

Thrombotic and Haemorrhagic Complications in Patients with Mechanical Heart Valve Prostheses Attending the Singapore General Hospital Anticoagulation Clinic

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Abstract

Introduction: This study evaluated the intensity of anticoagulation required for prevention of thromboembolic episodes with minimal haemorrhagic complications in patients with mechanical heart valve prostheses. **Materials and Methods:** The incidence of thrombotic and haemorrhagic events was retrospectively assessed in a series of 143 patients attending the anticoagulation clinic over a period of 67 months. Risk factors for haemostatic events were also analysed. **Results:** All embolic events occurred when the International Normalised Ratio (INR) was less than 2.2, suggesting an INR of 2.5 to 3.0 should be adequate for thromboembolic prophylaxis. Risk factors for embolic events were atrial fibrillation, mitral valve prosthesis and a previous thromboembolic event. Most embolic events involved the central nervous system with resultant permanent residual disability. Most major bleeding episodes occurred in the presence of underlying pathological states such as peptic ulcers or fibroids and were not related to the intensities of anticoagulation. There was no mortality or long-term morbidity associated with bleeding episodes. **Conclusions:** In agreement with recent data from other centres, a moderate intensity of anticoagulation of INR 2.5 to 3.0 is now recommended. Hence, with this lowered intensity of anticoagulation and better patient education, we hope that thrombotic as well as haemorrhagic complications will be reduced in future.

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Key words: Mechanical heart valves, Optimal INR

Introduction

Patients with mechanical heart-valve prosthesis receive lifelong anticoagulation.^{1,2} The management of these patients taking oral anticoagulants is aimed at achieving and maintaining adequate levels of anticoagulation to prevent thrombotic manifestations and at the same time to keep the risk of severe haemorrhagic complications to the minimum. This is particularly important for patients with mechanical heart valves in whom high intensity anticoagulation is recommended. The anticoagulation clinic in the Singapore General Hospital was started with the intention to provide patient education, close monitoring of prothrombin time/International Normalised Ratio (INR) and record all bleeding and thrombotic complications. The intensity of anticoagulation was based on recommendations in published studies;³⁻⁵ hence the initial intention to achieve an anticoagulation profile between INR of 3.0 to 4.5.

The aim of this study was to determine the degree of anticoagulation related to the thrombotic and haemorrhagic complications in patients with mechanical heart valve prosthesis attending the anticoagulation clinic. Risk factors

for haemostatic events were also analysed. The results of this study will help to determine the optimum range of anticoagulation for future management of our local population of patients.

Patients and Methods

One hundred and forty-three (143) patients (59 females and 84 males, median age 49 years, range 14 to 79 years) on warfarin for mechanical heart valve prosthesis (aortic 45; mitral 80; mitral-aortic 18) attending the anticoagulation clinic were assessed. Follow-up time in total was 61,521 patient-years with a median of 381 patient-years from January 1989 to July 1995. For each patient, the follow up time ranged from 0.5 to 5.6 years. Medication compliance and haemostatic events (thromboembolic and haemorrhagic complications) and the degree of anticoagulation as determined by the INR were documented during each consultation. The patients were monitored at intervals ranging from 1 week to 3 months.

Haemostatic events were recorded from both inpatient and outpatient case notes. Thrombotic events included

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transient ischaemic attack, stroke, myocardial infarction and peripheral artery occlusion. Thrombotic episodes were considered present if there were definite clinical features or with objective documentation such as CT scan, MRI, ECG and arteriograms. Haemorrhagic events included haematuria, epistaxis, muscle haematomas, gastrointestinal bleeding, spontaneous gum bleeding or prolonged bleeding after dental procedures, vaginal bleeding and intracranial haemorrhage. Haemorrhagic events were considered to be severe if there was hypotension, haemoglobin decreased by 2 g/L or more or when hospitalisation was required. Bleeding episodes that did not fulfil criteria for severe episodes were considered mild.

Data Analysis

The follow-up for each patient was defined as the person time at risk for the individual i.e. patient-years. The sum of the individual patient-years represented the total patient-years.

The anticoagulation profile of each patient was evaluated on the basis of time spent in the therapeutic range and was classified into the various groups:

- 1) INR between 2.5 to 3.5 for >90% of individual patient-years.
- 2) INR between 2.5 to 3.5 for 70% to 90% of individual patient-years.
- 3) INR between 2.5 to 3.5 for 50% to 69% of individual patient-years.
- 4) INR between 2.5 to 3.5 for <50% of individual patient-years.

Patients were considered over-anticoagulated if INR above 4.5 and under-anticoagulated if INR below 2.0.

The person-time incidence was obtained by dividing the number of haemorrhagic and thrombotic episodes by the total patient-years. The likelihood of haemorrhage and thrombosis according to risk factors (age, sex, previous haemorrhage and thrombotic events, hypertension, chronic

atrial fibrillation and underlying lesions) was calculated in univariate analysis as the odds ratio, i.e. the ratio of the incidence in exposed and unexposed patients. The standard chi-square test for association provided an approximate test of association.

Results

Patients Anticoagulation Profile (Table I)

Only 7% of patients were over-anticoagulated at INR >4.5 for maximum of 5% of their follow-up time. Most of our patients were not adequately anticoagulated; 53.3% of patient had INR of less than 2.0 for 20% to 50% of follow-up time while 27.3% of patients had INR of less than 2.0 for more than 50% of follow-up time. Non-compliance as the reason for subtherapeutic INR was frequently documented.

Haemorrhagic complications: There was a total of 17 severe bleeding episodes (4.03 per 100 patient-years). Ten were bleeding from the gastrointestinal tract of which all were associated with an underlying pathology (5 had gastric ulcers, 2 duodenal ulcers, 2 gastritis and 1 haemorrhoids). Four severe bleeding episodes were due to menorrhagia and for which underlying fibroids were diagnosed in all. There was 1 severe bleeding episode from a muscle haematoma after the patient received an intramuscular injection of a non-steroidal anti-inflammatory drug (NSAID) from a doctor who was unaware that the patient was on warfarin. There were 1 intracranial bleed and 1 gum bleed classified under severe bleeding for which no underlying disease or cause was found. Therefore, most severe haemorrhagic episodes were associated with underlying pathology such as peptic ulcers, haemorrhoids,

TABLE I: PATIENTS ANTICOAGULATION PROFILE

Anticoagulation profile	Number of patients n (%)
1) INR between 2.5 to 3.5 for >90% of individual patient-years	0 (0)
2) INR between 2.5 to 3.5 for 70% to 90% of individual patient-years	2 (1.4)
3) INR between 2.5 to 3.5 for 50% to 69% of individual patient-years	10 (7)
4) INR between 2.5 to 3.5 for <50% of individual patient-years	131 (91.6)
Under-anticoagulated >50% follow-up time	39 (27.3)
Under-anticoagulated 20% to 50% follow-up time	76 (53.3)

INR: International Normalised Ratio

TABLE II: NUMBER OF HAEMORRHAGIC EVENTS

	No. of events	pr-time inc
Total haemorrhagic events	80	20.2
Mild bleeding events	63	15.9
Severe haemorrhagic events	17	4.3

pr-time inc: person-time incidence rates per 100 patient-years

TABLE III: TYPES OF HAEMORRHAGIC EVENTS

Events	No. of mild events (pr-time inc)	No. of severe events (pr-time inc)
Gastrointestinal tract	7 (1.8)	10 (2.5)
Menorrhagia	14 (3.5)	4 (1.0)
Epistaxis	5 (1.3)	0 (0)
Muscle haematoma	8 (2.0)	1 (0.25)
Gums	10 (2.5)	1 (0.25)
Bruises	11 (2.8)	0 (0)
Brain	0 (0)	1 (0.25)

pr-time inc: person-time incidence rates per 100 patient-years

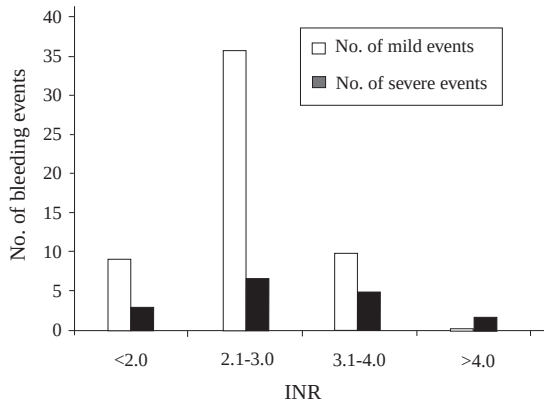


Fig. 1. Number of bleeding events and INR.

fibroids or concomitant medication with NSAIDs. None of the severe bleeding episodes was fatal. Mild bleeding episodes often resolved spontaneously without intervention (Tables II & III, Fig. 1).

There was no correlation between the INR and bleeding episodes and indeed most bleeding events occurred at sub-therapeutic and therapeutic intensity of anticoagulation.

Thrombotic complications: There was a total of 23 events in 14 patients (5.3 per 100 patient-years). Majority (20 out of 23) of embolic events involved the central nervous system and resulted in significant disabilities. Of the 3 cases of non-cerebral embolism, 1 was fatal while the other 2 had significant morbidity. These events occurred at INR of 1.0 to 2.2. Significant risk factors for thromboembolic complications were presence of atrial fibrillation, mechanical mitral valve prosthesis and a previous history of thromboembolism. Hypertension was not associated with an increase in thrombotic complications (Tables III & IV).

Discussion

Lifetime oral anticoagulation is recommended to reduce the risk of thromboembolic complications for patients with mechanical heart valve prosthesis.^{1,2} However, anticoagulation predisposes to bleeding. The anticoagulation clinic is a service specifically set up to manage these patients so that anticoagulation is well monitored. The rates of thromboembolism and haemorrhage in the setting of this service in its early years are being evaluated in this study. However, it must be emphasised that this is a retrospective study and the associated limitations must be taken into consideration in interpretation on data.

The recommended range of anticoagulation for mechanical heart valve prosthesis in overseas centres is INR of 3.0 to 4.5.³⁻⁵ Hence, our initial INR target was set at this range when the anticoagulation clinic was first set up in 1989. Paradoxically, this had resulted in poor compliance. The patients very often stopped taking warfarin on their

TABLE IV: THROMBOTIC EVENTS

	No. of events (pr-time inc)	Outcome
Transient ischaemic attacks	2 (0.5)	full recovery
	6 (1.5)	progressed to CVA
Embolic CVA	12 (3.0)	permanent disability
AMI	1 (0.25)	non fatal
Femoral artery embolism	1 (0.25)	non fatal
Mesenteric artery embolism	1 (0.25)	fatal

pr-time inc: person-time incidence rates per 100 patient-years

TABLE V: RISK FACTORS FOR THROMBOEMBOLISM

Risks factors	No. of persons	No. of events	P value
Previous thromboembolism			
Yes	16	6	0.0004
No	127	8	
Mechanical mitral valve			
Yes	88	14	0.018
No	45	0	
Atrial fibrillation			
Yes	71	12	0.01
No	72	2	
Hypertension			
Yes	36	3	ns
No	107	11	

ns: not significant

own accord when they developed bleeding symptoms; even for minor bruising and gum bleeding episodes or during menstruation. As a result, most patients were poorly controlled with 91.6% of patients having an INR of outside the range of 2.5 to 3.5 for more than 50% of the time. Poor compliance is the main reason for subtherapeutic range of anticoagulation. This prolonged subtherapeutic degree of anticoagulation accounts for the high incidence for thrombosis in our study population. The person-time incidence for thrombosis was 5.3 per 100 patient-years which was higher compared to other centres with reported person-time incidence of 0.6 to 4.0 per 100 patient-years.⁶⁻⁸ All thrombotic events occurred at an INR of less than 2.2. Mitral valve prosthesis, atrial fibrillation and a past history of thromboembolism are significant risk factors for thromboembolic phenomenon. In our study, most patients with thrombotic complications suffered long-term disabilities and this was fatal in 1 case. More effort is therefore required to ensure compliance.

The person-time incidence for severe haemorrhagic complications was 4.03 per 100 patient-years. This again is higher than others who reported 0.6 to 2.7 per 100 patient-years.⁶⁻⁸ Although there are studies to suggest that high intensity anticoagulation is associated with more major

bleeding events,^{6,7} our study showed no correlation between bleeding episodes and the degree of anticoagulation as reflected by the INR. Most haemorrhagic events occurred at therapeutic and subtherapeutic intensity of anticoagulation. Most patients with severe bleeding incidences had underlying organic lesions. This finding is similar to other reports in which many bleeds during anticoagulation are not related to the intensity of anticoagulation but to a local source that may be unmasked by anticoagulation therapy.^{9,10} However, the person-time incidence of mild haemorrhagic events was much higher at 15.9% compared to other reports;⁶⁻⁸ this reflects the low tolerance of our local patients to minor bleeding symptoms. Any bleeding symptoms would cause great distress to our patients and this led to poor compliance to warfarin therapy, which in turn gave rise to much higher thrombotic complications.

The range of INR at 3.0 to 4.5 has traditionally been recommended for patients with mechanical heart valves. Our study has clearly shown that our patients will not be able to tolerate and be compliant with this degree of anticoagulation. Besides, all thromboembolic episodes occurred at INR less than 2.2. More recent studies also support a reduction in intensity of anticoagulation with data to show that an INR between 2.5 to 3.5 is adequate for patients with prosthetic heart valves.^{8,11-13} At this range and with better patient education, we hope for better patient compliance and therefore a reduction in both haemorrhagic as well as thrombotic complications.

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