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Title of Study:

A Prospective Comparative Study of Rivaroxaban versus Warfarin in Patients with Mechanical Heart Valves

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STUDY SYNOPSIS

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A Prospective Comparative Study of Rivaroxaban versus Warfarin in Patients with Mechanical Heart Valves

1. General Information

Study Title

Rivaroxaban versus Warfarin in Patients with Mechanical Heart Valves

Principal Investigator

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Study Site

Department of Cardiac Surgery and Cardiology
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Rawalpindi, Pakistan

Study Duration

From regulatory approval until completion of one year of follow-up for the last enrolled participant. Approval granted on 12th Nov 2025 From DRAP Pakistan

2. Background and Rationale

Warfarin is the current standard for oral anticoagulation therapy in patients with mechanical heart valves However, achieving the ideal balance between effective anticoagulation and minimal bleeding risks demands regular coagulation monitoring, potential dietary constraints, and vigilant drug interaction monitoring. Moreover, warfarin requires frequent INR monitoring, which may be difficult for patients in remote areas or those with limited access to healthcare facilities. Furthermore, warfarin therapy can be associated with bleeding and thromboembolic complications despite careful monitoring. As alternatives to warfarin, oral direct-acting factor Xa inhibitors have gained approval for venous thromboembolism prophylaxis, treatment, and the reduction of stroke and systemic embolization

Rawalpindi Institute of Cardiology stands as a specialized cardiac training center where countless young and courageous patients undergo life-saving mechanical valve replacement surgeries. Yet their journey does not end in the operating room. After surgery, they must rely on lifelong anticoagulation, most commonly warfarin, which demands strict adherence and frequent INR monitoring. In Pakistan, a resource-limited country where INR facilities are scarce and often inaccessible, especially for patients traveling from remote and far-flung areas, this simple requirement becomes an overwhelming burden. Many rely on local general practitioners, unable to obtain regular INR testing, and as a result, they return to us in the emergency department with devastating complications such as stuck valves, leaving families shattered and clinicians forced to intervene urgently with treatments like streptokinase. These preventable tragedies form the emotional and clinical foundation of our trial. We seek a safer, more practical alternative, rivaroxaban, which does not require frequent INR monitoring and has fewer drug interactions.

In a pilot study of four to five patients who either could not tolerate warfarin or could not access INR testing due to geographic and socioeconomic barriers, rivaroxaban allowed them to be followed for a full year without returning with such complications. Their stability and improved quality of life strengthened our resolve. It is this lived reality, of patients lost in the gaps of our healthcare system, that drives the significance of our study and fuels the need to explore rivaroxaban as a viable alternative to warfarin. Within this clinical trial, only patients who have experienced bleeding complications secondary to warfarin therapy, or who have presented to the emergency department with warfarin-related complications, are being enrolled. Such patients are transitioned to alternative anticoagulation therapy, including rivaroxaban, as clinically indicated. Additionally, patients with limited access to regular INR monitoring due to geographic or logistical constraints are included in the study.

Rivaroxaban, a direct oral anticoagulant (DOAC), has been suggested as a potential alternative, as it does not require routine INR monitoring and may offer more convenient management. However, the safety and efficacy of rivaroxaban compared to warfarin in patients with mechanical heart valves remains inadequately explored, especially in terms of bleeding and thromboembolic complications. This study aims to compare these outcomes in patients switched from warfarin to rivaroxaban due to complications or inaccessibility to INR monitoring . we intend to prove use of rivoroxaban in metallic heart valves although it has already proven benefit in patients with DVT , pulmonary embolism. Our aim is to use tablet rivoroxaban in place of warfarin in patients with metallic heart valves with strict monitoring initially. If rivoroxaban can be used with same efficacy as warfarin we will make it a standard practice in our institute this will greatly help patients especially those who lack facility of frequent INR monitoring by blood samples and those who are unable to maintain optimal INR due to food and drug interactions.

3. Review of Preclinical and Clinical Evidence

Warfarin

Warfarin inhibits vitamin K epoxide reductase, leading to reduced synthesis of vitamin K-dependent clotting factors II, VII, IX, and X, as well as proteins C and S. Its broad anticoagulant effect has proven efficacy in mechanical heart valves but requires close monitoring and dose adjustment.

Rivaroxaban

Rivaroxaban is a direct factor Xa inhibitor that blocks thrombin generation and fibrin formation. It has predictable pharmacokinetics, rapid onset of action, and does not require routine coagulation monitoring.

Relevant Studies

- **Pilot Mechanical Valve Study (NCT02128841):** No thromboembolic or bleeding events over six months in low-risk patients receiving rivaroxaban.
- **RIWA Trial:** A randomized phase II/III pilot study comparing rivaroxaban and warfarin in mechanical heart valve patients; results pending.
- **Preclinical Porcine Model:** Demonstrated reduced valve thrombosis and platelet deposition with rivaroxaban.
- **EINSTEIN-DVT and EINSTEIN-PE Trials:** Established safety and efficacy of rivaroxaban in venous thromboembolism.

These data support further investigation of rivaroxaban in mechanical heart valve patients under controlled conditions.

4. Study Objectives

Primary Objective

To compare the incidence of thromboembolic and bleeding events over a 12-month period in patients with mechanical heart valves treated with rivaroxaban versus dose-adjusted warfarin.

Secondary Objectives

- To assess the safety profile of rivaroxaban in this population.
- To evaluate treatment adherence and feasibility, particularly in patients with limited access to INR monitoring.
- To assess prosthetic valve function using serial echocardiographic measurements.

5. Trial Design

This is a **single-center, prospective comparative study**.

Study Groups

1. **Rivaroxaban Group:**
   Patients switched from warfarin to rivaroxaban due to warfarin-related complications or inability to maintain regular INR monitoring.

2. **Warfarin Group:**
   Patients continuing dose-adjusted warfarin therapy with regular INR monitoring.

Sample Size

A total of **60 patients** with mechanical heart valves:

- 30 patients in the rivaroxaban group
- 30 patients in the warfarin group

Study Duration

Each participant will be followed for **12 months**.

6. Selection and Withdrawal of Subjects

Inclusion Criteria

- Age ≥18 years
- Mechanical aortic or mitral valve replacement
- History of thromboembolic or bleeding complications on warfarin, or limited access to INR monitoring
- Ability to provide informed consent

Exclusion Criteria

- Contraindication to rivaroxaban
- Hemorrhagic stroke or ischemic stroke within the past 3 months
- Severe renal impairment (creatinine clearance <30 mL/min)
- Known bleeding disorders or high bleeding risk

Withdrawal Criteria

- Occurrence of a serious adverse event requiring discontinuation
- Non-compliance with treatment or follow-up
- Withdrawal of consent

7. Treatment of Subjects

Rivaroxaban Group

- Rivaroxaban 20 mg once daily with aspirin 75 mg once daily
- Patients weighing >80 kg may receive rivaroxaban 15 mg twice daily

Warfarin Group

- Dose-adjusted warfarin therapy
- Target INR range: 2.5–3.5

- Regular INR monitoring per standard guidelines

8. Assessment of Efficacy

Efficacy will be assessed by the incidence of:

- Thromboembolic events (stroke, TIA, valve thrombosis, DVT, PE)
- Major and minor bleeding events

Major bleeding is defined as bleeding requiring medical intervention or hospitalization. Minor bleeding includes less severe bleeding not requiring intervention.

9. Assessment of Safety

Safety assessments include:

- Monitoring of adverse events
- Laboratory evaluations (renal function, liver enzymes, hematologic parameters)
- Serial echocardiographic evaluation of valve gradients and function

All serious adverse events will be documented and reviewed.

A **Data Safety Monitoring Board (DSMB)** will oversee patient safety and trial integrity.

10. Ethical Considerations

- The study will comply with the Declaration of Helsinki and GCP guidelines
- Approval will be obtained from the Institutional Review Board/Ethics Committee
- Regulatory approval from DRAP and NBC will be secured
- Written informed consent will be obtained from all participants
- Patient confidentiality will be maintained

11. Data Handling and Record Keeping

- Data will be collected using pre-designed case report forms
- Stored in a secure electronic database
- Records will be retained for at least five years
- Access limited to authorized personnel

12. Financing and Insurance

- Medications and investigations will be provided by the hospital
- Echocardiography and follow-up visits covered by institutional resources
- Management of complications will be provided by the hospital

13. Publication Policy

- Results will be published in peer-reviewed journals
- Findings will be presented at scientific meetings
- Authorship will follow standard ethical guidelines

14. Detailed Plan of Action Flow Diagram

RIVAROXABAN (XCEPT GROUP)	WARFARIN GROUP
Eligibility confirmed • Mechanical valve • Warfarin-related complication OR poor INR access Baseline: • Clinical exam • Labs (Hb, platelets, creatinine, LFTs) • Baseline Echocardiography	Eligibility confirmed • Mechanical valve • Suitable for warfarin Baseline: • Clinical exam • Labs (Hb, platelets, creatinine, LFTs) • Baseline Echocardiography
Initiation of XCEPT Protocol • Rivaroxaban 20 mg OD + Aspirin 75 mg • >80 kg: 15 mg BD • No routine INR monitoring	Warfarin Initiation / Continuation • Dose-adjusted warfarin • Target INR 2.5–3.5 • Regular INR monitoring
Early Safety Phase (Day 0–15) • Bleeding assessment • Thromboembolic symptoms • Renal & hepatic function if indicated	Early Safety Phase (Day 0–15) • INR monitoring & dose adjustment • Bleeding / thromboembolism assessment
Echocardiography Schedule • Baseline • Day 15 • Monthly up to 12 months (Valve gradients, leaflet motion, thrombus, LVEF)	Echocardiography Schedule • Baseline • Monthly up to 12 months (Valve gradients, leaflet motion, thrombus, LVEF)
Adverse Event Pathway • Major bleed / thrombosis → Hospitalization (length of hospital/ICU stay/frequency of hospital visits) • Warfarin dose modification • Drug adjustment or discontinuation • DSMB review	Adverse Event Pathway • Major bleed / thrombosis → Hospitalization (length of hospital/ICU stay/frequency of hospital visits) • Warfarin dose modification • DSMB review
Final Outcome Assessment at 12 Months • Thromboembolic events • Major & minor bleeding • Prosthetic valve function • Hospitalization (frequency and length of stay) • Mortality & treatment adherence	

15. Statistical Analysis Plan

This study **will be conducted** as an experimental comparative study with a total sample size of 60 patients, with 30 patients allocated to each treatment group. Statistical analysis **will be performed** using IBM SPSS Statistics. A p-value < 0.05 **will be considered** statistically significant, and all tests **will be two-tailed**.

Variables

Continuous Variables

Age, body mass index, baseline international normalized ratio (INR), hemoglobin level, platelet count, serum creatinine, peak and mean transvalvular gradients, left ventricular ejection fraction (LVEF), and pulmonary artery systolic pressure (PASP) **will be analyzed** as continuous variables.

Categorical Variables

Gender, type of mechanical valve, study group (rivaroxaban or warfarin), comorbidities, previous thromboembolic events, previous bleeding events, presence of thrombus or pannus, valve leaflet motion, degree of regurgitation, bleeding events, thromboembolic events, hospitalization, and mortality at 12 months **will be analyzed** as categorical variables.

Descriptive Statistics

Continuous variables **will be summarized** as mean ± standard deviation for normally distributed data and as median with interquartile range for non-normally distributed data. Categorical variables **will be expressed** as frequencies and percentages.

Normality Testing

Given the small sample size, non-parametric tests **will be predominantly used** for the analysis of continuous variables. Normality **will be formally assessed** using the Shapiro–Wilk test for key continuous variables, including:

- Age
- Body mass index
- Baseline INR
- Mean transvalvular gradient
- Left ventricular ejection fraction (LVEF)

Based on the results of the normality testing, appropriate parametric or non-parametric statistical tests **will be applied**.

Comparison Between Groups

Continuous Variables

- The independent samples *t*-test **will be used** for normally distributed variables.
- The Mann–Whitney *U* test **will be used** for non-normally distributed variables.

Categorical Variables

- The chi-square test **will be applied**

Analysis of Outcomes

Thromboembolic events and bleeding events **will be compared** between the two groups using Fisher's exact test. Echocardiographic parameters over follow-up **will be analyzed** using the Friedman test, with repeated measures ANOVA **being used** only when normality assumptions are satisfied.