

IMPACT OF CLINICAL PHARMACIST LED FIRST WARFARIN CLINIC IN YEMEN: A RETROSPECTIVE STUDY FROM A TERTIARY HOSPITAL

A Submitted Report to the Faculty of Pharmacy

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Dedication

We dedicate our research to our families specially our beloved parents, who they educate us and enabled us to reach at this level. Thank you for all the things you have done for us as we have grown up.

Moreover, we want to dedicate this research to our respected supervisors **Dr. Mohammed Abdullah Kubas and Dr. Abdusalam Al-Subari**

They were supported us one very step of our research durations. Without them, it could might never possible to complete this research project.

Our supervisors made us able to face different challenges and win those challenges. In addition, we wish to dedicate this research to our friends, nurses, pharmacists, doctors and the rest of the health practitioner.

Accreditation

This research discussed and accomplished successfully in 6/2/2022 and approved by:

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Abstract

Background: Many trials have compared anti-coagulation management provided by a pharmacist Led-Warfarin clinic versus usual physician care showing the role for clinical pharmacist in the management of anticoagulant therapy, and demonstrating excellent outcomes. In Yemen, there is no published research evaluating the role of pharmacist in providing pharmaceutical care for patients taking warfarin.

Objective: The objective of the study is to assess impact of clinical pharmacist led-warfarin clinic and Quality of Anti-coagulation effect TTR at UST hospital. **Setting:** This study was conducted at UST hospital in cardiac and internal medicine department's warfarin clinic. **Methods:** Clinical outcome data were collected through a retrospective chart review of all patients managed from (2015 to 2021) in the clinical pharmacist led-warfarin clinic at UST hospital, seventy-seven patients were randomly selected from adult patients on warfarin therapy was done by the clinical pharmacist for 3 months. the primary outcome for this study was the INR control, while the secondary outcomes were the bleeding events and hospitalization due to warfarin. **Results:** After the clinical pharmacist intervention there was significant improvement in INR control and TTR results and a significant reduction in incidence of bleeding after clinical pharmacist intervention. Hospitalization resulted by warfarin related complications (bleeding, high INR, low INR) was also significantly reduced. **Conclusion** Clinical pharmacists' intervention in warfarin therapy improves INR control and reduces bleeding and hospitalization, resulted by warfarin complications.

Keywords:

Warfarin clinic – Anticoagulation - Clinical pharmacist -Intervention -Yemen

Impact on practice:

- The involvement of a clinical pharmacist improves the anticoagulation management of patients in Yemen.
- Pharmacist can provide useful information to patients on anticoagulation therapy, in both written and verbal format.

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Table 1 Abbreviations**Abbreviations**

CYP	Cytochrome P450
INR	International Normalized Ratio
TTR	Time Within Therapeutic Range
PT	Prothrombin Time
APTT	Activated Partial Thromboplastin Time
CBC	Complete Blood Count
GFR	Glomerular Filtration Rate
AF	Atrial Fibrillation
VKA	Vitamin K Antagonists
ICH	Intracerebral Brain Hemorrhage
DOAC	Direct Oral Anticoagulant
LMWH	Low Molecular Weight Heparin
BID	Bis In Die
PO	Per Oral
MI	Myocardial Infarction
LV	Left Ventricular
CAD	Coronary Artery Disease
QUM	Quality Use Of Medicines
USTH	University of Science and Technology Hospital
CCU	Cardiac Care Unit
ICU	Intensive Care Unit
VHD	Valvular Heart Disease
DVT	Deep Venous Thromboembolism
DDI	Drug Interactions
DM	Diabetes Mellitus
PE	Pulmonary Embolism
HTN	Hypertension
HF	Heart Failure
ER	Emergency Room

Chapter One: Introduction

- Anticoagulant drugs are used to reduce the ability of the blood to clot. Major categories of anticoagulants include:
 - ✓ Heparin and Its Derivatives
 - ✓ Oral Anticoagulants
 - ✓ Antiplatelet Drugs
 - ✓ Direct Thrombin Inhibitors
 - ✓ Factor Xa Inhibitor Drugs
- The major oral anticoagulant used in the Yemen is the Coumarin compound warfarin.
- Warfarin is an oral anticoagulant with a delayed onset of effect that acts as a vitamin K antagonist. Vitamin K is essential for the conversion (carboxylation) of precursors to clotting factors II, VII, IX, and X into inactive clotting factors and for the synthesis of the naturally occurring anticoagulants, protein C and protein S. Warfarin displays nonlinear kinetics. Small-dose adjustments can lead to large changes in anticoagulant response. The dose of warfarin is determined by each patient's individual response to therapy and the desired intensity of anticoagulation. It is metabolized in the liver via several isoenzymes including CYP 1A2, 3A4, 2C9, 2C19, 2C8, and 2C18. (1)
- For several decades, warfarin has been the mainstay anticoagulation therapy that is used in the outpatient setting for the treatment and prevention of many thromboembolic disorders (2).
- Anticoagulation therapy with warfarin reduces major thromboembolic complications in patients with many common medical conditions, including atrial fibrillation, history of deep vein thrombosis, pulmonary embolism, and mechanical heart valves. (1). The effect of warfarin is monitored using the one-stage prothrombin time, for example, the INR. This test is sensitive chiefly to factors VII, II and X (and to a lesser extent factor V, which is not a vitamin K–dependent clotting factor). (3) . The therapeutic and adverse effects of warfarin depend largely on the percentage of time during which the INR is within the therapeutic range. (4)
- There are many challenges associated with warfarin therapy to achieve the target therapeutic concentration. These include, 1) The narrow therapeutic range, 2) The presence of many drug-drug, disease drug and food-drug interactions, 3) Genetic differences causing a significant variation in the dose–response, which require an individualized dosing regimen, 4) The altered sensitivity to warfarin in some clinical conditions and specific populations, and 5) The need for frequent laboratory monitoring to assess the efficacy and minimize the risk of bleeding events. (5)

- The time in the therapeutic range (TTR) is a measure of the percentage of time a patient's INR is within the target therapeutic range, which is used as a marker of the effectiveness of warfarin therapy and as a quality metric. Optimizing the percentage of time spent in therapeutic range for INR (TTR) can reduce the risk of hemorrhagic and thromboembolic events. reviewed TTR data from anticoagulation centers of 15 countries and reported that a TTR of at least 65% is required for optimum benefit of warfarin therapy. (22-23)

Indication of Oral Anticoagulant: -

- Prior to starting warfarin, it is appropriate to obtain the following baseline testing, if not already done: Baseline prothrombin time (PT) with international normalized ratio (INR) and baseline activated partial thromboplastin time (APTT). complete blood count (CBC) including platelet count, to obtain a baseline and identify thrombocytopenia. Serum creatinine, to estimate the glomerular filtration rate (GFR). Liver function tests, to identify potential alterations of warfarin metabolism (or hemostasis). Urine (or serum) pregnancy test for women of childbearing potential (due to risks of teratogenicity).

- The most indications of warfarin are :

{1} Atrial fibrillation Most patients with atrial fibrillation (AF) should receive long-term oral anticoagulation to decrease the risk of ischemic stroke and other embolic events. For most patients, the benefit from anticoagulation outweighs the associated increase in the risk of bleeding. For patients with AF starting VKA with no intra-cardiac thrombus or prior history of thromboembolism, the risk of a thromboembolic event during the several days typically required to achieve therapeutic anticoagulation with warfarin is generally very low. Thus, it is reasonable for outpatients to initiate warfarin without bridging. With high risk of thromboembolism (e.g., prior cerebrovascular event/transient ischemic attack or current intra-cardiac thrombus) and low risk of ICH, initiation of warfarin with a heparin bridging regimen may be reasonable in some clinical settings (e.g., patient who is hospitalized for another condition such as heart failure and has no acute stroke) although there is no high quality evidence to support this approach. For patients with AF who have been treated with warfarin with an annual time in the therapeutic range (TTR) of at least 65 percent, we suggest switching to a DOAC. However, it is reasonable to continue VKA in these patients. Exceptions to the general preference for use of DOAC rather than VKA in patients with AF with an indication for anticoagulation include: - Clinical settings in which VKA target international normalized ratio [INR] 2.0 to 3.0; TTR $\geq$ 70 percent) is the agent of choice and in which DOAC should not be used.

{2} Venous Thrombosis prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism initial dose 2-5mg. Initiate warfarin on day 1 or 2 of LMWH or unfractionated heparin therapy and overlap until desired INR. then discontinue heparin Check INR after 2 days and adjust dose according to result.

{3} Stroke and Thromboembolism prophylaxis and treatment of systemic embolic complication associated with atrial fibrillation. ACCP guidelines recommend dabigatran 150mg PO BID over adjust dose warfarin therapy for AF unless both AF and mitral stenosis are present Indication for indefinite treatment duration. Persistent or paroxysmal non-valvular AF in patients with a high risk of stroke: I.e., patients who have risk factors for stroke, such as prior ischemic stroke, transient ischemic attack, or systemic embolism or who have 2 of the following risk factors-age greater than 75 years, moderately or severely impaired left ventricular systolic. function and/or heart failure, history of hypertension, or diabetes mellitus Persistent or paroxysmal non-valvular AF in patients with an intermediate risk of ischemic stroke: patients who have 1 of the following risk factors-age >75 years, moderately or severely impaired left ventricular systolic function and/or heart failure, history of hypertension, or diabetes mellitus, AF and mitral stenosis.

{4} Cardiac Valve Replacement Prophylaxis and treatment of thromboembolic complications associated with cardiac valve replacement.

{5} Post Myocardial Infarction Reduction in the risk of death, recurrent MI, and thromboembolic events (e.g., stroke, systemic embolization) after MI INR and treatment duration maintain INR between 2 and 3

{6} Rheumatic Valve disease (off-label) with any of the following: Atrial diameter >55, Left atrial thrombus, AF and previous systemic embolism.

{7} Antiphospholipid antibody syndrome with previous arterial or venous thromboembolism.

{8} Systolic LV dysfunction without established CAD but with identified LV thrombus.

Table 2. This nomogram applies to warfarin initial dosing in an otherwise healthy adult without comorbidities that could affect warfarin metabolism.

DAY	INR	Warfarin dose (mg)
1		5
2		5
3	<1.5	10
	1.5-1.9	5
	2-3	2.5
	>3	0
4	<1.5	10

	1.5-1.9	7.5
	2-3	5
	>3	0
5	<2	10
	2-3	5
	>3	0
6	<1.5	12.5
	1.5-1.9	10
	2-3	7.5
	>3	0
<p>This protocol only applies to patients already taking warfarin and should not be used during the first - week of therapy.</p>		
INR	Adjustment in total (mg) of warfarin per week.	
≤1.5	Increase 15 percent per week.	
1.51 to 1.99	Increase 10 percent per week.	
2 to 3	No change.	
3.01 to 4	Decrease 10 percent per week.	
4.01 to 4.99	Hold one dose; restart with dose decreased by 10 percent per week.	
5 to 8.99	Hold until INR is 2 to 3; restart with dose decreased by 15 percent per week.	

Background About Clinical Pharmacy: -

- Clinical pharmacy practice is relatively a new discipline in pharmacy practice in which the emphasis is transferred from products oriented to patient-oriented practice. (6)
- However, the definition of clinical pharmacy or clinical pharmacy practice has not been universally standardized; hence different academic institutions and pharmaceutical societies have attempted to define it in their own perspectives. (7)
- In doing so, the discipline “clinical pharmacy” now has numerous meanings throughout world. (8)
- Few of the recognized definitions are as follows: Clinical Pharmacy is a health science discipline in which pharmacists provide patient care that optimizes medication therapy and promotes health, wellness, and disease prevention. Clinical Pharmacy practice is the practice of pharmacy as a part of a multi-disciplinary healthcare team directed at achieving QUM (Quality Use of Medicines). (9)

Background About Clinical Pharmacy Services: -

- Clinical pharmacy services were defined as those where pharmacists provide patient care that optimizes medication therapy, and promotes health, wellness, and disease prevention in all health care settings. (8)
- Clinical pharmacy services have been shown to identify clinically important drug-related problems, reduce the incidence of clinically important drug-related problems, improve patient education and concordance, improve prescribing, improve clinical outcomes and cost-effectiveness, and also reduce length of hospital stay. Clinical pharmacy is an integral component of medicines management. (10)
- Clinical pharmacy services are delivered to minimize the inherent risks associated with the use of medicines and pharmacists have been providing clinical pharmacy services to hospital-based patients for over 40 years. Clinical pharmacy services for individual patients, as described in the Standards, are required to support the objectives of national safety and quality initiatives. They facilitate the continuity of medication management when patients transition between care settings and are applicable in all healthcare sectors and care settings. (11)
- A study covering 1029 US hospitals was the first to indicate that both centrally based and patient-specific clinical pharmacy services are associated with reduced mortality rates. (12)

Background About Clinical Pharmacy in Yemen (Universities That Offer Clinical Pharmacy, Hospitals That Adopt Clinical Pharmacy Services): -

- In Yemen, clinical pharmacy services are only provided at few government and private hospitals. Most of the services are focusing on in-patient departments with limited services in the out-patient departments (e.g., warfarin clinic). However, some public and private universities have established the PharmD program with the aim to encourage clinical pharmacy services expansion in majority of healthcare institutions.
- The University of Science and Technology Hospital (USTH) is one of the leading healthcare institutions in Sana'a, Yemen. USTH serves a huge number of patients and is considered a referral hospital for the most complicated cases. In 2013, the clinical pharmacy unit was established at USTH to improve the quality of patient care and health outcomes. However, to our knowledge, the quality of clinical pharmacists' recommendations and services, and the perspective of physicians' perceptions toward clinical pharmacy services have not been evaluated in Yemen. (13)
- Hodeida University and one of the private colleges offer a doctor of pharmacy (PharmD) degree. The duration of a bachelor's degree program in all public and private colleges is 5 years. (14)

Background About University and Technology Hospital (USTH): -

- University of Science and Technology Hospital is one of the biggest and pioneer hospitals in Yemen which happened by developing and updating the equipment's continuously. The University of Science and Technology Hospital (USTH) is one of the leading healthcare institutions in Sana'a, Yemen. USTH serves a huge number of patients and is considered a referral hospital for the most complicated cases.
- The hospital has 108 beds on adults' medical wards, 10 beds in the ICU, and 8 beds in the CCU. The department of clinical pharmacy at USTH was established in January 2013 to provide patient care services in most critical departments, such as the intensive care unit (ICU), critical care unit (CCU), and male and female internal medicine wards. Since the establishment of the clinical pharmacy department, Two clinical pharmacist has been providing patient care services.

The Importance of Warfarin Clinic for Dose Optimization: -

- The use of warfarin requires individualized dosing and close laboratory monitoring to achieve optimal outcomes while minimizing the risk of serious adverse bleeding events. Multiple factors have been shown to affect anticoagulation control, such as warfarin dosage, drug-drug interaction, disease-drug interaction, food-drug interaction, patient compliance, patient knowledge and the setting of anticoagulation management. (15)

- Optimal anticoagulation therapy requires dedication and continuous patient education and monitoring. These requirements are time-consuming, and time is a resource that the majority of physicians lack due to their high workload and other responsibilities.
- Studies have demonstrated that when compared to traditional physician-based anticoagulation monitoring, pharmacist-managed anticoagulation services can improve anticoagulation quality outcomes [i.e., the time in the therapeutic range (TTR)] and clinical outcomes (i.e. efficacy and safety). (15)
- Additionally, pharmacist-managed Warfarin clinics have been demonstrated to improve patient satisfaction. (16)
- Thus, the management of anticoagulation by pharmacists could benefit both the patient (by providing them with the necessary care) and the physician (by freeing their time for other skilled tasks). Although pharmacist-managed anticoagulation monitoring services are not a novel practice in the context of developed countries, the model is not common place in developing countries.
- This study demonstrates that a warfarin clinic in a multi-disciplinary setting offer not only safe and effective treatment, but is superior with respect to increase anticoagulation control and decreased incidence of thromboembolic events. (17)

Aim of Study: -

1. Assessing the impact of clinical pharmacist led-warfarin clinic at UST Hospital.
2. The quality of anticoagulation effect TTR (time within therapeutic range) .
3. Bleeding and thrombosis events reported by patient.

Establishment of Warfarin Clinic: -

- The first pharmacist-managed Warfarin clinic under a collaborative practice agreement in Yemen was established at University of Science and Technology Hospital in 2015. The influence of this new service on clinical and patient-oriented outcomes had not been explored.
- A specific area in the cardiology clinic is allocated for a clinical pharmacist and a nurse with complete support of the medical staff.
- The clinic operates from 7 a.m. to 4 p.m., Saturday through Wednesday, as those are the regular working days in Yemen.
- A trained clinical pharmacist is responsible for the clinic's operation and acts as an agent for the referring physician within the approved protocol. A trained certified clinical pharmacist initiates, refills, and adjusts the dose of oral anticoagulation based on the approved protocol. In addition, the clinical pharmacist reviews the patients' medical chart, electronic profile, history, and orders laboratory tests as deemed necessary to

achieve therapeutic anticoagulation goals (e.g., INR, hemoglobin/ hematocrit, hepatic function, and renal function).

- Establishment of an anticoagulation service requires careful planning, development of high-quality standards and procedures, with input from local consultants, while recognizing the barriers which exist to developing such a service.
 - The main challenges of establishing the Warfarin clinic summarized in application of Anticoagulation services:
 - (1) Evaluating the organization's need to establish such a service.
 - (2) Identifying the stakeholders, they need to see the explanation for funding such a service.
 - (3) Find the right personnel to run the service.
 - (4) Continuously development of new skills and service chance throughout the health care organizations.
- (21)**

Chapter Two: Methods

Study Setting: -

The study was conducted at the University of Science and Technology Hospital's pharmacist managed Warfarin clinic. The University of Science and Technology Hospital is a general hospital that provides comprehensive, high-quality health care to people of all ages. The available care includes emergency care, general medicine, surgery and highly specialized treatments .

Study Design: -

This study comprised of the following :

A retrospective descriptive study of all patients who attended the clinic, and clinical outcome data were collected through a retrospective chart review of all of the patients who were managed at the clinic between (2015 and 2021).

Clinical Pharmacist's Intervention in Warfarin Clinic: -

- The intervention for clinical pharmacists in warfarin clinic were: Data collected included international normalized ratio (INR) results, indication for warfarin, minor and major bleeds, thromboembolic events, emergency room (ER) visits, and hospitalizations.
- Then patients' warfarin dose adjustments according to INR were done by the clinical pharmacist 'during each visit the dosage of warfarin was adjusted by clinical pharmacist for every patient according to INR results. Booking for the next visit was done according to patient's INR results if within the therapeutic range or not as follows:
- Patients with INR results within the therapeutic range without any obvious risk factor to alter INR (e.g., disease state, new medication that may interact with INR) were directed to visit the clinic and monitor INR after 4 weeks.
- Patients with higher or lower INR results than therapeutic range, and/or have a risk factor to alter their INR were directed to monitor INR more frequently (e.g., every 1–2 weeks) according to the guidelines, and clinical judgment.
- Patients received continuous verbal education and written information about warfarin and its effects and indications, dosage, adverse effects, interactions with food and common over the counter products (OTC), what to do if he/ she miss a dose, and the use during pregnancy and lactation. Patients were also educated about how to manage their diet, measure warfarin effect by INR test, the importance of regular INR monitoring, the adherence to warfarin, when to seek immediate medical attention, the importance of sticking to one brand of warfarin, and when to take their pills. (18)

Patient Reaches to Warfarin Clinic: -

Under the protocol, the patient remains under the care of a physician for all medical problems, and the physician is responsible for the decision to initiate or to discontinue anticoagulation therapy. After the decision to initiate anticoagulation is made, the physician establishes goals and the duration of treatment, identifies the target INR for the patient, and sends a referral directly to the pharmacist-based anticoagulation clinic. (19)

Patient Interview During Each Visit: -

- Patients on warfarin regimen should make schedule interview with their clinical pharmacists at warfarin clinics for the purpose of: warfarin dose optimization, patient education about drug- drug interactions, drug-food interactions and prevent serious side effects of warfarin over dose, as well as data for all patients during patient interview must be available through the computerized system include:
- Warfarin indication (e.g.: Atrial fibrillation/flutter, deep vein thrombosis or pulmonary embolism, Valvular disorder).
- Miscellaneous (i.e., cerebrovascular accident or transient ischemic attack, peripheral vascular disease).
- Patient demographics (age, gender).
- INR target.
- Comorbid conditions (e.g.: Diabetes mellitus Hypertension, Hyperlipidemia Coronary artery disease Heart failure).
- Concomitant medications.
- Adverse events (e.g., minor and major bleeding) should be assessed.
- Patient satisfaction. (18)

Duration of The Study and The Number of Patients: -

The total number of patients with complete medical records was 369 patients, then 292 patients excluded from the study.

From the total of 369 patients. 77 patients of them were included who were enrolled at the clinic over the duration were retrospectively evaluated. The selection criteria include adult patients on warfarin therapy for at least the previous 3 months on regular follow up in Cardiac and Internal Medicine's Warfarin Clinic at UST hospital.

Inclusion Criteria: -

- Age 18 years and above.
- At least have 3 months' follow-up.

Exclusion Criteria: -

- Age less than 18 years.
- Less than 3 months' follow-up.

Data Analysis: -

The data were analyzed using the Statistical Package for Social Sciences(SPSS) program, for Categorical data, frequency, and percentage.

Ethics Approval: -

This Study Was Approved by the Ethical Committee at the University of Science and Technology Hospital (Code: EAC/UST159).(20)

Chapter Three: Results

Subjects' Demographic and Habits: -

The highest percentages (54.5%) of patients taking warfarin were males. Regarding age, the highest percentage of patients (83.1%) was in the age below 65 years old and the lower percentage of patients (16.9%) was in the age group of 65 years and above. The mean age of patients was found to be (45.5 ± 16.9 years old). However, patients with no smoking, Khat chewing or tobacco less habits were (77.9%, 45.5%, 96.1%) respectively.

Bellow in table:

Table 3.Demographic data: -

Age	≥ 65	13(16.9 %)
	< 65	64(83.1 %)
Gender	Male	42(54.5%)
	Female	35(45.4 %)
Khat chewing	YES	31(40.3%)
	NO	35(45.5 %)
	Hx.	11(14.3 %)
Smoking	YES	05(6.5 %)
	NO	60(77.9 %)
	Hx.	12(15.6%)
Tobacco less habits	YES	02(2.60 %)
	NO	74(96.10 %)
	Hx.	01(1.30 %)

Indication of Warfarin: -

The most common indications: the highest percentage of indications for warfarin are: deep vein thrombosis 26 patients (33.8%), valvular heart disease 24 patients (31.2%), left ventricle thrombosis 8 patients (10.4%), cerebral thrombosis 9 patients (11.7%), pulmonary embolism 6 patients (7.8%), portal vein thrombosis 3 patients (3.9%), slow flow of blood 3 patients (3.9%), atrial fibrillation 1 patient (1.3%), myocardial infarction 1 patient (1.3%), and other thrombosis 1 patient (1.3%).

Target INR: -

The therapeutic INR target for (77.9%) of the patients was 2–3 and (22.1%) 2.5–3.5.

Duration of Treatment: -

Duration of therapy for (22.1%) of the patients were depended, (41.6%) long life, (15.6%) 1-6 months and (20.8%) 6-12 months.

Referral Clinic: -

The highest percentage of referral clinic to cardiac and internal medicine clinics as (31.17%), followed by vascular surgery clinics as (23.38%), and Neurological and internal medicine as (16.88%).

Table 4. The Referral clinics of patients was: -

Clinics	Percent%
• Cardiac and internal Medicine	31.17%
• Vascular Surgery	23.38%
• Neurology and Internal Medicine	16.88%
• Chest and Internal Medicine	6.49%
• Unknown	6.49%
• Cardiac surgery	5.19%
• Gastroenterology	3.90%
• Hematology and Internal Medicine	2.60%
• Internal Medicine	2.60%
• Nephrology and Internal Medicine	1.30%

Medical History: -

Regarding concomitant diseases. The highest patients having concomitant diseases were those having VHD (25) 32.5%, followed by DVT (24) 31.2%, then HTN (17) 22.1%, Cerebral thrombosis (17) 22.1%, and other diseases included HF (LV thrombosis) (13)16.9, CAD (10) 13.0%, PE (7) 9.1%, arrhythmia (5)6.5%, DM (4) 5.2%, Post surgery and fractures (4) 5.2%.

Hx. Of medications and DDI: -

Results show patients had at least one concomitant medication. The most 10 prescribed drugs were warfarin (58), followed by aspirin (28), then pantoprazole (23), and other medication, bisoprolol (16), atorvastatin (13), spironolactone (13), torsemide (9), digoxin (9), furosemide (9) and paracetamol (9).

Table 5 The most 10 drugs did interact with warfarin in 47 patients were divided into two parts: -

Increase Warfarin Effect		Decrease Warfarin Effect	
Name of drug	No. of Cases	Name of drug	No. of Cases
Aspirin	(24)	Spironolactone	(8)
Clopidogrel.	(6)	Oxcarbazepine.	(2)
Paracetamol	(6)	Azathioprine	(1)
Amoxicillin +clav.acid.	(4)	Carbimazole	(1)
Tramadol.	(4)	Prednisolone	(1)

Bleeding Assessment: -

Number of Patients That's Have High of Bleeding Assessment Score are (17), then Patients That's Have Moderate of Bleeding Assessment Score are (31), And Patients That's Have Low of Bleeding Assessment Score are (29).

Table6 . Bleeding assessment: -

Bleeding Assessment Score	Percent of Patient %
High	22.1%
Moderate	40.3%
Low	37.7%

Patient Already on Warfarin: -

The total number of patients was 77. Most of the patients were already on warfarin. Number of patients that's already to warfarin is 66, Number of patients that's not already to warfarin is 11.

Table 7 . Patients already on warfarin:

Patients already on warfarin	percent of patient%
Yes	85.7%
No	14.3%

Dose Change: -

Our finding for dose changes, is about the total number of patients during the first and second visit. The number of patients that has changes in dosage during the first visit is 10 (13.0%), and 67 (87.0%) of the patients did not have any dose change. The number of patients that has dose changes during the second visit is 6 (7.8%), and 71 (92.2%) of the patients they did not have any dose change.

Table 8 During all visit of patient. the most patients don't have any dose change:

Number of visits	Visit 1	Visit 2
Percent of patients have dose change	13.0%	7.8%
Percent of patients don't have dose change	87.0%	92.2%

TTR Result: -

The average time in the therapeutic range (TTR) was (51.44%). A 26 (33.77%) of patients from 77 patients that have TTR above 65%. The total number of patients with TTR less than 65% are 51 (66.23%).

Table 9.TTR results: -

No. patients with TTR above 65%	TTR percent %
1	71.18%
2	70.30%
3	67.80%
4	74.00%
5	86.50%
6	66.58%
7	89.22%
8	68.26%
9	100.00%
10	86.50%
11	71.70%
12	74.90%
13	93.77%
14	100.00%
15	100.00%
16	100.00%
17	70.34%
18	79.38%
19	91.53%
20	65.36%
21	67.85%
22	81.31%
23	76.01%
24	97.06%
25	68.10%
26	72.89%

Change in Medications: -

The change in medications that we noted is that. It happened to a small number of patients (a small percentage of them). We also, noted that, in the first visit the total number of 77 patients for whom only 14 patients were changed in medication, while 63 patients did not have any change in their medication. In the second visit the total number of patients was 77 while only 9 patients for which medication was changed only out of 77 patients. We conclude that the patients whose medication is changed are less than 20% out of the total number of patients.

Change in Eating: -

There was a change in eating patterns in second visit. About 8 patients had changes in eating, that present as (10.4%), and the number patients that did not have any change in eating patterns is about 69 that present as (89.6%).

Symptoms of Bleeding: -

Our finding for symptoms of bleeding the total number of 77 patients during first and second visit. Number of patients that has symptom of bleeding during the first visit are 6 patients (7.8%). And 71 (92.2%) of patients did not have any symptom of bleeding. Number of patients that has symptom of bleeding during the second visit are 5 (6.5%). And 72 (93.5%) of patient did not have any symptom of bleeding.

Table10 .During all visits of patients. Most of patients did not have any symptoms of bleeding

Number of visits	First Visit	Second visit
Percentage of patients who have symptoms of bleeding	7.7%	6.5%
Percentage of patients who did not have symptoms of bleeding	92.3%	93.5%

Symptoms of Thrombosis: -

In the second visit to 77 patients, the symptoms of Thrombosis that noticed was only 2 patients, and for the other 75 patients it is not known.

Hospitalization and Surgical procedures: -

Hospitalization resulted by warfarin related complications as general (bleeding, high INR, low INR) was significantly reduced in the second visit only a (1.30%) of patients had hospitalized after clinical pharmacist intervention. The percentage of patients having upcoming surgical or dental procedure are (2.60%).

Table 11.hospitalizations: -

Hospitalization resulted by warfarin related complications (bleeding, high INR, low INR)	Frequency	Percent %
Hospitalization During study	1	1.30 %
Surgical procedure.	2	2.60 %

Chapter Four: Discussion

- Warfarin is one of the most complex drugs prescribed worldwide, because of the need for individualized dosing, monitoring and its limited therapeutic range.
- In this study, we evaluated the outcomes of the first pharmacist managed warfarin clinic in Yemen. The first outcome which was evaluated, the time within therapeutic range.
- The most patients who referred to the warfarin clinic that run by clinical pharmacist they were with uncontrolled INR and they were on warfarin therapy in the first visit. The majority of them reached the target INR after the 2nd, 3rd, 4th of the follow-up visit. The percentage of INR tests in therapeutic range after the referral to warfarin clinic was significantly better than, the time before the referral to the clinic. And the average percent of the total number of TTR was (51.44%).
- Bleeding was the main adverse effect associated with warfarin therapy. Incidence of bleeding was significantly reduced (5 patients (6.5%) of total patients 77) after clinical pharmacist intervention in warfarin clinic compared to that before intervention.
- Also, a reduction of thromboembolism and all-cause mortality was observed after clinical pharmacist intervention in the warfarin clinic, where was the number of patients who suffered from thrombosis adverse effect just (2 patients form 77 patients).
- According to eating pattern of the patients, the effect of the clinic was very clear by the patients' adherence to the eating pattern that could affect the treatment, this improvement was as (81.82%) of patients they didn't have any change in the eating pattern.
- Also, for the patients who had a change in the dose, their percentage was (7.8%), and this indicates that the role of the warfarin clinic was very large in controlling the dose for patients.
- The change in medication that the patients were used (less than 20% of total number of patients).
- Some national guidelines set a target of TTR at 60% or above, while others define a TTR range of 58%–65% as acceptable to maximize warfarin efficacy and decrease its toxicity, (24). In our study, patients followed in the warfarin clinic had moderate TTR (51.44%), that mean half of the total patients get desired time therapeutic range ($\geq 65\%$). The outcome of percentage of time within the therapeutic range in this study indicated that pharmacists provided significantly better anticoagulation control of warfarin. When compare with Sultan Alghadeer study, 1: 33 patients were enrolled in pharmacist's -led clinic for anticoagulation management, the TTR was ($87.27\% \pm 3.82\%$) which mean higher than in our study. The result in our study influenced by many factors include: Small sample size, differences in demographic factors, including genetics, age, degree of education and geographic factors, the different Number in the Follow up visit for each patient and differences in indications, such as atrial fibrillation, deep vein thrombosis, pulmonary embolism, mechanical valve replacement and so on.

- The thromboembolic events were 2 events (2.6%) of total 77 patients in the second visit. also, the rate of major hemorrhagic events were 5 events (6.4%) of total 77 patients There are several similar studies that support these statistics, our results are in accordance with previously reported results [25, 26]. As an example, Witt and his colleagues reported that the percentage of patients with INR values more than 6 who developed major bleeding decreased due to pharmacist intervention from 6.31 to 1.19% per year [8]. Furthermore, in another study [19] statistically significant decrease in minor bleeding events was observed in the pharmacist-managed group (n = 4 versus n = 10, respectively), and a decrease in major bleeding events was observed, although it was not statistically significant.
- The optimal outcomes that were observed in first clinic are believed to driven by well - organized patient education contributes to improved compliance and greater understanding of anticoagulation therapy which produce higher INR value within the target range This significant improvement in INR control could be explained by the fact that the services provided by pharmacist offered close follow up for patients INR results and ensure that patients adhere to their regular visits as scheduled for anticoagulation monitoring and dosage adjustment so improved Continuity of follow-up, and there for improve management and INR control.as comparison , number of patients who are change in medications in second visit is 9 (11.69%) and 68 (88.31%) patients not change and in first visit, 14 (18.18%) patients who are change in medications and 63 (81.82%) patients not change. Patients were also educated about how to manage their diet, the importance of regular INR monitoring, and the adherence to warfarin, what to do if he/she miss a dose so no observed significant food-drugs interaction. As comparison, the percentage of patients who changed eating pattern are 8 (10.39%) and 6 (7.79%) change the dose in second visit but, 9 (11.69%) patients are change eating pattern and 11 (14.29%) change the dose in first visit.
- The result show that 47 (61.04%) patients use medication was enrolled drug- drug interactions that included drugs that increase effect of the warfarin are Aspirin p=24 (51.06%), Clopidogrel p=6(12.7%), paracetamol p=6 (12.7%), amoxicillin/clav.acid p=4 (8.5%), tramadol p=4 (8.5%), And drugs that decrease effect of the warfarin are spironolactone p=8 (17.0%), oxcarbazepine p=2 (4.25%), azathioprine p=1 (2.12%), carbimazole (1), prednisolone (1) and 30 (38.96%) patients not.
- There is another study conducted on 578 patients were enrolled in the ACC where the result of Implementation of the pharmacist-managed ACC in the eastern province of Saudi Arabia had a positive impact on patient care based on the improvements in the number of patients whose INR was within therapeutic The benefits of pharmacist-managed ACC include reductions in cost of care, concurrent interacting drugs, and adverse medication-related events while still achieving treatment goals. (27)

Limitation of Study:

- 1- The study was conducted in one hospital (UST hospital) in Sana'a, because there is no warfarin clinic in other hospitals.
- 2- Among the limitations of our study is that, the studied sample may not fully represent the general population receiving warfarin in Sana'a.

Chapter Five: Conclusion and Recommendations

Conclusion:

Clinical pharmacists' intervention in warfarin therapy improved the INR control by keeping it within the patient specific therapeutic range for (average: 51.44 %) of patients, the reduced warfarin related bleeding, and the reduced hospitalization resulted by warfarin complications. The clinical pharmacist's intervention effectively and safely improved the warfarin therapy at warfarin clinic in the University of Science and Technology Hospital (USTH), at the Cardiac Center. Future multi-central researches are needed to highlight and confirm the positive role of the pharmacist in warfarin clinics.

Recommendations:

1. Implementation of warfarin clinic at other hospitals is advisable.
2. Clinical pharmacist is qualified to run warfarin clinic.
3. Upgrading the clinic to cover all anticoagulation medications is needed.

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تأثير الصيدلاني السريري الذي قاد أول عيادة وارفارين في اليمن: دراسة رجعية أجريت على مستشفى من الدرجة الثالثة

بحث دراسي مقدم لكلية الصيدلة السريرية

مقترح طلبة البكالوريوس لاستفتاء متطلبات التخرج لدرجة البكالوريوس في الصيدلة السريرية

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دكتوراه في الصيدلة السريرية والممارسة الصيدلانية

دكتوراه في الكيمياء الدوائية السريرية.

رئيس قسم الصيدلة السريرية في مستشفى جامعة العلوم
والتكنولوجيا.

نائب عميد كلية الصيدلة السريرية في جامعة 21 سبتمبر.

يناير 2022

الخلاصة

قارنت العديد من التجارب بين الإدارة المضادة للتخثر التي تقدمها العيادة الصيدلانية Led-Warfarin، وبين الرعاية المعتادة التي يقدمها الطبيب، والتي بدورها تُظهر الدور الذي يلعبه الصيدلي السريري في إدارة العلاج المضاد للتخثر، وإظهار نتائج ممتازة. في اليمن، لا يوجد بحث منشور لتقييم دور الصيدلي في تقديم الرعاية الصيدلانية للمرضى الذين يتعاطون الوارفارين.

الهدف: يتمثل الهدف من هذه الدراسة في تقييم تأثير العيادة الصيدلانية السريرية وجودة تأثيرها لعلاج التخثر في مستشفى جامعة العلوم والتكنولوجيا. جرى الإعداد لهذه الدراسة في مستشفى جامعة العلوم والتكنولوجيا في عيادة الوارفارين للقلب والطب الباطني. **الطريقة:** تم جمع بيانات النتائج السريرية من خلال مراجعة الرسم البياني الاستعادي لجميع المرضى الذين تمت إدارتهم من (2015 إلى 2021) في عيادة الصيدلاني السريري led-warfarin في مستشفى جامعة العلوم والتكنولوجيا، تم اختيار سبعة وسبعين مريضاً بشكل عشوائي من المرضى البالغين الذين خضعوا للعلاج بالوارفارين من الصيدلي السريري لمدة 3 أشهر. كانت النتيجة الأولية لهذه الدراسة هي التحكم في مستوى الـ INR، بينما تمثلت النتائج الثانوية في حدوث حالات نزيف ودخول المستشفى بسبب الوارفارين. **النتائج:** بعد تدخل الصيدلي السريري، كان هناك تحسن كبير في إدارة مستوى الـ INR، وعلاج الـ TTR وانخفاض كبير في حدوث النزيف. تم أيضاً التقليل وبشكل كبير من حالات دخول المستشفى بسبب المضاعفات المرتبطة بالوارفارين مثل (النزيف، النسبة العالية من الـ INR، النسبة المنخفضة من الـ INR). **الاستنتاج:** إن تدخل الصيادلة السريريين في العلاج بالوارفارين يحسن من إدارة مستوى الـ INR ويقلل من حالات النزيف ودخول المستشفى الناتجة عن مضاعفات الوارفارين.