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Research Article

STUDY OF SAFETY AND EFFICACY OUTCOMES OF DOACS VS CONVENTIONAL ORAL ANTICOAGULATION IN PATIENTS WITH MITRAL STENOSIS

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A R T I C L E I N F O

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A B S T R A C T

Background: AF is associated with risk of thromboembolism events. DOACs are effective in preventing thromboembolism among AF patients. However patients with moderate to severe MS have been excluded from all pivotal studies. Warfarin remains only oral anticoagulants in such patients **Aim of the Study:** To validate efficacy and safety of DOACs vs COACs (Warfarin) in patients with mitral stenosis with Atrial fibrillation irrespective of severity of mitral stenosis. **Material & Methods:** The study was in 150 patients with rheumatic heart disease with mitral stenosis with AF regardless of severity. Prospective and hospital based study. **Results:** Among patients on DOACs 97.3% (36/37) treated with dabigatran and in conventional oral anticoagulation (COACs) 37.83% (14/37) and 62.14% (23/37) patients on warfarin and acenocoumarol respectively. Among COACs (warfarin) group two i.e.(5.4%)patients were developed ischemic stroke during follow up which was statistically insignificant as compared to DOACs group, in which no patient were developed ischemic stroke. Among COACs (warfarin) two patients i.e. 5.4% developed other bleeding manifestations such as nasal or gum bleeding and one patient i.e.2.7% patients developed other bleeding manifestations such gum bleeding which is statistically insignificant.

INTRODUCTION

AF is associated with risk of thromboembolism events. However patients with moderate to severe MS and mechanical prosthetic valves have been excluded from all pivotal studies[1] Warfarin remains only oral anticoagulants in such patients[2]. AF combined with moderate to severe MS requires mandatory anti-coagulations as it increases risk of stroke by 17 times Stroke or systemic embolism can be first manifestations of mitral stenosis even before development of other symptoms [3].In anticoagulation therapy using VKA, the lowest risk of complications is achieved by maximising the time in the optimum therapeutic range (TTR), with an international normalised ratio (INR). An INR range between 2 to 3.5 is the optimum range for most indications. The efficacy of warfarin in the prevention of thromboembolism can be hampered by poor quality anticoagulation mainly in developing countries so it is desirable to determine the efficacy of DOACs in patients with AF and mitral stenosis[4].

Aims and Objectives of Study

To validate efficacy and safety of DOACs vs COACs (Warfarin) in patients with mitral stenosis with Atrial fibrillation irrespective of severity of mitral stenosis.

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REVIEW OF LITERATURE

The normal mitral orifice area is 4 to 6 square centimeters. Under normal physiologic conditions, the mitral valve opens during left ventricular diastole to allow blood to flow from the left atrium to the left ventricle. The pressure in the left atrium and the left ventricle during diastole are equal. The left ventricle gets filled with blood during early ventricular diastole. The incidence of atrial fibrillation in mitral stenosis is 40%.Evidence from the Framingham study indicates that patients with RHD and AF have an 18-fold higher risk of stroke than age and blood pressure matched controls, while NVAF is associated with a five- to six-fold increase in stroke risk(5). The incidence of thromboembolism is most likely higher when mechanical heart valve is accompanied by AF. The presence of mechanical valve(s) of all types or locations without AF is associated with an 8.6% overall risk of thromboembolism, including a 1.8% risk of valve prosthesis thrombosis and a 4.0% risk of major embolism. Distribution of embolic events, with 63% being cerebral and 38% non-cerebral Wood *et al*. Demonstrated that in RHD patients with AF, approximately 60% of thromboemboli occurred in cerebral territories, while 40% occurred in other locations(6).

Table 1 Advantages of DOACs and warfarin

DOACs	COACs (warfarin)
Rapid onset of action	Potent anticoagulant affecting multiple coagulant factors
Predictable anticoagulant effect	Higher bioavailability
Specific coagulation enzyme target	Accurate monitoring of anticoagulant effect
Low potential for food interactions	Renal failure is not contraindication
Low potential for drug interaction	Reversal anticoagulant effect with vitamin k

Table 2 Disadvantages of DOACs and warfarin.

DOACs	COACs(warfarin)
Higher drug cost	Often require parenteral anticoagulant for bridging onset due to delayed and initial pro-coagulant activity
Increased risk of gastrointestinal bleeding	Delayed onset and loner half life
Higher rebound rate of VTE events in patients poor compliance	Narrow therapeutic index
Lack of availability of reversal agents	Variable response to dosing and Non-fixed regimens

Differing Definations of Valvular Atrial Fibrillation

The issue of ‘‘valvular atrial fibrillation’’ definition is relevant because most of these patients were excluded from recent trials testing NOACs in patients with atrial fibrillation. So NOACs have been registered and are currently indicated only for patients with so-called ‘‘Non-valvular atrial fibrillation’’. The reasons for excluding patients with ‘‘valvular atrial fibrillation’’ included uncertainties about whether the mechanism of thrombogenesis in such patients is similar to that occurring in the more common forms of ‘‘non-valvular’’ AF and so, whether similar anticoagulation strategy is appropriate. 2011-2012 American heart Association/American College of Cardiology/Heart Rhythm Society AF guidelines said that: ‘‘the historical term ‘non-valvular AF’ is restricted to cases in which the rhythm disturbance occurs in the absence of rheumatic mitral valve disease, a prosthetic heart valve or mitral valve repair’’(7).This was confirmed in the 2014 update, where non-valvular AF was defined as AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve or mitral valve repair (8). Warfarin is the only oral anticoagulant approved for use in patients with moderate to severe mitral stenosis and AF thus far..Maintaining a proper therapeutic range is important for the efficacy and safety of warfarin. Low INR control was influenced by the high intake of vitamin K rich foods and a high frequency of genetic polymorphisms in Asians. The REMEDY (Global Rheumatic Heart Disease Registry) trial showed that only a quarter of the patients had an international normalized ratio (INR) in a therapeutic range. Meanwhile, DOACs have better compliance due to fewer drug and food interactions, no need for INR monitoring, and a lack of fluctuation.

MATERIAL AND METHODS

Study design: Prospective study

All patients of rheumatic heart disease with mitral stenosis attended at department of cardiology Gandhi Hospital, were screened, to determine if they met the study criteria.

Duration: 7 months

Follow up: 1month, 6 months,1 year and 18 months

Sample size: 150 patients

Inclusion criteria

All patients with rheumatic heart disease with mitral stenosis with AF regardless of severity

Exclusion criteria

1. Patient undergone mitral valve replacement with mechanical valves
2. Patients with valvular heart disease with atrial fibrillation other than mitral stenosis

Source of data:

All the patients attended Department of cardiology, Gandhi Hospital, secunderabad,. Safety end points were occurrence of intracranial haemorrhage and efficacy end points were occurrence of systemic embolism or ischemic stroke after at least 3 weeks of treatment with DOACs.

Iinvestigations required are complete blood count, renal function test, bleeding time, clotting time, prothrombin time, activated partial thrombin time, inr, ecg, transthorasic echo. Follow up investigation: in selected patients CT BRAIN, MRI BRAIN if required.

Statistical Analysis

Qualitative data was represented in the form of frequency and percentage.

Association between qualitative variables was assessed by Chi-Square test with Continuity Correction for all 2 X 2 tables along with calculation of odds ratio (with 95%CI).
Quantitative data was represented using Mean ±SD.
Analysis of Quantitative data between the two groups was done using unpaired t-test.
A p-value < 0.05 was taken as level of significance.

RESULTS

Clinical characteristics: A total of 150 patients with vavular heart disease with atrial fibrillation screened between September 1st 2019 to 28 march 2021.

The 56 patients with valvular heart disease with atrial fibrillation other than mitral stenosis and 20 patients with mitral stenosis with atrial fibrillation who underwent mechanical valve replacement were excluded from study.

Table 3 Number of patients in DOACs and Warfarin group

Group	N	%
DOACs	37	50.0%
COACs(Warfarin)	37	50.0%
Total	74	100.0%

Table 4 Mean age group between DOACs and Warfarin group

Variables	Group	N	Mean	SD	SE	95% CI	P value
Age (years)	DOACs	37	47.16	13.24	3.13	- 6.96	5.50
	COACs(Warfarin)	37	47.89	13.64			

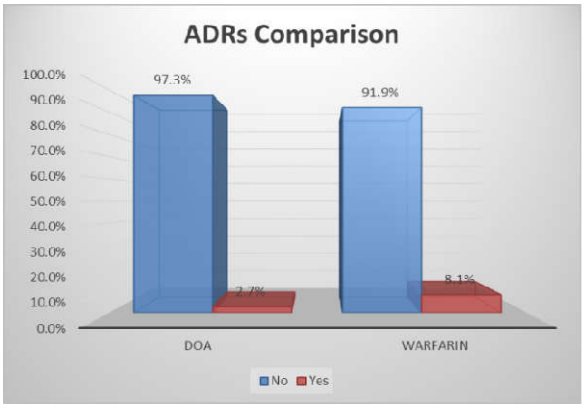
Table 5 Gender distribution between DOACs and Warfarin group

Gender	Group		Total
Gender	DOACs	COACs(Warfarin)	
Female	26	25	51
Female	70.3%	67.6%	68.9%
Male	11	12	23
Male	29.7%	32.4%	31.1%
Total	37	37	74
	100%	100%	100%

OR - 1.135; 95% CI - 0.424 - 3.04; p- value - 1.0

Table 6 Comparison of efficacy and safety outcomes between DOACs and Warfarin group

Outcomes	Group		Total	OR	95%CI		P value
	DOACs	COAC (warfarin)					
Ischemic stroke	0 0.0%	2% 5.4%	2% 2.7%	5.28	0.24	114	0.49
ICH	0 0%	0 0%	0 0%	NA	NA	NA	NA
Systemic Embolism	0 0%	0 0%	0 0%	NA	NA	NA	NA
Bleeding from other sources	1 2.7%	2 5.4%	3 4.1%	2.05	0.18	23.74	1.00



DISCUSSION

In this study rate of ischemic stroke were similar in DOACs and warfarin group. Conolly *et al* noted in patients with atrial fibrillation, dabigatran was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin(9). Kym jy *et al* studies shows the rate of thromboembolic events with DOACs therapy in patients with mitral stenosis and AF was significantly lower than that in the warfarin group(10). Among warfarin group 40% of patients had INR below therapeutic range so these patients more prone to thromboembolic outcomes.. In the study done by kim *et al* primary efficacy endpoint of ischemic stroke or systemic embolism over a mean follow-up of 27 months occurred in 4.19%/year of patients treated with warfarin compared with 2.22%/year treated with a DOAC, while the annualized rates of the primary safety outcome of intracranial haemorrhage occurred in 0.93% and 0.49% of patients in the warfarin and DOAC groups, respectively(10)

So there is need of large randomized trial with adequate follow up to apply these results as significant. In our study bleeding in the form of nasal, gum bleeding are similar in both groups DOACs and warfarin.

Linitations

1. This study is non-blinded study so there is possibility of selection bias.
2. In warfarin group 40% patient had INR below therapeutic range, patients under warfarin group are more prone to thromboembolic outcomes.
3. Safety and efficacy outcomes needs to be tested in large randomized trial, n this study, study population is too small to apply this outcomes in general population.

CONCLUSION

Observation in this DOACs are non-inferior to warfarin in preventing ischemic stroke in patients with CRHD with mitral stenosis with atrial fibrillation.

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