Cardiovascular Topics

Factors associated with sub-optimal control of anti-coagulation in patients with prosthetic heart valves taking oral anticoagulants in a sub-Saharan African setting

Tigist Chalachew, Dejuma Yadeta, Endale Tefera

Abstract

Background: Replacement of diseased valves reduces the morbidity and mortality rate associated with native valvular disease but comes at the expense of risking complications related to the implanted prosthetic device. Establishing the desired anticoagulation level in a sub-Saharan African setting may be a challenge.

Objectives: This study was conducted to determine the challenges of maintaining a desired level of anticoagulation and factors associated with sub-optimal anticoagulation in patients with prosthetic heart valves on chronic anticoagulation.

Methods: We reviewed 73 patients who had undergone prosthetic valve replacement for chronic rheumatic valvular heart disease and were taking warfarin. The follow up ranged from one to 13 years. We studied international normalised ratio (INR) profiles of the patients for the six months preceding the study and defined optimal control as an INR of 2.5–3.5. We aimed to determine if there were factors associated with sub-optimal control of INR.

Results: Forty-two patients (57.5%) were female. Mean age of the participants was 21.5 ± 3.1 years (range 14–25 years). Warfarin was the anticoagulant in 55 (75.3%) of the patients and 18 (24.7%) were on combined warfarin and aspirin anticoagulation. Thirty-five (47.9%) patients had optimal control of their INR. Educational level of primary school or less, distance from follow-up medical facility of more than 300 km, quarterly or less-frequent check-up visit, and public health institution as a source of free warfarin supply were found to be significantly associated with sub-optimal control of INR.

Conclusion: Educational level, distance from follow-up facility, number of follow-up visits and source of warfarin supply were found to be significantly associated with sub-optimal control of INR.

Keywords: anticoagulation, valve replacement, warfarin, sub-Saharan Africa, rheumatic heart disease

Submitted 20/12/18, accepted 27/4/19
Published online 24/5/19
Cardiovasc J Afr 2019; **30**: 316–320 www.cvja.co.za

DOI: 10.5830/CVJA-2019-024

Department of Pediatrics and Child Health, School of Medicine, Hawassa University, Hawassa, Ethiopia
Tigist Chalachew, MD

Department of Internal Medicine, Division of Cardiology, School of Medicine, Addis Ababa University, Addis Ababa, Ethiopia
Dejuma Yadeta, MD

Department of Pediatrics and Adolescent Health, Division of Cardiology, Faculty of Medicine, University of Botswana, Gaborone, Botswana
Endale Tefera, MD, endalet2008@gmail.com

Among patients who undergo cardiac valve replacement, approximately 60% receive mechanical valves, and replacement of a diseased heart valve with a prosthetic valve exchanges the native disease for potential prosthesis-related complications.[1,2] Replacement of diseased valves reduces the morbidity and mortality rates associated with native valvular disease but comes at the expense of risking complications related to the implanted prosthetic device.[3] These complications include primary valve failure, prosthetic valve endocarditis and thrombosis, thromboembolism, haemorrhage and mechanical haemolytic anaemia.[4-7] The frequency of serious complications depends upon the valve type and position and other clinical risk factors.[8] Thromboembolic and anticoagulation-related problems are by far the most frequent complications of mechanical valves.[1,2,8]

Chronic rheumatic heart disease is still prevalent and is a major public health problem in sub-Saharan Africa. In recent years, there has been a glimmer of hope for many patients to get surgical intervention in their local environment through locally established facilities,[9] overseas charity referrals or visiting surgical missions. However, determining the optimal strategy to treat such sub-Saharan African patients is a challenge.

Colleagues from Cameroun recently reported their experience with 233 patients who had undergone mechanical valve replacement.[9] Although the surgical results and mid-term event-free survival was good in their report, that may not be the case in other parts of sub-Saharan Africa, primarily due to issues related to anticoagulation. Tissue valves and valve repair strategies tend to be short lived because of the recurrence of

rheumatic fever, as many of these patients fail to comply with penicillin prophylaxis when their cardiac symptoms improve as a result of surgical intervention.

For those who get mechanical valves, the problem starts with regular availability of warfarin itself.[10] Once they are on warfarin, compliance, regular follow up and regular monitoring of their coagulation profile has been a challenge because of lack of facilities in almost all public institutions, and limited access to well-equipped medical facilities. This study aimed at determining factors associated with sub-optimal control of international normalised ratio (INR) in children and young adults who had received mechanical valve replacement for rheumatic valve disease in the last few years.

Methods

This was a cross-sectional study of patients with prosthetic heart valves who are on oral anticoagulation therapy. The study included patients younger than 25 years who were being followed up at the paediatric and adult cardiac clinics of Tikur Anbessa Hospital and the Children's Heart Fund Cardiac Centre, which is also located within the premises of Tikur Anbessa Hospital, Ethiopia.

The study was conducted from December 2014 to September 2015. The principal investigator collected data directly through interviewing patients and attendants and by reviewing medical records during this period. Socio-demographic data, including age, gender, patient's educational level, parental educational level, parental occupation, income, residence, and distance from follow-up health facility were collected on a pre-tested questionnaire.

Clinical data, including current cardiac symptoms, bleeding episodes, strokes, frequency of follow-up visits, frequency of INR determination, source of anticoagulant supply and compliance were collected. For those who missed doses of anticoagulants in the six months preceding the study, possible reasons were inquired.

Patient records were retrieved and reviewed for age at the time of surgery, pre-operative New York Heart Association (NYHA) functional class, indication for valve replacement, prosthetic valve position, type of prosthetic valve implanted, compliance with recommended follow-up visit, INR checks, major bleeding or thrombo-embolic events, and any post-surgical hospital admissions. Where there were discrepancies between patient reports and what had been documented in the medical records, we used the information documented in the records. Definition of adherence to follow-up visit, anticoagulant use and INR determination in this study was based on the doctor's recommendation for each individual patient. The institutional review committee approved the study.

INR determinations during the six-month period ranged from one in the case of some of the patients to multiple values in others. In those with multiple INR recordings, we determined to which side the majority of the readings pointed. There were few patients with mixed optimal and sub-optimal readings in this study.

Our definition of optimal anticoagulation range (2.5–3.5) is in the strict category. We chose the narrower range due to the realities of our setting where frequent follow up, determination of INR and adjustment of extreme boundaries of control is difficult. Although INR values of 2.5–4.9 are considered to be optimal by some,[2] the upper range of this value may have predisposed our patients to bleeding due to lack of frequent determination of their INR and subsequent dose readjustments. The risk of bleeding increases once INR increases above 4.5.[11] Therefore, using a point close to this value would probably have endangered our patients' lives. We did not adjust for valve position, namely mitral or aortic.

Statistical analysis

Data were entered into SPSS version 20 for Windows and analysed. Demographic data were analysed using descriptive statistics. Continuous variables are displayed as mean ± standard deviation (SD). Statistical significance was set at $p < 0.05$. The chi-squared test and binary logistic regression methods were used to test for association of factors to sub-optimal control of anticoagulation.

Results

A total of 73 patients were included in the study and 42 (57.5%) were female. Mean age of the participants was 21.5 ± 3.1 years (range 14–25 years) and mean follow-up period was 5.6 ± 2.5 years (range 1–13 years). Sixty-three of the patients (86.3%) were from urban areas while the rest were from semi-urban or rural areas. Of the 73 patients, 35 (47.9%) had optimal control of their INR. Table 1 shows the socio-demographic data and clinical characteristics of the patients at the time of valve-replacement surgery. With regard to educational status, 24 (32.9%) had primary school education, 29 (39.7%) had secondary education, 19 (26.0%) had higher education and only one patient was illiterate.

Valve brands used included St Jude mechanical valves in 40 (54.8%) patients, Edward's mechanical valves in 12 (16.4%), and other variants in 21 (28.8%) patients. Warfarin was the

Table 1. Baseline socio-demographic and clinical characteristics of patients with prosthetic heart valves on oral anticoagulation therapy

Characteristics	*Frequency*	*Percentage*
Gender		
Female	42	57.5
Male	31	42.5
Age categories at surgery (years)		
11–15	12	16.4
16–20	29	39.7
21–25	32	43.8
Residence		
Urban	63	86.3
Semi-urban	9	12.3
Rural	1	1.4
NYHA functional class (before surgery)		
I	–	–
II	12	16.4
III	29	39.7
IV	32	43.8
Indications for valve replacement (type of valve lesion)		
Severe MR	16	21.9
Severe MS	13	17.8
Severe AR	4	5.5
Multi-valvular lesions	40	54.8

MR: mitral regurgitation; MS: mitral stenosis; AR: aortic regurgitation.

anticoagulant in 55 (75.3%) of the patients and 18 (24.7%) were on combined warfarin and aspirin anticoagulation.

Only 30 (41.1%) patients reported perfect adherence to their medication, while the rest reported that they had missed a few to several doses in the preceding six months. The most common reason for missed doses was forgetfulness, accounting for about 22 (30.1%) of the cases, as reported by the patients themselves. The next most common one was shortage or unavailability of warfarin, accounting for 17 (23.3%) of the cases. Self-perceived side effects and other various reasons accounted for the rest.

Forty-nine (67.1%) patients reported that they had scheduled monthly visits with clinicians, while seven (9.6%) reported that they visited less than once in three months. Thirty-three (45.2%) of the patients reported that they hardly complied with frequency of INR checks as prescribed by their doctors, and the major reason given was cost and availability of the test. Table 2 shows responses and findings in patients with prosthetic heart valves on anticoagulant treatment.

Educational level of primary school or less, more than 300 km distance from follow-up medical facility, quarterly or less-frequent check-up visits, and source of free warfarin supply being from a public institution were found to be significantly associated with sub-optimal control of INR (Table 3). Multiple other factors, including young age, parental level of education, combination of warfarin and aspirin, missed anticoagulant doses and lack of dietary counselling showed a tendency towards an association but did not reach statistically significant levels.

A total of seven patients had major bleeding or stroke in the course of their treatment and four of these patients died as a result (Table 4). One of the fatalities had two episodes of stroke, for which she was admitted. This patient died on the third admission as a result of intracranial bleeding (patient #7).

Table 2. Socio-demographic and clinical characteristics of patients with prosthetic heart valves taking anticoagulants

Characteristics	*Frequency*	*Percentage*
Age at the time of study (years)		
11–15	6	8.7
16–20	16	23.2
21–25	47	68.1
NYHA functional class (at the time of study)		
I	61	88.4
II	7	10.1
III	1	1.5
IV	–	–
Prosthetic valve position		
Mitral	49	67.1
Aortic	9	12.3
Mitral and aortic	14	19.2
Other	1	1.4
INR control		
Optimal	35	47.9
Sub-optimal	38	52.1
Educational status of the patient		
≤ Primary education	25	34.3
Secondary education	29	39.7
Higher education	19	26.0
Parental education (best)		
≤ Primary education	34	46.6
Secondary education	13	17.8
Higher education	26	35.6
Distance from cardiology care clinic (km)		
≤ 150	55	75.3
151–300	4	5.5
> 300	14	19.2
Anticoagulant		
Warfarin alone	55	75.3
Warfarin + aspirin	18	24.7
Drug supply source		
Private	19	26.0
Public for payment	36	49.3
Public for free	18	24.7
Frequency of INR determination		
Every month	54	74.0
Every 2 months	4	5.5
Quarterly or longer	15	20.5
Laboratory facility for INR		
Private	73	100
Public	–	–
Missed doses (approximate)		
Never	30	41.1
1–2 doses per week	34	46.6
> 2 doses per week	9	12.3
Bleeding or thromboembolic complications	7	9.6

Table 3. Factors associated with sub-optimal control of INR in patients with prosthetic heart valves

Factors analysed for association	*Optimal control*	*Sub-optimal control*	p-*value*
Age at surgery (years)			
< 15	7	10	0.588
≥ 15	28	28	
Gender			
Female	21	21	0.813
Male	14	17	
Educational status of the patients			
≤ Primary education	6	19	0.003
≥ Secondary education	29	19	
Parental/caretaker education (best)			
≤ Primary education	14	20	0.350
≥ Secondary education	21	18	
Distance from follow-up facility (km)			
< 300	32	23	0.003
≥ 300	3	15	
Clinic visit frequency			
Once in a month	28	21	0.022
Once in a quarterly or less	7	17	
Approximate monthly income ($US)			
≤ 50	14	12	0.162
> 50	21	16	
Medications			
Warfarin alone	28	27	0.425
Warfarin + aspirin	7	11	
Source of medication supply			
Private or public for fee	30	25	0.047
Public for free	5	13	
Medication adherence counselling (as per patient's report)			
Yes	32	33	0.712
No	3	5	
Dietary counselling (as per patient's report)			
Yes	24	20	0.232
No	11	18	
Anticoagulant doses missed (approximate)			
None or < 1 dose per week	33	31	0.155
≥ 1 dose per week	2	7	

Table 4. Description of patients with prosthetic heart valves and thrombo-embolic events

Age (years)	*Gender*	*Educational status*	*Age at surgery (years)*	*Valve position*	*Duration of follow up*	*Type and number of events*		*Outcome*
						Bleeding	*Thrombo-embolism*	
18	*F*	Secondary education	16	Aortic	2 years	1	2	Alive, no sequelae
14	M	Primary education	14	Aortic and mitral	6 months	3	2	Alive, no sequelae
20	F	Primary education	20	Aortic	8 months	1	1	Alive, neurological sequelae
12	M	Primary education	11	Mitral	1 year	2	1	Deceased
15	F	Primary education	15	Mitral	6 months	1	1	Deceased
20	F	Primary	18	Mitral	2 years	1	1	Deceased
11	F	Primary education	9	Aortic and mitral	2 years	2	1	Deceased

Overall, 16 of the patients had hospital admissions after valve replacement surgery and the reasons included prosthetic valve endocarditis in eight patients, stroke in five and miscellaneous reasons in the rest.

Discussion

Our study showed that educational level of primary school or less, distance from follow-up medical facility of more than 300 km, check-up visit once quarterly or less frequently, and free drug supply from public institutions were significantly associated with sub-optimal control of INR in this group of patients, suggesting the need for interventions directed towards tackling some of these factors.

Review of the existing literature shows a lower level of knowledge consistently affects adherence to prescribed medicines.[12] Multiple other factors including young age, level of parental education, combination of warfarin and aspirin, and missed anticoagulant doses also showed a tendency towards an association, although not statistically significant, probably due to the small sample size of our study. The number of major bleeding/thrombotic events and mortalities in our study is also unacceptably high considering the small number of patients we are reporting on (Table 4).

A lower level of literacy may have influenced the patients' understanding of the nature of the clinical condition they are suffering from, the risks associated with sub-optimal anticoagulation, and the importance of adhering to medications and follow-up clinical visits, even when they do not have clinical symptoms. Longer travel to follow-up clinics and INR test facilities is even more important in sub-Saharan African settings where transportation facilities are not readily available or are too costly for most poor patients to afford, or travel is too difficult. It may be surprising that free drug supply from public facilities was associated with sub-optimal anticoagulation. However, the truth is that warfarin was rarely available in the public institutions, which means it was difficult for the patients to secure a regular and sustainable supply.

Optimisation of anticoagulation in populations with sub-optimal adherence to medication and follow up is a major challenge.[13] Adherence to follow-up care and medication is a challenge once patients are relieved of their cardiac symptoms.[14] Colleagues from Cameroon reported that their cohort of 233 patients with mechanical valves had freedom from neurological events and anticoagulation-related bleeding of 93.1 ± 2.1 and 78.9 ± 3.7%, respectively, at six years.[9] While it is difficult to directly compare our study with theirs due to the small number of patients and differences in methodology, the number of major stroke and bleeding events in our study was disproportionately high.

A study from Rwanda reported that no anticoagulation-related events occurred,[15] but the number of patients with valve replacement in that study was small and the follow up was relatively short. The South African group that compared adjusted-dose warfarin with pre-determined fixed-dose warfarin also reported there were significant numbers of major thrombotic and haemorrhagic events in their study population.[13] However, this study was also significantly different in methodology and cannot be compared with our study.

Our study has important limitations in methodology. We included all patients we could acquire during the study period. We did not know the exact number of patients with prosthetic valves due to lack of records. We did not calculate our sample size therefore our statistical tests should be taken with caution.

Besides the small size of the study population, the study was cross-sectional with only one encounter with each patient participant. We used medical records to determine the six-month INR profile. Some of these patients may have had a single INR determination within that period due to the compliance and logistical problems already mentioned. The ideal study design would have been a cohort study.

We only included patients who came for follow up during the study period. Finally, recall bias may also have been a limitation in our study. This study could prompt the hospital to re-organise record keeping of patients.

It is worth mentioning the inherent drawbacks of warfarin as an anticoagulant. Warfarin has marked individual variation in its metabolism and hence varying dosage requirements and the need for frequent monitoring.[16] However, there are no agreed guidelines on how frequently one should monitor anticoagulation in patients who are on chronic anticoagulation. Besides, warfarin has wide dietary and drug interactions, making it difficult to establish a desired level of anticoagulation. Fixed-dose warfarin has been shown to be better than adjusted-dose warfarin. Future studies may be required to determine the feasibility and safety of this strategy in our patients. It may also be worth considering the feasibility, affordability and effectiveness of novel anticoagulants (NOACs) in our setting.

Finally, it may be better to opt for valve repair surgery whenever possible,[14] although this strategy also has its own drawbacks in this part of the world. Besides the significantly high failure rate in advanced rheumatic heart disease, patients usually fail to comply with their monthly benzathine penicillin prophylaxis, putting themselves at risk of recurrence of acute rheumatic fever. Ideally, development of prosthetic heart valves that do not require anticoagulation may be a future solution to tackle some of these complex problems.

Conclusion

Low educational level, longer distance from medical facility, less frequent follow-up visits, and warfarin from public institutions were found to be significantly associated with sub-optimal control of INR in our study. These findings may help to develop initiatives such as implementing regular outreach clinics, training health workers in remote areas with task shifting, supplying INR self-determination devices, or other innovative ways that may be found to be feasible and effective. It may also be worth considering the feasibility, affordability and effectiveness of NOACs for such patients in our setting.

We thank the staff members of the paediatric and adult cardiac clinics and the children's Heart Fund Cardiac Centre for allowing us to conduct this study and assisting with the data collection. We are also grateful to all those practitioners who care for these patients over the years.

References

1. Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. *N Engl J Med* 1996; **335**: 407–416.
2. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation* 1994; **89**: 635–641.
3. Butchart EG, Gohlke-Bärwolf C, Antunes MJ, *et al.* Recommendations for the management of patients after heart valve surgery. *Eur Heart J* 2005; **26**: 2463–2471.
4. Kontozis L, Skudicky D, Hopley MJ, Sareli P. Long-term follow-up of St. Jude Medical prosthesis in a young rheumatic population using low-level warfarin anticoagulation: an analysis of the temporal distribution of causes of death. *Am J Cardiol* 1998; **81**: 736–739.
5. Deviri E SP, Wisenbaugh T, Cronje SL. Obstruction of mechanical heart valve prostheses: clinical aspects and surgical management. *J Am Coll Cardiol* 1991; **17**: 646–650.
6. Alpert JS. The thrombosed prosthetic valve: current recommendations based on evidence from the literature. *J Am Coll Cardiol* 2003; **41**: 659–660.
7. Wilson WR, Geraci JE, Danielson GK, *et al*. Anticoagulant therapy and central nervous system complications in patients with prosthetic valve endocarditis. *Circulation* 1978; **57**: 1004–1007.
8. Little SH, Massel DR. Antiplatelet and anticoagulation for patients with prosthetic heart valves. *Cochrane Database Syst Rev* 2003: CD003464.
9. Mve Mvondo C, Pugliese M, Ambassa JC, Giamberti A, Bovio E, Dailor E. Mechanical Heart valve replacement in a low-middle income region in the modern era: mid-term results from a sub-Saharan center. *Thorac Cardiovasc Surg* 2018 Jul 18. doi: 10.1055/s-0038-1666873. [Epub ahead of print].
10. Tefera E. Treatment of children with rheumatic heart disease in sub-Saharan Africa by overseas' medical missions: challenges left behind. *J Cardiol Clin Res* 2014; **2**: 1016.
11. Vahanian A, Alfieri O, Andreotti F, *et al*. Guidelines on the management of valvular heart disease: The joint task force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2012; **33**: 2451–2496.
12. Bowry ADK, Shrank WH, Lee JL, Stedman M, Choudhry NK. A systematic review of adherence to cardiovascular medications in resource limited settings. *J Gen Intern Med* 2011; **26**: 1479–1491.
13. Buchanan-Leel B, Levetan BN, Lombard CJ, Commerford PJ. Fixed-dose versus adjusted-dose warfarin in patients with prosthetic heart valves in a peri-urban impoverished population. *J Heart Valve Dis* 2002; **11**: 583–589.
14. Mvondo CM, Pugliese M, Giamberti A, *et al*. Surgery for rheumatic mitral valve disease in sub-saharan African countries: why valve repair is still the best surgical option. *Pan Afr Med J* 2016; **24**: 307.
15. Rusingiza EK, El-Khatib Z, Hedt-Gauthier B, *et al.* Outcomes for patients with rheumatic heart disease after cardiac surgery followed at rural district hospitals in Rwanda. *Heart* 2018; **104**: 1707–1713.
16. Pirmohamed M. Warfarin: almost 60 years old and still causing problems. *Br J Clin Pharmacol* 2006; **62**: 509–511.

… continued from page 315

References

1. Brink AJ. Editorial: CVJSA e-journal publication. *Cardiovasc J Sth Afr* 2003; **14**(2): 57–58.
2. Brink AJ. New impact factor and PubMed Central service from the *Cardiovascular Journal of Africa*. *Cardiovasc J Afr* 2012; **23**(7): 364.
3. Brink PA. Article visibility: journal impact factor and availability of full text in PubMed Central and open access. *Cardiovasc J Afr* 2013; **24**(8): 295–296.
4. Brink P. Measuring publication impact, and publishing and funding models. *Cardiovasc J Afr* 2016; **27**(6): 335.
5. Roldan-Valadez E, Salazar-Ruiz SY, Ibarra-Contreras R, Rios C. Current concepts on bibliometrics: a brief review about impact factor, Eigenfactor score, CiteScore, SCImago Journal Rank, Source-Normalised Impact per Paper, H-index, and alternative metrics. *Ir J Med Sci* 2019; **188**(3): 939–951.
6. 2017 Journal impact factor, Journal Citation Reports. Clarivate Analytics 2018.
7. 2016 Journal impact factor, Journal Citation Reports. Clarivate Analytics 2017.
8. WORLD POPULATION [Internet]. Worldometers 2019. [cited 2019 Dec 15]. Available from: https://www.worldometers.info/