THROMBOEMBOLIC AND BLEEDING COMPLICATIONS, RISK FACTORS INVOLVED AND ANTICOAGULANT ADEQUACY AMONG PATIENTS WITH MECHANICAL HEART VALVES AS SEEN AT MUHIMBILI NATIONAL HOSPITAL

A RETROSPECTIVE COHORT STUDY

BY

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A dissertation submitted in partial fulfillment of the requirements for the degree of Master of Medicine (Internal Medicine) of the University of Dar es Salaam

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CERTIFICATION

The undersigned that they have read and hereby recommended for acceptance by the University of Dar es salaam a dissertation entitled: ***"THROMBOEMBOLIC AND BLEEDING COMPLICATIONS, RISK FACTORS INVOLVED AND ANTICOAGULANT ADEQUACY AMONG PATIENTS WITH MECHANICAL HEART VALVES AS SEEN AT MUHIMBILI NATIONAL HOSPITAL"*** in partial fulfillment of the requirements for the degree of Master of Medicine (Internal Medicine) of the University of Dar es salaam.

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DEDICATION

"To my parents and my son Alphonce Jinai for their love and encouragements"

ABSTRACT

Background: Thromboembolic and bleeding complications are the main causes of morbidity and mortality in patients with mechanical heart valves. The magnitude and risk factors for these complications in Tanzania has not been established.

Methods: A retrospective cohort study was conducted among patients with mechanical heart valves operated from 1990 to 2003 attending the Muhimbili National Hospital. Information on occurrence and risk factors for thromboembolic and bleeding complications was obtained from medical records and interviews. Anticoagulation adequacy was assessed basing on the proportion of Prothrombin ratio measurements within the therapeutic ranges during the study follow-up.

Findings: Among the 232 study patients, 59 (25.4%) suffered a total of 83 thromboembolic episodes. The linearized incidence of minor (grade I and II) episodes was 5.5% person-years and 3.5 % person-years for major (grade III) episodes. In a multivariate Cox regression analysis, residing very far away from Dar es Salaam and mitral valve replacement were found to be predictors of thromboembolism. In a univariate logistic regression analysis, increased left ventricular diameters, mean aortic valves pressure gradient and reduced ejection fraction were significantly associated with thromboembolism.

The study also indicates that 87 (37.5%) patients suffered a total of 132 bleeding events. The linearized incidence rate of minor bleedings was 11.4% person-years while that of major bleeding was 2.9 % person-years. In the multivariate Cox regression of potential risk factors, those patients who attended both cardiac and anticoagulation clinic had less

episodes of bleeding complications compared to those who had attended cardiac clinic only. Patients who had no history of /coexisting bleeding disorder at baseline were found to have a reduced risk of bleeding complications compared to those who had.

The control of anticoagulation was poor only 35.5% of the Prothrombin ratio measurements were reflecting sustained adequate anticoagulation. Furthermore, during study period only 23.8% of the patients were able to maintain adequate anticoagulation for more than 56.5% (more than 80 percentile) of their Prothrombin ratio measurements. The occurrence of both thromboembolic and bleeding events was only significantly reduced when the level of anticoagulation adequacy was above 80 percentile.

Conclusions: The incidence of both thromboembolic and bleeding complications was high among study patients and was multifactor in nature. Most of the patients were either over or under anticoagulated. It is recommended to improve the anticoagulant adequacy among study patients.

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LIST OF ABBREVIATIONS

AF	Atrial Fibrillation
CT	Computerized Tomography
ECG	Electrocardiography
ECHO	Echocardiography
GELIA	The German Experience with Low Intensity Anticoagulation
HR	Hazard Ratio
INR	International Normalized Ratio
LAID	Left Atrial Internal Diameter
LMNPT	Log Mean Normal Prothrombin Time
LVEF	Left Ventricular Ejection Fraction
LVID (D)	Left Ventricular Internal Diameter during Diastole
LVID (S)	Left Ventricular Internal Diameter during Systole
MNH	Muhimbili National Hospital
MOH	Ministry of Health
MRI	Magnetic Resonance Imaging
NSAIDs	Non Steroid anti-inflammatory Drugs
U.K	United Kingdoms
USA	United States of America
WHO	World Health Organization

1. INTRODUCTION

Thromboembolic and anticoagulant related bleeding complications are the main causes of morbidity and mortality in patients with mechanical heart valves [1]. A review of articles published since 1979 indicates that thromboembolic and bleeding complications account for about 75% of valve-related complications in patients with mechanical heart valves [2]. In the US, thromboembolic complications occur in 13-17% of mechanical heart valves within five years of implantation and in 34-44% within fifteen years of implantation [3]. Anticoagulant-related bleeding complications of mechanical heart valves include major bleeding in 1-3% of patients per year and minor bleeding in 4-8% of patients per year [3]. In Tanzania, the incidence of these complications is not known and no study has been done to date.

Patients with mechanical heart valves receive life long, oral anticoagulant therapy to prevent thromboembolic complications, but this treatment is associated with an increased risk of bleeding [4]. The risks of thromboembolism and bleeding depend mainly on the adequacy of anticoagulation [4], however other factors may play a role. Thus it is important to identify the possible risk factors for these complications both before and during anticoagulant therapy to develop appropriate preventive strategies. Thus, this study was designed to determine the incidence and risk factors for thromboembolic and bleeding complications and assess the anticoagulation adequacy among patients with mechanical heart valves.

2. LITERATURE REVIEW

2.1 HEART VALVE REPLACEMENT

Approximately 70,000 heart valve replacement procedures are performed annually in USA. The indications for valve replacement range from rheumatic mitral valve stenosis, mitral regurgitation from "floppy" valves, and calcific aortic stenosis [5]. In United Kingdom, 6471 patients had first valve replacement in 1998 of whom 71.7% had aortic valve disease, while 28% had mitral valve diseases. The mean age for the first implant was 65.29 years [6].

From 1st April 1999 to 31st March 2000 just over 8,000 patients had surgery for valve disease (one third in combination with coronary surgery), representing about 20% of all cardiac surgical operations in the UK National Health Service units in that year. Replacement of the aortic valve alone was the commonest valve procedure, representing about 63% of all valve surgery [7].

Surgical practice for valvular heart disease varies around the world, depending on the predominant pathology encountered. In most of the developing countries where rheumatic valvular heart disease remains prevalent, the patients are often young. In most of the developed countries, patients present late in life (mean age of valve replacement of 65 years), valvular degenerative disease being common [7].

In East Africa, several patients have been reported to undergo valve replacement with success. In Kenya, at Kenyatta National Hospital, the main operative procedure performed for open-heart surgery between 1973 and 1998 was valve replacement accounting for about 50% of all cases [8]. Among 475 patients operated during that period, 41.2% of them had valve replacement. Mitral valve replacement was the commonest operative procedure accounting for about 32.1% of all open-heart surgery procedures. The mean age at surgery was 18.0 (±11.4) years.

2.1.1 The Situation of heart valve replacement in Tanzania

In Tanzania, open-heart surgery is not available. All patients requiring heart valve replacement are therefore sent abroad for surgery through sponsorship by the Ministry of Health (MOH) [9]. In the 1970's and 1980's, most of the patients for heart surgery were referred to UK and Italy. However since 1990's and now most of the patients are referred to India. A few patients are sent to South Africa and the United Kingdom. India was preferred because the operations are less expensive. Based on available data the commonest cause of heart valve replacement is rheumatic heart disease and mitral valve disease tops the list [10].

According to Muhimbili National Hospital records, between 1990 and 2002, a total of 600 patients were referred abroad through the MOH for surgical interventions due to cardiovascular causes. Of these, 40% (240) required valve replacement [9].

2.2 MECHANICAL HEART VALVES

The basic types of mechanical valves are (1) a ball-cage valve in which a spherical occluder is contained within a metal "cage" when the valve is open and fills the orifice in the closed position. The most common caged ball valve is Starr-Edwards valve [11], (2) a tilting disc valve where a single circular disk opens at an angle to the annulus plane, being constrained in its motion by a smaller "cage", a central strut, or a slanted slot in the valve ring and (3) a bileaflet valve where two semicircular disks hinge open to form two large lateral orifices and a small central orifice. Tilting disc valve models include the Medrotonic Hall valve, omniscience valve, and the discontinued Bjork–Shiley valve. Bileaflet valves include the St Jude (the most commonly implanted valve in the US).

2.2.1 Characteristics of prosthetic valves

Prosthetic valves differ from one another with regard to several characteristics, including durability, thrombogenicity, and hemodynamic profile [12]. With rare exceptions, mechanical valves are very durable, most lasting at least 20 to 30 years. In contrast, 10 to 20 % of homograft bioprostheses and 30% of heterograft bioprostheses fail within 10 to 15 years of implantation and require replacement. Patients under 40 years of age have a particularly high incidence of premature heterograft failure. [12]

Mechanical valves are thrombogenic and therefore require that the patient receive long-term anticoagulant therapy. 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].

For a valve of a given size, the heterograft bioprosthesis and caged-ball mechanical valve have the smallest effective orifice areas, whereas the homograft bioprosthesis has the largest, with an effective orifice area similar to that of a native valve [13]

On the basis of these characteristics, mechanical valves are preferred in patients who are young or have a life expectancy of more than 10 to 15 years, or who require long-term anticoagulant therapy for other reasons (e.g. atrial fibrillation)[12]. Bioprosthetic valves are preferred in patients who are elderly or have a life expectancy of less than 10 to 15 years, or who cannot (or will not) take long-term anticoagulant therapy.

2.2.2 Echocardiography evaluation of prosthetic valves.

Echocardiography (ECHO) evaluation is mandatory for prosthetic valve assessment. During ECHO examination of the patient with a prosthetic valve, attention is focused on the antegrade velocity across the valve in relation to the size, type and position of the implanted prosthesis [11]. A focus is also made on calculation of mean gradient and valve area when stenosis is suspected, estimation of chamber sizes, wall thickness, systolic function and a careful search for prosthetic valve regurgitation. Emphasis is also made on visualization of prosthetic valve function (motion), calcification and vegetations

2.2.2.1 Normal regurgitation

Even in normal prosthetic valve there is a small degree of valvular regurgitation in virtually all mechanical valves and in a high percentage (30% to 50%) of bioprosthetic valves [14]. This does not reflect valvular malfunction. On a transthoracic study, it may be difficult to separate normal from pathological prosthetic regurgitation due to reverberations from the metal. On color flow imaging, normal prosthetic regurgitation tends to be a uniform color with little variance, whereas pathologic regurgitation shows aliasing and variance with a "confetti-like" appearance to the flow pattern [14]. On continuous-wave Doppler examination, normal prosthetic regurgitation has low signal strength, may persist through only part of the cardiac cycle, and is spatially localized. However if pathological regurgitation is suspected, trans-esophageal imaging is superior to transthoracic approach and is needed in many aortic and all mitral valve prostheses

2.2.2.2 Prosthetic valve stenosis

The principles applied to evaluation of native valve stenosis also have been used for suspected stenosis of prosthetic valves [14]. From a continuous-wave Doppler recording of the antegrade velocity across the valve, obtained at a parallel intercept angle, maximum instaneous and mean pressure gradient can be calculated using the Bernoulli equation. Maximum and mean pressure gradients across bioprosthetic valves calculated by Doppler echo compare well with directly measured pressure gradient [15]. The situation is more complex for mechanical valves because of the differing fluid dynamics of each types of prosthesis. Thus even though, the correlation between Doppler and invasive pressure gradient measurement is high, the slope of regression line indicates

that the Doppler approach consistently "overestimates" the overall transvalvular gradient [16]. Again, a baseline study in the early postoperative period provides a base for comparison when subsequent valve dysfunction is suspected.

Echocardiography also allows calculation of the aortic valve area using the continuity equation based on the concept that the stroke volumes proximal to and in the stenotic orifice are equal [11]. It is important to understand that the invasive Gorlin formula and the noninvasive continuity equation, although both estimates of aortic valve area, are measuring different parameters [19]. The Gorlin equation is a measure of the anatomic orifice area, whereas the continuity equation is a measure of physiologic flow area of the vena contracta. As such, these equations would not be expected to yield identical results, but both provide reproducible, reliable data that can predict clinical outcome and guide patient management.

There are other methods for measuring aortic valve stenosis severity [11]. The normal area of the aortic valve area, obviously, is related to body size; for example, being smaller in children than adults. One approach to indexing the valve area to body size is to divide valve area by body surface area. Another approach is to delete the outflow tract cross-sectional area from the continuity equation, leaving the ratio of outflow tract velocity to aortic jet velocity. This velocity ratio is effectively indexed for body size as the valve area of the outflow tract is the expected normal valve area for that individual. Thus, a ratio close to 1 is normal, a ratio of 0.5 indicates a valve area half normal size, and a ratio of 0.25 is consistent with severe stenosis (i.e., a valve area one quarter

normal size). Some clinicians look at the "step up" in velocity across the valve, which is the inverse of the velocity ratio.

With prosthetic mitral valve, calculation of the valve area is used to assess the severity of stenosis [16] .The prosthetic valve areas can be estimated using the pressure half-time approach as for native mitral valve stenosis. Somewhat surprisingly, the empirical constant 220 also appears to provide a reasonable approximation of mitral valve area for mechanical prosthesis [11]. Continuity equation valve area also can be calculated for a mitral prosthesis (in the absence of mitral regurgitation) using the antegrade stroke volume across the aortic or pulmonary valve in question [11].

2.2.2.3 Prosthetic valve regurgitation

Transthoracic color Doppler flow imaging for prosthetic valve regurgitation can be helpful, particularly if a view can be obtained where the ultrasound beam has access to the chamber receiving the regurgitant flow without first transversing the valve prosthetic [17].Conventional pulsed Doppler can be used to detect prosthetic regurgitation, but a meticulous examination is needed with persistent repositioning of the sample volume in multiple views to detect the regurgitant signal [18].

Continuous-wave Doppler has the advantage of a wide beam size at the depth of a prosthetic valve and a high signal-to-nose ratio, enhancing the likehood that a weaker signal or eccentric jet (i.e. paraprosthetic regurgitation) will be identified.

When prosthetic regurgitation is detected, the first step in evaluation and interpretation is whether "normal" or pathologic prosthetic regurgitation is present [11]. While the normal

backflow across the valve represents a small volume of blood, the color jets on transesophageal imaging can be fairly large in area. Distinguishing features are the characteristic pattern of each valve type, a uniform color pattern rather than the mosaic flow disturbance seen with pathological regurgitation (increased antegrade velocity, chamber sizes and functions and pulmonary hypertension) to suggest significant regurgitation

2.3 MECHANICAL HEART VALVES AND THROMBOEMBOLIC COMPLICATIONS

2.3.1 Prosthetic valve obstruction

Prosthetic valve obstruction includes several pathological findings ranging from primary thrombosis, pannus formation and pannus formation plus secondary thrombosis [20]. The reported incidence of these complications ranges from 0.05% to 4.3 % patient-year, depending on the type, the valve position and the management of anticoagulation [21]. In mechanical valves, the risk is highest for tricuspid position, with an incidence of up to 20% patient-year, where as in patient with aortic or mitral prostheses the incidence is reported at between 0.2% and 6% per patient-year [21, 22]. These significant differences are probably a consequence of underreporting in studies because of inadequate follow up techniques and non-standardized postoperative anticoagulation regime [23]. The risk for prosthetic valve thrombosis appears to be twice as high in mitral as in aortic valve replacement. Though valve obstruction is most often thought to result from thrombosis, the role of pannus formation in causing obstruction is less well established [20]. In one study, 63.4% 213 patients who had valve replacement had pannus formation with secondary thrombosis in 31.1% of the patients [20].

Prosthetic valve thrombosis may manifest clinically with, dizziness, palpitations, pulmonary congestion, poor peripheral perfusion, or systemic embolization. In major thombotic events, patients have acute hemodynamic deterioration requiring immediate medical attention. Other patients have a more insidious onset and longer duration of symptoms (weeks to months) [24]. Physical examination may reveal a decreased intensity

of one or both metallic clicks or the presence of a new murmur. Decreased movement of the disk or poppet can be seen on cinefluoroscopy or echocardiography, and an increased transvalvular pressure gradient, a reduced orifice area, or valvular regurgitation can be detected with Doppler echocardiography or catheterization [24].

Findings from several studies [23, 24, 27] have shown that unstable anticoagulation may be the risk factors predisposing to clot formation after mechanical valve replacement.

2.3.2 Systemic thromboembolization

In patients with mechanical valves, the incidence of major embolization (resulting in death or a persistent neurological 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 [25]. The majority of the systemic embolizations manifest as cerebrovascular event [2]. Katsuhiko et al [1] found the incidence of cerebral infarction to be 0.8% patients-years. Koertkel et al showed the incidence of major thromboembolic complications per observation year to be 2.8 % [26]. During the 7-year follow up period in GELIA 5 study, 18 among 553 patients had 21 thromboembolic events after mitral valve replacement. Of these 9 patients had 10 severe (2 grade II and 8 grade III) events. Linearized rates for grade II and III thromboembolic events were 0.16% patient-years and 0.62 per patient-years, respectively [27]. Francisco J et al [28] showed linearized rates for the thromboembolism for mitral valve replacement, aortic valve replacement, and multiple valve replacement (in events % patient-years) were, respectively, as follows; 3.7 ± 0.9, 3.1 ± 0.8, and 3.9 ± 1.3;. The Actuarial

estimates of freedom from thromboembolism for mitral valve replacement, aortic valve replacement, and multiple valve replacement (at 5 years of follow-up for mitral valve replacement and aortic valve replacement and 4.5 years for multiple valve replacement) were, respectively, as follows: 88% ± 3%, 91%± 2%, and 86% ± 5 %. Cannegieter SC et al [25], in a case series, showed an incidence of thromboembolism of 0.5% per year with prosthetic aortic valves, 0.9% per year with prosthetic mitral valves, and 1.2% per year with both aortic and mitral valves.

2.3.3 Risk factors for systemic thromboembolism

The risk factors that increase the incidence of systemic embolism must be considered when defining the need for starting anticoagulant therapy in patients with cardiac valvular disease and prosthetic valves [30]. These factors include age, hypertension, diabetes, type and severity of valve lesion, presence of atrial fibrillation, low cardiac output, size of the left atrium (over 50mm on echocardiography) and previous thromboembolism. Secondly, the risk of embolization is increased with mitral-valve prostheses, caged-ball valves, and multiple prosthetic valves [31].

In one study Cannegieter SC et al [25] showed that prosthesis in mitral position increased the risk of thromboembolism almost twice as compared with aortic position. Tilting disc valves and bileaflet valves showed a lower incidence of major embolism than ball valves. Horstkotte et al [32] showed that, the incidence of thromboembolism of 6.5% patient-year and 3.9% patient-year with St Jude medical bileaflet in mitral and aortic positions respectively while maintaining the INR between 1.8 and 2.8. With tilting disk

valves the incidence of Thromboembolism was found to be 2.6%person-year and 1% person-year in mitral and aortic positions respectively at the INR of 2.5-4.5.

It has also been shown in patients with chronic moderate (grade II-1V) mitral regurgitation that, irrespective of left atrial size, the occurrence of atrial fibrillation (AF) is an independent predictor of thromboembolism [33]. Thromboembolic risk is considered three to four times greater in non anticoagulated patients with chronic AF than in patients with paroxysmal AF [34, 35]

2.3.3.1 Cardiac chamber dilatation and ventricular function

Enlargement of one or more cardiac and impairment in the left ventricular function have been associated with increased incidence of thromboembolic events [36] although it is difficult to prove an independent role of such mechanisms.

In patients with chronic mitral regurgitation, increased frequency of embolic events was observed in parallel with enlargement of the left atrium and left ventricular end diastolic diameter, as well as with decrease in left ventricular ejection fraction or cardiac index.

2.4 BLEEDING COMPLICATIONS AND THEIR RISK FACTORS

Bleeding is the most common complication of warfarin treatment occurring in about 6-39% of recipients annually [37]. Casselman FP et al [38] studied 249 patients who had undergone mitral valve replacement1963-1964 and found that 25% had the ball valve was implanted and disc valve in 75% of the patients. The mean follow up was 19.5+_9.4 years and 100% of them completed the study. About 40% of all patients had at least one bleeding episode and 29% had two postoperative events. The incidence of events was higher in the first 5 years after surgery.

A study by Cannegieter SC et al [2] found the incidence of major bleeding among patients with mechanical valve replacement on coumarin to be 1.45% person-year. Cannegieter SC [25] also studied a total of 1608 patients who were followed for 6475 patient-years. Intracranial and spinal bleeding occurred in 36 patients (0.57% patient-year) and major extracranial bleeding in 128 (2.1%patient-year).

In another study [39] that involved 102 patients with prosthetic valve in a 4 years follow up, hemorrhagic complications developed in 26 (25.5%) patients, 3 (2.9%) patients suffered from life threatening bleeding, such as cerebral bleeding and gastrointestinal bleeding and were defined as the major hemorrhagic group. Another 23 (22.5%) patients had minor bleeding complications such as nasal, gingival or subcutaneous bleeding and were defined as the minor hemorrhagic group.

Malcolm J et al found [40] unwanted bleeding events (linearised rate, 1.73% patient-year) occurring with a similar incidence to that in other Carbomedics valves [41, 42] and was similar to that reported with other bileaflet valves [43]. Huth C et al [44] reported a linearised rate of 1.5-2.5 % patient-year and 0.75-0.25 % patient-year for grade II and grade III (major) bleeding complications, respectively among patients with St. Jude medical aortic prosthesis receiving different intensities of oral anticoagulation. Pruefer D [45] found the incidence of severe bleeding to be 1.95 % patient-years for grade II and 0.55 %patients-years for grade III in patients with St.Jude medical mitral valve replacement.

It is notable that the incidence of bleeding complications is variable (0.2-7.4% patient-year) in most of the study populations [46]. This is a result of multiple inter-related factors including patient-physician and prosthetic-related factors, the definition of bleeding, the medical centre, and the patient cohort [46, 47].

Several published articles have also shown great variability on incidence of bleeding events on the bases of type of mechanical valve replaced. A search done by Cohn LH et al showed an incidence of 0.6-3.3% patient-year, 0.0-2.7% patient-year, 1.4-3.2% patient-year, 0.3-2.1% patient-year and 0.0-2.8 % patient-year among patients with Starr-Edward, Omnicarbon/Omniscience, Medrotonic hall, St Jude and Carbomedics, respectively [48].

The role of the type of medical clinic attended by the patients during follow up has also been found to influence the occurrence of bleeding complications. In a study done by Chiquette E et al [49], the incidence of significant bleeding (expressed as % patient-year) was 35% among patients who attended for anticoagulation in the usual medical clinic compared to 8.1% of those who attended specialised anticoagulant clinic. The incidence of major to fatal bleeding rate was 3.9% and 1.6% respectively.

Models have developed to estimate the risk of major bleeding [50]. They are based on identification of independent risk factors such as a history of stroke, a history of gastrointestinal bleeding, older age, and the higher level of anticoagulation. Stephan D et al [51] found that age didn't appear to be an important determinant of risk for bleeding in patients receiving warfarin with possible exception of age 80 years or older. Higher age as a risk factor for bleeding complication have also been reported by other studies [53, 54]

Regarding the position of valve replacement, no significant difference in occurrence of major bleeding was found among patients with aortic, mitral or double Carbomedics valve replacement [52]. Other studies have reported coronary artery disease, hypertension as risk factors for anticoagulant–related bleeding [53, 54].

2.5 MECHANICAL HEART VALVES AND ANTICOAGULANT THERAPY

Because of the risk of thromboembolism, patients with mechanical prosthetic valves require long-term anticoagulant therapy, which should be initiated as soon as possible after valve replacement (preferably within 6 to 12 hours). The efficacy of anticoagulant therapy was previously assessed with use of the prothrombin time, but variability in the sensitivity of the thromboplastin reagent prevented its standardization, so comparing results from different periods or laboratories was problematic. The prothrombin time is now converted to an international normalized ratio (INR). The INR is calculated from (patient's Prothrombin Time/mean normal Prothrombin Time) ^{ISI}, where ISI is the International Sensitivity Index, a comparison of the responsiveness of each laboratory's thromboplastin reagent to that of a reference reagent (established by the WHO), which is arbitrarily assigned an ISI of 1.0[55].

In patients with mechanical prosthetic valves, oral anticoagulant therapy reduces the incidence of thromboembolism but may increase the risk of hemorrhage [56, 57, 58]. Although the overall incidence of adverse events (thromboembolic or hemorrhagic) is lowest when the INR is from 2.5 to 4.9, some patients at high risk for thromboembolic complications benefit from more intense anticoagulation [4,37] whereas others require less intense therapy. For example, in those with a caged-ball valve or more than one mechanical prosthetic valve, the incidence of adverse events is lowest when the INR is from 4.0 to 4.9. Conversely, adverse events are infrequent when the INR is only 2.0 to 2.9 in patients with bileaflet-disk valves and 3.0 to 3.9 in those with single-tilting-disk

valves. Patients who are more than 70 years old have an increased incidence of bleeding complications when the INR exceeds 3.9, whereas younger patients generally tolerate more intensive anticoagulant therapy without increased complications.

Antiplatelet drugs have been administered with warfarin in an attempt to reduce the incidence of thromboembolic events without increasing the risk of bleeding [58]. Although some studies have suggested that dipyridamole reduces the incidence of thromboembolism when given with warfarin [59, 60] others have failed to confirm this [61] Aspirin (500 mg daily) combined with warfarin therapy (target INR, 2.6 to 7.5) is associated with an increased incidence of gastrointestinal bleeding (requiring transfusion or hospitalization) without a lower incidence of systemic embolization than that with warfarin therapy alone [60]. Various dosages of Aspirin have been evaluated in a number of clinical trials. Aspirin (75-150mg daily) combined with lower-intensity warfarin (target INR, 1.8 to 2.3) is associated with a reduced incidence of systemic embolization, but the incidence of gastrointestinal bleeding is still higher than with lower-intensity warfarin therapy alone [62.63].

Better results have been obtained when lower-dose aspirin (100 mg daily) is combined with warfarin (target INR, 3.0 to 4.5) in patients with mechanical heart valves or bioprosthetic valves who have atrial fibrillation or have had previous systemic embolization [64]. As compared with warfarin alone, lower-dose aspirin plus warfarin is associated with a marked reduction in the incidence of systemic embolization or death,

an increased incidence of minor bleeding (epistaxis, hematuria, and bruising), and a similar incidence of gastrointestinal or other major bleeding. Whether the combination of aspirin (100 mg daily) and lower-intensity anticoagulant therapy (target INR, 2.0 to 3.0) can further reduce the incidence of bleeding complications is unknown. In short, the addition of aspirin to warfarin in patients with prosthetic valves offers additional protection against thromboembolism at the risk of more frequent bleeding complications. Therefore, its use should be reserved for patients with a history or a high risk of systemic embolization or other conditions in which it is indicated (e.g., coronary artery or peripheral vascular disease).

2.5.1 Levels of Anticoagulant adequacy and influencing factors

Despite the variability in range of INR required to reduce thromboembolic complications with minimal bleeding complications, dose regime is generally adjusted to obtain the following INR ranges [65].

INR 2.0 to 3.0 target 2.5: Sinus rhythm, normal left atrium size, St. Jude Bileaflet aortic valve, Carbomedics bileaflet valve and Medtronic-Hall tilting aortic valve.

INR 2.5 to 3.5 target 3.0: Tilting disks, Bileaflet valve in mitral position, Bileaflet mechanical aortic valve plus atrial fibrillation.

INR 2.5 to 3.5 target 3.0 and aspirin (80 to 100mg/d): Caged ball valve, caged disk valve, additional risk factors and systemic embolism despite adequate anticoagulation.

Despite the use of warfarin in patients with prosthetic valves to prevent thromboembolic complications with minimal bleeding several factors also may potentiate/negate either of the complications. A study done by Wells PS et al [66] found warfarin's anticoagulant effect was potentiated by 6 antibiotics (cotrimoxazole, erythromycin, fluconazole, ionized, metronidazole, and miconazole); 5 cardiac drugs (amiodarone, clofibrate, propafenone, propranolol, and sulfinpyrazone); phenylbutazone; piroxicam; alcohol (only with concomitant liver disease); cimetidine; and omeprazole. Three patients had a hemorrhage at the time of a potentiating interaction (caused by alcohol, isoniazid, and phenylbutazone). A study by Chan [67] showed that All NSAIDs can prolong bleeding time by inhibiting platelet function. High-dose aspirin has a direct hypoprothrombinemic effect. Phenylbutazone and its analogs enhance the hypoprothrombinemic effect of warfarin through a pharmacokinetic interaction by inhibiting the hepatic metabolism of warfarin

The influence of vitamin K-rich vegetables on effectiveness has also been documented in a number of studies. Karlson B et al [68] found that when broccoli and spinach were given daily to patients receiving warfarin, the thrombotest values tended to rise above the upper therapeutic dose adjustment.

2.5.2 Managing oral anticoagulant therapy

Warfarin given at a frequency of once per day takes, 4-7 days to have its optimum effect [69]. Large loading doses do not markedly shorten the time to achieve a full therapeutic effect but cause rapid falls in the level of protein C, which may precipitate paradoxical thrombosis in the first few days of warfarin therapy. It is recommended that warfarin

therapy be started at an average maintenance dose of 5 mg compared with 10 mg, which usually is sufficient to lower the INR to 2.0 in 4 or 5 days [70]. Lower starting doses may be appropriate in elderly patients, those with liver disease or inadequate nutrition, and those at high risk for bleeding. Larger starting doses e.g. 7.5 to 10 mg may be selected if a rapid effect is urgently needed. A loading dose of warfarin is unnecessary for most patients.

2.5.3 Anticoagulation of patients with prosthetic valve replacement at MNH

The anticoagulation unit in the department of Hematology and Blood Transfusion provides anticoagulant service. Patients with prosthetic valves normally report at the anticoagulation clinic, Muhimbili National Hospital during their first week after coming back from Surgery. It was the only service in the country until recently when it was also available in a few private in Dar es Salaam and some referral hospitals. The clinic is run in an outpatient mode once per week. At registration at the anticoagulation clinic, each patient is given a booklet, which is filled with Prothrombin time ratio results, dosage of anticoagulant and complications reported. Patients also attend cardiac clinic once per week during the same time where they have their files for follow up documentations on history taking, physical findings, investigations and treatment given.

Warfarin is the only anticoagulant used at MNH. The 5mg daily dose of warfarin is the recommended maintenance dose for most of the patients. A few patients receive a 5mg and 10 mg alternate dose. Some of them are advised to skip the daily dose over the

weekends depending on the physician's decision based on laboratory values of Prothrombin ratios and the clinical condition of the patient. Counseling is done regarding restriction to some drugs and constant intake of foods such as cabbage, spinach, soybeans green vegetable etc. Patients are advised to stop warfarin temporarily or report to the physician if they experience bleeding episodes.

Monitoring of adequacy of anticoagulation at Muhimbili National Hospital is still based on measurements of Prothrombin ratio. It is recommended to maintain a Prothrombin ratio of 1.5-2 and 2-2.5 for mechanical valve on aortic and mitral positions, respectively. The use of international normalized ratio has not been put into practice though this is done in a few private hospitals due to the difficulty in getting standardized commercial reagents.

3. RATIONALE OF THE STUDY

Bleeding and thromboembolic disorders are the commonest complications seen in patients with mechanical valves on long-term anticoagulation therapy. Morbidity and mortality in these patients is mainly attributable to these complications.

Patients in Tanzania are operated outside the country in different settings and conditions with different type of valve replacement. The incidence of complications is not known in our setting. Therefore a better understanding of these complications is imperative to maximize on the therapeutic benefits. Knowledge of the incidence of complications and their possible associated risk factors would give the extent of its magnitude in this population and provide a basis for intervention measures targeting relevant associated factors at appropriate levels of health care.

Anticoagulation in patients with mechanical heart valves aims at minimizing thromboembolic complications. However no study in our setting has been done to assess the adequacy of anticoagulation monitoring in the operated patients. This study therefore addressed these problems, bearing in mind that the control of these complications would have a positive effect on the quality of life of our patients.

4. OBJECTIVES

4.1 Broad Objectives

To determine the incidence and risk factors of bleeding and thromboembolic complications and assess the adequacy of anticoagulation among patients with mechanical heart valves as seen at MNH

4.2 Specific objectives

1. To determine the incidence of bleeding complications among patients with mechanical heart valves
2. To determine the incidence of thromboembolic complications among patients with mechanical heart valves
3. To identify possible risk factors for bleeding complications among patients with mechanical heart valves
4. To identify possible risk factors for thromboembolic complications among patients with mechanical heart valves
5. To assess the adequacy of anticoagulation under routine conditions among patients with mechanical heart valves
6. To identify factors influencing the adequacy of anticoagulation among patients with mechanical heart valves.

5. METHODOLOGY

5.1 Study setting:

The study was conducted in the cardiac clinic, anticoagulant clinic and cardiology records section at the Muhimbili National Hospital, in Dar es Salaam, Tanzania. The Muhimbili National Hospital is a referral hospital which runs outpatient cardiac clinics every Friday afternoon and anticoagulant clinics every Tuesday morning.

5.2 Study design:

This was a retrospective cohort study aimed at determining the incidence and risk factors of thromboembolic and bleeding complications and assessing the adequacy of anticoagulation among patients with mechanical heart valves.

5.3 Study subjects and methods

The target population for the study included all patients with mechanical heart valves who were attending either the MNH cardiac or anticoagulant clinics. It is notable as a matter of practice that patients who attend the anticoagulant clinics at MNH are given booklets that contain records of complications, Prothrombin ratio and dose of warfarin. The patients were divided into two categories based on how information was collected.

Category 1; Inclusion criteria

1. Patients who had valve replacement from 1990 to 2003 and were attending the Muhimbili National Hospital but died or were lost to follow up for any reason before the time of the study.
2. Patients with mechanical valve on warfarin
3. Patients in whom it was possible to trace record of surgery and complications.

Exclusion criteria

1. Patients in whom it was not possible to trace records of surgery /complication
2. Patients who had been operated before 1990 and after 2003.

Category 2; Inclusion criteria

1. Patients who had valve replacement from 1990 to 2003 and were still attending clinic to the day of study
2. Patients with mechanical valve on warfarin
3. Patients in whom it was possible to obtain information both from medical records and interview
4. Patient/guardian gave informed consent to participate in the study.

Exclusion criteria

1. Refusal to give consent during interview
2. Patients in whom it was not possible to trace records of surgery /complication.
3. Patients who had been operated before 1990 and after 2003.

5.3.1 Sample size and sampling procedures

All 243 patients operated for mechanical heart valve replacement from 1990 to 2003 who were attending MNH were recruited in the study . Following lack of proper records 11 subjects were excluded from the study. The 232 subjects who met the inclusion criteria were divided into two categories of 43 subjects for category 1 and 189 subjects for category 2. Further sampling was done among category 2 patients for a new follow up Echocardiography examination. Due to the limitation of funds , only 100 of the patients interviewed by the investigator, had a new follow up echocardiography test. The patients were selected by random number tables.

5.3.2 End points of follow-up

For category 1, the follow-up commenced from the day of valve replacement to the last clinic visit after which the patients were lost to follow-up due to death, migration, or failure to attend clinic for any reason. The end point of follow up for category 2 was when the investigator in the follow up clinic visits has interviewed the patients.

5.4 Procedures for collecting information

Category 1

Records of baseline demographics, surgical and medical profiles, whether patients had bleeding or/and thromboembolic complications were obtained from the medical cardiology record section. But information on their Prothrombin ratio values and dose of warfarin was not collected as the patients keep them. The Information was entered in a structured questionnaire-1.

Category 2

Patients in this category were recruited during their visit at the anticoagulation and cardiac clinic as part of their routine follow up. Information was collected by scrutinizing hospital records; and the information collaborated at a face to face interview. Patients were also required to bring the booklets which contained records for Prothrombin ratio measurements and warfarin dosage. Patients were also required to provide further information on other drugs and food habits.

During each clinic visit, patients (or their guardians) were interviewed by the investigator to asses any complications that had/have developed from the time of surgery to the time the patient was interviewed. Some interviewed patients had electrocardiograph and echocardiography (ECHO) tests on top of the Prothrombin ratio. The anticoagulation booklets were utilized to assess adequacy of anticoagulation. Both information collected by records and interviews was entered in a structured questionnaire-2.

The collection of information from all eligible patients was conducted from 1st April 2004 to 30th November 2004.

5.6. Procedures and tools for determining Prothrombin ratio

Each patient interviewed by the investigator had Prothrombin time test done at the anticoagulant clinic where 4.5 mls of blood sample was collected in 0.5 ml of 3.13%. Sodium citrate. Samples of blood were then transported in containers for laboratory processing. Whole blood was centrifuged and the plasma removed. Then 0.1 ml of fresh

plasma was added to 0.1ml of rabbit thromboplastin. The formed mixture was warmed for 1-3 minutes at 37^0C. A solution of 0.1ml calcium chloride was added to the mixture; simultaneously starting the timer .The time taken to observe for the formation of fibrin gave the patient's Prothrombin time .The Prothrombin ratio was then calculated by dividing the patient's Prothrombin time to that of the control plasma.

5.7 Echocardiography procedures and tools

This was done under supervision of an experienced cardiologist using a HP Sonos 100 machine with a 2.5 Hz transducer for adult and a 5Hz transducer for children. At transthoracic approach, standard views were taken to assess for chamber sizes and left ventricular function. The prosthetic valve movements and valve integrity were assessed visually. Doppler studies were performed to assess pressure gradients across prosthetic mitral, aortic valves and the presence of regurgitation both on pulse wave Doppler and color flow mapping. The findings were compared to those obtained at the baseline ECHO examination to determine if there was a change in the measured values.

5.8 Determination of the thromboembolic and bleeding complications

This involved tracing complications recorded in the file for all patients. Additional collaborative information, by interview, was added for category 2 patients. This involved all complications that were related to warfarin. The time taken to develop the first complication from valve replacement was determined. Subsequent episodes that developed in the course of follow up were also recorded to obtain the commulative events

5.9 Identification of possible risk factors

Identification included the listing of possible risk factors for the patients before or at the time of valve replacement (baseline factors) and thereafter throughout the period of follow up. The listed factors were, age at valve replacement, sex, residence with reference to distance from Dar es Salaam, type of follow up clinic attended, valve type replaced, valve position replaced, duration of hospitalization postoperatively, past history /presence of diabetes mellitus, hypertension, stroke, ischemic heart disease and bleeding disorders. The aim was to assess whether these factors have a predictive role in development of thromboembolic and bleeding complications over time during follow up.

5.10 Assessment of adequacy of anticoagulation

Assessment of anticoagulation adequacy was based on the prothrombin ratio measurements that were recorded in the anticoagulation booklets. Each Prothrombin ratio measurement was assessed if it was within the therapeutic level, above or below it.

At a given time of anticoagulation monitoring, a Prothrombin ratio of a patient was considered to be within therapeutic ranges if either its value was 1.5-2 times the control value (for the patient with aortic valve replacement) or a value was 2-2.5 times the control value (for patient with mitral , double valve replacement or other additional risk factor for thromboembolism)

During interview each patient was asked if he/she had been exposed to a number of possible factors that might affect adequacy of anticoagulation. Information collected in hospital records was also used. This included warfarin dose and where it is obtained or bought and whether there was concurrent use of warfarin with aspirin, amiodarone; consumption of cabbage and green leafy vegetables.

5.11 Reducing recall bias and lack of proper records.

Only patients operated within the last 14 years were involved in the study as it was expected that most of the patients would be able to recall their experience and provide the required information. This interview was aimed at adding more information to that available in hospital records. It was also expected that the records of surgery, complications and anticoagulation monitoring could be traced easily. Almost all patients who were reffered abroad for operation during this period on government support ,their post-operatively records were available at the Ministry of Health and MNH.

5.12 Statistical analysis

The data were entered into a computer and analysed using the SPSS package software Version 12.0.1.The incidence rate of complications was reported as the number of complications per patient year of observation. The 95% confidence interval for the incidence rate was calculated using the Poisson distribution assumption.

Survival curves were obtained using the method of Kaplan and Meier to determine the freedom (survival) rate from either thromboembolic or bleeding complications. The time taken to develop a first complication since valve replacement was used for analysis.

Both univariate and multivariate Cox regression analysis was performed to identify possible risk factors with bleeding and thromboembolic complications being the dependent variable. The following independent variables were included for bleeding complications: Age at valve replacement, sex, residence with reference to distance from Dar es Salaam, type of follow up clinic attended, valve type, valve position, duration of hospitalization postoperatively and history/coexisting bleeding disorder and hypertension at the baseline. Independent variables for thromboembolic complications included; all the above variables plus any baseline past history/presence of diabetes mellitus, ischemic heart disease, stroke and atrial fibrillation.

A univariate and multivariate logistic regression analysis of cardiac chamber measurements, mean valve pressure gradient and left ventricular ejection fraction on thromboembolic complications was also done. Any increase in cardiac chamber measurements and mean valve pressure gradient or a decrease in left ventricular ejection

fraction (LVEF) as determined on ECHO examination compared to the baseline finding was taken as a risk factor for thromboembolism.

Adequacy of anticoagulation was analyzed in two ways. First, as percentages of all Prothrombin ratio tests done during the whole period of follow up to determine the proportion of tests which were within the therapeutic level, below or above it. Secondly, each patient was analyzed individually to determine the level of anticoagulation basing on the percentage of Prothrombin ratio measurements which were within the therapeutic range for the whole period of follow up. The level of anticoagulation was divided into four percentiles in which at 20 percentile the percentage of Prothrombin ratio that was within the therapeutic was from 0-28.6% and at more than 80 percentiles, it was more than 56.5%. A percentile of more than 80 was considered to be a high level of anticoagulation. These different levels of anticoagulation were then analyzed in a univariate logistic regression to determine their influence on occurrence of thromboembolic and bleeding complications.

Univariate logistic regression was also done to assess factors such as warfarin dose, source, food habits and drugs that could be associated with the high level of anticoagulation.

Continuous variables were presented as mean ± standard deviation. A p value of < 0.05 was considered statistically significant.

5.13 Definition of terms

Terms related to thromboembolic and bleeding complications

These complications were defined as major (grade III) and minor (grade I and II) events according to the adapted GELIA grading definition[27]

Minor thromboembolism (grade I and II) was defined as symptoms and signs of embolic cause that were observed and treated by the patient himself or treated in an outpatient mode.

Major thromboembolism (grade III) was defined as symptoms and signs of embolic cause that necessitated hospitalization.

Minor bleeding (grade I and II) was defined as any episode of bleeding such as minor epistasis, gum bleeding, purpura, bruising, menorrhagia etc that were observed and treated by the patients himself or treated in an outpatient mode and that was thought to be related to warfarin by the patient/ attending doctor.

Major bleeding (grade III) was defined as any episode of bleeding in any system of the body that could lead to death, hospital admission or blood transfusion and that was thought to be related to warfarin by the attending doctor.

Terms related to distance of residency from Dar es Salaam.

Dar es Salaam (DSM) is the largest city in Tanzania. Muhimbili national Hospital is a national referral hospital within this city and until recently the hospital was the only centre in the country running anticoagulant clinic for all patients with Prosthetic valves in the country

Near DSM. Residences close to DSM. The patient had to take 45min-3hrs to access the anticoagulant/cardiac clinic in DSM

Far from DSM. The patient had to take 4-12hrs to access the anticoagulant/cardiac clinic in DSM by public transport

Very far from DSM. The patient had take more than 12hrs to several days to access the anticoagulant/cardiac clinic in DSM by public transport

Terms related to food intake

Regular food intake. The food that was taken for at least 3 days in a week

Constant amount of food. The amount of food taken was nearly of the same quantity per meal.

Variable amount of food. The amount of food taken was of variable quantity per meal.

5.14 Limitations on the methodology

This was a retrospective study over period of time. This inevitably raises the concern of the availability of medical records and the ability to recall complications accurately. Although it is unlikely the major complications were missed, the registration and recall of minor complications might be limited despite the efforts to minimize it by supportive interview to some patients. The reported minor events may therefore be underestimated and the proportion of major events consequently overestimated.

Failure to trace some of the records might also influences the final results. However only 4.5% of the patients were excluded due to this limitation

Confirmation of some of the complications was mainly clinical. The use of CT scan, ECHO and angiography as confirmatory tests was limited to few patients as the majority of them could not afford the costs. CT scan was unavailable until recently. Angiography could be done to very few patients who were referred abroad. This made the confirmation of events such as ischemic versus hemorrhagic stroke and coronary emboli very difficult.

Even with these limitations in mind, the observed incidence may still be a good reflection of true incidence of complications and the results would serve as a reference for further recommendations to improve medical record section and availability of diagnostic facilities in the country.

5.14 Ethical consideration

Informed written consent was requested, from all subjects and the medical record section. Patients who were found to have complications at the time of interview were referred to a hematologist/cardiologist for further management. Patients for whom on ECHO were detected to have malfunctioning valves were assessed for further management by the cardiologists. Institutional ethical clearance was obtained from the Muhimbili University College of Health Sciences ethical committee.

6. RESULTS

6.1 Baseline characteristics

The study included that a total of 268 patients were operated for both mechanical and bioprosthetic heart valve replacements from 1990 to 2003. Following valve replacement 13 patients who didn't report at Muhimbili National Hospital to start follow up clinics and 12 patients who had bioprosthetic valves implanted were excluded from the study. The remaining 243 who had mechanical heart valves were recruited into the study but again 11 (4.5%) were excluded due to lack of proper records. The 232 (95.5%) subjects who met the inclusion criteria were divided into two categories of 43 (18.5%) subjects for category 1 and 189 (81.5%) subjects for category 2. The study found that 114 (49.1%) subjects had valves implanted in mitral positions, 66(28.4%) in aortic positions and 52 (22.4%) in both mitral and aortic positions.

A total of 143 (61.6%) of patients were females and 89 (38.4%) were males but the sex distribution of valve position replaced was not statistically different. The mean age at valve replacement was 18.8±9.8 years (Table 1). The mean duration of the study follow-up was 3.9± 2.2 years with a total duration of 919 patient-years.

Most of the study subjects were attending both cardiac and anticoagulation clinics (62.9%) and were operated in India (81.6) (Table 1).

The findings also indicate that about 50% of the patients had pure mitral valve replacement. Bileaflet tilting disks were replaced in majority of the patients (44.8%).

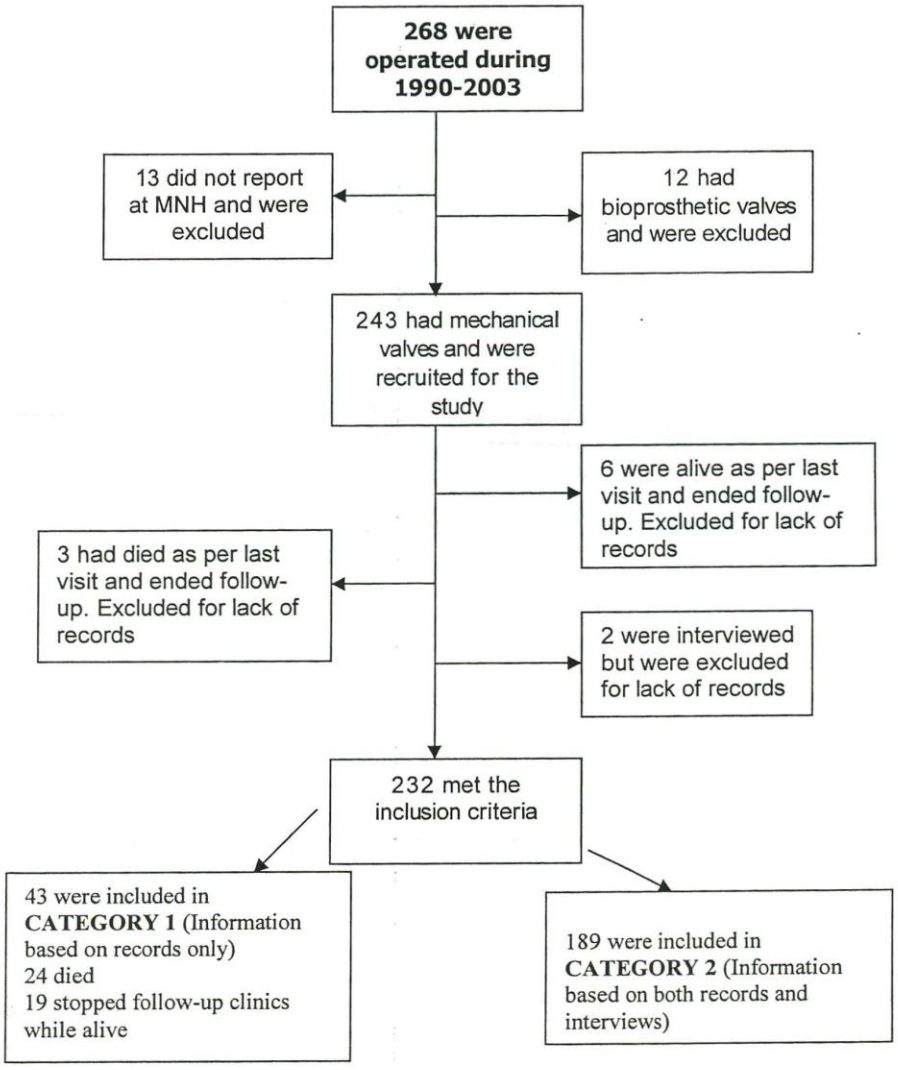

Figure 1. A flow chart for patients included in the study

The underlying valve pathology was mainly due to rheumatic process. Atrial fibrillation was the commonest coexisting medical condition occurring in about 32% of all patients at valve replacement

Table 1 Baseline characteristics by position of valve replaced

Variable	Total		Position of valve replacement					
			Aortic		Mitral		Aortic and Mitral	
	N	%	n	%	n	%	n	%
No of patients	232	(100)	66	(28.4)	114	(49.1)	52	(22.4)
Mean age at valve replacement(years)	18.8±9.8		17.8±8.7		19.9±10.4		17.7±9.6	
Female sex	143*	(61.6)	40	(28.0)	72	(50.3)	31	(21.7)
Residence								
Dar es Salaam (DSM)	80*	(34.5)	21	(26.3)	38	(47.5)	21	(26.2)
Near DSM	40	(17.2)	15	(37.5)	13	(32.5)	12	(30.0)
Far from DSM	31	(13.4	12	(38.7)	13	(41.9)	6	(19.4)
Very far from DSM	42	(18.1)	07	(16.7)	29	(69.0)	6	(14.3)
Changed residence	39	(16)	11	(28.3)	21	(53.8)	7	(17.9)
Follow up clinic attended								
Cardiac only	35	(15.1)	9	(25.7)	22	(62.9)	4	(11.4)
Anticoagulation only	23	(09.9)	5	(21.7)	11	(47.8)	7	(30.4)
Both clinics	146*	(62.9)	46	(31.5)	66	(45.2)	34	(23.3)
Changed Clinics	28	(12.1)	6	(21.4)	15	(53.6)	7	(17.9)
Type of valve								
Ball caged	56	(24.1)	4	(07.1)	41*	(73.2)	1	(19.6)
Single tilting disk	72	(31.1)	34	(47.2)	23	(31.9)	1	(20.9)
Bileaflet tilting disk	104	(44.8)	28	(26.9)	50	(48.1)	2	(25.4)
Underlying valve pathology								
Rheumatic	201*	(86.6)	50	(24.9)	106	*(52.7)	45	(22.4)
Non Rheumatic	31	(13.4)	16	(51.6)	8	(25.8)	7	(22.6)
Place of Surgery								
India	191*	(81.6)	4	(24.6)	9	(50.8)	47	(24.6)
Others	41	(18.4)	1	(46.3)	17	(41.5)	5	(12.2)
Past/coexisting medical condition								
Diabetes Mellitus	3	(1.3)	1	(33.3)	2	(66.7)	0	(0)
Hypertension	11	(4.3)	4	(30.0)	4	(40.0)	2	(20.0)
Ischemic heart disease	8	(3.4)	1	(12.5)	7	(87.5)	0	(0)
Stroke	5	(2.2)	0	(0)	5	(100.0)	0	(0)
Atrial fibrillation	73	(31.5)	15	(20.5)	51	(69.9)	6	(9.6)
Bleeding disorder	25	(10.8)	1	(44.0)	13	(52.2)	7	(4.0)

* Indicates p value < 0.05

The findings also indicated that mitral position was replaced in the majorities of the patients whose residency was very far from DSM. Mitral valve replacement was also common in patients who attended cardiac clinic only and those who had ball caged valve implanted (Table 1). The commonest indication for replacement was isolated mitral valve disease, which was indicated in 49% of all patients (Table 2).

Table 2 Indications of valve replacement

Variable	Frequency N=232 n	%
Indications for replacement		
Mitral regurgitation	51	22.0
Mitral stenosis	35	15.1
Aortic regurgitation	31	13.4
Aortic stenosis	29	12.5
Mitral regurgitation and stenosis	28	12.1
Mitral regurgitation and aortic stenosis	11	4.7
Mitral stenosis and aortic regurgitation	12	5.2
Mitral and aortic regurgitation	12	5.2
Mitral and aortic stenosis	17	7.3
Aortic regurgitation and stenosis	6	2.6

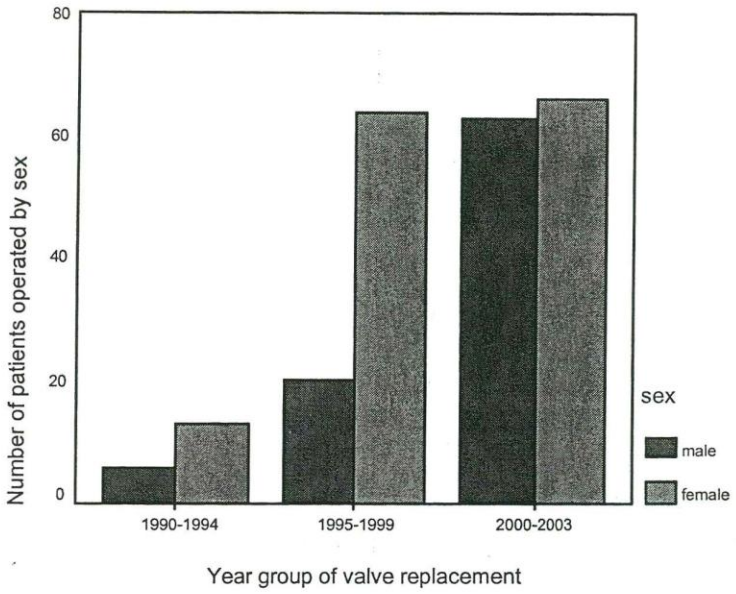

Figure 2 The number of subjects operated by sex per year group

Only a few patients were operated for valve replacement from 1990 to 1994(<20 per year). The majority were operated 1995-2003. More females than males were operated per year group and especially during 1995-199 when the number of females was about three-fold (Figure 2).

Incidence and risk factors for thromboembolic complications

Among 232 study subjects, 59 (25.4%) suffered a total of 83 thromboembolic events. There were 51 minor (grade II and I) episodes and 32 major (grade III) episodes. Among 83 episodes, 59 were experienced as the first events from valve replacement. The linearized incidence for minor episodes was 5.5% person- years and 3.5 % person -years for major episodes (Table 3).

Table 3 Linearized incidence of thromboembolism during follow up

Variable	Patients experienced TE events N=232		Number of TE events	Patients years of observation =919
	n	%		Incidence (95%CI)
Minor TE	38	16.3	51	5.5 (4.2-8.6)
Major TE	21	9.1	32	3.5 (2.1-4.9)
Combined TE	59	25.4	83	9.0 (7.2-11.2)

TE-Thromboembolic

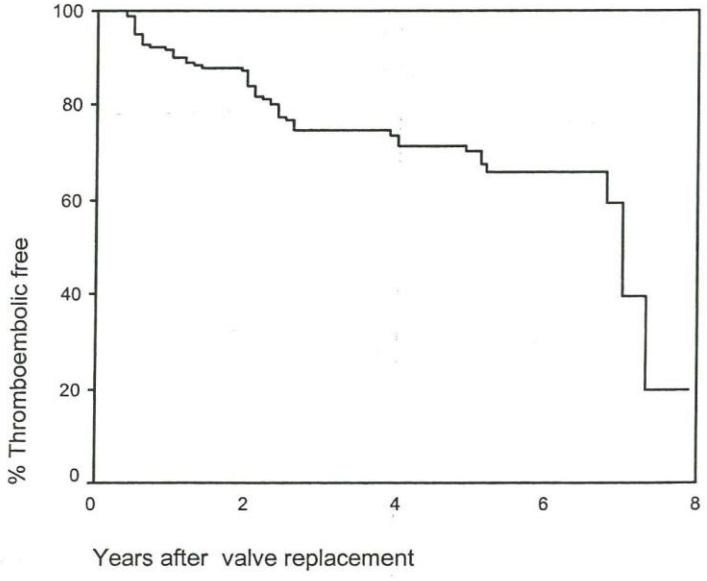

Figure 3 Time to first thromboembolic complications (Kaplan-Meier plot