Low-Intensity Anticoagulation in Mechanical Cardiac Prosthetic Valves*

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Retrospectively, we reviewed the charts of 101 patients at the University of Kansas Medical Center who received low-intensity anticoagulation for mechanical prosthetic valves implanted over a 17-yr period. The mean duration of follow-up was 4.6 yr, and the total duration of follow-up was 466.5 patient-yr. The patients' records were evaluated for evidence of hemorrhagic or thromboembolic complications. A prothrombin time ratio of 1.3 to 1.5 times control was considered to be low-intensity anticoagulation. There were three thromboembolic events or 2.9/100 patient-yr of follow-up at a prothrombin time ratio of less than 1.3, four thromboembolic events or 2.5/100 patient-yr of follow-up at 1.3 to 1.5 times control, four thromboembolic events or 2.2/100 patient-yr of follow-up at 1.6 to 2.0 times control, and no thromboembolic events at prothrombin time ratios greater than 2.0 times control. Hemorrhagic events occurred in three patients at a prothrombin time ratio of less than 1.3 times control or 2.8/100 patient-yr of follow-up, in six patients at 1.3 to 1.5 times control or 3.8/100 patient-yr of follow-up, in ten patients at 1.6 to 2.0 times control or 5.5/100 patient-yr of followup, and in two patients at 2.1 to 2.5 times control or 12.2/100 patient-yr of follow-up. The rate of hemorrhagic events at 2.5 times control was 470/100 patient-yr of follow-up. While not providing definitive proof, we believe that our retrospective study provides supportive evidence for the use of low-intensity anticoagulation in patients with mechanical cardiac prostheses.

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Thromboembolism is a common complication in patients who have had implantation of mechanical prosthetic heart valves. Warfarin anticoagulants have been utilized to prevent this complication, but these have been associated with a risk of spontaneous hemorrhage. Although many studies have been undertaken to ascertain the appropriate level of anticoagulation in patients with mechanical prosthetic valve implants, the optimal level of anticoagulation is still controversial.1,2 For many years, clinicians recommended that the prothrombin time ratio should be 2 to 2.5 times control. Although effective in the prevention of thromboembolism, the incidence of hemorrhage was high.

Recent studies have shown that the general use of less responsive rabbit brain thromboplastin in the performance of prothrombin times has resulted in excessive anticoagulation and increased the risk of bleeding.3 Hull and associates4 demonstrated that low-intensity anticoagulation was as effective as conventional anticoagulation in preventing recurrent thrombophlebitis, but was associated with fewer bleeding complications. Recently, Saour and associates5 reported a prospective study of low-intensity anticoagulation and conventional anticoagulation in patients with mechanical prosthetic valves and found equal protection from thromboembolism but a decrease in the number of bleeding complications with low-intensity anticoagulation.

In the early 1970s, we made the decision to use anticoagulation in our patients with mechanical prosthetic valves at a prothrombin time ratio of 1.3 to 1.5 times control. This was done intuitively because of our perception of excessive bleeding with conventional anticoagulation. The following is a retrospective analysis of our experience with what is now termed "low-intensity anticoagulation."

MATERIALS AND METHODS

The charts of the 416 patients who underwent mechanical prosthetic valve replacement surgery at the University of Kansas Medical Center from Jan 1, 1972 to Oct 1, 1986 were retrospectively reviewed to assess the adequacy of low-intensity anticoagulation. Of these patients, there were 101 whose anticoagulation was controlled during this 17-year period by the Division of Cardiovascular Diseases at the University of Kansas Medical Center for more than 6 wks after surgery. Patients were seen at regular intervals by one of the cardiology faculty, and a thorough history and physical examination were performed and recorded.

Patients' records were reviewed for hemorrhagic and thromboembolic events. Since some patients had elective and emergency visits or hospitalizations in other institutions, the complications that occurred when the anticoagulation was not controlled at the University of Kansas Medical Center were excluded from this study. This was done to assure that only the effect of low-intensity anticoagulation was assessed.

Hemorrhagic complications were defined as a bleeding event necessitating hospitalization, transfusion, anticoagulation reversal, or a surgical procedure to control or correct the bleeding. A thromboembolic event was defined as a transient or permanent neurologic deficit not explained by a coexisting disease process such as endocarditis. When it was available, cranial computerized axial tomography was reviewed for evidence of an intracranial hemor-

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rhage. Valve thromboses were included as thromboembolic events. The latter were diagnosed by cardiac catheterization, echocardiographic evaluation, surgical observation, or clinical presentation. Approximately 75 percent of the prothrombin times were determined in the University of Kansas Medical Center's central laboratory (using General Diagnostics Simplastin prior to 1982 and Dade Thromboplastin C after 1982). The frequency of prothrombin time tests were determined by the stability of the patient's prothrombin time level. Every prothrombin time was available for retrospective analysis, whether determined at the University of Kansas Medical Center's laboratory or at an outside hospital. When patients had prothrombin times determined at outside hospitals, they were usually determined at the same hospital every time for that particular patient. All prothrombin time tests performed at the University of Kansas Medical Center were recorded in the patients' charts and in a special anticoagulant file that was maintained in the cardiovascular office.

All charts and the anticoagulant file were available for review. All prothrombin times determined outside the University of Kansas Medical Center were performed in certified laboratories, and reports of these prothrombin times were forwarded to the cardiovascular office, and a permanent record was maintained in the anticoagulant file in the office of the Division of Cardiovascular Diseases. In total, 5,630 prothrombin times were reviewed. In general, prothrombin times were obtained monthly. Each patient's status was categorized at the end of the study as (1) alive, (2) dead, or (3) moved or changed physicians.

RESULTS

There were 123 prosthetic valves implanted in 101 patients, 2 of whom had valve replacement surgery twice. The total duration of follow-up was 466.5 patient-yr. The mean duration of follow-up was 4.6 yr, the median was 4.3 yr, and the 25th and 75th percentiles were 2.1 and 7.2 yr, respectively.

Six patients, all of whom had aortic Starr-Edwards prostheses implanted during 1972 and 1973, did not receive anticoagulation initially but later did have anticoagulation for the following reasons: (1) three patients had transient ischemic attacks; (2) one patient had a stroke; and (3) one developed atrial fibrillation. One additional patient was not followed initially at the University of Kansas Medical Center after discharge but received anticoagulation later from an outside physician. This patient eventually reentered the population at the University of Kansas Medical Center.

The mean duration of discontinuity in anticoagulation following surgery in these six patients from valve implantation to entering our study period ranged from 0.2 to 7.6 yr with a total duration of discontinuity of 18.9 patient-yr.

An additional seven patients had discontinuity in their follow-up from our study because of a change in physician or residence, with a range of 0.6 to 10.9 patient-yr and a total duration of discontinuity of 32.4 patient-yr. In these two groups the discontinuity of anticoagulation was excluded from analysis. The type of prosthesis and the position of implantation are reviewed in the following tabulation listing numbers of patients:

<table>
<thead>
<tr>
<th>Prosthesis Type</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic Björk-Shiley</td>
<td>25</td>
</tr>
<tr>
<td>Mitral Björk-Shiley</td>
<td>31</td>
</tr>
<tr>
<td>Aortic and mitral Björk-Shiley</td>
<td>14</td>
</tr>
<tr>
<td>Aortic St. Jude and mitral Björk-Shiley</td>
<td>2</td>
</tr>
</tbody>
</table>

![Figure 1: Numbers of prosthetic valve surgeries by year.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21637/)
Table 1—Thromboembolic Events

<table>
<thead>
<tr>
<th>Case, Sex, Age (yr)</th>
<th>Valve</th>
<th>Event</th>
<th>Outcome</th>
<th>PTR</th>
<th>Evaluation</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, F, 47</td>
<td>Aortic Björk-Shiley</td>
<td>Valve thrombosis</td>
<td>Repeat AVR</td>
<td>&lt;1.1</td>
<td>Cardiac catheterization surgery</td>
<td>...</td>
</tr>
<tr>
<td>2, F, 79</td>
<td>Aortic Starr-Edwards</td>
<td>Valve thrombosis</td>
<td>Died</td>
<td>&lt;1.1</td>
<td>No valve clicks; no valve motion on echo</td>
<td>Noncompliant alcoholic</td>
</tr>
<tr>
<td>3, F, 75</td>
<td>Aortic Starr-Edwards</td>
<td>Stroke; left parietal hemorrhage</td>
<td>Survived</td>
<td>1.9</td>
<td>CT of head; no hemorrhage</td>
<td>Atrial fibrillation after surgery</td>
</tr>
<tr>
<td>4, M, 42</td>
<td>Aortic Starr-Edwards</td>
<td>TIA; left-sided paresthesias</td>
<td>Aspirin (ASA) for 1 wk</td>
<td>1.4</td>
<td>...</td>
<td>Stroke when no warfarin after discharge</td>
</tr>
<tr>
<td>57</td>
<td>Aortic Starr-Edwards</td>
<td>TIA; left-sided paresthesias</td>
<td>Survived; increased warfarin sodium (Coumadin); IV heparin</td>
<td>1.2</td>
<td>...</td>
<td>As above</td>
</tr>
<tr>
<td>5, F, 55</td>
<td>Mitral Björk-Shiley</td>
<td>TIA; right-sided paresthesia</td>
<td>Dipyridamole (Persantine)</td>
<td>1.6</td>
<td>...</td>
<td>Atrial fibrillation before surgery</td>
</tr>
<tr>
<td>6, F, 70</td>
<td>Mitral Björk-Shiley</td>
<td>TIA; amaurosis</td>
<td>Dipyridamole (Persantine)</td>
<td>1.3</td>
<td>Mild carotid disease by Doppler</td>
<td>Atrial fibrillation after surgery</td>
</tr>
<tr>
<td>7, F, 69</td>
<td>Mitral Björk-Shiley</td>
<td>RIND; dysarthria</td>
<td>Already dipyridamole (Persantine)</td>
<td>1.3</td>
<td>CT of head; multiple old strokes</td>
<td>Atrial fibrillation before surgery; prior CVA before surgery</td>
</tr>
<tr>
<td>70</td>
<td>Mitral Björk-Shiley</td>
<td>RIND; dysarthria; blurred vision</td>
<td>Already dipyridamole (Persantine)</td>
<td>1.3</td>
<td>CT; no change from prior CT; carotid Doppler mild disease</td>
<td>As above</td>
</tr>
<tr>
<td>70</td>
<td>Mitral Björk-Shiley</td>
<td>Stroke</td>
<td>Died</td>
<td>1.8</td>
<td>CT</td>
<td>As above</td>
</tr>
<tr>
<td>8, F, 66</td>
<td>Aortic St. Jude; mitral Björk-Shiley</td>
<td>Amaurosis, 10 min</td>
<td>Dipyridamole (Persantine)</td>
<td>1.7</td>
<td>Seen by ophthalmology</td>
<td>...</td>
</tr>
</tbody>
</table>

The years when the surgery was performed are indicated in Figure 1. The principal characteristics of the population are reviewed in the following tabulation (numbers within parentheses are ranges):

- Mean age at time of operation, yr: 60 ± 13 (18-76)
- Duration of follow-up, yr: 4.6 ± 3.5 (0.3-13.6)
- No. of patients: 101
- Male patients: 48
- Left atrial enlargement (by chest radiography or echocardiography before surgery): 59
- Left atrial thrombus at surgery: 10
- Atrial fibrillation before surgery: 31
- Atrial fibrillation after surgery (additional patients who developed atrial fibrillation after surgery): 31
- Prior thromboembolic event: 11
- Anticoagulation prior to surgery: 21
- Prior cardiac surgery: 33
- Other associated cardiac surgery with valve replacement: 21

During the follow-up period the prothrombin time ratios (PTRs) were less than 1.3 times control 22.5 percent of the time, were 1.3 to 1.5 times control 34.1 percent of the time, were 1.6 to 2.0 times control 39.2 percent of the time, were 2.1 to 2.5 times control for 3.5 percent of the time, and were greater than 2.5 times control 0.7 percent of the time.

There were 11 thromboembolic events in eight patients (Table 1), including two valve thromboses. Both valve thromboses occurred with PTRs of less than 1.1 times control. One of these patients had emergent repeat surgery and survived; the other was a noncompliant alcoholic who died immediately following admission to the hospital.

Nine patients had neurologic events, but no patient had a noncerebral peripheral embolus. Only one of the patients had a long-term residual neurologic deficit (not a TIA or RIND) and eventually died from complications of the stroke.

There were 37 hemorrhagic events in 27 patients. In 12, the anticoagulation was reversed with fresh frozen plasma or vitamin K because of the severity of the hemorrhage. Eleven required a procedure to control the bleeding or to alleviate a complication resulting from the hemorrhage. The procedures were three craniotomies, two polypectomies by colonoscopy, one transurethral prostate resection, one thoracectomy, one colectomy, one hysterectomy, one colonoscopy, and one nasal packing, and one nasal cautery. In the remainder of the patients, the prothrombin time corrected spontaneously by withdrawing the warfarin therapy. The anatomic location of hemorrhagic events were as follows: intracranial, five; vaginal, three; urinary, six;
respiratory, five; nasal, one; gastrointestinal, nine; and musculoskeletal, four. Additionally, four combined hemorrhages occurred, as follows: musculoskeletal and nasal; gastrointestinal and nasal; gastrointestinal and urinary; and Mallory Weiss tear and intracranial hemorrhage.

Table 2 provides information about the circumstances of the six intracranial hemorrhages, including the PTR at presentation. Three were due to falls, including one patient who was an alcoholic. One patient had poorly controlled hypertension, and one had severe emesis with a resultant Mallory Weiss tear and a subarachnoid hemorrhage. In three of these episodes, the PTRs were substantially elevated.

At the end of the study, 60 patients were alive, one patient had repeat valve surgery at a hospital other than the University of Kansas, three were lost to follow-up, and 16 had moved or changed physicians. Of the 20 who died, one died of valve thrombosis and two of intracranial hemorrhages. One patient died following complications of an apparent embolic stroke. Five died suddenly due to unknown circumstances and nine of congestive heart failure, bacterial endocarditis, or complications of repeat valve surgery for nonembolic indications.

Table 3 indicates the relative PTRs when the patients presented with thromboembolic and hemorrhagic events. The parentheses indicate the events per 100 patient-yr. The incidence of thromboembolic events appears similar at different levels of anticoagulation except when PTRs were greater than 2.0.

**Discussion**

When mechanical valve prostheses were initially implanted, patients arbitrarily received anticoagulation to a prothrombin ratio of 2.0 to 2.5. This was the level used in the anticoagulation of patients with phlebitis, myocardial infarction, etc; however, due to the durability of the prosthetic valves, anticoagulant therapy was continued over many years, and bleeding complications became a major problem. Hull and associates first demonstrated that low-intensity anticoagulation was as effective as conventional anticoagulant therapy in decreasing the incidence of recurrent phlebitis; however, the bleeding complications were decreased fivefold. Since then, there have been other studies suggesting that lower intensity anticoagulation is appropriate for preventing thrombosis in patients with bioprosthetic valves and, more recently, in patients with mechanical prosthetic valves.

Saour and associates studied patients with mechanical prostheses at two levels of anticoagulation. The patients were divided prospectively into two groups, one with moderate-intensity anticoagulation with a PTR of 1.5 (INR, 2.65) and the second a high-intensity anticoagulation with a PTR of 2.5 (INR, 9). The embolic rates were approximately the same, ie, 4.0/100 and 3.7/100 patient-yr, respectively. This was accompanied by a substantial reduction in hemorrhagic episodes, 6.2/100 vs 12.1/100 patient-yr. The major bleeding episodes were reduced, 0.95/100 vs 2.1/100 patient-yr.

Our retrospective evaluation revealed similar results. We had an incidence of thromboembolic events of 2.5/100 patient-yr at low-intensity anticoagulation and 2.2/100 patient-yr at high intensity. Our incidence of hemorrhagic complications increased in frequency with PTRs greater than 1.5 times control.

**Limitations of the Study**

The clinical information in this retrospective study was obtained by reviewing patients' charts. Patients who were still being actively followed were personally contacted. A portion of the population had already died prior to the study review. We were unable to account for complications that occurred when patients were under the control of different physicians or when they were admitted to different hospitals in the area, such as when their anticoagulation was revised by physicians other than those in the University of Kansas Division of Cardiovascular Diseases for other surgical procedures.
Since this was a retrospective study, there was no fixed schedule of clinic visits or established routine follow-up for evidence of complications of anticoagulation. This is the reason that there is no category for minor hemorrhages. Minor bleeding events such as hemoptysis may not have been commented upon in clinic notes or might not have been recorded in a telephone message. The constant source of thromboplastin at the University of Kansas Medical Center removed major variability of thromboplastin as a reason for prothrombin time variation. Sudden variations in prothrombin times may have occurred due to a patient’s negligence, the addition of new medications, termination of long-term medications, and for unknown reasons.

Nevertheless, our data are consistent with the premise that a lower intensity of anticoagulation may be equally effective in preventing thromboembolic events while decreasing bleeding complications in patients with mechanical valve prostheses. This is consistent with other recent reports on this topic.

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REFERENCES
1 Stein PD, Kantrowitz A. Antithrombotic therapy in mechanical and biological prosthetic heart valves and saphenous vein bypass grafts. Chest 1989; 95:1075-17S
2 McGoon DC. The risk of thromboembolism following valvular operations: how does one know? J Thorac Cardiovasc Surg 1984; 88:782-96