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Incidence of thromboembolic and bleeding complications after heart valves replacement

Dr. Zakir Hussain[1], Dr. Rakia Parveen[2], Dr. Nazar Hussain[3]
[1-3] Department of Surgery, Distt Hospital Rajouri, Jammu and Kashmir, India

Abstract
Thromboembolic and bleeding complications is one of the most frequent complications of prosthetic heart valves and all the patients with these prosthesis need anticoagulation. Thromboembolism and bleeding are the consequences of inability to control the interaction between blood and synthetic material which was the major deterrent to earlier operations.
The study was conducted retrospectively in the department of Surgery at District Hospital Rajouri, J&K, India, in collaboration with Department of CVTS SKIMS-Soura to correlate the type of valve and antithrombotic drug used to predict thromboembolic and bleeding complications and also to devise ways and means to prevent these complications. 9 volume of patients' blood was collected in 1 volume of anticoagulant to find out the INR for anticoagulation titration. In total 466 patients were studied, 47.40% of the patients were in 31-40 years of age, 51.50% were male, 67.8% had undergone MVR.17.38% had undergone AVR and 14.8% had DVR done. Medtronic prosthesis was used in$1%, Bjork Shilly in27.5% of patients.
Nicomalone (Acitrome) was the anticoagulant drug used in OPD. In addition 220 patients were on aspirin also. 38.10% of patients needed just 2 mgs daily dose of Nicoumalone and only 0.21% needed 7mg daily. Stroke was the commonest complication observed in patients. In patients with MVR complications was observed in 10 patients with INR in range of <1.5 to >2.5 and all the patients with AVR/DVR complications were observed with INR range of 2.0 to 2.5. In patients with MVR having TE complications 0.94% died, mortality was 2.89% in patients with DVR.
In spite of all the precautions complications do occur. Anticoagulation after mechanical prosthesis is mandatory and Nicoumalone should be the drug of choice.

Keywords: thromboembolism, bleeding, prosthetic heart valve, MVR, AVR, DVR, medtronic, Bjork Shilley, prosthesis

Introduction
Thromboembolic and bleeding complication is the frequent complications of prosthetic heart valve replacements and all the patients with mechanical 'prosthetic heart valves require titration of anticoagulation as prophylaxis. Experience in patients without anticoagulation has been devastating. These complications are lower with modern valves than first generation valves.
The valvular thrombosis has multifectorial etiology which depends upon surgical technique, patients related factors, anticoagulation therapy and prosthetic designs. The thrombus formation on the valve maybe influenced according to Virchow's triad-by surface characteristics of prostheses (material and design), the blood flow (cardiac output, turbulence and stagnation) and characteristics of blood constituents of patient (hypercoagulability). Clinically this may result in significant disruption of valve function, a life threatening event. Likewise part of thrombus may embolise in the central or the peripheral arteries [6].
The patients with mechanical heart valve prostheses receive lifelong high intensity oral anticoagulation therapy to prevent thromboembolic complication but this treatment is associated with an increased risk of bleeding. The risk of thromboembolism and bleeding depends upon the intensity of anticoagulation. The optimal intensity i.e. the levels at which thromboembolic events are effectively prevented without bleeding are not known.
Consequent from the information studies, it is hardly possible to establish the risk of the romboembolism with reliability [4]. But in last few years marked progress has been made in the prevention of these events in patients with mechanical heart valves thus therapy becomes more effective and associated with less risks.
The introduction of INR has changed the management of anticoagulation therapy in these patients with prosthetic heart valve replacement. For these patients the INR is now used internationally for the management of oral anticoagulation therapy which has become more reliable, effective and relatively safe [5].
In bioprosthetic valves, thromboembolic events have been reported in first 3 months in patients without antithrombotic therapy, particularly in mitral position. Some investigators reported that 67% to 80% of patients had thromboemboli during first 3 months.
Anticoagulation therapy in these patients during pregnancy is devised to protect both mother and the foetus from antivitamin-K drugs induced embryopathy. So, Heparin should be used during first trimester to avoid the teratogenic potential of antivitamin-K drugs so as to reduce the incidence of spontaneous abortions. During 2nd and 3rd trimester antivitamin-K drugs can be used easily with no substantial risk to the foetus. At delivery and immediate postpartum period heparin has to be started again from 8th month of gestation [8].
The American Society of Consultants recommended the use of anticoagulant flow sheets for the patients on oral anticoagulation and the current recommendation for monitoring of (ORT) include monthly prothromb in time and INR ratio [13].
There were no guidelines for optimal therapeutic range of

oral anticoagulation therapy (OAT) in Japanese patients with mechanical heart valves. The target range of the INR for oral anticoagulation therapy was between 1.5-2.5, which was considered optimal range and was safe for thromboembolic and bleeding complications [9].

The risks of valves related complication varies with the type and position of the prosthesis. It is desirable to change the intensity of oral anticoagulation according to prosthetic valves type and its position. The intensity is optimal when PT-INR is 1.8-2.0 for bileaflet valve in mitral position and is 1.6-1.8 in aortic position [10]. The tilting disc valves needs more intensity of anticoagulation and needs additional anti platelet agents for the mitral position [10].

The results of PTI monitoring should be reported as INR. An INR of 2.0-3.0 is recommended therapeutic range for all indications except for the prevention of systemic embolism in patients with mechanical heart valves [11].

In last 20 years, many reports have been published but unfortunately the results vary greatly because of difference in patients' selection, definitions of end points methods of follow up, statistical analysis, type of intensity and efficacy of anticoagulation therapy. Therefore, in order to assess the anticoagulation therapy after mechanical heart valve replacement, this study was undertaken.

Review of Literature

In March 1960, the first successful replacement of an aortic valve was performed by Harken. In the following years many modifications have been made and the new designs were introduced to address specific deficiencies in these earlier devices [6]. Most modern prosthesis now offers good durability and haemodynamic characteristics.

However, they are inadequate with respect to thromboresistence. So modern oral anticoagulants are far from ideal. Every patient with more or less thrombogenic mechanical valves carries risk not only for valve thrombosis or systemic embolism, but also risk of bleeding which follows anticoagulation therapy. The thromboembolic and bleeding comprises 75% of complications occurring with mechanical heart valves (Edmund 1987). The decreased incidence of these complications in last several years are due to careful, consistent anticoagulation therapy, revision of indications of surgery and improved thromboresistance of the new heart valve prosthesis [14].

Edmund *et al.*, in review of article published in 1979 indicated that the thrombotic and bleeding complications accounts for about 50% of valve related complications in patients with bioprosthetic aortic and mitral valves, of which 75% of these complications occur in patients with mechanical valves [2]. Although compromised by lack of standard definition, variability in reporting and follow-up, the data suggests that the linearized rate of both thrombotic and bleeding complications in patient with aortic bioprosthesis is approximately half, that for aortic mechanical prosthesis (2% versus 4%) and it is equal for both bioprostheses and mechanical in mitral in position (approx. 4%), and for mechanical and bioprostheses aortic as well as mitral in combination [2]. However, linearised rate of fatal thrombotic and bleeding events are 2-4 times higher in patients with mechanical heart valve.

The short term warfarin anticoagulation or long-term use of platelet inhibitors, or both do not reduce incidence of thrombotic complication in patients with aortic bioprostheses but increases the risk of bleeding. For mitral bioprosthesis the prospective use of warfarin for 3 months or aspirin indefinitely is as effective in preventing thromboembolism as long-term warfarin.

Acute prosthetic valve endocarditis is associated with 13-40% incidence of thrombotic complications likewise recurrence rate of arterial emboli is high (20-30%) in patients with prosthetic valve who are not anticoagulated. Antuaes *et al.* analysed 1,000 patients in 3rd World with Hall valve prothesis (538 mitral and 463 aortic), which were implanted in 852 patients (mean age 30+15 years) and double valve replacements were performed in 209 patients. The 782 operative survivors were followed-up for 2 to 6.5 years (mean 3.5 years) for cumulative 2676 patient-years of follow up. The results of events were expressed in both lineared and acturial terms. There were systemic thromboembolism 3.3 and 85+2, thrombotic obstruction 1.2 and 95+1, prosthetic valve endocarditis 0.7 and 97+1 and anticoagulant related haemorrhage 0.7 and 98+1. So in these patients, thrombotic obstruction (71% of cases fatal), anticoagulant related haemorrhage (61% fatal) and prosthetic valve endocarditis (44% fatal) were most lethal complications [5].

Klepetko *et al.* in their study from September 1983 to April 1986, total of 451 patients were analysed for cardiac valve prostheses. The duromedics cardiac valve prostheses were implanted in 400 patients - 190 aortic, 157 mitral and 52 underwent double valve replacements. Follow-up was done on 337 patients surviving which represents 429 patients years. They found thromboembolism in 4 (0.9%), prosthetic valve endocarditis in 5 (1.2%), anticoagulantrelated haemorrhagein 10 (2.3%) and valve failure occurring 8 (1.8%) and they concluded that good clinical results were achieved with new type of duromedicsbileaflet cardiac prosthetic valves [6].

Cannegieter *et al.* in their analysis between 1970 and 1992, the data were collected from midline and current content database and by cross references. Total of 46 studies were found including 13,086 patients studied for 53,647 patients - years. They found incidence of embolism in absence of antithrombotic therapy 4 per 100 patient – year and with cumarin therapy it is reduced to 1 perpatient- years [19].

A prostheses mitral in position increases the risk almost twice as compared to aortic position. Tilting disc valve and bileaflet valve shows lower incidence of major embolism than caged ball valves [4].

Gohlke-Barwolf *et al.* in the article in German Z Kardial 2001 highlighted the number of new developments- like introduction of international normalized ratio (INR) for determination of intensity of oral anticoagulation. This therapy proposed by them was individualized, risk factor adjusted and prosthetic specific. They also gave the concept of self-monitoring of oral anticoagulation therapy [18].

Ezekowitz *et al.* (J Heart valve Dis 2002) made following recommendation to protect patients with prosthetic heart valves on oral anticoagulation from developing stroke:

1. For mechanical heart valve in aortic position with warfarin, an INR range should be between2.0-3.0.
2. For mitral position INR range of2.5-3.5 is recommended, an alternative INR of2.0-3.0 with combination of aspirin 80mg/day.
3. The patients with mechanical heart valve replacements with history of systemic embolization, an INR range of 2.5-3.5 with low dose aspirin (80- 100mg) was recommended. They also pointed out that the dose of

warfarin should not exceed 3mg/day in patients greater than 70 years of age [28].

Lecuru F *et al.* in their study in 1995 pointed out that the patients with mechanical heart valve replacements with pregnancy should be started with low molecular weight heparin from 5th week of gestation onwards. This therapy with heparin is an alternative to cumarin derivatives because of danger of warfarin embryopathy [8].

Matsuyama *et al.* in their analysis in 2002 in Japanese patients found that there were no guidelines for optimal therapeutic range of OAT in Japanese patients with mechanical heart valve replacements. A total of 214 patients were followed retrospectively after MVR (mean duration of 4.8 years), total duration 1027 patient- years; target INR range was 1.5-2.5. So total follow-up measurements of INR was obtained in which 76% INR range were within the recommended values. Thromboembolism occurring in 8 patients (0.8 per patient - years) and major bleeding in 5 patients (0.5 per patient - years) [9].

Lindblom *et al.* in their study in 1989 performed heart valve replacements in 208 patients with age group of 70-80 years - aortic (AVR) in 172, mitral in 20 and both in 16 cases. All valves were Bjork-Shiley type, all but 6 received (OAT) maintenance therapy. 100% follow-up comprise of 744 patient-years (mean 4 years). Actuarial survival was 79% at 5 years and 73% 8 years overall. They foundthat incidence of thromboembolism and of fatal bleeding complications were equal to that for younger group. So mechanical heart valve replacements and maintenance anticoagulationis safe even in elderly patients and eliminates need for re-replacement due to bioprosthetic degeneration [10].

Raskob *et al.* 1996, Department of Medicine and Biostatistics and Epidemiology, University of Iklahoma, USA pointed out that OAT is effective antithrombotic treatment for several indications. Thus the results of PTI monetring should be reported as International Normalized Ratio (INR). An INR of 2.0-3.0 is recommended therapeutic range for all indications except for prevention of systemic embolism in patient with mechanical heart valves and long-term treatment of patient with myocardial infarction, for whom an INR range of 2.5 to 3.5 is recommended [11].

Hasenkam *et al.* in their study in 1997 recommended self-management of OAT after heart valve replacements by the patients themselves. Total of 21 patients were enrolled in their study and followed for at least 9 months postoperatively. After heart valve replacements, the patients were trained in operating coagu-chek INR monitor to analyse capillary and whole blood samples. They were educated about INR valve (target INR range 2.0-3.0) and dosage adjustments of oral anticoagulants. The patients were fully capable of self-management after 30 weeks [12].

Butchart *et al.* in their study in 1988 between December 1979 to June 1987 performed total of 1004 Medtronic Hall valve replacements in 601 mitral, 398 aortic and 5 tricuspid in 847 patients. The 2640 patients-years of follow up were done. The prothrombin time ratios were reviewed for all patients (16,866 observations). The observations were made on the basis of international normalized ratio (INR) which was highly variable (lower 10th percentile 1.6, upper 10th percentile 3.9). However, the median INR was 2.6 which were therapeutically low. The follow up was done on the basis of 30 days, 180 days and 5 years acturial embolic free rates. The 30 and 180 days follow up of embolic free rates were 99.9%, 99.5% and 99% for aortic mitral and double valve replacements. For 5 years' follow up, the acturial ambolic free rates were 92, 84 and 83% respectively.

Heras *et al.* in their analysis in 1995 reported thromboembolic rates during first 10 days after operation upto 41% perpatient-years for the aortic bioprosthetic valves and 55% per patient-years for mitral position. Those patients who received only subcutaneous heparin 22,500 [U/day and aspirin 100mg/day for first 14-22 days. In them, the frequency of thromboembolic events were reduced to 3.5% per patient-years [16]. They investigated that during first 3 months of bioprosthetic valve insertion, ORT appears to diminish the prevalence of thromboembolism but thromboembolic events are not eliminated. Among patients with either aortic or mitral bioprosthetic valves, 1.9% of patient with an INR of 2.5-4.5 had thromboemboli during first 3 months, and 2.0% of patient with an INR of 2.0-2.3 had thromboemboli during this period [16].

Prophylaxis *at al* INR of 2.0-2.5 was associated with fewer bleeding complications than higher INR range. None with prosthetic valves in the aortic position had thromboemboli, but 5.0 to 5.1%with valves in the mitral position had thromboemboli [16].

Material & Methods

This study was conducted in the department of Surgery at District Hospital Rajouri, J&K, India, in collaboration with Department of CVTS SKIMS-Soura. The study conducted retrospectively on the patients with prosthetic heart valve replacements. The records of these patients with respect to chemical parameter, operation done and OAT started were fallowed.

All the patients, prospective as well as retrospective, were followed with detailed history, though general and systemic examination, laboratory investigations as-per proforma. They were screened for thromboembolic and bleeding complications. The patients with this complication were admitted and fully worked up with required investigations including coagulograms.

The patients with history suggestive of peripheral embolism were subjected to doplar ultrasonography and findings correlated with coagulogram. Those patients with history and examination suggestive of intracranial lesions such as headache, altered sensorium, blurring of vision, transient/loss of consciousness, weakness of any parts of body, aphasia, vomiting, convulsions, incontinence of urine or faeces, loss of vision and cranial nerve palcies, were subjected to the CT scan head and M.R. angiography as and when indicated/available.

Patients with history of bleeds like gastrointestinal bleed, haematamesis, malena, epistaxis, haemoptysis, petacheal spots on the body or internal organic haematoma, were fully evaluated. Patients with documented peripheral embolus were operated upon and embolectomies done. Patient with duodenal ulcer bleed and perforation was operated, under running of bleeding vessel with closure of perforation done.

Patient with documented SAH with hydrocephalus, was operated in this Institute and V-P shunt was performed. Those patients with strokes, were managed here by the departments of Neurology as well as Cardiovascular and Thoracic Surgery.

We take commercially available thromboplastin in another tube and then put 0.1ml of plasma into duplicate tubes. Wait for 3 minutes and add 0.2mlof thromboplastin calcium chloride mixture and start the stop watch so as to note the

clotting time. The same procedure is repeated for normal control plasma. The patients who were planned for prosthetic heart valve replacements were admitted in the ward. They were fully investigated, besides all investigations, preoperative coagulogram was done. On the second postoperative day, coagulogram was repeated and patients were put on oral anticoagulation therapy. Then daily coagulograms were done and anticoagulation therapy was titrated to the level of desired INR and was stabilized in about weeks' time.

The patients were discharged on the oral anticoagulation therapy stabilized on the basis of repeated coagulograms and desired INR range. The patient then followed with weekly coagulogram for 1 month; followed by fortnightly and then on monthly basis.

If patients are doing well, then followed every 3 monthly basis, on each visit detailed history is taken about the drug used, complaints if any and interventions.

In case the INR is not in the target range, ORT is changed (Titrated to achieve) the desired level. In our study, patients even with low INR values were without any complaints.

Observations

Total number of patients included in our study was 466.

- Mitral valve replacements: 316
- Aortic valve replacements: 81
- Double valve replacements: 69

The analysis is made on the basis of International Normalised Ratio (INR) and complications recorded according to INR range.

The age of patients ranged from 10-60 years. The peak age group was between 31- 40 years 221 (47.4%) followed by 21-30 years 112 (24%), 41-50 years 95 (20.3%), 10-20 years 21 (4.5%) and 51-60 years 17 (3.6%).

Table 1: Age Distribution of patients with Prosthetic Valve (n=466)

S. No.	Age in years	No. of patients	Percentage
1.	10-20	21	4.50
2.	21-30	112	24.00
3.	31-40	221	47.40
4.	41-50	95	20.30
5.	51-60	17	3.60

Out of 466 patients, in 316 MVR was done: males 145 (45.8%) and females 171 (54.1%). AVR were 81, out of 57 (70.3%) were males and 24 (29.6%) were females. DVR was done in 69 patients: 38 were males (55.0%) and 31 were females (38.2%). The sex-wise distribution of patients with valve replacements is shown in Table-2.

Table 2: Sex Distribution of patients with Prosthetic Valve (n=466)

S. No.	Types of Prosthesis	Males	%	Females	%
1.	MVR	145	45.8	171	54.1
2.	AVR	57	70.3	24	29.6
3.	DVR	38	55.0	31	38.2

The types of replacements are depicted in Table-3. MVR were done in 316 (67.8%), AVR in 81 (17.88%) and DVR in 69 (14.8%). MVR in tricuspid repair 2 (0.6%), AVR with tricuspid repair (1.2%) and DVR with tricuspid repair 2 (2.8%).

Table 3: Table showing types of Replacements Performed (n=466)

S. No.	Types of Prosthesis	Total No. of patients	Percentage
1.	MVR	316	67.8
2.	AVR	81	17.38
3.	DVR	69	14.8

Types of prosthesis used are shown in Table-4. Medtronic Hall valves were used in 378 patients (81.1%) followed by Bjork Shiley valves 82 (17.59%) and tissue valves in 6 (1.28%).

Table 4: Table showing types of Prostheses used (n=466)

S. No.	Types of Valve	No. of Valves	Percentage
1.	Medtronic hall valves	378	81
2.	Bjerk Shilley	82	17.5
3.	Tissue valves	6	1.28

The most commonly anticoagulant drug was nicoumalone 98.2% followed by nicoumalone with aspirin 220 (47.2%), nicoumalone with aspirin and dipyradamole in 125 (26.8%), nicoumalone with clopidogril in 45 (9.6%) and heparin in 3 patients 0.64% -.

Table 5: Table showing types of Anticoagulation Drugs Used

S. No.	Anticoagulation Drugs	No. of Patients
1.	Nicoumalone (Acitrom)	466
2.	Nicoumalone+Aspirin	220
3.	Nicoumalone+Aspirin+Dipyradanole	125
4.	Nicoumalone+Clopidragenil	45
5.	Heparin	3*

The dose of nicomalone was 2mg in 178 (38.3%), 3mg in 134 (28.7%), 1mg in 86 (18.5%), 4mg in 43 (9.2%), 5mg in 19 (4.07%), 6mg in 2 (0.42%) and 7mg in 1 patient (0.21%). The total number of complications were found in 19 patients out of 466 (4.0%). 7 patients had minor events like transient cerebral events in 3 patients (0.64%), peripheral embolism in 1 (0.2%), epistaxis in 1 (0.2%), 2 episodes of malena in 2 (0.4%). Rest of twelve patients had major complications. Comprising of peripheral embolus in 2 (0.4%), stroke in 6 (1.28%), intracerebral bleed in 1 (0.2%), SAH in 1 (0.21%) and duodenal ulcer bleed in 2 patients (0.4%).

Table 6: Table showing Complications in Total Number of Patients

S. No.	Complications	No. of Patients
1.	Peripheral embolization	3
2.	G.I. bleeding	3
3.	Epistaxis	1
4.	Stroke	6
5.	Transient cerebral events	3
6.	Intracerebral blood	1
7.	Petechial spots	1
8.	SAH with hydrocephalus	1
9.	Peripheral embolization with SAH	1
10.	Peripheral emboli with intracerebral bleed	1

The INR range in relation to complication in MVR is shown in Table 8. In INR range <1.5, 1 patients of 100 (1.0%) had complications. Similarly in INR range 1.5- 2.0, 3 out of 115 (0.86%), INR 2.0-2.5, 1 out of 72 (1.3%) and >2, 5, 1 out of 28 (3.5%).

Table 7: Table showing types of Surgical Interventions (n=19)

S. No.	Types of surgical intervention	Patients
1.	Peripheral embolectomies	2
2.	Under-running of bleeding vessel in duodenal bleeding ulcer	1
3.	Ventriculo-peritoneal shunt for SAH with hydrocephalus	1
4.	Peripheral embolectomy with VP shunt	1

INR-wise complications in AVR. In INR range of <1.5, 1 patient out of 8 had complication (12.5%), 1.5-2.0 INR,1 out of 33 patients (3.0%), 2.0-2.5, 1 out of 17 patients (5.8%) and >2.5 INR range, 1 out of 24 (4.1%).

In INR range <1.5; 4 patients had thrombolic (3.3%) and 2 had bleeding complication (1.7). In the ranges 1.5-2.0, 2.0-2.5, >2.5 the thrombolic and bleeding complication were 1.7 and 0.57%, 2.6% and 0.8% and 3.2% and 4.8% respectively. The highest mortality was observed in DVR 2/69 (2.8%), followed by 1.23% in AVR and 0.9% in MVR.

Table 8: Table showing INR Range-wise Complications (n=466)

S. No.	INR range	No. of Pts.	Percentage	Complications			
				Thrombo-embolism	%	Bleeding	%
1.	<1.5	118	25.3	4	3.3	2	1.69
2.	1.5-2.0	173	37.5	3	1.7	1	0.57
3.	2.0-2.5	113	24.5	3	2.6	1	0.8
4.	>2.5	62	13.3	2	3.2	3	4.8

Table 9: Table showing Mortality due to Thromboembolic and bleeding

S. No.	Type of valve	No. of patients	Deaths	%
1.	MVR	316	3	0.94
2.	AVR	81	1	1.23
3.	DVR	69	2	2.89

Discussion

The total number of patients in our study were 466 out of which 240 (51.5%) were male and 226 (48.40) were female, with male to female ratio of 1.06:1.0. Cannegieter *et al.* reported low risk of thromboembolism in younger age group and high risk in patients of more than 50 years of age [3]. In our study, low risk of thromboembolism was found in both younger age group and elderly patients which is in contrast to the study reported by Cannegieter *et al.* [19]. This can be explained on the basis of fewer numbers of patients in elder age group in our Study.

Felix *et al.* reported the incidence of thromboembolism of 0.8 per patient-years for women and 0.6 for men and risk of bleeding was 3.1 and 2.4 per patient-years for women and men respectively [21]. In our analysis, the results were similar for males but higher incidence of bleeding (1.7%) for females versus 0.9 per patient-years. The reason is explained on the basis that one patient with septicemia and another with acute renal failure had bleedings under this study [21].

In our study, majority of valve replacements was MVR (67.8%) followed by AVR (17.4%) and DVR (14.5%). Butchart *et al.* reported in their study MVR (59.91%) [15] which is similar in our study.

In our analysis, the risk of thromboembolism and bleeding was 4.1% in MVR as compared to AVR (3.7%). Cannegieter *et al.* found in their study the risk of thromboembolism was 5 times higher for MVR as compared to AVR [19]. They also reported incidence of thromboembolism 0.5/100 patient-years for AVR and 0.9/100 patient-years for MVR [19]. Antunes MI *et al.* demonstrated that the risks of thromboembolism were higher in mitral valve 3.1/patient-years as compared to 2.2 patient-yearsfor aortic valves [5]. The findings of these two studies are similar to that of our study.

The prosthetic heart valve replacements done in our study were Medtronic Hall valves 81.1% followed by Bjork-Shiley 17.59%. The incidence of thromboembolism with Medtronic Hall valve was 2.64% and with Bjork-Shiley it was 2.4%. In the study conducted by Kuntze *et al.*, the incidence of thromboembolism was 2.6 times higher for the Medtronic Hall valve as compared to Bjork-Shiley type [7]. However, in our study the rate of complication was approximately similar in both the types of valves. Since the Number of Bjork-Shiley valve replacements was fewer than Medtronic Hall valve (82 v/s 378), so we cannot compare the rate of complications in these types of valves.

The main anticoagulant drug used in our study was nicomaline (Acitrom) in 98.2% patients, followed by nicomaline with low dose aspirin 47.2%, nicomalone, dipyradamole and aspirin 26.8% and heparin in 0.64% patients. The dosage of anticoagulant drugs weretitrated with INR range to the level of desired target so that optimal INR levels are achieved for the types of prosthetic valves. In our study, the dose of nicomalone was 2mg in 38.2%, 3mg in 28.7%, 1 mg in 18.5% and 4mg in 9.2% of patients.

Butchart and Colleague used low intensity oral anti-coagulation in 847 patients and found low incidence of thromboembolism [15]. Ezekowitz *et al.* recommended different ranges of INR for different prosthetic valve positions and presence of additional risk factors. They also recommended aspirin in low doses in combination with oral anticoagulation therapy [20].

We used heparin as anticoagulation therapy in 3 pregnant patients. Ginsberg *et al.* recommended the use of heparin as anticoagulation therapy in pregnancy because of risk of the warfarin embryopathy [22]. Lecuru *et al.* also recommended the use of heparin in pregnancyin order to prevent the side effects (embryopathy) associated with cumarin Derivatives [8].

The overall incidence of complications in our study was 4.0%. Saour *et al.* reported an incidence of 3.85% which is similar to the incidence reported in our study [23]. The total number of events was 19 out of 466 patients. There were minor events in 7 patients (1.5%) comprising of transient cerebral events in 3 patients (0.64%), peripheral emboli in 1 patient (0.2%), epistaxis in one (0.2%) and two episodes of malena in 1 patient (0.42%). These minor events did not require any intervention. In rest of 12 patients (2.57%) major complications were encountered comprising of 2 cases of peripheral embolism (0.4%), 6 cases of stroke (1.28%), 1 case of massive intracerebral bleed (0.2%), 1 case of SAH (0.21%), 2 cases of duodenalulcer bleed (0.42%). All these cases required interventional management.

Klepetko *et al.* reported in their study the rate of thrombolism in 4 patients (0.9%), prosthetic valve endocarditis in 5 (1.2%) and anticoagulant related haemorrhage in 10 (2.3) [6]. Cannegieter *et al.* found the incidence of bleeding with cumarin derivatives 1.4/ patient-years, cerebral bleed 0.68/patient-years and peripheral embolus in 0.03 per patient-years [3].

The observation in the above studies is similar to our study except that the anticoagulant related haemorrhage was less in our study (1.28%) compared to 2.3%. But thromboembolism was more in present study (2.14) compared to 0.9%. The possible explanation for increased incidence of thromboembolismis that the INR range was lower than recommended.

In our study we have grouped the patients on the basis of INR ranges. The number of patients having INR range <1.5 was 25.3%, between 1.5 - 2.0 was 37.5%, between 2.0-2.5 was 24.2% and the range of >2.5 was 13.3%. The incidence of thromboembolism and bleeding observed in these INR ranges was 3.3 and 1.69%, 1.7 and 0.57%, 2.6 and 0.8% and 3.2 and 4.8% respectively.

Heras *et al.* in their study among the patients with either aortic or mitral valve found that 1.9% of patients with an INR of 2.5-4.5 had thromboembolic and 2.0% of patients with an INR of 2.0-3.0 had thromboembolic [16]. the observation in these studies is similar to our analysis.

Matsuyama *et al.* in their study in Japanese patients found that there were no guidelines for OAT, the target INR range was 1.5-2.5 which was achieved only in 76% of patients. The thromboembolism occurs at 0.8 per patient-years and major bleeding at 0.5 per patient-years [9]. Antunes *et al.* demonstrated in their study the rate of systemic embolism 3.3%, thrombotic obstruction in 1.2%, prosthetic valve endocarditis in 0.7% and anticoagulant related haemorrhage in 0.7 % [5]. In our study, we have done two embolectomies (femoral and aorto-illac), one under running of bleeding vessel in duodenal ulcer bleed and one V.P. shunt for SAH. Mortality because of these complications in our study was 1.28%. Overall, it was more with the double valve replacements (2.8%). It was observed that thromboembolism was 21% fatal and bleeding 10.5% fatal (15). Butchart *et al.* observed in their studies that 60% of thromboembolism left no residual deficit and 75% of bleeding events require no treatment. Only 11%of thromboembolic and 7% of bleeding events were fatal. The analysis in our study is similar to that of Butchart *et al.* [15].

Conclusion

Thromboembolic and anticoagulant related bleeding remains one of the most frequent complications of heart valve replacements. Thromboembolic and bleeding complication affects the long term course of patients with heart valve replacement.

The patients with mechanical heart valve replacements require lifelong anticoagulation therapy. Anticoagulation therapy prevents thromboembolism but increases the risk of bleeding. The most commonly used anticoagulant drug was nicomalone followed by low dose aspirin.

Complete coagulogram was the most commonly performed investigation for titration of therapy (OAT). The International Normalized Ratio (INR) was the most important parameter for titrations of anticoagulation therapy.

The INR range between 1.5-2.5 was safe associated with less complication. The cerebral stroke was most commonly encountered complication during our analysis (1.28%). The double valve replacement carries greater risk of complications than single valve.

References

1. Henry Edmunds L Jr. Thrombotic and bleeding complications of prosthetic heart valves. Ann Thoracic Surg. Oct. 1987; 44:430-45.
2. Henry Edmunds H Jr, Richard E, Clark Lawrence H, Cohn Garyl Grunkemeier *et al.* Guidelines for reporting morbidity and mortality after cardiac valve operation. Ann Thorasic Surg. 1996; 62:932-35.
3. Cannegieter SC, Rosenthal FR, Wintzen AR, Van Dermeer FJN *et al.* Opeimal oral anti coagulant therapy in patients with mechanical heart valves. New England Journal of Medicine. July. 1995; 333(1):11-17.
4. Eric Buchart G, Peter Lewis A, Cary Grunkemeier L, Nihal Kulatilake *et al.* Lowrisk of thrombosis and serious embolic events despite of low-intensity anticoagulation. Circulation. 1988;78(Suppl. 1):1-66-1-77.
5. Antunes MJ, Wessels A, Sadowski RG, Schultz JG, Vanderonck KM, Olivira JM, Fernandes *et al.* Medtronic-Hall valve replacementin third world population group: A review of performance of 1000 prostheses. J. Thorac Cardiovasc Surg. 1988; 95:980-93.
6. Klepetko W, Mortiz A, Khunl-Brady G *et al.* Implantation of the Duromedics bileaflet cardae valve prosthesis in 400 patients. Ann Thorac Surg. 1987; 44:303-9.
7. Carl EE, Kuntze Blackstone H, Tjarli Ebel *et al.* Thromboembolism and mechanical heart valve. A randomized study revisited. Ann Therac Surg. 1998; 66:101-7.
8. Lecuru F, Taurelle R, Desnos M, Ruscillo MM *et al.* Use of anticoagulants during pregnancy. Presse Med May. 1995; 24(19):901-4.
9. Matsuyama K, Matsumoto M, Surgita T, Nishizawa J, Yoshida K, Totuda Y, Matusuo T *et al.* Anticoagulant therapy in Japanese patients with mechanicalheart valves. Circ J Jul. 2002; 667(7):668-670.
10. Lindblom D, Lindblom U, Ivert T *et al.* Heart valve replacements in septuagenarians. Scad J Thorac Cardiovfasc Surg. 1989; 323(1):29-32.
11. Roskob GE *et al.* Oral anticoagulant therapy. Deptt. of Medicine and Biostatistics and Epidemiology, University of Oklahoma, Health Science Centre, Oklahoma City, USA, 9: Curr Opin Hematol Sept. 1996; 3(5):361-4.
12. Hesenkam JM, Kimose HH, Knudsen L, Gronnes by H, Halborg J, Christensen TD Attermann *et al.* Self management of oral anticoagulant therapy after heart valve replacement. 10: Eur J Cardiothorac. 1997; 11(5):935-42.
13. Raul Altman, Jorge Rouvier, Enrique Gurfinkel, Oscar Ortencio *et al.* Comparison of two levels of anticoagulant therapy in patients with substitute heart valves. J.Thorac Cardiovasc. Surg. 1991; 101:427-31.
14. Cannegieter SC, Ronsondool IR, Biet E *et al.* Thromboembolic and bleeding complication in patients with mechanical heart valves. Circulation Feb. 1994; 89(2):635-641.
15. Butchart EG, Lewis PA, Grunkemeier GL, Kulatilake *et al.* Low risk of thrombosis and serious embolic events

despite of low intensity anticoagulation. Circulation. 1999; 78(pt 2):166-77, Ee M7.
16. Heras M, Chesebro JH, Fuster V *et al.* High risk of early thromboemboli after bioprosthetic cardiac valve replacement. J Am Coll Cardiol. 1995; 25:1111-19.
17. Renard PW *et al.* Update on warfarin monitoring, use of an anticoagulation flow sheet. Consult Pharm. 1995; 10:826.
18. Gohlke-Barwolf C *et al.* Current recommendations for prevention of thromboembolism in patients with heart valve prostheses:30Z Kasdid. 2001; 90(suppl 6):112-17.
19. Cannegieter SC MD Rosendaal MD Briet EB *et al.* Thromboembolic bleeding complications in patients with mechanical heart valve prostheses. Circulation. 1994; 89:635-41.
20. Dwight C, Mc Goon MD, Rosendaal MD, Briet E *et al.* Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation. 1994; 89:635-41.
21. Flix JM, Van der Meer MD, Frits R, Rosendaal MD, Jan P, Vandenbroucke MD, Emest *et al.* Bleeding complication on oral anticoagulant therapy. Arch Intern Med. 1993; 153:1557-62.
22. Ginsberg JS, GreerI Hirsh J *et al.* Use of antithrombotic agents during pregnancy. 4: Chest. 2001; 119(Suppl. 1):122S-131S.
23. Saour JN, Sieck JO, Mamo LAR, Gallus *et al.* Trial of different intensities of anticoagulation in patients with prosthetic heart valves. N Engl J Med. 1990; 322:428-372.
24. Wilson DB, Dunn MI, Hassanein K *et al.* Low intensity anticoagulation in mechanical cardiac prosthetic valves. Chest. 1991; 100:1553-57.
25. Van der Meer FJM, Rosendaal FR, Vancerbrucke JP *et al.* Bleeding complications in oral anticoagulant therapy, an analysis of risk factors. Arch Intern Med. 1993; 153:1557-62.
26. Duxbury BM *et al.* Therapeutic quality control leading to further clinical assessmentoforal anticoagulation. Acta Haemat. 1986; 76:65-67.
27. Hirsh J, Greer I *et al.* Antithrombotic therapy during pregnancy. Chest. 2001; 221(Suppl. If):2438-45S.
28. Ezekowitz MD *et al.* Anticoagulation management of valve replacement patients. Department of Medicine, MCP Hehnemann University, Philadelphia, USA. 28, J Heart Valve Dis. 2002; 11(suppl. 1):S560-60.