Aniticoagulation in Patients Following Prosthetic Heart Valve Replacement

Raja Parvez Akhtar, FRCS,1 Abdul Rehman Abid, FCPS,2 Hasnain Zafar, MBBS,1 and Jawad Sajid Khan, FRCS1

Purpose: To identify optimum international normalized ratio (INR) levels and required warfarin doses and anticoagulation-related complications in patients following mechanical prosthetic valve replacement.

Materials and Methods: Five hundred and seven patients were prospectively followed up for 10 years (2008.5 patient-years). Anticoagulation-related complications were classified into hemorrhage and thromboembolism.

Results: Two hundred and ninety-two (57.6%) were males and 215 (42.4%) were females with a mean age of 29.5 ± 11.32 years. A total of 268 (52.9%) patients had mitral, 96 (18.9%) had aortic and mitral, and 76 (15%) had aortic valve replacement (AVR). Valves implanted totaled 345 (68%) ball and cage, 126 (24.9%) bileaflet, and 36 (7.1%) single disc. There were 10,669 total visits, with mean INR 2.6 ± 0.59 and mean warfarin 5.17 ± 1.6 mg. Sixty-four (3.2% per patient-years) events occurred during follow-up, of which 23 (1.13% per patient-years) events were due to thromboembolism and 41 (2.04% per patient-years) to bleeding. Atrial fibrillation occurred in 12 (52.4%) patients having thromboembolic events and in 24 (58.5%) suffering from bleeding complications. Among thromboembolic events, valve thrombosis occurred in 9 patients (0.44% per patient-years) and cerebrovascular accidents (CVAs) in 14 (0.69% per patient-years). Atrial fibrillation was present in 7 (77.8%) patients in the valve thrombosis group and in 5 (35.7%) in the CVA group. Of 41 bleeding events, 8 (0.39% per patient-years) were minor episodes, 20 (0.99% per patient-years) were major episodes, and severe hemorrhage occurred in 5 (0.34% per patient-years). Intracranial hemorrhage leading to CVA was seen in 8 patients (0.34% per patient-years). There were 22 (1.1% per patient-years) fatal hemorrhages and 15 (0.74% per patient-years) fatal thromboembolic events. In-hospital mortality was 25 (4.9%), and 62 (12.2%) were late deaths; of these, 37 (7.3%) were anticoagulation related.

Conclusions: Anticoagulation for mechanical heart valve replacement can be managed with INR levels of 2–2.5 with acceptable hemorrhagic and thromboembolic events. (Ann Thorac Cardiovasc Surg 2009; 15: 10–17)

Key words: rheumatic heart disease, prosthetic heart valve, anticoagulation, international normalized ratio, valve thrombosis

Introduction

Rheumatic heart disease (RHD) is endemic in Pakistan with a prevalence of 5.7 in 1,000.10 A significant proportion of patients with RHD is ≤ 20 years.11 There is an accelerated deterioration of valves in rheumatic fever (RF) because of repeated recurrences of RF leading to severe debilitation and early death.2 Most patients present late and undergo mechanical valve replacement because
of severely diseased valves not suitable for open repair or percutaneous valvuloplasty. The decision regarding a mechanical valve versus a bioprosthesis is based on factors like patient age, overall longevity of the valve, relative contraindications to anticoagulation, and lifestyle. RF and a young age at the time of operation are possible factors in early bioprosthetic valve failure.

The implantation of an artificial valve exposes the patient to an increased risk of valve thrombosis and embolism; thus lifelong oral anticoagulation therapy is imperative. The occlusion of a prosthetic valve has been reported to occur in 1%–13% of cases. There is an estimated 4–8 per 100 patient-year rate of major thromboembolism in patients not receiving long-term anticoagulation therapy. The administration of antiplatelet therapy reduces this risk to 2.2 per 100 patient-years and oral anticoagulation therapy reduces this risk further, to 1 per 100 patient-years. Factors leading to an increased risk of thromboembolism include number of valves replaced, type of valve implanted (greater in ball-and-cage variety), mitral valve replacement (MVR), atrial fibrillation, left atrial enlargement, left ventricle (LV) dysfunction, clotting disorder, and prior embolic event.

Because the risks of thromboembolism and bleeding, an optimal intensity of anticoagulation is defined as the level where both of these complications are lowest. Recently, the American College of Cardiology recommended a target international normalized ratio (INR) of 2.5–3.5 for patients with high-risk aortic valve replacement (AVR), MVR, and INR of 2.0–3.0 for low-risk AVR. Saour et al. reported no increase in thromboembolic events with low-dose anticoagulation. It has been reported that a high-intensity (INR: 7.4–10.7) versus low intensity (INR: 1.9–3.6) shows no difference of thromboembolism, but a high incidence of bleeding events.

Studies done in Asian populations have reported a marked decrease in bleeding and effective prevention of thromboembolism with low-dose anticoagulation (INR: 1.4–2.0) in patients of prosthetic valve replacement. Oriental patients have a greater tendency to bleed with anticoagulation therapy than Western patients do because of differences in race, coagulation characteristics, diet, and lifestyle. The current recommendation for Asian patients is low-intensity anticoagulation because they seem to be less vulnerable to thromboembolic disease than Caucasians are.

Keeping in view the Chinese and Japanese experience, we decided to report optimum INR levels and required warfarin-dose and anticoagulation-related complications in our patients undergoing mechanical valve replacement.

Materials and Methods

From June 1994 to June 2006, a prospective follow-up with clinical assessment, INR measurement, recording of thromboembolic and hemorrhagic events, and echocardiography was carried out in 507 consecutive patients undergoing mechanical valve replacement for RHD. Informed consent was taken from all patients. The practice at our institute has been to manage an INR of 2.0–3.0. With this in mind, we proceeded to record all INR levels, warfarin doses, and events in our patients from 1994. Follow-up ranged from 0.16 to 12.08 years, (mean 3.96 ± 3.33 years, median 3.42 years) with a cumulative follow-up of 2008.5 patient-years.

There were 292 (57.6%) males and 215 (42.4%) females, with a mean age of 29.5 ± 11.32 years. Mitral valve disease was present in 268 (52.9%) patients, aortic and mitral valve disease in 96 (18.9%) patients, and aortic valve disease in 76 (15%) patients (Table 1). Atrial fibrillation was present in 259 (51.1%) patients. A total of 419 (82.6%) were in New York Heart Association (NYHA) class IV, 9 (1.8%) were in NYHA class III, and 79 (15.6%) were in NYHA class II prior to surgery. A total of 127 (25%) had moderate pulmonary hypertension, and in 54 (10.7%) it was severe. A total of 345 (68%) had a ball-and-cage valve (B&C) implanted, 126 (24.9%) had bileaflet valves, and 36 (7.1%) had single disc valves.

Operative technique

Cardiopulmonary bypass was established using a membrane oxygenator and moderate systemic hypothermia. Myocardial preservation was with St. Thomas' Hospital solution until 1997; thereafter blood cardioplegia was used, repeated every 20–25 min. The types of mechanical valves implanted were Starr-Edwards, St. Jude Medical, CarboMedics, and Sorin. Until December 2003, we used a Starr-Edwards ball valve because it was the least expensive available. Since then, only bileaflet valves have been used because of their considerable reductions in price. MVR was performed via standard left atrial exposure, using semicontinuous 3/4 Prolene sutures. AVR was carried out using an oblique...
aortotomy and interrupted pledgetted Ethicon Ethibond Excel 2/0 sutures (Johnson & Johnson, Piscataway, NJ, USA).

**Postop**
Postoperatively, all patients were moved to the intensive care unit (ICU). After removal of chest drains on the 1st postoperative day, 5,000 units of unfractionated heparin (Heparin Sodium Injection, USP; Pharmacia & Upjohn Company, Kalamazoo, MI, USA) were injected subcutaneously every 8 hours, and oral warfarin therapy (COUMADIN®; DuPont Ethical Pharmaceuticals, MA, USA) was commenced. Heparin was continued until the INR was >2. Patients were maintained at an INR of 2.0–3.0. All patients were assessed by 2-D and color Doppler echocardiography (Toshiba 6000 Power Vision; Toshiba Medical Systems Corp., Otawara, Japan) preoperatively, postoperatively in the ICU, and prior to discharge.

**Follow-up and anticoagulation**
At discharge, they were counseled on oral anticoagulation and rheumatic prophylaxis. Follow-up echocardiography was performed at 3 months and then yearly unless otherwise indicated. Anticoagulation was monitored by checking the prothrombin time and INR; if required, patients were admitted until the optimum INR was achieved, and followed up weekly until the proper control of INR was assured.

**Study end points**
The primary end point was anticoagulation-related complications classified into thromboembolic and hemorrhagic complications. Valve thrombosis, central nervous system complications, and bleeding events were defined, according to guidelines for reporting morbidity after cardiac valvular operations by Edmunds et al.17)

The secondary end points were mortality and early postoperative complications. Mortality was divided into early and late mortality. Early mortality was defined as patient death in-hospital immediately postoperation or during index hospital admission. Late mortality was death of the patient after discharge at home or death in the hospital after 30 days following readmission.

The early postoperative complications included pericardial effusion large enough to cause hemodynamic compromise requiring pericardiocentesis and wound infection occurring during the index hospital admission. Females of child-bearing age who conceived were followed up until the completion of pregnancy. They were anticoagulated with warfarin sodium to maintain an INR of 2.0–2.5. They were informed of anticoagulation-related hazards and possible warfarin embryopathy. In the beginning of our study all were subjected to subcutaneous Heparin 6–8-hourly doses for the first 12 weeks followed by oral warfarin therapy until the last 15 days of pregnancy, when the patient was admitted.

<table>
<thead>
<tr>
<th>Table 1. Epidemiological characteristics of the study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Age mean years</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>Isolated mitral valve disease</td>
</tr>
<tr>
<td>Isolated aortic valve disease</td>
</tr>
<tr>
<td>Aortic and mitral valve disease</td>
</tr>
<tr>
<td>Mitral and tricuspid valve disease</td>
</tr>
<tr>
<td>Aortic mitral and tricuspid valve disease</td>
</tr>
<tr>
<td>Aortic valve with IHD</td>
</tr>
<tr>
<td>Mitral valve with IHD</td>
</tr>
<tr>
<td>Mitral and aortic valve disease with IHD</td>
</tr>
<tr>
<td>Mitral and tricuspid valve disease with IHD</td>
</tr>
<tr>
<td>Mitral valve with other associated lesions, such as ASD and PFO</td>
</tr>
<tr>
<td>Prosthesis implanted</td>
</tr>
<tr>
<td>Ball and cage</td>
</tr>
<tr>
<td>Single disc</td>
</tr>
<tr>
<td>Bileaflet</td>
</tr>
</tbody>
</table>

IHD, ischemic heart disease; ASD, atrial septal defect; PFO, patent foramen ovale.
and switched to unfractionated heparin (UFH) therapy. Since then this has changed in later pregnancies because with this regime we had a high incidence of valve thrombosis. Now we continue with oral warfarin until the 34th week when the patient is admitted and switched to intravenous heparin keeping activated partial thromboplastin time (aPTT) at 2 times control. Warfarin is restarted 24 hours after delivery at the pre-delivery dosage along with I/V heparin until we achieve the therapeutic range of INR.

**Statistical Analysis**

The data were analyzed by using SPSS 14.0 (Statistical Package for Social Sciences, Version 14.0) for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as percentages, and continuous variables were expressed as mean ± standard deviation. Events were defined as thromboembolic and hemorrhagic complications. Linearized event rates were calculated by dividing the total number of events by the patient-years of follow-up.

**Results**

Three hundred and fifty-two (69.4%) patients are alive and having regular follow-up, but 7 (1.4%) never reported back, and we were unable to obtain complete clinical follow-up on 61 (12%).

A total of 64 (3.2% per patient-years) events occurred over the follow-up period. Among them, 36 (56.3%) patients had atrial fibrillation, and 28 (43.8%) were in sinus rhythm. A total of 23 (1.3% per patient-years) events were due to thromboembolism, and 41 (2.04% per patient-years) were due to bleeding. In thromboembolic events, 12 (52.2%) patients had atrial fibrillation, and 24 (58.5%) suffering from bleeding complications had associated atrial fibrillation. Among thromboembolic events, 9 (0.44% per patient-years) patients had valve thrombosis, and 14 (0.69% per patient-years) had cerebrovascular accidents (CVAs). In valve thrombosis patients, 2 had a disc, 6 had B&Cs at mitral, and 1 had a B&C at the aortic position (Fig. 1). Out of these, 7 (77.8%) patients had atrial fibrillation and 2 (22.2%) were in sinus rhythm. There were 6 mortalities, 4 (66.7%) had atrial fibrillation. Three patients having thrombosed valves were pregnant, of which 2 were on subcutaneous heparin during the first trimester it was in the early days of the study. Two patients survived after emergency valve replacement, and one died soon after arrival at the hospital. One patient with a thrombosed bileaflet valve was given injection streptokinase 1.5 million units (Injection Streptase®; Aventis Behring GmbH, Marburg, Germany) with good results. Except for pregnant patients, all patients had poor compliance to anticoagulation therapy despite repeated counseling. Fourteen (0.69% per patient-years) patients had CVAs, of which 5 (0.25% per patient-years) had transient ischemic attacks (TIAs), and 9 (0.44% per patient-years) patients had CVAs with delayed recovery (Table 2). Among patients with CVAs, 5 (35.7%) had atrial fibril-
lation, 1 (20%) had TIA, and 4 (44.4%) had CVAs with delayed recovery. Fifteen (0.74% per patient-years) were fatal thromboembolic events with associated atrial fibrillation in 8 (53.3%) patients.

Forty-one (2.04% per patient-years) hemorrhagic events were recorded. Twenty-six (5.1%) had MVR; of these, 11 (1.99%) had B&Cs, 9 (1.78%) bileaflet, 4 (0.78%) B&Cs with tricuspid valve repair (TVR), and 2 (0.39%) with single disc valves. Nine (1.78%) patients had AVR, 4 (0.78%) ball-and-cage, 3 (0.59%) bileaflet, and 2 (0.39%) single disc valves. Six (1.18%) had double-valve replacements (MVR + AVR); 2 (0.39%) had B&Cs, and 4 (0.79%) had bileaflet valves (Fig. 2). Of these events, 8 (0.39% per patient-years) were minor bleeding episodes, 20 (0.99% per patient-years) were major episodes, and severe hemorrhage occurred in 5 (0.34% per patient-years). Intracranial hemorrhage leading to CVA was seen in 8 (0.39% per patient-years). There were 22 (1.1% per patient follow-up years) fatalities resulting from hemorrhage.

The mean INR levels and warfarin doses were calculated individually for all valves used (Table 3). The INR and warfarin doses of each patient were recorded at each visit, and these were totaled to get an average value for each patient. They were than added, and mean INR and warfarin doses were calculated for the cohort. There were a total of 10,669 visits, (1–107 visits per patient) and (mean of 22.84 ± 19.67) visit per patient. A mean INR of 2.6 ± 0.59 was maintained on a mean warfarin dose of 5.17 ± 1.6 mg. INR was in therapeutic range in 7,346 (68.85%), and in 3,323 (31.15%) visits, INR was either ≤2.0 or ≥5.0 (Table 4). In 1,282 (12%) visits, INR was <1.5, and this was associated with 9 (0.44% per patient-years) CVAs. In 1,604 (15%) visits similarly, INR was 1.6–1.9, and this was associated with 5 (0.24% per patient-years) TIA. All of the above patients were on irregular medication. In 437 (4%) visits, INR was >5; 33 (1.64% per patient-years) hemorrhagic events were recorded, and of these 5 (0.24% per patient-years) were severe hemorrhages and 4 (0.19% per patient-years) were intracranial bleeds leading to CVAs. Most bleeding events occurred during the first year of study. Mean INR in 259 patients having atrial fibrillation was 2.56 ± 0.58, which was maintained on a mean warfarin dose of 5.14 ± 1.51 mg, whereas the mean INR level of 248 patients in sinus rhythm was 2.69 ± 0.87, which was maintained on a mean warfarin dose of 5.21 ± 1.68 mg.

Twenty-five (4.9%) patients died within 30 days. Sixty-two (12.2%) were late deaths. Of these, 37 (7.3%) were anticoagulation related.

<table>
<thead>
<tr>
<th>Type of valve operation</th>
<th>Mean INR level</th>
<th>Mean warfarin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVR</td>
<td>2.63 ± 0.8</td>
<td>5.09 ± 1.55</td>
</tr>
<tr>
<td>AVR</td>
<td>2.45 ± 0.46</td>
<td>5.40 ± 1.74</td>
</tr>
<tr>
<td>MVR + AVR</td>
<td>2.77 ± 0.63</td>
<td>5.12 ± 1.51</td>
</tr>
<tr>
<td>MVR + TVR</td>
<td>2.54 ± 0.46</td>
<td>5.34 ± 1.57</td>
</tr>
</tbody>
</table>

INR, international normalized ratio; MVR, mitral valve replacement; AVR, aortic valve replacement; TVR, tricuspid valve repair.

<table>
<thead>
<tr>
<th>INR level</th>
<th>Events n (%/patient-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.5</td>
<td>TIA 5 (0.24)</td>
</tr>
<tr>
<td>1.6–1.9</td>
<td>CVAs 9 (0.44)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>Bleeding 33 (1.64)</td>
</tr>
<tr>
<td></td>
<td>CVA 4 (0.19)</td>
</tr>
</tbody>
</table>

INR, international normalized ratio; TIA, transient ischemic attack; CVA, cerebrovascular accident.
Discussion

At present there is no study showing what the optimal level of anticoagulation is for our patients. What is the incidence of anticoagulation-related complications? What level of INR is therapeutic for our patients?

A total of 507 patients with mechanical heart valve were followed, and we observed a low incidence of thromboembolic complications with an INR range of 2.6 ± 0.59. Our results are consistent with other Asian studies. Zhou et al.13) from China have reported after CarboMedics valve implantation a linearized rate of 5.83% per patient-years bleeding and 0.26% per patient-years thromboembolic events. The mean INR in this study was 1.68 ± 0.38. The authors concluded that low-dose anticoagulation (1.4–2.0) for patients with prosthetic valves could effectively prevent thromboembolism and markedly decrease bleeding events. Although our INR was higher, 68% of our patients had B&Cs, which are known to be more thrombogenic than the disc valves. We did not observe a significant increase in thromboembolic events.

In 805 Chinese patients receiving St. Jude Medical valves, Sun et al.12) reported a lower incidence of thromboembolism than of bleeding on an INR of 2.0–2.5. During follow-up, 47 anticoagulant-related hemorrhages occurred; thromboembolism occurred in 10 cases, and there were 3 mechanical valve thromboses. Our level of INR is comparable to their patients. In our study, 41 hemorrhagic events occurred, of which 22 were fatal, and 23 thromboembolic events occurred, of which 17 were fatal. Valve thrombosis occurred in 9 patients, 3 of whom were pregnant. Two patients were on subcutaneous heparin 7 patients had subtherapeutic INR levels and were on irregular warfarin of these 5 patients died.

Four studies from Japan13–16) have advocated an INR of 1.5–2.5. These studies have shown a low incidence of thromboembolic complications. In a retrospective study of 214 MVR patients, Matsuyama et al.13) reported thromboembolism in 8 patients and major bleeding in 5 on this INR. Mori et al.14) studied 102 patients with prosthetic valve, and no thromboembolic complications occurred. Hemorrhagic events occurred in 26 patients. Nineteen percent of the patients had an INR of <2.5, and 54% had an INR of 2.5–3.5. These studies have recommended that a low intensity of anticoagulation is needed for Asian patients because they are less vulnerable to thrombotic disease than Caucasians are. Chenhsu et al.18) from Taipei, noted a higher incidence of bleeding in patients having a mean INR of 1.9.18)

Koertke et al.,19) from Germany, have reported that a low-dose INR self-management has low hemorrhagic complications without increasing the risk of thromboembolism. They divided the study population into two groups. Group I received low-dose anticoagulation with a target INR of 1.8–2.8 for AVR and 2.5–3.5 for mitral or double valve replacement. Group II received the standard dose with a target INR of 2.5–4.5 for all heart valve prostheses. The rates of thromboembolic events and bleeding complications were lower in Group I as compared to Group II. Koertke et al.19) recommended a low-dose INR self-management for all patients in whom permanent anticoagulation therapy is indicated.

Hering et al.,20) have reported that low-intensity anticoagulation with a target INR of 2.0–3.5 is safe for patients with St. Jude Medical prosthesis in the aortic position as well as in the mitral position. They used three distinct levels of anticoagulation: 2.0–3.5, 2.5–4.0, and 3.0–4.5. With a higher INR range, there were no differences with regard to bleeding or thromboembolic complications. AREVA study21) reported 380 patients randomized to INR levels of 2.0–3.0 vs. 3.0–4.5. The incidence of thromboembolism was similar in the two groups. However, there were less bleeding episodes in the group with less intensive oral anticoagulation. We agree with this because we maintained our patients in a range of 2.0–2.5. Although this is lower than the recommendations of American College of Cardiology/American Heart Association (ACC/AHA), we have not seen a high incidence of anticoagulation-related complications. Meschengieser et al.22) compared anticoagulation-related complications in two groups, one with low-intensity INR of 2.5–3.5 in combination with oral aspirin 100 mg/day, and the second group having high-intensity anticoagulation alone (INR: 3.5–4.5). Thromboembolic events were similar in the two groups; however, major bleeding episodes were markedly less frequently observed in the group with low-intensity anticoagulation. The studies by Hering et al.,20) AREVA,21 and Meschengieser et al.22) included St. Jude Medical valves; however, most of our patients had Starr Edward’s valves at the mitral position.

John et al.,23) from India, have reported their experience with Starr Edward’s valves. With an INR of 2.65 they observed an incidence of 0.5/100 patient-years for thromboembolic events and 0.31/100 patient-years for hemorrhagic events. Our hemorrhagic event rate of
et al.23) did, which could probably be due to the racial
lislism and hemorrhagic episodes on low INR than Gödge
hemorrhagic events. We observed fewer thromboembo-
lic events. We observed fewer thromboembolism and hemorrhagic episodes on low INR than Gödge
et al.23 did, which could probably be due to the racial
dietary differences of our population in comparison
to the West. Our findings suggest that our patients are
less prone to complications on a low INR (2–2.5) in
comparison to patients in the West. This is comparable
to our colleagues in Japan and China, who recommend
an INR of 2–2.5.

Conclusions

This is the first time that a prospective follow-up study
with mechanical prosthetic valves has been done and
data recorded and analyzed in Pakistan. We agree with
our Asian colleagues about low-dose warfarin. Patients
with mechanical heart valves can be managed with an
INR level of 2.0–2.5 with acceptable hemorrhagic and
thromboembolic events.

Study limitations

We unfortunately are unable to compare our results
with different INR levels prior to this study because we
have no follow-up data. This is due to inadequate record
keeping and low patient appearance. Because we now
have a baseline, we can investigate the overall incidence
of hemorrhage and thromboembolism with a different
INR range, i.e., 1.6–1.9, 2–3, and 3–4, and compare
results. Because the current study is from a single center,
a single surgeon, and a small group, we would benefit
from extending this to a multicenter study with a differ-
ent INR range.

We have been using Starr Edward’s valves in most of
our patients because of their cost-effectiveness in com-
parison to the bileaflet valves now accepted worldwide.
Our two groups, B&C and bileaflet, are unequal, so we
were unable to compare their outcomes.

References

1. Rizvi SF, Khan MA, Kundi A, Marsh DR, Samad A,
et al. Status of rheumatic heart disease in rural Paki-
2. John S, Ravikumar E, John CN, Bashi VV. 25-year
experience with 456 combined mitral and aortic valve
3. American College of Cardiology; American Heart
Association Task Force on Practice Guidelines (Writ-
ing Committee to revise the 1998 guidelines for the
management of patients with valvular heart disease);
Society of Cardiovascular Anesthesiologists, Bonow
RO, Carabello BA, et al. ACC/AHA 2006 guidelines
for the management of patients with valvular heart
disease: a report of the American College of Cardiolo-
y/American Heart Association Task Force on Practice
Guidelines (writing Committee to Revise the 1998
guidelines for the management of patients with
valvular heart disease) developed in collaboration with
the Society of Cardiovascular Anesthesiologists
endorsed by the Society for Cardiovascular Angiogra-
phy and Interventions and the Society of Thoracic
Long-term evaluation of Carpentier Edwards porcine
bioprosthesis for rheumatic heart disease. J Thorac
TG, et al. Early postoperative anticoagulation after
mechanical valve replacement: a systematic review.
6. Sharma N, Grover A, Radotra BD. Prosthetic cardiac
valve replacement: management problems. Asian
7. Cannegieter SC, Rosendaal FR, Briët E. Throm-
boembolic and bleeding complications in patients
with mechanical heart valve prosthesis. Circulation
1994; 89: 635–41.
8. Hirsh J, Dalen JE, Anderson DR, Poller L, Bussey H,
et al. Oral anticoagulants: mechanism of action, clinical
9. Saour JN, Sieck JO, Mamo LA, Gallus AS. Trial of
different intensities of anticoagulation in patients


