



Outcomes of Patients with a Mechanical Heart Valve and Poor Anticoagulation Control on Warfarin

Isabelle Johansson^{1,2} Alexander P. Benz^{1,3} Tanya Kovalova¹ Kumar Balasubramanian¹
 Bianca Fukakusa⁴ Matthew J. Lynn⁵ Nikhil Nair⁶ Omaike Sikder⁷ Kashyap Patel⁸ Sai Gayathri⁹
 Marlene Robinson¹⁰ Colin Hardy¹ Jessica Tyrwhitt¹ Sam Schulman¹⁰ John W. Eikelboom¹
 Stuart J. Connolly¹

¹Population Health Research Institute, Hamilton Health Sciences, McMaster University, Ontario, Canada

²Division of Cardiology, Department of Medicine K2, Karolinska University Hospital Solna, Karolinska Institutet, Stockholm, Sweden

³Department of Cardiology, University Medical Center Mainz, Johannes Gutenberg-University, Mainz, Germany

⁴Division of Cardiology, Department of Pediatrics, The University of British Columbia, Vancouver, Canada

⁵Department of Medicine, University of British Columbia, Vancouver, Canada

⁶Division of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Canada

Address for correspondence Isabelle Johansson, MD, PhD, MSc., Population Health Research Institute, David Braley Cardiac, Vascular and Stroke Research Institute, 237 Barton St., East, Hamilton, ON L8L 2X2, Canada (e-mail: isabelle.johansson@phri.ca).

⁷Division of Medicine, School of Nursing, McMaster University, Hamilton, Canada

⁸Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada

⁹Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Canada

¹⁰Department of Medicine and Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, Canada

Thromb Haemost

Abstract

Background Patients with a mechanical heart valve (MHV) require oral anticoagulation. Poor anticoagulation control is thought to be associated with adverse outcomes, but data are limited.

Objective To assess the risks of clinical outcomes in patients with a MHV and poor anticoagulation control on warfarin.

Patients/Methods We conducted a retrospective study of consecutive patients undergoing MHV implantation at a tertiary care center (2010–2019). Primary outcome was a composite of ischemic stroke, systemic embolism, or prosthetic valve thrombosis. Major bleeding and death were key secondary outcomes. We constructed multivariable regression models to assess the association between time in therapeutic range (TTR) on warfarin beyond 90 days after surgery with outcomes.

Results We included 671 patients with a MHV (80.6% in aortic, 14.6% in mitral position; mean age 61 years, 30.3% female). Median follow-up was 4.9 years, mean TTR was 62.5% (14.5% TTR <40%, 24.6% TTR 40–60%, and 61.0% TTR >60%). Overall rates of the primary outcome, major bleeding, and death were 0.73, 1.41, and 1.44 per 100 patient-years. Corresponding rates for patients with TTR <40% were 1.31, 2.77, and 3.22 per 100 patient-years. In adjusted analyses, every 10% decrement in TTR was associated with a 31% increase in hazard for the primary outcome (hazard ratio [HR]:

Keywords

- ▶ mechanical heart valve
- ▶ outcomes
- ▶ stroke
- ▶ TTR
- ▶ VKA

received

April 18, 2023

accepted after revision

September 22, 2023

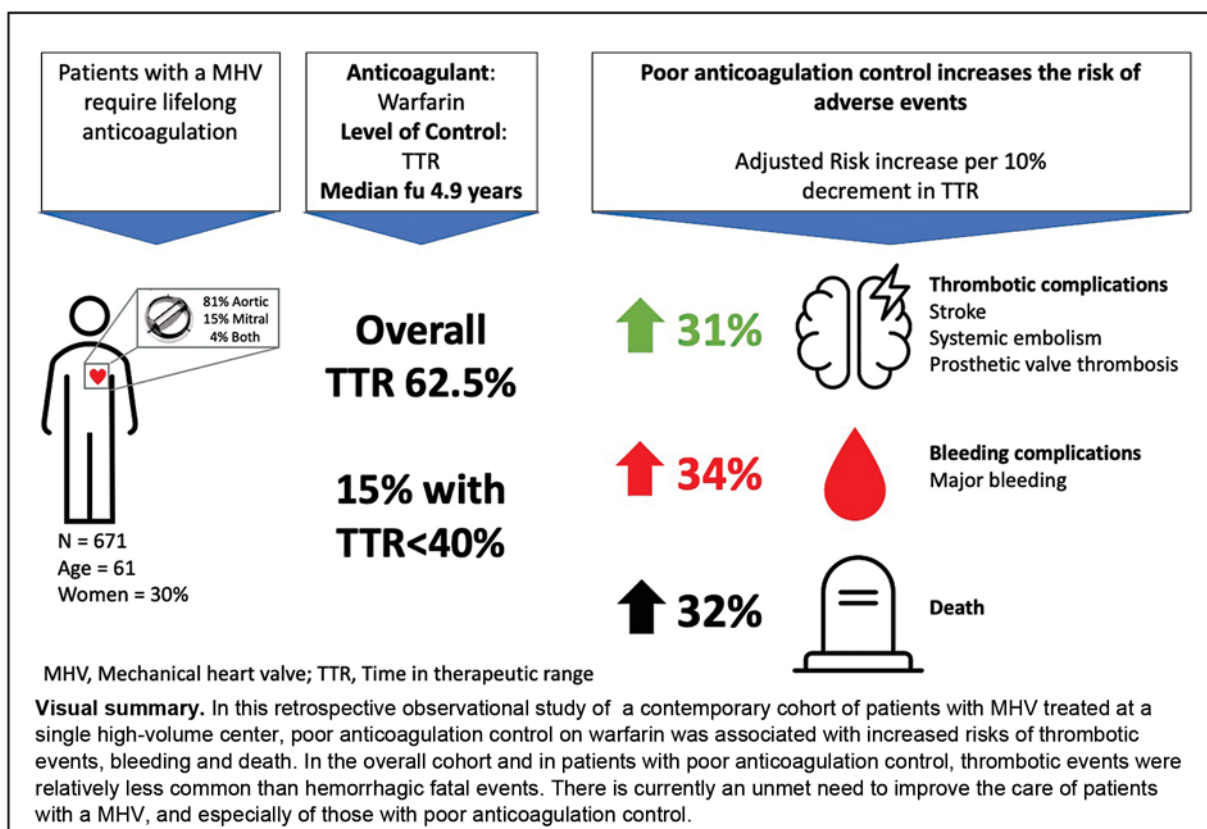
DOI <https://doi.org/10.1055/s-0043-1777827>

ISSN 0340-6245.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



1.31, 95% confidence interval [CI]: 1.13–1.52), 34% increase in major bleeding (HR: 1.34, 95% CI: 1.17–1.52), and 32% increase in death (HR: 1.32, 95% CI: 1.11–1.57).

Conclusion In contemporary patients with a MHV, poor anticoagulation control on warfarin was associated with increased risks of thrombotic events, bleeding, and death.

Introduction

Patients with a mechanical heart valve (MHV) prosthesis require lifelong oral anticoagulation due to thrombogenicity of the device.^{1,2} Only vitamin K antagonists (VKAs) such as warfarin are currently approved for this indication. Limitations of VKAs include a narrow therapeutic window, highly variable individual dose–response relationship, and multiple drug and food interactions. As a result, they require frequent blood testing and dose adjustments to maintain the international normalized ratio (INR) in a therapeutic range that provides an optimal balance between the risks of thrombotic and bleeding events.^{1,2}

Time spent in the therapeutic range (TTR) is a measure of the quality of anticoagulation control on a VKA. A large body of evidence links poor TTR with adverse outcomes in patients with atrial fibrillation (AF) or venous thromboembolism,^{3,4} but data in patients with a MHV are limited. In this study, we therefore aimed to explore the risks of important clinical outcomes according to the quality of anticoagulation control on a VKA in a contemporary cohort of patients undergoing implantation of a MHV prosthesis in the aortic or mitral

position, or both. We were specifically interested in describing the outcomes of patients with poor INR control in whom alternative treatments strategies might be considered and tested.

Methods

The primary objective of this study was to determine the risk of thrombotic events, major bleeding, and death in patients with a MHV and in whom there is poor INR control.

Study Population/Data Sources

This was a retrospective single-center observational database linkage study undertaken at the Anticoagulation Clinic at the Hamilton General Hospital, Hamilton, Ontario (Canada), a tertiary care level university clinic. Interventions are coded according to the Canadian Classification of Intervention [CCI] coding system. This enables the determination of all contacts with physicians and hospitals using unique encoded identifiers and linked administrative databases. The Anticoagulation Clinic at the Hamilton General Hospital monitors INR and warfarin dosing using the software

DAWN AC, Version 7, 4S Information Systems Ltd, Cumbria, England, United Kingdom. The DAWN database records serial INR measurements enabling prospective follow-up of anticoagulation control.

We identified all patients who underwent aortic- or mitral-valve replacement and received a bi-leaflet MHV prosthesis at the Hamilton General Hospital from January 1, 2010 through December 31, 2019 [CCI codes 1.HV.90.LA-CF** and 1.HV.90.WJ-CF-N**]. We extracted demographic and clinical data at the time of MHV implantation as well as follow-up data from subsequent hospital and outpatient visits linked to their unique encoded identifiers. We thereafter identified all MHV patients who were managed at the Anticoagulation Clinic at the Hamilton General Hospital during that period. We extracted clinical information and INR results from the DAWN AC database until February 1, 2021. Through individual-level data linkage, we selected patients that were identified in both databases (i.e., the hospital administrative and the DAWN AC databases). Patients receiving a VKA other than warfarin were excluded. Patient selection is detailed in ►Fig. 1.

For the final patient population, we undertook a comprehensive manual chart review to extract data on clinical information and events spanning the period from their MHV implantation (January 2010 through December 2019) to 90 days after the last recorded INR. A grace period of 90 days after the last INR was applied to catch events that occurred soon after the last recorded INR. The manual data extraction was conducted by six trained assistants, familiar with the unique electronic medical record systems, using electronic data extraction forms. To assure consistency of collected data, each assistant received extensive training prior to initiating the data extraction. The training included

individual and group sessions with information on outcomes of interest, test cases, and written supporting documentation. The local principal investigators (I.J. and A.P.B.) assured the fidelity of the data collection protocol by performing reviews in duplicate for randomly selected patient charts allotted to each student and for patient charts where there were doubts. All events were adjudicated by trained physicians using standard definitions, and any uncertainty was adjudicated in duplicate and if needed, discussed with senior investigators.

Anticoagulation Control

We used INR values beyond 90 days after the MHV implantation until last recorded INR value for each patient. The landmark at 90 days was selected because INR may be less well controlled during the first 90 days postoperatively and because factors related to the surgery itself are believed to be a major contributor to the high risk of thromboembolism during this period.^{5,6} We evaluated the quality of anticoagulation control by means of TTR calculated using linear interpolation according to the Rosendaal method,⁷ separately for individuals according to their therapeutic INR ranges. Individual INR ranges were those set by the treating physician based on guideline recommendations and concomitant risk factors. For the purpose of the present analysis, we grouped INR ranges into lower INR range ($n = 516$), including patients with target INR 1.5 to 2.5 ($n = 22$) and 2.0 to 3.0 ($n = 494$), and higher INR range ($n = 155$), including those with target INR 2.5 to 3.5 ($n = 154$) and 3.0 to 4.0 ($n = 1$).

To describe baseline characteristics and to explore the risk of clinical outcomes according to anticoagulation control, we categorized patients in three groups of TTR: very poor, TTR <40%; poor, TTR 40 to 60%; and good, TTR >60% over the full

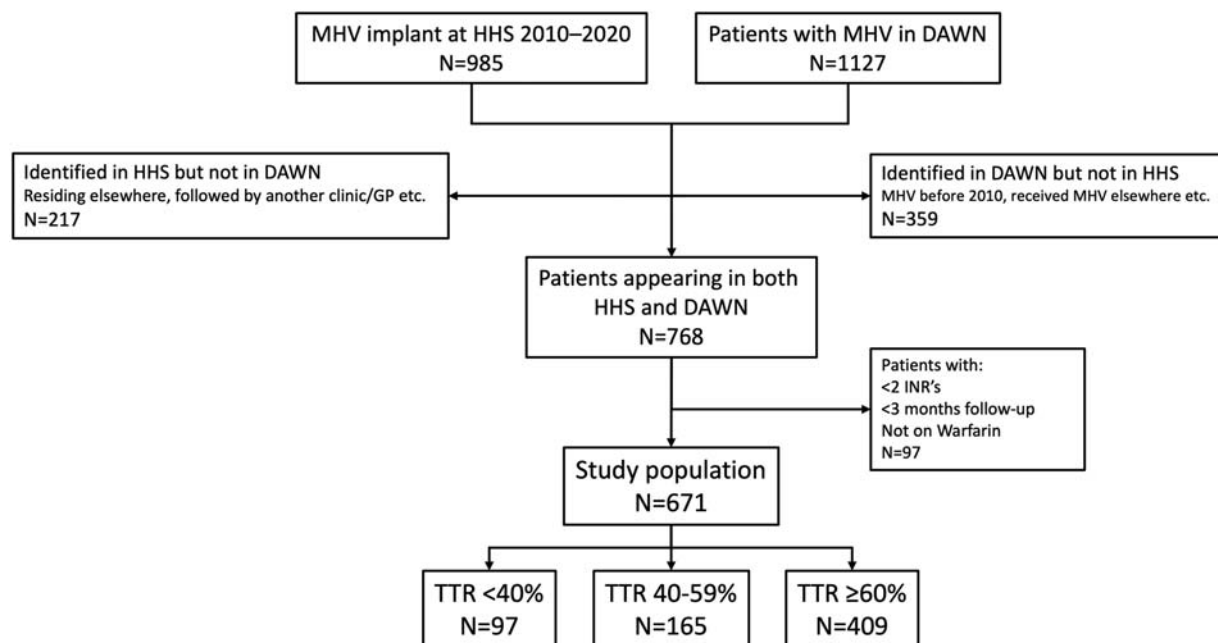


Fig. 1 Patient selection from Hamilton Health Sciences (HHS) administrative databases and from DAWN anticoagulation software database for the Thrombosis Clinic at Hamilton General Hospital. Dotted lined boxes indicate excluded patients. MHV, mechanical heart valve; TTR, time in therapeutic range.

duration of follow-up. There is no accepted standard cut-off for defining good, poor, and very poor TTR, respectively. These categories are therefore based on previous data from MHV cohorts^{8,9} and AF populations^{10–12} and further informed by clinical expertise.

Outcomes and Definitions

The primary outcome was a composite of ischemic stroke, systemic embolism (SE), or prosthetic valve thrombosis. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria,¹³ and deaths were key secondary outcomes. Other secondary outcomes included a composite outcome of ischemic stroke, SE, prosthetic valve thrombosis, major bleeding, transient ischemic attack (TIA), myocardial infarction (MI), deep vein thrombosis (DVT), or pulmonary embolism (PE), its individual components as well as ISTH clinically relevant nonmajor bleeding. Outcome definitions are listed in the ►Supplementary Material (available in the online version).

Statistical Analysis

We summarized distributions of baseline patient characteristics overall and stratified by TTR-groups; TTR <40%, 40 to 60%, and >60%. Continuous variables are presented as means and standard deviations (SDs) and categorical variables as counts and proportions. We used ANOVA to evaluate differences between means for normally distributed variables, and Fisher's exact test or Chi-square test for differences in frequency distribution for categorical variables. We calculated event rates and 95% confidence intervals (CIs) per 100 patient-years overall and by TTR group, censoring patients at the time of the event, or else at the date of the last INR, whichever came first. We further visualized time to events with cumulative incidence function curves, accounting for the competing risk of death where appropriate (truncated at 6 years) and formally compared incidence rates with Gray's tests for the primary and secondary thromboembolic and bleeding outcomes, and with log-rank test for death. We evaluated event rates per 100 person-years, and 95% CIs, per 10% decrements in TTR and visualized the output with smoothed continuous event rate plots. We further used regression models to assess the association between anticoagulation control (presented as hazard ratio [HR] per 10% decrement in TTR) and outcomes; the Fine-Gray model for nonfatal outcomes to evaluate the sub-distribution hazard function using death as a competing event, and Cox proportional hazards model to evaluate the risk of death. HRs for the associations between 10% decrements in TTR and outcomes were evaluated in unadjusted and adjusted analyses (model 1: adjusted for age and sex; model 2: adjusted for age, sex, therapeutic INR range, and valve position). The variables in the multivariable model were selected based on known prognostic importance in this patient population. The assumption of proportional hazards was assessed by visual inspection of the survival curves, and by including a time-treatment interaction term in the regression model (time log-transformed). Since the groups with TTR 40 to 60% and >60% had substantially longer follow-up periods than those

with TTR <40%, we undertook a sensitivity analysis for all outcomes analyses in which we truncated the follow-up time at 5 years for all patients (hence censoring any event which happened after that). The significance of the interaction was tested at 5% type I error level. A two-sided *p*-value of <0.05 was considered statistically significant. Data were analyzed using SAS statistical software version 9.4

Ethical Considerations

This study was conducted in accordance with the declaration of Helsinki. The study received approval from Hamilton integrated Research Ethics Board (HiREB) with a waiver for patient consent because of the retrospective type of analysis of administrative data. All investigators involved in data abstraction had received appropriate privacy protection training and the required certification.

Results

We identified 768 individuals with sufficient available data (►Fig. 1). After excluding 95 patients with a follow-up duration at our institution of less than 90 days after MHV implantation (1 patient died, the remainder were followed by other clinics), and 2 patients that were taking a VKA other than warfarin, the final study population comprised 671 patients. Patient characteristics, overall and stratified by TTR group, are shown in ►Table 1. The average age was 60.9 (SD: 11.4) years and 30.3% were women. The majority (80.6%) had their valve prosthesis in the aortic position, 14.6% in the mitral position and 4.8% in both aortic and mitral positions; 27.1% had AF, 31.3% coronary artery disease, and 30.4% hypertension. Concomitant antiplatelet therapy at baseline was recorded in 45% of the patients.

The overall mean TTR over the duration of follow-up was 62.5% (SD: 19.6); however, 14.5% (*n* = 97) had a TTR <40%, 24.6% (*n* = 165) had a TTR between 40 and 60%, while 61% (*n* = 409) had TTR >60%. Patients with poorer TTR were younger, more often treated according to a higher INR range (49.5% of those with TTR <40%, 37.6 and 11.0% in those with TTR 40–60% and TTR >60% respectively, *p* < 0.001), and relatively more often had received a MHV in the mitral position (25.8%, 23.0% and 8.6% going from the poorest TTR [<40%] to the best [>60%], *p* < 0.001). The distribution of sex and comorbidity pattern did not significantly differ between the TTR groups.

Clinical Outcomes

The last day of follow-up was February 1, 2021. By then, 470 patients were actively followed by the clinic while 201 were inactive (had moved or transitioned to family practice or another outpatient clinic, or had died). The group of patients with very poor TTR were to a larger extent inactive or had died by the end of the study period compared with the patients with better anticoagulation control (50.5% of those with TTR <40%, 37.0 and 22.2% in those with TTR 40–60% and TTR >60% respectively, *p* < 0.001). The median duration of treatment from the landmark at 90 days after MHV implantation through the last day of follow-up was 4.9 (interquartile

Table 1 Baseline information and treatment overall and stratified by TTR group

	Overall	TTR			p-Value
		<40%	40-60%	>60%	
Variable	N = 671	N = 97 (14.5%)	N = 165 (24.6%)	N = 409 (61.0%)	
Demographics					
Age, y	60.9 ± 11.4	58.1 ± 11.6	61.1 ± 12.1	61.5 ± 11.0	0.04
Female sex	203 (30.3)	38 (39.2)	51 (30.9)	114 (27.9)	0.09
BMI ^a	30.2 ± 6.8	28.7 ± 6.9	30.1 ± 6.9	30.7 ± 6.7	0.11
LVEF ^a	56.3 ± 9.2	55.5 ± 8.6	55.9 ± 8.1	56.6 ± 9.7	0.54
Valve position					
Aortic	541 (80.6)	66 (68.0)	112 (67.9)	363 (88.8)	<0.001
Mitral	98 (14.6)	25 (25.8)	38 (23.0)	35 (8.6)	<0.001
Both	32 (4.8)	6 (6.2)	15 (9.1)	11 (2.7)	0.0039
Comorbidities					
Atrial fibrillation	182 (27.1)	25 (25.8)	47 (28.5)	110 (26.9)	0.88
Hypertension	204 (30.4)	28 (28.9)	50 (30.3)	126 (30.8)	0.93
Heart failure	77 (11.5)	15 (15.5)	22 (13.3)	40 (9.8)	0.20
Diabetes	129 (19.2)	16 (16.5)	35 (21.2)	78 (19.1)	0.64
Coronary artery disease	210 (31.3)	24 (24.7)	58 (35.2)	128 (31.3)	0.21
Creatinine ^a , µmol/L	92.8 ± 61.6	98.4 ± 65.1	101.5 ± 93.3	87.9 ± 40.7	0.08
eGFR ^a mL/min/1.73 m ²	76.3 ± 21.7	73.7 ± 24.7	74.1 ± 25.1	77.8 ± 19.3	0.11
Hemoglobin level ^a , g/L	123 ± 22.2	115.8 ± 22.6	121.6 ± 23.1	125.2 ± 21.3	0.0009
Treatments					
Antiplatelet ^b	302 (45.0)	38 (39.2)	66 (40.0)	198 (48.4)	0.09
Amiodarone	37 (5.5)	4 (4.1)	9 (5.5)	24 (5.9)	0.79
INR target					
Lower INR target ^c	516 (76.9)	49 (50.5)	103 (62.4)	364 (89.0)	<0.001
Higher INR target ^d	155 (23.1)	48 (49.5)	62 (37.6)	45 (11.0)	<0.001
TTR %	62.5 ± 19.6	28.3 ± 11.1	51.2 ± 5.8	75.2 ± 9.9	<0.001
Treatment status at the end of follow-up, n (%)					
Active	470 (70.0)	48 (49.5)	104 (63.0)	318 (77.8)	<0.001
Inactive/deceased	201 (30.0)	49 (50.5)	61 (37.0)	91 (22.2)	<0.001
Warfarin treatment duration ^e , median years	4.9 (2.3–7.3)	2.3 (1.0–4.8)	5.0 (2.3–7.2)	5.5 (3.1–8.0)	<0.001

Abbreviations: BMI, body mass index; INR, international normalized ratio; LVEF, left ventricular ejection fraction; SD, standard deviation; TTR, time in therapeutic range; VKA, vitamin K antagonist.

Note: Values are n (%), mean ± SD, or median (interquartile range).

^aMissing data for BMI (n = 242); LVEF (n = 109); creatinine (n = 5); eGFR (n = 5); hemoglobin (n = 5).

^bAspirin and/or clopidogrel.

^cLower INR target: 22 had INR target range 1.5–2.5 and 494 had INR target range 2.0–3.0.

^dHigher INR target: 154 had INR target range 2.5–3.5 and 1 had INR target range 3.0–4.0.

^eStart of follow-up on day 90 postsurgery.

range [IQR]: 2.3–7.3) years (► **Table 1**). Patients in the poorest TTR group had the shortest median duration of follow-up, which gradually increased with better TTR group (2.3 [IQR: 1.0–4.8] years in TTR <40%, 5.0 [2.3–7.2] years in TTR 40–60%, and 5.5 [3.1–8.0] in TTR >60%, $p < 0.001$).

Counts and event rates per 100 patient-years for the primary and secondary outcomes are reported in ► **Table 2**. There were 24 patients with a primary thromboembolic

outcome (ischemic stroke, SE, or prosthetic valve thrombosis) and 45 patients with a first major bleeding outcome, translating into an incidence rate of 0.73 (95% CI: 0.49–1.10) and 1.41 (95% CI: 1.04–1.91) events per 100 person-years, respectively. Further, 73 patients had a secondary composite outcome (ischemic stroke, SE, prosthetic valve thrombosis, acute MI, major bleeding, TIA, PE, or DVT), with an incidence rate of 2.34 (95% CI: 1.83 to 2.98) events per 100 person-years. There were

Table 2 Total events and proportions, and event rate and 95% confidence interval (CI) per 100 person-years for the primary and secondary outcomes, overall and stratified by TTR groups, from day 90 post-valve implantation to end of follow-up^a

	Overall, N = 671		TTR ^a < 40%, N = 97		TTR ^a 40–60%, N = 165		TTR ^a > 60%, N = 409	
	N (%)	Event (95% CI) per 100 person-years	N (%)	Event (95% CI) per 100 person-years	N (%)	Event (95% CI) per 100 person-years	N (%)	Event (95% CI) per 100 person-years
Primary outcomes								
Ischemic stroke ^b /SE/prosthetic valve thrombosis	24 (3.6)	0.73 (0.49–1.10)	4 (4.1)	1.31 (0.48–3.57)	8 (4.8)	1.02 (0.50–2.07)	12 (2.9)	0.55 (0.31–0.98)
Secondary outcomes								
Major bleeding	45 (6.7)	1.41 (1.04–1.91)	8 (8.2)	2.77 (1.35–5.72)	15 (9.1)	2.01 (1.18–3.42)	22 (5.4)	1.02 (0.66–1.56)
Ischemic stroke ^b /SE/prosthetic valve thrombosis/MI/major bleeding/TIA/DVT/PE ^c	73 (10.9)	2.34 (1.83–2.98)	11 (11.3)	3.85 (2.06–7.22)	24 (14.5)	3.28 (2.13–5.06)	38 (9.3)	1.81 (1.29–2.52)
Death	48 (7.2)	1.44 (1.07–1.93)	10 (10.3)	3.22 (1.67–6.19)	16 (9.7)	1.99 (1.19–3.34)	22 (5.4)	0.99 (0.65–1.52)
Stroke (all)	25 (3.7)	0.76 (0.51–1.14)	3 (3.1)	0.97 (0.31–3.07)	8 (4.8)	1.01 (0.50–2.06)	14 (3.4)	0.64 (0.38–1.10)
Ischemic	18 (2.7)	0.55 (0.34–0.87)	2 (2.1)	0.65 (0.16–2.63)	6 (3.6)	0.75 (0.33–1.71)	10 (2.4)	0.46 (0.24–0.86)
Hemorrhagic	6 (0.9)	0.18 (0.08–0.40)	1 (1.0)	0.32 (0.04–2.31)	1 (0.6)	0.12 (0.02–0.89)	4 (1.0)	0.18 (0.07–0.49)
Prosthetic valve thrombosis	5 (0.7)	0.15 (0.06–0.36)	2 (2.1)	0.65 (0.16–2.65)	0 (0.0)	–	3 (0.7)	0.14 (0.04–0.42)
Myocardial infarction	8 (1.2)	0.24 (0.12–0.49)	2 (2.1)	0.65 (0.16–2.62)	4 (2.4)	0.51 (0.19–1.36)	2 (0.5)	0.09 (0.02–0.36)
Bleeding (any)	66 (9.8)	2.12 (1.64–2.73)	10 (10.3)	3.54 (1.84–6.81)	22 (13.3)	3.03 (1.94–4.75)	34 (8.3)	1.61 (1.14–2.29)
Bleeding, nonmajor clinically relevant	28 (4.2)	0.87 (0.59–1.26)	3 (3.1)	0.99 (0.31–3.13)	11 (6.7)	1.43 (0.78–2.63)	14 (3.4)	0.65 (0.38–1.10)

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; MI, myocardial infarction; PE, pulmonary embolism; SE, systemic embolism; TIA, transient ischemic attack; TTR, time in therapeutic range.

^aFollow-up starting at day 90. TTR was calculated using linear interpolation (Rosendaal method), and individual target (2.0–3.0 or 2.5–3.5).

^bIschemic stroke or undetermined stroke (undetermined stroke, $n = 1$).

^cThere were 15 TIA, 3 SEs, and 0 DVT or PE.

48 deaths during the active follow-up period, corresponding to an incidence rate of 1.44 (95% CI: 1.07–1.93) per 100 person-years. During the follow-up time, 25 patients had a stroke (of which 6 were hemorrhagic and 1 undetermined), 5 had a prosthetic valve thrombosis, 3 had SE, 8 had a MI, and 15 had a TIA. No patient experienced a DVT or PE.

Outcomes According to Quality of Anticoagulation Control

The incidence rates for most outcomes were highest in the group with the poorest anticoagulation control (►Table 2). A primary thromboembolic outcome occurred in 1.31 (95% CI: 0.48–3.57) per 100 person-years in those with TTR <40%, becoming less common with improving TTR to 1.02 (95% CI: 0.50–2.07) and 0.55 (95% CI: 0.31–0.98) per 100 person-years in those with TTR 40 to 60% and >60%, respectively. A major bleeding event occurred in 2.77 (95% CI: 1.35–5.72) per 100 person-years in those with TTR <40% versus 2.01 (95% CI: 1.18–3.42) and 1.02 (95% CI: 0.66–1.56) per 100 person-years in those with TTR 40 to 60% and >60%, respectively. A secondary composite outcome was seen in 3.85 (95% CI: 2.06–7.22) per 100 person-years among those with TTR <40% versus 3.28 (95% CI: 2.13–5.06) and 1.81 (95% CI: 1.29–2.52) per 100 person-years in those with TTR 40 to 60% and >60%, respectively. Death rates were also considerably more common in those with very poor TTR; 3.22 (95% CI: 1.67–6.19) per 100 person-years in those with TTR <40% compared with those with better anticoagulation control (1.99 [95% CI: 1.19–3.34] and 0.99 [95% CI: 0.65–1.52] per 100 person-years for TTR 40–60% and >60%, respectively).

As depicted in the cumulative incidence function curves (►Fig. 2A–D), after accounting for the competing risk of death, time-to-first event did not differ significantly between the three groups according to TTR for the primary thromboembolic outcome (►Fig. 2A, Gray's test $p=0.21$) but did significantly differ for major bleeding, with worse outcomes in the poorer TTR groups (►Fig. 2B, Gray's test $p=0.049$). Further, the time-to-first secondary composite outcome differed significantly between the TTR groups (►Fig. 2C, $p=0.042$) and for death (►Fig. 2D, $p=0.0013$).

Looking at TTR as a continuous variable depicted as smoothed continuous event rate plots, event rates gradually decreased with improving TTR for both the primary thromboembolic (►Fig. 3A) and bleeding outcomes (►Fig. 3B). Corresponding unadjusted and adjusted HRs for the primary and secondary outcomes per 10% decrement of TTR are tabulated in ►Table 3. The HR for having a thromboembolic event was 1.31 (95% CI: 1.13–1.52) following full adjustment in the Fine-Gray competing risk analysis. Corresponding adjusted HR for a major bleeding event was 1.34 (95% CI: 1.17–1.52) and for a secondary composite outcome, HR 1.30 (95% CI: 1.16–1.46). Trends for these outcomes were consistent in sensitivity analyses using Cox models. The adjusted HR for the risk of death was 1.32 (95% CI: 1.11–1.57) per 10% TTR decrement.

The sensitivity analysis using a truncated follow-up time of 5 years did not alter our results.

Discussion

We explored the risks of thrombotic events, bleeding, and death according to the quality of anticoagulation control on warfarin in a contemporary cohort of consecutive patients undergoing implantation of a MHV in the aortic or mitral position from 2010 to 2019. All patients were managed at a single, high-volume Canadian tertiary care center. Our key findings were: first, very poor anticoagulation control, defined as a TTR <40%, is not uncommon (approximately 15% of patients with a MHV). Second, poor anticoagulation control was associated with increased risks of thrombotic events, major bleeding, and death. Third, hemorrhagic and fatal events were relatively more common than a composite of ischemic stroke, SE, or prosthetic valve thrombosis, irrespective of the quality of anticoagulation control.

Patients with advanced mitral or aortic valvular heart disease often will require valve replacements. MHV prosthesis implantation remains one of the most used treatment methods, especially if patients are considered unsuitable candidates for a percutaneous procedure, surgical repair, or implantation of a bioprosthetic valve.^{1,2} Compared to bioprosthetic valves, MHVs are more durable and therefore often preferred in younger patients. However, MHVs are inherently thrombogenic. Patients with such a device therefore require lifelong oral anticoagulant therapy to mitigate the risk of thromboembolic events. Currently, VKAs (e.g., warfarin) remain the only approved drug class for this indication.^{1,2} VKAs have a narrow therapeutic window and maintaining patients in the therapeutic range can be challenging, even in a high-resource setting. Overall, mean TTR of patients included in our study, managed by a specialized anticoagulation clinic, was 62.5%. This is comparable to contemporary studies of MHV patients treated with warfarin (mean TTR: 54.9–61.6%),^{14–16} while considerable variation in anticoagulation control is seen in low-resource settings (mean TTR: 29.8–53%).^{17,18} Notably, pivotal, closely monitored, DOAC versus warfarin trials in patients with AF achieved a mean TTR of 55 to 65%.^{19–23} However, our observed TTR is lower than the overall TTR (72.5%; 74.2% in aortic MHVs and 66.7% in mitral MHVs) seen in a nationwide Swedish MHV cohort similarly managed with a computer-aided warfarin dosing program.⁸ The TTR variations across studies are not fully explained but are probably largely attributed to differences in study design and study populations such as distribution of INR targets, proportion with mitral MHVs, mean age, comorbidity burden, anticoagulation monitoring strategy, and organization of health care. Our analysis extends previously published data on anticoagulation control especially for the group with very poor anticoagulation control. About one in six patients included in our study had a TTR <40%, and an additional one in four with a TTR of 40 to 60% suggesting that there is still a considerable proportion of patients with a MHV whose anticoagulation control on a warfarin is suboptimal, even in a high-income, high-volume setting. An even higher proportion of patients with poor INR control is suspected in lower resource settings. For example, Erba and colleagues in their single-center

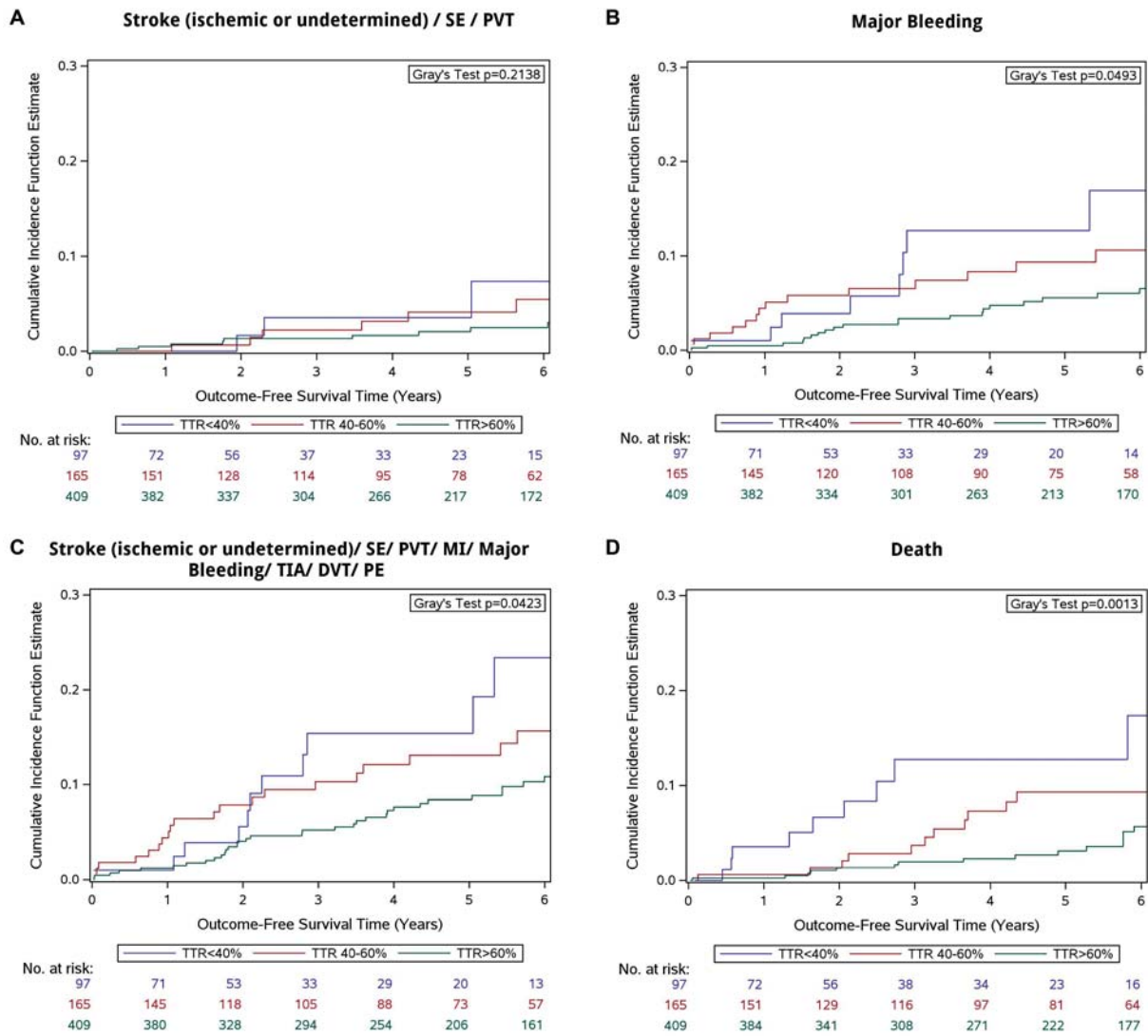


Fig. 2 Clinical outcomes, by TTR category. Cumulative incidence function curves for the primary composite thromboembolic outcome (A), major bleeding (B), secondary composite thromboembolic or bleeding outcome (C), and all-cause death (D). (A) to (C) calculated keeping death as the competing event. TTR category ranges are <40%, 40 to 60% and, >60%, with higher TTR indicating better anticoagulation control. TTR, time in therapeutic range.

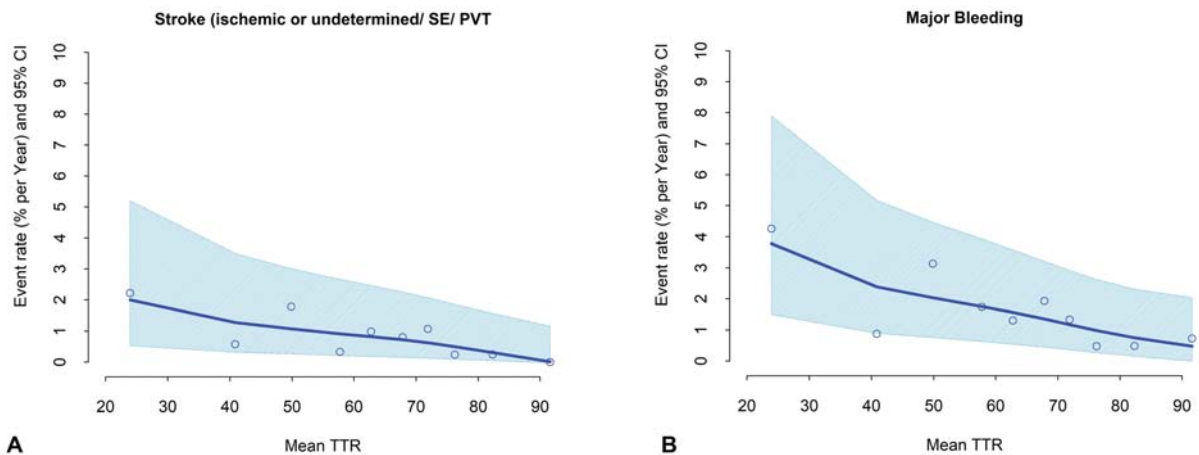


Fig. 3 Hazard of clinical outcomes by decreasing mean TTR. Smoothed continuous event rate plots for (A) the primary thromboembolic outcome (stroke [ischemic or undetermined], systemic embolism [SE] or prosthetic valve thrombosis [PVT]) and (B) major bleeding. TTR, time in therapeutic range.

Table 3 Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the primary and selected secondary outcomes by 10% TTR decrements and competing risk

	Unadjusted		Adjusted Model 1		Adjusted Model 2	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Stroke ^a /SE/prosthetic valve thrombosis						
TTR per 10% decrement, competing risk: death	1.35 (1.10–1.66)	0.0045	1.34 (1.18–1.53)	<0.0001	1.31 (1.13–1.52)	0.0003
Major bleeding						
TTR per 10% decrement, competing risk: death	1.24 (1.08–1.43)	0.0026	1.31 (1.17–1.48)	<0.0001	1.34 (1.17–1.52)	<0.0001
Stroke ^a /SE/prosthetic valve thrombosis/MI/major bleeding/TIA/DVT/PE						
TTR per 10% decrement, competing risk: death	1.24 (1.11–1.38)	0.0002	1.28 (1.16–1.42)	<0.0001	1.30 (1.16–1.46)	<0.0001
Death						
TTR per 10% decrement	1.32 (1.13–1.54)	0.0005	1.34 (1.14–1.56)	0.0002	1.32 (1.11–1.57)	0.0021

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; MI, myocardial infarction; PE, pulmonary embolism; SE, systemic embolism; TIA, transient ischemic attack; TTR, time in therapeutic range.

Note: Follow-up starting at day 90. TTR was calculated using linear interpolation (Rosendaal method), and individual target (2.0–3.0 or 2.5–3.5). Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, INR target, and valve position.

^aIschemic or undetermined.

cohort ($n = 3647$) from a hospital clinic in Khartoum found that a quarter of the patients had a TTR <37%.¹⁷ In addition, a trial evaluating the direct factor Xa inhibitor rivaroxaban in patients with AF and rheumatic valvular heart disease, which mostly recruited from countries in Africa and South East Asia, found a mean TTR on a VKA prior to study entry as low as approximately 35%.²⁴ This poses a particular problem since MHVs are often implanted in younger patients with advanced rheumatic valvular heart disease, a disease that is mostly seen in low- and middle-income countries.^{25,26}

In our study, patients with a TTR <40% were at increased risk of thrombotic complications. The rate of a composite outcome of ischemic stroke, SE, or prosthetic valve thrombosis was 1.31 per 100 patient-years, which was higher than the risk of patients with a TTR between 40 and 60%, and considerably higher than those with TTR >60% (corresponding event rates 1.02 and 0.55 per 100 patient-years, respectively). Similarly, rates of major bleeding and death in patients with a TTR <40% (2.77 and 3.22 per 100 patient-years) were also clearly increased compared to those with better anticoagulation control. It is notable that major bleeding and death were relatively more common than thrombotic complications, even in our fairly young population of MHV patients (mean age 61 years) and irrespective of the quality of anticoagulation control. Thrombotic events were relatively rare even in the group of patients with very poor TTR (<40%). Underlying reasons for these observations are not fully understood; however, they are in line with previous findings from other observational cohorts from high-income settings,^{23,27} while observations from lower income settings show a higher incidence of thrombotic events compared to major bleeding events.^{17,18} Potential reasons may be variations in risk factors. Patients in our cohort and similar tend to be of older age with a larger comorbidity burden and therefore potentially have a higher predisposition of bleeding

events compared to thrombotic events. Conversely, patients in lower income settings are more often younger with rheumatic heart disease as the reason for their MHV prosthesis. They tend to have fewer comorbidities potentially putting them at a lower risk of bleeding but at a larger risk of thrombotic complications given the more often mitral position of the MHV, known to be inherently thrombogenic.

In the primary analysis that accounted for the competing risk of death, each 10% decrement in TTR was associated with 31% (95% CI: 13–52%) increased hazard of ischemic stroke, SE, or valve thrombosis. Furthermore, TTR was a powerful and independent predictor of major bleeding and death (HR: 1.34, 95% CI: 1.17–1.52 and HR: 1.30, 95% CI: 1.16–1.46, respectively). These contemporary observations add to findings from previous studies linking poor TTR with adverse clinical outcomes,^{8,15–17,23,27,28} and continue to motivate finding new ways to improve anticoagulation control for MHV patients.

Considering our findings, and given the inherent limitations of VKA therapy, there is a clear and currently unmet need to improve care of patients with a MHV, and especially of those with poor anticoagulation control. There have been several efforts to directly improve the quality of INR control. Notable examples include algorithmic approaches based on weekly dosing of warfarin, which have proven successful in other settings,^{29,30} and the widespread use of point-of-care testing.³¹ However, although VKA treatment of patients treated at our center were managed with a validated dosing algorithm, the proportion of patients with a TTR <40% was as high as approximately 15%. Alternative INR target ranges have been proposed to improve TTR and clinical outcomes but require further safety and efficacy evidence before their incorporation into practice guidelines. Higher therapeutic ranges for VKA therapy, e.g., INR 2.5 to 3.5 or 3.0 to 4.0, which are sometimes used in patients with a MHV in the mitral position or in the

presence of additional risk factors, have been associated with an excess in event rates, especially bleeding.²⁷ Further, evidence suggests that a lower therapeutic range might yield a net benefit to patients with a MHV, because it may be easier to reach and maintain, and potentially reduces bleeding.^{32–34} This is particularly important as contemporary implants might be less thrombogenic than historical devices. In our study, the rate of thrombotic outcomes was lower than we had anticipated, even in the group with poorest anticoagulation control while the risk of bleeding was more concerning, especially in the poorer TTR groups. Interestingly, patients with the higher INR ranges in our study were overrepresented in the very poor anticoagulation control (50% TTR <40% vs. 38% in TTR 40 to 60% and 11% in those with the best TTR >60%) lending further support to lower therapeutic ranges as a way forward. At least one ongoing randomized controlled trial is evaluating an alternative range of INR 1.5 to 2.5 against standard of care in patients with a MHV in aortic position beyond 3 months after surgery (LIMIT, ClinicalTrials.gov, identifier NCT03636295).¹⁴ Finally, if proven effective and safe in patients with a MHV, the direct oral anticoagulants (DOACs) could overcome several of the limitations of VKA therapy. However, the phase 2 REALIGN trial, which evaluated the oral thrombin inhibitor dabigatran versus warfarin, was terminated prematurely because of an excess of both thromboembolic and bleeding events in patients randomized to dabigatran.³⁵ This prompted the U.S. FDA to issue a black box warning prohibiting the use of all DOACs in patients with a MHV. Interestingly, the REALIGN trial did not show an excess risk of event rates with dabigatran in a population of patients with at least 90 days since implantation.³⁵ Further disappointment came in September 2022 when the PROACT Xa, testing regular-dose apixaban against warfarin in large cohort of patients with >3 months since implantation of a single MHV type (On-X, CryoLife, Inc.) in the aortic position, had to stop prematurely due to an excess of thromboembolic events in patients receiving apixaban.³⁶ Emerging data from small, open-label pilot studies suggest that the oral factor Xa inhibitor, rivaroxaban, could be a candidate drug to be systematically evaluated in the setting of a large scale, randomized clinical trial, especially in patients beyond 90 days since surgery.^{37,38} Our data suggest that patients with poor anticoagulation control on a warfarin, i.e., those with TTR <40%, are likely to derive the greatest absolute benefit from a pharmacological alternative. In the future, the novel drug class of oral factor XI inhibitors that are currently not yet available for routine use could be evaluated for a broad range of indications, including the prevention of thrombotic events in patients with a MHV. Further studies should also continue to evaluate whether alternative, hopefully lower INR targets can lead to improved outcomes and better quality of life for patients with MHVs.

Strengths and Limitations

The main strengths of our study are the inclusion of consecutive patients treated between 2010 and 2019, the availability of longitudinal INR data, the same computer-aided anticoagulation dosing regimen for all patients for the entire

study period, and assessment of the major outcomes by adjudicators that were blinded to the quality of anticoagulation control. Our study also has several limitations. First, this was an observational study of patients treated at a single, albeit specialized center, and sample size and number of outcome events were limited. The limited number of outcome events also meant that we were not able to adjust for comorbidities or concomitant medications in our outcome analyses. Second, our study is unable to establish causality between TTR and outcomes, and results are likely subject to residual confounding. Third, there is some chance of under-reporting of outcome events, because some events may have led to hospitalization outside of our clinical network.

Conclusion

In a contemporary cohort of patients with a MHV treated at a single high-volume center, poor anticoagulation control on warfarin was associated with increased risks of thrombotic events, bleeding, and death. In the overall cohort and in patients with poor anticoagulation control, thrombotic events were relatively less common than hemorrhagic and fatal events. Randomized trials are needed to improve outcomes of patients with a MHV and poor anticoagulation control on a VKA.

What is known about this topic?

- Patients with a mechanical heart valve (MHV) require lifelong oral anticoagulation with warfarin.
- Poor anticoagulation control has been linked with increased risks of both thrombotic and bleeding events in other populations, but data in patients with a MHV are limited.

What does this paper add?

- This was a retrospective cohort study of 671 consecutive patients undergoing MHV implantation from 2010 to 2019 at a tertiary care center, with longitudinal data of INR control for a median of 4.9 years. Using regression analysis, we explored the risks of thrombotic events, major bleeding, and death according to the quality of warfarin anticoagulation control beyond 90 days following surgery.
- Our key findings were that (1) very poor anticoagulation control (time in therapeutic range [TTR] <40%) was present in as much as 15% of patients, (2) suboptimal anticoagulation control was associated with increased risks of thrombotic events, major bleeding, and death, and (3) hemorrhagic and fatal events were relatively more common than a composite of ischemic stroke, systemic embolism, or prosthetic valve thrombosis, irrespective of the quality of anticoagulation control.
- There is a clear and currently unmet need to improve the care of patients with a MHV, and especially of those with poor anticoagulation control.

Authors' Contribution

A.P.B. and S.J.C. conceived the study idea. I.J., A.P.B., S.J.C., and J.W.E. designed the study. C.H. developed the study database. I.J., A.P.B., M.R., S.S., J.W.E., B.F., K.P., M.J.L., S.G., O.S., and N.N. conducted the data collection and data extraction. T.K. and K.B. conducted the data analyses and developed tables and figures with inputs from I.J., A.P.B., S.S., J.W.E., and S.J.C. I.J. and A.P.B. wrote the first draft of the manuscript with further inputs from J.W.E., S.S., and S.J.C. All authors read and approved the final version of the manuscript.

Funding

This study was supported by the Hamilton Health Sciences' New Investigator Fund, Swedish Heart Lung Foundation, Stockholm County Council, AstraZeneca, and Swedish Society of Cardiology also supported this project.

Conflict of Interest

I.J. has received consultancy fees from AstraZeneca, Novo Nordisk, and Boehringer Ingelheim and is supported by unrestricted research grants from Stockholm County Council, Swedish Heart-Lung Foundation, AstraZeneca, and Swedish Society of Cardiology. J.W.E. has received honoraria and/or research support from Anthos, AZ, Bayer, BI, BMS, DSI, Idorsia, Janssen, Merck, and Pfizer. M.R. has received honoraria support in the past from Bayer, BI, and Pfizer. S.S. has received research funding from Octapharma and honoraria from Alexion, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Pfizer, and Sanofi. S.J.C. has received honoraria or research grants from Bayer, BMS, Pfizer, AstraZeneca, Javelin, Daiichi Sankyo. The remaining authors have no conflicting interests to report.

References

- Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;143(05):e72–e227
- Vahanian A, Beyersdorf F, Praz F, et al; ESC/EACTS Scientific Document Group. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur J Cardiothorac Surg* 2021;60(04):727–800
- Wan Y, Heneghan C, Perera R, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ Cardiovasc Qual Outcomes* 2008;1(02):84–91
- Mearns ES, Kohn CG, Song JS, et al. Meta-analysis to assess the quality of international normalized ratio control and associated outcomes in venous thromboembolism patients. *Thromb Res* 2014;134(02):310–319
- Sousa-Uva M, Head SJ, Milojevic M, et al. 2017 EACTS guidelines on perioperative medication in adult cardiac surgery. *Eur J Cardiothorac Surg* 2018;53(01):5–33
- Laffort P, Roudaut R, Roques X, et al. Early and long-term (one-year) effects of the association of aspirin and oral anticoagulant on thrombi and morbidity after replacement of the mitral valve with the St. Jude medical prosthesis: a clinical and transesophageal echocardiographic study. *J Am Coll Cardiol* 2000;35(03):739–746
- Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993;69(03):236–239
- Grzymala-Lubanski B, Svensson PJ, Renlund H, Jeppsson A, Sjölander A. Warfarin treatment quality and prognosis in patients with mechanical heart valve prosthesis. *Heart* 2017;103(03):198–203
- Pastori D, Lip GYH, Poli D, et al; Italian Federation of Anticoagulation Clinics (FCSA) Determinants of low-quality warfarin anticoagulation in patients with mechanical prosthetic heart valves. The nationwide PLECTRUM study. *Br J Haematol* 2020;190(04):588–593
- Haas S, Ten Cate H, Accetta G, et al; GARFIELD-AF Investigators. Quality of vitamin K antagonist control and 1-year outcomes in patients with atrial fibrillation: a global perspective from the GARFIELD-AF registry. *PLoS One* 2016;11(10):e0164076
- Reiffel JA. Time in the therapeutic range for patients taking warfarin in clinical trials: useful, but also misleading, misused, and overinterpreted. *Circulation* 2017;135(16):1475–1477
- Pokorney SD, Simon DN, Thomas L, et al; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: results from ORBIT-AF registry. *Am Heart J* 2015;170(01):141–148, 148.e1
- Schulman S, Kearon C Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3(04):692–694
- Menichelli D, Poli D, Antonucci E, et al; The Italian Federation Of Anticoagulation Clinics Fcsa. Comparison of anticoagulation quality between acenocoumarol and warfarin in patients with mechanical prosthetic heart valves: insights from the nationwide PLECTRUM study. *Molecules* 2021;26(05):1425
- Zulkifly HH, Pastori D, Lane DA, Lip GYH. Anticoagulation control and major adverse clinical events in patients with operated valvular heart disease with and without atrial fibrillation receiving vitamin K antagonists. *J Clin Med* 2023;12(03):1141
- Havers-Borgersen E, Butt JH, Vinding NE, et al. Time in therapeutic range and risk of thromboembolism and bleeding in patients with a mechanical heart valve prosthesis. *J Thorac Cardiovasc Surg* 2020;159(01):74.e4–83.e4
- Erba N, Tosetto A, Langer M, et al. Oral anticoagulant management of patients with mechanical heart valves at the Salam Centre of Khartoum: observations on quality of anticoagulation and thrombotic risk. *Thromb Res* 2022;219:155–161
- Botsile E, Mwita JC. Incidence and risk factors for thromboembolism and major bleeding in patients with mechanical heart valves: a tertiary hospital-based study in Botswana. *Cardiovasc J S Afr* 2020;31(04):185–189
- Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361(12):1139–1151
- Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365(10):883–891
- Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365(11):981–992
- Giugliano RP, Ruff CT, Braunwald E, et al; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369(22):2093–2104
- Poli D, Antonucci E, Pengo V, et al; Italian Federation of Anticoagulation Clinics. Mechanical prosthetic heart valves:

- quality of anticoagulation and thromboembolic risk. The observational multicenter PLECTRUM study. *Int J Cardiol* 2018; 267:68–73
- 24 Karthikeyan G, Connolly SJ, Ntsekhe M, et al; INVICTUS Investigators. The INVICTUS rheumatic heart disease research program: rationale, design and baseline characteristics of a randomized trial of rivaroxaban compared to vitamin K antagonists in rheumatic valvular disease and atrial fibrillation. *Am Heart J* 2020;225:69–77
 - 25 Watkins DA, Johnson CO, Colquhoun SM, et al. Global, regional, and national burden of rheumatic heart disease, 1990–2015. *N Engl J Med* 2017;377(08):713–722
 - 26 Karthikeyan G, Guilherme L. Acute rheumatic fever. *Lancet* 2018; 392(10142):161–174
 - 27 Grzymala-Lubanski B, Labaf A, Englund E, Svensson PJ, Själander A. Mechanical heart valve prosthesis and warfarin - treatment quality and prognosis. *Thromb Res* 2014;133(05):795–798
 - 28 Vestergaard AS, Skjøth F, Larsen TB, Ehlers LH. The importance of mean time in therapeutic range for complication rates in warfarin therapy of patients with atrial fibrillation: a systematic review and meta-regression analysis. *PLoS One* 2017;12(11): e0188482
 - 29 Van Spall HG, Wallentin L, Yusuf S, et al. Variation in warfarin dose adjustment practice is responsible for differences in the quality of anticoagulation control between centers and countries: an analysis of patients receiving warfarin in the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial. *Circulation* 2012;126(19):2309–2316
 - 30 Grzymala-Lubanski B, Själander S, Renlund H, Svensson PJ, Själander A. Computer aided warfarin dosing in the Swedish national quality registry Auricula - algorithmic suggestions are performing better than manually changed doses. *Thromb Res* 2013;131(02):130–134
 - 31 Heneghan C, Ward A, Perera R, et al; Self-Monitoring Trialist Collaboration. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. *Lancet* 2012;379(9813):322–334
 - 32 Torella M, Torella D, Chiodini P, et al. LOWERing the INTensity of oral anticoagulant Therapy in patients with bileaflet mechanical aortic valve replacement: results from the “LOWERING-IT” Trial. *Am Heart J* 2010;160(01):171–178
 - 33 Puskas J, Gerdtsch M, Nichols D, et al; PROACT Investigators. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. *J Thorac Cardiovasc Surg* 2014;147(04):1202–1210, discussion 1210–1211
 - 34 Gupta S, Belley-Cote EP, Sarkaria A, et al. International normalized ratio targets for left-sided mechanical valve replacement. *Thromb Haemost* 2018;118(05):906–913
 - 35 Eikelboom JW, Connolly SJ, Brueckmann M, et al; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;369(13):1206–1214
 - 36 Wang TY, Svensson LG, Wen J, et al. Apixaban or warfarin in patients with an On-X mechanical aortic valve. *NEJM Evid* 2023;2(07): Doi: 10.1056/EVIDoa2300067
 - 37 Roost E, Weber A, Alberio L, et al. Rivaroxaban in patients with mechanical heart valves: a pilot study. *Thromb Res* 2020;186:1–6
 - 38 Duraes AR, de Souza Lima Bitar Y, Schonhofen IS, et al. Rivaroxaban versus warfarin in patients with mechanical heart valves: open-label, proof-of-concept trial-the RIWA study. *Am J Cardiovasc Drugs* 2021;21(03):363–371