THE IMPACT OF CLINICAL PHARMACIST MANAGED ANTICOAGULATION MANAGEMENT SERVICE VERSUS ROUTINE MEDICAL CARE ON THE CLINICAL OUTCOME OF ATRIAL FIBRILLATION PATIENTS: AN EGYPTIAN PILOT STUDY.

BY

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ABSTRACT

Aim. To assess impact of pharmacist managed anticoagulation management service on Egyptian atrial fibrillation patients' anticoagulation management, incidence and severity of bleeding events and thromboembolic events, incidence of warfarin drug and food interactions.

Methods. Prospective, randomized, controlled study. Patients presenting to Cardiology Department, Ain Shams University Hospitals, Cairo, from November 2012 to February 2014, were assessed for eligibility. Inclusion criteria; newly diagnosed AF patients who would receive anticoagulation with warfarin, aged 18- 80 years, moderate to high risk of developing stroke. Exclusion criteria; patient with renal disorder or on renal dialysis, pregnancy or lactation, dementia, moderate to severe hepatic disorder, valvular heart disease, clinically significant active bleeding, recurrent DVT or PE. Patients were randomly assigned to; control (routine medical care group); 30 atrial fibrillation patients subjected to regular care, or study (pharmacist group); 30 atrial fibrillation patients subjected to pharmacist managed anticoagulation management service. For both groups; demographics, anticoagulation knowledge assessment questionnaire (AKA) and INR were assessed initially and patients given a side effect self-reporting card. Study group was subjected to a systematic anticoagulation management and education. Follow up was done continuously for 6 months for both

groups and final evaluation included; percentage time in therapeutic range (TTR), anticoagulation knowledge assessment questionnaire (AKA), side effect, warfarin drug and food interaction reporting.

Results.

Groups were compared and there was no significant difference between them at baseline. After 6 months, study group's TTR levels were significantly ($p< 0.001$) higher as compared to control group. The patients' AKA score was significantly ($p< 0.001$) increased in study group compared to control group. Study group had a significantly lower frequency of bleeding ($p<0.001$) and no significant difference in thromboembolic ($p= 0.154$) or nonspecific episodes ($p= 0.303$) versus control group, Study group had a significantly lower frequency of warfarin drug interactions ($p= 0.004$) and no significant difference in frequency of warfarin food interaction ($p= 0.17$) versus control group.

Conclusion. Pharmacist managed anticoagulation management service improved patients' INR control, frequency of acute complications, frequency of warfarin drug interactions and patients' level of anticoagulation education.

Keywords. Anticoagulation management service, pharmacist, INR control.

Introduction:

Atrial Fibrillation (AF) is a heart rhythm disorder of the atria associated with deadly and debilitating consequences including heart failure, stroke, poor mental health, reduced quality of life and death ***(Stewart et al., 2002)***. The prevalence of atrial fibrillation is increasing particularly in developing countries due to the aging population ***(Go et al., 2003)***. Estimate of global prevalence of AF increases with age, from 0.5% at 40–50 years, to 5–15% at 80 years ***(Naccarelli et al., 2009).*** AF is estimated to affect 2.3 -5.1 million people in the US and 4.5 million people in the EU ***(Go et al., 2003) (Miyasaka et al., 2006).***AF is associated with increased rates of death, stroke and other thrombo-embolic events, heart failure and hospitalizations, degraded quality of life, reduced exercise capacity, and left ventricular [LV] dysfunction. Death rates are doubled by AF, independently of other known predictors of mortality ***(Marini et al., 2005)***. Only antithrombotic therapy has been shown to reduce AF-related deaths.AF increases an individual's risk of suffering a stroke by five times making it the most powerful independent risk factor for stroke ***(Marini et al., 2005)***. Moreover, strokes in patients with AF tend to be more severe than in non-AF patients ***(Jorgensen et al.,***

1996). They are more frequently fatal ***(Steger et al., 2004)*** and are more likely to lead to disability ***(Iqbal et al., 2005)***, increased healthcare costs ***(Winter et al., 2009)*** and extended hospital care than strokes in patients without AF ***(Jorgensen et al., 1996).***
Two treatment approaches cornerstone the management of AF. One is to correct the faulty heartbeat, and the other is to manage the risk of stroke by preventing the formation of clots in the fibrillating heart ***(Iqbal et al., 2005).***

Warfarin has been shown to reduce the risk of stroke in patients with AF in both clinical trials and clinical practice. Importantly, warfarin has proven efficacy in reducing the risk of severe, fatal or disabling strokes. In addition, anticoagulation with warfarin has been demonstrated to be cost-effective in patients with AF & a moderate-to- high risk of stroke ***(Fuster et al., 2006).*** However, warfarin administration is associated with major, well-recognized drawbacks. Despite the useful anticoagulant activity, warfarin has a narrow therapeutic index in which it is both safe and effective. Maintaining warfarin within this range is also complicated by interactions with food and other drugs that can significantly alter blood levels of warfarin regardless of the dose taken ***(Hart et al., 2000).*** For monitoring, usually the INR (International Normalized Ratio) is the standard test which represents the ratio between the test result and a standard pro-thrombin time ***(Fuster et al., 2006).***

Many patients have a poor understanding of AF as a disease and its pharmacotherapeutic requirements. In a study by Lip and colleagues, it was reported that 37% of documented chronic AF patients were unaware that they had AF and nearly half didn't know why they were taking warfarin. A similar number didn't know they were at risk of clots that could cause stroke. Sixty percent felt that their underlying condition (AF) was not severe***. (Lip et al., 2010)***

An extensive international survey conducted by the patient organization, AntiCoagulation Europe (ACE), revealed that a quarter of the surveyed patients did not remember receiving any information on AF at diagnosis, and over one-third felt that their doctor could have told them more regarding their medication and how it would affect their lives. Particular lack of awareness among patients was noted with regard to the potential interactions of warfarin with common over-the-counter medicines and herbal remedies. ***(Anticoagulation Europe, 2009)***
In the US, Anticoagulation Management Service is one of the standards of care offered

to patients on anticoagulation. It employs a focused and coordinated approach to managing anticoagulation ***(Macik, 2003).***They have sometimes been considered the gold standard of warfarin management ***(Macik, 2003)*** helping to increase the time that a patient's INR values are within the target range, improve the overall cost-effectiveness of therapy, increase patient adherence and provide valuable information for both healthcare professionals and patients ***(Ansell et al., 2007).*** However, in Egypt till now anticoagulation management service is lacking with only routine medical care availability that lacks proper patient education, follow up and monitoring for adverse drug events. The current situation has initiated our proposal to investigate the impact of such service on patient outcome. Another obstacle to achieving good control of anticoagulation among atrial fibrillation patients in Egypt is the relatively poor structure and processes of care in government hospitals and primary health care units.

The role of pharmacists has changed dramatically over the past 30 years with a change in the pharmacy practice concept from being a product-oriented practice to a patient-oriented one. The Pharmacist has become an integral member in the health care team.

Many studies that have included pharmacists as providers of anticoagulation management service have shown positive impact on patients' anticoagulation control and overall outcome ***(Chiquette et al., 1998; Holden and Holden, 2000; Baker, et al., 2006; Poon et al., 2007; Garwood et al., 2008).***

In Egypt, the clinical pharmacists' role in anticoagulation management service is still underutilized and under investigated.

The aim of the current study was to evaluate the role of a pharmacist managed anticoagulation management service on atrial fibrillation patients' INR control, frequency of acute complications, drug and food interactions and level of anticoagulation education.

Patients & methods:

Design:

prospective randomized controlled study, according to research ethics committee guidelines.

Setting:

Cardiology department, Ain Shams University Hospitals, Cairo.

Patients:

All patients presenting to the cardiology department were assessed for eligibility and present study was carried out From November 2012 to February 2014.

Inclusion criteria:

newly diagnosed AF patients, who received warfarin, aged 18- 80 years, moderate to high risk of developing stroke.

Exclusion criteria:

patient with renal disorder or on renal dialysis, pregnancy or lactation, dementia, moderate to severe hepatic disorder, valvular heart disease, clinically significant active bleeding, recurrent DVT or PE. Eligible patients were randomly assigned to:

Control (routine medical care group):

30 patients were observed by the clinical pharmacist and evaluated at baseline, monthly and at study end.

Study (Pharmacist group):

30 patients subjected to a thorough clinical pharmacist anticoagulation management and were evaluated at baseline, monthly and at study end.

Methods:

All reported investigations in the current study have been carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000.The ethical committee of Ain Shams University approved the study. All patients were informed of study protocol and only those who consented to participate were enrolled.

A. Baseline Evaluation:

At enrollment, through a face to face interview, pharmacist gathered the following information for both groups: a **full history taking** (Medical, medication, family and social histories and demographic data), **Laboratory data** (INR, CBC, and Serum creatinine), CHA_2DVASC and HASBLED scores and patients' anticoagulation knowledge assessment questionnaire (AKA). The questionnaire was done to evaluate patients' basic level of knowledge and practice about anticoagulation. The AKA included 29 questions (with a pass score of 21), 15 questions of which are deemed by the investigators to be relevant to INR control. This questionnaire assessed the various basic anticoagulation knowledge items with a total score of 29 points (AKA 1 score) and assessed anticoagulation knowledge items that are relevant to INR control with a

total score of 15(AKA 2 score). Clinical pharmacist interviewed the patient through a face to face interview and allocated the score according to patients' answer.

Score allocation. Each question was provided with a model answer, and patients' scores were allocated according to coverage of model answers' contents (Table 1).

Table 1. ***Anticoagulation Knowledge Assessment (AKA) Questionnaire***

Q.no	The questions and model answers
1	Which one of these medications is recommended if you are taking Marevan (warfarin) and want relief from a headache? a. Advil b. Motrin c. Aspirin d. Tylenol
2	Which of the following food items would interfere with your Marevan (warfarin) medication? a. Bacon b. Broccoli c. Bananas d. Peeled cucumbers
3	3. While on Marevan (warfarin) medication, in which of the following would you go directly to the emergency room? a. Small bruises b. Your appetite dramatically increases c. Nosebleed which will not stop bleeding d. Gums which bleed for a few seconds after brushing teeth
4	You just remembered that you forgot to take your evening Marevan (warfarin) medication dose last night. You would— a. skip the dose of Marevan (warfarin) you missed b. take the missed Marevan (warfarin) dose right now c. wait and take 2 doses of Marevan (warfarin) this evening d. take one-half of the missed dose of Marevan (warfarin) right now
5	While on Marevan (warfarin) you— a. should not eat spinach b. can eat spinach one time a month c. can eat as much spinach as you would like whenever you would like d. can eat spinach but need to eat the same amount regularly every week
6	While out with friends for dinner, you have just finished your third glass of wine. This amount of alcohol consumed in a single evening will— a. cause a decrease in your INR b. cause an increase in your INR c. not affect you or your Marevan (warfarin) in any way d. make you sick when taking Marevan (warfarin) medication

7	While in your pharmacy, you notice multivitamins are on sale. After some thought, you decide that you may need a multivitamin. You would— a. purchase the multivitamin and begin taking it regularly b. not take a multivitamin because it will cause a blood clot while taking Marevan (warfarin) c. start taking it and bring the multivitamin to your next Marevan Clinic visit to show the pharmacist d. purchase the multivitamin but not start taking it until you talked with the pharmacist at your Marevan Clinic
8	If you ran out of your prescription for your Marevan (warfarin) you would— a. borrow Marevan (warfarin) from a friend, as long as it is the same dose as yours b. call and ask for refills for that day so you do not miss a dose of Marevan (warfarin) c. wait until your next appointment that is just a few days away to get a new prescription d. do nothing because you have taken Marevan (warfarin) long enough, otherwise there would be more refills on your prescription
9	Which of the following is an effect of Marevan (warfarin) medication that will most likely be experienced? a. Stroke b. Leg Clot c. Bruising d. Blood in the urine
10	You have a cold, which includes a runny nose and cough. You— a. could safely take Nyquil to help get rid of the runny nose and cough b. take your friend's medication that he/she uses for a bad cold because he/she is also on Marevan (warfarin) medication c. would call the Marevan Clinic and tell him/her you are on Marevan (warfarin) medication and ask what you can take for your cold d. decide it is safer to suffer through the cold because most cold medications will interact with your Marevan (warfarin) medication
11	When making a dental appointment while taking Marevan (warfarin) medication, you need to remember you— a. cannot have procedures done on your teeth while taking Marevan (warfarin) b. must tell your dentist you are taking Marevan (warfarin) well in advance of having any procedure done c. can have procedures done and there is not a need to tell the dentist about the Marevan (warfarin) d. can have the dental procedure done if when you arrive at your dental appointment you tell the dentist you are taking Marevan (warfarin)
12	When the need arises to take an antibiotic (to get rid of an infection) while taking Marevan (warfarin), you need to— a. take half of the prescribed length of therapy, and then call the Marevan clinic b. refuse to take any new medication because you are taking Marevan (warfarin) c. wait until your next Marevan clinic visit and then tell the pharmacist about the antibiotic d. call the Marevan Clinic right away and let them know you are starting a new

	medication
13	Marevan (warfarin) works— a. in my liver to make my blood thicker b. in my liver to make my blood thinner c. in my kidneys to make my blood thicker d. in my kidneys to make my blood thinner
14	The best time of day for me to take my Marevan (warfarin) is— a. at lunchtime b. in the evening c. in the morning before breakfast d. any time of day when I remember
15	Which of the following is an effect of my Marevan (warfarin) medication that I will most likely experience if my INR is too high? a. A clot in the leg b. Minor bleeding c. Clot in the lung d. Bleeding in the brain
16	Which of the following drinks can decrease the effectiveness of your Marevan (warfarin)? a. Deans 2% low-fat milk b. Hershey's chocolate shake c. Tropicana orange juice d. Ensure nutritional supplement
17	17. While taking Marevan (warfarin), which of the following represents a situation when you should go to the emergency room? a. You cough up blood b. Your nose bleeds slightly while blowing it c. Your gums bleed after brushing your teeth then it stops quickly d. You have cut yourself while shaving and you control the bleeding
18	Your neighbor brings over this great "all natural" herbal supplement she just bought from her chiropractor. She swears that this helps all her aches and pains and recommends that you take it when you ache. Your decision is to— a. take her advice, realizing that you could use this herbal supplement b. start taking the herbal supplement and tell your pharmacist at the next office visit c. ask your pharmacist if the herbal supplement will interact with your medications before you take it d. avoid taking herbal supplements altogether because all medications interact with Marevan (warfarin)

19	Once you have reached a stable Marevan (warfarin) dose, a PT/INR blood test— a. should be checked once a year b. should be checked once every 3 months c. should be checked at least once every 4 weeks d. does not need to be checked once you are on a stable Marevan (warfarin) dose
20	The results of your PT/INR test tells the pharmacist— a. how thick or thin your blood is while taking Marevan (warfarin) b. how well your kidneys are working since taking Marevan (warfarin) c. what your average blood sugar level was since taking Marevan (warfarin) d. how much alcohol you have been drinking since taking Marevan(warfarin)
21	While taking Marevan (warfarin), you should call your Marevan Clinic when you get: a. a backache b. an upset stomach c. a tension headache d. diarrhea for more than 1 day
22	While on Marevan (warfarin) you need to be routinely monitored for which of the following: a. PT/INR tests b. Potassium levels c. Blood glucose levels d. Kidney function tests
23	Which of the following may have a significant effect on how well your Marevan (warfarin) works? a. Changes in your mood b. Changes in sleep habits c. How much water your drink d. Using over the counter medications
24	While taking Marevan (warfarin), which of the following should lead you to the emergency room? a. Loss of appetite b. Brown loose stools c. Urine becomes red in color d. A quarter size bruise on your arm
25	25. Which of the following foods could affect how well your Marevan (warfarin) works? a. Celery b. Carrots c. Cole slaw d. Green beans
26	You have generic and brand Marevan (warfarin) tablets at home that are both the same dose. You should— a. take both because they work differently b. take only brand or generic, but not both c. not take either until you call the Marevan Clinic d. alternate days by taking brand on one day and generic on the next day

27	Once your Marevan (warfarin) is stopped, how long does it take to get the medication to get out of your system? a. 5 hours b. 5 days c. 5 weeks d. 5 months
28	After starting Marevan (warfarin), how long (in months/years) would you expect to be taking Marevan (warfarin)? a. 1 year b. 1 month c. It depends on each person's needs d. If you start Marevan (warfarin), you will have to be on the medication for the rest of your life
29	Which of the following activities are more risky while taking Marevan (warfarin)? a. Playing football, because you can hit your head b. Taking a bath, because soap interacts with Marevan (warfarin) c. Playing cards because using your hands a lot will cause a blood clot d. Walking a lot, because exercise is not good for you while taking Marevan (warfarin)

Correct answers are underlined.
Items that were deemed relevant by the study investigators for inclusion in sensitivity analyses of knowledge with INR control are shaded in gray.
INR = international normalized ratio; PT=prothrombin.

Baseline education:

1. For both groups:

- Patients were given the follow up side effects reporting card.

- The follow up card was used for patients' self -assessment and reporting of the frequency of bleeding, thromboembolic and non-specific events/ day during the 6 months period. The main events reported were; minor bleeding (bleeding gum, epistacsis), internal bleeding (bruises), major bleeding (haematepsis, blood in urine/stool/vomit), thromboembolic (DVT, leg change color/vessels appear, pulmonary embolism), non-specific (leg pain, leg swell, dyspnea, chest pain, hypotension, tachycardia, dizziness, headache, skin rash, nausea, and other).

The numbers of events were summed up to give the frequency of bleeding, thromboembolic and non-specific events.

- Patients were educated about using the follow up event card, the expected events & how to report them.

2. For the study group:

- Follow up events card education

- A Structured anticoagulation education first was performed by the clinical pharmacist to cover the basic atrial fibrillation knowledge, warfarin use and common side effects, warfarin drug and food interactions.

B. Follow up assessment:

During the 6 months period ***(Jack et al., 2003; Ansell et al., 2014)***, **patients in both groups** were assessed monthly or more frequent when required according to INR value as follows;

1. INR value recording.
2. Assessment of reasons of out of range INR readings whether (warfarin drug interaction, warfarin food interaction, illness, non compliance, improper dosing or testing, unknown and starting dose)
3. Patient follow-up event card assessment and giving new cards.
4. Assessment of frequency of bleeding, thromboembolic and non-specific events.
5. Assessment of occurrence of warfarin drug or food interaction.
6. Recording of cause and number of days of hospitalization if occurred.
7. Decision of the time of the next visit according to each patient INR status.

Patients in study group were additionally assessed for

1. Their educational level and education was reinforced as individually required by patients.
2. Stability of INR value in range and readjustment of warfarin dose if required.

Patients in control group were referred to their physician if the INR value was out of range to be adjusted by means of the physician.

C. End of study assessment:

After the 6 months of study duration, both groups were assessed for the following;

1. INR levels
2. Patients anticoagulation knowledge assessment Questionnaire (AKA)
3. Follow up event card assessment
4. Determination of incidence of hospitalization
5. End of study laboratory data (INR, CBC, Serum creatinine)
6. Calculation of percentage of time in therapeutic INR range

D. Statistical methods

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 17. Numerical data were summarized using means and standard deviations or median & ranges. Categorical data were summarized as percentages. Comparisons between the two groups were done using the Mann-Whitney test. The Chi-square or the Fisher's exact tests for small sample size were used to compare between the groups with respect to categorical data. Repeated measures analyses of variance were done to study the differences between groups and change with time.

P-values are two-sided. P-values < 0.05 were considered significant and P-values < 0.001 were considered highly significant.

E. Materials (Drugs):

Warfarin: Marevan®, available in different strengths (1mg, 3mg and 5mg), uncoated tablets; each tablet contains warfarin sodium, lactose, maize starch, maize starch pregelatinised, purified water, and sodium starch glycolate and magnesium stearate, manufactured by GlaxoSmithKline, Egypt.

Results:

From November 2012 to February 2014 the present study was carried out on 60 non-valvular atrial fibrillation patients who fit the inclusion criteria and were randomly assigned to control or study group. All the 60 patients who started the study completed till the end of the study.

Baseline Evaluation

At baseline, both groups were comparable in their baseline parameters with no significant difference between them **(Table 2)**.

Table 2. Patients' demographics and baseline data in both groups

Parameter	Control group (n=30)	Study group (n=30)	P value
Age; mean ± S.D	63.4± 7.4	62.4± 7.1	0.584
Sex			
Male; n (%)	14 (46.7 %)	13 (43.3%)	0.795
Female; n (%)	16 (53.3%)	17 (56.7%)	
Comorbidities type			
DM; n (%)	12 (40%)	8 (26.7%)	
HTN; n (%)	14 (46.7%)	16 (53.3%)	
Hypothyroidism; n (%)	1(3.3%)	1(3.3%)	
COPD; n (%)	1(3.3%)	0(0%)	
Gout; n (%)	1(3.3%)	0(0%)	
Hypercholesterolemia; n (%)	1(3.3%)	2(6.7%)	
Smoking; n (%)	3(10%)	2(6.7%)	
BPH; n (%)	2(6.7%)	1(3.3%)	
Hyperthyroidism; n (%)	1(3.3%)	0(0%)	
Number of complication			
· None · One disease · Two diseases · > Two diseases · No of comorbidities median (range)	6 (20%) 15 (50%) 6 (20%) 3(10%) 1(0-3)	7(23.3%) 18 (60 %) 3(10%) 2(6.7%) 1(0-3)	0.352
Questionnaire score			
AKA1	9.7±2.8	7.9±2.6	0.061
AKA2	3.6±2.1	3.4±1.8	1.0
Laboratory Data			
S.Cr mg/dL	0.8 ± 0.12	0.85 ± 0.16	0.378
Plt*1000/mcL	275.1± 64.2	262± 59.8	0.82
INR	1.12 ± 0.16	1.12 ± 0.16	0.867
CHA_2D_2VASC score	2± 0.69	1.97± 0.76	0.854
HAS BLED score	1± 0.69	1.3 ± 0.72	0.954

1. **After treatment evaluation**

a. Percentage time in therapeutic INR range (TTR %)

After 6 months of implementing pharmacist managed anticoagulation managed service, there was a significant difference in percentage TTR levels between the 2 groups. The study group's TTR% was higher than the control group with a high significant difference ($p < 0.001$).

The mean (SD) TTR% was 38% (11%) for the control group versus 68% (8%) for the study group **(Table 3** and **Figure 1).**

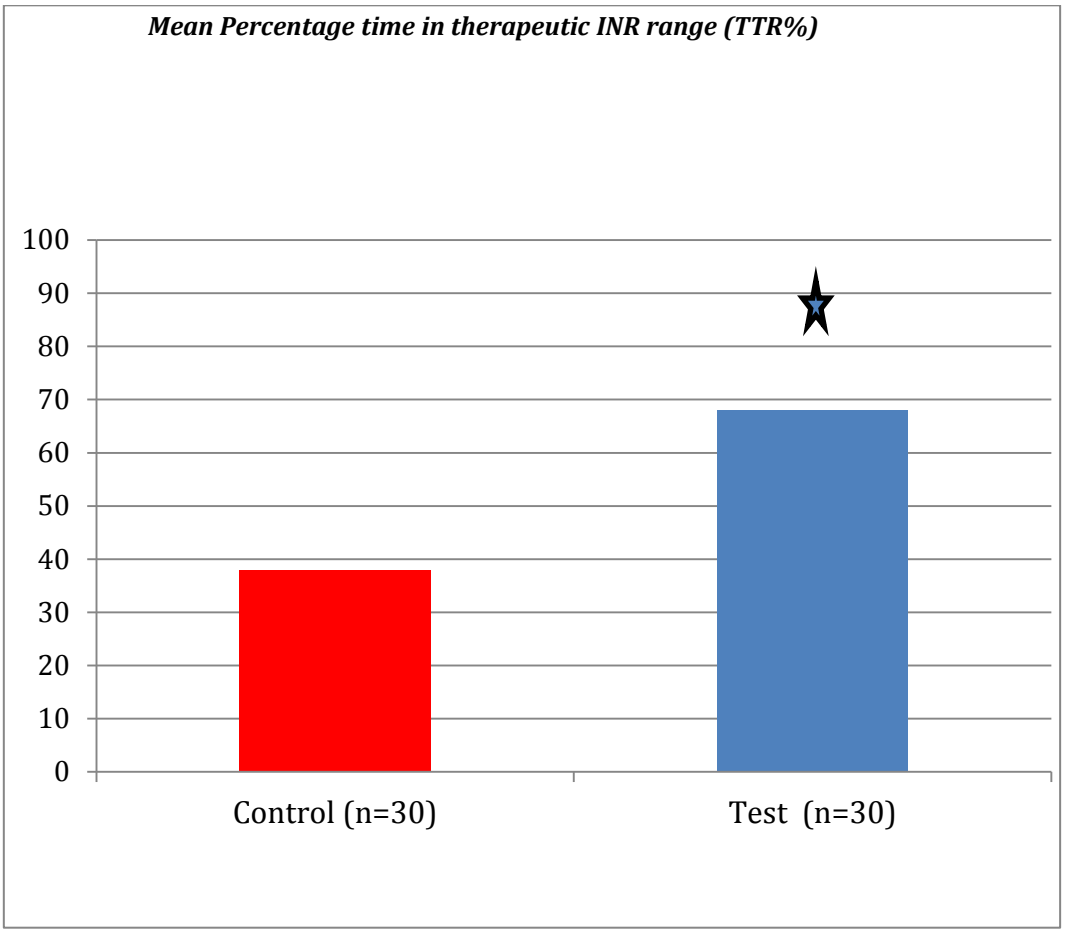

Figure1. Patient Percentage of Time in INR range in both groups.

Statistical test; Unpaired T-test

★ p value< 0.05 is considered significant

b. Patient anticoagulation knowledge assessment questionnaire (AKA)

At baseline, there was no significant difference in the AKA 1 or AKA 2 scores between the 2 groups, while at the end of the study, there was a significant increase in AKA1 and AKA2 scores with time in both groups. The control group's scores increased with time but much less than the study group. The study group's scores significantly increased ($p < 0.001$) with time after the implementation of the anticoagulation management service **(Table 3 and Figure2).**

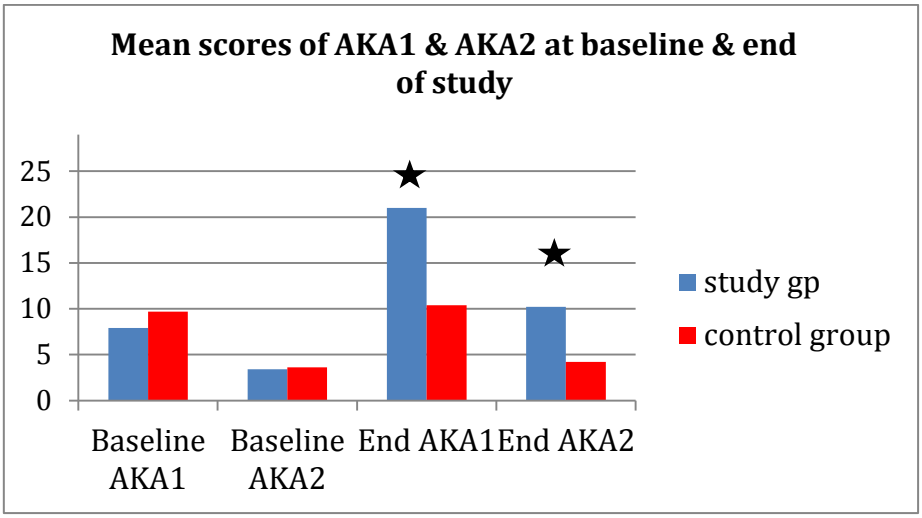

Figure2. Patient Anticoagulation knowledge assessment questionnaire (AKA) in both groups over time.

Statistical test; ANOVA with repeated measures

★p value< 0.05 is considered significant

c. Incidence of side effects

1. Number of events

The median number of events in the 6 months period was highly significantly lower (p<0.001) in the study group (4; range: 2-7) relative to the control group (5; range: 3-10) **(Table 3).**

2. Frequency of bleeding events over 6 months

The median frequency of bleeding events over the 6 months period was significantly lower (p<0.001) in the study group (0.5; range: 0-4) relative to the control group (2; range: 0-9) **(Table 3).**

3. Frequency of thrombo embolic events over 6 months

There was no significant difference (p=0.154) in the median frequency of thromboembolic events in the 6 months period between the study group (0; range: 0-0) relative to the control group (0; range: 0-2) **(Table 3).**

4. Frequency of non-specific events over 6 months

There was no significant difference (p=0.303) in the median frequency of non-specific events in the 6 months period between the study group (3; range: 1-5) relative to the control group (2; range: 0-10) **(Table 3).**

d. ***Incidence of hospitalization:*** There was no significant difference between both groups in the percentage of patients who were hospitalized **(Table 3).**

e. ***Frequency of warfarin drug interaction:***

The median frequency of warfarin drug interaction in the 6 months period was significantly lower (p=0.004) in the study group (0; range: 0-2) relative to the control group (0.5; range: 0-3) **(Table 3).**

f. ***Frequency of warfarin food interaction***

There was no significant difference between both groups in the incidence of warfarin food interaction **(Table 3).**

g. ***Number of out of INR range reading***

The mean number of out of INR range readings in the 6 months period was highly significantly lower (p<0.001) in the study group (3.4; SD= 1) relative to the control group (7.3; SD= 1.8) **(Table 3).**

h. ***Reasons of out of INR range reading***

1. The median frequencies of **Non-Compliance** as a reason of out of INR range reading is highly significantly lower in study group(0; range:0-2) than control group (2; range:0-4) **(Table 3).**
2. The median frequencies of **Improper Dosing or testing** as a reason of out of INR range reading is highly significantly lower in study group(0; range:0-0) than control group (2; range:0-5) **(Table 3).**
3. The median frequency of **Warfarin drug interaction** as a reason of out of INR range reading is significantly lower in study group(0; range:0-2) than control group (1; range:0-3) **(Table 3).**
4. There was no significant difference between study and control group in the median frequencies of **Warfarin food interaction**, **Illness**, **Start dose** and **unknown** as reasons of out of INR range readings **(Table 3).**

Table 3. Patients outcomes in both groups and over time.

Parameter	Groups				Analysis of Variance		
	Study (n=30)		**Control (n=30)**		**Effect**	**P value**	**Significance**
	Mean	**S.D**	**Mean**	**S.D**			
1. Percentage of Time in Therapeutic INR Range (%)							
TTR %	68%	8%	38%	11%	Group	*<0.001	Yes
2. Patient Anticoagulation knowledge assessment questionnaire (AKA)							
AKA1 Base	7.9	2.6	9.7	2.8	**Group**	*<0.001	Yes
					Time	*<0.001	Yes
AKA1 End	21	2.4	10.4	3	**Time* group**	*<0.001	Yes
AKA2 Base	3.4	1.8	3.6	2.1	**Group**	*<0.001	Yes
					Time	*<0.001	Yes
AKA2 End	10.2	1.9	4.2	2	**Time* group**	*<0.001	Yes

	Median	**Min**	**Max**	**Median**	**Min**	**Max**	**Mann-Whitney Test**	
							P value	**Significance**
3. Frequency of Events								
Bleeding Events	0.5	0	4	2	0	9	*<0.001	Yes
Thromboembolic	0	0	0	0	0	2	0.154	No
Non specific	3	1	5	2	0	10	0.303	No
4. Incidence of Hospitalization								
No.of Hospitalization records	0	0	1	0	0	1	0.165	No
5. Incidence of Warfarin Interaction								
No of Drug Interaction	0	0	2	0.5	0	3	*0.004	Yes
No of food interactions	0	0	2	0	0	3	0.170	No
5.Frequency of Out of range readings								
No of out of range readings	3	2	6	7	4	10	*<0.001	Yes
6. Reasons of Out of INR range readings								
Warfarin drug interaction	0	0	2	1	0	3	*0.002	Yes
Warfarin Food interaction	0	0	2	0	0	3	0.17	No
Illness	0	0	1	0	0	2	0.621	No
Non-Compliance	0	0	2	2	0	4	*<0.001	Yes
Improper Dosing	0	0	0	2	0	5	*<0.001	Yes
Unknown	0	0	2	0	0	3	0.084	No
Start dose	2	1	4	2	0	4	0.708	No

Discussion:

Atrial Fibrillation is a heart rhythm disorder of the atria associated with deadly and debilitating consequences including heart failure, stroke, poor mental health, reduced quality of life and death ***(Stewart et al., 2002).***

Two treatment approaches cornerstone the management of AF. One is to correct the faulty heartbeat, and the other is to manage the risk of stroke by preventing the formation of clots in the fibrillating heart ***(Iqbal et al., 2005).***

Warfarin has been shown to reduce the risk of stroke in patients with AF in both clinical trials and clinical practice. Importantly, warfarin has proven efficacy in reducing the risk of severe, fatal or disabling strokes. In addition, anticoagulation with warfarin has been demonstrated to be cost-effective in patients with AF & a moderate-to- high risk of stroke ***(Fuster et al., 2006).***

However, warfarin administration is associated with major, well-recognized drawbacks. Despite the useful anticoagulant activity, warfarin has a narrow therapeutic index in which it is both safe and effective. Maintaining warfarin within this range is also complicated by interactions with food and other drugs that can significantly alter blood levels of warfarin regardless of the dose taken ***(Hart et al., 2000).***

The pharmacist role in the healthcare team has proven to be influential and resulted in positive patient outcomes ***(Garwood et al. ,2008)***. Moreover, this role was also evident in the provision of anticoagulation management in several parts of the world, yet this role is still underutilized and its outcome not properly investigated in Egypt. To our knowledge, this is the first Egyptian study to investigate the impact of pharmacist managed anticoagulation management service on non valvular atrial fibrillation patients' outcome.

At baseline, patients in both groups were comparable in INR and AKA scores. After implementing the pharmacist managed anticoagulation management service, the study group, showed a significant higher time in therapeutic range relative to control group, indicating the positive impact of pharmacist managed anticoagulation management service.

Similarly, Garwood and colleagues, in their retrospective medical record review to study quality of anticoagulation care in patients discharged from a pharmacist-managed anticoagulation clinic after stabilization of warfarin therapy in outpatient

clinics have shown that on transition to physician-managed care a significant decrease in percentage of international normalized ratios (INRs) in target range and patient satisfaction with clinical care provided by the anticoagulation clinic was significantly higher before transition to physician-managed care ***(Garwood et al. ,2008)***

Moreover, **Chiquette et al. (1998)** in a prospective study design compared the impact of anticoagulation clinic with usual medical care in: anticoagulation control, patient outcomes, and health care costs. Results showed a significant more time in range and had lower rates of significant bleeding, major to fatal bleeding and thromboembolic events in the pharmacist led group versus the control group.

Similarly, **Baker et al. (2009)** assessed the quality of warfarin control in atrial fibrillation patients in the United States in a Meta-analysis that included 8 studies and a total of 14 unique warfarin- treated groups. Meta-regression suggested that AF patients treated in a community usual care setting compared with an anticoagulation clinic spent 11% less time in range.

Warfarin is more likely to be used safely by a patient who is aware of the potential for drug and diet interactions, understands the need for monitoring, and can recognize the signs of over- and under- anticoagulation. Anticoagulation education, a cornerstone in the management process of atrial fibrillation has resulted in improved patients' INR control, increased well being and reduced acute and chronic complications ***(AntiCoagulation Europe, 2009; Macik, 2003).***

Poor knowledge leads to non-adherence to medication therapy, leading to poor INR control and negative outcomes ***(AntiCoagulation Europe, 2009)***.

Our study has assessed atrial fibrillation patients' basic knowledge and practice. Both groups were not significantly different in their AKA1 and AKA2 scores at baseline. At the end of the study, the AKA1 and AKA2 scores increased in the pharmacist and control groups, yet the increase in the pharmacist managed group was significantly higher than the regular care group. Moreover, the increase of change in both scores from baseline was significantly higher in the pharmacist managed group versus the regular care.

Our results are in accordance with a prior prospective study of ***Lane et al. (2006)*** evaluating effects of an educational intervention program on Patient knowledge and perceptions of atrial fibrillation and anticoagulant therapy. After a brief educational

intervention a significant improvement in patient's knowledge of the target INR range and factors that may affect INR levels.

Similarly, in a prospective study to evaluate patients' knowledge of warfarin and its relationship to anticoagulation control, ***(Tang et al., 2003)*** it was found that there was a positive correlation between patients' warfarin knowledge and the number of INR values that was within the target range and concluded that patients' warfarin knowledge, a determinant of anticoagulation control, was generally poor. More attention should be given to the education of elderly and illiterate patients.

In the contrary, a cross-sectional study with 156 randomly sampled patients from physician- and pharmacist-managed anticoagulation clinics found that there was no significant differences between physician- and pharmacist-managed anticoagulation clinics' patients on their knowledge but patients in pharmacist-managed anticoagulation clinics were found to have better INR control compared to physician-managed anticoagulation clinics' patients ***(Hasan et al.,* 2011**).

All of these results confirm previous conclusions that good knowledge about atrial fibrillation, need for anticoagulation, warfarin, medication or diet interaction, compliance, possible side effects and treatment modifications is necessary in the effective self-management of atrial fibrillation.

It has been repeatedly confirmed in previous studies***, (AntiCoagulation Europe, 2009; Macik, 2003)*** that patient education has great efficiency in improving INR control and reducing acute complications of anticoagulation.

Results of the current study has shown a significantly lower frequency of patient-reported bleeding, thromboembolic or non specific events in the pharmacist educated group versus the control group, indicating the positive impact of pharmacist managed anticoagulation management service on frequency of acute complications.

These findings are in accordance with prior results of Chiquette et al. (1998) and ***Wilson et al. (2003)***, that demonstrated that intensive anticoagulation control can keep more INR readings in therapeutic range and prevent complications of anticoagulation***.(Chiquette E1,1998)(Wilson SJ1,2003)***

Similarly, A pilot follow-up study used a before-after comparison between anticoagulation management service led by pharmacists and by a primary-care general

practitioner (GP) it concluded that pharmacist-led anticoagulation care resulted in significant improvements in TTR ***(Harrison et al.,2014).***

Same results were found in a retrospective cohort study to evaluate warfarin management by pharmacists compared with physicians through an inpatient anticoagulation management service (AMS). It was clear that the pharmacist-managed patients demonstrated a lower incidence of supratherapeutic INRs and significantly more time within goal ***(Chilipko and Norwood, 2014).***

Conclusion:

The current study showed that pharmacist provided anticoagulation management service was associated with significantly higher % of TTR, higher levels of anticoagulation knowledge and practice and a lesser frequency of bleeding, thromboembolic events.

Hence, we recommend that pharmacist role in anticoagulation management service & education should be highly enforced and nationally implemented as it can contribute to more anticoagulation control, awareness and lesser complications.

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تأثير خدمة متابعة منع تخثر الدم بواسطة الصيدلي الاكلينيكي بالمقارنة بالرعاية الطبية الروتينية على المردود الإكلينيكي لمرضى الرجفان الأذيني : دراسة تجريبية مصرية

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الملخص:

هدف البحث . تقييم تأثير خدمة متابعة منع تخثر الدم مقابل الرعاية الطبية الروتينية لمرضى الرجفان الأذيني عن طريق مراقبة منع تخثر الدم و مراقبة حدوث وشدة أحداث النزيف و أحداث انسداد الأوعية الدموية و أيضا الكشف عن تفاعلات دواء الوارفارين مع الأدوية و الغذاء.

المرضى و طريقة الدراسة تضمنت الدراسة ٦٠ من مرضى الرجفان الأذيني و المترددين على قسم القلب – مستشفيات جامعة عين شمس – القاهرة- مصر.و هم بالغون من سن ١٨ إلى ٨٠ سنة، مرضى الرجفان الأذيني حديثي التشخيص، ولديهم خطر متوسط أو عالي لحدوث السكتة الدماغية و يستثنى منهم النساء الحوامل و المرضعات، مرضى الكبد، مرضى الكلى و الغسيل الكلوي، العته ، أمراض صمام القلب ، نزيف نشط، تجلط وريدي عميق أو انسداد رئوي متكرر.

وتم تقسيم المرضى الذين تنطبق عليهم معايير الاشتمال عشوائيا إلى مجموعتين :المجموعة الأولى هي مجموعة المراقبة (30 مريض) وتم توفير الرعاية الطبية الروتينية لهم و المجموعة الثانية مجموعة الدراسة(30 مريض) وتم تقديم خدمة متابعة منع تخثر الدم لهم من قبل الصيدلي الإكلينيكي.وتم الحصول على الموافقة المسبقة على كل من المريض قبل إدراجها في الدراسة وفقا لإعلان هلسنكي.

تم تقييم جميع المرضى قبل الدخول إلى الدراسة عن طريق تجميع بيانات كاملة لهم كالعمر و الجنس ، الادوية الحالية و الماضية ، تاريخ المرض و مضاعفاته، التاريخ المرضى، وظائف الكبد و الكلى، صورة دم كاملة، تقسيم خطر السكتة الدماغية عن طريق حساب درجة CHA2DS2VASc ، حساب خطر النزيف عن طريق حساب درجة HAS-BLED.و تقييم الوعي الذاتي عن طريق استبيان (AKA) لتقييم مستوى المرضى ومعرفتهم كيفية استخدام مضادات التخثر.المتابعة تمت بشكل مستمر لمدة ٦ أشهر لكلا المجموعتين و التقييم النهائي شمل ؛ قياس

نسبة الوقت الذي يقضيه المريض في نطاق ال INR العلاجي (TTR)، استبيان تقييم المعرفة، نسبه حدوث الاعراض الجانبية والمضاعفات الحادة و نسبه حدوث تفاعلات دوائية أو غذائية.

النتائج. فى بداية الدراسة كانت المجموعتين متماثلين فى; قياس نسبة السيولة، استبيان تقييم المعرفة .بعد ٦ أشهر وجد أن نسبة الوقت الذي يقضيه المريض في نطاق ال INR العلاجي للمجموعة الثانية أعلى من المجموعة الاولى وكان الفرق ذو دلالة احصائية ($P < 0.001$).وكانت هناك زيادة ذو دلاله احصائية($P < 0.001$) في تقييم استبيان المعرفة (AKA) بالمقارنة مع مستوياتها في بداية الدراسة لكلا المجموعتين ، لكن كانت الزيادة أعلى في المجموعة الثانية. ظهرت المجموعة الثانية انخفاضا كبيرا($P < 0.001$) في تكرار حدوث وشدة أحداث النزيف مقارنة بالمجموعة الاولى.وكانت المجموعة الثانية أقل بكثير في تكرار حدوث تفاعلات دواء الوارفارين مع الأدوية وكان الفرق ذو دلالة احصائية ($P = 0.004$) مقارنة بالمجموعة الاولى.وأيضا كانت المجموعة الثانية أقل بكثير في تكرار عدم الالتزام بالدواء وأخذ جرعات خاطئة كأسباب خروج نسبة السيولة عن نطاق ال INR العلاجي وكان الفرق($P < 0.001$) ذو دلالة احصائية.

الاستنتاج. تقديم خدمة متابعة منع تخثر الدم بواسطة الصيدلي لمرضى الرجفان الأذيني ادى الى تحسن فى نسبة الوقت الذي يقضيه المريض في نطاق ال INR العلاجي ، درجة المعرفة والممارسة للمرضى ، و انخفاض نسبه حدوث المضاعفات الحادة و التفاعلات الدوائية