

Incidence and risk factors for thromboembolism and major bleeding in patients with mechanical heart valves: a tertiary hospital-based study in Botswana

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Abstract

Introduction: Mechanical heart valve (MHV) prostheses increase the risk of thromboembolic complications. While warfarin anticoagulation reduces this risk, its use increases the risk of bleeding. We sought to estimate the rate of thromboembolic and bleeding complications among patients with MHVs at a tertiary hospital in Botswana. Factors associated with bleeding and thromboembolic complications are also described.

Methods: This retrospective cohort study involved a cohort of patients with MHV at Princess Marina Hospital who were operated on before September 2017. The study documented bleeding and thromboembolic events since the valve replacement, patients' demographic information, co-existing medical conditions, drug history and details of valve replacement. Using the recent international normalised ratio (INR) results, each patient's time in therapeutic range (TTR) was calculated to assess the level of anticoagulation control.

Results: The study enrolled 142 patients with a mean (SD) age of 42 (12) years and a median (IQR) duration since valve replacement of four years (1.8–10.0). The median (IQR) TTR was 29.8% (14.1–51.0) and only 14.8% of the patients had an optimal anticoagulation control. The rates of major bleeding and thromboembolic complications were 1.5 per 100 person-years and 2.80 per 100 person-years, respectively. A longer duration of warfarin use was associated with an increased risk of both bleeding ($p = 0.008$) and thromboembolic complications ($p = 0.01$).

Conclusion: Bleeding and thromboembolic complications were common in MHV prosthesis patients in this study. Long duration of anticoagulation, albeit sub-optimal control, was a risk factor for bleeding and thromboembolic complications in these patients. Therefore, long-term efforts are necessary to address these complications and possibly improve the quality of life of these patients.

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Rheumatic heart disease (RHD) remains the leading cause of cardiovascular disease in developing countries, including

Botswana.¹⁻⁴ The disease affects young people and has been the main reason for valve replacement in sub-Saharan Africa.⁵

Because of their longevity, mechanical heart valves (MHVs) are preferred to bio-prostheses in most patients with RHD.⁶ As MHVs increase the risk of thromboembolic complications, these patients require life-long warfarin anticoagulation.^{7,8} While warfarin is effective and the only anticoagulant used for thromboembolic prophylaxis in patients with MHVs, it has a narrow therapeutic window.⁹ It may be difficult to achieve the desired anticoagulation without excess risk of bleeding.⁹ Therefore, patients with MHVs are at increased risk of both bleeding and thromboembolic complications.^{10,11}

The rates of major bleeding and thromboembolic complications after implantation of MHVs are 1–3.9 per 100 patient-years and 1.3–1.6 per 100 patient-years, respectively.^{7-9,12-14,16} Generally, the rates of bleeding and thromboembolic complications vary across settings, due to differences in the levels of anticoagulation control and the population studied.^{12,13,17} A combination of both non-genetic and genetic factors influence the inter-individual and ethnic variability in warfarin responses and the quality of anticoagulation.¹⁸ Differences in the two genes responsible for warfarin pharmacokinetics and pharmacodynamics, cytochrome P450 2C9 (*CYP2C9*) and vitamin K epoxide reductase complex 1 (*VKORC1*) account for up to 30% of the variability in warfarin dose among Caucasians and 10% among blacks.

The quality of anticoagulation is often measured by the patient's average time in therapeutic range (TTR), which correlates with bleeding and thromboembolic complications.²⁰⁻²² Achieving optimal anticoagulation control has been a challenge, especially in developing countries, due to system-related problems.^{17,21} Unsustainable availability of medications, including warfarin, long distance to the centralised international normalised ratio (INR) testing centres, and underfunded health systems in developing countries are some of the problems.^{23,25}

A recent study reported optimal anticoagulation control in only 15% of warfarin-treated patients in our setting.¹⁷ Consequently, the majority of our patients have an elevated risk of warfarin-related complications.¹⁵ However, there is a lack of data on the frequency of bleeding and thromboembolic complications among patients with MHVs in our setting. This information is imperative in managing our increasing number of patients with MHV prostheses. As a result, this study sought to determine the rate of both major bleeding and thromboembolic complications and associated factors among patients with MHVs at a tertiary hospital in Botswana.

Methods

This retrospective cohort study was conducted at the warfarin clinic of Princess Marina Hospital (PMH). PMH is a tertiary

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hospital in Gaborone, the largest city and capital of Botswana with a population of about 232 000 inhabitants.²⁵ The warfarin clinic runs once weekly and serves about 30 patients per week (roughly 40% have MHVs).

INR testing and consultations occur on the same day. Warfarin tablets are available in PMH and also in the peripheral clinics. The study cohort consisted of patients aged ≥ 18 years who were on warfarin for at least 30 days and with at least three INR readings.

Ethical approval was obtained from the University of Botswana, Ministry of Health and wellness, and PMH ethical review boards. All participants provided informed consent before their inclusion in the study.

Data were collected between September 2017 and January 2018 from consecutive patients with MHVs at PMH. Through personal interviews and a review of medical records, patients' age, gender, residence, occupation, level of education, co-existing medical conditions and drug history were documented. Other information was the presence or absence of known risk factors for thromboembolic events such as hypertension, diabetes mellitus and human immunodeficiency virus (HIV) infection. Information on operated valves and dates of replacement were extracted from patients' medical records. As most patients underwent valve replacements outside Botswana, data on the type (model) of MHVs were unavailable because of inaccessibility of surgical notes.

Study outcomes were the occurrence of any bleeding and thromboembolic events since the valve replacement. Due to different times of follow up in different patients, the rates of bleeding and thromboembolic complications are presented as events per 100 patient-years. Major bleeding was defined as overt bleeding leading to a decrease in the haemoglobin level of at least 2 g/dl or transfusion of at least two units of packed red blood cells, occurring at a critical site such as intracranial, intraspinal, intra-ocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome.²⁶ Thromboembolic complications included ischaemic stroke, transient ischaemic attack, myocardial infarction, pulmonary embolism, deep-vein thrombosis and systemic embolism.²⁷

Using recent INR readings, each patient's time in therapeutic range (TTR) was calculated to assess the level of anticoagulation control using the Rosendaal method.²² TTR is the number of person-days that each patient stayed within an INR of 2.5 to 3.5, divided by the total number of person-days on warfarin.²² We used INR values from at least two valid intervals separated by 56 days (eight weeks) or less, without an intervening hospitalisation. Individual patient's TTRs were used to calculate the overall TTR for the clinic. A TTR value below 65% is defined as poor anticoagulation control.^{28,30}

Statistical analysis

Data were entered and analysed using SPSS for Macintosh, version 24.0 (IBM Corporation). Continuous variables are presented as mean with standard deviation (SD) for normally distributed data, and median with interquartile range (IQR) for asymmetrical distribution. Categorical and nominal variables are presented as absolute and relative frequencies (%). Comparisons of demographic and clinical characteristics between patients with and without thromboembolic and bleeding complications were analysed with independent *t*-tests, Mann-Whitney *U*- or

Pearson's χ^2 tests. A two-sided *p*-value of < 0.05 was considered statistically significant.

To assess for independent predictors for bleeding and thromboembolic complications, a multivariate logistic regression model was used. All factors with a *p*-value < 0.25 on bivariate analysis were added to the multivariable model. We report adjusted odds ratios (ORs), 95% confidence intervals (CIs) and *p*-values.

Results

The study included 142 patients whose mean (SD) age was 42 (12) years (Table 1). The majority of participants were female, and over two-thirds of the patients were less than 50 years old. Many participants (56%) resided in Gaborone and the majority had formal education. About 44.4% of the participants were unemployed and with no regular source of income. The most common co-morbidities were hypertension, atrial fibrillation and HIV (all on antiretroviral therapy). Ninety per cent of participants had either mitral or aortic valve replacement. The median (IQR) duration since valve operation was four years (1.8–10.0). A total of 568 blood INR tests were assessed, with only 28.1% of them being in the therapeutic range. The median (IQR) TTR was 29.8% (14.1–51.0) and about 14.8% of the patients had a TTR $\geq 65\%$.

Twenty (14.1%) patients reported significant bleeding events, and the rate of major bleeding was 1.5 per 100 patient-years (Table 2). Gastrointestinal bleeding was the commonest major bleeding event.

Thromboembolic events occurred in 32 (22.5%) patients. Overall, the rate of occurrence of thromboembolic complications was 2.8 per 100 person-years. Of the 32 patients with thromboembolic events, 25 (78.1%) had stroke/TIA and seven (21.9%) had valve thrombosis. Hypertension ($p = 0.451$), atrial fibrillation ($p = 0.879$), HIV ($p = 0.568$) and diabetes ($p = 0.510$) were not associated with thromboembolic events. Also, there was no gender difference in bleeding and thromboembolic complications.

Thromboembolic events were more common among people in Gaborone than those from outside the city ($p = 0.044$). Patients with a longer duration of warfarin use were more likely to suffer bleeding and thromboembolic events than those with a shorter duration. On multivariate analysis, the duration of warfarin use (OR 1.06, 95% CI: 1.01–1.11) and an increased level of education (OR 2.25, 95% CI: 1.17–4.33) were independent predictors of bleeding complications (Table 3).

Discussion

In this study, 14.1 and 22.5% of patients with MHV prostheses reported major bleeding and thromboembolic complications, respectively. The rate of major bleeding was 1.5 events per 100 person-years while that of thromboembolic complications was 2.8 events per 100 person-years.

The rate of major bleeding in our cohort is lower than the rates previously reported in other settings, with event rates as high as 3.9 per 100 person-years.^{12,31} It is, however, difficult to compare bleeding complication rates across studies because of the variation of factors such as patient characteristics, study methods, duration of follow up and the level of anticoagulation control.

Table 1. Baseline characteristics of enrolled patients with MHVs at PMH, Gaborone (n = 142)

Characteristics	All patients (n = 142)
Gender, n (%)	
Female	97 (68.3)
Male	45 (31.7)
Mean age (SD), years	42 (12)
Age groups (years), n (%)	
≤ 30	28 (19.7)
31–50	72 (50.7)
> 50	42 (29.6)
Residence, n (%)	
Gaborone	80 (56.3)
Outside Gaborone	62 (43.7)
Level of education, n (%)	
No formal schooling	13 (9.2)
Primary school	29 (20.4)
Secondary school	66 (46.5)
University/college	34 (23.9)
Marital status, n (%)	
Not married	106 (74.6)
Currently married	36 (25.4)
Monthly income, n (%)	
No income	63 (44.4)
< 1 000 Pula	14 (9.9)
1 000–4 000 Pula	38 (26.7)
> 4 000 Pula	27 (19.0)
Employment, n (%)	
Employed	77 (58.0)
Unemployed	61 (42.0)
Co-morbidities, n (%)	
Hypertension	40 (30.3)
Atrial fibrillation	30 (21.1)
HIV	25 (17.1)
Heart failure	21 (14.8)
Diabetes mellitus	2 (1.4)
Valves operated, n (%)	
Mitral	73 (66.4)
Aortic	26 (23.6)
Tricuspid	2 (1.8)
Dual (mitral/aortic)	7 (6.4)
Triple (mitral/aortic/tricuspid)	2 (1.8)

One Botswana Pula was equivalent to 0.09757 American dollars during the time of study.
PMH, Princess Marina Hospital; HIV, human immunodeficiency virus; SD, standard deviation.

Since the most common cause of valvular heart diseases in our setting is rheumatic heart disease, our participants were young and predominantly female.^{2,32,33} The mean age of participants in the large Swedish cohort of patients with MHVs was 63 years, older than in our study.¹⁵ Old age and the high burden of co-morbid conditions most likely predisposed the Swedish patients to bleeding than in our young population. Given the young age of our cohort, the reported rate of bleeding events was high and should call for vigilant monitoring of our patients. We also observed that the risk of bleeding was incremental with longer duration of warfarin use.

Similar to a previous study in our clinic, the majority of our participants had sub-optimal anticoagulation control.¹⁷ As a result, individuals with a longer duration of warfarin use in our setting are more likely to be exposed to prolonged periods of sub-optimal anticoagulation control than those with a shorter

Table 2. Difference in bleeding and thromboembolic complications by gender among patients with MHVs at PMH, Gaborone (n = 142)

Complications	All (n = 142)	Male (n = 45)	Female (n = 97)	p-value
Major bleeding complications, n (%)	20 (14.1)	8 (17.8)	12 (13.4)	0.389
Intracranial bleeding	3 (15)	2 (25.0)	1 (8.3)	0.537
Intra-ocular	1 (5)	0	1 (8.3)	1.000
Gastrointestinal	10 (50)	4 (50.0)	6 (50.0)	1.000
Haematuria/menorrhagia/epistaxis	6 (30)	2 (25.0)	4 (33.4)	1.000
Thrombotic complications, n (%)	32 (22.5)	10 (31.2)	22 (68.8)	0.711
Stroke/TIA	25 (78.1)	7 (70.0)	18 (81.8)	0.662
Valve thrombosis	7 (21.9)	3 (30.0)	4 (18.2)	0.580

PMH, Princess Marina Hospital; TIA, transient ischaemic attack; MHVs, mechanical heart valves.

duration. Hence, there is an incremental increase in bleeding risk with a longer duration of warfarin use. Decentralisation of INR testing centres and emphasis on patient education are necessary steps for the achievement of anticoagulation control.^{33,34}

Table 3. Factors associated with bleeding and thromboembolic complication rates of patients with MHVs on warfarin

Characteristics	Thromboembolic		p-value	Major bleeding		p-value
	No (n = 110)	Yes (n = 32)		No (n = 122)	Yes (n = 20)	
Age, mean (SD), years	43.1 (12.9)	41.0 (11.9)	0.59	43.3 (12.7)	39 (11.9)	0.04
Valve duration, median (IQR), years	3 (1.0–7.0)	8.5 (2.3–15.8)	0.01	5 (3–11)	3 (1.6–7)	0.08
TTR, median (IQR), years	30.2 (14.0–54.0)	25.6 (14.3–39.1)	0.26	30.1 (15–49)	20.5 (13.3–55.2)	0.50
Residence, n (%)						
Gaborone	57 (51.8)	23 (71.9)	0.04	70 (57.4)	10 (50.0)	0.54
Outside Gaborone	53 (48.2)	9 (28.1)		52 (42.6)	10 (50.0)	
Education, n (%)						
No formal education	11 (10.0)	2 (6.3)	0.048	11 (9.0)	2 (10.0)	0.87
Primary school	26 (23.6)	3 (9.4)		26 (21.3)	3 (15.0)	
Secondary school	52 (47.3)	14 (43.8)		57 (46.7)	9 (45.0)	
University/college	21 (19.1)	13 (40.6)		28 (23.0)	6 (30.0)	
Marital status, n (%)						
Not married	80 (72.7)	26 (81.3)	0.33	91 (74.6)	15 (75)	0.97
Currently married	30 (27.3)	6 (18.7)		31 (25.4)	5 (25)	
Monthly income, n (%)						
No income	51 (46.4)	12 (37.5)	0.51	58 (47.5)	5 (25.0)	0.10
< 1 000 Pula	11 (10)	3 (9.4)		13 (10.7)	1 (5.00)	
1 000–4 000 Pula	30 (27.3)	8 (25.0)		31 (25.4)	7 (35.0)	
> 4 000 Pula	18 (16.4)	9 (28.1)		20 (16.4)	7 (35.0)	
Current smoker, n (%)	3 (2.7)	2 (6.3)	0.34	5 (4.1)	0	0.36
Alcohol intake, n (%)	6 (5.5)	5 (15.6)	0.06	9 (7.4)	2 (10.0)	0.68
HIV positive, n (%)	20 (18.2)	2 (6.3)	0.73	25 (20.5)	0	0.03
Valve operated, n (%)						
Mitral	73 (66.4)	21 (65.6)	0.83	83 (68.0)	11 (55.0)	0.004
Aortic	26 (23.6)	8 (25.0)		30 (24.6)	4 (20.0)	
Tricuspid	2 (1.8)	0		1 (0.8)	1 (5.0)	
Dual (mitral/aortic)	7 (6.4)	3 (9.0)		8 (6.6)	2 (10.0)	
Triple (mitral/aortic/tricuspid)	2 (1.8)	0		0	2 (10.0)	

One Botswana Pula was equivalent to 0.09757 American dollars during the time of study.
IQR, interquartile range; SD, standard deviation; MHVs, mechanical heart valves.

While there is evidence that female gender, smoking and low income are associated with bleeding complications, none of these factors had an association with bleeding complications in the current study.^{35,36} The above factors affect the anticoagulation effect of warfarin and consequently lead to bleeding complications. Unfortunately, our study was not powered enough to detect the influence of these factors on the risk of bleeding.

In our study, the incidence of thromboembolic complications was 2.8 per 100 person-years, higher than the rate of one to two per 100 patient-years in the Western world cohorts.^{8,16} This is concerning as our cohort was younger than those in the developed world, whose thromboembolic complications are likely to be influenced by several co-morbidities that are risk factors for atherosclerosis. For this reason, our results suggest a high rate of thromboembolic complications in our young population with MHV prostheses. These complications were not associated with hypertension or atrial fibrillation.

Like bleeding complications, prolonged exposure to sub-optimal levels of anticoagulation in our cohort may partly explain the high rate of thromboembolic complications among our patients. Patients with sub-optimal levels of anticoagulation often present with a clear predominance of over-anticoagulation.²¹ This fact most likely explains a preponderance of thromboembolic over major haemorrhagic events in our cohort.²³

The observation of a two-fold increased risk of thromboembolic complications in those with education compared to those who were uneducated may be explained by the fact that educated patients are more likely to reside in the city and hence survive thromboembolic complications because of their proximity to healthcare services. Although ageing, smoking, female gender and alcohol intake are linked to an increased risk of bleeding and thromboembolic complications, these factors were neutral in the present study.^{20,35} Again, the young age of our participants may have influenced the findings.

We are aware of the limitations of our study. Being a retrospective study, it was not possible to document complications as they happened. Furthermore, selection bias cannot be excluded in this study design, as fatal warfarin-related complications that led to mortality were likely to be missed. Also, patients' ability to recall events may have been limited, especially those with minor impacts. However, we reviewed the medical records to confirm all reported complications. Also, because of a variable number of days between each patient's visit, the TTR calculation might have over- or underestimated time in therapeutic window. As most operations were not done in Botswana, information on the type (model) of valves was missing. Lastly, being a hospital-based study, patients with severe morbidity that limited their clinic attendances were likely to be missed.

Conclusion

This study shows high rates of bleeding and thromboembolic events in a young cohort of patients with MHVs in a developing country. Also, most of the patients had poor anticoagulation control. Efforts aiming at improving the care of patients with mechanical valves are necessary to reduce the burden of complications in this young population. Decentralisation of INR testing to their local facility might be one way of improving anticoagulation in these patients.

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