



COMPLICATIONS OF WARFARIN IN PATIENTS WITH MECHANICAL MITRAL VALVE REPLACEMENT

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Abstract

Background: Warfarin remains the standard anticoagulant following mechanical mitral valve replacement (MVR); however, bleeding and thromboembolic events continue to pose significant clinical challenges. This study evaluated warfarin-related complications and anticoagulation monitoring in our local setting. **Methods:** This prospective observational study was conducted over nine months at Ibn Al-Nafees Teaching Hospital. Among 104 patients undergoing mechanical MVR with or without concomitant aortic valve replacement, 19 who developed warfarin-related complications were analyzed. Clinical characteristics, INR values, and adverse events were prospectively recorded. **Results:** The cohort comprised 13 females and 6 males (age range 18–65 years). Minor bleeding predominated (14 patients), while major complications (stroke) occurred in two patients, including one fatal case. All affected patients had elevated International Normalized Ratio (INR) values (4.0–10.0). The annualized major complication rate was 2.6% per patient-year, and minor bleeding occurred at 18% per patient-year. Rheumatic valve disease, preoperative atrial fibrillation, renal impairment, and low educational level were common among patients with complications. Events were more frequent after discharge, though this was not statistically significant. **Conclusion:** Warfarin-related complications after mechanical MVR were mainly minor bleeding events and were consistently associated with over-anticoagulation. Multiple comorbidities and limited patient education may contribute to INR instability. Structured anticoagulation monitoring and enhanced patient education may improve dose control and reduce complications.

Keywords: [Warfarin](#), [complications](#), [mitral valve](#), [heart valve prostheses implantation](#), [international normalized ratios](#)

Main Subjects: [Cardiothoracic](#)

Introduction

Warfarin remains the cornerstone of long-term anticoagulation in patients undergoing mitral valve replacement (MVR), particularly in those receiving mechanical prostheses, for whom lifelong therapy is essential to prevent thromboembolic events.¹ Despite its well-established efficacy, warfarin is associated with a narrow therapeutic window,² marked interindividual variability, and numerous drug–drug and drug–food interactions, making optimal anticoagulation difficult to achieve.¹ Consequently, patients are exposed to a continuous risk of both hemorrhagic and thromboembolic complications, especially when the international normalized ratio (INR) deviates from the recommended therapeutic range.

Patients with MVR constitute a high-risk group, as they typically require higher target INR levels compared with other indications for anticoagulation.³ Bleeding events, valve thrombosis, systemic embolization, and anticoagulation-related hospital readmissions remain important causes of morbidity and healthcare utilization in this population. These risks are further amplified by common comorbid conditions such as atrial fibrillation, renal impairment, advanced age, and limited

health knowledge,^{1,4} all of which may adversely affect anticoagulation control and clinical outcomes.

Effective warfarin therapy depends on regular INR monitoring, appropriate dose adjustment, patient adherence, and adequate education regarding medication interactions and dietary considerations.¹ However, maintaining stable anticoagulation remains challenging in routine clinical practice, particularly in resource-limited settings where access to monitoring facilities and structured anticoagulation services may be inconsistent. As a result, warfarin-related complications continue to pose a significant clinical burden worldwide.

This study was conducted to evaluate the spectrum and rate of warfarin-related complications in patients following MVR in our local setting and to compare these findings with those reported in the existing literature. By identifying common adverse outcomes and associated clinical factors, this work aims to provide context-specific data and contribute to a better understanding of anticoagulation-related risks, thereby supporting strategies to improve patient safety and long-term management.

Patients and Methods

Study Design and Setting

This study was conducted as a prospective observational cohort study at Ibn Al-Nafees Teaching Hospital for Cardiothoracic and Vascular Surgery, Baghdad, Iraq, over a period of 9 months, from February 1, 2023, to October 31, 2023.

During the study period, patients undergoing mitral MVR (**Figure 1A**) or combined mitral and aortic valve replacement with mechanical prosthetic valves (**Figure 1B**) (n=104) were prospectively monitored for warfarin-related adverse events. Only patients who developed warfarin-related complications were included in the final analysis.

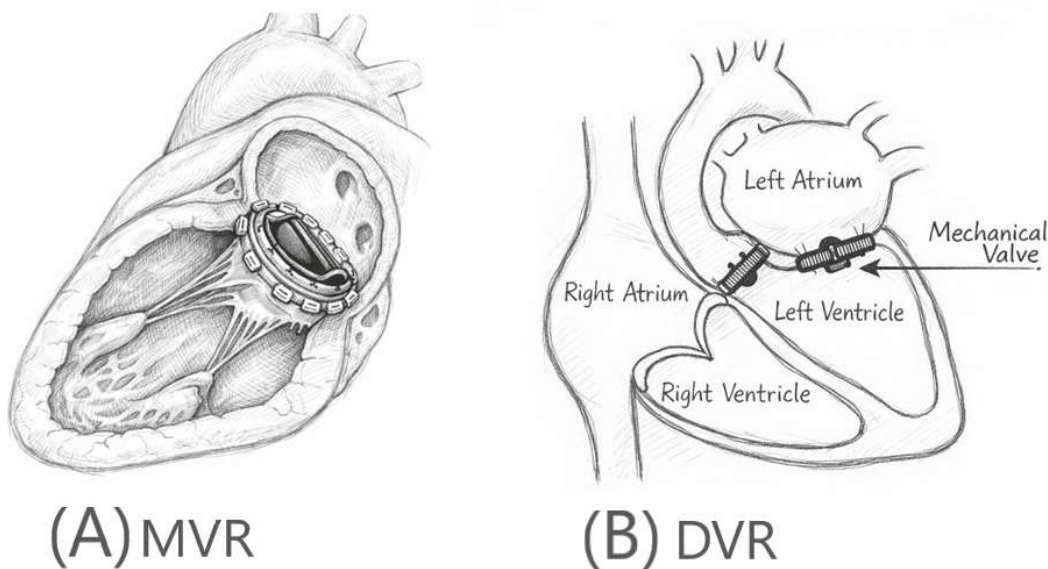


Figure 1(A): Mechanical valve in the mitral position. **(B)** Mechanical prostheses in both the aortic and mitral positions.

A total of 19 patients met the inclusion criteria, comprising 13 females and 6 males, with an age range of 18–65 years. According to the timing of complication occurrence, patients were categorized into two groups:

- **Inpatient group:** 6 patients who developed complications during their

hospital stay

- **Outpatient group:** 13 patients who developed complications after hospital discharge during follow-up at the consultation clinic.

Anticoagulation and Follow-up

All patients received oral warfarin therapy following valve replacement surgery. Postoperatively, warfarin dosing was adjusted to maintain a target international INR of 2.0–4.0, in accordance with the institutional protocol for MVR or double valve replacement (DVR). INR levels were monitored regularly, initially daily during hospitalization and subsequently at each scheduled outpatient visit, to guide dose adjustments and ensure therapeutic anticoagulation. INR values > 4.0 were considered elevated. Patients were prospectively followed throughout their hospital stay and during post-discharge outpatient visits. Monitoring and documentation of warfarin-related complications were performed by a dedicated senior clinician, ensuring consistent and accurate data collection.

Clinical and demographic data were collected prospectively by a dedicated senior house officer using a structured data collection form. The following variables were recorded:

- Demographic data, including age, sex, and level of education.
- Etiology of valvular heart disease, classified as rheumatic or non-rheumatic.
- Associated medical conditions, including atrial fibrillation (AF), renal failure, hypertension (HTN), diabetes mellitus (DM), and ischemic heart disease (IHD).

- Warfarin-related complications, documented either during hospitalization or after discharge, were classified as major or minor. Major complications included cerebrovascular accidents (CVA) and significant gastrointestinal or other site bleeding requiring hospitalization and blood transfusion. Minor complications comprised mild hematuria and ecchymoses, which were managed conservatively.

The primary outcome of the study was the pattern and type of warfarin-related complications, with a comparative analysis between the inpatient and outpatient settings.

Statistical Analysis

Due to the small sample size and low expected cell counts, Fisher's exact test was used to compare categorical variables between inpatients and outpatients. A two-tailed P value < 0.05 was considered statistically significant.

The study protocol was reviewed and approved by the local ethical and scientific committee of Ibn Al-Nafees Teaching Hospital for Cardiothoracic and Vascular Surgery. The study was conducted in accordance with the Declaration of Helsinki, and patient confidentiality was strictly maintained. All data were anonymized prior to analysis. Informed

consent was obtained from the patients involved in the study.

Results

During the 9-month study period, 104 patients underwent mechanical MVR with or without concomitant aortic valve replacement. Of these, 19 patients (13 females and 6 males; age range 18–65 years) developed warfarin-related complications and constituted the study cohort. According to the timing of complication occurrence, 6 patients developed complications during hospitalization (inpatients), while 13 developed complications after discharge during outpatient follow-up. The majority of patients had rheumatic mitral valve disease (16/19), severe valve lesions (16/19), and preoperative AF (15/19). Renal impairment was present in 16 patients. These are shown in **Table I**.

Table I shows some of the patients' characteristics.

Age range		18-65 years.
Gender		13 female & 6 males
Outpatients vs. Inpatients		13 vs. 6
Etiology of MVD (Rheumatic vs. non-rheumatic)		16 vs. 3
Type of lesion (Severe vs. Moderate)		16 vs. 3
MVR vs. DVR		17 vs. 2
Preoperative Atrial Fibrillation		15 vs. 4
Preoperative Renal Impairment		16
Educational Level	No formal education	7
	Primary school	10
	Secondary school	2

The comorbidities are shown in **Table II**. All patients included in this analysis (n = 19) demonstrated elevated INR values ranging from 4.0 to 10.0, of whom 16 developed clinical complications, as shown in **Table III**. No statistically significant differences were observed between inpatient and outpatient groups for any complication category.

Table II: The Comorbidities

Comorbidity	Number
Hypertension	8
Diabetes Mellitus	6
Ischemic Heart Disease	2
None	5

Table III: Warfarin-related complications

Complication		Outpatients (n=13)	Inpatients (n=6)	P value
Major (n=2)	Non-fatal CVA	1	0	P = 1.000
	Fatal CVA	1	0	P = 1.000
Minor (n=14)	Ecchymosis	6	3	P = 1.000
	Hematuria	4	1	P = 1.000

As mentioned earlier, during the 9-month study period, 104 patients underwent mechanical MVR $\pm$ DVR, corresponding to approximately 78 patient-years of follow-up. Two patients experienced stroke, one of which was fatal, yielding an annualized major warfarin-related complication rate of 2.6% per patient-year (95% CI: 0.3–9.2%). Fourteen patients developed minor bleeding events (nine ecchymoses and five episodes of mild hematuria), resulting in a minor complication rate of 18% per patient-year (95% CI: 9.8–30.3%). The overall warfarin-related complication rate was therefore 20.5% per patient-year (95% CI: 11.7–33.3%). Elevated INR values were documented in all 19 affected patients, indicating over-anticoagulation rather than representing clinical complications per se. When stratified by setting, complications were observed more frequently among outpatients than inpatients (13 vs. 6), likely reflecting longer exposure following hospital discharge rather than an intrinsically higher outpatient risk; however, this difference was not statistically significant (P = 1.000, Fisher's exact test).

Discussion

Mechanical prosthetic valves have been used in MVR for more than six decades,

evolving from early ball-and-cage designs to contemporary bileaflet valves with improved hemodynamics and durability. Despite these advances, mechanical valves remain inherently thrombogenic, particularly in the mitral position due to lower flow velocities and larger atrial chambers, necessitating lifelong anticoagulation.⁵ Consequently, thromboembolic and bleeding complications continue to be major determinants of morbidity and mortality following mechanical MVR.

Warfarin remains the standard anticoagulant for patients with mechanical heart valves, exerting its effect through inhibition of vitamin K–dependent clotting factors (II, VII, IX, and X). However, its narrow therapeutic window and susceptibility to dietary influences, comorbid conditions, and drug interactions result in substantial interindividual variability. Maintaining INR within the therapeutic range, therefore, remains challenging, and deviations are associated with either bleeding or thromboembolic events.⁶ In the present study, all patients who developed complications demonstrated elevated INR values, highlighting over-anticoagulation as the principal mechanism underlying adverse events.

Minor bleeding represented the most frequent complication in our cohort, while

major events were relatively uncommon. The annualized major complication rate of 2.6% per patient-year aligns with previously reported outcomes in mechanical mitral valve populations, whereas minor bleeding predominated, reflecting the clinical burden of less severe but frequent warfarin-related adverse effects. Although complications appeared more common among outpatients, this likely reflects longer exposure following hospital discharge rather than an intrinsically higher outpatient risk, a finding supported by the absence of statistical significance between groups.

The predominance of female patients and rheumatic etiology in this study reflects the epidemiology of valvular heart disease in rheumatic-endemic regions, in contrast to high-income countries where degenerative valve disease predominates.⁷ This highlights the continued reliance on mechanical valve replacement in relatively young patients in our setting, with lifelong dependence on anticoagulation therapy and its attendant risks.

Preoperative AF and renal impairment were highly prevalent among affected patients. Both conditions are known to destabilize anticoagulation control: AF increases thromboembolic risk and INR variability, while renal dysfunction alters warfarin pharmacokinetics and heightens bleeding susceptibility. Although subgroup analysis

was limited by sample size, these comorbidities likely contributed to anticoagulation instability and underscore the need for individualized dosing strategies and closer INR surveillance in high-risk patients.

Low educational attainment was another notable feature of this cohort, with only two patients having secondary-level education. Limited health literacy may adversely affect patients' understanding of warfarin therapy, recognition of adverse effects, and adherence to prescribed regimens.^{1,2} Previous studies from Iraq and elsewhere have demonstrated that structured pharmacist-led anticoagulation programs significantly improve INR control, medication adherence, and time within the therapeutic range.^{4,6,8,9} Such models may be particularly beneficial in settings where routine monitoring is inconsistent and patient education is limited.

Comorbid conditions including HTN, DM, and IHD may further increase vulnerability to complications through potential drug interactions and altered pharmacodynamics. Elevated INR values were observed in all affected patients and appeared more pronounced among outpatients, possibly reflecting variability in laboratory measurements or follow-up practices after discharge. These findings emphasize the importance of reliable INR monitoring systems, careful medication

review, and ongoing patient education, particularly during the transition from inpatient to outpatient care.

Despite advances in valve design and anticoagulation monitoring, warfarin-related complications remain a substantial clinical burden following mechanical MVR. Although direct oral anticoagulants have transformed anticoagulation in other clinical contexts, they have not demonstrated safety or efficacy in patients with mechanical valves, leaving warfarin as the only approved option. Future strategies aimed at safer anticoagulation—including structured monitoring programs, individualized dosing algorithms, enhanced patient education, and development of less thrombogenic prosthetic valves—are essential to improving long-term outcomes in this population.

Limitations of the Study

This study has several limitations. The small sample size, single-center design, and relatively short follow-up period limited statistical power and precluded meaningful subgroup analyses, thereby restricting the generalizability of the findings. Variability in outpatient INR measurements may also have influenced the assessment of anticoagulation control. Future multicenter studies with larger cohorts and longer follow-up are warranted to validate these findings and better characterize

anticoagulation-related risks after mechanical MVR.

Strengths of the Study

Despite these limitations, this prospective observational study has several important strengths. Real-time documentation enabled accurate capture of warfarin-related complications, and data collection by a dedicated senior clinician ensured consistency and clinical reliability. Furthermore, the study reflects real-world practice in a tertiary cardiothoracic center within a resource-limited setting, enhancing its relevance to similar healthcare environments. The inclusion of contextual factors such as educational level and comorbidities provides additional insight into challenges of anticoagulation management in this population.

Conclusions

Warfarin-related complications following mechanical MVR remain a significant clinical concern, with minor bleeding representing the most frequent adverse

event. Elevated INR levels were observed in all affected patients, reflecting over-anticoagulation rather than therapeutic failure. Rheumatic valve disease, AF, renal impairment, and low educational status were common among patients experiencing complications. These findings highlight the importance of structured anticoagulation monitoring, individualized dose adjustment, and enhanced patient education. Establishing dedicated anticoagulation services may improve INR control and reduce warfarin-related morbidity in this high-risk population.

List of Abbreviations

MVR – Mitral Valve Replacement

DVR – Double Valve Replacement

INR – International Normalized Ratio

AF – Atrial Fibrillation

HTN – Hypertension

DM – Diabetes Mellitus

IHD – Ischemic Heart Disease

CVA – Cerebrovascular Accident (Stroke)

IRB – Institutional Review Board

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Data Collection and Analysis: 1, 2, 3

Responsibility for Statistical Analysis: 2

Writing the Article: 2

Critical Review: 1, 2

Final Approval of the Article: 1, 2, 3

Each author believes that the manuscript represents honest work and certifies that the article is original, is not under consideration by any other journal, and has not been previously published.

Availability of Data and Material: The corresponding author is prompt to supply datasets generated during and/or analyzed during the current study on wise request.

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