

Major Hemorrhagic and Thromboembolic Complications in Patients with Mechanical Heart Valves Receiving Oral Anticoagulant Therapy

Przemysław Trzeciak,¹ Marian Zembala,² Lech Poloński¹

¹3rd Department of Cardiology and ²Department of Cardiac Surgery and Transplantology, Silesian Center for Heart Disease, Zabrze, Poland

ABSTRACT

Introduction: Patients with mechanical heart valve prostheses are obligated to receive lifelong oral anticoagulant therapy to prevent thromboembolic complications; however, this treatment is associated with an increased risk of bleeding. The aim of this study was to evaluate the frequency of major hemorrhagic and thromboembolic complications in patients with mechanical heart valves who received oral anticoagulant therapy.

Materials and Methods: The analysis involved 225 patients who underwent successful surgery in 2000; the mean (\pm SD) follow-up period was 43.3 ± 9.2 months. Aortic, mitral, and double valve replacement was performed in 128 (56.7%), 70 (31.1%), and 27 (12.1%) of the patients, respectively. There were 128 men (57.3%), and the mean patient age was 57.9 ± 18.8 years. The following data were assessed: rate of major hemorrhagic and thromboembolic complications, frequency of international normalized ratio (INR) rate measurements, and percentage of results within the therapeutic range.

Results: Major hemorrhagic and thromboembolic complications occurred in 25 patients (11.1%). Seventeen patients (7.5%) survived, and 8 (3.6%) died of the complications. Major hemorrhagic and thromboembolic complications occurred in 17 patients (7.6%) and 8 patients (3.6%), respectively. The mean time between sequential measurements was 4.3 ± 3.0 weeks, and of all the INR values collected, 42.4% were within, 31.3% were below, and 26.3% were above the target ranges.

Conclusions: Patients with a mechanical heart valve prosthesis receiving acenocoumarol are susceptible to major hemorrhagic and thromboembolic complications, some of which lead to death. Despite the danger related to these complications, patients receiving anticoagulant therapy still have difficulty achieving INR values within the therapeutic range.

INTRODUCTION

Many of the problems associated with heart valve replacement have been eliminated through 4 decades of

incremental improvements in the materials, design, and manufacture of prostheses, in surgical techniques, and in postoperative management. Patients with mechanical heart valve prostheses are obligated to receive lifelong oral anticoagulant therapy to prevent thromboembolic complications, but this treatment is associated with an increased risk of bleeding [Cannegieter 1995]. Despite advances in technology and perioperative care, thromboembolic and hemorrhagic complications are still associated with a significant rate of postoperative mortality and morbidity and remain an unresolved problem [Horskotte 1993a]. Although oral anticoagulation with coumarin derivatives has been used therapeutically for 60 years [Link 1959] and for 40 years in patients with prosthetic heart valves, there are still only a limited number of publications concerning the problem of thromboembolic and hemorrhagic complications after heart valve replacement. Whereas studies on the design of drug therapy are published regularly, publications concerning the field of related heart valve diseases and the most common dangers have been extremely rare thus far [VA 1985]. In many areas of patient management after valve surgery, randomized trials and meta-analyses do not exist. The few randomized trials that do exist are narrowly focused with small numbers, have limited general applicability, and do not lend themselves to meta-analysis because of widely divergent methodologies and patient characteristics [Butchart 2005]. The definition, classification, and occurrence of thromboembolic and hemorrhagic complications in patients with artificial heart valve prostheses are different in many studies.

The scope of the problem and the number of mechanical heart valves implanted in Poland are inestimable. The first prosthetic valve implanted in Poland was in 1964 [Dziatkowiak 2006]. Despite the growing number of patients with mechanical heart valve prostheses, thromboembolic and hemorrhagic complications are largely ignored. According to data from the Registry of the Club of Polish Cardiac Surgeons, 3365 heart valve replacements and 1619 heart valve replacements concomitant with coronary artery bypass grafting (CABG) were performed in Poland in 2005 [Raport 2006].

In our study, we have observed the occurrence of major hemorrhagic and thromboembolic complications in patients after mechanical heart valve replacement. In the following sections, we assess the frequency of international normalized ratio (INR) measurements and the adequacy of anticoagulation therapy within the therapeutic range.

Received July 5, 2009; received in revised form September 22, 2009; accepted October 5, 2009.

Correspondence: Dr. Przemysław Trzeciak, MD, 3rd Department of Cardiology, Medical University of Silesia, Silesian Centre for Heart Disease, 2 Szpitalna Str., 41-800 Zabrze, Poland; +48-32-3733700; fax: +48-32-2732679 (e-mail: przemyslaw.t@wp.pl).

Table 1. Baseline Clinical Characteristics of the Patients*

Characteristic	
NYHA class	2.6 ± 0.8
Duration of symptoms, mo	53.4 ± 64
LVEF	44% ± 8.9%
Atrial fibrillation, n	45 (20%)
Previous stroke, n	9 (4%)
Previous myocardial infarction, n	17 (7.6%)
Diabetes mellitus, n	19 (8.4%)
Hypertension, n	85 (37.8%)
Cigarette smoking, n	70 (31.1%)
Mean BMI, kg/m ²	28.4
Hypercholesterolemia, n	21 (9.3%)

*Data for New York Heart Association (NYHA) class, duration of symptoms, and left ventricular ejection fraction (LVEF) are presented as the mean ± SD. BMI indicates body mass index; diabetes mellitus, fasting glucose >126 mg% or normal on hypoglycemic therapy; hypertension, blood pressure >140/90 mm Hg or controlled with hypotensive therapy; cigarette smoking, current or stopped for <1 year; hypercholesterolemia, cholesterol level >200 mg%.

MATERIALS AND METHODS

Study Population

The study population consisted of 225 patients who underwent at least one successful mechanical valve replacement at the Department of Cardiac Surgery and Transplantology in the Silesian Center for Heart Disease, Zabrze, Poland, between January and December 2000.

Aortic, mitral, and double valve (aortic plus mitral) replacements were performed in 128 (56.9%), 70 (31.1%), and

27 (12%) of the patients, respectively. Associated procedures were performed in 56 patients (24.9%), including CABG in 46 patients (20.4%) and tricuspid annuloplasties in 10 patients (4.4%). The mean age (±SD) of the 225 patients at the time of their procedure was 53.7 ± 18.8 years, and 128 (57.3%) of them were men. Other baseline characteristics of the patients are summarized in Table 1.

Intensity of Oral Anticoagulation

All 225 patients with mechanical prosthetic heart valves received oral anticoagulant therapy with acenocoumarol. Treatment was usually initiated on the second postoperative day after chest tube removal. Anticoagulation intensity was measured by the INR. Patients with aortic valve replacement (AVR) without atrial fibrillation were generally advised to maintain an INR between 2.0 and 3.0. Patients with mitral valve replacement (MVR) and atrial fibrillation were generally prescribed to maintain an INR within the range of 2.5 to 3.5. Patients after an additional CABG procedure received an oral anticoagulant and aspirin, usually at a dosage of 75 or 150 mg/d. After patient discharge from the hospital, oral anticoagulation was administered by general practitioners, internists, or, less frequently, cardiologists or cardiac surgeons.

Follow-up

The mean follow-up period was 43.3 ± 9.2 months (range, 1-52 months). Follow-up data were gathered from medical and hospital records, physician and cardiologist/cardiac surgeon records, and direct telephone interviews with patients and relatives. Patients without telephones were asked to complete a questionnaire and return it by mail. All patients were requested to send copies of additional information about hospital admission (such as discharge letters) and the results of the last 10 INR measurements.

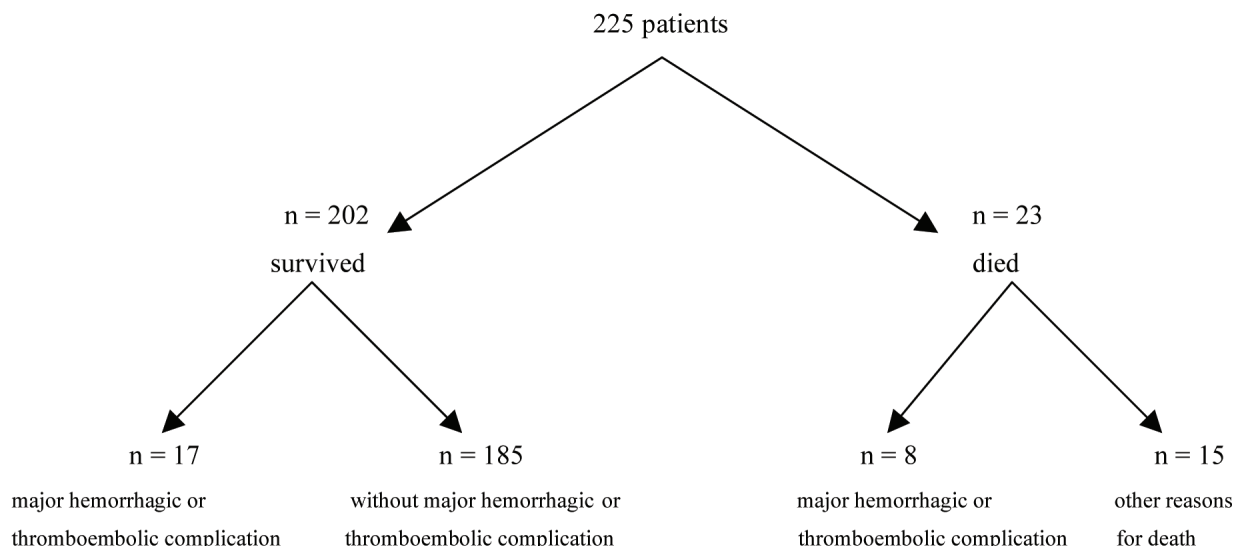


Figure 1. Incidence of major hemorrhagic and thromboembolic complications in 225 patients after mechanical valve replacement.

Table 2. Cause of Death in 23 Patients*

Cause of Death	MVR (n = 14), n	AVR (n = 8), n	DVR (n = 1), n	Total (N = 23), n
Cerebral bleeding	3	3 (1)	—	6
Dysfunction of prosthetic valve	3	—	—	3
Sudden cardiac death	2 (1)	—	1	3
Infective endocarditis	2 (1)	—	—	2
Pulmonary embolism	1	1 (1)	—	2
Congestive heart failure	—	2 (1)	—	2
Neoplasm	—	2 (1)	—	2
Trauma	1	—	—	1
Peritonitis	1 (1)	—	—	1
Unknown	1 (1)	—	—	1

*Parentheses indicate number of patients treated with oral anticoagulant and aspirin. MVR indicates mitral valve replacement; AVR, aortic valve replacement; DVR, double valve replacement.

Definitions of Major Hemorrhagic and Thromboembolic Complications

The main outcome variables were hemorrhagic and thromboembolic complications during the follow-up period. Major hemorrhagic complications comprised the following: (1) cerebral bleeding as determined by computed tomography (CT) scan or postmortem examination; (2) overt gastrointestinal bleeding; (3) occult gastrointestinal bleeding if endoscopic studies were performed; (4) retroperitoneal bleeding documented by CT scan; (5) ocular bleeding with blindness; and (6) bleeding that reduced the hemoglobin concentration by 2 g/dL or that required the transfusion of ≥ 2 units of blood.

Major thromboembolic complications included the following: (1) cerebral embolism, defined as an unexpected neurologic or visual deficit, either transient (transient ischemic attack, ie, totally reversible in <24 hours; or reversible ischemic neurologic deficit, ie, totally reversible within 3 weeks) or permanent (complete stroke), with cerebral hemorrhage excluded by CT scan; (2) peripheral embolism, defined as the occurrence of an acute ischemia caused by arterial embolism, as determined by angiography or surgery; (3) visceral embolism, defined as an acute occlusion of a visceral artery as determined by angiography or postmortem exam; (4) coronary embolism, defined by an acute myocardial infarction (typical electrocardiographic changes and elevated cardiac enzymes) in patients with normal arteries, as previously determined by angiography; and (5) valve thrombosis, as determined by 2-dimensional cardiac ultrasound or surgery in a patient with a previously normal echocardiogram. All complications that occurred during hospitalization that were due to a different therapeutic or diagnostic procedure were excluded.

Frequency of INR Measurements and Adequacy of Anticoagulation Treatment

The information regarding the frequency of INR measurement was obtained from telephone interviews and mail-in

questionnaires. The adequacy of anticoagulation treatment was evaluated from medical records and the results of the last 10 INR measurements sent in by the patients.

Statistical Analysis

Values were expressed as mean \pm SD unless otherwise indicated.

RESULTS

Of the 225 study participants, 23 (10.2%), including 10 women, died during the mean follow-up period of 43 ± 9.2 months: 14 with MVR, 8 with AVR, and 1 with double valve replacement (DVR). Eight of the dead patients had undergone concomitant CABG and were taking an oral anticoagulant and aspirin after surgery. Causes of death are presented in Table 2.

Among the 225 patients, major hemorrhagic and thromboembolic complications occurred in 25 patients (11.1%), including 11 women. Seventeen (7.5%) of these patients survived, and 8 (3.6%) died from these complications (Figure 1). Major hemorrhagic and thromboembolic complications occurred in 17 patients (7.6%), and 8 patients (3.6%), respectively.

The types of hemorrhagic and thromboembolic complications, for both the living and dead patients, are shown in Table 3.

The frequency of INR measurements and the adequacy of anticoagulant treatment were assessed only for the surviving patients. The mean time between 2 measurements was 4.3 ± 3.0 weeks. Of all the INR values collected, 42.4% were within, 31.3% were below, and 26.3% were above target ranges. The distribution of INR value ranges is shown in Figure 2.

Oral anticoagulation was administered mainly by general practitioners and internists; on rare occasions they were administered by cardiologists and cardiac surgeons. The mean time between 2 visits to the cardiologist was 5.7 ± 5.2 months.

Table 3. Major Hemorrhagic and Thromboembolic Complications Occurring during the Follow-up Period*

Major Complications	Nonfatal, n				Fatal, n				Nonfatal + Fatal, n			
	MVR	AVR	DVR	Total, n	MVR	AVR	DVR	Total, n	MVR	AVR	DVR	All, n
Hemorrhagic												
Cerebral bleeding	—	3 (2)	—	3 (2)	3	3 (1)	—	6	3	6 (3)	—	9 (3)
Gastrointestinal bleeding	1	6 (1)	—	7 (1)	—	—	—	—	1	6 (1)	—	7 (1)
Bleeding requiring transfusion	—	1 (1)	—	1 (1)	—	—	—	—	—	1 (1)	—	1 (1)
Thromboembolic												
Cerebral embolism	2 (1)	3	1	6 (1)	—	—	—	—	2 (1)	3	1	6 (1)
Valve thrombosis	—	—	—	—	2	—	—	2	—	—	—	—
Peripheral embolism	—	—	—	—	1	1 (1)	—	2 (1)	1	1 (1)	—	2 (1)
Total	3 (1)	13 (4)	1	17 (5)	6	4 (2)	—	10 (1)	7 (1)	17 (6)	1	25 (7)

*Parentheses indicate number of patients taking oral anticoagulant and aspirin. MVR indicates mitral valve replacement; AVR, aortic valve replacement; DVR, double valve replacement.

DISCUSSION

Hemorrhagic and thromboembolic complications are one of the main causes of morbidity and mortality in patients after mechanical valve replacement [Cortelazzo 1993; Horskotte 1993a, 1993b; Cannegieter 1995; Acar 1996; Aris 1996; Fiore 1998; Massel 2001; Butchart 2002; Ansell 2004; Levine 2004]. The number of clinical studies that assessed bleeding and thromboembolic complication rates in patients with a mechanical heart valve prosthesis is limited [VA 1985; Cortelazzo 1993; Horskotte 1993a, 1993b; Cannegieter 1995; Acar 1996; Aris 1996; Fiore 1998; Massel 2001; Butchart 2002; Ansell 2004; Levine 2004]. The intensity of the target anticoagulation level is different for many of these studies, and the definitions of major hemorrhagic and thromboembolic complications are inconsistent [VA 1985; Saour 1990; Cortelazzo 1993; Horskotte 1993a, 1993b; Turpie 1993; Acar 1996; Altman 1996; Aris 1996; Meschengieser 1997; Pengo 1997; Fiore 1998; Massel 2001; Butchart 2002; Van Nooten 2003; Ansell 2004; Levine 2004]. The reader must be aware of these discrepancies when interpreting the results from these clinical studies.

Saour et al [1990] randomized patients to receive either warfarin therapy at a target INR of 2.65 or very high-intensity warfarin therapy (target INR, 9.0). The rate of major bleeding during a 3.5-year follow-up period in the former treatment group was 3.3%, compared with 7.2% in the latter group ($P = .27$). In the trial conducted by Acar et al [1996], 380 patients were randomized for treatment with acenocoumarol at a target INR range of either 2.0 to 3.0 or 3.0 to 4.5. The rate of major bleeding over 2.2 years in the lower-intensity group was 9.0%, compared with 12.0% in the higher-intensity group ($P = .29$). Thromboembolic events occurred in 5.3% of the patients in the group with an INR of 2.0 to 3.0 and in 4.7% of the patients in the group with an INR of 3.0 to 4.5 ($P = .78$). In a trial conducted by Pengo et al [1997], 205 patients were randomized to receive treatment with either warfarin or acenocoumarol at a target INR of 2.5 to 3.5 or 3.5 to 4.5, with a mean follow-up period of 3 years. The rate of major bleeding was 3.8% in the former group, compared with 11% in the latter group ($P =$

.019); the rate of thromboembolism episodes was 5.8% in the former group and 5.9% in the latter ($P =$ not significant [NS]). In our analysis, major hemorrhagic and thromboembolic complications during a 3.6-year follow-up period occurred in 7.6% and 3.6% of the patients, respectively. It is worth noting that 20.4% of the patients in our analysis were taking oral anticoagulants in addition to aspirin. Because of nonoptimal control of anticoagulation and the high risk of hemorrhagic and thromboembolic complications, we significantly reduced the number of mechanical heart valve prosthesis implantations in lieu of biological valves in the last years.

The addition of aspirin to vitamin K antagonists in anticoagulation therapy after mechanical valve replacement has been investigated in a number of studies. In a blinded trial, Turpie et al [1993] compared warfarin (INR, 3.0 to 4.5) with warfarin combined with 100 mg of aspirin. The rate of major bleeding after 2.5 years of follow-up was 10.3% in the warfarin-alone group, compared with 12.9% in the warfarin-plus-aspirin group ($P = .43$). Major embolic complications occurred in 7.1% of the patients from the warfarin-alone group, compared with 2.7% of the patients in the warfarin-plus-aspirin group. Altman et al [1996] compared 2 different dosages of aspirin (100 mg/d versus 650 mg/d) in patients receiving acenocoumarol at an INR of 2.0 to 3.0 and followed the patients up for a mean of 24.1 and 21.7 months, respectively. The rate of major bleeding in the lower-dose aspirin group was 7.2%, compared with 9.4% in the higher-dose group ($P = .4$). The incidences of systemic embolism in the low- and high-dose aspirin treatments were 0.9% and 1.9%, respectively ($P =$ NS). Meschengieser et al [1997] compared acenocoumarol alone (INR, 3.5 to 4.5) with a combination of acenocoumarol at a lower intensity (INR, 2.5 to 3.5) and 100 mg of aspirin. The rate of major bleeding after a median follow-up period of 23 months was 4.5% in the monotherapy group, compared with 2.3% in the combined-therapy group ($P = .27$). The incidence of embolism was 2.7% in the former group and 2.8% in the latter. Laffort et al [2000] compared treatment with vitamin K antagonist alone (INR, 2.5 to 3.5) with a combination of a vitamin K antagonist and aspirin (200 mg/d)

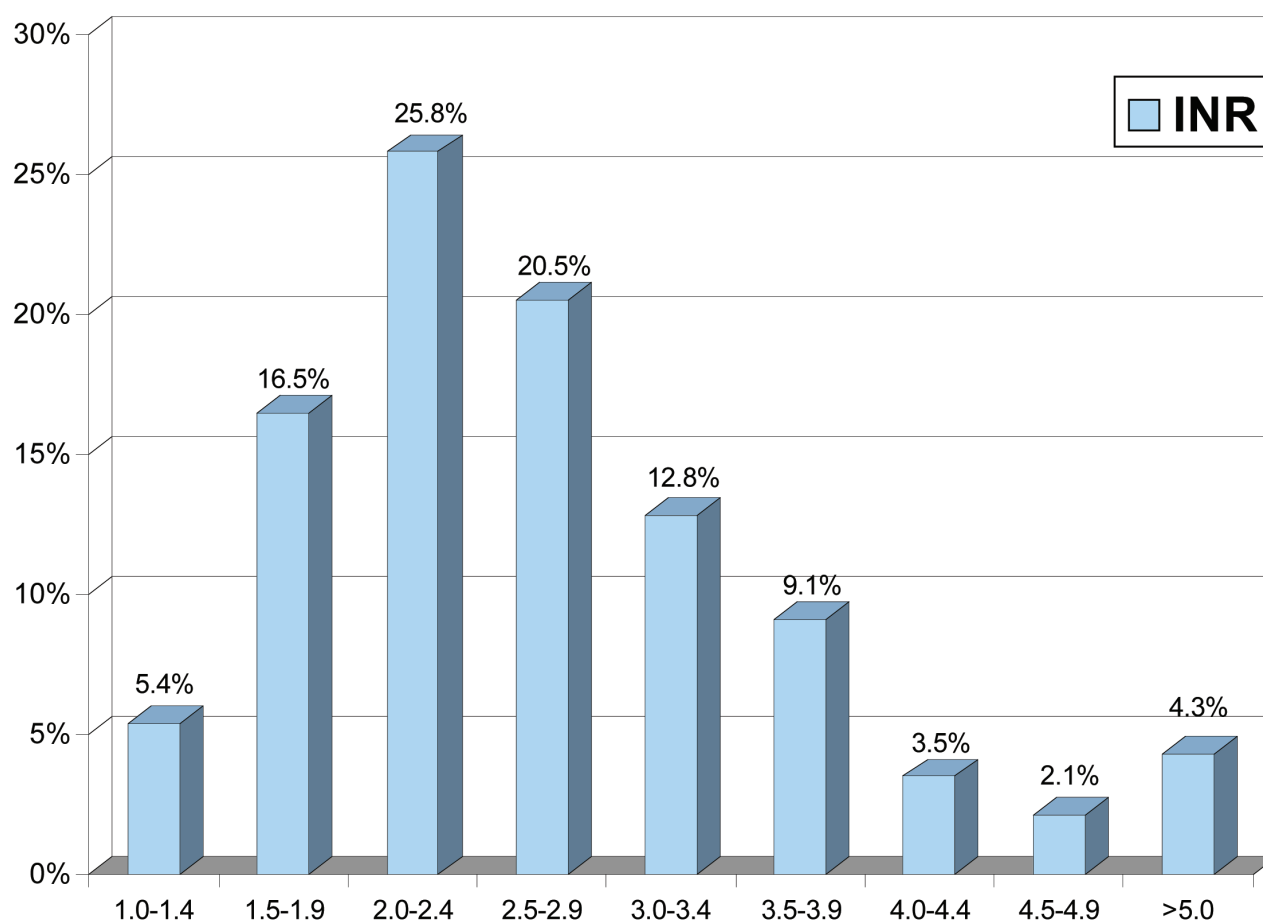


Figure 2. Distribution of values for the international normalized ratio (INR) based on the last 10 INR measurements.

for 1 year. The rate of major bleeding was 8.3% in the monotherapy group and 19.2% in the combined group ($P = .02$).

The most significant factor influencing the frequency of hemorrhagic complications, the frequency of thromboembolic complications, and survival after prosthetic valve replacement is the adequacy of anticoagulant therapy. Butchart et al [2002] showed that high anticoagulation variability was the most important independent predictor of reduced survival after mechanical valve replacement. Altman et al [1996] showed that anticoagulant therapy was adequate in 70% of patients treated with an oral anticoagulant (with a target INR range of 2.0 to 3.0) and aspirin (at a daily dose of 100 mg). In these adequately treated patients, 17% of the INR values were lower than the target range, and 13% were higher. Meschengieser et al [1997] noticed that the adequacy of anticoagulant therapy (target INR, 3.5 to 4.5) in the third year of follow-up was only 37%, whereas 38% of the INR values were lower than the target range and 25% were higher [Meschengieser 1997]. In the Butchart et al study [2002], 75.5% of the INR values were within the target range. Of the 24.5% of the INR values that were outside the range, 12% were below and 12.5% were above the therapeutic level [Butchart 2002]. In the study of Hering et al [2005], 90.2% of the total number of INR measurements made during the follow-up period were within

the therapeutic INR range of 2.0 to 4.5, which is the lowest erratic INR ever published. In our retrospective study of all the INR values collected, 42.4% were within, 31.3% were below, and 26.3% were above the target range. It is worth noting that patients from these cited studies generally had their systematic INR controlled in clinical centers. The majority of our patients lived far away from the clinical center, and many of them could not receive frequent INR measurements. Poor INR control can explain why cerebral bleeding was the most common cause of death in our population.

Adequacy of anticoagulation therapy is strongly correlated with the frequency of INR measurements. Horskotte et al [1993a] specifically addressed this issue in a study of 200 patients with mechanical valves, in which the percentage of INRs within the target range varied from 48%, when monitoring occurred at a mean interval of 24 days, to 89%, when monitoring occurred at a mean interval of every 4 days. In our study, the mean time between sequential measurements was 3.4 ± 5.9 weeks.

To improve the management of patients taking oral anticoagulants, some countries offer anticoagulation clinics [Landefeld 1989; Cortelazzo 1993; Bussey 1996; Chiquette 1998]. Cortelazzo et al [1993] assessed the incidence of thromboembolic events and major hemorrhagic complications in patients

with a mechanical heart valve prosthesis before and after enrollment at an anticoagulation clinic. The incidence of major hemostatic complications was significantly lower when patients attended the clinic: 1.0% versus 4.9% per patient-year for hemorrhage and 0.6% versus 6.6% per patient-year for thrombosis. These differences were due to 3 main factors: better regulation of the oral anticoagulant dosage, continuous patient education, and early identification of clinical risk factors for thrombosis and hemorrhage. More than 70% of the patients were maintained in the therapeutic range of anticoagulation [Cortelazzo 1993].

In summary, patients with mechanical heart valve prostheses treated with acenocoumarol are susceptible to major hemorrhagic and thromboembolic complications, some of which lead to death. Despite the risk of complications, patients still have difficulty achieving INR values within the therapeutic range. To reduce the incidence of hemorrhagic and thromboembolic events, we hypothesize that patients may require more frequent INR control; however, our assertion requires further investigation.

REFERENCES

- Acar J, Jung B, Boissel JP, et al. 1996. AREVA: multicenter randomized comparison of low-dose versus standard-dose anticoagulation in patients with mechanical prosthetic heart valves. *Circulation* 94:2107-12.
- Altman R, Rouvier J, Gurfinkel E, Scazzioti A, Turpie AG. 1996. Comparison of high-dose with low-dose aspirin in patients with mechanical heart valve replacement treated with oral anticoagulant. *Circulation* 94:2113-6.
- Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. 2004. The pharmacology and management of the vitamin K antagonists. The seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 126:204S-33S.
- Aris A, Igual A, Padro JM, et al. 1996. The Spanish Monostrut Study Group: a ten year experience with 8,599 implants. *Ann Thorac Surg* 62:40-7.
- Bussey HL, Chiquette E, Amato M. 1996. Anticoagulation clinic care versus routine medical care: a review and interim report. *J Thromb Thrombolysis* 2:315-9.
- Butchart EG, Gohlke-Barwolf C, Antunes MJ, et al. 2005. Recommendations for the management of patients after heart valve surgery. *Eur Heart J* 26:2463-71.
- Butchart EG, Payne N, Li HH, Buchan K, Mandana K, Grunkemeier GL. 2002. Better anticoagulation control improves survival after valve replacement. *J Thorac Cardiovasc Surg* 123:715-23.
- Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJM, Vandenburghe JP, Briet E. 1995. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med* 335:11-7.
- Chiquette E, Amato MG, Bussey HL. 1998. Comparison of an anticoagulation clinic with usual medical care. *Arch Intern Med* 158:1644-7.
- Cortelazzo S, Finazzi G, Viero P, Remuzzi A, Parenzan L, Barbui T. 1993. Thrombotic and hemorrhagic complications in patients with mechanical heart valve prosthesis attending an anticoagulation clinic. *Thromb Haemost* 69:316-20.
- Dziatkowiak AJ. 2006. Outlined history of the development of the world and Polish cardiac surgery. *J Physiol Pharmacol* 57(suppl 1):43-105.
- Fiore AC, Barner HB, Swartz MT, et al. 1998. Mitral valve replacement: randomized trial of St. Jude and Medtronic Hall prostheses. *Ann Thorac Surg* 66:707-13.
- Hering D, Piper C, Bergemann R, et al. 2005. Thromboembolic and bleeding complications following St. Jude Medical Valve replacement: results of the German experience with low-intensity anticoagulation study. *Chest* 127:53-9.
- Horskotte D, Bergemann R, Althaus U, et al. 1993. German experience with low intensity anticoagulation (GELIA): protocol of a multi-center randomized, prospective study with the St. Jude Medical valve. *J Heart Valve Dis* 2:411-9.
- Horskotte D, Schulte H, Bircks W, Strauer B. 1993. Unexpected findings concerning thromboembolic complications and anticoagulation after complete 10 year follow up of patients with St. Jude prostheses. *J Heart Valve Dis* 2:291-301.
- Laffort P, Roudaist R, Rogues X, et al. 2000. Early and long-term (one-year) effects of the association of aspirin and oral anticoagulant on thrombi and morbidity after replacement of the mitral valve with the St. Jude medical prosthesis: a clinical and transesophageal echocardiographic study. *J Am Coll Cardiol* 35:739-46.
- Landefeld S. 1989. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. *Am J Med* 87:144-52.
- Levine MN, Raskob G, Beyth RJ, Kearon C, Schulman S. 2004. Hemorrhagic complication of anticoagulant treatment. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 126(suppl):287S-310S.
- Link KP. 1959. The discovery of dicumarol and its sequels. *Circulation* 19:97-107.
- Massel D, Little S. 2001. Risks and benefits of adding anti-platelet therapy to warfarin among patients with prosthetic heart valves: a meta-analysis. *J Am Coll Cardiol* 37:569-78.
- Meschengieser SS, Fondevilla CG, Frontroth J, Santarelli MT, Lazari MA. 1997. Low-intensity oral anticoagulation plus low-dose aspirin versus high-intensity oral anticoagulation alone: a randomized trial in patients with mechanical prosthetic heart valves. *J Thorac Cardiovasc Surg* 113:910-6.
- Pengo V, Barbero F, Banzato A, et al. 1997. A comparison of a moderate with moderate-high intensity oral anticoagulant treatment in patients with mechanical heart valve prostheses. *Thromb Haemost* 77:839-49.
- [Raport]Raport Klubu Kardiologów Polskich. 2006. Kardiolog i Torakochirurg Pol 3:108-9.
- Saour JN, Sieck JO, Mamo LAR, Gallus AS. 1990. Trial of different intensities of anticoagulation in patients with prosthetic heart valves. *N Engl J Med* 322:428-32.
- Turpie AG, Gent M, Laupacis A, et al. 1993. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med* 329:524-9.
- [VA]VA Cooperative Study Group on Valvular Heart Diseases. 1985. Prognosis in valvular heart disease. I. Description of purpose, organization, data collection techniques, estimates of statistical power and criteria for termination of patient entry. *Control Clin Trials* 6:51-74.
- Van Nooten GJ, Van Belleghem Y, Caes F, et al. 2003. Lower-intensity anticoagulation for mechanical heart valves: a new concept with the ATS bileaflet aortic valve. *J Heart Valve Dis* 12:495-502.