Adequate Intensity of Warfarin Therapy for Korean Patients with Mechanical Cardiac Valves

In Kyung Yoon[1], Kyung Eun Lee[1], Jin Koo Lee[2], Byung Chul Chang[2], Hye Sun Gwak[1]

[1] College of Pharmacy & Division of Life and Pharmaceutical Sciences, Ewha Woman's University, Seoul, [2]Department of Thoracic & Cardiovascular Surgery, Yonsei University Medical Center, Seoul Korea

Background and aim of the study: **The study aim was to identify adequate therapeutic ranges of the International Normalized Ratio (INR) in Korean patients receiving warfarin after prosthetic mechanical heart valve replacement.**
Methods: **Retrospective chart reviews were conducted of 818 patients for a total follow up period of 8,100 patient-years; all details of major complication events of thromboembolism and bleeding were recorded. The INR-incidence of complication curve was plotted, and an adequate INR determined from the intersections of 95% confidence interval (CI) curves of complication rates to ensure the lowest incidences of both thromboembolic and bleeding complications. An analysis of a subgroup of patients with atrial fibrillation (AF) was performed to evaluate the complication occurrence.**
Results: **A total of 69 complications occurred, of which 36 were thromboembolic events and 33 were bleeding. The adequate ranges of INR were determined as: 2.0-2.5 for patients with aortic or mitral valve replacement; 2.1-2.6 for those with aortic plus mitral valve replacement; and 2.3-2.8 for those with tricuspid valve replacement with or without other valves. It has been shown that, by keeping the INR levels within these therapeutic ranges, complication risks could be significantly reduced by up to 51%. The overall incidence of complications was increased if the patients had AF (hazards risk (HR) = 1.27, 95% CI = 1.05-1.52).**
Conclusion: **The study results may provide evidence for the application of low-intensity warfarin therapies in Asian patients, including Koreans. In addition, the method of determining adequate INR levels by using INR-incidence of complications curves might be employed in many clinical settings.**

The Journal of Heart Valve Disease 2013;22:102-109

Anticoagulation therapy after mechanical heart valve replacement is inevitable, due to the inherent thrombogenicity of the mechanical valves (1,2). Although the lifelong use of oral anticoagulation significantly reduces the occurrence of thromboembolic complications, it also causes bleeding risks and, indeed, thromboembolic and bleeding complications are the main causes of late mortality and morbidity in patients with mechanical heart valve prostheses (3,4). Thus, the adequate intensity of oral anticoagulation may be defined as the level where both thromboembolic and bleeding complication rates are the lowest (5).

Warfarin sodium (3-(α-acetonylbenzyl)-4-hydroxycoumarin) is a vitamin K antagonist that is the most widely used oral anticoagulant drug for preventing cardiovascular diseases after ischemic stroke and thromboembolism related to atrial fibrillation (AF), artificial heart valve replacement, deep-vein thrombosis, and pulmonary embolism (6). However, because of the large inter-individual variations in its dose requirements, warfarin requires continuous patient monitoring and education in order to achieve desirable outcomes (7). Currently, the International Normalized Ratio (INR) of the prothrombin time is the most widely used measurement to determine the clotting tendency of blood.

Thromboembolic hazards are related to not only the type of mechanical valve implanted, but also to a variety of concomitant patient-related clinical factors, such as AF (8). Since the introduction of prostheses with improved designs (e.g., bileaflet mechanical valves) during the late 1970s, it has been proposed that

I. K. Yoon. and K. E. Lee contributed equally to these studies

Address for correspondence:
Hye Sun Gwak, College of Pharmacy & Division of Life and Pharmaceutical Sciences, Ewha Woman's University, 11-1 Daehyun-Dong Seodaemun-Gu, Seoul 120-750, Korea
e—mail: hagwak@ewha.ac.kr

a less-intensive oral anticoagulation therapy could result in the successful prevention of bleeding complications, without any significant increase in thromboembolic events (9-11). Moreover, especially in Asian people, a lower intensity of anticoagulation is recommended because of differences in race, in coagulation characteristics, lifestyle (including diet), and their vulnerability to thromboembolic diseases (12-16).

Although the effectiveness of low-intensity anticoagulation therapy in bileaflet mechanical valve prostheses has been noted in several Korean studies (17,18), there are as yet no specific guidelines for adequate therapeutic levels of anticoagulation in Korean patients who have undergone bileaflet mechanical heart valve replacement. An adequate intensity of anticoagulation therapy is still widely disputed, and a less-intensive therapy is now carried out empirically in many Korean hospitals, though without a basis of any evidence (17-19).

Hence, the study aim was to identify adequate therapeutic ranges of INR in Korean patients receiving warfarin as anticoagulation therapy following mechanical heart valve replacement.

Clinical material and methods

Patients and data collection

Retrospective chart reviews were conducted of a total of 818 patients who had undergone prosthetic mechanical heart valve replacements with St. Jude Medical (SJM) mechanical valves at the Severance Cardiovascular Hospital of Yonsei University Medical Center between January 1984 and December 2008, and had been followed up continuously at the outpatient clinic of the hospital. All patients had received a single brand of warfarin (Coumadin®) for their anticoagulation therapy since the day of surgery, with a target INR range of 1.8 to 3.0 by empirical evidence of the center; 1.8 to 2.5 for patients with aortic valve replacement (AVR), and 2.0 to 3.0 for those with mitral valve replacement (MVR), AVR plus MVR (double) replacement, and tricuspid valve replacement (TVR) with or without other valves.

Anticoagulation complications

Anticoagulation-related complications were classified into thromboembolic events including valve thrombosis and embolism and bleeding events according to the guidelines of Akins et al. (20).

Valve thrombosis referred to any thrombus not caused by infection attached to or near an operated valve that obstructed part of the blood flow path, interfered with valve function, or was sufficiently large to warrant treatment. Embolism was any embolic event that occurred without infection after the immediate perioperative period. The manifestations of embolism were neurologic events or non-cerebral embolic events. Neurologic events included any central and new neurologic deficits that occurred after the patient had emerged from anesthesia. Non-cerebral embolic events were an embolus documented intraoperatively, at autopsy, or clinically that produced signs or symptoms by complete or partial blockade of a peripheral artery. A bleeding event was any episode of major bleeding that caused hospitalization, permanent injury or death, or necessitated transfusion (20).

INR assessments

The mean INR was calculated for the replaced valve types as an independent predictor of thromboembolic and bleeding events. In order to determine the incidences of thromboembolism and hemorrhage according to INR levels, the measured INR values were divided into five sections in order of their levels: <1.75, 1.75-2.25, 2.25-2.75, 2.75-3.25, and >3.25. The INR-incidence of complication curves were plotted using the middle value of INR from the five sections (1.5 and 3.5 in the case of <1.75 and >3.25, respectively), and the adequate INR was determined from intersections of 95% confidence interval (CI) curves of complication rates to ensure the lowest incidences of both thromboembolic and bleeding complications. Adequate ranges were validated by comparing the complication rates of INR within the ranges to those of INR under or over the ranges.

All major complications were reviewed independently by a physician-investigator at the Yonsei Cardiovascular Research Institute. The INR at the time of an event was obtained from the hospital records; if values had not been determined or were unavailable, the last INR record was used. The electronic medical records of patients were reviewed for complication histories, INR measurements, and the clinical conditions of patients, including any comorbidity of atrial fibrillation.

Approval to conduct the study was granted by the Ethics Committee of the Yonsei University Medical Center Institutional Review Board.

Statistical analysis

All data were analyzed using the Statistical Package for Social Sciences Version 12.0 for Windows (SPSS 12.0K; SPSS Inc., Chicago, IL, USA). Complication rates were expressed as linearized incidences per 100 patient-years (pt-yr). All data were expressed as the mean ± SD, while 95% CIs for incidences were computed based on the assumption of a Poisson distribution (21). A chi-square test was used for the detection of statistically significant differences in complication rates between groups. A p-value <0.05 was considered to be statistically significant.

J Heart Valve Dis
Vol. 22. No. 1
January 2013

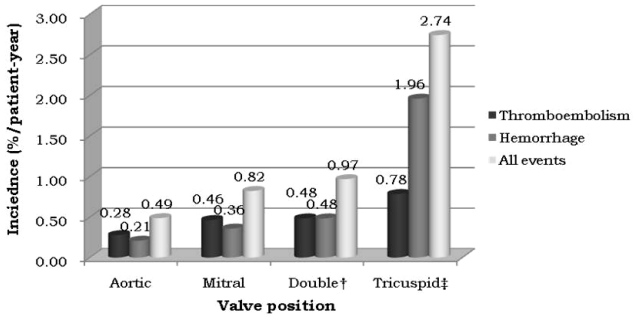

Figure 1: Incidences of thromboembolic and bleeding events in each valve position. †, Aortic plus mitral valve replacement; ‡, tricuspid valve replacement with or without other valves.

Table I: Characteristics of the study patients (n = 818).

Characteristic	Value
Age at surgery (years)*	45 ± 13
Gender (n)	
Male	348 (43)
Female	470 (57)
Valve position (n)	
Aortic	179 (22)
Mitral	428 (52)
Double†	181 (22)
Tricuspid‡	30 (4)

*Mean ± SD.
Values in parentheses are percentages.
†, AVR plus MVR; ‡, TVR with or without other valves.

Results

The patient group included 348 males (43%) and 470 females (57%), with a mean age at surgery of 45 ± 13 years. Numbers of patients with AVR, MVR, AVR plus MVR (double) valve, and TVR (with or without other valves) were 179 (22%), 428 (52%), 181 (22%), and 30 (4%), respectively. The baseline characteristics of the patients are listed in Table I.

The patients were followed until June 2009, after their heart valve replacement. The follow up period ranged from six to 252 months, and the total follow up was 8,100 pt-yr. On average, patients were monitored at intervals of 2.7 months. In total, the INR was measured 36,497 times, with an average of 45 ± 27 times per patient. A total of 41 deaths occurred during the follow up period. Twenty of these deaths were valve-related, but no fatality was caused by any complications of anticoagulation therapy. The mean duration of follow up was 96 ± 71, 122 ± 68, 110 ± 70, and 98 ± 61 months for patients with AVR, MVR, AVR plus MVR, and TVR with or without other valves, respectively. Those patients who discontinued their regular clinic visits for more than 12 months were considered to be lost to follow up; hence, the completion rate of total follow up was 94.5%.

A total of 69 complications occurred over the follow up period (0.85% per pt-yr) (see Table II). Among these were included 36 thromboembolic events (0.44% per pt-yr), incorporating 28 cases of cerebral infarction (0.35% per pt-yr). Bleeding complications occurred in 33 patients (0.41% per pt-yr), including 16 intracranial bleedings (0.20% per pt-yr).

There were four thromboembolic and three bleeding events among patients with AVR, with incidences of 0.28% and 0.21% per pt-yr, respectively. Thromboembolic and bleeding events occurred in 22 patients (0.46% per pt-yr) and 17 patients (0.36% per pt-yr) with MVR, in eight patients (0.48% per pt-yr) and eight patients (0.48% per pt-yr) with AVR plus MVR, and in two patients (0.78% per pt-yr) and five patients (1.96% per pt-yr) with TVR with or without other valves, respectively. The incidences of both thromboembolic and bleeding events were lowest in patients with AVR (Fig. 1).

The incidences of complications in each INR section are shown in Figure 2. All four thromboembolic events among patients with AVR were cerebral infarctions, which occurred at INR levels below 2.25. Bleeding events, including two cases of intracranial bleeding and one case of gastrointestinal bleeding, occurred at INR levels above 2.25. As the INR levels increased, the thromboembolic rates decreased and bleeding rates increased (Fig. 2A). The INR level at the point of intersection was 2.23, while those of the 95% CI curves were 2.20 and 2.27.

Among patients with mitral valve prostheses there were 17 cases of cerebral infarction, four of valve thrombosis, and one case of mesenteric infarction.

Table II: Characteristics of major complications.

Complications	No. of events	Incidence (%/pt-yr)
Thromboembolism		
Embolism		
Cerebral infarction	28	0.35
Mesenteric infarction	1	0.02
Valve thrombosis	7	0.09
Total	36	0.44
Bleeding episodes		
Intracranial bleeding	16	0.20
Gastrointestinal bleeding	7	0.09
Hematoma	6	0.07
Urogenital bleeding	3	0.04
Retroperitoneal bleeding	1	0.02
Total	33	0.41

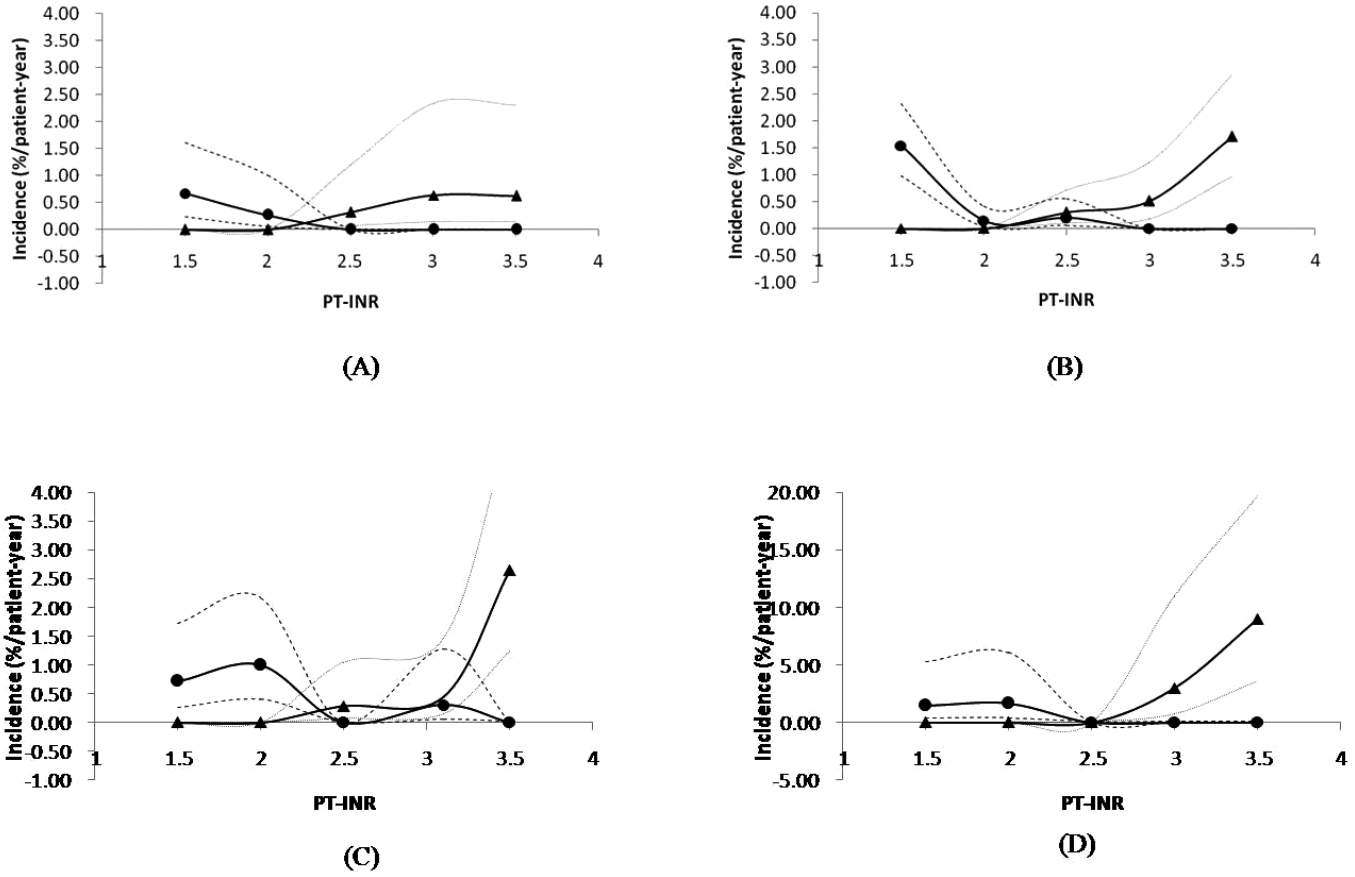

Figure 2: Incidences of thromboembolic and bleeding complications in patients with AVR (A), MVR (B), AVR plus MVR (C), and TVR (D). The middle values of INR from the five sections (1.5 and 3.5 in the case of <1.75 and >3.25, respectively) were used. -▲-, bleeding complications; -●-, thromboembolic complications; - - - - , 95% CI of bleeding complications; ·····, 95% CI of thromboembolic complications.

Thromboembolism occurred when the INR levels were below 1.75, except for four cases of cerebral infarction. Bleeding events, including nine intracranial bleeds, three urogenital bleeds, three hematomas, one gastrointestinal bleeding, and one retroperitoneal bleeding, occurred at INR levels above 2.25. As depicted in Figure 2B, the thromboembolic and bleeding rates had opposite tendencies in relation to the INR levels, and the complications crossed each other at an INR level of 2.20; the points of intersection in the 95% CI curves were 2.05 and 2.35.

The incidences of complications in patients with double valve replacement included five cases of cerebral infarction and three of valve thrombosis. Bleeding events occurred in eight cases, including three events of intracranial bleeding, three of gastrointestinal bleeding, one hematoma, and one event of urogenital bleeding. The incidences of complications had an intersection at an INR level of 2.36, and those of the 95% CI curves were 2.32 and 2.40 (see Fig. 2C).

The two thromboembolic events identified among patients with TVR with or without other valves were cerebral infarctions, which occurred at INR levels below 2.25. There were five bleeding events, with two cases of intracranial bleeding, two of gastrointestinal bleeding, and one hematoma. All hemorrhages occurred when the INR levels were above 2.75. Only one INR intersection of 2.50 was attained in both the mean graph and 95% CI curves of thromboembolic and bleeding complications (see Fig. 2D).

The adequate therapeutic ranges of INR for warfarin therapy in Korean patients with SJM prosthetic heart valve replacements were established on the basis of target INR values, which were derived from the intersection of 95% CI curves of complication rates in Figure 2. The adequate therapeutic ranges were determined to center the target INR values at a confined distance of 0.5: 2.0-2.5 for AVR and MVR, 2.1-2.6 for AVR plus MVR, and 2.3-2.8 for TVR with or without other valves.

J Heart Valve Dis
Vol. 22. No. 1
January 2013

Table III: Hazard ratios of complications in patients with prosthetic heart valve replacement.

Valve position	Desired TR	Complication	Outside TR*			Within TR*	HR§	95% CI
			Under	Over	Total			
Aortic	2.0-2.5	All events	4 (0.73)#	2 (0.40)	6 (0.57)	1 (0.25)‖	0.72	0.62-0.83
		Thromboembolism	4 (0.73)#	0 (0.00)	4 (0.38)	0 (0.00)‖	0.50	0.49-0.51
		Bleeding	0 (0.00)#	2 (0.40)	2 (0.19)	1 (0.25)¶	1.16	0.83-1.63
Mitral	2.0-2.5	All events	20 (1.23)#	17 (0.91)#	37 (1.06)	2 (0.16)‖	0.57	0.53-0.61
		Thromboembolism	20 (1.23)#	1 (0.05)	21 (0.60)	1 (0.08)‖	0.57	0.52-0.62
		Bleeding	0 (0.00)**	16 (0.85)#	16 (0.46)	1 (0.08)‖	0.59	0.52-0.66
Double†	2.1-2.6	All events	6 (0.97)#	8 (1.30)#	14 (1.13)	2 (0.48)‖	0.71	0.64-0.79
		Thromboembolism	6 (0.97)#	1 (0.16)	7 (0.57)	1 (0.24)‖	0.71	0.62-0.82
		Bleeding	0 (0.00)#	7 (1.14)#	7 (0.57)	1 (0.24)‖	0.71	0.62-0.82
Tricuspid‡	2.3-2.8	All events	2 (1.69)#	5 (6.25)#	7 (3.53)	0 (0.00)‖	0.49	0.48-0.50
		Thromboembolism	2 (1.69)#	0 (0.00)	2 (1.01)	0 (0.00)‖	0.50	0.49-0.50
		Bleeding	0 (0.00)	5 (6.25)#	5 (2.52)	0 (0.00)‖	0.49	0.49-0.50

*No. of complications (incidence, % per pt-yr); †, Aortic plus mitral valve; ‡, Tricuspid valve replacement with or without other valves; §, Hazard ratio of 'within TR' group, compared to 'outside TR' group; ‖p <0.0001 compared to 'outside TR' group; ¶p = 0.365 compared to 'outside TR' group; #p <0.0001 compared to 'within TR' group; **p <0.05 compared to 'within TR' group. CI: Confidence interval; HR: Hazards ratio; TR: Therapeutic range.

The adequate ranges were validated by comparing the complication rates of INR within the ranges to those of INR under or over the ranges. Patients in the 'within therapeutic' group had statistically significantly lower thromboembolic rates compared to those of the 'under therapeutic range' group. Compared to the 'over therapeutic range' group, significantly lower incidences of bleeding events were obtained in the 'within therapeutic range' group, except in patients with AVR. The hazard ratios (HRs) of complications by valve type are summarized in Table III. It was shown that, by keeping INR levels within therapeutic ranges, the complication risks could be significantly reduced by up to 51% in patients with SJM heart valve prostheses.

In order to examine the influence of INR fluctuation on complication occurrences in warfarin therapy, the standard deviations of INR measurements in patients with thromboembolic or bleeding complications were compared to those in complication-free patients. Patients with complications showed a greater fluctuation of INR measurements than those without complication histories, of which the mean of standard deviations in INR was 0.92 ± 0.34 and 0.86 ± 0.64 in patients with and without experiences of complications, respectively, despite the lack of statistical significance of the difference, with a p-value of 0.383.

The influence of AF on the complication occurrence in patients with mechanical heart valve prostheses was evaluated by comparing the incidences of thromboembolic and bleeding events of patients with normal sinus rhythm (NSR) and those of patients with AF (see Table IV). In total, 389 patients (48%) were found to have AF, with 42 complication events occurring in the AF subgroup (61% of the total complications). In patients with double-valve replacement, increased incidence rates in both complications were observed in the AF subgroup. In patients with AVR and MVR, the thromboembolic rates were increased in the AF subgroup, whereas the bleeding rates decreased; the TVR group showed an opposite tendency compared to those with AVR and MVR. Overall, the complication rates increased statistically significantly if patients had AF (p = 0.007, HR = 1.26, 95% CI = 1.05-1.52), especially thromboembolism (p = 0.017, HR = 1.35, 95% CI = 1.02-1.77). However, the incidence of bleeding events failed to show any statistically significant difference between the AF subgroup and the NSR group (p = 0.126).

Discussion

The incidence of complications shows differences among implanted valve positions as a result of structural differences inside the heart. Aortic valve prostheses are known to have lower complication rates compared to other prostheses. Indeed, in a long-term multicenter follow up study with SJM mechanical valve prostheses (22), the average incidences of thromboembolism were 0.53% per pt-yr for AVR, 1.64% per pt-yr for MVR, and 0.79% per pt-yr for double-valve replacement. Severe bleeding complication rates were 0.51%, 0.55%, and 1.31% per pt-yr, respectively. In a previous long-term follow up study using SJM mechanical valve prostheses (23), the incidences of thromboembolism in AVR, MVR and double-valve

Table IV: Comparisons of thromboembolic and hemorrhagic complications in patients with and without atrial fibrillation (AF).[*]

Valve position	Parameter	NSR	AF	p-value
Aortic	No. of patients	162	17	
	Complication events	6 (0.48)	1 (0.51)	0.763
	Thromboembolism	3 (0.24)	1 (0.51)	0.002
	Bleeding	3 (0.24)	0 (0.00)	<0.0001
Mitral	No. of patients	164	264	
	Complication events	16 (0.84)	21 (0.74)	0.425
	Thromboembolism	6 (0.31)	14 (0.49)	0.044
	Bleeding	10 (0.52)	7 (0.25)	0.002
Double[†]	No. of patients	93	88	
	Complication events	4 (0.51)	13 (1.50)	<0.0001
	Thromboembolism	3 (0.38)	5 (0.58)	0.041
	Bleeding	1 (0.13)	8 (0.93)	<0.0001
Tricuspid[‡]	No. of patients	10	20	
	Complication events	1 (1.66)	7 (3.59)	<0.0001
	Thromboembolism	1 (1.66)	2 (1.03)	0.0001
	Bleeding	0 (0.00)	5 (2.57)	<0.0001
Total	No. of patients	429	389	
	Complication events	27 (0.67)	42 (1.02)	0.007
	Thromboembolism	13 (0.32)	22 (0.54)	0.017
	Bleeding	14 (0.35)	20 (0.49)	0.126

[*]Variables are given as number (incidence, % per pt-yr); [†], AVR plus MVR; [‡], TVR with or without other valves.
NSR: Normal sinus rhythm.

replacement were 0.33%, 0.54%, and 0.53% per pt-yr, respectively. Typically, the bleeding rates were 0.25%, 0.35%, and 0.38% per pt-yr, respectively.

In the present study, the AVR group also showed the lowest incidences in both complications, compared to other valve replacement groups. On the other hand, patients with TVR were found to have higher complication incidences than those with other valve replacements.

Because of the risk of complications, the anticoagulation intensity should be controlled in an adequate range, where the number of incidences of both thromboembolic and bleeding complications are the lowest. Since the late 1970s, when bileaflet mechanical valves were first introduced, it has been reported that blood flow was more laminar and thromboembolic events were considerably reduced (24,25). This brought about a clinical apprehension regarding the bleeding risks with previously recommended target INR levels. However, studies suggesting less-intensive anticoagulation levels have been continuously reported (9-11).

Although several studies have identified similar target INR values to those of the present study (26,27), well-conducted and up-to-date guidelines on anticoagulation levels after mechanical valve replacement have recommended higher levels. Notably, the American College of Chest Physicians (ACCP) 2004 Guideline (1) recommends an INR of 2.5-3.5 for most patients with mechanical prosthetic valves, and 2.0-3.0 for those with bileaflet mechanical valves (e.g., the SJM device) in the aortic position. The American Heart Association/American College of Cardiology (AHA/ACC) guidelines 2006 (28) suggest an INR of 2.0-3.0 for patients with mechanical aortic valves and no risk factors (including AF), and 2.5-3.5 for the others. The adequate therapeutic ranges of INR evaluated in the present study were noticeably lower, though this might be explained by ethnic differences, as the guidelines are based mainly on studies with Caucasians. It is known that Asians are less vulnerable to thrombotic diseases than Caucasians (29).

Studies of Asian populations have suggested considerably lower intensities of warfarin therapy after implanting mechanical valve prostheses. In a retrospective study of 214 Japanese patients with MVR, a target INR range of 1.5-2.5 was reported to be safe for both thromboembolic and bleeding complications (14).

In Chinese patients with CarboMedics valve implantations (12), an INR range of 1.4-2.0 was concluded to be optimum, while a retrospective study with 805 Chinese patients receiving SJM valves reported lower incidences of thromboembolism and bleeding, with an INR between 2.0 and 2.5 (13), which was exactly the same as found in the AVR and MVR groups of the present study.

The mean age at surgery in the present study was 45 ± 13.3 years, which was less than that reported elsewhere by Butchart et al. (30) (ca. 65 years) and Toole et

al. (31) (ca. 55 years). Thus, the results of the present study cannot be compared directly to those of other studies with older patients. A recent study compared the complication rates between patients with a low INR target (1.5-2.5) and a conventional INR target 2.0-3.0); in this case, the patients were of a similar age (50 years) to those in the present study. The study results revealed that a low INR target was safe and practical in low-risk patients after bileaflet mechanical AVR. Although the thrombotic event rates were similar in the two groups, a significant reduction in bleeding events was apparent in the low-INR group (32).

Fluctuation in the INR is known to be a risk factor for complications in warfarin therapy (33). In the present study, however, there was no significant influence of INR fluctuation on complication rates in warfarin therapy, although patients with complications showed a greater fluctuation of INR.

Atrial fibrillation is not only the most common significant cardiac rhythm disorder, but also an important independent risk factor for ischemic stroke. The influence of AF on thrombotic events is well known, and in the present study those patients with a comorbidity of AF were found to have a greater risk of thromboembolism, which was consistent with prior findings (34,35).

Study limitations

The main limitation of the study was the small number of collected INR values per patient, which could have resulted in a large variability of follow up among patients. The failure to have sufficient statistical power due to extremely low complication rates might represent an additional limitation of the study.

In conclusion, this is the first long-term follow up study of a large population to investigate adequate anticoagulation levels in Korean patients with SJM mechanical heart valve prostheses. The adequate INR values were as follows: 2.0-2.5 for patients with AVR or MVR, 2.1-2.6 for those with AVR plus MVR, and 2.3-2.8 for those with TVR with or without other valves. The results of the study can be considered as evidence for the application of low-intensity warfarin therapies in Asian patients, including Koreans. Moreover, it is expected that the method used to determine optimal INR levels, via the INR-incidence of complications curves, could be utilized in many clinical settings.

References

1. Salem DN, Stein PD, Al-Ahmad A, et al. Antithrombotic therapy in valvular heart disease - native and prosthetic: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:457S-482S
2. Cannegieter SC, Torn M, Rosendaal FR. Oral anticoagulant treatment in patients with mechanical heart valves: How to reduce the risk of thromboembolic and bleeding complications. J Intern Med 1999;245:369-374
3. Stein PD, Alpert JS, Copeland J, Dalen JE, Goldmann S, Turpie AG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest 1992;102:445S-455S
4. Levine MN, Hirsh J, Landefeld S, Raskob G. Hemorrhagic complications of anticoagulant treatment. Chest 1992;102:352S-363S
5. Bodnar E. A critical assessment of thrombosis and embolism reporting methods. In: Butchart EG, Bodnar E (ed.) Thrombosis, embolism and bleeding. ICR Publishers, London, 1992:476-484
6. Wang TL, Li HL, Tjong WY, et al. Genetic factors contribute to patient-specific warfarin dose for Han Chinese. Clin Chim Acta 2008;396:76-79
7. Perini JA, Struchiner CJ, Silva-Assunção E, et al. Pharmacogenetics of warfarin: Development of a dosing algorithm for Brazilian patients. Clin Pharm Ther 2008;84:722-728
8. Horstkotte D. Abnormal cardiac anatomy and physiology. In: Butchart EG, Bodnar E (ed.) Thrombosis, embolism and bleeding. ICR Publishers, London, 1992:31-69
9. Horstkotte D, Schute HD, Bircks W, Strauer BE. Lower intensity anticoagulation therapy results in lower complication rates with the St. Jude Medical prosthesis. J Thorac Cardiovasc Surg 1994;107: 1136-1145
10. Saour JN, Sieck JO, Mamo LA, Gallus AS. Trials of different intensities of anticoagulation in patients with prosthetic heart valves. N Engl J Med 1990;322:428-432
11. Wilson DB, Dunn MI, Hassanin K. Low-intensity anticoagulation in mechanical cardiac prosthetic valves. Chest 1991;100:1553-1557
12. Zhou XM, Zhuang W, Hu JG, Li JM, Yu JF, Jiang L. Low-dose anticoagulation in Chinese patients with mechanical heart valves. Asian Cardiovasc Thorac Ann 2005;13:341-344
13. Sun X, Hu S, Qi G, Zhou Y. Low standard oral anticoagulation therapy for Chinese patients with St. Jude mechanical heart valves. Chin Med J 2003;116:1175-1178
14. Matsuyama K, Matsumoto M, Sugita T, et al. Anticoagulation therapy in Japanese patients with mechanical mitral valves. Circ J 2002;66:668-670
15. Kudo T, Kawase M, Kawada S, et al. Anticoagulation after valve replacement: A multicenter retrospective study. Artif Organs 1999;23:199-203

16. Kitamura M, Koyanagi H, Kawada S, et al. Optimum anticoagulation control after bileaflet mechanical valve replacement: A prospective multi-institutional study. Kyobu Geka 1999;52:1001-1004
17. Kim CW, Kim YT. Anticoagulation management after mitral valve replacement with the St. Jude Medical prosthesis. Korean J Thorac Cardiovasc Surg 1998;31:1172-1182
18. Kim US, Kim GB, An H, et al. A clinical study of isolated aortic valve replacement with CarboMedics and St. Jude prostheses. Korean J Thorac Cardiovasc Surg 1998;31:781-786
19. Lee BK, Lee JY, Jeong YM, Lee MK, Kim KB, Ahn H. Determination of practical dosing of warfarin in Korean outpatients with mechanical heart valves. Korean J Thorac Cardiovasc Surg 2005;38:761-772
20. Akins CW, Miller DC, Turina MI, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008;135:732-738
21. Bellocco R, Pagano M. From the binomial to Poisson distribution. Nutrition 1997;13:842-843
22. Hering D, Piper C, Bergmann R, et al. Thromboembolic and bleeding complications following St. Jude Medical valve replacement. Chest 2005;127:53-59
23. Chang BC, Lim SH, Kim DK, et al. Long-term results with St. Jude Medical and CarboMedics prosthetic heart valves. J Heart Valve Dis 2001;10:185-195
24. Horstkotte D, Bodnar E. Bileaflet prostheses. In: Bodnar E, Frater RWM (ed.) Replacement cardiac valves. Pergamon, New York, 1991:201-228
25. Butchart EG. Prostheses-specific and patient-specific anticoagulation. In: Butchart G, Bodnar E (ed.) Thrombosis, embolism and bleeding. ICR Publishers, London, 1992:293-369
26. Koertke H, Zittermann A, Wagner O, et al. Efficacy and safety of very low-dose self-management of oral anticoagulation in patients with mechanical heart valve replacement. Ann Thorac Surg 2010;90:1487-1494
27. Emery RW, Erickson CA, Arom KV, et al. Replacement of the aortic valve in patients under 50 years of age: Long-term follow-up of the St. Jude Medical prosthesis. Ann Thorac Surg 2003;75: 1815-1819
28. Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2006;114:e84-e231
29. Akhtar RP, Abid AR, Zafar H, Khan JS. Anticoagulation in patients following prosthetic heart valve replacement. Ann Thorac Cardiovasc Surg 2009;15:10-17
30. Butchart EG, Ionescu A, Payne N, Giddings J, Grunkemeier GL, Fraser AG. A new scoring system to determine thromboembolic risk after heart valve replacement. Circulation 2003;108:II68-II74
31. Toole JM, Stroud MR, Kratz JM, et al. Twenty-five year experience with the St. Jude Medical valve prosthesis. Ann Thorac Surg 2010;89:1402-1409
32. Torella M, Torella D, Chiodini P, et al. Lowering the intensity of oral anticoagulant therapy in patients with bileaflet mechanical aortic valve replacement: Results from the 'Lowering-it' trial. Am Heart J 2010;160:171-178
33. Fihn SD, Mcdonell M, Martin D, et al. Risk factors for complications of chronic anticoagulation. Ann Intern Med 1993;118:511-520
34. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133:546S-592S
35. Reynolds MW, Fahrback K, Hauch O. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: A systematic review and meta-analysis. Chest 2004;126:1938-1945