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Thromboprophylaxis of stroke in atrial fibrillation: into the crux of anticoagulant therapy in current scenario

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ABSTRACT

Amid the arrhythmias confronted in clinical practice Atrial Fibrillation is ineluctable. Stroke is grim complication of Atrial Fibrillation due to its inherent prospective for occlusion of cerebral vessels. Hence physicians subjugate the situation by referring thromboprophylaxis. With this study we aim to characterize the anti-thrombotic medication profiles and also to determine the efficacy of anticoagulant therapy used for thromboprophylaxis's in solicitous patients. A prospective study of observational nature was carried out in a tertiary care referral hospital for a period of one and half years to yield a total of 260 patients. The anti thrombotic drugs and dosages selected at the discretion of the treating cardiologist was audited during the study period and was used to evaluate the efficacy of anticoagulants. Study revealed that 72% of the subjects received anticoagulation. There was a preponderance of warfarin in about 89% of the population followed by apixaban in 2% and dabigatran in 9%. In warfarin anticoagulated group dosage gamut included 2 to 5 mg where38.46%, 23% and 38.46% patients achieved target INR when treated with 2mg, 3mg and 4mg respectively whereas the percentage in 110mg dabigatran therapy accounts for about 67%. Stroke prevention in Atrial fibrillation is exigent part in the management of cardiac patients. A forestall towards appropriate thromboprophylaxis can extricate the patients from humongous clinical complications and financial burden put upon the subject in the advancement of the disease condition. From days of yore warfarin has demonstrated its efficacy and has ensconced overriding position in the markets of India.

INTRODUCTION

Amid the arrhythmias confronted in clinical practice Atrial Fibrillation is ineluctable[1]. Stroke is the grim complication of Atrial Fibrillation due to its inherent prospective for occlusion of cerebral vessels[2]. Predominance of Atrial Fibrillation escalates with age obnubilating approximately 0.4% to 2% of the population[3]. The tribulation from Atrial Fibrillation will incite the occurrence of stroke as high as five to seven fold intensified risk when allegorized with respect to general population. The prognosis of stroke as a complication of Atrial Fibrillation is unendurable. Hence physicians subjugate the situation by referring subjects for thromboprophylaxis as a comprehensive management of Atrial Fibrillation[4]. The superior pharmaceutical category most widely used for thromboprophylaxis are Vitamin K antagonists. Warfarin, presently though not the only recourse for thromboprophylaxis, many physicians relate its use as pragmatic. Three new oral anticoagulants are now progressively acknowledged as alternative in fallback of traditional vitamin K antagonist therapy. Dabigatran is the premiere anticoagulant approved for stroke prevention in Atrial Fibrillation succeeded by rivaroxaban and apixaban. Rapid onset, predictable pharmacokinetics, and no need for routine anticoagulation monitoring entices physician to NOAC therapy in the current era[1]. Patients net clinical wellbeing has to be given cardinal importance while arriving at decision making with regard to thromboprophylaxis. Top tier management of Atrial Fibrillation always hubs around appropriate choice of thromboprophylaxis and the assessment of stroke as well as bleeding risk[4]. Antithetical to non AF related stroke the economic burden (average direct cost per patient) is consequentially higher in stroke that evolves as a complication of Atrial Fibrillation[5].

Warfarin breakthrough in 1933, have influenced the discipline

of medicine tremendously. Since then warfarin and Vitamin K antagonists have been extensively utilized in clinical practice[6].The role of warfarin for stroke prevention in Atrial Fibrillation can be explained by its inhibitory action on Vitamin K epoxide reductase. This inhibitory action halts the effective synthesis of biologically active forms of vitamin Kdependent clotting factors (II, VII, IX, and X) together with the regulatory factors scilicet protein C and protein S. The oral bioavailability of warfarin exceeds 95% and takes approximately 26-36 hours to attain its peak activity. The 20-60 hours half life of warfarin makes it to be administered once daily with less than 1% excreted renally[2,7].The effectiveness of warfarin is clinically defied by its complication namely hemorrhage[8]. Incessant surveillance of coagulation status is imperative to indemnify the subjects from complications and to secure utmost efficacy[9]. Multiple interactions of Vitamin K antagonist with food and other drugs and the requisite for reiterant laboratory monitoring make its use unwieldy[10]. Albeit no longer the sole option, Vitamin K antagonist still overrules its primacy owing to its reasonably lower cost andcolossal experience. They still predominatein choice for therapy of sizeable proportion of diseases[9].

The advent of NOAC era has not only made the selection of anticoagulants for thromboprophylaxis of stroke in Atrial Fibrillation enticing but also contentious[6]. The NOAC classification encompasses the following drugs videlicet dabigatran, rivaroxaban, endoxaban and apixaban. Dabigatran is the first NOAC to be approved in 2010 and was made accessible in Italy. It is the lone novel oral anticoagulant in the direct thrombin inhibitors category that is being used for stroke thromboprophylaxis in Atrial Fibrillation[11]. The anticoagulant effect is rapid and often erratic. The pharmacokinetic profile supports twice daily administration at doses of 110 mg or 150 mg with an oral bioavaliablity of 6.5%. 80% of the administered dose is excreted through kidneys with a half life of 12 to 17 hours. Regular monitoring of coagulation status is redundant with dabigatran which makes its choice preferential[12]. Howbeit recent studies have reported an heightened risk of coronary events with dabigatran[13].

The direct factor Xa inhibitor category of NOAC includes rivaroxaban which was the introductory drug to be approved and made accessible commercially in Europe and Canada in 2008. It exerts its anticoagulant action by inhibiting the single integrant of the coagulation cascade namely Xa with a bioavailability ofmore than 80%[14,15]. The accustomed prescription claims a dose of 10 mg to be administered daily.The zenith activity is seen in about 2-4 hours with a elimination half life of 5-9 hours[15]. In the chronology of discovery apixaban is the second drug in the direct factor Xa inhibitor category to be approved in Europe in 2011 and in the United States in 2012[16].*The risk of major hemorrhage*as gauged in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial has uncloaked a 31% reduction in comparison to that of warfarin among the AF patients[17,18].The oral bioavailabilty of apixaban is roughly 50% for doses upto 10 mg with a time to peak activity of about 3-4 hours and a half life of 12 hours[15]. The third one edoxaban (Lixiana, Savaysa) was ratified in Japan in 2011 and in Europe and the USA in 2015[19].The half life nudges around 6-11 hours for 10-150 mg single dose making it to be administered once daily. The oral bioavailability is approximately 62% for 60mg dose with a time to peak activity of about 1-2 hours[15].

Contemplating the clinical practice guidelines published by the American College of Cardiology, the American Heart Association, the American College of Chest Physicians, and the European Society of Cardiology, AF patients at a risk for stroke and serious bleedingshould generally accrue an anticoagulant (usually a vitamin K antagonist) or antiplatelet regimen (usually acetylsalicylic acid)[20]. With this study we aim to characterize the anti-thrombotic medication profiles and also to determinine the efficacy of anticoagulant therapy used for thromboprophylaxis's in solicitous patients.

METHODOLOGY

The study was designed as a prospective study of observational nature. A tertiary care referral hospital was decided to serve as the study setting. The study lasted for a period of one and half years to yield a total of 260 patients. Subjects seeking services from the department of cardiology for the diagnosis of Atrial Fibrillation were pondered for inclusion in the study.

Preparatory to data collection the criteria for including and excluding the subjects were decided. The specifications for inclusion were age above 18 years and all newly and existing cases with specific diagnosis of Atrial Fibrillation. The exclusion criteria stated knock-back of critically ill patients with high rate of mortality less than one month and patients with Acute Coronary Syndrome. Transient Atrial Fibrillation due to reversible causes like infection, alcoholic intoxication and post operative Atrial Fibrillation and subjects with hyperthyroidism were not considered for the study.

The nature, type and intension of the study were explained to the patient by direct interaction in patient's vernacular language. Apprising subject was followed by informing the participants about where and how the data will be used. Subjects were provided sufficient time to decide whether or not to participate in the study. Written informed consent was then obtained from voluntary subjects.

To facilitate and expedite the data collection, a data collection form was concocted beforehand. Reported cases confirmed with ECG by the physician were identified and critically analyzed to compile the requisite information. Demographic details and complete history of the patients was obtained from medication charts and personal interview with patients and their attendants. The anti thrombotic drugs and dosages selected at the discretion of the treating cardiologist was audited during the study period and was used to evaluate the efficacy of thromboprophylaxis in Atrial Fibrillation patients.The anticoagulant selected, the dose, duration and adverse drug reactions associated with the selected drugs were evaluated for efficacy.

Data collected from the study was tabulated in Microsoft Excel 2010 and were keyed into the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) computer software version 20 for windows and analyzed by appropriate statistical methods. Statistical analysis was both descriptive at 95% confidence level (CI). Continuous variables were analyzed using the mean, percentage and standard deviation.

RESULT

Data from a total of 260 patients were mustered to make the population for the study.

Anticoagulation for stroke prevention is ineludible in the management of Atrial Fibrillation. Patients with stroke, after being stratified for their risk score, were subjected to anticoagulation. Study population revealed that 72% of the

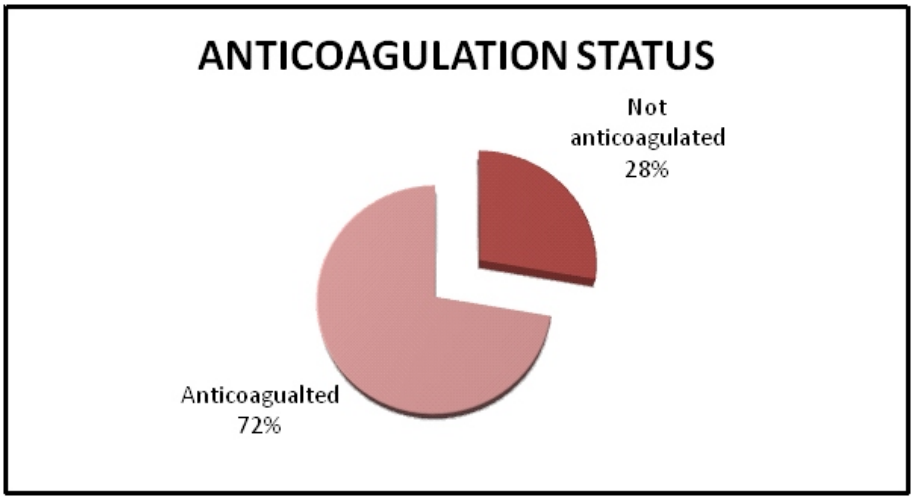

Fig. 1: Anticoagulation status of study subjects

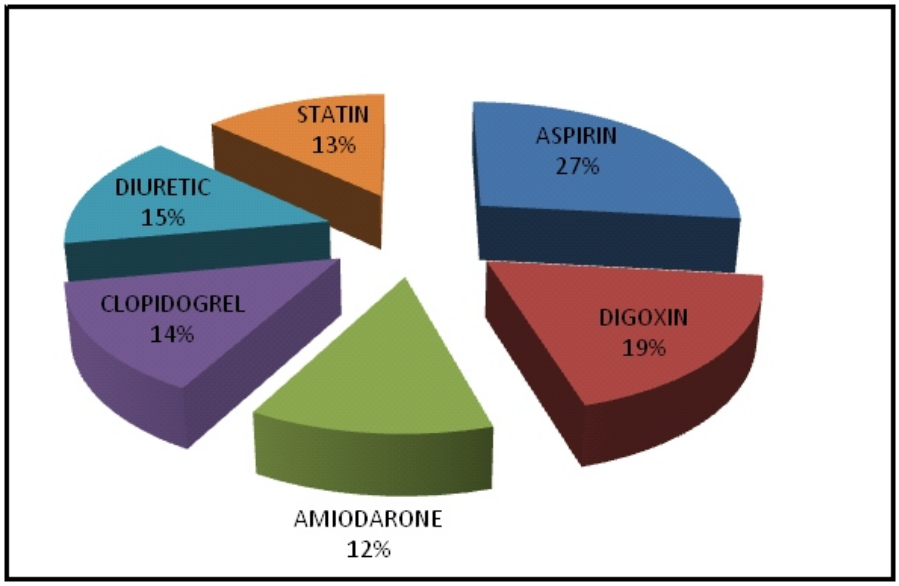

Fig. 2: Other Medications Used In Study Population

subjects received anticoagulation for thromboprophylaxis (Figure 1). Apart from anticoagulants, other medications received by the subjects as an adjuvant therapy includes aspirin, digoxin, clopidogrel, amiodarone, diuretic and statins. Aspirin was received by 27% of the study population and digoxin by 19%. 15% of the population received diuretic and 14% received clopidogrel. 12% of the study population received statins and amiodarone (Figure 2).

Physicians often experience bewilderment in the choice of anticoagulants between vitamin K antagonist and NOAC. Major anticoagulants used for thromboprophylaxis among the patient population in the study setting were warfarin, dabigatran and apixaban. There was a preponderance of warfarin in the study population in about 89% of the population followed by apixaban in 2%. Dabigatran was the alternative option in subjects who experienced adverse reactions from warfarin therapy. Precisely 9% of the population shifted from warfarin to dabigatran during the proposed study period in the concerned population (Figure 3).

In the warfarin anticoagulated group which comprises of 72.2% of the study population (n=188) the dosing of warfarin was disparate. The dosage gamut included 2 to 5 mg. 27.7% of the study population received 2mg dose whereas 23.1% received 3mg dose and 20.0% and 1.5% received 4mg and 5mg fitly.

The dosing range was correlated with achievement of target INR during the stipulated time period to evaluate the efficacy. Findings reveal that 38.46%, 23% and 38.46% patients achieved target INR when treated with 2mg, 3mg and 4mg warfarin respectively (Figure 4).

In the interim of second follow up, 24 subjects among the total

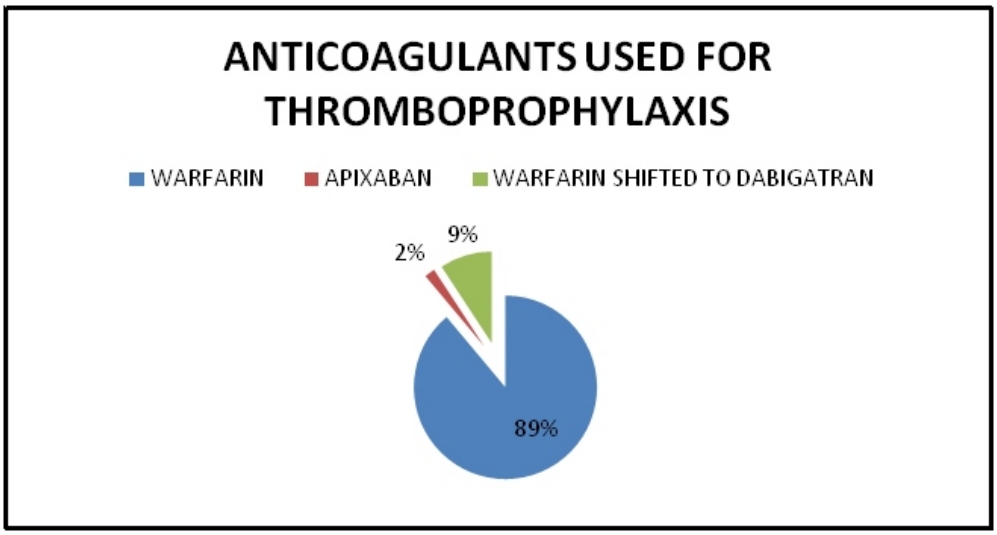

Fig. 3: Choice of anticoagulants used for thromboprophylaxis

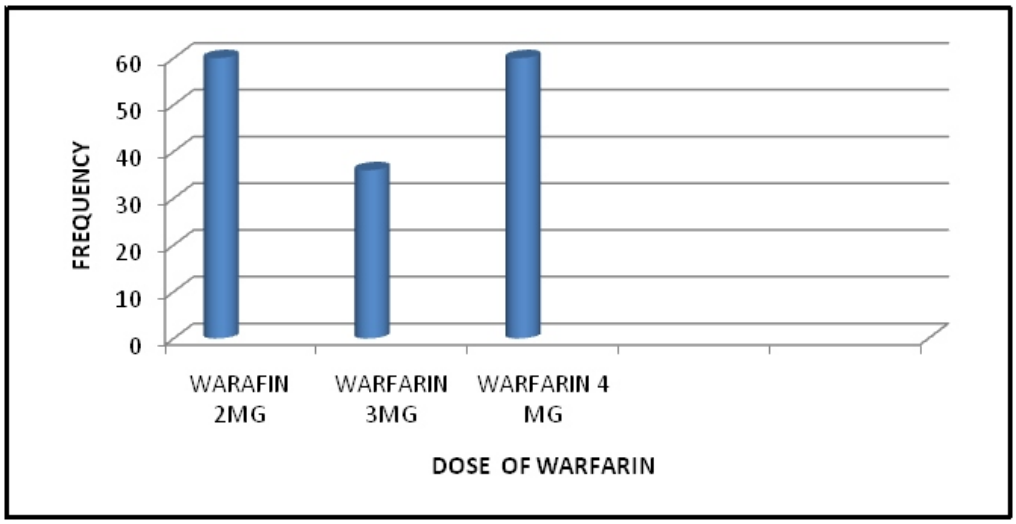

Fig. 4: Warfarin- Dose INR Relationship

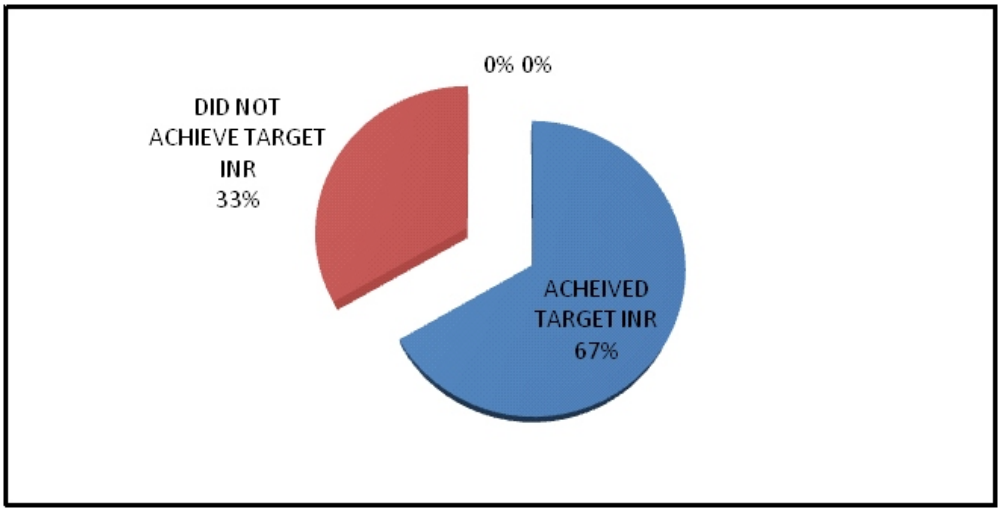

Fig. 5: Dabigatran- Dose INR Relationship

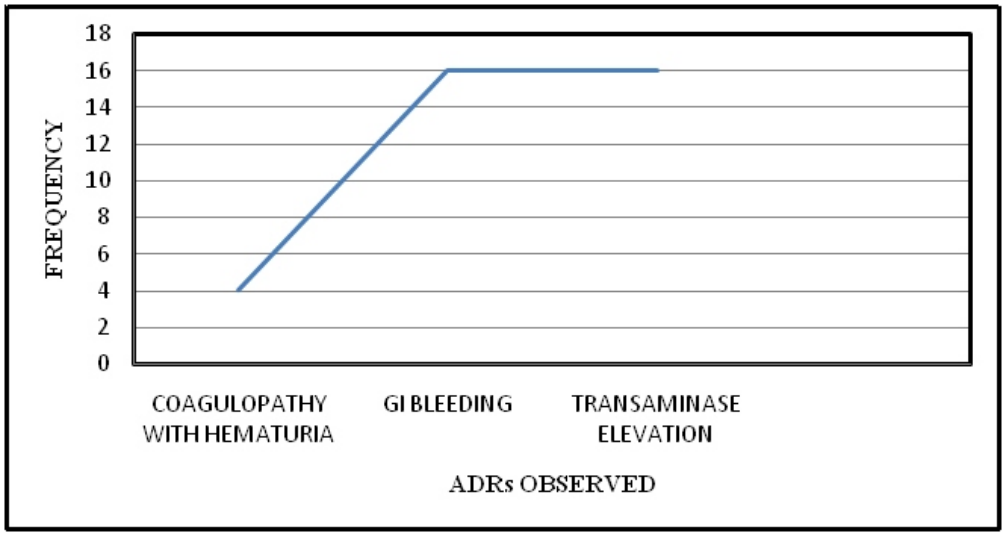

Fig. 6: ADRs observed among study subjects treated with warfarin

of 184 subjects who received the warfarin therapy discontinued the prophylaxis owing to adverse effects. The subjects were advised to take up with the dabigatran at a dose of 110mg as a shift in course from warfarin. The percentage of patients who achieved target INR of 2-3 while on dabigatran therapy accounts for about 67% (Figure 5).

Observation of ADR in the study population being treated with warfarin descried coagulopathy with hematuria, GI bleeding and transaminase elevation. Coagulopathy with hematuria was noted in 4 subjects whereas GI bleeding was discerned in 16 subjects. Elevation in serum transaminase levels was espied in 16 subjects (Figure 6). Causality assessments based on Naranjo ADR probability scale rated 67% of the adverse events as possible and 33% of the adverse events as probable.

DISCUSSION

The study aims to epitomize the efficacy of anticoagulants used for thromboprophylaxis of stroke in Atrial Fibrillation. On the basis of convenience sampling who confirmed to the preset inclusion and exclusion criteriaa total of 260 subjects sufficed the study.

The mainstay in the long term management of Atrial Fibrillation revolves around the anti-thrombotic therapy for prevention of stroke in subjects of advanced stage. The results of our study revealed that 72% of the patients received anticoagulants for thromboprophylaxis to prevent the complication of AF. When compared with the study conducted by Aarti A. Patel et al[20] (2012), where only 35% received vitamin K antagonists and 16,617 (65%) did not receive any anticoagulant among the total of 25,710 patients, the finding of our study conflicted in that that a higher proportion of patients received anticoagulants for thromboprophylaxis.

An overlook on concomitant medications used by study subjects divulged that the most commonly encountered medication was aspirin 27% of patients, followed by 19% of the subjects who received digoxin. 15% received diuretic and 14% received clopidogrel in addition to thromboprophylatic therapy. 12% each received amiodarone and statins as an adjuvant therapy. Aspirin use among Atrial Fibrillation subjects are anticipated due to its antiplatelet actions that adjuncts the antithrombotic therapy.

Contemplating the anticoagulants therapy, where warfarin and novel oral anticoagulants serves as an option to choose in between, there was an envisaged supremacy of warfarin use in the study population. Novel oral anticoagulant use in the study population was limited to dabigatran and apixaban. To precisely define the warfarin dominance 89% of the subjects were treated this Vitamin K antagonist. The novel oral anticoagulant use can be compiled as 2% of apixaban and 9% of dabigatran use, which was mainly a shift from warfarin therapy owing to ordeal of an adverse event. Deliberation of the study findings with the study conducted by Torben Bjerregaard Larsen et al[21] (2016) where the study population was distributed according to the treatment type included 57% of study subject with warfarin, 21% with dabigatran and 10 % with apixaban. The possible explanation of the conflicting results could be the relatively increased cost of dabigatran and apixaban when compared to warfarin along with the decreased market popularity of dabigatran in North Kerala.

The warfarin anticoagulated bracket within the study population was dosed from 2-5 mg based on their individual requirements upon deliberation by the physician. Dosing of 2mg were felt appropriate for 27.7% whereas 23.1% were advised a dose of 3mg. 4mg and 5 mg doses of warfarin was intimated for 20% and 1.5% of the study population respectively. The achievement of INR with the prescribed dose was scrutinized to evaluate the efficacy of warfarin therapy among the study subjects. The percentage of patients who attained target INR of 2-3 as when appraised during the second follow up among a total of 184 patients who were continued with warfarin therapy depicts 60 (38.46%), 36 (23%) and 60 (38.46%) patients achieved target INR when treated with 2mg, 3mg and 4mg warfarin respectively. The second follow up also rendered 24 subjects who shifted from warfarin to dabigatran therapy. Efficacy in terms of achievement of INR within the range of 2-3 in dabigatran subgroup accounted for approximately 67% while in 33% of the dabigatran use population, the NOAC failed to demonstrate its efficacy.

Observation of ADR is in exorable part of any drug therapy. As anticipated in the thick of warfarin anticoagulated subjects, 36 cases of adverse drug reactions was observed. The observed ADR among the patient population includes coagulopathy with hematuria, GI bleeding and transaminase elevation. This is

mainly due to the hemorrhagic tendency that warfarin possess. Amid the patient population, 4patient developed coagulopathy with hematuria. Transaminase elevation as a consequence of hepatic damage and GI bleeding was observed in 16 patients each.Rating of adverse drug reaction on Naranjo ADR probability scale bestowed 24 possible and 12 probable cases. According to the study conducted by Stuart J. Connolly et al[10] (2009), the rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group that received 110 mg of dabigatran. The possible explanation for findings from our study could be due to the wide popularity of warfarin as an anticoagulant used for thromboprophylaxis in patients with Atrial Fibrillation that sufficient sample of dabigatran use population couldn't be mustered to identify the nature of ADR with dabigatran therapy.

CONCLUSION

Stroke prevention in Atrial fibrillation is exigent part in the management of cardiac patients. A forestall towards appropriate thromboprophylaxis can extricate the patients from humongous clinical complications and financial burden put upon the subject in the advancement of the disease condition. With this study we aim to characterize the anti-thrombotic medication profiles and also to determine the efficacy of anticoagulant therapy used for thromboprophylaxis's in solicitous patients.Within the limitations of the observational nature of the study, the finding of our study was unswerving to the note that anticoagulation is a crucial requirement for averting stroke in AF patients.

From days of yore warfarin has demonstrated its efficacy and has ensconced an overriding position in the markets of India as an established anticoagulant. Still in the NOAC era the hold of warfarin in clinical practice was not shattered. The preference for warfarin as an anticoagulant of choice still lingers in the minds of physician. But its potential for adverse events and ordeals faced by subjects cannot be curtained at least after the advent of novel oral anticoagulants. Limitations in dose variability and need for frequent monitoring associated with Vitamin K antagonist have prompted the physician to focus and enhance the knowledge about novel oral anticoagulants.There is a need to accomplish this goal at the earliest to improve the anticoagulation status of concerned patients not at the cost of compromising the efficacy. The dawn of NOAC in markets augmented by better risk stratification schemes prognosticates a revolutionary transition in the anticoagulation selection. These advances in AF treatment will optimisticallydecipher into improved outcomes for patients, especially as experience with the new agents grows.

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