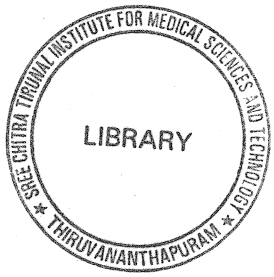
Stroke in Patients with Mechanical Valve Prostheses- A Long Term Follow Up Study



Thesis submitted in partial fulfillment of the rules and regulations for DM Degree Examination of Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram

By

Dr. Atma Ram

Resident in Neurology

Month and Year of Submission: October 2008

CERTIFICATE

I, Dr. **Atma Ram** hereby declare that I have actually carried out the project under report.

Place: Thiruvananthapuram

Signature:

Date: 6-10-2008

Dr. Atma Ram
Resident in Neurology

Forwarded. He has carried out the project under report.

Signature:

Dr. C SARADA for

Dr. K. Radhakrishnan
Senior Professor & Head,
Department of Neurology

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INTRODUCTION

Stroke is the second leading cause of death and a major cause of disability worldwide[1]. Two-thirds of stroke deaths worldwide occur in developing countries[2]. Cardioembolic stroke is thought to be one of the more preventable types of strokes. It accounts for quite significant proportion of stroke especially in young patients, accounting for about one fourth of all strokes in various studies[3,4]. According to previously defined guidelines[5], a potential cardiac source of embolism can divided into three groups: (1) Cardiac wall abnormalities (2) Mitral or aortic valve abnormalities and (3) Arrhythmias.

Several recent studies conducted in India have highlighted the unacceptably high prevalence of Rheumatic Heart Disease (RHD) among children and adolescents[6,7]. Overpopulation, overcrowding, poverty, and poor access to medical care are undoubtedly the main reasons for the high prevalence of RHD in India. With the high prevalence of symptomatic rheumatic valvular heart disease, valve replacement is carried out extensively across the country. The heart valves, ravaged by the rheumatic process are often so damaged that these are no longer suitable for lasting repair procedures and need to be replaced with prosthetic heart valves. Since majority of heart valve replacement in India are for rheumatic valvular heart disease, in younger age, mechanical heart valves are the preferred choice[8]. In contrast, in Western countries where degenerative disease in elderly is prime indication for valve replacement, biological valves are preferred.

Stroke can occur as both an intraoperative and a postoperative complication of valve surgery, although the mechanisms differ. Intraoperative strokes are typically the result of cerebral hypoperfusion or embolization related to procedural issues such as bypass or vessel clamping. Cerebral hypoperfusion is usually due to intraoperative hypotension or decreased cardiac output. Emboli are not uncommon during cardiac surgery, most often occurring as either air emboli or atherosclerotic emboli[9]. Air emboli can arise from open cardiac chambers and enter the arterial circulation to the brain, while atherosclerotic emboli break off during clamping and manipulation of degenerated valves[10].

The mechanism of stroke in the postoperative period, however, is most often embolus secondary to direct valve thrombosis, left atrial thrombus (especially in patients in atrial fibrillation), or infected valves with subsequent septic embolism to the brain[11].

Prosthetic heart valve forms an important source of emboli. Mechanical valves, which are composed primarily of metal or carbon alloys, are classified according to their structure as caged-ball, single-tilting-disk, or bileaflet-tilting-disk valves, differ in their mechanical and surface properties. The thrombogenic potential is highest in patients with caged-ball prostheses, lowest in patients with bileaflet-tilting-disk prostheses, and intermediate in those with single-tilting-disk prostheses[12]. So optimum level of anticoagulation may differ based on the type of prosthetic valve used.

Thrombus formation on the valve may be influenced – according to Virchow's triad -by surface characteristics of the prostheses (material and design), blood flow (cardiac output, turbulence, and stagnation), and characteristics of the blood constituents of the patient (hypercoagulability).

In patients with mechanical valves, the incidence of major embolization (resulting in death or a persistent neurologic deficit) is roughly 4 percent per patient-year in the absence of antithrombotic therapy, 2 percent per patient-year with antiplatelet therapy, and 1 percent per patient-year with warfarin therapy[13], with the majority of embolizations manifesting as cerebrovascular events[14].

Clinically, this may result in significant disruption of valve function, a life-threatening event. Likewise, parts of the thrombus may embolize to peripheral arterial sites. These emboli usually involve the central nervous system, resulting in a spectrum of effects ranging from minor and transient to sometimes-fatal events. To prevent these complications, life-long oral anticoagulation (Vitamin K antagonist- VKA) therapy is recommended in all patients[15],[16] however this treatment introduces a risk, which can be severe or fatal bleeding[17], especially when the anticoagulation is inappropriate. Cannegieter et al.[18] described, on the basis of a discrepancy between targeted and achieved international normalized ration (INR), the relationship between the effectiveness of anticoagulation and the actually achieved intensities. The study showed that the optimal intensity of anticoagulation, resulting in the fewest adverse events, lies between INR levels of 2.5 and 4.9. The incidence of the events rises sharply above or below this range. As a target range, they recommended an INR of 3.0 to 4.0 for both aortic and mitral valves, although it was shown that the risk of thromboembolic complications appears to vary with the position of the valve.

Patients with prostheses in the mitral position have a significantly higher risk of thromboembolic complications than those with aortic valve prostheses[19]. Based on this discrepancy, a minor discrimination in anticoagulation intensity was recommended between aortic and mitral valves with advice for

a higher target range was advised for mitral valve. However, these latest guidelines are based on only a few studies. Thus, the range of optimal intensity of VKA is an ongoing matter of debate, moreover because it is difficult to assess the individual risks of thromboembolism and bleeding in an individual patient. According to the AHA/ACC/ACCP recommendations, the target INR is 2.0-3.0 for Medtronic Hall valve in the aortic position in patients with no other risk factors, and 2.5-3.5 for all other prosthetic valve in aortic position as well as for prosthetic valve in mitral position[20].

Drugs, herbs and multivitamin supplements can alter the absorption, pharmacokinetics or pharmakodynamics of VKA[21]. Nonsteroid anti-inflammatory drugs in combination with VKA seem to be the most dangerous because of availability without prescription and use without medical consultation. Patients on VKA therapy are sensitive to changing dietary intake of vitamin K, which is supplied from phylloquinones in plants or from vitamin K-containing medicines.

In our country, meticulous monitoring of PT INR (Prothrombin test with INR) is challenging because of several factors, including local availability of testing facility, reliability of test methodology, medication compliance, and irregular follow-up. Our Institute being tertiary referral centre for cardiological, neurological and vascular disorders, cardioembolic stroke forms a significant proportion of stroke, especially in young adults. Valve replacement surgery is being done on a regular basis for over 3 decades at our institute, and patients are followed up regularly. Medical records are archived systematically, and therefore our Institution is ideally suited to study the frequency of complications especially stroke and to identify the predisposing factors involved.

REVIEW OF LITERATURE

In the past 40 years, many reports have been published on the risks of thromboembolic and bleeding complications[22,23,24,25,26,27]. Unfortunately, in these series vary greatly because of differences in patient selection, definitions of end points, methods of follow-up and statistical analysis, and type, intensity, and efficacy of anticoagulation therapy[28]. A meta analysis study for thromboembolic and bleeding complications in patients with mechanical heart valve prostheses was published in 1994[29]. This meta analysis found an incidence of major embolism in the absence of antithrombotic therapy of 4 per 100 patient-years. With antiplatelet therapy this risk was 2.2 per 100 patient-years, and with cumarin therapy it was reduced to 1 per 100 patient-years. This risk varied with the type and the site of the prostheses. Prostheses in mitral position increased the risk almost twice as compared with the aortic position. Tilting disc valves and bileaflet valves showed a lower incidence of major embolism than caged ball valves. An incidence of major bleeding was found in patients treated with cumarin derivatives of 1.4 per 100 patient-years.

MECHANICAL Vs BIOPROSTHESES

In a study from Canada for characterization of late stroke occurrence, approximately 20% of patients with valve prostheses have an embolic stroke by 15 years after valve replacement[30]. Linearized embolic stroke rates were 1.3% ± 0.2% per year in patients with aortic bioprostheses, 1.4% ± 0.2% per year with aortic mechanical valves, 1.3% ± 0.3% per year with mitral bioprostheses, and 2.3% ± 0.4% per year with mitral mechanical valves (p = 0.002, vs other implant types). Ninety-seven patients, or 37.5% of those who

had an embolic stroke, died with stroke as a primary or contributing cause at a mean of 1.6 ± 2.7 years after the event.

MECHANICAL PROSTHESES

Starr-Edwards Valve- Godje et al studied 30 years follow up in 416 patients with Starr Edwards Prostheses (SEP) placed in mitral and aortic position[31]. Aortic valves were replaced 286 and the mitral valve in130. Only 65.7% of patients with Starr-Edwards aortic valves received VKA therapy. The therapeutic goal was to maintain the prothrombin time at 25% to 30% (international normalized ratio, 3.0 to 4.0). Patients with mitral valves were treated with phenprocoumon in 90.7% of cases. 30 years follow-up was possible for 241 patients (84.2%) with AVR and 117 patients with MVR(90.0%). Early mortality was 17.1% for AVR and 10.0% for MVR. Thromboembolic events with AVR observed 36 times with only 67.5% patients receiving VKA therapy, corresponding to a linearized rate of 1.36% per patient-years. Patients with MVR suffered a thromboembolic complication in 20 cases, with a linearized rate of 1.25% per pt-y. Anticoagulant-related hemorrhage was recorded in 28 cases in AVR (1.06% per pt-y) and in 9 cases in MVR (0.56% per pt-y).

Medtronic-Hall Valve Prostheses- Svennevig et al studied a retrospective cohort analysis of 816 consecutive patients undergoing aortic valve replacement with the Medtronic-Hall valve[32]. During the first 10 years of this study, all incidents of morbidity (eg, thromboembolism, valve, thrombosis, bleeding, leak, endocarditis) were counted. Linearized rates of thromboembolic complications, warfarin-related bleeding, and endocarditis were 1.5%, 0.7%, and 0.16%/patient-year, respectively.

Akins et al reported long term outcome in patients undergoing aortic or mitral or both valve replacement with the Medtronic-Hall valve[33]. Operative

mortality for the total group was 4.6% (18/391). The operative mortality by valve position was 2.9% for AVR (0.9% for 110 isolated AVR), 4.3% for MVR (3.6% for 84 isolated MVR), and 10.6% for DVR (8.9% for 45 isolated DVR). Late deaths occurred in 40 (14.3%) of the 280 hospital survivors followed up long-term. Linearized mortality was 2.5% per patient-year for hospital survivors of AVR and 4.4% per patient-year for hospital survivors of MVR. Thromboembolism was documented in ten events in 10 patients after AVR: five after isolated AVR, four after AVR + CABG, and one after composite AVR + ascending aortic replacement. The linearized rate for thromboembolism after AVR was 1.3% per patient-year, and the 10-year actuarial event-free rate was 87.3% ± 4.4%. Thromboembolism after MVR was reported on nine occasions in 8 patients. The linearized rate for thromboembolism, including the valve thrombosis, after MVR was 2.1% per patient-year, and the 10-year actuarial event-free rate was 90.8% ± 3.2%. The linearized rate for anticoagulant-related hemorrhage following AVR was 1.7% per patient-year, and the ten-year actuarial event-free rate was 80.0 ± 7.5%. The linearized rate for anticoagulant-related hemorrhage after MVR was 1.9% per patient-year, and the 10-year actuarial event-free rate was 85.6% ± 4.9%

Chitra Heart Valve (CHV) - The Chitra tilting disc valve was developed in India to meet the need for a low-cost cardiac valve[34]. In the clinical trial, linearized rate of late thromboembolism was 6.2%/patient-year (pt-yr), anticoagulant related hemorrhage 0.54%/pty and infective endocarditis 0.54%/pty. At two years, the total actuarial survival was 89.5%.

In a multicentre study done in India, 306 patients underwent isolated aortic (AVR, n = 101) or mitral valve replacement (MVR, n = 205) at six institutions in India[35]. The early mortality rate was 6.9%. A total of 285

survivors were followed up and total follow up was 1212 patient-years (pt-yr) (AVR, 445 pt-yr; MVR, 767 pt-yr). There were 52 late deaths (4.3%/pt-yr;-AVR 2.2%/pt-yr; MVR 5.5%/pt-yr). Embolic episodes occurred in 25 patients (seven after AVR, 1.6%/pt-yr; 18 after MVR, 2.4%/pt-yr). Full recovery from such episodes occurred in all 25 patients (except one patient who died) without any residual neurological deficits. Bleeding events occurred in four patients with AVR with linearized rate for bleeding being 0.9+/-0.5% and 3 patients with MVR with linearized rate for bleeding being 0.4+/-0.2%. Out of these 7 patients, 4 patients expired due to cerebral hemorrhage with a mortality of 57.1% in case of bleeding CNS events. The higher incidence of thromboembolism and the very low incidence of anticoagulant related hemorrhage illustrate the difficulty in the management of anticoagulant therapy in a developing country.

Limited data is available from another study on CHV by Nagarajan et al[36]. 144 patients were followed up (a total of 622 patient- years of follow-up) with clinical and echocardiographic evaluation. There were 11 patients (7.2%) with thrombo-embolic episodes, 5 of whom had major events and the rest were minor with a linearized rate of 1.8 percent patient- year, out of them 8 were thromboembolic stroke. 3 had major stroke and 5 had minor stroke.

Another study from India from Tata Main Hospital, Jamshedpur reported data of 88 patients who had undergone valve replacement surgery in various cardiothoracic centers in the country[37]. Total follow up period was 462 patient-years. The incidences of thrombotic complications with Starr-Edwards, St. Jude and Medtronic-Hall valves placed in mitral, aortic or both the sites were studied. In the single valve replacement group, St. Jude valve in mitral position had the highest thromboembolic risk (including valve

thrombosis) of 12.5 per 100 patient-years. In the double valve replacement group, all the three prostheses had high thrombotic risk: St. Jude 22.2, Medtronic-Hall 12.5 and Starr-Edwards 8.6 per 100 patient-years. Cumulative thrombotic risk in this series was 4.9 per 100 patient-years out of which about 1/4th (6 out of total 23 thrombotic events) were cerebral thromboembolism. Sub-therapeutic anticoagulation was the key factor for thrombotic complications.

AGE & LONG-TERM OUTCOME OF VALVE REPLACEMENT

Young Adults

In one study in young adults, the early overall perioperative mortality were 16 of 500 patients (3.2%)[38]. Long-term survival was significantly worse after double valve replacement than after either aortic or mitral replacement (HR: 2.2; 95% CI: 1.1, 4.5; P=0.03). On the other hand, there was no significant difference in survival between patients who underwent AVR versus those who underwent MVR, but in either implant position there was no survival difference between the 4 subclasses of prostheses examined. Four strokes occurred in the early postoperative period in the cohort; 2 involved AVR patients (0.6%) and 2 occurred in MVR patients (1.3%). In the chronic phase, the 10-year cumulative incidence of late postoperative embolic stroke was 6.3±2.4% for mechanical AVR patients, 6.4±2.9% for bioprosthetic AVR patients, 12.7±3.9% for mechanical MVR patients, 3.1±3.1% for bioprosthetic MVR patients, and 16.1±9.4% for mechanical DVR patients. No significant independent effect was observed with respect to prostheses type or subclass.

Middle Age

Kulik et al studied[39] patients aged 50–65 years for the long-term outcomes of mechanical versus bioprosthetic valves. Ten-year survival was 73.2 ± 4.2% after mechanical AVR, 75.1 ± 12.6% after bioprosthetic AVR, 74.1 ± 4.6% after mechanical MVR, and 77.9 ± 7.4% after bioprosthetic MVR (*P* = NS). The 10-year freedom from late postoperative stroke was 90.0 ± 2.7% for mechanical AVR patients, 97.6 ± 1.7% for bioprosthetic AVR patients, 87.9 ± 4.1% for mechanical MVR patients, and 91.1 ± 5.0% for bioprosthetic MVR patients. There was no difference in the stroke risk between mechanical and bioprosthetic valves in either implant position.

Ruel et al[40] studied long term outcome in mechanical versus prosthetic valve in age< 60 years. The 20-year freedom from death attributable to ischemic or hemorrhagic stroke was 97.9±1.2% in tissue AVR patients, 83.9±4.9% in mechanical AVR patients, 96.1±1.9% in tissue MVR patients, and 85.6±5.3% in mechanical MVR patients. After adjusting for coronary artery disease and atrial fibrillation, the use of a mechanical valve was a significant risk factor for dying from stroke in either implant position (for AVR, HR: 7.0; for MVR, HR: 4.5; both *P*<0.02).

ANTICOAGULATION & LONG-TERM OUTCOME

Wolkanin-Bartnik J et al[41] reported relation of INR and oral anticoagulant complications. There was no significant difference in therapeutic range in patients with complications and event free patients. Significant differences were found when a shorter period of time-3 months preceding the incident was analyzed compared with the average results of measurements of event free patients. The risk of thromboembolic and hemorrhagic complications

was dependent on high fluctuation of INR values in the period of 3 months before the event.

OTHER DEMOGRAPHIC FACTORS FOR STROKE IN GENERAL

Stroke risk factors in young – In a study on stroke in young patients in north India [42], cardioemblism was the most common risk factor accounting for 29.4% (32/109) of cerebal infarction patients including 3 of prosthetic valve patients over 9 year duration.

Socioeconomic status- in a study on correlation with socioeconomic status, incidence and outcome of stroke, it was demonstrated that incidence and the case-fatality ratio of first ischemic stroke events were higher in persons with low socioeconomic status (SES) than in persons with high SES[43]. In this study education level also to an extent affected the incidence and outcome with patients having secondary or higher level of education had lower incidence and better outcome. . In another study in elderly women[44], the low SES was associated with higher incidence of stroke. There was a strong association among elderly women between socioeconomic status and stroke. The association could only partly be explained by known risk factors.

Education level –Avendano et al[45] studied education level in patients with stroke at ages 65 to 74 years; lower education and income were associated with higher stroke incidence. The standardized stroke incidence rates in those with low education or income were twice as high as in those with high education (HR=2.07, 95% CI, 1.04 to 4.13) or income (HR=2.08, 95% CI, 1.01 to 4.27).

The role of these demographic factors in Prosthetic Valve related embolic strokes have not been adequately examined in the previous studies.

AIMS AND OBJECTIVE

1. To ascertain the incidence of cerebrovascular accidents in patients over a five-year period following implantation of mechanical heart valve and
2. To systematically analyze the possible role of various factors.

MATERIAL AND METHOD

This retrospective cohort study was conducted at the Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Trivandrum, Kerala in South Indian state. This tertiary referral centre for cardiological, neurological and vascular disorders receives patients from all over Kerala as well as the neighboring state of Tamil Nadu. Our study is a retrospective cohort study where all consecutive patients operated in the department of Cardio-Vascular and Thoracic Surgery (CVTS) for mechanical valve replacement between July 1999 and December 2002 were enrolled.

Their initial follow up data for next five years from the date of surgery were retrieved. The standard guidelines were followed in collecting data to study the complications[46]. Medical records were reviewed carefully for all the patients. Patients were seen periodically initially three months after surgery and then annually in a dedicated valve clinic, where a history focused on the occurrence of valve-related complications and the determination of functional status, physical examination, electrocardiogram (ECG), chest radiograph, and international normalized ratio (INR) were performed and interpreted by a physician.

For the patients who were not currently in follow up, attempts were made to contact via letters and telephone. These patients were called for follow up and were personally interviewed with verification of medical documents. For the patients who mentioned inability to come, were interviewed over telephone for the health status and complications in 5 years after surgery with questions specifically directed for symptoms of stroke or transient ischemic attack (TIA) in this duration. Patients who could not be contacted by letters or telephone, though had completed initial five year

follow up, medical records were verified for any documentation of complication, specially stoke. The patients who had lost to follow up before completing five years of follow up, attempts were made to trace them by letters. In case if they did not turn up despite repeated attempts, the medical records were verified to look for documentation of cerebrovascular complications during the available follow up period.

The patient's demographic data including age at the time of surgery, sex, religion, dietary habits, education level, employment status, residence and socio-economical status were noted. The patients were also interviewed for the knowledge regarding use of anticoagulation, related complications, frequency of monitoring prothrombin time and about regularity of oral anticoagulation medication. The type of oral anticoagulation used was also noted.

At the time of discharge patients were given were counseled about the oral anticoagulant use and potential complications and also written details of the precautions to be taken was given in local language. Patients were advised to repeat Prothrombin (PT) test at least once in a month once INR stabilize. INR values were collected from medical records of the patients who were testing prothrombin tests in this institute. For the patients who were doing prothrombin tests elsewhere were asked to bring their prothrombin test reports with INR. For patients who were missing monitoring frequently and were not doing as per advice after surgery, the possible reasons were asked including financial reason, distance of nearby good laboratory.

To assess the quality of oral anticoagulant treatment, Rosendaal Method for percentage of time in therapeutic range (%TTR) was used[47]; a method in which INR-specific person-time is calculated by incorporating the frequency of INR measurements and their actual values, and assuming that changes

between consecutive INR measurements are linear over time. A formula was designed to calculate percentage of time in therapeutic range automatically based on Rosendaal method. The time interval between two consecutive values of PT INR was taken as maximum of 14 weeks as in patient with stable INR prothrombin test.

A 1998 guideline from the British Committee for Standards in Haematology states: "For rapid anticoagulation with warfarin, daily INR measurement for a minimum of 4 day is recommended. Having achieved an INR in the desired therapeutic range the INR should continue to be monitored weekly until control is stable. Thereafter the frequency of recall can be extended. Extension of recall up to 12 weeks is acceptable"[48]. A review paper on INR intervals of measurement published in 2000 from a hematology department in West Sussex suggests that for selected patients the interval between INR tests can be safely extended to 14 weeks with the potential for longer intervals[49].

Medical records were reviewed for the type of surgery whether emergency surgery or elective surgery including first or redo valve implantatation surgery. The site of valve, type of valve and size of valve were noted.

The numbers of cerebrovascular complications were noted. Strokes were characterized either as embolic or as an intracranial bleeding event based on the primary mechanism and CT appearance of the lesion. Thromboembolic ischemic stroke including TIAs were taken as primary outcome. Patients with intraceberal hemorrhage were analyzed separately.

Patients with stoke were divided in two groups

1. Perioperative stroke – Perioperative stroke was taken separately from follow up stroke as per guidelines[39]. Patients who awaken after operation with a new stroke or stroke occurring during recovery from

anaesthesia or any stroke with in one week of surgery was taken as perioperative stroke.

2. Stroke in follow up – the stroke occurring during follow up (after one week the surgery) was taken as late stroke.

Each episode of stroke was classified into transient ischemic attacks, minor stroke –with near complete recovery with follow up modified Rankin score (mRS)[50] of 1-2 and major stroke with follow up (mRS) of 3 or more at last follow up.

INR value at that time of stroke was specially looked for from medical records of the patient. INR at admission or last INR value before stroke but not more than seven days before stroke was noted. Preceding INR values were also noted with percentage of time in therapeutic range was calculated in the preceding 3-4 months.

Whether patient was admitted in hospital or managed as out patient was noted. In case an imaging was done, the findings were noted as normal or abnormal.

In case of patient on antiplatelets, the type of antiplatelet and indication whether before due to cardiac cause like coronary artery disease or after an episode of stroke in patients on anticoagulation was noted. It was specially noted whether patient was antiplatelets regularly after surgery or was taking intermittently.

An attempt was made to note for other possible risk factors of stroke particularly diabetes mellitus, systemic hypertension and dyslipidemia.

The number of patients who expired during the study period was also noted. Thirty-day mortality (also termed perioperative mortality) i.e. death within 30 days of operation regardless of the patient's geographic location was

specially noted. The cause of death wherever available was noted. It was categorized into four main subgroups,

(a) Death due to cerebrovascular complication

(b) Cerebrovascular complication might have contributed to the death

(c) Death clearly had no relation to cerebrovascular complication

(d) Cause of death was not available.

STATISTICAL ANALYSIS

Statistical analysis was done with SPSS software version 15.0. For univariant analysis Fisher Exact T test and Pearson Chi-Square was used. For multivariant analysis logistic regression analysis was used. $P<0.05$ was taken as statistically significant. Finally Kaplan Meir survival analysis was done to calculate patients at risk of stroke in relation to time.

RESULTS

A total of 400 patients underwent surgery for prosthetic valve replacement in the period of July 1999 to December 2002. in case of three patients bioprostheses was used for valve replacement and hence were excluded. The remaining 397 patients comprised study population. These patients were followed up for next 5 years from the time of valve replacement.

A total of 56 patients (14%) expired during the study period. Of the remaining 341 patients, 290 patients completed the five-year follow up. Total 290 patients completed the five-year follow up. One hundred and ninety of these patients were interviewed by the author-166 by face to face and 24 by telephonic interview. For the remaining 100 patients, follow up was obtained through review of medical records. Fifty-one patients (12.8%) failed to complete 5 years follow up. Twelve of these 51 patients (21%) belonged to the neighboring state of Tamilnadu, many of them residing more than 500 kilometers from Trivandrum, and could not be contacted, while another 6 patients belong to other states distant from Kerala. It is possible that these patients are being followed up by local physicians. Although the remaining 33 patients belonged to Kerala, all attempts to contact them failed: letters sent to 10 patients returned from respective post offices due to change of address. For the remaining 22 patients, no information was available, despite repeated attempts to contact them through letters. Twelve of these patients had completed at least one year of follow up.

Complete follow up was therefore available for 87.2% (346/397) of the patients, close to the international standard of 90% required for such studies. Total follow up was 1884 patient-years (pt-yr).

PRIMARY OUTCOME

Thromboembolic cerebrovascular events including TIAs occurred in total 68 patients.10 patients had perioperative stroke and 58 patients had late stroke in follow up.

Perioperative stroke- 10 patients had perioperative stroke. Perioperative stroke was 2.5% (10/397). Total 5 patients had undergone AVR, MVR in 4 patients and DVR in one patient. Only patient expired due to perioperative complication. Rest of the 9 patients recovered completely and none of these patients had recurrence of stroke in follow up. There was no death directly related to perioperative stroke.

Late ischemic stroke- Late ischemic stroke occurred in 58 patients in follow up. These 58 patients were analyzed for possible risk factors for stroke in follow up. 11 patients had stroke recurrence in follow up. 9 patients had total 2 strokes, one patient had 3 strokes and one patient had 5 strokes, forming a total of 73 strokes during in 5 years follow up period.

These 73 episodes of stroke occurred in the 1884 patient-years follow up period, with a linearized rate of 3.9 per 100 patient-years (% pt-yrs).

DEMOGRAPHIC FACTORS

AGE- Mean age at the time of surgery of the entire cohort was 36.5 years (SD-13.2) with youngest patient being 4 year old and eldest patient being 68 year old. Most patients belonged to the fourth and fifth decade. Stroke occurred most frequently in the fifth and seventh decades, but this was not statistically significant.

Table 1

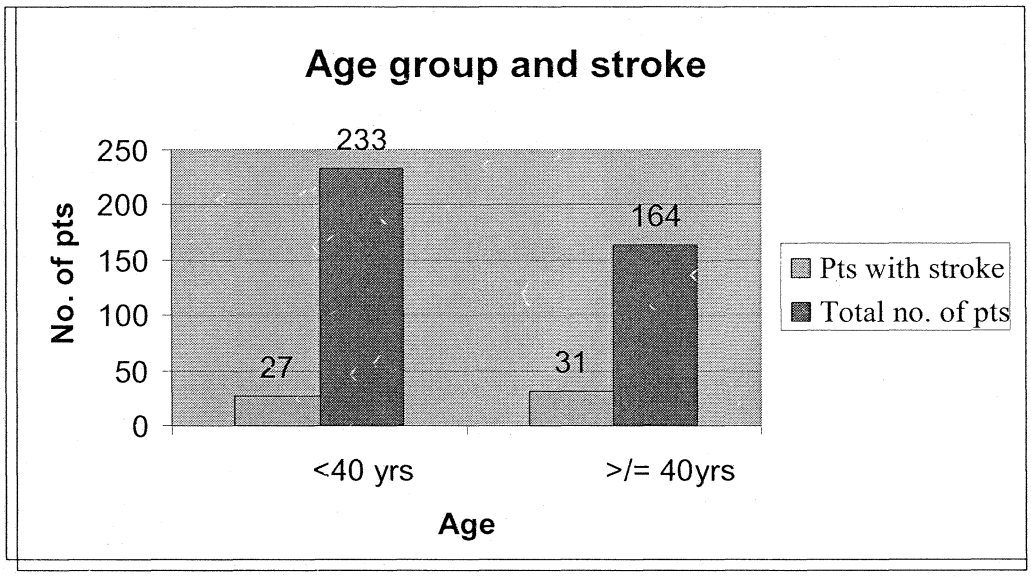
Age Group analysis Age			Outcome		
			Stroke	No Stroke	Outcome
Age Group	1 <20	Count	3	41	44
		Percentage	6.8%	93.2%	100.0%
	2 20-29	Count	8	65	73
		Percentage	11.0%	89.0%	100.0%
	3 30-39	Count	16	100	116
		Percentage	13.8%	86.2%	100.0%
	4 40-49	Count	20	71	91
		Percentage	22.0%	78.0%	100.0%
	5 50-59	Count	7	50	57
		Percentage	12.3%	87.7%	100.0%
	6 >=60	Count	4	12	16
		Percentage	25.0%	75.0%	100.0%
Total		Count	58	339	397
		Percentage	14.6%	85.4%	100.0%

Elderly vs. younger age group- age groups were divided in young age i.e. <40 years and old age >/= 40 years . Of the 233 patients aged <40 years, 27 patients (11.6%) developed stroke. Of the 164 patients aged > 40 years, 31 (19%) developed stroke. Though stroke was more common in patients >40 years, this was not statistically significant (p=0.127) in univariant analysis.

Table 2

Age Group analysis			Outcome		
			Stroke	No Stroke	Total
Age Group	1	<40 years	27	206	233
		% within	11.6%	88.4%	100.0%
	2	>=40 years	31	133	164
		% within	18.9%	81.1%	100.0%
Total		Count	58	339	397
		% within	14.6%	85.4%	100.0%

Figure 1



Gender- of 397 patients, 211 (53.1%) were males and 186 (46.9%) were females. Of the 58 patients with stroke, 30 were females and 28 were males. Stroke was more common in females but it was not statistically significant (p=0.421).

Figure 2

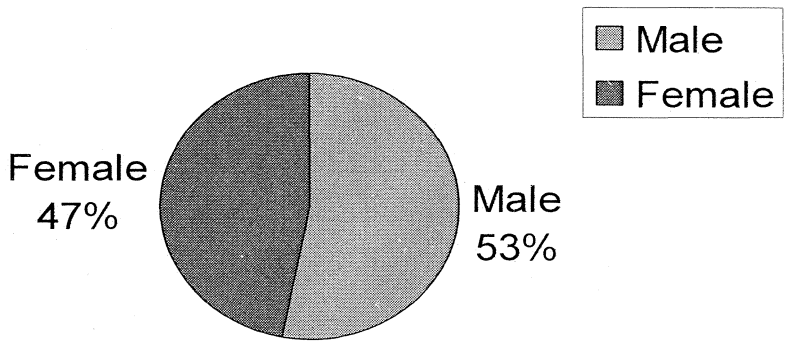
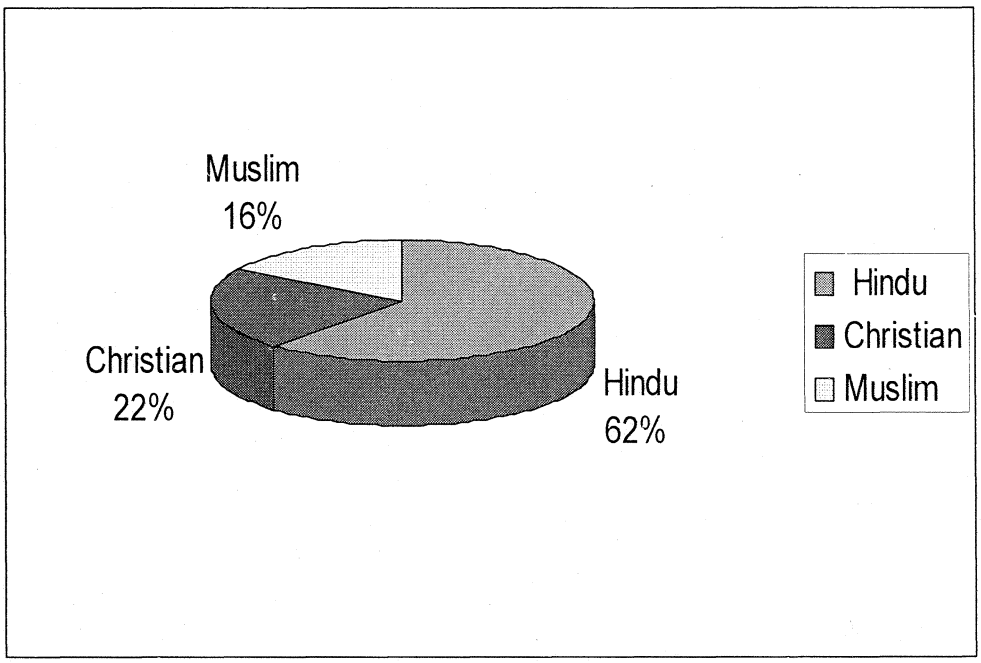


Table 3

Gender and stroke risk			Outcome		Total patients
			Stroke	No stroke	
Sex	1	Male	28	183	211
		% within	13.3%	86.7%	100.0%
	2	Female	30	156	186
		% within	16.1%	83.9%	100.0%
Total		Count	58	339	397
		% within	14.6%	85.4%	100.0%

Religion –Religion data was available for 355 (89.4%) patients. Majority (61.7%) were Hindus, followed by Christians (22 %) and Muslims (16.3%). For some of the (10.6%, N=42) patients, religion data was not available.

Figure 3

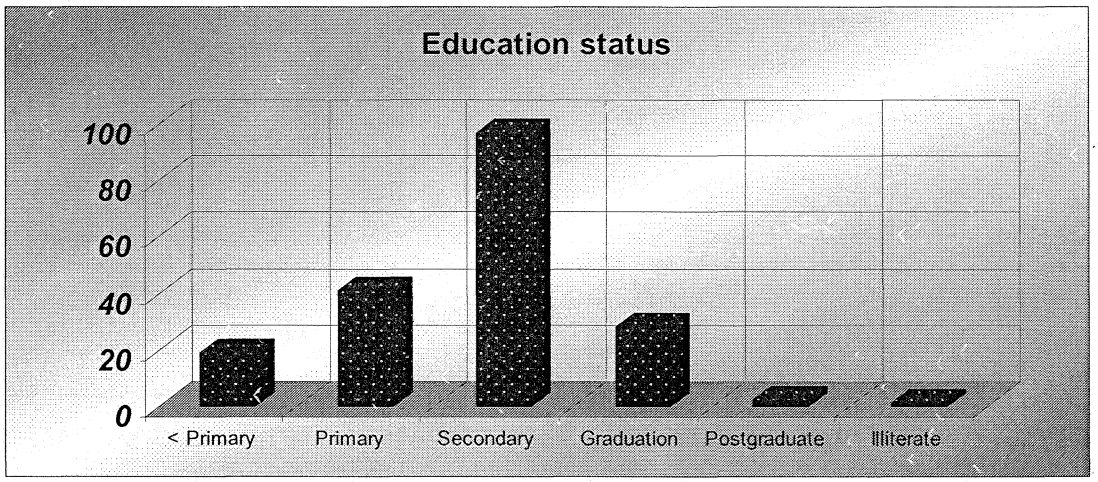


Education Status-Data on the education status was available for 188/397 patients (47.4 %). Primary education was taken as completed schooling of 5 years duration, while secondary education was taken as completed ten years of schooling. Majority (51.6%) had completed secondary level of education and 16% were either graduates or postgraduates. Remaining patients had either had either just received primary education (21.8%) or had not completed primary education (10%). Only one patient was totally illiterate, indicating overall good education status.

Table 4

Education Status		Frequency	Percent	Valid Percent	Cumulative Percent
1	< Primary	19	4.8	10.1	10.1
2	Primary	41	10.3	21.8	31.9
3	Secondary	97	24.4	51.6	83.5
4	Graduation	28	7.1	14.9	98.4
5	Postgraduate	2	.5	1.1	99.5
6	Illiterate	1	.3	.5	100.0
7	Total	188	47.4	100.0	
Missing		209	52.6		
Total		397	100.0		

Figure 4



Educational status was known in 31(53.4%) patients with stroke. Among the patients who had education equal to or less than primary level, 16.7% developed stroke and among the patients who had completed

secondary education, 16.4% had stroke. It indicates that lower level of education was not a risk factor for stroke.

Table 5

Education and stroke risk			Outcome		Total
			Stroke	No Stroke	
Education	1. </= Primary	Count	10	50	60
		% within	16.7%	83.3%	100.0%
	2. >/= Secondary	Count	21	107	128
		% within	16.4%	83.6%	100.0%
Total		Count	31	157	188
		% within	16.5%	83.5%	100.0%

Employment Status- data was not available for 51.6% (205/397) of patients. Of the available data of 192 patients, majority (54.2%) of patients were unemployed. Data on employment status was available for 31 patients with stroke. There was no significant difference among the patients who are employed and those who were unemployed. Employment status may be related to functional cardiac status also.

Table -6

Employment status		Frequency	Percent	Valid Percent	Cumulative Percent
1	Not employed	104	26.2	54.2	54.2
2	Employed	49	12.3	25.5	79.7
3	Self employed	39	9.8	20.3	100.0
	Total	192	48.4	100.0	
Missing		205	51.6		
Total		397	100.0		

Socio-Economic Status-Each patient at the time of registration in this institute was categorized according to income group of the patients.

Category A means family annual income of less than 4800/- Indian rupees. Category B1 means family annual income of 4800- 8400/- rupees. Category B means family annual income of 8400- 14400/- rupees. Category C means family annual income of 14400/- 24000/- rupees. Category D means family annual income of more than 24000/- rupees.

Table 7

Income category		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	A category	119	30.0	30.0	30.0
	B1	42	10.6	10.6	40.6
	B	73	18.4	18.4	58.9
	C	24	6.0	6.0	65.0
	D	139	35.0	35.0	100.0
	Total	397	100.0	100.0	

One hundred and sixty-one patients (40.6%) belonged to low socioeconomic group (Category A and B+), 97 (24.4%) belonged to middle economic group (category B and C), and the remaining 139 patients (35%) belonged to higher economic group (Category D). Majority of low income patients (119/161, 75%) belonged to very poor economic category, usually below poverty line. There was no statistically significant difference in stroke incidence between different socioeconomic categories (p=0.081), although stroke occurred more frequently in Category C patients.

Table 8

Socio-economy status and stroke risk			Outcome		
			Stroke	No Stroke	Total
Income category	A	Count	14	105	119
		% Within	11.8%	88.2%	100.0%
	B1	Count	8	34	42
		% Within	19.0%	81.0%	100.0%
	B	Count	6	67	73
		% Within	8.2%	91.8%	100.0%
	C	Count	7	17	24
		% Within	29.2%	70.8%	100.0%
	D	Count	23	116	139
		% Within	16.5%	83.5%	100.0%
Total		Count	58	339	397
		% Within	14.6%	85.4%	100.0%

Residential Status- Residential status data (urban/ rural) was available in 283 patients (71.3%), and for 39/58 patients with stroke. For others, it was not possible to ascertain the residential status from the given address. Majority (75.6%) of the patients belonged to rural background, rest 24.4% were from urban background. Of the 69 patients from urban background, 5 patients had stroke (7.2%), while 34 of 214 patients (15.9%) from rural background had stroke. Although more patients from rural background had stroke, difference was not statistically significant (p=0.074).

Table 9

		Frequency	Percent	Valid Percent	Cumulative Percent
1	Urban	69	17.4	24.4	24.4
2	Rural	214	53.9	75.6	100.0
	Total	283	71.3	100.0	
Missing		114	28.7		
Total		397	100.0		

Figure 5

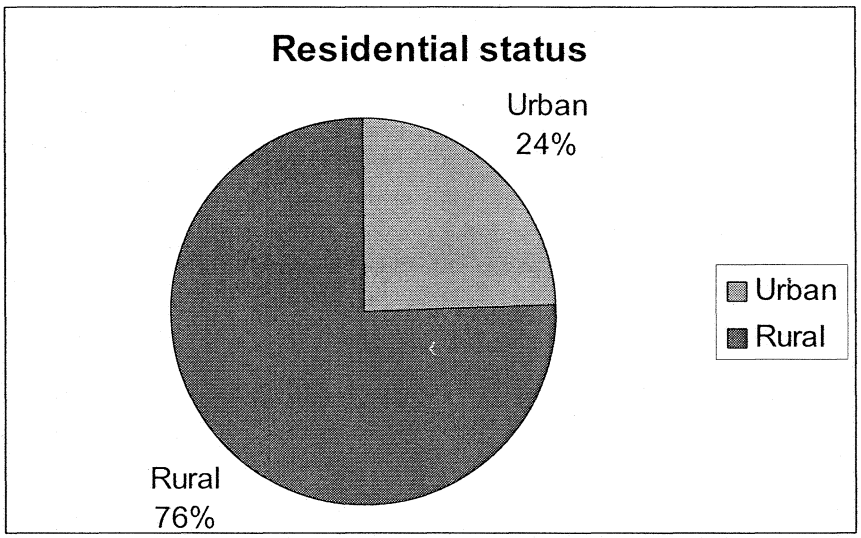


Table 10

Residential status and stroke risk			Outcome		Total
			Stroke	No Stroke	
Residential status	Urban	Count	5	64	69
		% within	7.2%	92.8%	100.0%
	Rural	Count	34	180	214
		% within	15.9%	84.1%	100.0%
Total		Count	39	244	283
		% within	13.8%	86.2%	100.0%

SURGERY- Thirty-three patients underwent emergency valve replacement, while others (n=364) underwent elective surgeries. Twenty patients with previous valve replacement underwent re-do surgery.

Concomitant coronary artery bypass grafting was undertaken in 10 patients, while 18 patients underwent closure of ventricular septal defect, and 11 patients underwent closure of atrial septal defect along with valve replacement.

Mortality-A total of 56 patients (14.1%) expired during the 5 years of follow up. Out of total expiry, majority of the patients were having MVR (41), followed by AVR (10) and lastly DVR (5). Mortality rate was high among MVR patients (19.2%), followed by AVR (9%), least being with DVR (6.8%). Seventeen (30.4%) patients expired in perioperative period i.e.

within one month of surgery, nine of whom had undergone emergency valve replacement.

Of the 33 patients who underwent emergency valve replacement surgery, 10 (30.3%) patients expired: 9 (90%) expired in the perioperative period and one patient 3 years after surgery.

Perioperative mortality- 17 patients expired in perioperative period i.e. within one month of surgery forming a perioperative mortality rate of 4.3 %. 9 of these 17 patients with perioperative mortality had emergency surgery done for valve replacement. Perioperative mortality was 2.2% (8/364) for the elective patients and 27.3% (9/33) for patients with emergency valve replacement.

Emergency MVR was performed in 23 of the 33 patients (70%): perioperative mortality occurred in 5 (21.7%). Two of 6 patients (33%) with emergency AVR expired in perioperative period. Four patients had emergency DVR, 2 (50%) of whom died perioperatively, indicating high mortality for emergency AVR and DVR.

Late mortality- 39 patients (69.6% of total expiry) expired in follow up with linear mortality rate of 2.1% patient-years. The cause of late mortality in 39 patients was as follows.

Table 11

Cause of late expiry		Frequency	Valid Percent	Cumulative Percent
1.	only due to stroke	2	5.1	5.1
2.	stroke + systemic cause	3	7.7	12.8
3.	other cause	25	64.1	76.9
4.	unknown	9	23.1	100.0
	Total	39	100.0	

Two patients (5.1%) expired due to fatal stroke. One had malignant infarct while the other developed hemorrhagic transformation. Both patients expired within one week of the stroke. Both had SEP as mitral valve prostheses. First patient had completed 3 years of surgery and the other had completed 4 year of surgery.

First patient had suffered total 5 strokes, and three of them occurred while the INR at admission was within range but with infrequent monitoring of PT-INR and poor compliance to VKA. His INR was 65% TTR in the next 10 months after 4th stroke and was doing fine. But in next 6 months his time interval between INR monitoring was significantly long (9-13 weeks) and INR was only 30% TTR just preceding the fatal stroke and at the time of this fatal stroke his INR was only 1.57.

The second patient had no complication prior to this stroke. She was operated for ASD repair along with MVR using SEP. She was on oral anticoagulation and antiplatelets. No PT INR values were available for this patient before stroke. Her INR at the time of stroke was only 1.48. She developed hemorrhagic conversation of stroke.

Two patients had stroke in the preceding few days prior to expiry but cause of death was not directly attributed to stroke. Both had SEP heart valve prostheses. Other patient expired with in 1 week of stroke. Though INR at that time was not available, patient was admitted subsequently and he expired secondary to systemic infection and septicemia.

25 patients expired either due to documented cardiac complication or due to other systemic complication but had no stroke in the preceding few weeks. Cause of death was not clear in rest of 9 patients.

Type of valve surgery- Replacement of mitral valve was done in 213/397 (53.6%), aortic valve in 111/397 (28%) patients, and double valve replacement (both aortic and mitral) in 73/397(18.4%) indicating that majority of the surgery for valve replacement was done for mitral valve followed by aortic valve.

Only three varieties of valves were used. 1. The Starr–Edwards's caged ball (SEP) 2.The Medtronic–Hall tilting disc valve (MH) and 3. The Chitra tilting disc valve (CHV).

Total valves used in 397 patients were 470, of which SEP was most commonly used, in 287(61%) (21/111 AVR, 201/213 MVR and in case of DVR at aortic position in 4/73 and mitral position 61/73). This was followed by Medtronic Hall valve (MH) in 142 (30.3%) (74/111 AVR, 10/213 MVR, and in DVR at aortic position in 53/73 and mitral position 5/73) and lastly Chitra Heart valve (CHV) in 41 (8.7%) (16/111 AVR, 2/213 MVR, and in DVR at aortic position in 16/73 and mitral position 7/73)

Table 12

Type of valve	AVR	MVR	DVR		Total
			AVR	MVR	
CHV	16	2	16	7	41
MH	74	10	53	5	142
SEP	21	201	4	61	287
Total	111	213	73	73	470

Stroke in relation to valve- A total of 68 patients had stroke, in 12 patients stroke occurred within one month and out which in 10 patients it occurred within one week and strokes within one week were taken as perioperative complication. Perioperative stroke rate was 2.5% (10/397); none of the patient had follow-up stroke. Therefore, only stroke as a long term complication of anticoagulant therapy in mechanical valve patients were analyzed in detail in relation to valve and prostheses.

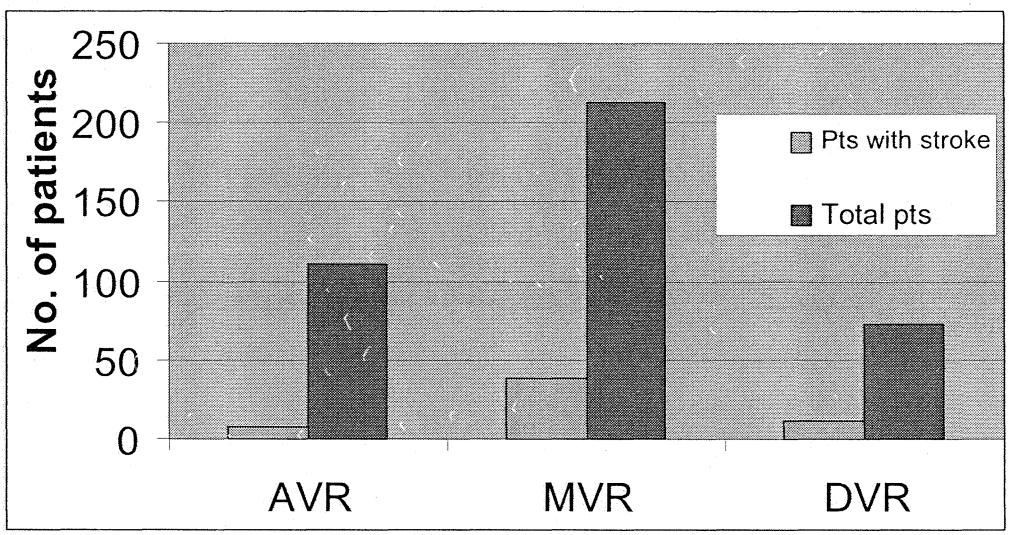
Total number of patients with late complication after surgery as stroke was 58. Out of 111 patients with AVR, 7 developed strokes; of 213 patients with MVR, 38 developed stroke; and of 73 patients with DVR 13 patients developed stoke. Overall risk for stroke was 7.2% in AVR, 17.8% for MVR and 16.4% for DVR. Patients with MVR had the highest risk of stroke, which was statistically significant ($p<0.05$).

Table 13

Type of vave replacement			Outcome		Total
			Stroke	No Stroke	
Valve	1. AVR	Count	8	103	111
		% within Valve	7.2%	92.8%	100.0%
	2. MVR	Count	38	175	213
		% within Valve	17.8%	82.2%	100.0%
	3. DVR	Count	12	61	73
		% within Valve	16.4%	83.6%	100.0%
Total		Count	58	339	397
		% within Valve	14.6%	85.4%	100.0%

Chi-square tests	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	6.853(a)	2	.032
N of Valid Cases	397		

Figure 6



AVR and Stroke -If we analyze late stroke of the 58 patients in relation to AVR, total 7 had AVR forming 12.7% of patients with stroke. If individual valve was compared at aortic position, 5.4% of the patients with MH valve had stroke while 6.3% of the patients with CH valve had stroke as compared to patients with SEP prostheses where14.3 % had stroke indicating higher chances of stroke with SEP. But this difference was not statistically significant (p=0.375)

Table 14

AVR and Stroke			Outcome		
			Stroke	No Stroke	Total
AVR prostheses	1 CHV	Count	1	15	16
		% within	6.3%	93.8%	100.0%
	2 MH	Count	4	70	74
		% within	5.4%	94.6%	100.0%
	3 SEP	Count	3	18	21
		% within	14.3%	85.7%	100.0%
Total		Count	8	103	111
		% within	7.2%	92.8%	100.0%

MVR and Stroke-Comparing the type of valve prostheses at mitral position, none of the two patients with CHV valve had stroke, while stroke occurred in 20% of the patients with MH prostheses and 17.9% of the patients with SEP, indicating that both MH and SEP prostheses at mitral valve had a

higher propensity for development of stroke, but this was not statistically significant p=0.792).

Table 15

Stroke in MVR			Outcome		Total
			Stroke	No Stroke	1
Prostheses	1 CHV	Count	0	2	2
		% within	.0%	100.0%	100.0%
	2 MH	Count	2	8	10
		% within	20.0%	80.0%	100.0%
	3 SEP	Count	36	165	201
		% within	17.9%	82.1%	100.0%
Total		Count	38	175	213
		% within	17.8%	82.2%	100.0%

Stroke in DVR- Twelve patients with DVR had stroke. Correlation of stroke with type of valve prostheses was complex. If patients had both aortic and mitral valve as CHV then there was no stroke –0/7 patients. If patient had both valves as MH, again there was no stroke –0/5 patients but if both valves were SEP, the stroke was 25% (1/4). If the valve were of different types at different sites, CHV at aortic and SEP at mitral position, stroke incidence was 11.1% (1/9) and if MH at aortic and SEP at mitral position, stroke incidence was 20.8% (10/48). Overall features suggest that in case of DVR, use of SEP either at single position or at both positions carries a higher risk of stroke. This difference was however not statistically significant.

Table 16

Stroke in DVR			Outcome		Total
			Stroke	No Stroke	1
Prostheses	1. CH+CH	Count	0	7	7
		% within	.0%	100.0%	100.0%
	2. CH+SEP	Count	1	8	9
		% within	11.1%	88.9%	100.0%
	3. MH+MH	Count	0	5	5
		% within	.0%	100.0%	100.0%
	4. MH+SEP	Count	10	38	48
		% within	20.8%	79.2%	100.0%
	5. SEP+SEP	Count	1	3	4
		% within	25.0%	75.0%	100.0%
Total		Count	12	61	73
		% within	16.4%	83.6%	100.0%

Type of prostheses irrespective of position and stroke-in attempt to correlate association of stroke incidence among all three different prostheses, irrespective of valve position, a comparative analysis was done, in which in case of DVR, if two different prostheses used, were excluded.

Table 17

All surgeries with single type prostheses			Outcome of Pts		Total
			Stroke	No Stroke	
Prostheses type	1 only CHV	Count	1	24	25
		% within	4.0%	96.0%	100.0%
	2 only MH	Count	6	83	89
		% within	6.7%	93.3%	100.0%
	3.Only SEP	Count	40	186	226
		% within	17.7%	82.3%	100.0%
Total		Count	47	293	340
		% within	13.8%	86.2%	100.0%

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	8.622(a)	2	.013
N of Valid Cases	340		

Isolated CH valve prostheses were used in 25 patients and only one had a stroke indicating risk of 4% with CH valve. In patients with isolated MH, out of 89 patients, 6 had stroke indicating risk of 6.7%. In patients with isolated SEP, out of 226 patients with MVR, 40 patients developed stoke

indicating risk of 17.7%. Risk for stroke was lowest in patients with CH as compared to MH and risk was highest with SEP. Out of total available data of 340 prostheses, patients with SEP had a statistically significant increased risk of stroke ($p<0.05$).

Caged Ball valve versus Tilting disc-In attempt to see the comparison of tilting disc alone with versus combination with caged ball valve or isolated caged ball valve, irrespective of position of valve in relation to occurrence of stroke, Stroke was more common in patients with caged ball valve either used alone or in combination with tilting disc valves than tilting disc valves. SEP alone or in combination with MH/CHV was found to have statistically significant higher risk than MH or CH ($p=.002$)

Table 18

Cagged Ball vs Tilting Disc valves			Outcome		
			Stroke	No Stroke	Total
Prostheses Types	1. Tilting Disc valves	Count	8	115	123
		% within prostheses	6.5%	93.5%	100.0%
	2. Cagged Ball	Count	50	224	274
		% within prostheses	18.2%	81.8%	100.0%
Total		Count	58	339	397
		% within prostheses	14.6%	85.4%	100.0%

ANTICOAGULATION AND STROKE-

All the patients on discharge were given written information about the use of anticoagulation in regional language and were also counseled. Patients were advised to repeat their INR at least monthly. There were three types of VKA therapy used.

1. Warfarin(Warf)
2. Phenindione (Dindivan)
3. Acenocoumarol (Acitrom)

Data is available for 349 patients for type of vitamin K antagonist tablets. Majority of the patients (252, 72.2%) were taking Phenindione while 65 (18.6%) patients were on Warfarin (Warf) and rests of 32 (9.2%) patients were taking Acenocoumarol. Stroke frequency was maximum in patients taking tablet Acenocoumarol - 21.9%, followed by Phenindione -15.5% and least with Warfarin - 12.3% but this difference was not statistically significant(p=0.472)

Table 19

Type of anticoagulation			Outcome		Total
			Stroke	No Stroke	
Last VKA	1. Warfarin	Count	8	57	65
		% within	12.3%	87.7%	100.0%
	2. Dindivan	Count	39	213	252
		% within	15.5%	84.5%	100.0%
	3. Acitrom	Count	7	25	32
		% within	21.9%	78.1%	100.0%
Total		Count	54	295	349
		% within	15.5%	84.5%	100.0%

Knowledge about VKA therapy- importance of oral anticoagulation and its potential complications with emphasis on stroke-related symptoms were especially enquired from patients who were personally interviewed. Of the available data of 184 patients, Only 75 (40.8%) patients had detailed knowledge regarding various potential complications related to over-or under anticoagulation, and the need for meticulous monitoring of INR. Sixty-four patients (34.8%) had some knowledge about the various possible complications, but 24.5% (45 patients) had no knowledge at all about the risks.

Table 20

Knowledge about anticoagulation		Frequency	Percent	Valid Percent	Cumulative Percent
1	no awareness	45	11.3	24.5	24.5
2	some awareness	64	16.1	34.8	59.2
3	fully aware	75	18.9	40.8	100.0
	Total	184	46.3	100.0	
Missing System		213	53.7		
Total		397	100.0		

On data analysis knowledge about anticoagulation was found to have no relation with risk of stroke.

VKA compliance and stoke-Limited data of 169 patients was available for the compliance of oral anticoagulants. 110 patients (65.1%) had very good

compliance with VKA, while 23 (13.6%) patients with poor compliance and rest 36 (21.3%) patients were missing VKA occasionally. Overall 2/3 rd patients had very good compliance and 1/7th patient had poor compliance.

Table 22

Compliance with VKA		Frequency	Percent	Valid Percent	Cumulative Percent
Regularly	1 very regular	110	27.7	65.1	65.1
	2 frequently missed	23	5.8	13.6	78.7
	3 Miss occasionally	36	9.1	21.3	100.0
	Total	169	42.6	100.0	
Missing	System	228	57.4		
Total		397	100.0		

PT/INR monitoring-Adequate data enough to analyze for percentage in therapeutic range was available only for 84 patients. Majority of the rest interviewed patients (106/190) were not monitoring their INR charting enough to analyze. Reason for not doing INR monitoring was financial problem in 47 (44.3%) and non availability of good quality laboratory to test prothrombin test in 17(16.3%) patients. No clear reason was available for rest of the patients.

Total numbers of INR values including all patients were 3064, with a mean of 36.8 (SD-19.3) PT INR values for each patient. Mean days of repeating INR was 37 (SD-13.5) days, Out of total 89930 days of available

INR data for all patients, INR was in therapeutic range for 41518.05 days indicating total of 46.2% TTR (percentage of time in therapeutic range).

It was difficult to analyze relation of stroke with anticoagulation in view of the fact that data was available only for 84/397 (~ $1/5^{th}$) of the patients. Out of which only 21 patients developed stroke during follow up. These 21 patients developed total 31 strokes during follow up. There was no data available for INR in the preceding 3 months of stroke during 15 of these episodes. It indicates that these patients had not tested their prothrombin time in the preceding 3 months. In rest of the 16 strokes, %TTR was less than 40% in 75% (12/16) patients in the preceding 3 months before stroke,. Though one patient also had stroke while his INR in the preceding 4 months was 86% TTR and at the time of stroke also, his INR was 2.58 (in therapeutic range).

Overall there was a trend for the patients with stroke having either low percentage of time in therapeutic range in the preceding three months or not monitoring there prothrombin time for continuously many months.

Prothrombin Time at the time of Stroke- In patients with perioperative stroke, the PT value was available in 6/10 patients and INR was less than 2.0 in all patients except one patient with DVR who had INR = 2.07 at the time of stroke indicating INR was less than therapeutic range in all of these patients at the time of stroke

A total of 73 strokes happened in 58 patients with follow up stroke. Prothrombin time with INR data at the time of stroke was available in 49/73 (67.1%) of follow up strokes. PT was less than 2 in 22 episodes, 2-2.5 in 10 episodes, and between 2.5 to 3.5 in 12 episodes. 5 episodes happened when INR was more than 3.5.

Position, type of heart valve and stroke: Total 9 strokes occurred in patients with AVR with INR at the time of stroke available for 7 patients. 3 strokes occurred with MH prostheses (target INR 2-3); one patient had PT INR in range at the time of stroke -INR 2.2, other 2 patients had INR below range- 1.0 & 1.78. With CHV, Stroke occurred in only in one patient with INR of 1.0. With SEP, 3 stokes happened, all at 1.87, 1.9 and 1.38.

With MVR (target INR 2.5-3.5), total 50 strokes occurred. INR data at the time of stroke is available for 34 patients. Stoke occurred in one patient with MH occurred at INR 2.07. With SEP- total stroke 33 happened, where INR data is available, 20 Strokes with INR <2.5; 8 strokes with INR between 2.5-3.5; and 5 strokes with INR above 3.5.

With DVR – a total of 14 strokes occurred, 4 with INR <2.5 and 4 strokes with INR in therapeutic range (2.5-3.5). Rest of the 6 patients INR was not available at the time of stroke.

Overall 13 (26.5%) strokes occurred when INR was in therapeutic range and 5 (10.2%) embolic strokes happened when INR was above the therapeutic range but majority (63.3%) strokes happened when INR was below therapeutic range.

Other Vascular Risk Factors (DM/HTN/Dyslipidemia) and stroke- Other risk factors of stroke were found in 56 patients out of which, 22 were having diabetes and equal no of patients had systemic hypertension and 12 patients and dyslipidemia. In analysis of stroke in relation to these risk factors , presence of any of these factor was associated with increased risk of stroke but it was not statically significant(p=.15).

Table 23

Other medical illness and stroke DM/HTN/Dyslipidemia			Outcome		
			Stroke	No Stroke	Total
Other Illness	1.present	Count	12	44	56
		% within	21.4%	78.6%	100.0%
	2 absent	Count	43	264	307
		% within	14.0%	86.0%	100.0%
Total		Count	55	308	363
		% within	15.2%	84.8%	100.0%

4 of these patients had both diabetes and hypertension ,one (25%) of them developed stroke, two of the patients had diabetes mellitus and dyslipidemia and one (50%) developed stroke, indicating presence of more risk factor is associated with increased risk of stroke but data was small enough to analyze statistically.

Antiplatelets and stroke-Data was available for 365 patients, of which only 24 patients were taking antiplatelets, mainly for cardiac indications (associated coronary artery disease). In 7 more patients on antiplatelets, the indication was not clear and it was given intermittently. In relation to the stroke with antiplatelets, patients on regular antiplatelets were less likely to develop stroke but this was not statistically significant.

Table 24

Antiplatelets and stroke			Outcome		Total
			Stroke	No Stroke	
Taking antiplatelet	1Regular	Count	3	21	24
		% within	12.5%	87.5%	100.0%
	2 Irregularly	Count	1	6	7
		% within	14.3%	85.7%	100.0%
	3 Never	Count	53	281	334
		% within	15.9.1%	84.1%	100.0%
Total		Count	57	308	365
		% within	15.6%	84.4%	100.0%

Relation to drug interaction- was difficult to analyze as other medications used by the patients most often were, beta blockers, calcium channel blockers, diuretics, penicillin, digitalis and ACE inhibitors. None of these medications is known to cause significant drug interaction with oral anticoagulants.

Table 25

Multivariant analysis- Logistic regression test

	B	S.E.	Wald	df	P Value	Odds Ratio	95.0% C.I.for Odds Ratio	
	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
Age Group	.602	.302	3.984	1	.046	1.827	1.011	3.300
Income Group	.173	.189	.838	1	.360	1.189	.821	1.724
Prosthesis	1.024	.406	6.349	1	.012	2.783	1.255	6.171
VKA	-.056	.337	.028	1	.868	.946	.489	1.829
Sex	.054	.303	.032	1	.858	1.056	.583	1.912
Constant	-4.743	1.116	18.051	1	.000	.009		

a Variable(s) entered on step 1: Age Group, Income Group, Prosthesis, VKA, Sex.

After logistic regression method, adjusted odd ratios were maximum (2.783, 95% CI-1.255-6.171) for caged ball prostheses (SEP) prostheses followed by age group of more than or equal to 40 years (1.827, 95% CI 1.011-3.3). It indicates highest risk for stroke in patients prosthetic valves was SEP prostheses (p=0.12) followed by age group of >/= 40 years (p=0.46) patients.

Outcome of stroke –

Perioperative stroke- there was total 10 patients with perioperative stroke. 5 (50%) patients had recovered almost completely at the time of last follow up with mRS of 0 to 1. One patient had some residual deficits with mRS of 2. Four patients expired, three patients expired during recovery period of stroke due to other systemic complications and one patient expired 6 weeks after stoke.

Stoke in follow up – in 58 patients, out of total 73cerebral ischemic events occurred with following details.

1. Twenty-one were TIAs
2. Forty-four were minor stroke with minimal residual deficits.

3. Six strokes were major enough to cause some disability.

4. Two Strokes were fatal and resulted in expiry. (See details in mortality). Including these two patients, total 6 patients died with stroke as a primary or contributing cause. 3 developed some other systemic problem in recovery from stroke and cause of death was not known in other patient.

Majority of patients made near complete recovery with no residual deficits. MRS was zero for 24 patients, 1 for 21 patients and 2 for 6 patients. Only one patient had mRS of 3.

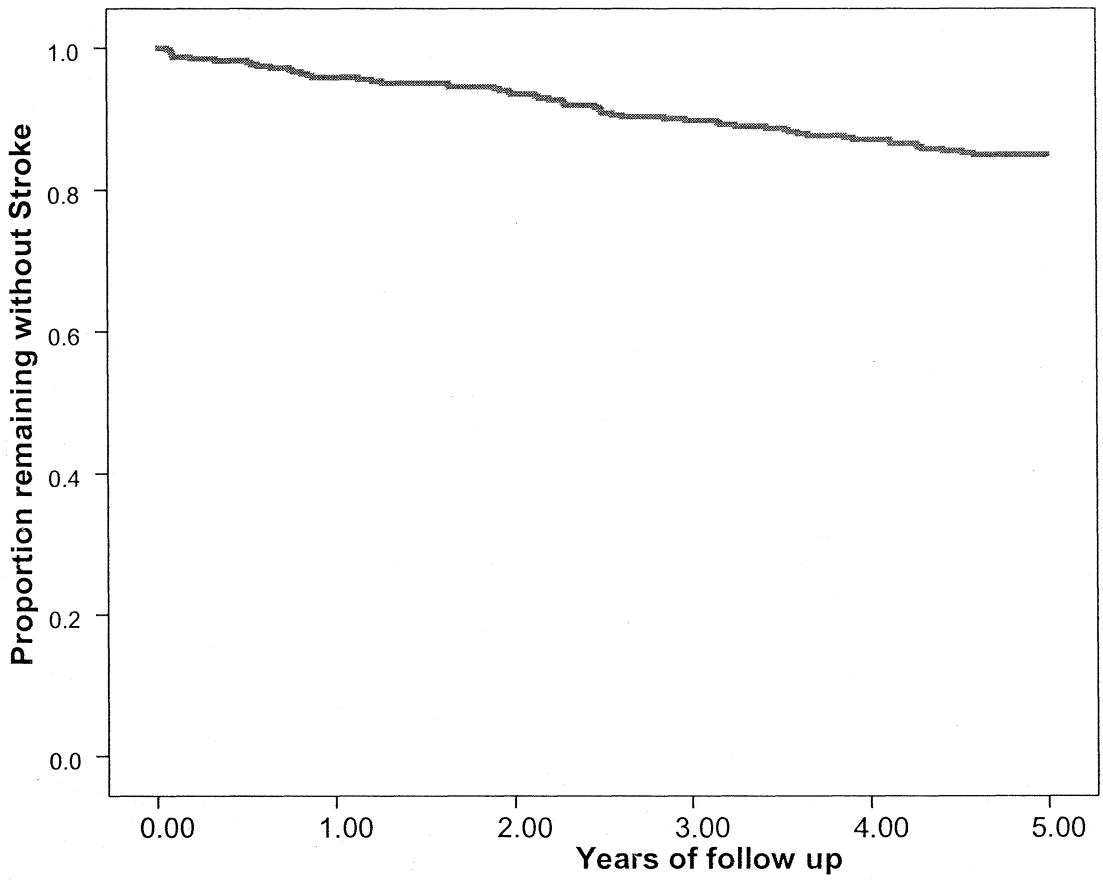
Table 26

Modified Rankin score	0	1	2	3	4	5	6	Total
Pts with perioperative stroke	1	4	1				4	10
Pts with stroke in follow up	24	21	6	1			6	58
Total Patients	25	25	7	1			10	68

It indicates that though the embolic stroke was the main complication in current study, overall outcome was good with 83.8% (57/68) patients with stroke having mRS of </=2.

Kaplan Meir Survival analysis-In relation to time, 95.7 % patients were free from stroke at one year, 93.3% patients were free from stroke at 2 years, 89.7% patients were free from stroke at 3 years, 87% patients were free from stroke at 4 years and 84.7% patients were free from stroke at 5 years of follow up.

Kaplan Meir Survival curve



Intracerbral hemorrhage- In our study there were only three patients with documented intracerebral hemorrhage, one patient had two episodes of subarachnoid hemorrhage within a gap of few days. Both the time prothrombin time was lower than therapeutic range 1.69 and 1.57, Patient was under treatment for culture negative infective endocarditis. He expired due to massive bleed with mass effect. Though cerebral angiography was not performed, in view of the presentation, it is likely that he had mycotic aneurysm with rupture as the cause rather than CNS bleed secondary to over-anticoagulation.

One other patient had intracerebral bleed with documented aneurysm after 11 month of follow up and expired due to infective endocarditis and intracerebral bleed.

Third patient had subdural hematoma due to high INR (3.74) and recovered completely in follow up. She had one episode of thromboembolic stroke at one month of follow up with INR 1.18 at the time of stroke. There was INR data available in between these episodes.

DISCUSSION

In the current study, 397 patients with prosthetic valve replacement were followed up for consecutive 5 years from the date of surgery. Complete follow up data was available for 87.2% patients with 12.8% dropouts during this period. Total follow up was 1884 patient-years. Most of the dropouts belonged to distant places or even to neighboring states, these patients rather would have preferred to have local follow up. Thus distance could be one factor accounting for some of these dropouts.

Mortality- A total of 56 patients (14.1%) expired during the follow up period, including 17 patients who expired in the perioperative period (perioperative mortality) and 39 patients during the subsequent follow up period. Stroke was primarily responsible for death in 2 patients and secondarily in 5 patients.

Perioperative mortality was 4.2%. Most of the early postoperative mortality (9/17) occurred in patients who underwent emergency valve replacement. For elective valve replacement perioperative mortality rate was 2.2 %. In the published literature, perioperative mortality ranged from 4.1%[51] to 6.9%[35], though figures for emergency valve replacement, as a separate group was not mentioned.

Late mortality in the current study was 2.1 per 100 patient-years, which was similar to other studies where mortality ranged from 2.5% per patients years for AVR to 4.4% for MVR[33] and 4.6% per patients years for all valve positions[13]

Ischemic stroke – The study was primarily designed to ascertain the incidence of cerebrovascular events as primary outcome. A total of 68

patients had ischemic stroke, 10 patients had perioperative (within one week of surgery) and 58 patients had late stroke.

Perioperative stroke- Perioperative stroke rate was 2.5% (10/397); and interestingly none of these patients had stroke in the subsequent follow up period, probably indicating a better subsequent care following an early adverse medical event or could be attributed to different mechanism responsible for early and late stroke. The incidence of perioperative stroke was similar to other studies.

Various studies have mentioned perioperative stroke risk, which varying from 0.5% to 5.7% depending on many other factors including age, associated surgery including concomitant coronary artery bypass grafts (CABG) etc[52]. Ruel et al[38] reported incidence of early postoperative stroke as 0.6% in patients with AVR and 1.35 with MVR, taking only major stroke into consideration.

In a study looking at all cerebral ischemic events in patients undergoing AVR and concomitant CABG has documented perioperative cerebral ischemic events of 4.5% which included 2.9% major stroke and 0.5 % TIA's and 1.1% RIND[53]. The present study included all cerebrovascular events including TIAs and the incidence of perioperative cerebral ischemic events was similar to the published data in literature.

The early perioperative stroke is a well-mentioned complication. The risk for thrombus formation associated with prosthetic heart valves is up to seven times greater within the first month after valve replacement than during the subsequent months and years, irrespective of the intra-cardiac position of the device[54]. Underlying pathophysiological factors are activation of the extrinsic and intrinsic coagulation systems by synthetic surfaces of the extracorporeal circulation, or by contact of blood with foreign surfaces

(sutures, sewing ring, occluder), or at sites of collagen or denuded tissue. Intraoperative strokes are typically the result of cerebral hypoperfusion due to intraoperative hypotension or decreased cardiac output or embolization related to bypass or vessel clamping. Emboli most often occur as either air emboli or atherosclerotic emboli[6].

Prothrombin time and INR at perioperative stroke

The method of optimal anticoagulation in perioperative period had been an issue of debate. During the initial phase of oral anticoagulation, INR even in the therapeutic range does not necessarily indicate sufficient anticoagulation because of the different half-lives of the coagulation factors[55]. Puri et al[56] found early low-dose oral anticoagulation alone as the safest regimen in early perioperative period with a low thromboembolic risk. Early supplementation with either UFH or LMWH, according to them, significantly increases the risk of hemorrhagic complications, without reducing the risk of thromboembolic events. In the present study INR at the time of stroke was available in 6 patients and all of them had INR below therapeutic range.

Late stroke during follow up

A total of 58 patients had 73 episodes of stroke in the follow up period, with a linearized rate of 3.9 per 100 patient-years (% pt-yrs). In relation to valve replacement it was 1.7 % pt-yrs for AVR, 4.9 % pt-yrs for MVR and 4.2% pt-yrs for DVR.

Other studies have mentioned thromboembolic events (including major and minor, peripheral and CNS) in the range of 1-1.8 per100 patient-years[13]. Akins et al[53] reported thromboembolic complication specifically as stroke of 1.1 per 100 patients-years, while Ruel et al[38] reported late stroke as 1.4% (AVR) to 2.3% (MVR) per 100 patient-years. Butchart et al[57] reported both

major and minor thromboembolic strokes. The linearized rates of minor events (transient or reversible ischemic attacks) were 1.7%/y for AVR, 3.2%/y for MVR, and 2.8%/y for DVR. The linearized rates of major stroke were 0.6%/y for AVR, 0.8%/y for MVR, and 0.6%/y for DVR. Total thromboembolic cerebrovascular events ranged from 2.3% to 4% per year. Vink et al[58] in a metanalysis of total thromboembolic events (not specified for stroke), noted incidence ranging from 0.1% to 3.7 % per 100 patient years with overall rate of 1% to 1.3% for AVR and 1.6% to 2% for MVR.

From India, only limited data is available for stroke in relation to prosthetic valves. Sankarkumar et al[35] in a multicentre study reported thromboembolic events of 1.6%- 2.4% /patient–years, while Bharat V.[37] reported a thromboembolic risk of (including valve thrombosis) 4.9 per 100 patient-years in a small number of patients (88 patients with 462 patient- years follow up).

Overall, our study showed an apparently higher incidence of cerebrovascular events as compared to other studies, especially in relation to MVR. This may be spurious, as we have included all events including TIAs as primary endpoints, and the latter formed 28.2% of total events.

However use of SEP was more frequent in our patients especially in MVR, which is now known to be more thrombogenic and currently is not a preferred prostheses in most of the places. The higher incidence of stroke in the present study definitely warrants a larger preferably prospective study looking at various factors including re-evaluation of postoperative medical management issues.

Vascular risk factor analysis-

Age and sex

Patients more than 40 years of age had more strokes than younger ones (18.9% vs 11.6%); though it was not statistically significant in univariate analysis but logistic regression analysis showed a significant Odd ratio for age.

Ruel et al[30] has reported that age more than 75 years was an independent risk factor for embolic stroke regardless of the site of implant or type of prostheses. The embolic stroke risk was 1.9 times higher in elderly patients with aortic prostheses, regardless of other risk factors and valve type, and 3.1 times higher for elderly patients with mitral prostheses. However atheroembolic or small vessel arteriosclerotic strokes could have contributed to the total figure in this study. So the trend in our study, observed between two groups, around 40 years of age, is less likely to be confounded by the presence of atherosclerotic disease and becomes more significant.

Female gender was an independent risk factor for embolic stroke in patients with aortic or mitral prostheses[30]. Women with prosthetic valves had approximately 1.7 times the embolic stroke risk of men, despite adjustment for other risk factors.

In our study also females had more strokes as compared to males (16.1% vs 14.6%), though it was not reaching statistical significance.

Other demographic factors

Educational status, employment status and socioeconomic status are also reported as risk factor in relation to stroke in general[43,44] but there was no statistically significant risk noted with these factors in prosthetic valve patients for stroke in our study.

In relation to residential status, stroke was more in rural background patients in our study but without any statistical significance. Higher risk in rural patients can be explained by lack of good quality medical/laboratory facility locally, especially for monitoring of PT INR.

To prove or disprove the role of these factors with regards to incidence of cardio embolic stroke larger study involving more number of patients is required.

Type and site of prostheses

For occurrence of stroke in patients with mechanical prosthetic valve, most significant risk factor was Starr-Edward Prostheses and location at mital valve. This is similar to observations from most of the studies[30, 33]. Only one study has reported more strokes following AVR than MVR[31].

In relation to type of prostheses used, the risk of stroke was maximum with SEP, followed by MH and least with CHV and this difference was statistically significant (p=0.013). Similar findings with caged-ball being more thrombogenic than tilting disc have been reported in other studies also [12, 29]. The more striking observation in our study is the performance CHV with regards to incidence of incidence of embolic cerebrovascular complications.

Hemorrhagic strokes

Only one patient in our study had intracranial bleed, subdural hematoma developing de novo, at an INR of 3.74. No one else had anticoagulation related CNS bleed.

Current study reports significantly higher incidence of ischemic strokes compared to hemorrhagic ones. A similar finding has been reported earlier

from this institute with thromboembolic episodes being more than ten times of anticoagulant related hemorrhage[34].

This probably indicates a tendency for maintaining INR on the lower side of therapeutic range. Tendency for under-anticoagulation is reported in another Indian study also. Kakkar et al[59] reported overall under anticoagulation for most period of anticoagulant treatment. Of a total of 1631 prothrombin time ratios and International Normalized Ratios recorded, only 17.8% were in the therapeutic range with 73% being sub-therapeutic.

Though CNS bleeding is reported as less common, the mortality rate is significantly higher than ischemic events in patients with prosthetic valve[35] and also raises difficult management issues.

With no studies showing higher incidence of bleeding when the guidelines for anticoagulation are strictly followed, physicians should be encouraged to maintain anticoagulation in the recommended range, rather than keeping it sub-therapeutic for fear of bleeding complications. However the international guidelines regarding optimal levels of anticoagulation can extrapolated to Indian population as such is debatable.

Anticoagulation and stroke

Less than 50% patients were having adequate knowledge about need of anticoagulation and its potential complications. Rest had either partial or no knowledge about the possible complications including stroke. Though not noted to associate with stroke statistically in the present study, this observation indicates the need to educate these patient and the caregivers adequately.

The average time interval between consecutive PT INR monitoring in this study was 37 days (SD-13.5). There is no clear-cut guideline for accepted time interval for monitoring PT INR. American Heart Association in

conjunction with the American College of Cardiology produced a foundation guide to warfarin therapy in 2003 and advised for a maximum gap of 4 weeks in patients with stable INR[60]. In a recent study a gap of 3 weeks is recommended[61].

In relation to INR, it was difficult to derive any conclusion with the available data. But patients with stroke have not monitored INR continuously for few weeks or their INR values were low at the time of stroke or %TTR was low in the preceding weeks. This variation in achieving target INR could be attributed to a variety of factors, including noncompliance in taking the correct dose regularly due to illiteracy, inadequate information, poverty, or at times due to laboratory variations.

Butchart E G et al[62] reported considerable variation in anticoagulation intensity in comparison of embolic episodes, yet it proved impossible to relate embolic episodes to levels of anticoagulation, whether the INR data was looked at in terms of the overall INR record for the patient, or only the values preceding the embolic event. There was no association found between the occurrences of a thromboembolic event with any of the following: (1) Mean level of INR, (2) Median level of INR, (3) 25th percentile of INR, (4) INR in the 6 months preceding a TE event, (5) INR immediately preceding a TE event.

From the present study, though it was not possible to correlate INR and stroke in view of inadequate data, some important observations could be made out.

1. Majority of the patients had inadequate knowledge about the importance of regular monitoring. Only one fifth of the patients were maintaining proper INR charts.

2. The frequency of checking PT/INR was far less than recommended a mean value of 37 days (SD-13.5).
3. Many patients with stroke had not monitored their PT INR even for 3-4 months continuously before stroke, which may be one of the most important risk factor for stroke in these patients.
4. Most of the stroke (74%) occurred while PT INR were less than therapeutic range, though single value at the time of stroke may not be the only responsible factor but still it again indicate poor management of anticoagulation.
5. There was a tendency of keeping the INR in lower side of recommended range, which has resulted in more ischemic events.

In a recent metanaysis from 45 studies involving 71,065 subjects, Overall, 44% (95% confidence interval [CI] 39%–49%) of hemorrhages occurred when INRs were above the therapeutic range, and 48% (95% CI 41%–55%) of thromboemboli took place when below it[63]. This study concluded that improving anticoagulation control could decrease the likelihood of almost half of all anticoagulant-associated adverse events.

A recent randomized, multicenter trial evaluated a structured teaching and self-management program for anticoagulated patients in comparison with conventional anticoagulation management by family physicians and found not only more INR values in the target range but also higher patient satisfaction scores on a quality-of-life questionnaire[64].Anticoagulation self-management can improve INR profiles up to 2 years after prosthetic valve replacement and reduce adverse events.

Current indications of prosthetic rather than biologic valve implantations may be extended if the benefit of INR self-management is shown by future studies with longer follow-up[65]

Because most of the adverse events occur in the period of under- or over-coagulation, it is plausible to assume that the risk for embolism and bleeding will decrease with a more stable level of anticoagulation. In addition, a major effect of anticoagulation control on the long-term survival was shown in a recent study[66], demonstrating that a high variability in INR was the strongest independent predictor of reduced survival. This observation emphasizes the importance of adequate management of anticoagulation.

Several developments in therapeutic quality control have improved the safety and efficacy of VKA therapy. Monitoring of VKA therapy by a specialized anticoagulation clinic reduces the bleeding and thromboembolic event rates. More recently, home testing of the intensity of anticoagulation by means of a portable coagulometer that performs an INR on a single drop of capillary blood has become available. The INR home testing appears to be a safe and efficient anticoagulation control method, which results in a higher percentage of target range values compared with the conventional laboratory-based testing regimen [67,68]

Noncompliance to medication is another risk factor. IN-RANGE study, a study on patient adherence in relation to oral anticoagulants has described poor adherence as a potentially major source of poor anticoagulation control[69].

To conclude, potential for optimal anticoagulation to improve survival in patients with prosthetic heart valves seems enormous and may outweigh the influence of other factors.

Traditionally, surgeons seek technical solutions to improve long-term survival for their patients, but in the case of valve-replacement surgery, ensuring good long-term anticoagulation control is likely to have the greatest effect on survival. It is no longer sufficient simply to begin a patient on VKA and hope for the best. Cardiac surgeons and physicians caring for patients with prosthetic valves have a major responsibility to ensure that their patients receive the best possible anticoagulation management.

CONCLUSION

Our study reports a slightly higher incidence of strokes in patients with mechanical prosthetic valve, compared to published literature. However the trend of these complications with regards to type and location of prosthesis is similar. Based on our observations, certain recommendations can be made to improve management of anticoagulation and thus the long term outcome of these patients.

Recommendations

1. The awareness of patients and caregivers regarding need for compliance, monitoring and potential complications of VKA therapy need to be improved by appropriate education and counseling.
2. Patients need to be encouraged to maintain proper record of PT /INR.
3. Calculating %TTR for each patient appears to be promising in assessing the adequacy of anticoagulation over a span of time (which can guide like Hb1Ac in case of diabetes mellitus and could alert the patient in case of low TTR) and would be of help in guiding the overall management.
4. Complications, if any, should be interpreted in relation to both INR and TTR, so that a safer TTR can be calculated for individual patient.
5. Patients with age more than 40 years, patients with prosthetic valve in Mitral location and patients with Star Edward Prosthesis need closer monitoring.
6. Educating patients, caregivers as well as the primary care physicians is of utmost importance for optimal management of anticoagulation and thus assuring an event free survival.
7. A prospective study involving a larger cohort with systematic follow up is likely to clarify areas that were less clear in the present study.

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