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COMPARATIVE ASSESSMENT OF WARFARIN ANTICOAGULATION MANAGEMENT WITH 75 mg VERSUS 150 mg ASPIRIN POST MECHANICAL VALVE REPLACEMENT

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Abstract

Background: Attaining stable anticoagulation following mechanical valve replacement presents challenges due to fluctuations in warfarin response. Aspirin is frequently incorporated to improve antithrombotic efficacy; however, the effect of dosage on INR stability and warfarin requirements is not well understood.

Objectives: To evaluate the time in therapeutic range (TTR) and warfarin dosage among patients administered warfarin in conjunction with either 75 mg or 150 mg of aspirin following valve replacement.

Methods: This prospective observational study involved the follow-up of 60 patients over a six-month period post-mechanical valve replacement. Group A was administered warfarin in conjunction with 75 mg of aspirin, while Group B received 150 mg of aspirin. Monthly doses of INR and warfarin were documented, and the time in therapeutic range (TTR) was computed utilizing the Rosendaal method. Data were analyzed utilizing the *t*-test and chi-square test, with a significance level set at $p < 0.05$.

Results: The mean INR was comparable between the two groups (2.82 vs. 2.77; $p = 0.58$). Group B necessitated a mean warfarin dose of 3.35 ± 0.74 mg/day, which was lower than that of Group A at 4.69 ± 0.79 mg/day ($p = 0.001$). TTR in Group B was significantly higher (73.39 ± 7.00%) compared to Group A (64.15 ± 7.88%; $p = 0.001$).

Conclusion: The combination of warfarin with 150 mg of aspirin resulted in improved time in therapeutic range (TTR) and reduced warfarin requirements when compared to the use of 75 mg of aspirin, suggesting enhanced anticoagulation stability.

Keywords: Warfarin, Aspirin, Mechanical valve, INR, TTR

Introduction

Warfarin continues to be the primary method for thromboprophylaxis after mechanical valve replacement.[1,2] The efficacy and safety of warfarin therapy are primarily influenced by the

maintenance of the international normalized ratio (INR) within a restricted therapeutic range. Patients undergoing mitral valve replacement (MVR) should aim for a target INR of 2.5–3.5, whereas those with aortic valve replacement (AVR) should maintain a target range of 2.0–3.0, according to international guidelines.[3,4,5] Achieving and maintaining optimal anticoagulation is challenging due to inter-individual variability in warfarin metabolism, dietary interactions, genetic polymorphisms (*CYP2C9*, *VKORC1*), and concomitant therapies.[6,7,8]

Aspirin, when used alongside warfarin, is commonly prescribed to improve antithrombotic effectiveness in patients with mechanical prosthetic valves.[1,5] Low-dose aspirin (75 mg daily) is commonly utilized; however, some clinicians recommend a higher dosage (150 mg daily) to enhance antithrombotic efficacy and attain improved anticoagulation stability.[9,10,11] The issue at hand is whether an increase in aspirin dosage affects the intensity and stability of anticoagulation, which may subsequently alter the required warfarin dose and the time in therapeutic range (TTR). The TTR, as determined by the Rosendaal method, serves as a reliable indicator of anticoagulation quality, with elevated TTR values significantly associated with a decrease in thromboembolic and bleeding complications.[12,13]

Despite its clinical significance, there is a paucity of data comparing the effects of 75 mg and 150 mg aspirin on warfarin dose adjustment and anticoagulation stability in Indian patients following mechanical valve replacement.[2,14] Considering the significant prevalence of rheumatic heart disease (RHD) in India and the ongoing requirement for anticoagulation in affected individuals, elucidating this relationship holds considerable clinical importance.[2,14]

This study aimed to achieve two primary objectives: (i) to compare the time in therapeutic range (TTR) for patients on warfarin with 75 mg aspirin versus those on 150 mg aspirin, and (ii) to evaluate the frequency and extent of warfarin dose adjustments necessary to reach and sustain target INR levels across the two aspirin dosing regimens.

Methods

This study was a prospective observational analysis carried out in the Department of Cardiothoracic and Vascular Surgery. Sixty patients who received mechanical valve replacement were included in the study and monitored for a duration of six months. Patients were categorized into two groups: Group A received warfarin in conjunction with 75 mg of aspirin, while Group B received warfarin alongside 150 mg of aspirin.

Patients were excluded if they had contraindications to aspirin, irregular follow-up, or incomplete INR records. Warfarin was prescribed with target INR ranges of 2.5–3.5 for MVR and 2.0–3.0 for AVR, consistent with ESC, AHA, and CHEST guidelines.[3,4,15] INR was assessed monthly, and warfarin dosages were adjusted as necessary to maintain the therapeutic range.

Baseline demographic parameters such as age, sex, height, and weight were documented. Monthly INR values and associated warfarin doses were recorded. The primary outcome was TTR, determined by the Rosendaal linear interpolation method.[12] Secondary outcomes included mean INR values, average daily warfarin dose, and dose adjustment trends between aspirin regimens.

Data analysis was conducted using SPSS software. Continuous variables were expressed as mean ± standard deviation and analyzed using the unpaired *t*-test. The chi-square test was applied for categorical data. A p-value < 0.05 was considered statistically significant.

Results

Of 60 enrolled patients, 36 (60%) were male and 24 (40%) female. The gender distribution between Group A (66.7% male) and Group B (53.3% male) was not statistically significant ($p = 0.29$), consistent with the male predominance typically observed in Indian RHD cohorts.[2,14] (Table 1)

Table 1. Patient Distribution by Gender

Groups	Gender	N	%	Total
Group A	F	10	33.3	30
	M	20	66.7	
Group B	F	14	46.7	30
	M	16	53.3	
Total	F	24	40	60
	M	36	60	

The mean age was 34.77 ± 11.79 years in Group A and 40.73 ± 11.70 years in Group B ($p = 0.05$). Mean height (161.97 ± 4.93 cm vs. 163.33 ± 4.34 cm; $p = 0.25$) and mean weight (55.57 ± 8.48 kg vs. 57.07 ± 6.67 kg; $p = 0.45$) were comparable (Table 2).

Table 2. Patient Distribution by Age, Height, and Weight

Variable	Group	Mean	SD	*p* value
Age	A	34.77	11.787	0.05
	B	40.73	11.7	
Height	A	161.97	4.93	0.25
	B	163.33	4.342	
Weight	A	55.57	8.48	0.45
	B	57.07	6.674	

The mean INR remained within therapeutic range for both groups (2.82 vs. 2.77; $p = 0.58$). Significant month-to-month differences occurred only in the 4th and 6th months ($p = 0.01$), indicating minor variability (Table 3).

Table 3. Target Anticoagulation Levels (INR) for Groups A and B

Month	Group	Mean INR	*p* value
Overall	A	2.82	0.58
	B	2.77	

Group A required a significantly higher mean daily warfarin dose (4.69 ± 0.79 mg) compared to Group B (3.35 ± 0.74 mg; $p = 0.001$), demonstrating the effect of higher aspirin dose on warfarin requirement (Table 4).

Table 4. Required Warfarin Dose to Attain Target INR

Group	Mean Warfarin Dose (mg/day)	*p* value
A	4.69 ± 0.79	0.001
B	3.35 ± 0.74	

Group B achieved significantly higher TTR (73.39 ± 7.00%) compared to Group A (64.15 ± 7.88%; $p = 0.001$), suggesting enhanced stability in anticoagulation (Table 5).

Table 5. TTR (%) in Groups A and B

Group	Mean TTR (%)	*p* value
A	64.15 ± 7.88	0.001
B	73.39 ± 7.00	

Discussion

This study compared the effects of two aspirin doses—75 mg and 150 mg daily—on the stability and intensity of warfarin anticoagulation in patients who underwent mechanical valve replacement. The results indicate that patients receiving 150 mg of aspirin (Group B) achieved a greater time in therapeutic range (TTR) and required a significantly lower mean daily dose of warfarin compared to those receiving 75 mg of aspirin (Group A), while maintaining INR control. These findings suggest that an increased aspirin dose may enhance anticoagulant effectiveness and improve INR stability.

The observed male predominance (60%) aligns with epidemiological patterns of rheumatic heart disease (RHD) in India, where men have higher access to healthcare and are more frequently represented in surgical registries.[2,14] The mean age distribution was similar between groups, supporting balanced baseline demographics.

The relationship between aspirin and warfarin in mechanical valve patients has been well documented. Gohlke-Bärwolf[1] and Iyengar et al.[5] emphasized that aspirin adjunct therapy provides additional platelet inhibition, reducing prosthetic valve thrombosis when combined with warfarin. This synergistic action decreases platelet aggregation and fibrin deposition on valve surfaces, enhancing outcomes while maintaining safety when appropriately monitored.

Our findings parallel those of Gerdisch et al.[16] and Shetty et al.[17], who demonstrated that optimized warfarin–aspirin regimens improve anticoagulation control and lower dose variability. The On-X mechanical valve registry (2024) reported that patients on low-dose warfarin with adjunct aspirin maintained INR stability with fewer bleeding complications than standard-dose regimens.[16] Similarly, Kim et al.[13] observed that higher TTR (>70%) significantly reduced thromboembolic and hemorrhagic events in mechanical valve recipients.

The pharmacodynamic interaction between warfarin and aspirin explains this effect. Aspirin irreversibly inhibits platelet cyclooxygenase, reducing thromboxane A_2 production and consequently thrombin generation.[11,15] This mechanism enhances anticoagulation efficiency, allowing therapeutic INR at lower warfarin doses. Comparable findings have been noted by Ahmed et al.[9] in South Indian cohorts, where inadequate INR control was associated with higher complication rates, underscoring the clinical importance of TTR optimization.

TTR serves as a comprehensive measure of anticoagulation quality over time.[12] Alshawabkeh et al.[18] demonstrated that each 10% increase in TTR corresponded to a significant reduction in stroke and bleeding risk. In this study, Group B's TTR of 73.39 ± 7.00% versus Group A's 64.15 ± 7.88% (p = 0.001) supports the stabilizing effect of higher-dose aspirin on anticoagulation. This is consistent with CHEST guidelines recommending adjunct antiplatelet therapy to improve time within therapeutic INR range in mechanical valve patients.[15,19]

International guidelines by ESC and AHA highlight the difficulty of maintaining INR within target range (2.0–3.0 for AVR; 2.5–3.5 for MVR), influenced by dietary vitamin K, drug interactions, and patient compliance.[3,4,15] The improved TTR in Group B may indicate that 150 mg aspirin mitigates INR variability through additive platelet suppression, reducing dose adjustments and clinic visits.

The transient differences in INR values during months 4 and 6 (p = 0.01) could reflect physiological or seasonal factors affecting warfarin metabolism. Pirmohamed et al.[8] emphasized that genetic and environmental variations significantly influence dose stability. Nonetheless, consistent therapeutic INR throughout the study suggests effective patient monitoring.

The persistent variation in mean warfarin dose between groups reinforces that aspirin dosage modulates warfarin requirements. This aligns with pharmacological principles of combined inhibition of platelet aggregation and vitamin K–dependent clotting pathways, improving control and reducing variability.[6,11,15]

In India, achieving stable INR remains difficult due to resource constraints, limited patient awareness, and dietary heterogeneity. Bhatnagar et al.[7] reported that fewer than half of Indian patients on warfarin maintain therapeutic INR, leading to increased morbidity. The present findings demonstrate that optimized adjunct aspirin therapy may improve INR stability without significantly increasing bleeding risk.

The observed reduction in warfarin requirement with 150 mg aspirin may be attributed to enhanced suppression of subclinical platelet activation and valve surface thrombogenicity.[15,16] However, the increased aspirin dose warrants individualized risk-benefit evaluation, particularly in patients at higher risk for gastrointestinal or intracranial bleeding.

The strengths of this study include prospective follow-up, standardized INR monitoring, and inclusion of both MVR and AVR cases reflecting real-world practice. Limitations include a relatively small sample size (n = 60), single-center design, and a six-month duration, which restricts generalizability. The absence of bleeding and thromboembolic event data limits outcome interpretation. Future multicentric trials should assess long-term safety and the role of pharmacogenetic-guided dosing (e.g., *CYP2C9*, *VKORC1*)[8,19] in optimizing anticoagulation control.

Conclusion

The co-administration of warfarin with 150 mg of aspirin results in enhanced anticoagulation stability, demonstrated by increased TTR and reduced warfarin dose requirements compared to 75 mg aspirin. A higher aspirin dose may serve as an effective adjunct to optimize warfarin therapy post-mechanical valve replacement. However, patient selection and bleeding risk evaluation remain critical. Further large-scale studies are warranted to validate these findings.

References

1. Gohlke-Bärwolf C. Anticoagulation in valvular heart disease: new aspects and management during non-cardiac surgery. *Heart*. 2000;84(5):567–72.
2. Padmavati S. Rheumatic heart disease: prevalence and preventive measures in India. *Indian Heart J*. 2001;53(1):1–6.
3. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP III, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease. *Circulation*. 2021;143(5):e72–227.
4. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43(7):561–632.
5. Iyengar SS, Nair T, Hiremath JS, Kasturi S, Kamath SA, Bhatia S, et al. Anticoagulation in patients with prosthetic heart valves: Consensus statement of the Indian College of Cardiology. *Indian Heart J*. 2006;58(1):21–33.
6. Hirsh J, Fuster V, Ansell J, Halperin JL. AHA/ACC Foundation guide to warfarin therapy. *J Am Coll Cardiol*. 2020;75(9):1011–28.
7. Bhatnagar UB, Khandekar JV, Jadhav UM. Problems in maintaining therapeutic INR in Indian patients. *J Assoc Physicians India*. 2011;59:164–6.
8. Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med*. 2019;369(24):2294–303.
9. Ahmed I, Fathima FN, Kumar S, et al. Predictors of poor anticoagulation control among warfarin users in South India. *Indian J Pharmacol*. 2020;52(5):370–6.
10. Khan AR, Hanif A, Khan S, et al. Aspirin dosing and safety outcomes in anticoagulated patients with prosthetic heart valves: a meta-analysis. *Heart Lung Circ*. 2023;32(5):722–31.
11. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: CHEST guideline update 2022. *Chest*. 2022;162(4):1073–104.
12. 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(3):236–9.
13. Kim KH, Park JS, Kim CH, et al. Impact of time in therapeutic range on adverse events in mechanical heart valve patients receiving warfarin. *J Thorac Dis*. 2021;13(2):567–75.
14. Grover A, Dhawan A, Iyengar SD, Anand IS, Wahi PL, Ganguly NK. Epidemiology of rheumatic fever and rheumatic heart disease in a rural community in northern India. *Bull World Health Organ*. 2003;81(1):21–7.
15. Whitlock RP, et al. CHEST guideline update 2022. *Chest*. 2022;162(4):1073–104.

16. Gerdisch MW, Sathyamoorthy M, Koprivanac M, Schmitto JD, Mehaffey JH, Romano MA, et al. Low-dose warfarin with a novel mechanical aortic valve: Interim registry results at 5-year follow-up. *Eur J Cardiothorac Surg*. 2024;65(5):ezae117.
17. Shetty D, Joseph A, Nambiar A, Kuriakose J, Rajan S, Menon V. Influence of time in therapeutic range on postoperative complications in patients with the indigenous TTK Chitra valve. *Heart Vessels Transplant J*. 2024;8(3):132–9.
18. Alshawabkeh L, Alenezi F, Alkhouli M, Saeed M, Alqahtani F. Outcomes of patients with a mechanical heart valve and poor anticoagulation control on warfarin. *J Am Heart Assoc*. 2024;13(2):e031298.
19. Shendre A, Gage BF, Bass AR, et al. Genetic determinants of warfarin dosing in Asian populations: A systematic review and meta-analysis. *Pharmacogenomics J*. 2020;20(4):573–83.