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RISK OF BLEEDING IN ATRIAL FIBRILLATION PATIENTS TAKING ANTICOAGULANTS

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Abstract
Atrial fibrillation is an irregular heart rate that occurs when the two upper chambers of heart experience chaotic electrical signals. Factors associated with an increased risk of thromboembolic events in patients with atrial fibrillation include increasing age, poor left ventricular function, previous myocardial infarction, hypertension and past history of a thromboembolic event. Atrial fibrillation patients should be considered for anticoagulation or antiplatelet therapy based on their age, the presence of other risk factors for stroke and the risk of complications from anticoagulation. In general, patients with risk factors for stroke should receive warfarin anticoagulation, regardless of their age. In patients who are under age 65 and have no other risk factors for stroke, either aspirin therapy or no therapy at all is recommended. In this study we discuss the issues involved in the risk of bleeding in association with atrial fibrillation and the indications for anticoagulation therapy. A study was conducted in Cardiology In-patient Department of a Tertiary care hospital. Patient details were collected using data collection forms. HAS BLED score were used. Out of 150 patients, rivaroxaban was used in 82 patients and using SPSS version 20 software, results were calculated. Results obtained illustrate that patients using combination therapy of oral anticoagulants and antiplatelets were at higher risk of bleeding compared to other patients and patients with hypertension were at higher risk of bleeding than non-hypertensive patients. It is crucial to find an effective and equally safe treatment to reduce bleeding risk in atrial fibrillation patients taking anticoagulants.

Keywords: Anticoagulation, Atrial fibrillation, Bleeding, HAS BLED score, Thromboembolic.

Introduction

Atrial fibrillation (AF) is an abnormal heart rhythm characterized by rapid and irregular beating of the atrial chambers of the heart [1]. It is a type of supraventricular tachycardia that is often seen as short periods of abnormal beating which become longer over time. Atrial fibrillation can also start as other forms of arrhythmias such as atrial flutter and then transform into atrial fibrillation. Often episodes are asymptomatic. There may be palpitations, fainting, dizziness, shortness of breath, or chest pain [2]. The disease is associated with an increased risk of heart failure, dementia, and stroke [3]. The most common risk factors for atrial fibrillation are High blood pressure and valvular heart disease. Other risk factors include excess alcohol intake, tobacco smoking, diabetes mellitus, and thyrotoxicosis. A diagnosis is made by checking the pulse and may be confirmed using an electrocardiogram. No P wave and an irregular ventricular rate is what a typical electrocardiogram in atrial fibrillation looks like [4]. Medications to slow the heart rate to normal range or to convert the rhythm to normal sinus rhythm are what the treatment of atrial fibrillation often includes. Alternately, electrical cardioversion can also be used to convert atrial fibrillation to a normal sinus rhythm and is often used in emergency cases where the patient is unstable. Recurrence in some patients can be prevented by ablation. If the patient has a low risk of stroke, no specific treatment is required, though aspirin or an anti-clotting drug may be considered. For those at moderate to high risk of stroke, anti-clotting medications like, warfarin and direct oral anticoagulants are recommended. While these anticoagulants reduce stroke risk, they increase rates of major bleeding. Atrial fibrillation is the most frequently encountered cardiac arrhythmia [5].Guidelines intensely and consistently recommend anticoagulation in patients with AF and risk factors for cardio embolic events to lessen the likelihood of stroke or thromboembolism [6]. A 64% reduction in stroke and a 26% reduction in mortality have been seen with the use of oral anticoagulation therapy [7]. When considering thromboprophylaxis, management decisions need to be individualized balancing the risk of stroke against the risk of serious hemorrhage. This has led to the analysis of net clinical benefit comparing ischemic stroke with intracranial hemorrhage.

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Thromboembolic events, resulting from atrial stasis and poorly adherent mural thrombi, are complications of atrial fibrillation. Of which, the occurrence of an embolic stroke is the most serious complication. Approximately 15% of all strokes in the United States can be attributed to atrial fibrillation [8]. The average rate of ischemic stroke in patients with atrial fibrillation who are not receiving antithrombotic therapy is approximately 5% per year [8-9]. Stroke can precede the onset of documented atrial fibrillation, probably as a result of undetected paroxysms prior to the onset of established atrial fibrillation. The risk of stroke significantly increases with age, with the annual attributable risk increasing from 1.5% in individuals 50 to 59 years of age to almost 24% in those 80 to 89 years of age [8]. Patients with concomitant atrial fibrillation and rheumatic heart disease are at particularly high risk for stroke, with their risk being increased 17-fold compared to patients in sinus rythym [8]. Other risk factors for stroke identified from recent trials are increasing age, previous myocardial infarction, hypertension and history of previous thromboembolic event [10]. Thus, the assessment of bleeding risk has been given more importance. In this study we have used HAS-BLED (H-Hypertension, A-Abnormal renal/liver function, S- Stroke, B-Bleeding, L-Labile INR, E-Elderly, D-Drugs or alcohol) score to evaluate the risk of bleeding in atrial fibrillation patients receiving anticoagulants, to enhance clinical decision making, as recommended in current guidelines.

Materials and methods

Despite good progress in the management of patients with atrial fibrillation, this arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world. Additionally, the number of patients with atrial fibrillation is predicted to rise abruptly in the years to come. The European Society of Cardiology Guidelines for the management of atrial fibrillation recommend considering five areas in the assessment of patients who have been newly diagnosed with atrial fibrillation. These domains are:

- Hemodynamic instability or limiting, severe symptoms;
- Presence of precipitating factors and underlying cardiovascular conditions;
- Stroke risk and need for anticoagulation;
- Symptom assessment and decision for rhythm control [11].

A. If atrial fibrillation <48 hours, anticoagulation prior to cardioversion is unnecessary; may consider transesophageal echocardiogram if patient has risk factors for stroke.

B. Ablation may be considered for patients who fail or do not tolerate ≥1 antiarrhythmic drug.

C. Chronic antithrombotic therapy should be considered in all patients with atrial fibrillation and risk factors for stroke regardless of whether or not they remain in sinus rhythm.

Determining the risk of stroke and bleeding in atrial fibrillation patients: Atrial fibrillation is characterized by extremely rapid and disorganized atrial activation leading to irregular heart beat and other abnormal changes in the heart such as chamber distension. These factors may contribute to formation of blood-clots which can lead to stroke and other thromboembolic events. To prevent such complications anticoagulation therapy is advised, however they confer an increased risk of bleeding. Hence when initiating chronic antithrombotic therapy in patients with atrial fibrillation it is important to assess the risk of stroke and the risk of bleeding to select the most appropriate regimen.

Clinical risk scores for bleeding: For the assessment of bleeding risk many different scores have been developed, mainly in patients on vitamin K antagonists.

These include:-

- HAS-BLED Score (H-Hypertension, A-Abnormal renal/liver function, S- Stroke, B-Bleeding, L-Labile INR, E-Elderly, D-Drugs or alcohol)
- $HEMORR_2HAGES$ Score (hepatic or renal disease, ethanol abuse, malignancy history, older age (>75years), reduced platelet count, re-bleeding risk, hypertension uncontrolled, anemia, genetic factors, excessive fall risk, stroke history) (Table 1). [12]

Clinical risk scores for stroke: The assessment of risk of stroke is foremost in developing a proper treatment regimen for atrial fibrillation. Numerous risk factors have been used to make a stroke risk classification system, which has classified patients as to having low, moderate and high risk stroke, so that the patients at highest risk can be considered for warfarin therapy. Many of these risk factors were derived from inadequately conducted trails, where only <10% of patients screened were randomized, and many risk factors were not systematically looked for, nor consistently defined. With the availability of the other oral anticoagulants that are alternatives to warfarin, there is the need to be more inclusive of common stroke risk factors, to focus more on identification of 'truly low risk patients' with atrial fibrillation who do not

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need any antithrombotic therapy. Indeed, the 2012 focused update to the European Society of Cardiology guidelines [12] recommends stroke risk assessment using the CHA2DS2-VASc (C-Congestive Heart failure, H-Hypertension, A-Age ≥75 (doubled), D-Diabetes, S-Stroke (doubled), V-Vascular disease, A-Age 65–74, S-Sex (female)) score, and strongly emphasizes a clinical practice shift with more focus on identifying the 'truly low-risk' patients with atrial fibrillation, instead of trying to identify 'high-risk' patients. These 'truly low risk' patients are those patients who have CHA2DS2-VASc score=0 and they do not need any antithrombotic therapy (Table 2).

Anticoagulants used for stroke prevention and the associated risk of bleeding: Ischemic strokes in atrial fibrillation patients can be prevented and life can be prolonged with the use of oral anticoagulants. To minimize stroke risk, anticoagulants are superior to no treatment or just aspirin in patients with different profiles [13]. The bleeding risk on aspirin is not different to the bleeding risk on vitamin K antagonists or non-vitamin K antagonist oral anticoagulants therapy, while vitamin K antagonists and non-vitamin K antagonist oral anticoagulants, but not aspirin, effectively prevent strokes in atrial fibrillation patients. Oral anticoagulants should be used in most patients with atrial fibrillation because the net clinical benefit is almost universal, with the exception of patients at very low stroke risk. In spite of this evidence, underutilization or hasty termination of oral anticoagulants therapy is still commonly seen.

In a study carried out shows that geriatrics with atrial fibrillation are at increased risk of thromboembolic stroke (4% to 15% per year), depending on the presence of certain clinical factors, including left ventricular dysfunction, history of hypertension, history of stroke or transient ischemic attack, diabetes mellitus, and increasing age. The risk of stroke can be reduced by using combination of thrombolytic with anticoagulants and aspirin. Risk factors for major bleeding due to anticoagulants are NSAIDS (Non-Steroidal Anti-Inflammatory Drugs), hypertension, trauma, stroke, head injury, improper INR (International Normalized Ratio) status, aging, thrombocytopenia, alcoholism and poor medication compliance and increased bleeding. Therefore, all persons with AF more than 75 years should be considered for anticoagulation unless a contraindication exists. [14] Another study claimed that dabigatran may cause gastrointestinal adverse effects such as dyspepsia which may in turn cause increased risk of gastrointestinal bleeding. In this study they reviewed that 7 patients developed severe hemorrhage (3 cases of fatal gastrointestinal hemorrhage i.e. 81 years old patients). Depending upon different doses of dabigatran with other anticoagulants, major bleeding was seen in 1 to 3% of patients. Connolly et al study reported that the occurrence of major bleeding was 2 % annually in dabigatran group receiving dose of 110 mg, bid (with life-threatening bleeding of 1.2%) and 3 % annually in dabigatran group receiving dose of 150 mg, bid (with life-threatening bleeding of 1.4%. On the other hand, ulcerogenic drugs, increased age, Helicobacter pylori infection are also responsible for dabigatran-induced bleeding. At last, dabigatran should not be used in patients with its risk factors in order to avoid further bleeding events. [15] A study included various data sources which are used to compare major bleeding and stroke among atrial fibrillation (non valvular) patients on non–vitamin K antagonist oral anticoagulants or warfarin. A retrospective study of atrial fibrillation (non-valvular) patients who started apixaban, dabigatran, rivaroxaban, or warfarin was conducted in which total of 434 046 patients were included in matched cohorts (37 693 dabigatran-rivaroxaban, 37 314 apixaban-dabigatran, 36 990 dabigatran-warfarin, 125 068 rivaroxaban-warfarin, 107 236 apixaban-rivaroxaban, 100 977 apixaban-warfarin patient pairs).According to this study apixaban, dabigatran and rivaroxaban were associated with lower rates of stroke/systemic embolism compared with warfarin. Apixaban and dabigatran had lower rates of major bleeding while rivaroxaban had higher rate of major bleeding compared to warfarin. To evaluate risk of stroke/systemic embolism and major bleeding across matched cohorts Cox models were used. An increased rate of major bleeding was observed in atrial fibrillation patients using warfarin (Vitamin K antagonist) when compared to patients with no anticoagulant treatment or placebo. Therefore according to this study non vitamin K antagonist oral anticoagulants had lower rates of stroke/systemic embolism and major bleeding compared to warfarin. [16] Another study compared the safety and efficacy of apixaban with warfarin in which adults were chosen as eligible participants with non valvular atrial fibrillation. Apixaban was associated with better safety (RR 0.58; CI 0.52–0.66) profile compared with warfarin (RR 0.93; CI 0.70–1.24) with few major bleeding events, but no difference in efficacy was noted. Besides, apixaban also reduces stroke/systemic embolism. Similar studies were searched in the Cochrane Central Register of Controlled Trials, MEDLINE, Pub Med, and clinicaltrials.gov. In these studies Cochrane risk of bias tool and SIGN methodology was used to assess risk of bias and RevMan software was used to determine the effect size and perform meta-analysis. Thus anticoagulant therapy should be selected based on the risk factor profile

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of the patient. [17] Recent study provides strategy for management of atrial fibrillation patients by selecting most appropriate anticoagulant treatment according to patient's characteristics and preference in order to assess the individual risk factors for ischemic and bleeding events. For this purpose, several risk scores have been developed to predict thromboembolic and hemorrhagic risk. They reported a strategy for management of atrial fibrillation patients in specific clinical situations; 1.History of acute coronary artery disease (undergoing cardiac revascularization) 2.History of major bleeding 3.Restart anticoagulation after acute ischemic stroke, 4. If required switch to another antithrombotic regimen. CHADS2 (cardiac embolic stroke risk stratification) score was 1st approved score which classified patients into three groups as low (0 point), moderate (1–2 points) and high (3–6 points) risk for stroke and ≥2 score indicates that patient can receive anticoagulation treatment . This score was then refined into CHA2DS2-VASc score (personalized risk stratification for atrial fibrillation patients). The stroke rate was 2.99% per annum for ATRIA (C-statistic= 95% confidence interval), CHADS2 (C-statistic = 0.70 (0.69–0.71)) and CHA2DS2-VASc(C-statistic = 0.68 (0.67–0.69) score in 60,594 patients. The ATRIA score had a net reclassification improvement of 0.23 compared with CHA2DS2-VASc. According to this study, ATRIA score performed better than CHADS2 and CHA2DS2-VASc score, mainly in the identification of low-risk patients. To predict the risk of major bleeding HAS BLED score was developed (ICH, hospitalization, hemoglobin decrease > 2 g/L, and/or transfusion) in a population of 3,978 patients (atrial fibrillation) with 1 year of follow-up, showing a good predictive ability (C statistic 0.72) ≥3 score indicates high risk of a major bleeding. The HEMORRAHAGES score has a global modest predictive accuracy (c statistic of 0.67), with a bleeding rate increasing up to 12.3 per 100 patient-years (with vitamin K anticoagulants (7.2%/year) and non vitamin K anticoagulants (6.4%/year) with ≥5 points in atrial fibrillation patients, this was reported during a mean follow up of 33.6 months. During a mean follow up of 33.6 months, 357 bleeding events occurred. Of these, 261 in the VKA (7.2%/year) and 96 (6.4%/year) in the NOAC group. Patients with CLD on vitamin K anticoagulants experienced a higher rate of major bleeding (14.3 vs. 5.6%) as compared to those on NOACs (5.8 vs. 9.5%) group. In specific settings, such as patients with CKD and in patients needing a combination therapy along with antiplatelet drugs, risk of major bleeding is still an evolving clinical scenario. Therefore, according to this study non vitamin K oral anticoagulants have significantly reduced the risk of major bleeding (such as intra-cranial hemorrhage). [18]

Various studies reported anticoagulation-related bleeding complications in patients with atrial fibrillation. They identified following patient characteristics as risk factors (according to national guidelines) for anticoagulation-related bleeding complications in atrial fibrillation patients: advanced age, anemia (OR 2.5, 95%CI 1.6–3.8) or history of bleeding (RR 2.4, 95%CI 1.7–3.3), cerebrovascular disease, previous history of myocardial infarction, uncontrolled hypertension, previous history of ischemic heart disease and medication history of antiplatelet agents. The significant risk factors which were not recognized include diabetes mellitus, gender and hypertension. Intracranial hemorrhage or occurrence of any bleeding event (it might be major or minor bleeding) was considered as outcome of this study. In a study of over 10,000 anticoagulated atrial fibrillation patients, 1.5% of major bleeding events, of which 0.3% intracranial hemorrhage were reported in a yearly incidence. In similar study of 6777 atrial fibrillation patients receiving both anticoagulant and anti-platelet therapy, 1.1% of major bleeding events, of which 0.6% intracranial hemorrhages were reported per year along with 11.8% of minor bleeding events. Further research in this area is to be needed to balance the risks and benefits of anticoagulation in atrial fibrillation patients. [19] A study carried out was associated with the different antithrombotic drugs that aim to determine which antithrombotic therapy is most effective and safest for each patient. In this study the risk of bleeding of direct non vitamin K oral anticoagulants (DOACs) was compared with warfarin (vitamin K anticoagulant) in non valvular atrial fibrillation patients. Their findings shows that: Increased risk of gastrointestinal bleed was seen with Rivaroxaban and Dabigatran compared to warfarin and direct vitamin K oral anticoagulants, Rivaroxaban also showed evidence of increased risk of major bleeding and all-cause mortality compared with the other DOACs and warfarin, while Apixaban showed equal or lower risk of major bleeding and all-cause mortality compared with DOACs and warfarin. Increased risk of intra-cranial hemorrhage was seen with Rivaroxaban, while decreased risk was seen with Dabigatran. Among the 3 DOACs (apixaban, rivaroxaban, dabigatran), apixaban has consistently shown lower rate of major bleed risk compared with the other DOACs and with warfarin. [20]

A study included patients with advanced age (24,788); heart failure (29,297), having CHADS 2 score ≥3 (31,203) and atrial fibrillation in randomized clinical trials were evaluated for safety and efficacy of direct oral anticoagulants (DOACs) by using risk index (RI). In order to choose DOACs or warfarin in

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atrial fibrillation patients the risk index is used as a tool to facilitate clinicians. In patients treated with DOACs or warfarin with stroke or systemic embolism had same risk index. Dabigatran (elderly: RI = 0.21; HF: RI = 0.19; CHADS 2 score ≥3: RI = 0.28) and Apixaban (HF: RI = 0.14; CHADS 2 score ≥3: RI = 0.23; elderly: RI = 0.25) had higher bleeding risk indexes (RIs) compared to rivaroxaban. Rivaroxaban had the lowest RI of major bleeding (HF: RI = 0.05; CHADS 2 score ≥3: RI = 0.04; elderly: RI = 0.09). In the management of patients with atrial fibrillation and CHADS 2 score ≥3, advanced age and HF, the use of direct oral anticoagulants (DOACs) is reasonable alternative to vitamin K antagonists. [21]

For this study, SPSS version 20 software was used to obtain the results with P value <0.05 is considered significant since the Confidence I is 95%.

Results

This study has a sample size of 150 patients. The ages of patients in our study ranged between 21-90 years. Out of 150 patients, 1% belonged to the age group of 21-30 years; 13% were between 31-40 years of age; 16% were between 41-50 years of age; 23% were between 51-60 years of age; 27% were between 61-70 years of age; 19% were between 71-80 years of age and 1% was between 81-90 years of age.

25% patients were prescribed with OAC alone; 7% patients were prescribed with OAC+NSAIDS; 63% patients were prescribed with OAC + Antiplatelets and 5% patients were prescribed with OAC + Antiplatelets + NSAIDS. P value calculated by chi square test was found to be 0.0087. Statistically significant difference was found (Figure 1).

Bleeding risk was compared based on age group and was found that age group 51-60 years were at higher probability to develop moderate risk of bleeding (+2) and age group 61-70 years were at higher probability to develop higher risk of bleeding (3+) (Figure 2).

Gender based bleeding risk revealed that 1 male was at low risk of bleeding (0); 63 males were at moderate risk of bleeding (1-2); 45 males were at higher risk of bleeding (3+) compared to 1 female at low risk of bleeding (0); 27 females at moderate risk of bleeding (1-2) and 13 females at higher risk of bleeding (3+). Considering age group, oral anticoagulants were prescribed highly in age group of 61-70 years (N=40) and least prescribed in the age group of 21-30 years (N=2).

On the basis of distribution of oral anticoagulants among all patients in accordance to gender, 109 males were prescribed with oral anticoagulants out of which were given Rivaroxaban and 41 females were prescribed with oral anticoagulants out of which were given Rivaroxaban.

Comparing the bleeding risk between Non-vitamin K antagonist (Rivaroxaban) and Vitamin K antagonist (Warfarin), patients prescribed with Warfarin were directly at high risk of bleeding compared to Rivaroxaban (Figure 3).

Group I was categorized as patients <65 years and Group II was categorized as patients ≥65 years. Results have shown that group I patients were preferably at low risk of bleeding compared to group II patients. P value calculated by chi square test was found to be <0.0001. Statistically significant difference was found (Figure 4).

Group A was categorized as Hypertensive patients and Group B as Non-hypertensive patients. Results depicted that group A patients were at high risk of bleeding compared to group B patients. P value calculated by chi square test was found to be 0.0026. Statistically significant difference was found (Figure 5).

Discussion

Anticoagulation therapy reduces the risk of stroke, thus the American College of Cardiology Guideline recommends oral anticoagulants for management of patients with atrial fibrillation with moderate to high risk of stroke. HAS-BLED score can guide physicians in informed decision making and providing adequate follow-up and monitoring. Based on the results from our study we conclude that patients prescribed other medications such as antiplatelets and NSAIDS along with oral anticoagulants, age ≥65 years and medication history of hypertension were at higher risk of bleeding in accordance to HAS BLED score. Among non-vitamin K antagonist and vitamin K antagonist, non-vitamin K antagonist was found to have less evidence of bleeding compared to vitamin K antagonist. This provides a new insight and can guide physicians in informed decision making and providing adequate follow-up and monitoring.

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Tables and Figures

I. HAS-BLED stands for H-hypertension, A-abnormal renal/liver function, S- stroke, B-bleeding, L-labile INR, E-elderly, D-drugs or alcohol. This score is used as one of the tools to evaluate the risk of bleeding in atrial fibrillation patients taking anticoagulants.

HAS-BLED	**Score**
Hypertension (systolic >160mmHg)	1
Abnormal renal/liver function	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Age (>65 years)	1
Drugs (concomitant NSAIDS, aspirin) or alcohol	1 or 2
Maximum score	9

II. CHA2DS2-VASC stands for C-congestive heart failure, H-hypertension, A-age ≥75 (doubled), D-diabetes, S-stroke (doubled), V-vascular disease, A-age 65–74, S-sex (female). It is one of the tools to evaluate risk of stroke in Atrial fibrillation patients.

CHA_2DS_2-VASc	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age (>75 years)	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI,PAD, or aortic plaque)	1
Age (65-74 years)	1
Sex category (i.e. female gender)	1
Maximum score	9

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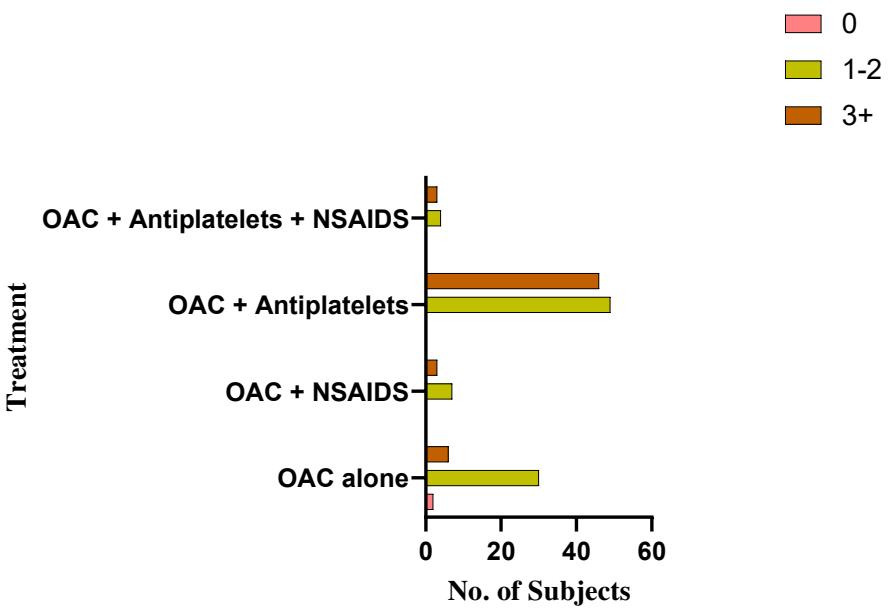
III.



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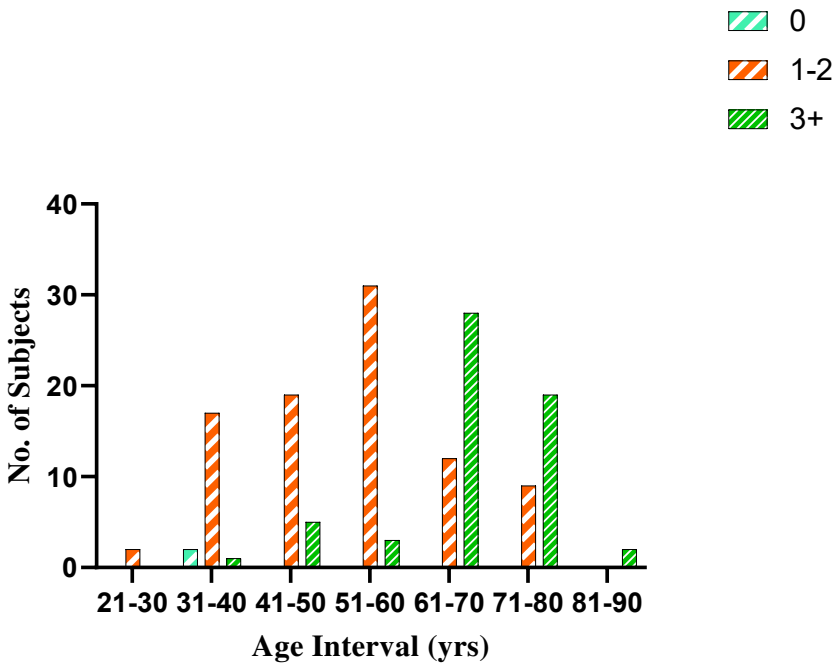

V.

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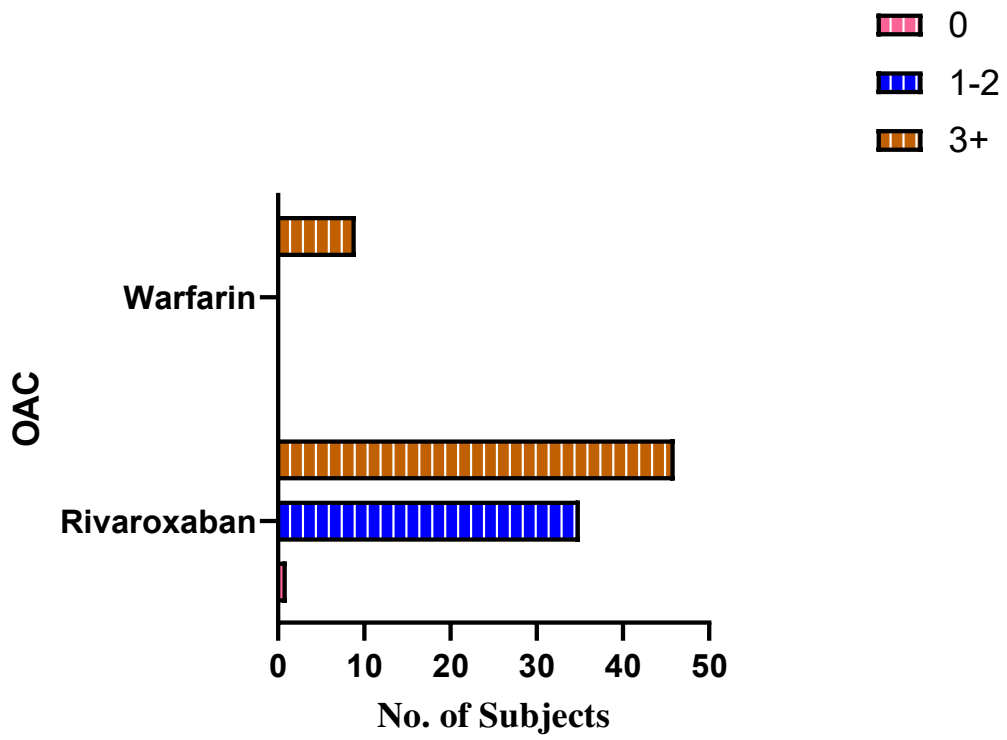

VI.

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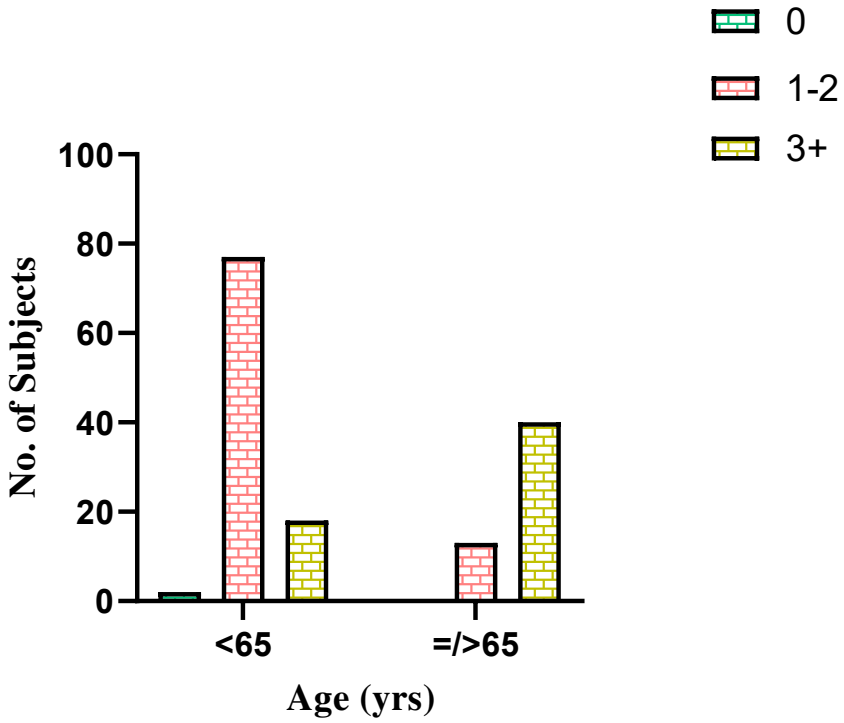

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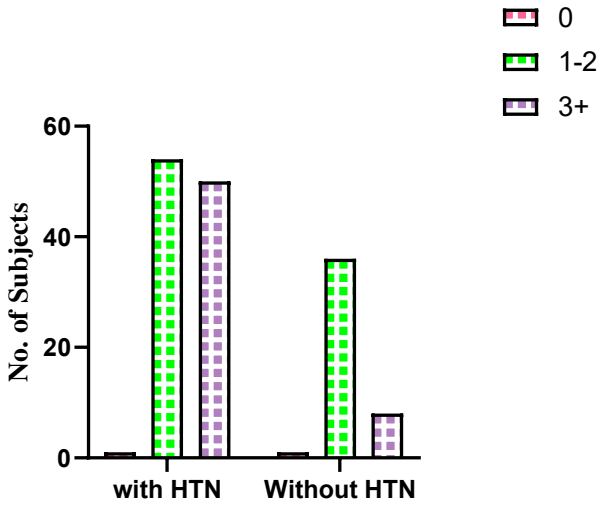

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Table and figure titles and legends:

Table I. HAS-BLED score for bleeding

Table II. CHA2DS2-VASC score for risk of stroke

Figure III. Comparison between Bleeding Risk In Patients Based On Treatment

Figure IV. Bleeding Risk Based On Age

Figure V. Comparison of Bleeding Risk Between Rivaroxaban (Non Vitamin K Antagonist) And Warfarin (Vitamin K Antagonist)

Figure VI. Comparison of Bleeding Risk Between 2 Age Groups (Group 1 – Age <65 Years And Group 2 – Age >65 Years)

Figure VII. Comparison of Bleeding Between 2 Groups (Group A - With Hypertension (HTN) And Group B – Without Hypertension (HTN))

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