endocarditis between January 1963 and January 1976. All prostheses were of the Starr-Edwards type. We judged the complication to have been present according to criteria described previously. 19 Briefly, these criteria were at least two of the following: (1) two or more separate blood cultures positive for the same organism; (2) histopathologic evidence of bacterial endocarditis in surgical or autopsy specimens; and (3) two or more of the following clinical signs—fever, development of a new regurgitant murmur, newly developed splenomegaly, or peripheral embolism.

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Before the onset of prosthetic-valve endocarditis, all patients had been receiving continuous anticoagulant therapy. Once the diagnosis of prosthetic-valve endocarditis was established, the decision to continue or discontinue the use of anticoagulants was arbitrary, based entirely on the physicians' uncertainties about the efficacy and safety of their use in patients with prosthetic-valve endocarditis. In no case were anticoagulants discontinued because of other cardiac or CNS complications that independently would have increased the risk of using anticoagulant therapy. In all cases where anticoagulant therapy was discontinued, the administration was stopped promptly after diagnosis of prosthetic-valve endocarditis and was not reinstituted until antimicrobial therapy for prosthetic-valve endocarditis was completed.

Accordingly, patients were divided into two groups: those who received inadequate anticoagulant therapy or none throughout the course of antimicrobial therapy for prosthetic-valve endocarditis and those who received adequate anticoagulant therapy throughout the duration of antimicrobial therapy or until the onset of CNS complications.

Adequate anticoagulant therapy was defined as administration of coumarin drugs to maintain prothrombin time at ≥ 1.5 times normal. It is well recognized that prothrombin time may fluctuate in patients who are receiving anticoagulant therapy with coumarin drugs. This is especially likely to occur in critically ill, hospitalized patients because of drug-drug interactions, difficulty in tolerating oral medication, and other factors. In all patients who were treated with anticoagulant therapy, effort was made to maintain prothrombin times ≥ 1.5 times normal. In frequently, patients had prothrombin times < 1.5 times normal. Such levels never continued more than three consecutive days, and none of the patients with these brief periods of inadequate control developed CNS complications.

One patient's local physician advised discontinuance of Coumadin when the diagnosis of prosthetic-valve endocarditis was suspected. When the patient arrived at the Mayo Clinic two days later, the prothrombin time was 1.2 times normal. Therapy with heparin (5,000 units intravenously...
Adequate anticoagulants ranged from therapy that the 52 patients; was (table 1). or embolism in those without those of continuance and periods the hospital. Three with signs of therapy.

CNS complications were defined as seizures or clinical signs of CNS thromboembolism.

Results

Adequate anticoagulant therapy was administered to 38 of the 52 patients; 14 patients did not receive anticoagulant therapy that was adequate by our criteria.

The ages of patients treated with anticoagulants ranged from 19 to 71 years, averaging 47; and ages of those without adequate anticoagulants ranged from 11 to 70, averaging 46 (table 1). None of the 52 patients had a history of thromboembolism or a seizure disorder before the onset of prosthetic valve endocarditis. Controlled arterial hypertension was present in four patients treated with anticoagulants and in one of those treated without anticoagulants. None of these five patients developed CNS complications.

Clinical signs of CNS complications occurred in 8% of patients with adequate anticoagulant therapy and in 71% of those without (fig. 1). The onset of CNS complications occurred from 7 to 23 days (mean 17 days) after discontinuance of anticoagulants. Six patients had transient periods of prothrombin times ≥ 3.0 times normal, and one of these six developed CNS complications. No patient developed new CNS complications during the two months following reinstitution of anticoagulant therapy.

Among the three patients who developed CNS complications while receiving adequate anticoagulant therapy, the anticoagulant therapy was discontinued in two at the onset of the complications. In the third, whose prothrombin time was 3.3 times normal at the onset of the complications, anticoagulant therapy was continued. All three died. CNS complications did not occur in the single patient who received simultaneous heparin and Coumadin therapy for three days.

The numbers of patients with infected aortic, mitral, or multiple prostheses who did and did not receive adequate anticoagulant treatment are shown in table 2. Among those without adequate anticoagulants, the frequency of CNS complications with infected mitral and aortic prostheses was similar.

Seven patients had infected cloth-covered Starr-Edwards prosthetic valves (5 aortic, 2 mitral). Anticoagulant therapy was discontinued in two of these (1 aortic, 1 mitral), and both subsequently developed CNS complications.

The infective organism, time of onset of infection, mortality, and number of patients with CNS complications are shown in table 3. Among these categories, the two groups of patients are distributed in similar proportions.

Mortality was 47% among those with adequate anticoagulants and 57% among those without. Autopsy was performed after 14 of the 18 deaths of patients with adequate anticoagulant therapy and after all eight deaths of patients without. The frequency of pertinent autopsy findings is shown in figure 2. The frequency of CNS emboli or infarction was higher in cases without anticoagulant therapy: the eight autopsies revealed such lesions in seven — multiple bland infarcts in four and multiple bland and hemorrhagic infarcts in three. The 14 autopsies on patients who died after adequate anticoagulant treatment revealed CNS thromboemboli in six — multiple bland infarcts in five and multiple hemorrhagic infarcts in one. None of the emboli was septic.

Among the patients who had signs of CNS complications ante mortem, autopsy indicated that such complications were the primary cause of death in all three patients with adequate anticoagulant treatment and in five of the 10 without. Of these five, three had massive intracerebral hemorrhagic infarcts at postmortem examination and the other two had multiple intracerebral thromboembolic bland infarcts with cerebral edema. Of the three with adequate anticoagulant therapy, one had marked cerebral edema and tentorial hemorrhage with secondary subarachnoid hemorrhage, but no CNS emboli. The second, who had had a prothrombin time 3.3 times normal at the onset of CNS symptoms, was the single patient treated with anticoagulant therapy.

### Table 1. Age Distribution

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Adequate anticoagulants (no. pts)</th>
<th>Not adequate anticoagulants (no. pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–19</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>20–29</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>30–39</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>40–49</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>50–59</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>60–69</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>&gt;70</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 2. Valve Infected and Patients with Central Nervous System Complications

<table>
<thead>
<tr>
<th>Anticoagulants</th>
<th>Aortic</th>
<th>Mitral</th>
<th>Multiple</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate</td>
<td>3/26</td>
<td>0/10</td>
<td>0/2</td>
</tr>
<tr>
<td>Not adequate</td>
<td>7/10</td>
<td>3/4</td>
<td>—</td>
</tr>
</tbody>
</table>

*Number with complications/number at risk.

![Figure 1](http://circ.ahajournals.org/)

Incidence of clinical evidence of central nervous system complications in cases of prosthetic-valve endocarditis without (PVE–ACT) and with (PVE+ACT) adequate anticoagulant therapy.
therapy who had fatal intracerebral hemorrhage from thromboemboli. And the third (not shown in figure 2) had a subdural hematoma thought to be the result of a fall six months earlier, but no evidence of extension of the hematoma or of CNS thromboemboli. This death was attributed to cerebral edema.

Among the fatal cases without signs of CNS complications ante mortem, three of the 15 with adequate anticoagulants had bland CNS thromboembolic infarcts at autopsy; the single patient without adequate anticoagulants who died without CNS signs did not have abnormal CNS findings at autopsy. Conversely, in all of the patients who had signs of CNS complications and came to autopsy, postmortem CNS findings were abnormal.

**Discussion**

Our data suggest that anticoagulant therapy does not appreciably increase morbidity or mortality in patients with prosthetic-valve endocarditis. On the contrary, in our patients, the risk of major clinical CNS complications was increased and the mortality was higher when anticoagulant therapy was discontinued. CNS complications occurred nine times more frequently in patients with prosthetic-valve endocarditis when anticoagulant therapy was discontinued or given in subtherapeutic dosage than when adequate anticoagulant therapy was continued.

Thromboembolic episodes are believed to occur less frequently in association with cloth-covered prosthetic valves than with valves not cloth-covered. The number of our patients with infected cloth-covered valves is too small for accurate assessment of the desirability of anticoagulant therapy in patients with cloth-covered prosthetic-valve infections. However, CNS complications developed in the two patients with cloth-covered valves in whom anticoagulant therapy was discontinued.

Among our patients treated adequately with anticoagulants, only one death was attributed directly to the anticoagulant therapy. Karchmer (personal communication) described six patients with late-onset prosthetic-valve endocarditis treated with anticoagulant therapy who had massive intracerebral hemorrhage or hemorrhagic infarcts. Five of these died as a direct consequence of the event, and three of the five had had prothrombin times in excess of two times normal. In our study, 10 patients without adequate anticoagulant therapy developed signs of CNS complications and five of them died. In all five, the CNS event was thought to be the primary cause of death; at autopsy, three of these five patients were found to have massive intracerebral bleeding caused by thromboembolism.

The use of anticoagulants in patients who have had cerebral emboli is controversial. From retrospective analysis, some investigators thought that use of anticoagulants in these circumstances increased the risk of CNS hemorrhage, and they suggested that anticoagulants be withheld for three weeks after the occurrence of cerebral emboli. Other authors, from retrospective studies, believed that use of anticoagulants in such cases decreased morbidity and mortality associated with cerebral emboli and suggested that anticoagulants be administered within 48 hours of the event.  

We are unaware of any controlled prospective study of the use of anticoagulants in patients who have had cerebral emboli. From our data, we believe that the risk of cerebral damage from emboli is greater when anticoagulant therapy in patients with prosthetic-valve endocarditis is discontinued. However, our data are not sufficient to establish

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**Table 3. Prosthetic Valve Endocarditis: Time of Onset of Infection, Microbiologic Etiology, Mortality, Central Nervous System Complications**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Adequate anticoagulants (no. pts)</th>
<th>Not adequate anticoagulants (no. pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early onset</td>
<td>Late onset</td>
</tr>
<tr>
<td></td>
<td>Mortality* CNS complications</td>
<td>Mortality CNS complications</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>4/4</td>
<td>3/4</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>4/4</td>
<td>0/6</td>
</tr>
<tr>
<td>Viridans streptococci</td>
<td>0</td>
<td>1/5†</td>
</tr>
<tr>
<td>Group D streptococci</td>
<td>1/1</td>
<td>2/4</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>1/1</td>
<td>0/2</td>
</tr>
<tr>
<td>Corynebacterium</td>
<td>0</td>
<td>1/2</td>
</tr>
<tr>
<td>Peptococcus</td>
<td>0</td>
<td>0/1</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>0</td>
<td>1/1</td>
</tr>
<tr>
<td>Total</td>
<td>10/10</td>
<td>8/28†</td>
</tr>
</tbody>
</table>

*Deaths/patients at risk.*
†Alcaligenes faecalis also isolated from one patient.
guidelines for the use of anticoagulants in patients with prosthetic-valve endocarditis who develop CNS complications while receiving anticoagulants. One must weigh the risk of additional cerebral emboli should anticoagulants be discontinued against the risk of intracranial hemorrhage complicating emboli should anticoagulants be continued.

In our series the onset of CNS complications occurred seven to 23 days (mean 17 days) after discontinuance of the use of anticoagulants, so it appears unlikely that cerebral emboli would occur within the first few days after the use of anticoagulants is stopped. Should patients with prosthetic-valve endocarditis who are receiving anticoagulants develop CNS complications, we believe one prudent course might be to temporarily discontinue the use of anticoagulants, observe the patient for clinical or laboratory evidence of intracranial hemorrhage and, if none occurs, reinstitute anticoagulants, preferably within 48 to 72 hours after the onset of the initial CNS complication. Prothrombin time frequently remains elevated for this length of time or longer after discontinuance of anticoagulants. While the prothrombin time hypothetically may not be in the so-called therapeutic range, this lower level of anticoagulation may nonetheless reduce the likelihood of new cardiac-valve thrombogenesis until anticoagulant therapy is resumed.

References
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W R Wilson, J E Geraci, G K Danielson, R L Thompson, J A Spittell, Jr, J R Washington, 2nd and E R Giuliani

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