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Observations on quality of anticoagulation and thrombotic risk

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Oral anticoagulant management of patients with mechanical heart valves at the Salam Centre of Khartoum: Observations on quality of anticoagulation and thrombotic risk

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ABSTRACT

Introduction: Rheumatic heart disease with mechanical heart valve (MHV) replacement is common in Africa. However, MHV requires long-life anticoagulation and managing this can be challenging.

Methods and results: We report data of a prospective observational study conducted between August 2018 and September 2019 in MHV patients in the Salam Centre for Cardiac Surgery built in Khartoum, by Emergency, an Italian Non-Governmental Organization, to evaluate the quality of anticoagulation control and the risk of thrombotic complications.

Results: We studied 3647 patients (median age 25.1 years; 53.9 % female). Median Time in Therapeutic Range (TTR) was 53 % (interquartile range 37 % to 67 %) and 70 thrombotic events (rate 1.8 × 100 pt-years [95 % CI 1.38–2.23]) were recorded. Among patients in the first quartile of TTR (≤37 %), we recorded 34/70 (48.6 %) of all thrombotic events (rate 3.7 × 100 pt-years [95 % CI 2.5–5.1]), with a high mortality rate (2.2 × 100 pt-years [95 % CI 1.3–3.3]). In patients with guideline-recommended TTR (≥65 %) the event rate was 0.8 × 100 pt-years for thrombotic events [95 % CI 0.3–1.5] and 0.4 × 100 pt-years for mortality [95 % CI 0.1–0.9].

Multivariable analysis showed that having a TTR in the lowest quartile (≤37 %) and being noncompliant are significantly associated with increased thrombotic risk. Aspirin use or different valve type did not influence the thrombotic risk. Almost 40 % of all thromboembolic complications could have been potentially prevented by further improving VKA management to obtain a TTR > 37 %.

Conclusion: The thrombotic risk of MHV patients on VKAs living in a low-income country like Sudan is associated with low quality of anticoagulation control. Efforts should be made to decrease the number of non-compliant patients and to reach a guideline-recommended TTR of ≥65 %.

1. Introduction

In low-income countries, cardiac diseases confer a major healthcare problem among adults and children [1–3]. In sub-Saharian countries, a high incidence of rheumatic heart disease and congenital heart disease among children and young adults has been reported [3]. In addition,

Abbreviations: CI, confidence interval; FCSA, Italian Federation of Anticoagulation Clinics; INR, International Normalized Ratio; IQR, interquartile range; MHV, mechanical heart valve; NGO, Non-Governmental Organization; TTR, Time in Therapeutic Range; VKA, vitamin K antagonists.

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many countries have a limited number of affordable surgery and cardiology services.

The main burden of acquired cardiac diseases is related to rheumatic heart disease, which is nowadays very rare in Western countries, instead it is endemic in low-income and middle-income countries, accounting for >350,000 deaths per year [1].

In African countries, access to cardiac surgery is scarce [4–6], and in the VALVAFRICA register, only 27 of 1200 Western and Central African patients (2.2 %) requiring surgical intervention were ultimately operated [7]. For this reason, many foreign cardiosurgical missions operate in African countries with their equipment, mainly to treat patients with congenital heart disease and rheumatic heart disease [8]. However, these projects are often limited to surgical interventions without an adequate follow-up. In particular, managing long-life anticoagulant therapy (OAT) after mechanical heart valve (MHV) replacement remains a challenging issue.

The difficulties of managing oral anticoagulant treatment with Vitamin K antagonists (VKAs) for MHV are well-known [9], and the use of direct oral anticoagulants in this setting is not recommended [10]. Oral anticoagulant treatment management in low-income countries is even more complex, and the few organizations operating in Africa dealing with MHV patients reported a generally low quality of VKAs management [11–15].

The Salam Centre for Cardiac Surgery was built and is operated in Soba Al Hilla (Khartoum –Sudan) by Emergency, an Italian Non-Governmental Organization (NGO) operating worldwide, mainly in war regions and several African countries. Since April 2007, high-quality and free-of-charge medical and cardio-surgical treatment has been offered to patients. In the frame of this project, an oral anticoagulant treatment clinic has been organized to manage MHV patients after surgery.

In this paper, we present the results of a prospective observational study conducted in the oral anticoagulant treatment clinic of the Salam Centre between August 2018 and September 2019 in patients with MHV on VKAs to evaluate the quality of the anticoagulation control and the risk for thrombotic events during anticoagulation.

2. Methods

Khartoum's Salam Centre for Cardiac Surgery, Sudan, Africa, is a hospital for cardiac surgery that started operating in April 2007. The characteristics of the Salam Centre have been previously described [16]. The study has been approved on May 14th 2020 by the Ethical Committee of the University of Milan.

2.1. Patients

Patients in need of cardiac surgery for MHV implantation reach the Centre directly or after referral by Sudanese physicians or other local EMERGENCY-NGO hospitals. Within a Regional Program [16], a network has been implemented with other African countries to offer treatment for patients living outside Sudan. All patients undergo a screening evaluation visit and are required to accept periodic follow-up visits and follow an adequate lifestyle, particularly concerning the need for long-term anticoagulation therapy. Counselling is ensured by national health staff to overcome the language barrier. The surgery, hospital stay, subsequent INR measuring with oral anticoagulant treatment management, and warfarin supply are ensured to all patients free of charge.

2.2. OAT management

Since 2010, the outpatient oral anticoagulant treatment monitoring program was supported by dedicated software (PARMA and PARMA GTS, Werfen, Milan, Italy) in which 'patients' demographic and clinical data are recorded. The software suggests the oral anticoagulant treatment dose prescription using a calculation algorithm previously validated in a multicentre study [17]. For this specific project, a collaboration between Emergency and the Italian Federation of Anticoagulation Clinics (FCSA) was defined in 2017. An expert FCSA physician (N.E.) spent 12 months in the Salam Centre to improve and evaluate the OAC outpatient program outcomes.

The International Normalized Ratio (INR) range has been assigned according to the American Heart Association and American College of Cardiology guidelines published in 2014 [18]. Patients with mechanical aortic valves without risk factors for thromboembolism were maintained at a target INR of 2.5, and patients with mitral or mitral-aortic valves at an INR target $\geq$ 3.0. Adult patients received aspirin treatment if not contraindicated; furthermore, the target INR is increased by 0.5 in case of thrombotic events despite a good quality anticoagulation control. The quality of anticoagulation control was calculated as time in therapeutic range (TTR), with the linear interpolation method of Rosendaal and colleagues [19].

After MHV surgery discharge, patients receive face-to-face and written education at the Salam OAT clinic. Patients living in Khartoum or the surrounding area come to the Salam Centre for blood sampling and INR measurement with an automatic instrument (STA Compact Stago) that uses a rabbit brain thromboplastin (NeoPTimal). Patients living in areas far from the Salam Centre perform the INR measurement at a local laboratory and send the INR results back to the Salam oral anticoagulant treatment Clinic either by phone or by a photo with the phone app "WhatsApp" In any case, patients are triaged by a national nurse overseeing previous warfarin dose reports, patient clinical conditions, and compliance with the oral anticoagulant treatment prescription. Patients receive the daily warfarin dosage and the next INR control date by a trained physician; patients usually also obtain the number of warfarin tablets needed for the scheduled time interval. Patients who missed the INR control receive a phone call after two weeks, one month, and three months if necessary.

2.3. Data collection

Data were collected from August 1st, 2018, to September 30th, 2019. Patients on long-term anticoagulation were excluded from the study cohort if less than three months of observation time was available after August 1st, 2018.

To allow the calculation of TTR, for patients who started warfarin before August 1st, 2018, the INRs measured from May 1st, 2018 were included in the analysis. Patients were defined as uncompliant when INR controls were missing for >3 months. Follow-up was defined uncomplete when <3 visits were available after August 1st, 2018.

Patients included in the Regional Program were followed by the anticoagulation centre of the Salam Centre in the first month after surgery. After that, anticoagulation was managed in their own country.

Every thrombotic and major bleeding event was recorded in the database. Thrombotic events were considered all objectively confirmed episodes of transient ischemic attack/ischemic stroke confirmed by computed tomography or magnetic resonance imaging, valve thrombosis detected by transthoracic echocardiography and confirmed by fluoroscopy, or peripheral embolism (sudden onset of arterial occlusion in the extremities or abdomen, confirmed by physical examination or Doppler ultrasound). Major bleeding events were classified according to International Society of Thrombosis and Haemostasis criteria [20].

Patients were censored when an adverse event occurred or when the follow-up at the Salam Centre was stopped. Patients were considered "lost to follow-up" 6 months after missing of the planned INR test.

2.4. Statistical analysis

Baseline characteristics were summarized with descriptive statistics: categorical variables were reported as counts and percentages, and continuous variables were expressed as the median and interquartile

range (IQR). Comparisons were performed with the Fisher exact test (for categorical data) or the Mann-Whitney test (for non-normally distributed data). The incidence rate of adverse events was calculated as the number of events per 100 patient-years of observation, and rate ratios were given with their 95 % confidence intervals (CIs). The observation time ended at the end of the study or the occurrence of a major vascular outcome or death.

The association between risk factors and major vascular outcomes was tested with Cox regression over eight prespecified variables considered relevant to modulate thrombotic risk. The variables were: patient's age (divided as below/above 14 years old), TTR (divided into quartiles), sex, presence of atrial fibrillation, target INR (divided as 2.5 or ≥3), concurrent aspirin treatment, type of MHV (high risk being considered the presence of mitral or double MHV) and patient's compliance. Since the cohort was heterogeneous as to the time elapsed from the first VKA assumption and start of the observation, all individual observations were first split into three-month periods, and a time-dependent variable (time from VKA start, coded as lower or higher than six months) was added to the model. Proportional hazards assumptions were checked using weighted residuals [21]. Finally, we computed time-based population attributable fractions based on Cox regression estimates for variables showing a significant statistical association [22,23].

We used SPSS v. 25 (SPSS Inc., Chicago, IL, USA) for descriptive analysis and R v. 4.03 (R Foundation, Vienna, Austria) for data processing and regression modelling.

3. Results

By August 1st, 2018, 3967 patients were receiving VKAs for MHV at the Salam oral anticoagulant treatment clinic. We excluded 320 patients with unavailable follow-up (see Fig. 1). A total of 3647 patients were followed from August 1st, 2018, to September 30th 2019. Out of these, 334 (9.2 %) started VKA during the observation period (inception cohort), and 3313 (90.8 %) were on long-term oral anticoagulant treatment (long-term cohort). Overall, 305 (8.4 %) patients were defined as not compliant, and 98 (2.7 %) were lost to follow-up (see Fig. 1).

Patients had a median age of 25.1 years (range: 4 to 66 years) at surgery, and 1964 (53.9 %) were women. Most patients (n = 3392, 93.0 %) were Sudanese, whereas 255 (7.0 %) came from other African countries. Excluded patients were more frequently males and belonging to the Regional Program compared to included patients. No differences were found concerning the type of valve and antithrombotic treatment between the two groups. The clinical characteristics of included and excluded patients are reported in Table 1.

During the follow-up period, 78 patients died (2.3 %), 46 among included patients (rate 1.2 × 100 pt-years), and 32 among excluded patients (rate 19.2 × 100 pt-years); we were unable to find out both the cause of death and the occurrence of thromboembolic events in those excluded from the study.

In the included cohort, the median TTR was 53 % (IQR 37 %–67 %). During follow-up, 70 thrombotic events (incidence rate 1.8 × 100 pt-years [95 % CI 1.38–2.23]) were recorded. The type of thromboembolic events is reported in Table 3. Females accounted for 42/70 events (60.0 %), and a blocked valve was the more frequent thrombotic complication recorded.

Characteristics of patients according to the TTR quartiles or a TTR = 0 (very low quality of anticoagulation) are reported in Table 2. Only 36 patients (30.3 % aged 12 to 14 years) were included in the TTR = 0 group. Overall, nine thrombotic events (rate 25.0 × 100 pt-years [95 % CI 12.1–42.2]) and three deaths with a mortality rate of 8.3 × 100 pt-years [95 % CI 1.7–22.4] were recorded in the TTR = 0 group.

Among patients belonging to the first quartile of TTR (including patients with TTR = 0), 28.9 % of patients were aged <14 years, 93.6 % of patients had an INR target ≥3.0, and 19.6 % of patients were uncompliant according to the definition of our study. The rate of thrombotic events was 3.7 × 100 pt-years, for a total of 34 events (48.6 % of all thrombotic events recorded in the study) [95 % CI 2.5–5.0]. Similarly, the mortality rate was higher in comparison to patients with a TTR > 37 %. The percentage of patients aged <14 years decreased progressively across the four quartiles, varying from 28.9 % of the first quartile to 9.5 % of the fourth. In addition, the number of patients for whom a high INR target was chosen decreased from 93.6 % in the first quartile to 72.9 % in the fourth quartile, according to the low quality of anticoagulation achieved in patients with an INR target ≥3.0. Finally, among patients in the first TTR quartile, 19.2 % were noncompliant to treatment: this percentage decreases to ≤5.0 % among patients belonging to the other three quartiles.

In patients with guideline-recommended TTR (≥65 %) the event rate was 0.8 × 100 pt-years for thrombotic events [95 % CI 0.3–1.5], 1.7 × 100 pt-years for major bleedings [95 % CI 0.9–2.6], and 0.4 × 100 pt-years for mortality [95 % CI 0.1–0.9].

The multivariable analysis of risk factors associated with the thrombotic events is reported in Fig. 2. Having a TTR in the lowest

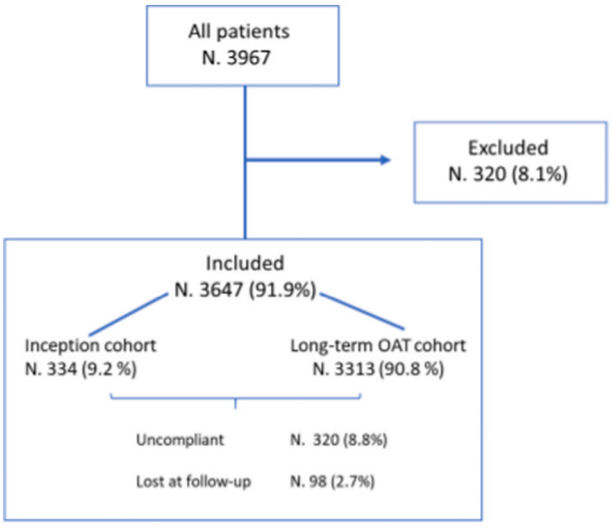

Fig. 1. Flow diagram of the study.
OAT, oral anticoagulant treatment.

Table 1
Characteristic of patients.

	Included	Excluded
N	3647	320
Women, N (%)	1964 (53.9)	135 (42.2)
Age at surgery, years, median (range)	25.1 (4–66)	25.6 (17.3–35.6)
Patients < 14 years, N (%)	636 (17.4)	70 (21.9)
Follow-up, years, median (range)	1.1 (0.1–1.2)	0.2 (0.0–1.2)
Total follow-up time (pt-years)	3940	167
Country of origin, N (%)		
Sudan	3392 (93.0)	196 (61.2)
Khartoum	965 (28.4)	44 (22.4)
Regional program	255 (7.0)	124 (38.8)
Prosthetic valve position, N (%)		
Mitral	2026 (55.5)	162 (50.6)
Aortic	541 (14.8)	44 (13.8)
Mitral + aortic	1080 (29.6)	114 (35.6)
Atrial fibrillation, N (%)	854 (23.4)	58 (18.6)
Target INR, N (%)		
2.5	498 (13.7)	39 (12.2)
3.0	3002 (82.3)	274 (85.6)
>3.0	147 (4.0)	7 (2.2)
Associated aspirin treatment, N (%)	3024 (83.9)	265 (82.8)
% TTR, median (IQR)	53 (37–67)	NA

IQR, Interquartile Range; NA, not available; TTR, Time in Therapeutic Range.

Table 2
Characteristics of patients and adverse events according to Time in Therapeutic Range (TTR) quartiles.

	TTR = 0	1st quartile TTR ≤37 %[a]	2nd quartile TTR 38–52 %	3rd quartile TTR 53–66 %	4th quartile TTR ≥67 %	Total population
N	33	924	893	884	946	3647
Women, N (%)	16 (48.5)	524 (58.7)	523 (58.6)	484 (54.8)	415 (43.9)	1964 (53.9)
Total follow-up time (pt-years)	36	926	956	957	1032	3940
Age at surgery, years, median (range)	25 (12–60)	26 (5–66)	26 (4–63)	25 (4–61)	27 (5–62)	25.1 (4–66)
Patients < 14 years, N (%)	10 (30.3)	267 (28.9)	158 (17.7)	121 (13.1)	90 (9.5)	636 (17.4)
Country of origin, N (%)						
Sudan	29 (87.9)	825 (89.3)	836 (93.6)	830 (93.9)	901 (95.2)	3392 (93.0)
Khartoum	10 (30.3)	190 (20.6)	205 (23.0)	253 (28.6)	318 (33.6)	965 (28.4)
Regional program	4 (12.1)	99 (10.7)	57 (6.4)	54 (6.1)	45 (4.8)	255 (7.0)
Prosthetic valve position, N (%)						
Aortic valve	6 (18.2)	68 (7.4)	72 (8.1)	35 (15.3)	266 (28.1)	541 (14.8)
Mitral and mitro-aortic valve	27 (81.8)	856 (92.6)	821 (91.9)	749 (84.7)	680 (71.9)	3106 (85.2)
Target INR, N (%)						
2.5	6 (18.2)	59 (6.4)	59 (6.6)	124 (14.0)	256 (27.1)	498 (13.7)
≥3.0	27 (81.8)	865 (93.6)	834 (93.4)	760 (86.0)	690 (72.9)	3149 (86.3)
Median INR (range)	1.3 (1.1–3.7)	2.3 (1.1–4.6)	2.6 (1.6–3.9)	2.7 (1.6–3.9)	2.8 (1.5–3.7)	2.6 (2.4–2.8)
Associated aspirin treatment, N (%)	28 (84.8)	785 (85.0)	717 (80.3)	742 (83.9)	780 (82.5)	3024 (82.9)
Atrial fibrillation, N (%)	7 (21.2)	181 (19.6)	225 (25.2)	228 (25.8)	220 (23.3)	854 (23.4)
Uncompliant patients, N (%)	27 (81.8)	177 (19.2)	45 (5.0)	41 (4.6)	42 (4.4)	305 (8.4)
Lost at follow-up, N (%)	5 (15.2)	52 (5.6)	16 (1.8)	17 (1.9)	13 (1.4)	98 (2.7)
Major bleeding, N (rate ×100 pt-years)	0	20 (2.2)	26 (2.7)	22 (2.3)	17 (1.7)	85 (2.2)
Thrombotic events, N (rate ×100 pt-years)	9 (25.0)	34 (3.7)	15 (1.6)	13 (1.4)	8 (0.8)	70 (1.8)
Death, N (rate ×100 pt-years)	3 (8.3)	20 (2.2)	8 (0.8)	14 (1.5)	4 (0.4)	46 (1.2)

[a] Includes patients with TTR = 0.

Table 3
Thromboembolic events during observational period.

Thrombotic events	
N (rate ×100 pt-years; 95 % CI)	70 (1.82; 1.38–2.23)
Women, N (%)	42 (60.0)
Age at surgery, years, median (range)	27 (19–41)
INR related to the event ≤1.7, N (%)[a]	23 (52.3)
Type of thrombotic events, N (%)	
Blocked valve	39 (55.0)
Stroke	18 (26.0)
TIA	6 (9.0)
Stroke+blocked valve	7 (10.0)
Fatal	7 (10.0)

[a] Available in 44/70 patients.

Table 4
Characteristics of patients and adverse events according to compliance to treatment.

	Uncompliant	Compliant
N	305	3342
Total follow-up time (pt-years)	332	3608
Males, N (%)	172 (56.4)	1511 (45.2)
Women, N (%)	133 (43.6)	1831 (54.8)
Age at surgery, years, median (range)	26 (6–60)	26 (4–66)
Patients < 14 years, N (%)	79 (25.9)	557 (16.7)
TTR 1st quartile, N (%)	177 (58.0)	747 (22.4)
Country of origin, N (%)		
Sudan	280 (91.8)	3112 (93.1)
Khartoum	58 (19.0)	908 (27.2)
Regional program	25 (8.2)	230 (6.9)
Target INR, N (%)		
2.5	51 (16.7)	447 (13.4)
≥3.0	254 (83.3)	2895 (86.6)
Associated aspirin treatment, N (%)	248 (82.9)	2684 (84.4)
Atrial fibrillation, N (%)	54 (17.7)	800 (23.9)
Major bleeding, N (rate ×100 pt-years)	3 (0.9)	82 (2.3)
Thrombotic events, N (rate ×100 pt-years)	14 (4.2)	56 (1.6)
Death, N (rate ×100 pt-years)	4 (1.2)	42 (1.2)
Inception cohort, N (%)	18 (5.9)	366 (11.0)
Lost at follow-up, N (%)	33 (10.8)	65 (1.9)

TTR, Time in Therapeutic Range.

quartile (corresponding to a TTR ≤37 %) and being noncompliant were significantly associated with increased thrombotic risk. A smaller, non-significant trend for lower risk in patients with higher INR target was observed. The risk of thromboembolic events in relation to TTR is reported in Fig. 3. The thrombotic risk was comparable in patients taking aspirin with respect to patients who did not take aspirin. Similarly, no difference was found between patients with aortic valves compared to patients with mitral or mitral-aortic valves.

Over the considered observation period, the multivariate population attributable fractions were 28 % (95 % CI 10.1–46.4), and 12.1 % (95 % CI 0.7–23.6) for TTR in the lower quartile and uncompliant behaviour, respectively. Therefore, about 40 % of all thromboembolic complications could have been potentially prevented by further improving oral anticoagulant treatment management quality.

The clinical characteristics of patients belonging to the uncompliant patients are detailed in Table 4. Briefly, uncompliant patients had an unsatisfactory quality of anticoagulation control (TTR 31 %) and a high rate of adverse events. Moreover, 25.9 % of them were aged ≤14 years.

4. Discussion

Our study is the first report on a large cohort of young patients on anticoagulant treatment with warfarin after MHV implantation in low-income countries. The overall thrombotic risk of this cohort of patients is acceptably low, despite the low quality of anticoagulation achieved. Overall, thrombotic risk in low-income countries was similar to those reported in Western country cohorts [24–27].

The Salam Centre for Cardiac Surgery of Khartoum was created by Emergency NGO, to assist as much as possible Africans who require cardiac surgery. All treatments are free, and all patients coming from African countries can get access to the hospital. In most cases, patients who reach Salam Centre are young, with valvular rheumatic heart diseases. Therefore, many MHV implantations have been performed since the starting of the clinical activities in April 2007. Conversely, MHV implantation in Western countries is progressively decreasing because the population of patients requiring cardiac surgery is old, and the use of biological heart valves is preferred, mainly to avoid long-term anticoagulation [28,29].

To date, patients with MHV are excluded from the use of direct oral anticoagulants, due to the negative results obtained when tested [30].

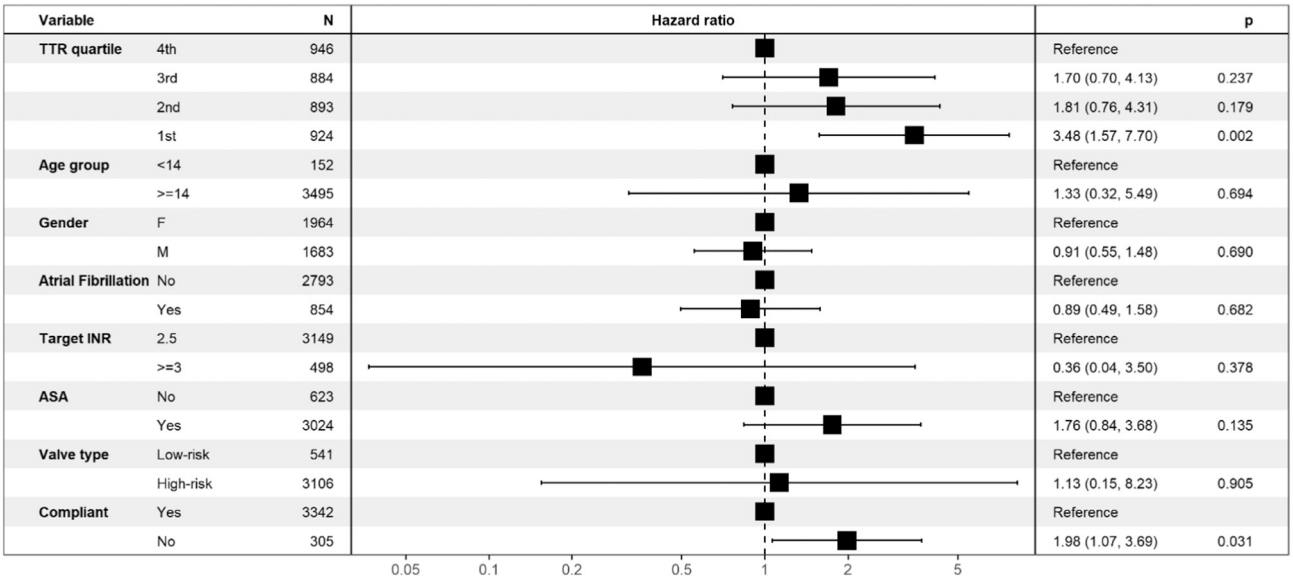

Fig. 2. Multivariable analysis of risk factors associated with thrombotic events.
ASA, acetylsalicylic acid; TTR, Time in Therapeutic Range.

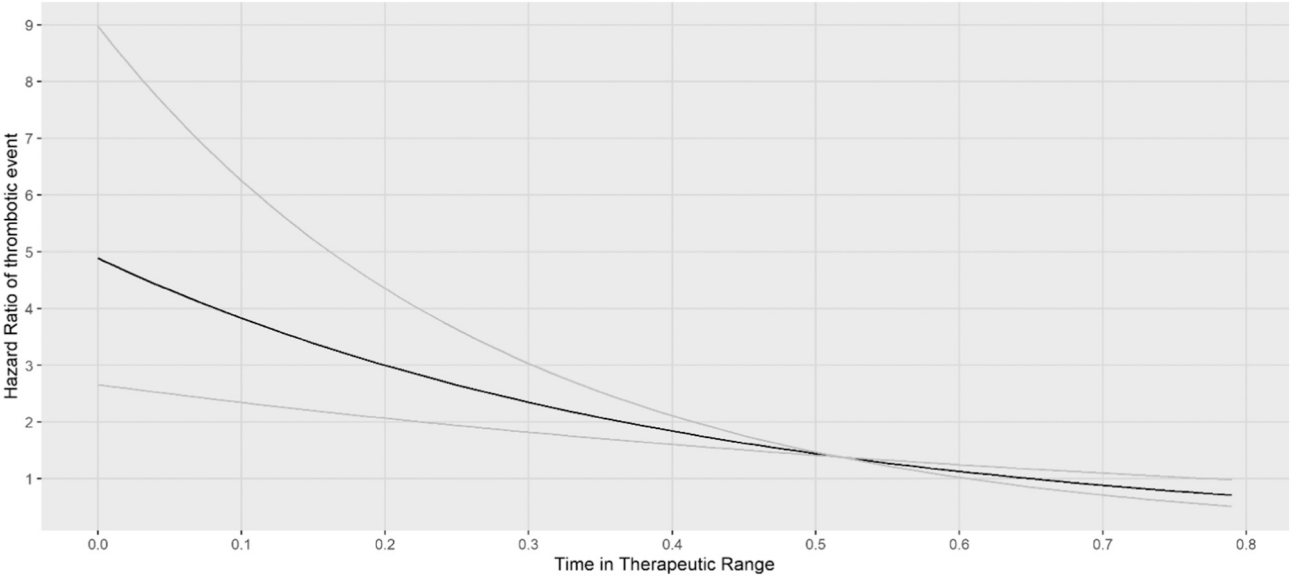

Fig. 3. Risk of thromboembolic events in relation to Time in Therapeutic Range (TTR). Hazard ratio is plotted as a continuous function from a Cox regression model with TTR adjusted for the same variables reported in Fig. 2. Baseline relative risk is set to a TTR value equal to 0.65.

Moreover, a very recently published study demonstrated that treatment with vitamin K antagonists led to a lower rate of cardiovascular events or death than rivaroxaban therapy, without a higher rate of bleeding [31]. Therefore, until new therapeutic strategies will be identified, all efforts should be made to give them VKAs treatment in the safer and simplest way possible. Warfarin management is challenging, and its use in developing countries is even more difficult than in Western countries due to inadequate clinical services or the lack of any health system. Even performing an INR measurement may be challenging due to the low number of laboratories, the expense, and scarce transportation services [32]. In addition, VKA supply is not regularly available in all African countries. The low literacy level and the difficulty in understanding the importance of this treatment may further contribute to poor adherence [7].

Only limited data are available about the quality of oral anticoagulant management after MHV implantation in African countries [11–15]. The available studies included a low number of patients and reported TTR ranging from 29 % to 48.5 %, except for a Kenyan study that included only 15 MHV patients of high social level who reach a TTR of 77 % [11]. The cost of the test, the unavailability of warfarin, the time spent for INR measuring could contribute to the overall poor quality of OAT control.

In our cohort, the analysis of TTR indicates on low-quality anticoagulation cohort, with a median TTR of 53 %. However, a lower quality of anticoagulation in MHV patients compared to patients with atrial fibrillation or venous thromboembolism has been reported also in Western countries cohorts [27,33]. The poor quality of the anticoagulation shown in MHV patients seems to be independent from the experience of treating physicians. Indeed, oral anticoagulant treatment clinics with good quality of anticoagulation reported poor quality only in MHV patients [27,33,34]. One possible explanation for this counterintuitive difference could be the INR range. When anticoagulation is

performed for stroke prevention in atrial fibrillation or venous thromboembolism, the intensity of anticoagulation refers to an INR range of 2.0 to 3.0; instead, a more intense anticoagulation is recommended for MHV patients. These patients were usually maintained at an INR range of 2.5 to 3.5, and even higher when a high thrombotic risk is estimated, and the quality of anticoagulation is progressively lower as the intensity of anticoagulation rises.

The recent Italian nationwide PLECTRUM [27] study reported a median TTR of 60 %, in patients with MHV which is low with respect to the standard usually achieved in the Italian OAT clinics [33]. In this study the TTR increased to 71.2 % among patients maintained at INR range of 2.0 to 3.0. Similarly, a median TTR of 74 % was reported in a recent Swedish study in patients maintained at INR 2.0–3.0 [26]. The finding of a poor anticoagulation in patients with higher INR ranges has been previously described in the PLECTRUM cohort [35]. High intense anticoagulation is probably associated with an unstable anticoagulant response, leading to more frequent INR testing, and higher risk of adverse events.

Women and children showed the worst quality of anticoagulation, which suggests a social fragility of these patients. For many women and children, it is extremely difficult to regularly check INR, because of the diminished access to social and economic resources. Indeed, patients living near the Salam Centre showed a better quality of anticoagulation as they could check INR easier than other included patients. Distance from hospitals with a consequent reduced access to clinical care has been reported to negatively influence health status [32,36]. On the contrary, a study conducted among a small group of MHV patients did not find any significant association between TTR and the distance from the Centre [37]. However, the study was retrospective and excluded >50 % of patients due to lack of data; moreover, it included patients living <50 km from the hospital, a distance that is not comparable with the huge distances many Sudanese people experience from health facilities. Over the observation period, the multivariate population attributable fractions showed that almost 40 % of all thromboembolic complications could have been potentially prevented by further improving quality of VKA management. The great majority of thrombotic events occurred in patients included in the first quartile of TTR, corresponding to a TTR < 37 %. Instead, the difference between patients belonging to the other three quartiles, was not clinically relevant. Therefore, efforts should be directed firstly to ameliorate the treatment in this group of patients, whereas for the other patients there is no need for a strict INR control. However, it should be noted that patients with very good TTR (≥65 %) carry the lowest risk for adverse events, in particular thrombotic events and mortality.

More than 80 % of patients in this study were also treated with aspirin, according to the North-American Guidelines published in 2014 [18]. However, the rate of thromboembolic events was not different between patients taking and not taking aspirin at the multivariable analysis. The European guidelines [28] do not recommend the routine use of aspirin in MHV patients, and our data supports this recommendation. Accordingly, the recently published American College of Cardiology/American Heart Association guidelines do not recommend the routine use of aspirin in addition to VKA [38]. Published studies suggested that the benefit of aspirin could be in patients with advanced age and/or with an elevated risk of coronary artery disease, probably due to the reduction of atherothrombotic events [39,40]. The young age of our patients could explain the inefficacy of aspirin found in this study.

Our study has several limitations. First, the study has an observational design: both the use of aspirin and the intensity of anticoagulation were decided by the treating physicians based on the estimated thrombotic risk and based on their own clinical experience. Second, about 8 % of patients have been excluded from the analysis on the quality of anticoagulation. An elevated number of deaths and adverse events occurred among these patients, but 40 % of them were included in the Regional Program, which means that they were followed in their own country.

The strength of our study is the availability of a large cohort of patients prospectively followed, with a small percentage of patients that were lost.

In conclusion, the thrombotic risk of MHV patients on VKAs living in a low-income country like Sudan is associated with low quality of anticoagulation control with implications in terms of thromboembolic events. Efforts should be made to optimize TTR by increasing the number of good-compliant patients.

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Data availability statement

Technical appendix, statistical code, and dataset available from the corresponding author at polida@aou-careggi.toscana.it.

The lead authors (NE and DP) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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CRediT authorship contribution statement

NE and DP conceived and designed the study. NE, SAA, EG, SL, FM, AM, ACS acquired and analysed the data, which was interpreted by NE, DP, AS, AT, GP and ML. NE e DP drafted the manuscript. AS, AT, GL, ST and ML revised the article critically for important intellectual content. All authors read the final version of the manuscript and gave approval for it to be published. NE had access to study data, takes responsibility for the integrity of study data and for the accuracy of data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. NE and DP are the guarantors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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