



EFFECTIVENESS AND SAFETY COMPARISON OF WARFARIN AND DABIGATRAN IN ATRIAL FIBRILLATION

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ABSTRACT

Key Words

Dabigatran, Atrial fibrillation, Anti coagulant, Hemorrhagic, Vitamin-K, Warfarin



Atrial fibrillation or irregular heartbeat than can lead to blood clots, stroke, heart failure, and other heart related complications. Atrial fibrillation can be simply defined as a condition where in the upper chambers of the heart will have a disturbed or altered functioning which in turn will most commonly lead to stroke. According to a systemic review of the world literature on the prevalence and incidence of atrial fibrillation by circulation journals, population based studies of atrial fibrillation published from 1980-2010 the incidence of atrial fibrillation ranges between 0.21-0.41 per 1,000 persons/year. Permanent atrial fibrillation occurs in approximately 50% of patients and paroxysmal and persistent atrial fibrillation in 25% each. Atrial fibrillation is frequently associated with cardiac disease and comorbidities. This study explains about the effectiveness of dabigatran over warfarin. Dabigatran (150mg BID) has been associated with lower rates of stroke than warfarin in trials of atrial fibrillation, by using PT/INR and stroke analysis. The objective of the study was to compare the incidence of stroke, bleeding, and myocardial infarction in patients receiving dabigatran versus warfarin in practice. The study conducted was a retrospective cohort study. Patients administered with dabigatran or warfarin therapy between November 2010 and May 2014 were taken into consideration. Patients were administered in case of ischemic stroke, myocardial infarction, intra cranial bleeding, extra cranial bleeding identified from hospital claims among propensity score matched starting treatment with dabigatran or warfarin. Among 150 patients stating dabigatran therapy, study population accounted for total 150 patients with a clinical condition of atrial fibrillation were assessed to compare the safety profile and efficacy of between two anti-coagulant drugs used. Total study population has been divided in two groups, one group has 88 patients who were administered with Warfarin and the others were administered with dabigatran consisting of 62 patients who are using dabigatran. In the study risk of bleeding has been estimated using two scales HAS-BLED scale and CHA₂DS₂-VASc score. Trivial information has found in both the scales significant difference was found between two study groups, risk of bleeding associated with atrial fibrillation was found to be slightly more in warfarin administered group than that of dabigatran (150mg) where in 110 mg has no advantage. This study found that mean warfarin doses declined predictably with age and were not affected by sex.

INTRODUCTION:

Atrial fibrillation (also called AFib or AF) is a quivering or irregular heartbeat (arrhythmia) that can lead to blood clots, stroke, heart failure and other heart-related complications. Atrial fibrillation can be simply defined as a condition; where in the upper chambers of the heart will have a disturbed or altered functioning which in turn will most commonly lead to Stroke - A condition diagnosed by the irregular blood supply to the brain due to formation of clot (or) a hemorrhagic condition. Normally, your heart contracts and relaxes to a regular beat. In atrial fibrillation, the upper chambers of the heart (the atria) beat irregularly instead of beating effectively to move blood into the ventricles. This irregular heartbeat or the irregular functioning of the atria will result in formation of clots inside the blood vessels of the heart - thrombus. If a clot or thrombus breaks off, enters the bloodstream and lodges in an artery leading to the brain, a stroke results. The prevalence of AF is increasing due to our greater ability to treat chronic cardiac and non-cardiac diseases, and the improved ability to suspect and diagnose atrial fibrillation. There an increase in the present time, the prevalence of AF (2%) is double that reported in the last decade. The prevalence of AF varies with age and sex. AF is present in 0.12%–0.16% of those younger than 49 years, in 3.7%–4.2% of those aged 60–70 years, and in 10%–17% of those aged 80 years or older. In addition, it occurs more frequently in males, with a male to female ratio of 1.2:1. However, some people with atrial fibrillation do not have heart abnormalities. Treatment of atrial fibrillation can be a very simple task. Per say, if the atrial fibrillation is caused due to hypothyroidism, treating the thyroid condition in the patient can actually treat the underlying cause of atrial fibrillation. Other Symptoms include:

congenital heart diseases, Lung diseases, previous heart surgery and sleep apnea also might lead to atrial fibrillation.

Aim: The aim of the study is to assess whether warfarin reduces the risk of stroke in patients with atrial fibrillation but increases the risk of hemorrhage and is difficult to use. Also, to check if the new Non Vit-K anti coagulant - dabigatran (a new oral direct thrombin inhibitor) gives a better efficient outcome with reduced side effects.

Objectives: To assess the gender-wise distribution of the effect of warfarin and dabigatran. To assess the age-wise distribution of the effect of warfarin and dabigatran.

To assess distribution of depression based on the types of cardiovascular diseases and To assess the effect of alcoholism on the drugs used for atrial fibrillation and To assess the efficacy of warfarin and dabigatran and to assess the time taken to reach therapeutic effect of warfarin and dabigatran.

MATERIALS AND METHODS

Study protocol: It is a prospective study conducted for a period of 5 months and about 150 patients, met the study criteria were included in the study. The required data was collected from the patients through direct interview using standard questionnaires and also from patients' respective case sheets. The acquired data was evaluated based on the respective questionnaire scales and was used to measure the severity of atrial Fibrillation and their increasing chances for stroke.

Study Site: The study was conducted at Yashoda Hospital, Secunderabad, Telangana, India.

Study design: It is a prospective observational study, wherein standard

questionnaire tools i.e. CHA₂DS₂ VASc and HAS-BLED were used to diagnose the severity of stroke in atrial fibrillation.

Study Period: Study was conducted for 6 months.

Study population: A total of 150 patients were included in the study, out of which 44 patients belonged to in-patient department (IPD) and 106 patients belonged to out-patient department (OPD).

Study criteria

Inclusion Criteria: All the patients above the age of 45 years were included in the study. All male and female patients, with atrial fibrillation using warfarin and dabigatran, who were able to answer the given questionnaires, were included.

Exclusion Criteria: Patients below the age of 45 years. Patients without any cardiac complications. Disabled and mentally challenged individuals with or without cardiac complications (who cannot answer the questionnaire).

Methodology: Two standard questionnaires were taken into consideration to assess depression in cardiac patients which are listed as below: CHA₂DS₂-VASc Score for Atrial Fibrillation Stroke Risk: is a clinical prediction rules for estimating the risk of stroke in patients with non-rheumatic atrial

fibrillation (AF). This score is used to determine whether or not treatment is required with anticoagulation therapy or anti platelet therapy, since atrial fibrillation can cause stasis of blood in the upper heart chambers, leading to the formation of a mural thrombus that can dislodge into the blood flow, reach the brain, cut off supply to the brain, and cause a stroke. A high score corresponds to a greater risk of stroke, while a low score corresponds to a lower risk of stroke. The CHADS₂ score is simple and has been validated by many studies. In clinical use, the CHADS₂ score (pronounced "chads two") has been superseded by the CHA₂DS₂-VASc score ("chads vasc"), which gives a better stratification of low-risk patients. HAS-BLED score for major bleeding risk: HAS-BLED is a scoring system developed to assess 1-year risk of major bleeding in patients with atrial fibrillation. It was developed in 2010 with data from 3,978 patients in the Euro Heart Survey. Major bleeding is defined as being intracranial bleedings, hospitalization, hemoglobin decrease >2 g/dL, and/or transfusion. Assessment of bleeding risk in AF using the HAS-BLED bleeding risk schema as a simple, easy calculation, whereby a score of ≥3 indicates "high risk" and some caution and regular review of the patient is needed.

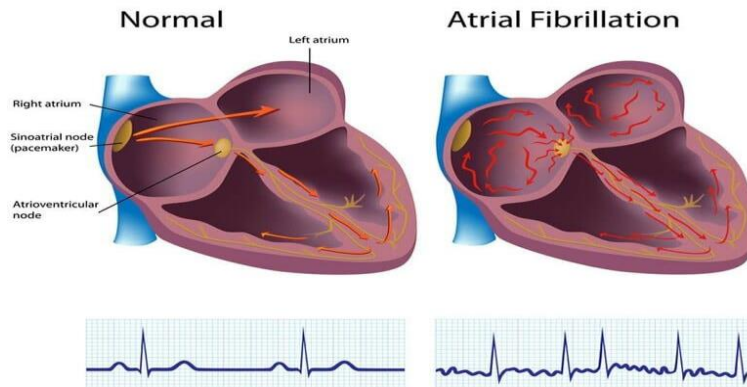


Figure 1: A diagrammatic representation of heart with Afib and to a normal heart

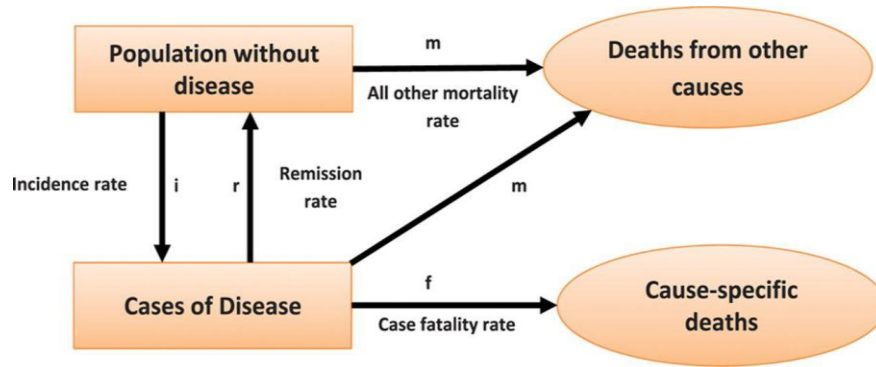


Figure 2: Epidemiological flow charts about the disease

Abnormalities (or) damage to the heart’s structure are the most common cause for atrial fibrillation possible causes of atrial fibrillation can be:

POTENTIAL CAUSES OF AFIB



Figure 3: Abnormalities

KNOW YOUR STROKE RISK			
CHA2DS2-VASc Risk	Score	CHA2DS2-VASc Score	Adjusted stroke rate (% / year)
		0	0
CHF or LVEF <40%	1	1	1.3
Hypertension	1	2	2.2
Age > 75	2	3	3.2
Diabetes	1	4	4
Stroke / TIA / Thromboembolism	2	5	6.7
Vascular Disease	1	6	9.8
Age 65-74	1	7	9.6
Female	1	8	6.7
		9	15.2

CHF = congestive heart failure; TIA - transient ischemic attack; LVEF = left ventricular ejection fraction.

Figure 4: CHA₂DS₂-VASc Score

Condition	Points
H – Hypertension	1
A – Ab(N) liver/renal	1 point each
S – Stroke	1
B – Bleeding	1
L – Labile INRs	1
E – Elderly (>65)	1
D – Drugs or ETOH	1 point each

Figure 5: HAS-BLED score

Table 1: Age wise distribution

Age interval	N=150	Percentage (%)
41-50	38	25
51-60	45	30
61-70	36	24
71-80	24	16
81-90	07	05

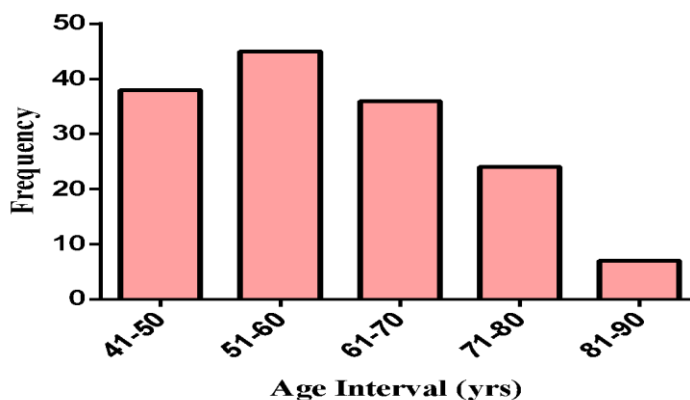


Figure 6: Age Wise distribution (n=150)

The graph illustrates the population distribution in different age groups. 25% of the patients fall under age group 41-50, whereas 30 % of them belong to age group 51-60 .24% are between 61-70 years of age. Remaining population is aged more than 70 years.

Table 2: Gender wise age distribution

Gender	N	Percentage	Minimum	Maximum	Median	Mean ± SD	P value
Male	67	45	42	84	56	58.61±10.92	0.1243
Female	83	55	42	82	61	61.42±11.19	

P value calculated by independent T test

The above table says that statistically significant difference was not found in the age between the genders.

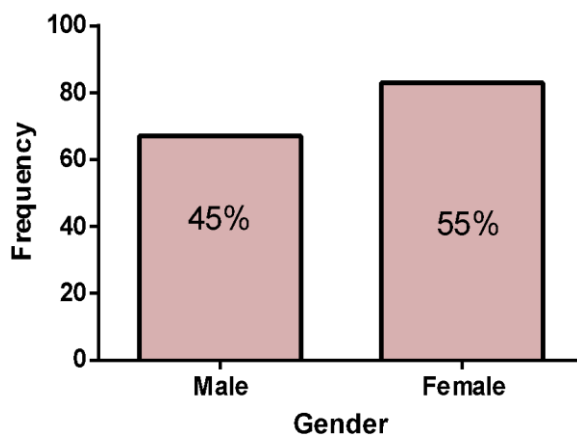


Figure 7: Gender distribution

The above graph shows gender distribution among the total study population more than 50% of population in this study.

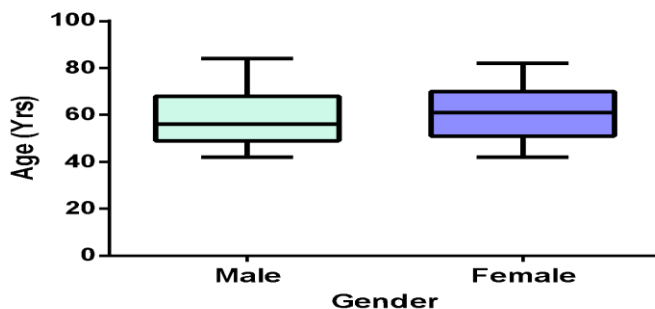


Figure 8: Gender based age distribution

Table 3: Proportion of drugs used

Drugs	Male	Female	P value
Warfarin	39	49	0.9185
Dabigatran	28	34	

The above table represents Chi-square test where P value is calculated. Statistically significant difference was not found.

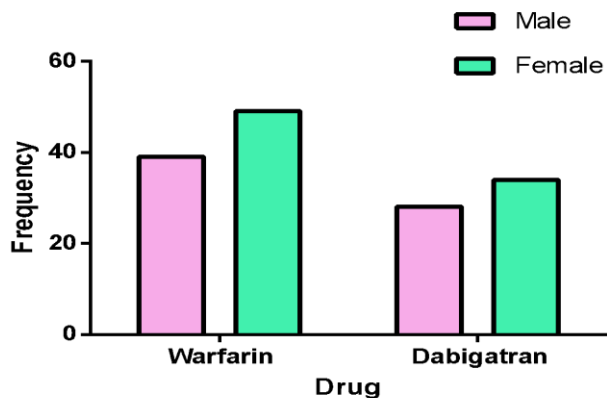


Figure 9: Proportion of drugs used in the study population

The above table depicts the two groups of population where one group is administered with warfarin and another group administered with dabigatran.

Table 4: Alcoholic habit based distribution

Drugs	Yes	No	P value
Warfarin	16	72	0.5072
Dabigatran	14	48	

The above table represents a P value calculated by Chi-square, statistically significant difference was not found frequency of people with alcohol abuse in both the groups is less, 30 patients are addicted to alcoholism out of total population.

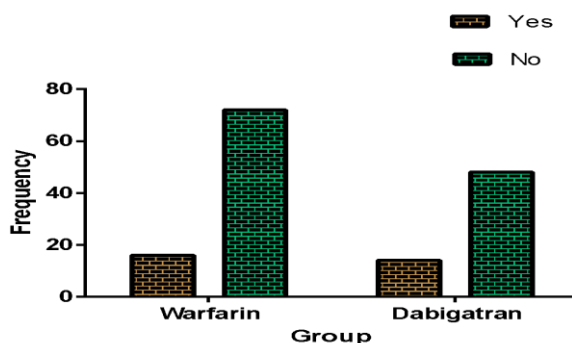


Figure 10: Alcoholic habit based distribution

The above graph depicts the population percentage addicted to alcohol, 20% patients out of total population are alcohol abused it includes 18% of patients from warfarin group and 22% patients of dabigatran.

Table 5: Proportion of Side Effects in the Study Population

Drugs	Yes	No	P value
Warfarin	83	05	<0.0001
Dabigatran	11	51	

The above table represents P value calculated by Chi-square test for occurrence of side effects in two groups of treated patients. Statistically significant difference was found which shows that side effects are seen more in warfarin treated patients.

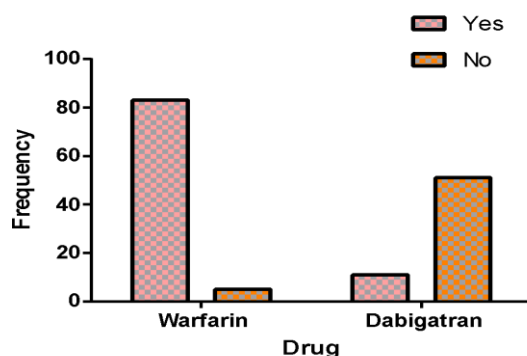


Figure 11: Proportion of side effects

The above graph depicts the occurrence of side effects in both the groups of patients. It states that high incidence of side effects were observed in warfarin used patients.

Table 6: Duration taken to achieve therapeutic effect (Days)

Drug	N	Percentage (%)	Minimum	Maximum	Median	Mean ± SD	P value
Warfarin	88	59	05	07	06	6.11±0.76	
Dabigatran	62	41	02	05	3.5	3.37±0.83	<0.0001

The graph represents the P value calculated by independent t test to obtain therapeutic efficacy between two anti coagulant drugs in this study. Statistically significant difference was found in the days taken to achieve therapeutic effect between the groups.

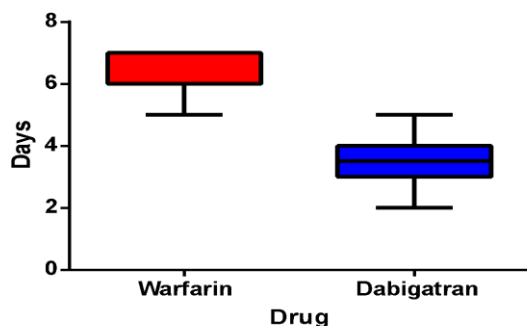


Figure 12: Duration taken to achieve therapeutic effect (Days)

The above graph illustrates a therapeutic efficacy comparison between warfarin and dabigatran. Dabigatran takes less duration to show its therapeutic effect that of warfarin according to study data.

Table 7: Inter group comparison of HAS-BLED score

Score	Warfarin (N=88)	Dabigatran (N=62)	P value
<3	31	34	0.0170*
≥3	57	28	

The above table represents P value calculated by Chi-square test for an inter group comparison done for two drugs complications or risk using HAS-BLED score. Statistically significant difference was found. Risk rate is higher in case of warfarin administration.

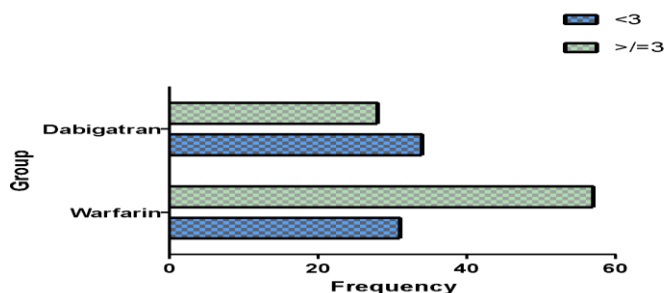


Figure 13: Inter group comparison of HAS-BLED score

The above graph shows that risk of bleeding is more in patients with atrial fibrillation when they are treated with warfarin than those who treated with dabigatran.

Table 8: Inter group comparison of CHA₂DS₂-VASc score

Score	Warfarin (N=88)	Dabigatran (N=62)	P value
<2	15	20	0.0301*
≥2	73	42	

The above table gives P value calculated by Chi-square test which was performed to assess the risk of bleeding in two groups of patients using CHA₂DS₂-VASc score. Statistically significant difference was found between both the groups. Risk is higher in case of warfarin administered patients.

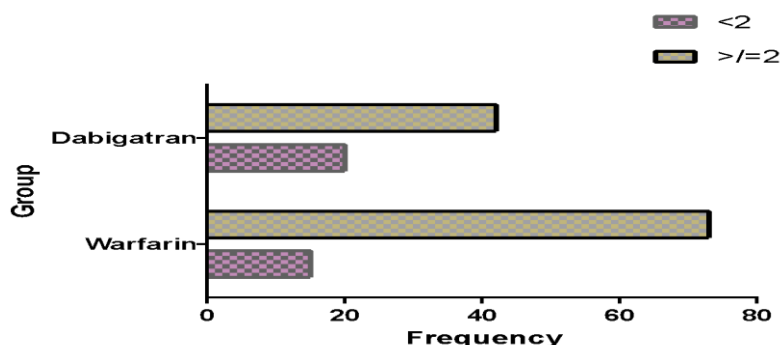


Figure 14: Inter group comparison of CHA₂DS₂-VASc score

The above graph illustrates a relationship between risk of bleeding and administration of anticoagulants in atrial fibrillation patients. Higher risk is found in patients with warfarin administration from the scale used.

A calculated HAS-BLED score is between 0 and 9 and based on eight parameters with a weighted value of 0-2. The HAS-BLED mnemonic stands for

- Hypertension
- Abnormal renal and liver function
- Stroke
- Bleeding
- Labile INR
- Elderly
- Drugs or alcohol

RESULTS

- Sample Size = 150
- Group I- Warfarin
- Group II-Dabigatran
- Software used: SPSS version 17
- P value <0.05 is considered significant since the CI is 95%

The graph illustrates the population distribution in different age groups. 25% of the patients fall under age group 41-50, whereas 30 % of them belong to age group 51-60 .24% are between 61-70 years of age. Remaining population is aged more than 70 years.

DISCUSSION: Study population accounted for total 150 patients with a clinical condition of atrial fibrillation were assessed to compare the safety profile and efficacy between two anticoagulant drugs used. Total study population has been divided in to two groups, one group has 88 patients who were administered with Warfarin and another group consists of 62 patients who are using dabigatran. From the Table-1 people between age group 50-60 are reported with higher percentage, patient's population is

least distributed in age group 80-90. From Figure-2 females are reported with a bit higher percentage in the study than males. From Figure-5, out of 88 Warfarin using patients 18% are alcoholic and 23% of patients administered with dabigatran were alcoholic. Totally 20% of patients in the conducted study are alcoholic. Side effects associated with warfarin are noticed to be higher; from Table-5 statistically significant difference was found which shows that side effects are seen more in warfarin treated patients than that of dabigatran in the study. Appearance of side effects in dabigatran administered patients is low when compared with that of warfarin from Figure 6, which concludes that using dabigatran as an anticoagulant in the population is safer than warfarin. From the study it is evident that dabigatran takes less duration to show its therapeutic effect on patient condition. Dabigatran achieved its therapeutic effect in minimum of two days whereas for warfarin it took minimum of 5 days according to the study (Table 6). In this study risk of bleeding has been estimated using two scales HAS-BLED scale and CHA₂DS₂-VASc score. In both the scales significant difference was found between two study groups, from Tables 7 & 8, risk of bleeding associated with atrial fibrillation was found to be more in warfarin administered group than that of dabigatran.

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CONFLICT OF INTEREST: Author declares that there is no conflict of interest to disclose.

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