An-Najah National University

Faculty of Graduate Studies

TRENDS OF ANTICOAGULANT PRESCRIPTION IN DIFFERENT HOSPITALS IN THE WEST BANK OF PALESTINE: A RETROSPECTIVE STUDY

By

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Dedication

The study is dedicated to those who believe in me and show me the path to success, with endless support, assistance, and encouragement, to my mother, my sisters, and brothers, I dedicate this work.

To all the hidden hands that helped me and never denied me.

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Thanks to God first and last, always and forever

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I want to express my sincere gratitude to my family, who have always supported me and believed in my potential. Thank you to my parents for fostering a love of learning and always being there for me through all of my successes and setbacks.

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

TRENDS OF ANTICOAGULANT PRESCRIPTION IN DIFFERENT HOSPITALS IN THE WEST BANK OF PALESTINE: A RETROSPECTIVE STUDY

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

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TRENDS OF ANTICOAGULANT PRESCRIPTION IN DIFFERENT HOSPITALS IN THE WEST BANK OF PALESTINE: A RETROSPECTIVE STUDY

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Abstract

Background: Today, cardiovascular disease and thromboembolic events are the leading cause of death worldwide. Anticoagulants are increasingly popular in the prevention and treatment of thromboembolic events associated with atrial fibrillation, venous thromboembolism, deep vein thrombosis, and pulmonary embolism. In orthopedic departments, anticoagulants are frequently used in orthopedic surgery such as hip replacement and bone fracture as a prophylaxis from thromboembolism. In gynecology, anticoagulants are commonly used in pregnant women who have a high risk for thrombosis or have multiple miscarriages due to thrombosis.

Objectives: This study was conducted to, evaluate trends in prescribing oral and parenteral anticoagulants in different Palestinian hospitals and visualize the increasing or decreasing trends in prescribing oral and parenteral anticoagulants in different Palestinian hospitals.

Methodology: Prescription data of anticoagulants, including injectable and oral forms were retrospectively collected from Avicenna and dhis databases from 2019 -2023 in Hebron in the west bank. Comparisons were made on the use pattern of anticoagulants based on indications and years.

Results: A total of 5121 patients were enrolled in the study. The mean age was (39.4 ± 18.0 years). The majority of patients were female (81.5%). There were increasing patterns in the total number of anticoagulant prescriptions. The prescriptions of novel oral anticoagulants (rivaroxaban, apixaban, and dabigatran) have significantly raised since 2020 with p-value <0.001 for rivaroxaban and apixaban, while the warfarin

prescriptions have decreased. Rivaroxaban accounted for 63% of oral anticoagulants prescription followed by apixaban (26.6%) and warfarin (8.8 %). Regarding injectable anticoagulants, heparin had constant use over the study period while enoxaparin prescription increased especially in the obstetric population. Enoxaparin use in the post-partum population increased from 11.2% in 2019 to 22.9% in 2023 and from 11% to 24.4% in pregnant women with thrombophilia mutations.

Conclusion: Key findings indicate a significant rise in the prescription of novel oral anticoagulants, mostly due to their favorable pharmacokinetic and pharmacodynamic profile, the convenience of use, and less need for monitoring as compared to older therapies. As well as a notable rise in the prescription of enoxaparin in pregnant and postpartum women. With the potential to improve patient outcomes, the changing patterns in anticoagulant use are suggestive of a more significant shift in the treatment of thromboembolism disorder. Nevertheless, to maximize anticoagulant treatment for patients, continued investigations are required.

Keywords: Prescription trend, warfarin, NOACs, enoxaparin, thrombophilia.

Chapter One

Introduction

1.1 Background

Worldwide, venous thromboembolism (VTE) and atrial fibrillation (AF) -related thromboembolism episodes are the main causes of morbidity and mortality. Venous thromboembolism (VTE) is a condition referring to blood clots in the veins. The most common cardiovascular disease after myocardial infarction (MI) and stroke is venous thromboembolism (VTE). One occurrence of VTE is thought to occur for every 1000-person year (1). Leg-deep vein thrombosis (DVT) is the most common site of VTE, pulmonary embolism (PE), which happens when a thrombus embolizes into the pulmonary arteries, is a potentially fatal consequence of DVT(2).

VTE is more known as an older-age disease and does not occur always in adolescents. The incidence rate of VTE is higher in men than women. A third of DVT patients will experience post-thrombotic syndrome and a third of VTE patients will experience a recurrence within ten years (2). This emphasizes the socioeconomic burden of VTE on healthcare systems and how crucial it is to manage it including avoiding recurrence (3).

Although there are several patterns (such as the Caprine score and Padua Prediction Score) for accessing VTE risk, none of them have undergone validation (4). Risk assessment takes into account both the surgical procedure and patient characteristics. Geerts's risk classification is widely used, which compromises the following risk factors, Surgery, major trauma or lower-extremity injury, Cancer, Venous compression, central venous catheterization, Pregnancy and post-partum period, Contraceptive, selective estrogen receptor modulators, Erythropoiesis-stimulating agents, acute medical illness, inflammatory bowel disease, Immobilization, lower-extremity paresis, Nephrotic syndrome, thrombophilia, Paroxysmal nocturnal hemoglobinuria, myeloproliferative disorder, Obesity, increasing age and previous VTE (5).

1.1.1 Management of VTE

The main goal of VTE treatment was to lower the risk of fatal PE by preventing thrombus expansion and embolization as well as the recurrence of VTE episodes (6).

Pharmacotherapy and non-pharmacotherapy strategies, such as leg elevation, ambulation, vena cava filters, compression socking, and intermittent pneumatic compression, are available as prophylactic measures for VTE, pharmacotherapy is anticoagulation that includes unfractionated heparin, low molecular weight heparin (LMWH), synthetic anticoagulant (fondaparinux), vitamin K antagonist (warfarin) and direct oral anticoagulants such as rivaroxaban, apixaban, dabigatran and edoxaban (7).

Given its demonstrated ability to prevent VTE onset and recurrence, anticoagulation is the cornerstone of VTE therapy, it is advised as first-line treatment for almost all individuals with acute PE or DVT (6).

For years, the standard care for treating acute VTE involved fondaparinux or low molecular weight heparin subcutaneously followed by vitamin K antagonist (warfarin) orally. recurrent VTE can be effectively prevented with this regimen (8).

With a relative risk reduction of almost 85% when compared to placebo, warfarin is efficient in preventing recurrent VTE (9). However, because of its limited therapeutic range and comparatively high likelihood of bleeding, VKA treatment needs continuous monitoring. In specialist clinics, only 60% of INR level is within the therapeutic range (10). A metal analysis in 2010 revealed a case fatality of severe bleeding of 13.4% and a significant risk of intracranial hemorrhage (1.1 per 100 patients – years) (11). Furthermore, because VKA has a delayed onset of action, parenteral anticoagulation is necessary for immediate therapy of VTE. (12). These issues encouraged drug developers to develop new classes of anticoagulant medications.

For the acute and long-term therapy of VTE, a novel class of drugs known as direct oral anticoagulants (DOAC) are currently available for clinical use. Comparing DOAC to the conventional regimen with LMWH and warfarin, large clinical trials have demonstrated that DOAC is both safe and efficacious in the management of VTE (13).

The European Medicine Agency (EMA) and the Food Drug Administration (FDA) have already approved four DOAC rivaroxaban, apixaban, edoxaban, and dabigatran for the treatment of VTE. Because DOACs are administered in fixed doses and do not require routine monitoring, it significantly simplify the management of VTE. Additionally, a meta-analysis showed that the DOAC was linked to decreased bleeding risk (12).

In 2012, the direct factor Xa inhibitor rivaroxaban was authorized for the treatment of VTE. Two large open-label trials (Einstein DVT and Einstein PE) showed that rivaroxaban was effective in treating acute DVT and PE (11). Rivaroxaban demonstrated a comparable bleeding rate to LMWH and warfarin in both trials. Other direct factor Xa inhibitor is apixaban, approved for VTE in 2014, a double dummy double-blind trial called AMPLIFY study tested apixaban, apixaban at both treatment dosages decreased the risk of recurrent VTE in a comparable manner without raising the bleeding risk (14).

A direct thrombin inhibitor, dabigatran, was approved in 2014 for VTE treatment, dabigatran was found to be non-inferior to conventional treatment in two double-blind, double-dummy studies (RE-COVER and RE–cover II), and there were no change in the incidence of bleeding risk (15).

Clinical recommendations have been published by healthcare organizations for the evaluation and prevention of VTE risk. These recommendations cover the assessment of patients' risk factors, available treatment, dose, and duration of treatment. To improve healthcare team worker’s compliance with clinical recommendations certain institutions have also introduced a clinical decision support system for VTE prophylactic during hospitalization (16).

1.1.2 VTE and Orthopedic

According to the literature, 10 % - 40 % of patients who undergo orthopedic surgery experience a DVT or PE, which is linked to a high risk of VTE (17). anticoagulants are frequently used in orthopedic surgery such as hip replacement and bone fracture as a prophylaxis from thromboembolism such as PE (18).

According to available data, pulmonary embolism (PE) accounts for half of postoperative mortality in total hip arthroplasty (THA). while deep vein thrombosis (DVT) is the most common postoperative complication in total knee arthroplasty (TKA) (19). Even though VTE can occur following any major surgery, orthopedic patients are particularly susceptible because of several prothrombotic processes, including venous injuries, heat from cement polymerization, decreased venous emptying during or after surgery, coagulation activation from tissue and bone damage, and immobilization after surgery (20).

VTE prophylaxis needs to be extended since clinical, pathological, and epidemiological evidence indicates that the risk period of VTE starts during and lasts long beyond hospitalization (19). However, the thrombosis may take days or weeks to form and the majority of symptomatic DVT cases normally happen after hospital discharge. unfortunately, it is currently impossible to identify which orthopedic patients will experience VTE.

The risk of VTE decreased from 4.3% to 0.53% in patients 35 days after major orthopedic surgery when thromboprophylaxis was prescribed before hospital discharge (20).

There are two categories of prophylactic techniques, mechanical and pharmacological, prophylaxis should be started as soon as possible after surgery and continued until the risk diminishes (19). The fundamental components of thromboembolism prevention and treatment are anticoagulant, unfractionated heparin, low molecular weight heparin (enoxaparin), and VKA (warfarin) are the most common pharmacological VTE prophylactic used in orthopedic patients (19, 20). DOACs such as rivaroxaban, apixaban, and dabigatran have become more popular than conventional management in orthopedics, because of their more favorable pharmacokinetic and pharmacodynamic profile and convenience of administration (12, 21).

1.1.3 VTE and obstetrics

One of the leading causes of morbidity and mortality during pregnancy and the postpartum period is venous thromboembolism (VTE). The prevalence of VTE in pregnancy is 0.8-2.0 per 1000 pregnancies and accounts for 1.1 deaths per 100,000 pregnancies (22). although PE accounts for 10-15% of pregnancy-associated maternal

mortality in high-income countries and causes the majority of VTE-related morbidity, DVT accounts for the majority of pregnancy-associated VTE (23). The prevention of obstetric venous thromboembolism is an important and complex clinical decision but is addressed in clinical practice guidelines.

One of the most prevalent hypercoagulable conditions in the general population is pregnancy. It represents an increased level of coagulation factors (such as factors V, VII, VIII, X, XII, fibrinogen, and von Willebrand factor). Decreased free level and activity of protein S, and developed resistance to activated protein C are the causes of this alteration (24). Because plasminogen activator types 1 and 2 (PAI -1, PAI-2) are produced in greater amounts in pregnancy, fibrinolytic activity decreases. Later in pregnancy, uterine constriction of the pelvic vein and the inferior vena cava exacerbates the venous stasis caused by hormone-mediated vasodilation, which begins in the first trimester (25). Hypercoagulability is an evolutionary mechanism thought to reduce hemorrhage at the time of childbirth or pregnancy loss (24).

According to some estimates,10-14 VTE events occur for every 10000 deliveries in pregnant women (24). the prevalence of VTE rises in the 1st trimester, slightly above the general population, rises to a greater degree in the 3rd trimester, and peaks in the first two weeks following birth (3). About half of all VTEs related to pregnancy are following delivery (26). although VTE can occur for up to 12 weeks after birth, the majority of these events happen within six weeks (24).

Many risk factors are associated with pregnancy that can potentiate VTE occurrences such as caesarean delivery, assisted reproductive technologies, stillbirth, preterm birth, preeclampsia, obstetric hemorrhage, and postpartum infection. Irritable bowel disease, systemic lupus erythematosus, sickle cell anemia, and preexisting diabetes mellitus are also medical conditions linked to either antepartum or postpartum VTE (27). Antepartum VTE is not always correlated with BMI, but postpartum VTE is more common in obese patients with BMI above 35 or who are also immobilized.

Recurrent episode accounts for 4-25 % of pregnancy-associated VTE (24). The risk of VTE is around 100 times higher in pregnant women with a history of VTE who do not receive thromboprophylaxis during pregnancy than in pregnant women without a history of VTE (28).

Recurrent VTE during pregnancy appears to be more common among women with prior VTE or using estrogen than in women whose previous VTE was kinked to non-hormonal risk factors or unprovoked VTE (29).

In the post-partum population, the appropriate recommendations are gathered in recent guidelines for the prevention and treatment of obstetric-associated VTE (30). Regardless of predisposing factors or thrombophilia status, they advise prophylactic LMWH for six weeks after delivery in women with combined thrombophilia, homozygous FVL or prothrombin, ATIII deficiency, antiphospholipid antibodies, and a history of VTE. According to these guidelines, several risk factors, including C-section, age > 35, BMI>30 kg\m2, post-partum hemorrhage or infection, preeclampsia, smoking, strict bed rest + BMI>25 kg\m2 before delivery, and anemia predispose women to postpartum VTE. According to the guidelines, LMWH prophylaxis should be considered for 10 days to 6 weeks, depending on the absolute VTE risk for each risk factor (29).

1.1.3.1 Recurrent pregnancy loss and thrombophilia

Over 50% of VTE cases that occur during pregnancy are linked to an underlying thrombophilia (31). These disorders include genetic mutations that alter the activity of clotting factors as well as prothrombotic disorders that result from endogenous anticoagulants. The thrombophilia gene mutation in pregnancy can cause maternal and fetal complications such as recurrent miscarriage, preeclampsia, fetal loss, and hypertensive pregnancy complications (32). Early or late in the gestational period, recurrent pregnancy loss (RPL) (miscarriage) is a serious issue and has both psychological and social concerns for women who have RPL.

According to clinical research, the primary underlying pathophysiological mechanism causing uteroplacental insufficiency and ultimately pregnancy loss is hypercoagulation (33). Thrombophilia can be acquired, inherited, or both of them.

The American Society of Reproductive Medicine defines recurrent miscarriage or recurrent pregnancy loss (RPL) as two or more unsuccessful pregnancies (34). Chromosomal abnormalities, uterine structural abnormalities, endocrine disorder, chronic medical and surgical disease, and thrombophilia disorder, particularly in the 1st

trimester, are some of the RPL reasons. 50-70% of RPL cases do not have a definitive etiology (35).

RPL is frequently caused by thrombophilia and it represents 40-50% of cases (36). pregnancy causes hypercoagulability, which can worsen if the mother has thrombophilia. This can result in clots in the placental blood vessels, leading to the restriction of fetal growth and \ or fetal death, and insufficient blood flow in the mother blood flow, which can cause deep vein thrombosis (33). due to these issues, anticoagulants have a lot of popularity for the management of RPL.

The inherited thrombophilia disrupts the placental function by causing arterial and \ or venous thrombosis at the fetal-maternal connection. Additionally, some clotting factors, including factors V and VIII are thought to be inhibited by activated proteins C and S, if these proteins' activity is reduced, the inhibition of the clotting mechanism is reduced or removed. So, arterial or venous thrombosis can occur, and this mechanism may be the cause of RPL related thrombophilia (37).

A family history of excessive clotting is typically present in cases with hereditary or genetic thrombophilia. A gene mutation such as factor v Leiden, hyperhomocysteinemia (MTHFR) mutation, prothrombin mutation, antithrombin III deficiency (ATIII), or a protein S and \ or protein C deficiency, are more frequently used to confirm the thrombophilia diagnosis (38).

The two most prevalent inherited thrombophilia, factor V Leiden (FVL) and the prothrombin gene (G20210A) mutation (PGM), these genes are linked to 40% and 17% of pregnancy-associated VTE respectively (39). The association between gene mutation that leads to hyperhomocysteinemia and RPL related to VTE is still controversial (40).

As we mentioned, one of the most prevalent known inherited thrombophilia is factor V Leiden. This genetic disorder is autosomal dominant and arises from a single point mutation in the gene for factor V. The mutation results in a replacement of Arginine (R) with Glutamine (Q) in one of the factor V cleavage sites for Activated Protein C (APC) where APC acts (41). APC is unable to destroy the factor V species that result from this substitution. The hypercoagulable state and increased risk of thrombosis are explained by the fact that the rate at which APC inactivates FVL is 10-20 times slower than the rate at which normal FV degrades (42). Heterozygous factor V Leiden (FVL) mutation

raises the relative risk of thrombosis in the general population by 1.8-2.6 times (43). The activated protein C (APC) resistance of the factor V protein, which results from the mutation at particular locations of APC cleavage. Results in a malfunctioning anticoagulant system that shifts the balance toward unregulated coagulation (42).

Factor V Leiden mutation may be heterozygous or homozygous, heterozygous form is the most common type of FVL mutation, this genetic mutation's heterozygosity raises the probability of thrombosis by roughly 7 times, while its rare homozygosity raises the risk by almost 20 times (44).

A mutation in the prothrombin G20210A gene greatly raises the likelihood of venous thrombophilia, which may lead to placental thrombosis and infarction. This condition raises the possibility of miscarriage because of inadequate utero–placental perfusion (45). In heterozygous patients, a mutation in the prothrombin gene will promote the production of thrombin and clot formation, increasing their risk of clotting by two times compared to non-carriers (46).

Regarding the MTHFR gene that causes hyperhomocysteinemia, The MTHFR gene is an important enzyme for folate and homocysteine metabolism. This gene plays a significant role in converting 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, Mutations in the MTHFR gene lead to decreased activity of the enzyme and substantially cause hyperhomocysteinemia (40). MTHFR is most commonly characterized by two polymorphisms, C677T and A1298C (47). many studies show that the MTHFR polymorphism is not associated with RPL, so the relationship between MTHFR and RPL is still questionable (40, 47).

Because the basic incidence differs among ethnic groups, the prevalence of hereditary thrombophilia may also vary. In the general population, thrombophilia prevalence ranges from 1.1% in Lebanon to 2.5% in India (48).

Thrombophilia is categorized into three groups according to what the protein or genes mutated, high risk thrombophilia includes antithrombin III, protein C, and protein S deficiencies, moderate risk includes factor V Leiden and prothrombin mutation, while the low risk is hyperhomocysteinemia (38).

Hypercoagulable conditions related to different etiologists are known as acquired thrombophilia, because of the underlying physiological change. The risks are heightened during pregnancy in particular. Antiphospholipid syndrome (APS) is the most frequent cause of acquired thrombophilia during pregnancy (49). Numerous medical and obstetric difficulties have been linked to complicated multisystem conditions known as APS, and recent research provides further light on the pathophysiology of APS. Anticardiolipin antibodies and lupus anticoagulants are the two most clinically significant antiphospholipid antibodies linked to thromboembolism and RPL (50).

In 2023, the American Society of Hematology guidelines published recommendations about the scenarios that require thrombophilia testing. These scenarios include, patients with previous VTE episodes, patients with cerebral or splanchnic venous thrombosis in settings where anticoagulation would be discontinued, patients with a family history of ATIII, protein C or protein S deficiency, pregnant women with a family history of high-risk thrombophilia type and patients with cancer who are at low or intermediate risk of thrombosis (22, 51).

In pregnant women, a thrombophilia test panel is required upon certain conditions, such as three or more consecutive miscarriages, history of VTE, and family history of 1st-degree relative of VTE (22). The thrombophilia test done in pregnancy should contain the following gene, factor V Leiden, prothrombin, protein C functional activity level, protein S free, total and functional, antithrombin heparin cofactor assay, and anti-phospholipid antibodies (22).

In addition to the regimen's effectiveness and maternal safety, the potential complications that any medication poses to the fetus must be taken into account while choosing the best treatment for VTE during pregnancy. Anticoagulant treatment may cause teratogenicity, bleeding, and fetal loss. Because these drugs are unable to pass through the placenta, LMWH and UFH are safe anticoagulant options in pregnancy (52). VKA (warfarin) can cause previous complications since it can pass the placenta. Enoxaparin is more commonly prescribed in pregnancy than UFH because it is more convenient, has fewer side effects, is easier to use, and is less expensive (53).

Many clinicians currently use low molecular weight heparin (LMWH) to manage RPL related to thrombophilia. After Sanson et al revealed that thrombophilia is linked to a significant risk of fetal loss in the early and late stages of pregnancy, this treatment became more popular in the late '90s (54). The LMWH dosage in obstetrics population for VTE prophylaxis is based on the patient's weight (38).

1.1.4 Atrial Fibrillation and VTE

One of the heart arrhythmias that occur most commonly is atrial fibrillation, about 25% of adults will experience AF at some point in their life (55). Regarding atrial fibrillation and thromboembolism-related episodes. In individuals with atrial fibrillation (AF), atrial thromboembolic events, such as ischemic stroke and systemic embolism are linked to a higher risk of significant potentially fatal consequences (56). VTE and AF are prevalent conditions, especially in the elderly (57). VTE has a 1 in 8 lifetime risk whereas AF has a 1 in 4 lifetime risk (58, 59). So, there is a significant morbidity and mortality associated with both VTE and AF. Therefore, much of the effort has gone into improving stroke risk stratification to identify AF patients who need oral anticoagulants (57).

However, several risk factors are frequently identified in AF patients and that contributes to the elevated risk of arterial thrombotic events are also known to be linked to the development of DVT and PE. Age, sex, diabetes mellitus, heart failure, vascular disease, and ischemic stroke are some of these risk factors (60). one in fact, the incidence of VTE is higher in women under the age of 55 than in men, and patients over 75 have a 5-fold higher chance of developing VTE than patients under 50 (61).

Hemodynamic alterations induced by AF may encourage the development of VTE. AF leads to PE through right atrial thrombosis or VTE through concomitant procoagulant status (62). the majority of earlier research documented a causative relationship between AF and VTE. More recent research suggests that AF and VTE may be reciprocal or co-occurring. According to Lutsey et al, there may be a reciprocal association between AF and VTE, they discovered that patients with VTE have about twice the chance of developing AF, and patients with AF have about twice the chance of developing VTE (63).

Anticoagulant medications may have additional advantages in reducing VTE, even though their primary goal in AF patients is to prevent stroke and systemic embolism. Given that VTE primarily affects the elderly and individuals with comorbidities, this is very crucial. Oral anticoagulation in AF patients to prevent stroke (64), may be beneficial to VTE protection. While anticoagulation to prevent VTE recurrence can provide additional AF protection (65).

Before 2010, the primary medication for treating VTE and secondary prevention, as well as the primary preventive measure against stroke in patients with AF, was the conventional oral anticoagulant warfarin. Since receiving FDA approval for human use in 1954, warfarin has dominated the oral anticoagulant market for treating VTE and preventing stroke in NVAF for 50 years (66). Warfarin lowers the risk of thromboembolic consequences in AF and VTE, but it also has a limited therapeutic window and interacts with medication and food that need regular INR checks, which affects its effectiveness and patient compliance. Due to these drawbacks, NOACs with a wider therapeutic window, no routine monitoring, and comparable efficacy with warfarin have been developed.

As mentioned previously, Dabigatran, the first NOAC, was authorized for use in humans by the FDA in 2010. There are now four NOACs that are licensed for clinical use, dabigatran, rivaroxaban, apixaban, and edoxaban, which expand the available options of OAC for human use. NOACs have more consistent anticoagulation, more stable pharmacokinetic profile, fewer drug-food interactions, an equal or greater impact on lowering mortality and vascular complications, and a lower incidence of cerebral hemorrhage than warfarin (12).

NOACs were tested as warfarin substitutes in four randomized trials that included 71683 AF patients. The results showed that NOAC significantly decreased mortality by 10%, massive hemorrhage by 14%, fatal hemorrhage by 51%, and stroke or systemic embolism by 19% when compared to warfarin. Large randomized clinical trials demonstrated that NOACs dabigatran, rivaroxaban, apixaban, and edoxaban are as effective as traditional treatment warfarin in preventing stroke and cardiac embolism complications in NVAF patients (67).

In 2020, the guidelines suggested that NOAC be the 1st choice medication for preventing stroke in AF patients, instead of warfarin (64). Furthermore, the overall risk of severe bleeding in AF patients with NOAC was as high as 3% per year, which is still an unacceptable level, even with relative risk reduction (67). In May 2018, the FDA authorized Andexanet alfa as a reversal agent for the factor FXaIs, apixaban, and rivaroxaban. For dabigatran, they developed idarucizumab as an inhibitor for dabigatran (68).

In general, the recommended anticoagulant drugs for AF and VTE have gradually evolved from warfarin priority to NOACs. With further research, the application of NOACs is gradually expanding.

1.1.5 Heart Failure and VTE

Heart failure (HF) is an increasingly prevalent condition, with an estimated 6 million patients with HF in the United States. According to available data, heart failure causes a hypercoagulable state that is not only linked to fatalities, systemic embolism, and stroke. but also increase the risk of both DVT and PE. This is could because patients with acute and chronic HF have higher amounts of pro-thrombotic and pro-inflammatory cytokines (69)..

Additionally, heart failure is linked to a nearly two-fold increase in the incidence of VTE in both hospitalized and outpatient settings. Left ventricular wall motion abnormalities in patients with systolic dysfunction predispose to local thrombosis due to blood stasis as does atrial fibrillation (AF) which leads to blood stasis in regions of the atria. Anticoagulation therapy has been used to avoid catastrophic occurrence due to the significant risk of thromboembolism in HF patients with AF (69). many randomized clinical trials showed that NOAC was more popular used in HF than warfarin due to the difficulties of warfarin use mentioned previously, with equivalent effectiveness and lower bleeding risk.

1.1.6 Acute Coronary Syndrome and Anticoagulation

In the developed world, cardiovascular disease is the most common cause of mortality. The most popular invasive therapeutic cardiac technique is revascularization such as percutaneous coronary intervention (PCI), which is crucial in the management of ischemic heart disease. There is now more interest in using anticoagulation in

conjugation with antiplatelet (ASA and clopidogrel or prasugrel) for patients with chronic coronary syndrome, especially those who have had ACS and PCI. Following coronary stenting, thrombotic risk can arise from several causes, including prothrombotic circumstances associated with the patient's underlying features, local thrombotic risk activation caused by stent and PCI outcomes, and chronic atherosclerotic disease manifestations that are distant from the procedure (70).

In the acute phase of ACS, the coagulation cascade is activated. Both thrombin and factor Xa play a significant role in this cascade, leading to clot formation. Achieving an appropriate balance between the inherent advantages of anticoagulant medication and the elevated risk of bleeding is crucial for their use in clinical practice. An increase in bleeding was found to outweigh the therapeutic benefits of warfarin when combined with antiplatelets in earlier investigations. In recent years, new oral anticoagulants (NOACs) have been created; some of these have been studied for secondary prophylaxis following ACS. The previous studies showed that, when used with conventional antiplatelet therapy, rivaroxaban is the first oral anticoagulant to enhance outcomes in ACS without increasing lethal bleeding. Identifying the "sweet spot" for net therapeutic benefit (71). However when apixaban (5 mg twice a day) was added to antiplatelet therapy in high-risk patients following an acute coronary syndrome, the incidence of severe bleeding events increased while the frequency of recurrent ischemic events did not significantly decrease (72).

About dabigatran, the composite end outcome of cardiovascular death, nonfatal MI, or stroke did not differ between the dabigatran and placebo groups when used in conjunction with dual antiplatelet treatment for secondary prevention in patients with ACS. It should be mentioned, nevertheless, that recent investigations have indicated that individuals using dabigatran may be at higher risk for MI and ACS (73).

1.1.7 VTE and COVID-19

At the end of 2019, the world faced a different era or pandemic, the COVID-19 pandemic. During this period, anticoagulants were widely prescribed. Coagulation and thrombosis are two of the many manifestations of severe acute respiratory syndrome coronavirus 2 (SAR – COV 2) that causes COVID-19. These symptoms can sometimes be the only indicator of a SARS-CoV-2 infection and may manifest earlier or later in the

course of the illness. These symptoms are caused by venous thromboembolism (VTE), which is more common in hospitalized patients, particularly those in intensive care units (74).

Additionally, other types of micro- or macro-vasculature emboli, including venous and arterial thrombosis, have been reported during this pandemic. Serious side effects, including neurological and cardiac issues, have nearly always been the consequence of this viral infection's hypercoagulable state. Higher platelet counts and D-dimer values are typically associated with coagulopathy in severe SARS-CoV-2 infections than in severe non-COVID-19 pneumonia cases (74, 75).

It has been estimated that the majority of COVID-19 cases that progress to a catastrophic stage are caused by the severe hypercoagulability seen in patients. Anticoagulants are therefore crucial medications for the treatment of this potentially fatal illness. However, as the pandemic has spread, a wealth of knowledge regarding the need for these drugs has emerged. Initially, it was thought that anticoagulant medication could only increase in-hospital survival for COVID-19 intubated patients and those with higher D-dimer levels or a high sepsis-induced anticoagulant score (76).

Later research, however, revealed that anticoagulants may help reduce the requirement for mechanical ventilation in moderately unwell SARS-CoV-2 patients. It is crucial to understand that heparin compounds have anticoagulatory effects as well as anti-inflammatory, anti-arrhythmic, immunomodulatory, antiviral, and anti-complementary actions (77).

Importantly, direct oral anticoagulants (DOACs) including dabigatran, apixaban, rivaroxaban, and edoxaban are not suitable for critically ill COVID-19 patients (hospitalized mainly) because of their lengthy half-lives and unexpected and unstable metabolic effects in patients with acute illnesses. Nonetheless, they might be perfect for COVID-19 patients who need ongoing or extended anticoagulation following hospitalization. So, in COVID hospitalized patients the recommended or preferred anticoagulant is UFH or LMWH (78).

1.2 Literature Review

The prescribing of anticoagulants is an area of active clinical research. So, it is important to understand the factors that drive local decision-making (79). Multiple studies showed that the DOACs are more effective, have less side effect, and need less monitoring test comparing to warfarin.

It was noticeable that the prescription rate of both anticoagulants (injectable and oral form) has increased for in and outpatients at the Palestinian hospitals. Oral anticoagulants for cardiovascular diseases and thromboembolic events. Injectable anticoagulants (enoxaparin) for pregnant and postpartum women.

unfortunately, no studies have been done in our country to date in order to assess the direction of prescribing these drugs, but globally this phenomenon has been studied in various countries such as England, China and others**.** In England, this topic was studied and published in 2021 and evaluated the prescribing pattern of the direct oral anticoagulants (DOACs) and warfarin, cost implication of the increasing prescribing DOACs and reporting the side effect between 2009-2019 and they also compared the prescribing trends of four DOACs and warfarin to better understand the regional differences in DOACs prescribing. The prescribing of DOACs (compared to total anticoagulants) has increased from 16% in 2015 to 62% in 2019, in contrast, warfarin prescribing has declined since 2015. This study has noticed an increase in the general use of anticoagulants over years and the prescribing of DOACs has excessed the prescribing warfarin (80).

Other study that similar to those in England was done in China, the study included a total of 189,006 prescriptions of 67 hospital in 6 years and showed that warfarin prescription has decreased, 92% of cost for DOACs and the most common used of DOACs was rivaroxaban and dabigatran, as an end result, the used of DOACs has increased rapidly, so they recommend increasing the attention on the use of DOACs (18).

Also, in five years just, the prescribing of DOACs was increased from 9% to 74%, while warfarin was declined from 91% to 26% in English primary care, this is maybe not only due to the switching of existing patients, but also from the initiation of newly

diagnosed patients on these medications, So, the total prescriptions of anticoagulant has nearly doubled from the approval of DOACs until 2019 (79).

In June 2022, a meta-analysis study that was published in Scopus concluded that the propotion of oral anticoagulants use worldwide almost doubled following DOACs introduction (81).

Regarding injectable anticoagulants especially enoxaparin, no global studies were conducted to assess the trends of prescribing enoxaparin in the obstetric population (pregnancy and postpartum women). However, many studies compared the effectiveness and complication of enoxaparin use in standard risk-stratified groups versus a more selective group of the postpartum population. A study was conducted in earlier 2024 showed that decreased rates of wound hematomas without elevated rates of postpartum VTE were linked to a more targeted or selective risk-stratified approach to an enoxaparin thromboprophylaxis program for VTE (82).

There was no significant difference in VTE or thromboembolism between patients receiving and not receiving prophylactic anticoagulation, according to a study by Ferresetal that found a significantly higher rate of wound separation (6.8% vs. 3.6%) in patients receiving chemoprophylaxis following the implementation of an institutional practice guideline for postoperative thromboprophylaxis in 2509 patients undergoing cesarean sections (83).

About enoxaparin in pregnant women with thrombophilia. Current research points to thrombophilia as a contributing factor rather than a cause of venous thromboembolism and placenta-mediated pregnancy complications. Thrombophilia screening is still debatable because there is limited evidence that anticoagulation medication helps with all placenta-mediated pregnancy complications or with all genetic mutations that were tested. Universal screening is not necessary because of the minimal absolute risk of placenta-mediated pregnancy complications and gestational venous thromboembolism with heritable thrombophilia (84).

As we mentioned above, the choice of anticoagulant has a financial implication such as number of hospitalizations, serious side effects, and monitoring tests of warfarin and others, that may lead to form a heavy burden to the Ministry Of Health (MOH) and patients themselves. According to one of cost-effectiveness study of oral anticoagulant

that done in South Korea, the DOACs were the most cost effective than warfarin in many cases (85).

1.3 Problem statement

For decades, warfarin, the oldest oral anticoagulant, was used to prevent thromboembolic events. However, the introduction of new oral and parenteral anticoagulants has provided physicians with other therapeutic options and changed their directions in prescribing oral and parenteral anticoagulants.

For enoxaparin use, many studies showed that the prescribing of enoxaparin in the obstetric population was not always justified, and many issues related to thrombophilic pregnant and postpartum women were still controversial.

In clinical practice, anticoagulants are increasingly prescribed for in and out patients in the Palestinian hospitals. The use of these anticoagulants could be associated with heavy burden on both individual and society. Currently, little is known on the trends in prescribing oral and parenteral anticoagulants in different Palestinian hospitals.

1.4 Research questions

1. What is the pattern of anticoagulants use in different Palestinian hospitals?

2. Which anticoagulants are frequently used? and for what indications?

1.5 Objectives

This study was conducted to:

- Evaluate trends in prescribing oral and parenteral anticoagulants in different Palestinian hospitals.

- Visualize the increasing or decreasing trends in prescribing oral and parenteral anticoagulants in different Palestinian hospitals.

- Identify the most commonly prescribed oral and parenteral anticoagulants and determine the prescription of oral and parenteral anticoagulants in different conditions.

1.6 Significance of the study

The findings of this study could be helpful in informing prescribers, pharmacologists, clinical pharmacists, other healthcare providers, insurance companies, and other decision makers about the growing or declining trends in prescribing oral and parenteral anticoagulants in different Palestinian hospitals. The findings might also help inform decision makers in health authorities who might be interested in developing guidelines for prescribing oral and parenteral anticoagulants.

Chapter Two

Methodology

2.1 Study design

Prescription data of anticoagulants, including injectable and oral forms were retrospectively collected from Avicenna and dhis databases from 2019 -2023 in Hebron in the west bank of Palestine. The prescription data involved in this study was collected from inpatients and outpatients' records. In this study, inpatients and outpatients' prescriptions, including heparin, enoxaparin, warfarin, rivaroxaban, apixaban, and dabigatran. The study was based on quantitative data and statistical analysis to evaluate prescribing trends. We collected data from electronic health records in hospitals and healthcare centers.

Prescription data of anticoagulants for all results in this study were extracted from the Avicenna database in hospitals. In addition, the prescription data of enoxaparin in pregnancy was extracted from the DHIS2 database in health care centers, Avicenna database involves outpatients and inpatients information, including past medical history, past drugs history, past surgical history, current diagnosis, and current prescribed drugs, DHIS2 database also involves past medical history, past surgical history, past drug history, thrombophilia genes test and concomitant medications.

2.2 Study settings

The data was collected from southern regions of west bank including Yatta Governmental Hospital, Alia Governmental Hospital, and Halhul Health Care Center in the West Bank of Palestine.

The sample was collected from November 2023 to June 2024.

Figure 1

Represents a map including hospitals and health care center

2.3 Participants

- **Inclusion criteria**

We included any patient diagnosed with conditions needed prescribing anticoagulant therapy and throughout the study period (2019-2023), at least one anticoagulant prescription.

- **Exclusion criteria**

We included any patients with incomplete data.

This study included all patients who were prescribed oral or parenteral anticoagulants regardless of the clinical indication that might include AF, venous thromboembolism (PE or DVT), post CAD, MI, orthopedic surgery, post-partum and pregnant women who have high risk for thrombosis. Oral anticoagulants include warfarin and DOAC (rivaroxaban, apixaban, and dabigatran), parenteral forms are enoxaparin and heparin. The prescription data of other OACs were not available such as edoxaban as it was not available in our country. Patients were eligible for inclusion if they were prescribed anticoagulant drugs during the study period.

2.4 Variables

Many variables are extracted from the electronic record system, 1st of them is patient demographic data such as age, sex, address, and medical history, 2nd one is clinical data such as an indication of anticoagulant (AF, DVT, PE, post-CS, and others) and year of hospitalization, the last one was anticoagulant details such as type of anticoagulant, dosing, duration and side effects.

2.5 Data collection

A data collection form created for this study was used as shown in (Appendix D). The data collection form has collected the variables needed for this study mentioned above.

2.6 Bias

Even with this study's robust methodology, several possible biases could affect the findings. Because the study is retrospective, it may undergo selection bias, many patients were prescribed anticoagulants in outpatient clinics (private) or private hospitals and were not included in our study. incorrect categorization of disease, the patient demographic, or anticoagulant type might result from inaccurate data coding in the electronic health record, this is called information bias and may lead to erroneous findings regarding usage patterns, another form of information bias is missing data, the databases could not contain all necessary details about crucial factors including treatment adherence and compliance that may affect the validity of the study. Prescriber bias also plays a role in a finding, preferences, or experiences of clinicians, and has an impact on the choice of anticoagulant, some physicians could favor more modern medications or this may be due to the medical representative of drugs (competition in the market).

2.7 Data analysis

The data was entered and analyzed using the Statistical Package for Social Sciences program (IBM-SPSS) version 21. Patient demographic and medication information was gathered using descriptive statistics. Continuous data were compared using T-tests, while categorical variables were compared using chi-square tests

The data was stratified by age groups, type of anticoagulants, and diagnosis, statistical significance was set at p-value < 0.05 for all tests.

2.8 Ethical consideration

All facets of the research protocol, encompassing the retrieval and utilization of clinical information pertaining to patients, received approval from both the Institutional Review Boards (IRB) (2023\20) and local health authorities. The IRB ethically approved this study by the College of Graduate Studies and the Education in Health and Scientific, Research Unit, the Palestinian Ministry of Health (Appendix A). All patient's information was anonymized and managed in compliance with privacy and data collection laws.

2.9 Confidentiality

We confirm that the collected data and information in this study will be used for clinical research only. Information will be confidential and will not be used for any purpose other than that of this study.

Chapter Three

Results

3.1 Sociodemographic and clinical characteristics

In this study, a total of 5,121 patients who received anticoagulants were included in this analysis. The mean age of the patients was 39.4 ± 18.0 years (the median was 33.0 [26.0, 51.0] years).

Of the patients, 4,172 (81.5%) were female and 3,587 (70.0%) were included from the Yatta governmental hospital; The other patients were included from healthcare centers in Hebron and Halhul regions. The patients are from different regions of Palestine, including northern, center, and southern regions (Figure 1).

Of the patients, 2,224 (43.4%) had a relevant past medical history. Of all patients, 893 (17.4%) had hypertension, 785 (15.3%) had diabetes mellitus, 100 (2.0%) had diabetic foot ulcers, and 178 (3.5%) were smokers.

Table 1 displays the characteristic of the patients and past medical history.

Table1

Characteristics of the patients and past medical history

Variable	N	%
Governorate/region		
Yatta	3587	70.0
Hebron	1361	26.6
Halhul	173	3.4
Sex		
Male	949	18.5
Female	4172	81.5
Age (years)		
< 18	70	1.4
18-30	2071	40.4
30-50	1694	33.1
50-65	659	12.9
≥ 65	627	12.2
Past medical history	2224	43.4
Diabetes mellitus	785	15.3
Diabetic foot ulcer	100	2.0
Hypertension	893	17.4
Hyperlipidemia	70	1.4
Smoking	178	3.5
Drug/food allergy	53	1.0

Anticoagulants were prescribed to 2,457 (48.0%) patients post a Cesarean section, 456 (8.9%) post-vaginal delivery, 348 (6.8%) patients during pregnancy, 83 (1.6%) patients during *in vitro* fertilization, and 105 (2.1%) patients after abortion. In addition, anticoagulants were given to 327 (6.4%) patients who tested positive for thrombophilia, 576 (11.2%) patients who presented with symptoms of a heart attack, 450 (8.8%) patients who received cardiac catheterization, 505 (9.9%) patients who had vascular disease, and 364 (7.1%) who had orthopedic surgery. Moreover, anticoagulants were given to 228 (4.5%) patients who had stroke, 199 (3.9%) who had covid /pneumonia, 174 (3.4%) who had heart failure, 125 (2.4%) who had chronic kidney disease, 98 (1.9%) who had hysterectomy, 46 (0.9%) who had deep venous thrombosis, 28 (0.5%) who had atrial fibrillation, and 10 (0.2%) who had pulmonary embolism. These details are shown in Table 6.

3.2 Prescription of anticoagulants and antiplatelets

In this study, 5,106 (99.7%) patients received enoxaparin and 114 (2.2%) received heparin. On the other hand, 128 (2.5%) received rivaroxaban, 54 (1.1%) received apixaban, 18 (0.4%) received warfarin, and 3 (0.1%) received dabigatran. In addition, 565 (11.0%) also received acetylsalicylic acid. These details are shown in Table C3 (Appendix C).

3.3 Trends in prescribing anticoagulants and antiplatelets

Over the study period (2019-2023), there has been an increasing trend in prescribing enoxaparin (Figure 2A). On the other hand, there has been no observable increasing trend in prescribing heparin. Over the study periods, there has been an increasing trend in prescribing oral anticoagulants, notably, rivaroxaban and apixaban (Figure 2B). From 2020 to 2021, there has been a sharp increase in prescribing rivaroxaban and apixaban. In the period between 2020 to 2021, there has been an observable drop in prescribing acetylsalicylic acid (Figure 2C). However, there has been an observable increase in prescribing acetylsalicylic acid after 2021. Figure 2 shows trend in prescribing anticoagulants and antiplatelet over the study period.

Figure 2

Trends in prescribing injectable anticoagulants (A), oral anticoagulants (B), and acetylsalicylic acid (C) over the study period (2019-2023)

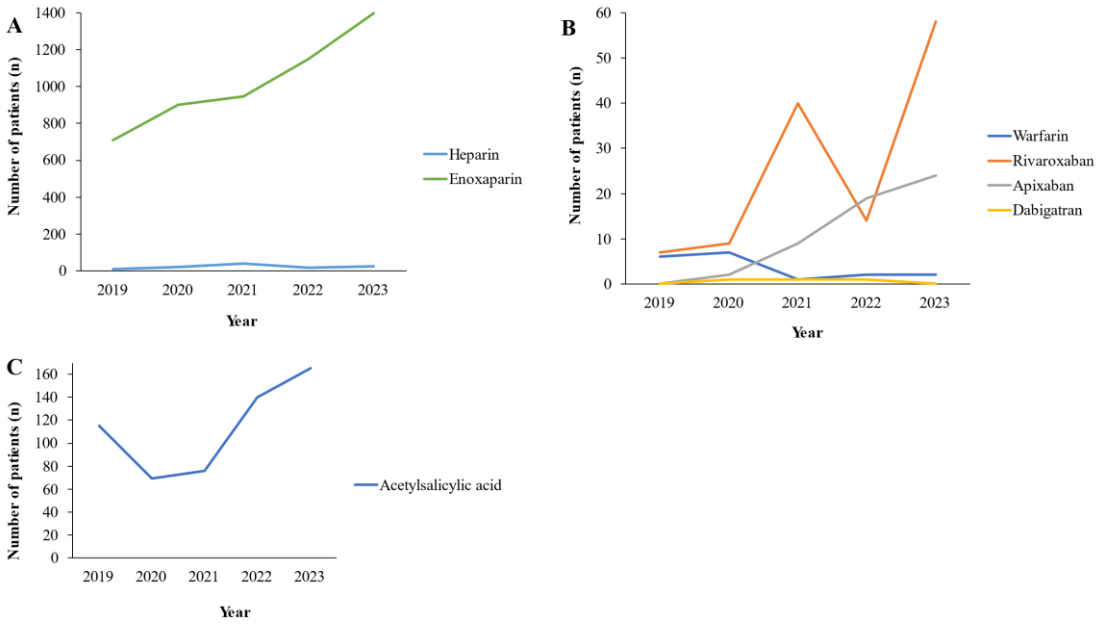
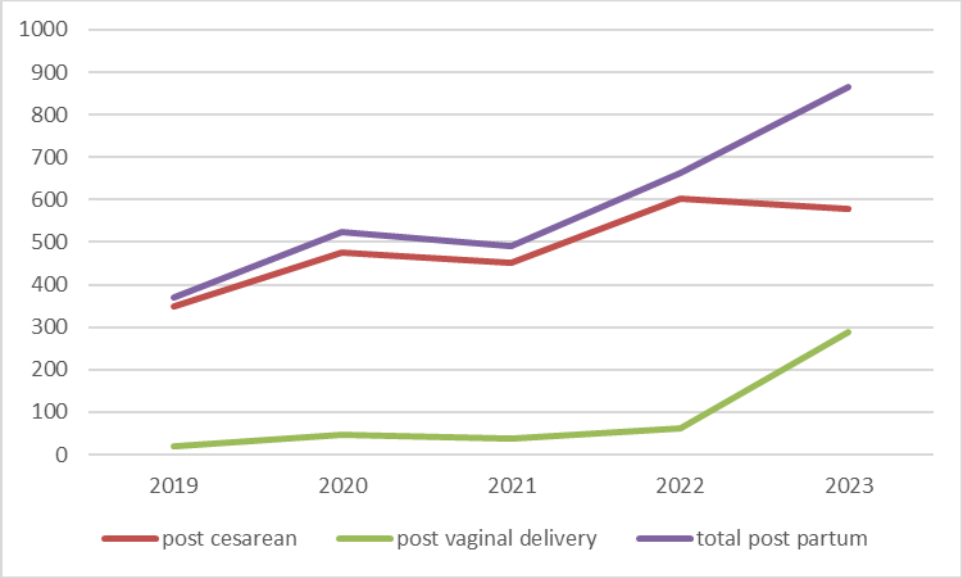


Figure 3

Represent trend of enoxaparin use in post-partum population



3.4 Outcomes of the Patients

Of the patients, 130 (2.5%) died. The most common cause of death was cardiopulmonary arrest. The other causes included Sepsis/septic shock, Stroke, and consequences of COVID-19. The causes of mortality are shown in Table C4 (in Appendix C).

3.5 Association between anticoagulants and patient variables

3.5.1 Association between prescribing enoxaparin and variables of the patients

Chi-square/Fisher's exact tests showed that the patients who had hypertension, diabetes mellitus, diabetic foot ulcer, vascular disease, and chronic kidney disease were less likely to be prescribed enoxaparin compared to the patients who did not have these diseases. On the other hand, the patients who had Cesarean section were more likely to be prescribed enoxaparin. These associations are shown in Table 2.

Table 2

Association between prescribing enoxaparin and variables of the patients

		Enoxaparin				
		No		Yes		
Variable	Category	n	%	n	%	p-value
Hypertension	No	8	0.2	4220	82.4	0.008
	Yes	7	0.1	886	17.3	
Diabetes mellitus	No	9	0.2	4327	84.5	0.018
	Yes	6	0.1	779	15.2	
Diabetic foot	No	13	0.3	5008	97.8	0.034
	Yes	2	0.0	98	1.9	
Vascular disease	No	10	0.2	4606	89.9	0.012
	Yes	5	0.1	500	9.8	
Post a Cesarean section	No	13	0.3	2651	51.8	0.007
	Yes	2	0.0	2455	47.9	
Chronic kidney disease	No	10	0.2	4986	97.4	< 0.001
	Yes	5	0.1	120	2.3	

In addition, t-tests showed that the patients who were prescribed enoxaparin were significantly younger than those who were not prescribed enoxaparin (39.4 ± 18.0 vs. 50.1 ± 19.4, p-value = 0.021).

3.5.2 Association between prescribing heparin and variables of the patients

Chi-square/Fisher's exact tests showed that the patients who were older, had diabetes mellitus, had hypertension, stroke, vascular disease, atrial fibrillation, pulmonary embolism, heart failure, pneumonia, chronic kidney disease, received acetylsalicylic acid, and those who died were more likely to have received heparin. On the other hand, the patients who were female, pregnant, had Cesarean section, had delivery, tested thrombophilia positive, and those who received anticoagulants lately were less likely to received heparin compared to the other patients. These associations are shown in Table 3.

Table 3

Association between prescribing heparin and variables of the patients

		Heparin				
		No		Yes		
Variable	Category	n	%	n	%	p-value
Sex	Male	901	17.6	48	0.9	< 0.001
	Female	4106	80.2	66	1.3	
Age (years)	< 18	69	1.3	1	0.0	< 0.001
	18-30	2069	40.4	2	0.0	
	30-50	1673	32.7	21	0.4	
	50-65	626	12.2	33	0.6	
	≥ 65	570	11.1	57	1.1	
Year	2019	706	13.8	10	0.2	< 0.001
	2020	884	17.3	20	0.4	
	2021	907	17.7	41	0.8	
	2022	1135	22.2	18	0.4	
	2023	1375	26.9	25	0.5	
Diabetes mellitus	No	4282	83.6	54	1.1	< 0.001
	Yes	725	14.2	60	1.2	
Hypertension	No	4183	81.7	45	0.9	< 0.001
	Yes	824	16.1	69	1.3	
Stroke	No	4795	93.6	98	1.9	< 0.001
	Yes	212	4.1	16	0.3	
Vascular disease	No	4547	88.8	69	1.3	< 0.001
	Yes	460	9.0	45	0.9	
Atrial fibrillation	No	4982	97.3	111	2.2	0.023
	Yes	25	0.5	3	0.1	
Pulmonary embolism	No	4999	97.6	112	2.2	0.020
	Yes	8	0.2	2	0.0	
Pregnancy	No	4660	91.0	113	2.2	0.011
	Yes	347	6.8	1	0.0	
Post a Cesarean section	No	2552	49.8	112	2.2	< 0.001
	Yes	2455	47.9	2	0.0	
Postpartum	No	4551	88.9	114	2.2	0.001
	Yes	456	8.9	0	0.0	
Thrombophilia positive	No	4681	91.4	113	2.2	0.015
	Yes	326	6.4	1	0.0	
Heart failure	No	4866	95.0	81	1.6	< 0.001
	Yes	141	2.8	33	0.6	
Pneumonia	No	4833	94.4	89	1.7	< 0.001
	Yes	174	3.4	25	0.5	
Chronic kidney disease	No	4923	96.1	73	1.4	< 0.001
	Yes	84	1.6	41	0.8	
Acetylsalicylic acid	No	4478	87.4	78	1.5	< 0.001
	Yes	529	10.3	36	0.7	
Death	No	4910	95.9	81	1.6	< 0.001
	Yes	97	1.9	33	0.6	

In addition, t-tests, showed that the patients who were prescribed heparin were significantly older than those who were not prescribed heparin (63.4 ± 16.6 vs. 38.8 ± 17.7 years, p-value < 0.001). The APTT value of the patients who were prescribed heparin were significantly higher than those who were not prescribed heparin (87.7 ± 402.5 vs. 35.4 ± 31.0, p-value < 0.001).

3.5.3 Association between prescribing dabigatran and variables of the patients

Chi-square/Fisher's exact tests showed that older patients, those who had atrial fibrillation, deep venous thrombosis, and pulmonary embolism were more likely to be prescribed dabigatran. These associations are shown in Table 4.

Table 4

Association between prescribing dabigatran and variables of the patients

		Dabigatran				
		No		Yes		
Variable	Category	n	%	n	%	p-value
Age (years)	< 18	70	1.4	0	0.0	0.039
	18-30	2071	40.4	0	0.0	
	30-50	1694	33.1	0	0.0	
	50-65	657	12.8	2	0.04	
	≥ 65	626	12.2	1	0.02	
Atrial fibrillation	No	5091	99.4	2	0.04	0.016
	Yes	27	0.5	1	0.02	
Deep venous thrombosis	No	5073	99.1	2	0.04	0.027
	Yes	45	0.9	1	0.02	
Pulmonary embolism	No	5109	99.8	2	0.04	0.006
	Yes	9	0.2	1	0.02	

In addition, t-tests showed that the patients who were prescribed dabigatran were significantly older than those who were not prescribed dabigatran (64.0 ± 13.0 vs 39.4 ± 18.0 years, p-value = 0.018).

3.5.4 Association between prescribing warfarin and variables of the patients

Chi-square/Fisher's exact tests showed that the patients who were older, had a past medical history, had stroke, vascular disease, deep venous thrombosis, and had pulmonary embolism were more likely to received warfarin. On the other hand, the patients who were female, received anticoagulants recently, and those who had

Cesarean section were less likely to be prescribed warfarin. These association are shown in Table 5**.**

Table 5

Association between prescribing warfarin and variables of the patients

		Warfarin				
		No		Yes		
Variable	Category	n	%	n	%	p-value
Sex	Male	940	18.4	9	0.2	0.002
	Female	4163	81.3	9	0.2	
Age (years)	< 18	70	1.4	0	0.0	< 0.001
	18-30	2068	40.4	3	0.1	
	30-50	1691	33.0	3	0.1	
	50-65	650	12.7	9	0.2	
	≥ 65	624	12.2	3	0.1	
Year	2019	710	13.9	6	0.1	0.008
	2020	897	17.5	7	0.1	
	2021	947	18.5	1	0.0	
	2022	1151	22.5	2	0.0	
	2023	1398	27.3	2	0.0	
Past medical history	No	2891	56.5	6	0.1	0.046
	Yes	2212	43.2	12	0.2	
Stroke	No	4878	95.3	15	0.3	0.043
	Yes	225	4.4	3	0.1	
Vascular disease	No	4605	89.9	11	0.2	0.001
	Yes	498	9.7	7	0.1	
Atrial fibrillation	No	5077	99.1	16	0.3	0.004
	Yes	26	0.5	2	0.0	
Deep venous thrombosis	No	5068	99.0	7	0.1	< 0.001
	Yes	35	0.7	11	0.2	
Pulmonary embolism	No	5095	99.5	16	0.3	0.001
	Yes	8	0.2	2	0.0	
Post a Cesarean section	No	2646	51.7	18	0.4	< 0.001
	Yes	2457	48.0	0	0.0	

In addition, t-tests, showed that the patients who were prescribed warfarin were significantly older than those who were not prescribed warfarin (51.3 ± 17.6 vs 39.4 ± 18.0 years, p-value = 0.005).

3.5.5 Association between prescribing apixaban and variables of the patients

Chi-square/Fisher's exact tests showed that the patients who were older, received anticoagulants recently, had diabetes mellitus, hypertension, were smokers, had vascular disease, atrial fibrillation, deep venous thrombosis, pulmonary embolism, orthopedic surgery, chronic kidney disease, heart failure, presented with symptoms of heart attack, had chest pain, was diagnosed with noncardiac chest pain, was discharged on muscle relaxants or proton pump inhibitors, and received acetylsalicylic acid were more likely to be prescribed apixaban. On the other hand, the patients who were female, pregnant, had Cesarean section, delivered, and those who tested thrombophilia positive were less likely to receive apixaban. These association are shown in Table C2 **.**

In addition, t-tests, showed that the patients who were prescribed apixaban were significantly older than those who were not prescribed apixaban (66.1 ± 16.1 vs 39.1 ± 17.8 years, p-value < 0.001).

Table 6

Rational use of anticoagulants and blood coagulation tests

Rationale for anticoagulant therapy use		
Post a Cesarean section	2457	48.0
Postpartum	456	8.9
Pregnancy	348	6.8
In vitro fertilization pregnancy	83	1.6
Abortion	105	2.1
Thrombophilia positive	327	6.4
Symptoms of heart attack	576	11.2
Received cardiac catheterization	450	8.8
Vascular disease	505	9.9
Orthopedic surgery	364	7.1
Fracture	183	3.6
Stroke	228	4.5
Covid 19/pneumonia	199	3.9
Heart failure	174	3.4
Chronic kidney disease	125	2.4
Hysterectomy	98	1.9
Deep venous thrombosis	46	0.9
Atrial fibrillation	28	0.5
Pulmonary embolism	10	0.2
Other	337	6.6
Blood coagulation tests	Median [IQR]	
International Normalized Ratio (INR)	1.1 [1.0, 1.2]	
Prothrombin time (PT), sec	13.0 [12.5, 15.0]	
Activated Partial Thromboplastin Time (aPTT), sec	33.0 [30.0, 36.2]	

3.5.6 Association between prescribing rivaroxaban and variables of the patients

Chi-square/Fisher's exact tests showed that the patients who were older, received anticoagulants recently, had diabetes mellitus, hyperlipidemia, hypertension, were smokers, had stroke, vascular disease, atrial fibrillation, deep venous thrombosis, pulmonary embolism, orthopedic surgery, fracture, heart failure, pneumonia, chronic kidney disease, chest pain, was diagnosed with noncardiac chest pain, was discharged on muscle relaxants and proton pump inhibitors, received acetylsalicylic acid, and died

were more likely to have received rivaroxaban. On the other hand, the patients who were female, pregnant, had Cesarean section, had delivery, and tested thrombophilia positive were less likely to receive rivaroxaban. These associations are shown in Table C6.

In addition, t-tests, showed that the patients who were prescribed rivaroxaban were significantly older than those who were not prescribed rivaroxaban (59.2 ± 18.2 vs 38.9 ± 17.7 years, p-value < 0.001).

Table 7

Association between abortion \ IVF pregnancy, year, multiparity, and genetic polymorphisms\ mutations

		Abortion		*In vitro* fertilization pregnancy		
Variable	Category	n	%	n	%	p-value
Year	2019	21	13.3	0	0.0	0.002
	2020	21	13.3	0	0.0	
	2021	27	17.1	1	0.6	
	2022	29	18.4	11	7.0	
	2023	40	25.3	8	5.1	
Multiparity	No	73	46.2	16	10.1	0.022
	Yes	65	41.1	4	2.5	
Polymorphism/mutation						
Homozygous MTHFR (A1298C)	No	124	78.5	13	8.2	0.007
	Yes	14	8.9	7	4.4	
4G/5G PAI	No	136	86.1	17	10.8	0.015
	Yes	2	1.3	3	1.9	
Homozygous PAI	No	115	72.8	20	12.7	0.047
	Yes	23	14.6	0	0.0	
1a/1a HPA	No	103	65.2	10	6.3	0.023
	Yes	35	22.2	10	6.3	

3.5.7 Association between prescribing acetylsalicylic acid and variables of the patients

Chi-square/Fisher's exact tests showed that the patients who had diabetes mellitus, diabetic foot ulcer, hyperlipidemia, hypertension, were smokers, had stroke, vascular disease, atrial fibrillation, pulmonary embolism, abortion, pregnancy, in vitro fertilization pregnancy, presented with symptoms of heart attack, tested thrombophilia positive, had heart failure, pneumonia, chronic kidney disease, chest pain, noncardiac chest pain, had cardiac catheterization, had unsuccessful pregnancy, and died were more

likely to have received acetylsalicylic acid. On the other hand, the patients who were female, received anticoagulants recently, had Cesarean section, delivery, and had hysterectomy were less likely to received acetylsalicylic acid. These association are shown in Table C7 (in appendic C).

In addition, t-tests showed that the patients who were prescribed acetylsalicylic acid were significantly older than those who were not prescribed acetylsalicylic acid (53.9 ± 20.0 vs 37.6 ± 16.9 years, p-value < 0.001).

Table 8

Association between dose of enoxaparin, year, and genetic polymorphisms\ mutations

		Received 40 and 80 mg doses together				
		No		Yes		
Variable	Category	n	%	n	%	p-value
Year	2019	14	8.1	8	4.6	<0.001
	2020	18	10.4	6	3.5	
	2021	21	12.1	9	5.2	
	2022	39	22.5	2	1.2	
	2023	26	15.0	30	17.3	
Heterozygous	No	92	53.2	34	19.7	0.026
fibrinogen	Yes	26	15.0	21	12.1	

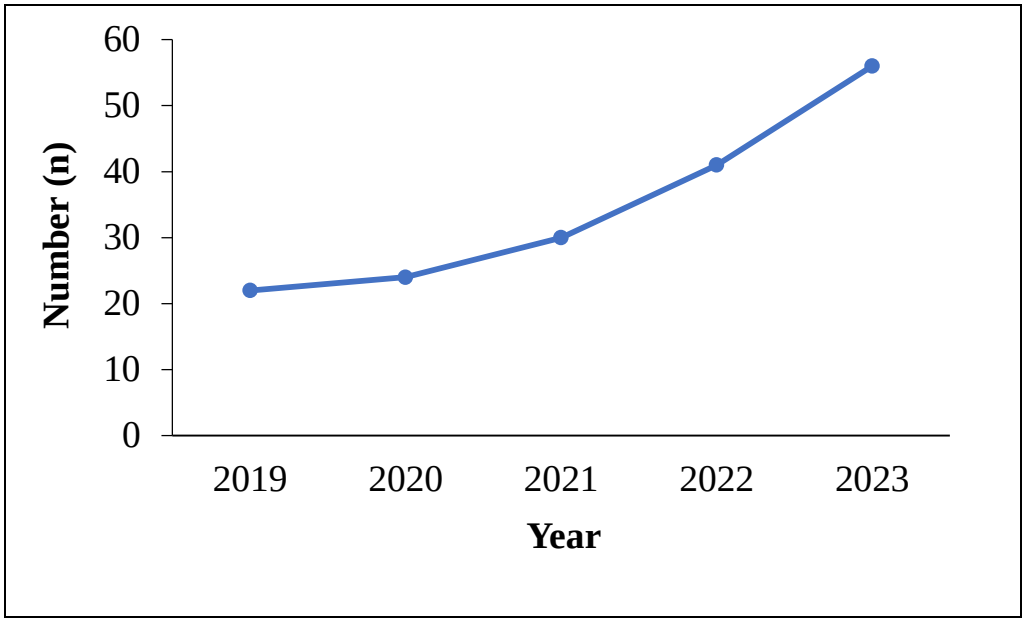
3.6 Enoxaparin in pregnant women with thrombophilia mutations

3.6.1 Trends in prescribing enoxaparin over the study period and characteristics of the women

In this study, genetic polymorphisms and mutations related to enzymes, proteins, and other factors affecting blood coagulation were available for 173 women. The mean age of the women was 29.3 ± 5.9 years. The tests were done in the period between 2019 and 2023. There was a trend in prescribing enoxaparin in thrombophilic pregnant women over the period between 2019-2023 as shown in Figure 4.

Figure 4

Trend in prescribing enoxaparin in thrombophilic pregnant women over the study period



Of the women, 138 (79.8%) had abortions and 20 (11.6%) had *in vitro* fertilization pregnancy. High percentage of the women (31.8%) received enoxaparin at a dose of 80 mg and were ordered to divide the dose because of the unavailability of 40 mg doses. Of the women, 4 (2.3%) had vascular disease, hypertension, and lupus anticoagulant.

Of the women, 136 (78.6%) received acetylsalicylic acid and 30 (17.3%) received progestins. Details of the reasons for receiving enoxaparin, doses, past medical history, and medications are shown in Table 9.

Table 9

Reasons for receiving enoxaparin, doses, past medical history, medications, and pregnancy outcomes

Variable	N	%
Reason for receiving enoxaparin		
Abortion	138	79.8
In vitro fertilization pregnancy	20	11.6
Received 40 and 80 mg doses together		
No	118	68.2
Yes	55	31.8
Past medical history		
Vascular disease	4	2.3
Hypertension	4	2.3
Lupus anticoagulant	4	2.3
Ischemic stroke	1	0.6
Single abortion only	28	15.6
Fetal death only	15	8.6
Other medications		
Acetylsalicylic acid	136	78.6
Progestin	30	17.3
Levothyroxine	3	1.7
Pregnancy outcome		
Unsuccessful	22	12.7
Successful	151	87.3

3.6.2 Prevalence of genetic polymorphisms and mutations related to enzymes, proteins, and other factors affecting blood coagulation

In this study, heterozygous MTHFR (C677T) was the most commonly prevalent (35.3) genetic polymorphism \ mutation among the women, followed by heterozygous factor v Leiden and heterozygous MTHFR (A1298C) with the same percentage (32.9). the prevalence of genetic polymorphisms \ mutations related to enzymes, proteins, and other factors that affected blood coagulation is shown in Table C5 (in appendix C).

3.6.3 Associations between the variables of the women, pregnancy outcomes, dose of enoxaparin, and use of other medications

Of the women, 151 (87.3%) had successful pregnancies and 22 (12.7%) had unsuccessful pregnancies. There was a significant rend in successful pregnancies over the study period as shown in Table 10.

Table 10

Pregnancy outcomes over the study period

		Pregnancy				
		Unsuccessful		Successful		
Variable	Category	n	%	n	%	p-value
Year	2019	4	2.3	18	10.4	0.006
	2020	4	2.3	20	11.6	
	2021	9	5.2	21	12.1	
	2022	3	1.7	38	22.0	
	2023	2	1.2	54	31.2	

3.6.4 Association between abortion \ IVF pregnancy, year, multiparity, and genetic polymorphisms\ mutations.

The women who had multiparity were significantly older than the women who had a single birth (32.9 ± 4.9 vs 26.5 ± 5.0 years, p-value < 0.001). On the other hand, the women who received progestins were significantly younger than those who did not receive progestins (27.2 ± 6.5 vs 29.7 ± 5.7 years, p-value = 0.034).

There was an increasing trend in abortions and in vitro fertilization pregnancy over the study period (p-value = 0.002). Similarly, the women who had homozygous MTHFR (A1298C), I/D ACE, 4/5G PAI, and 1a/1a HPA polymorphisms/mutations were more likely to have in vitro fertilization pregnancy. On the other hand, the women who had multiparity were more likely to have abortions. These associations are shown in Table 7.

3.6.5 Associations between dose of enoxaparin, year, and genetic polymorphisms/mutations

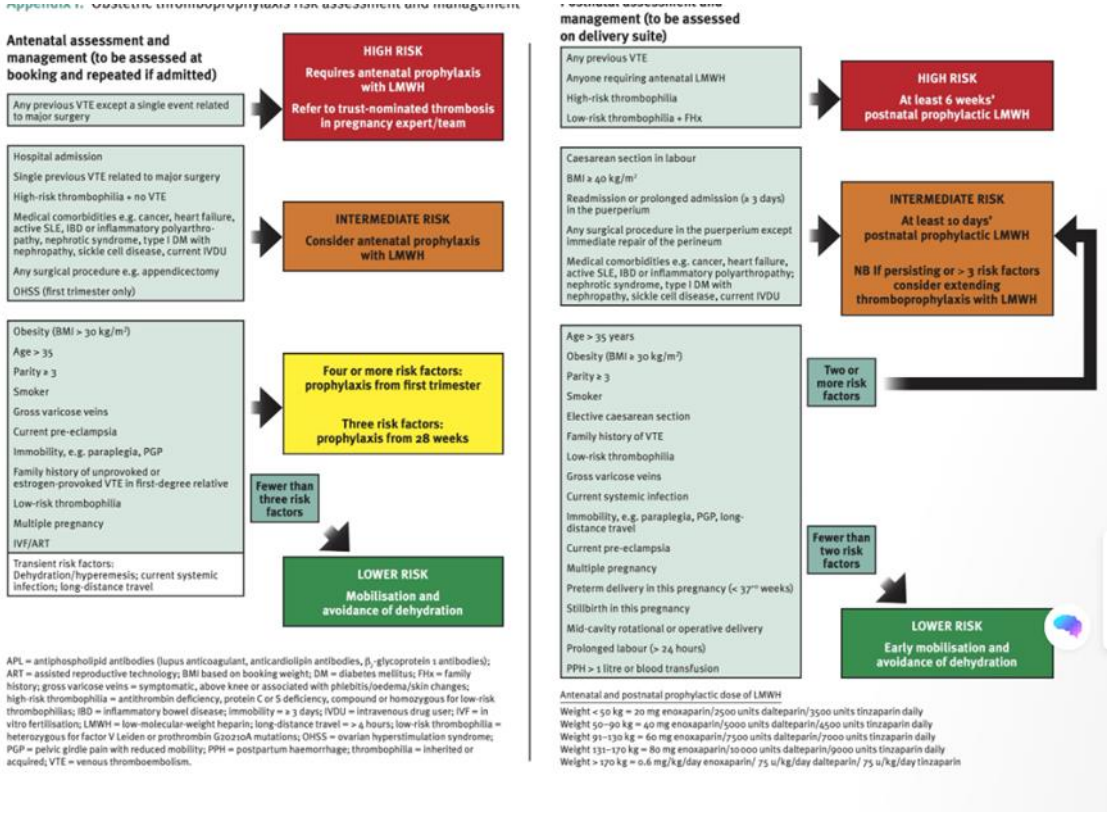
There was an increasing trend in receiving enoxaparin at a dose of 80 mg and being ordered to divide the dose because of the unavailability of 40 mg doses over the study period. Similarly, the women who had heterozygous fibrinogen polymorphisms/mutations were more likely to have received enoxaparin at a dose of 80 mg and were ordered to divide the dose because of the unavailability of 40 mg doses. These associations are shown in Table 8.

3.6.6 Association between the use of aspirin and genetic polymorphisms\ mutations

The women who had homozygous MTHFR (A1298C) were less likely to receive acetylsalicylic acid as shown in Table C 8 (in appendix C).

Figure 5

Guidelines of use enoxaparin postpartum



Chapter Four

Discussion and Conclusion

4.1 Discussion

Nowadays, cardiovascular disease and thromboembolic events are the leading cause of death worldwide (18). Anticoagulants are increasingly used in the prevention and treatment of thromboembolic events associated with atrial fibrillation (AF), venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE) (80). In orthopedic departments, anticoagulants are frequently used in orthopedic surgery such as hip replacement and bone fracture as a prophylaxis from thromboembolism such as PE. In gynecology, anticoagulants are commonly used in pregnant women who have a high risk for thrombosis or have multiple miscarriages due to thrombosis (18).

Anticoagulants including heparin, LMWH (enoxaparin), warfarin, and the newer oral anticoagulants such as rivaroxaban and dabigatran, among others, are commonly prescribed in different clinical settings for a variety of clinical indications (18).

This retrospective study was conducted to evaluate trends in prescribing oral and parenteral anticoagulants in different Palestinian hospitals, identifying the most commonly prescribed oral and parenteral anticoagulants and determining the prescription of oral and parenteral anticoagulants in different conditions in the period between (2019-2023).

It is noticeable that the prescriptions rate of the anticoagulant has increased for in- and outpatients at the Palestinian hospitals, but unfortunately no studies were done in our country until this moment to assess the direction of prescribing these drugs, but globally this phenomenon has been studied in various countries such as England, China and others. In England, this topic was studied and published in 2021 to evaluate the prescribing pattern of the direct oral anticoagulants (DOACs) and warfarin, cost implication of the increasing prescribing DOACs and reporting the side effect between 2009-2019 and they also compared the prescribing trends of four DOACs and warfarin to better understand the regional differences in DOACs prescribing, the prescribing of DOACs (compared to total anticoagulants) has increased from 16% in 2015 to 62% in 2019, in contrast, warfarin prescribing has declined since 2015, so this study has noticed

an increase in the general use of anticoagulants over the years and the prescribing of DOACs has excessed warfarin prescription (80). Other study that similar to those in England was done in China, the study included a total of 189,006 prescriptions of 67 hospital in 6 years and showed that warfarin prescription has decreased, 92% of cost for DOACs and the most common used of DOACs was rivaroxaban and dabigatran, as an end result, the used of DOACs has increased rapidly, so they recommend to increase the attention on the use of DOACs(18). Also, in five years just, the prescribing of DOACs was increased from 9% to 74%, while warfarin was declined from 91% to 26% in English primary care, this is maybe not only due to switching of existing patients, but also from initiation of newly diagnosed patients on these medications, So, the total prescriptions of anticoagulant was nearly doubled from the approval of DOACs until 2019 (79).

In June 2022, the meta-analysis study that was published in Scopus concluded that the proportion of oral anticoagulants use worldwide almost doubled following DOACs introduction (81). These studies demonstrated just trends of oral anticoagulants, but our study demonstrated two forms of anticoagulants, oral form and injectable form, so it is the first study that conducted two forms of anticoagulant.

The choice of anticoagulant has a financial implication such as number of hospitalizations, serious side effect, monitoring tests of warfarin and others, that maybe lead to form a heavy burden to MOH and patient itself. According to one of cost effectiveness study of oral anticoagulant that done in South Korea, the DOACs were the most cost effective than warfarin in many cases (85).

Our study includes 5121 patients from different regions of the West Bank, including northern, center, and southern regions. Of the patients, 4,172 (81.5%) were female, which explains the low percentage of smokers in the sample (3.5%) because in our country the majority of smokers are men, not women.

The mean age of the patients was 39.4 ± 18.0 years, which means that the majority of the sample was within youth age, this is due to the majority of the population (more than half) were postpartum women and pregnant women (in reproductive age), 1.4% of the sample with the age < 18 years, these represent younger patients who have

undergone orthopedic surgery or cystectomy, the rest of sample are older age (50->65) who have multiple diseases and need to management by anticoagulants.

This study demonstrated the rising trend in both injectable anticoagulants including enoxaparin and heparin and oral anticoagulants including warfarin and NOAC (rivaroxaban, dabigatran, and apixaban). In the west bank, with regard to injectable form, enoxaparin prescriptions have climbed dramatically since 2019 and heparin prescriptions have remained steady**,** regarding oral form (NOAC), warfarin has been steadily declining since 2020, however NOAC has surged dramatically since 2020, rivaroxaban was the most common prescribed of NOAC followed by apixaban, while dabigatran was the least common prescribed of NOAC **.**

Of all samples, 203 patients were prescribed oral anticoagulants (warfarin, rivaroxaban, apixaban, and dabigatran) as an outpatient anticoagulant, majority of them prescribed inpatients injectable anticoagulants (enoxaparin or heparin), 128 (63%) prescribed rivaroxaban, 54 (26.6%) prescribed apixaban, 18 (8%) prescribed warfarin and the rest prescribed dabigatran 3 (1.4%).

The first part of our study was included patients diagnosed with cardiovascular and thromboembolism disease mainly, these were used to evaluate the trends of prescribing oral anticoagulants, the old one warfarin and the newer NOAC (apixaban, rivaroxaban, and dabigatran). The results showed the rising trends in overall prescriptions for NOACs. warfarin has been steadily declining since 2020. however, NOAC have surged dramatically since 2020, rivaroxaban was the most commonly prescribed of NOAC followed by apixaban, while dabigatran was the least commonly prescribed of NOAC (Figure 1B). Of all samples, 128 (2.5%) received rivaroxaban, 54 (1.1%) received apixaban, 18 (0.4%) received warfarin, and 3 (0.1%) received dabigatran. Previous Studies have been done taking into account the patterns of OAC usage in various nations and areas. Similar patterns of sharply rising NOAC use were noted in the decade following their introduction, demonstrating the widespread acceptance and preference of clinicians for NOAC use worldwide due to improved safety profile and ease of use rather than warfarin (86).

Many thromboembolic conditions are prevented and treated using oral anticoagulants, (either warfarin or NOAC), such as AF, VTE (DVT OR PE), prosthetic heart valves, post orthopedic surgery (hip or knee replacement), peripheral vascular disease and acute coronary syndrome (12, 17, 66, 71). These conditions are more common in advanced age, and many studies showed the prevalence of these conditions was higher in older ages. For example, a study that was published in 2023 showed that both AF prevalence (6.4% at 65-69 years to 28.5% at ≥85 years) and incidence (14.2 per 1000 PY at 65-69 years to 50.8 per 1000 PY at ≥85 years) increased with age (87). Therefore, it is typical that the majority of usage of these medicines are in the older age group, which our study was indicated, as the T Test showed in warfarin, rivaroxaban, apixaban, and dabigatran, t-tests showed that the patients who were prescribed rivaroxaban were significantly older than those who have not prescribed rivaroxaban (59.2 ± 18.2 vs 38.9 ± 17.7 years, p-value < 0.001), t-tests, showed that the patients who were prescribed apixaban were significantly older than those who have not prescribed apixaban (66.1 ± 16.1 vs 39.1 ± 17.8 years, p-value < 0.001), t-tests, showed that the patients who were prescribed warfarin were significantly older than those who were not prescribed warfarin (51.3 ± 17.6 vs 39.4 ± 18.0 years, p-value = 0.005), t-tests, showed that the patients who were prescribed dabigatran were significantly older than those who have not prescribed dabigatran (64.0 ± 13.0 vs 39.4 ± 18.0 years, p-value = 0.018).

Over the past few decades, the usage of oral anticoagulants (OACs) has changed dramatically in response to new health issues, modifications to clinical practice recommendations, and advancements in drug research (79, 86). The rising usage of direct oral anticoagulants (DOACs) such as rivaroxaban, apixaban, and dabigatran over traditional medications like warfarin was part of our study, which evaluated trends of OAC prescriptions. Switch to DOACs from Warfarin.

In the past, warfarin dominated the anticoagulant treatment market for conditions such as venous thromboembolism (VTE), atrial fibrillation (AF), and patients with artificial heart valves. Nonetheless, the usage of DOACs has grown significantly in recent years. There are various reasons for this change, The first one is a better safety profile, when compared to warfarin, DOACs are linked to less cerebral hemorrhages and bleeding problems (12). They are easier to use, especially in outpatient settings, because they don't require frequent INR monitoring and have consistent dosages (10). The 2nd is

convenience, because DOACs have predictable pharmacokinetics and don't require routine laboratory testing, they are more convenient for patients and healthcare professionals than warfarin, which necessitates frequent monitoring and dietary restrictions (12). The last one is clinical Efficacy, Numerous extensive studies (such as ROCKET-AF and ARISTOTLE) have shown that DOACs are as effective as warfarin in lowering the risk of stroke and systemic embolism in individuals with atrial fibrillation while also lowering the risk of bleeding. DOAC adoption has accelerated as a result of this body of evidence (88, 89).

Despite the lack of guidelines over the most recommended NOAC, our data showed since 2020, rivaroxaban has been prescribed more frequently than dabigatran and apixaban, which is consistent with studies from other nations (90). Except in 2022, the predominant prescribed is apixaban. Furthermore, rivaroxaban's strong marketing approach and promotion could have been a significant contributing cause to its commanding market dominance.

Although, its delayed market introduction, apixaban was the most prescribed NOAC in England and Norway (80). in contrast to our study's majority share of rivaroxaban. Furthermore, since NOACs are strongly recommended over warfarin in many treatment indications by current clinical guidelines and because patients who receive NOACs have been shown to have higher adherence and satisfaction than those who receive warfarin. It is anticipated that an increasing number of patients will be initially prescribed NOACs rather than warfarin (10, 12) .

In this investigation, the prescription volume of dabigatran was extremely low and minimally increased during the study period, while it is the first NOAC approved by the FDA. Several reasons play a role of why dabigatran is the least prescribed one, GI side effects, compared to some other NOACs, such as apixaban, dabigatran is linked to a higher risk of gastrointestinal (GI) side effects, specifically dyspepsia (indigestion) and an increased risk of GI hemorrhage (91). Requirements for dosage, Rivaroxaban and certain apixaban dosages can be taken once daily, while dabigatran must be taken twice daily, for long-term drug adherence, patients and prescribers frequently favor the simplicity of once-daily dosage. Renal clearance, Patients with renal impairment are less likely to benefit from dabigatran because it is mainly eliminated by the kidneys. The use of other NOACs, such as apixaban, is expanded since they are thought to be

safer for individuals with impaired renal function (92). Market competition, because apixaban and rivaroxaban have been more extensively promoted and some clinical trials have demonstrated their effectiveness and tolerability, doctors are more likely to choose them, so compared to other NOACs, dabigatran is given less frequently as a result of these variables as well as patient and provider preferences.

The data we analyzed covered the period through 2020 - 2021, which overlapped with the COVID-19 epidemic. Given the significant changes in clinical treatment throughout this time, this might have affected DOAC use rates, due to the high frequency of thrombotic consequences is a characteristic of (SARS-CoV-2) infections. Increased blood levels of coagulation activation and inflammatory markers are associated with the course of the disease. Prophylactic anticoagulation lowers the risk of thromboembolism in hospitalized COVID-19 patients (74, 77). the most prescribed NOAC for covid 19 was in our sample rivaroxaban, 17% of covid 19 patients were discharged on rivaroxaban. Apixaban was not prescribed for COVID-19 in our sample, this may be due to the small number of COVID-19 patients included in our study, the majority of COVID patients were referred to other hospitals, and these hospitals were not included in our data.

Regarding the demographic characteristics of patients who received rivaroxaban, the majority of patients were men, representing 61.7% of patients while 38.3 were women, this may be due to the different CVD prevalence of men and women, the incidence of CVD in women is usually lower than in men (93). and corresponds to the population of the ROCKET AF pivotal study of rivaroxaban, where 60% of patients were men (94).

As we described previously, during the study period, rivaroxaban was predominant except in 2022, it was noted that the use of apixaban was dominant, as we believe, the cause was the introductions of two local brands of apixaban, which allowed commercial competition to exist with the directions of describing oral anticoagulants.

According to our data, 46% of AF patients were prescribed apixaban, in comparison to 25% prescribed rivaroxaban and 7% for warfarin, For NVAF patients who accept twice-daily doses, observational evidence consistently favors apixaban over rivaroxaban and dabigatran as the preferred first choice DOAC (95). Apixaban is a good choice for long-term anticoagulation in NVAF patients due to its effectiveness and safety profile,

especially in lowering severe bleeding. This is reinforced by the recent introduction of affordable generic versions (95).

Clinical investigations like the EINSTEIN-DVT and EINSTEIN-PE studies have validated the widespread use of rivaroxaban in the treatment of VTE. Its widespread use, particularly in outpatient treatment settings, is a result of its once-daily dosing choice and convenience of administration (96). which is consistent with what was found in our study that 30% and 40% of DVT and PE respectively were described rivaroxaban while 19% and 30% were prescribed apixaban. However, current studies encourage the use of apixaban more than rivaroxaban due to its favorable safety profile (97).

Regarding orthopedic surgery, our data showed that 10% of them prescribed rivaroxaban while just 2% prescribed apixaban, this may be explained by the French study that observed differences between rivaroxaban and apixaban in orthopedic surgery and showed that rivaroxaban had a greater influence on routine coagulation tests and reduced the maximum thrombin concentration more efficiently (98).

Many studies showed that apixaban is the most preferable DOAC for stroke, due to the lower risk of intracranial hemorrhage compared to VKA and rivaroxaban (99). Our study showed that rivaroxaban is more commonly used in stroke than apixaban or warfarin at 6.5%, 3.95, and 1.3%, respectively. Preference for warfarin is already known and mentioned previously, but the preference for rivaroxaban over apixaban is not consistent with what was found in the studies. The possible reasons for these findings are, that stroke patients have swallowing issues after an attack and apixaban requires two times daily dosing, so, rivaroxaban is more convenient for patients. FDA approved rivaroxaban earlier than apixaban, this reason may play a role in the clinician's decision about what DOACs prescribe for stroke. another reason may be marketing competition and physicians' preferences.

Even in the absence of atrial fibrillation, patients with heart failure (HF) are known to be at risk for ischemic stroke and systemic embolism due to impaired left ventricular ejection fraction (LV-EF) (69). Anticoagulation treatments involving Vitamin K antagonists (VKA) proved inadequate since the risk of significant bleeding was greater than the potential benefit of reducing stroke (100). In patients with atrial fibrillation, non-vitamin K oral anticoagulants (NOACs) are a successful and generally safer

method of preventing strokes. NOACs may also have a favorable risk-benefit profile in patients with heart failure (101). While the more focused COMMANDER-HF trial was neutral on overall ischemia benefit, the COMPASS trial indicated a possible benefit for rivaroxaban in HF patients with sinus rhythm (100). our data showed the same percentage of HF patients (6%) were prescribed rivaroxaban or apixaban, while no one with HF was prescribed warfarin because they are more convenient (no need for monitoring), have fewer medication interactions, and have superior safety profiles (lower risk of bleeding), apixaban and rivaroxaban are becoming more and more popular over warfarin for anticoagulation in heart failure patients.

About heparin, Chi-square/Fisher's exact tests showed that the older patients had diabetes mellitus, hypertension, stroke, vascular disease, atrial fibrillation, pulmonary embolism, heart failure, pneumonia, chronic kidney disease, received acetylsalicylic acid, and those who died were more likely to have received heparin. On the other hand, the patients who were female, pregnant, had Cesarean section, had delivery, tested thrombophilia positive, and those who received anticoagulants lately were less likely to receive heparin compared to the other patients, in addition, t-tests, showed that the patients who were prescribed heparin were significantly older than those who were not prescribed heparin (63.4 ± 16.6 vs. 38.8 ± 17.7 years, p-value < 0.001). these results were in harmony with the CVD and critical conditions are more common in older populations due to many physiological changes, these conditions are more related to the male sex group rather than female. So, for several reasons, including safety in cases of renal failure, its ease of dosage adjustment, and its capacity to rapidly reverse its impact in the event of bleeding, heparin is recommended among the elderly. It is a solid and dependable choice for this age group because it can be used to treat a variety of serious medical disorders that older people face.

The second part of this study discusses the prescription pattern of enoxaparin in the obstetric population. Prescription trends of enoxaparin were rising mainly in two populations that I have studied. The first was a pregnant women population with a risk of thrombosis like thrombophilia mutation that causes recurrent miscarriage, and the second was a post-partum population.

Two or more consecutive spontaneous miscarriages that typically happen before 20 weeks of gestation are known as recurrent pregnancy loss (RPL). The estimated prevalence of RPL in women of reproductive age ranges from 0.5% to 3.0%, making it a prevalent and complex disorder (34). Because of the condition's variability, the cause of RPL is poorly understood and difficult to identify. Parental chromosomal abnormalities, anatomical abnormalities, thrombophilia, endocrinological problems, immunological variables, and nutrition/environmental factors are all probable causes of RPL. However, only 50% of individuals have these causes identified, and the other 50% are still unknown (35).

Early pregnancy requires a delicate equilibrium between coagulation and fibrinolysis, and thrombophilia has been suggested as a factor in the pathophysiology of RPL. Procoagulant factors rise and anticoagulant levels fall during pregnancy, making it hypercoagulable. Numerous obstetric problems, including RPL, stillbirth, fetal development restriction, preeclampsia, and placental abruption, are linked to inherited thrombophilia (33).

An estimated 50% of VTE cases during pregnancy and the postpartum period are thought to be related to thrombophilia. Pregnancy-related VTE episodes and hereditary thrombophilia are known to have major implications for both the mother and the fetus (38).

Numerous studies have reported associations between RPL and thrombophilia, which include acquired conditions like antiphospholipid antibodies and patients who produce lupus anticoagulants, as well as hereditary conditions linked to deficiencies in natural coagulation inhibitors (antithrombin III, protein S, and protein C) or mutations in the factor v Leiden genes or prothrombin (38).

The FVL mutation causes the single amino acid replacement Arg506Gln, which makes the protein resistant to cleavage and, consequently, inactivated by activated protein C (APC) and increases susceptibility to clotting (42). Homozygote carriers of this mutation have a 50–100 times increased risk of venous thrombosis. Plasma prothrombin levels are raised by the prothrombin gene mutation (G20210A). The blood-clotting system may then become unbalanced as a result. A mutation in the prothrombin G20210A gene greatly raises the likelihood of venous thrombophilia, which may lead to

placental thrombosis and infarction. Owing to inadequate uteroplacental perfusion, this condition raises the chance of miscarriage (46). Many studies around the world showed that there is a significant association between factor v Leiden and prothrombin mutation (102, 103).

The LMWH (enoxaparin) is the favorable anticoagulant that is commonly used in pregnant women with thrombophilia mutation during pregnancy and post-partum, other anticoagulants such as heparin and warfarin are not recommended in pregnancy due to fetal and maternal comorbidities (52, 53).

Our finding shows that the Enoxaparin use in pregnant thrombophilia patients has increased between 2019 – 2023 due to the increasing thrombophilia mutation among pregnant women in this period. which requires using enoxaparin as a prophylaxis to prevent any maternal comorbidities related to thrombophilia mutation. The thrombophilia panel mutation in pregnancy is required upon certain comorbidities, such as a history of VTE or three subsequent miscarriages (22, 51).

In our study, we had a percentage of women who have had a single abortion and have no past maternal comorbidities such as fetal death (15.6%), (8.6%) respectively; however, they were asked to do a thrombophilia panel. Therefore, we assumed that the reason for the increase in thrombophilia mutation among pregnant women in West Bank was over screening of the thrombophilia panel. The over screening of the thrombophilia panel included not only whom to do the thrombophilia panel but also what are the genes that must be tested in this panel. The genes that play a role in thrombosis risk for pregnant women if they have a mutation are factor v Leiden and prothrombin (mentioned above), (congenital thrombophilia is associated with early and recurrent thrombosis and increased risk of thrombosis, particularly if combined with additional factors , Factor V Leiden accounts for 40–50% of thrombosis, and prothrombin G20210A is considered the second most common cause of genetic mutation causing thrombophilia (39, 102, 103). When one of them is homozygous or combined two heterozygous. so the test panel must contain a gene that is mentioned above and Protein C functional activity level, Protein S free, total, and functional levels, and Antithrombin-heparin cofactor assay (22).

In the thrombophilia panel for our sample, the 8 gene mutations were included in addition to factor v Leiden and prothrombin, the other genes are MTHFR, ACE, PAI, GPIIIa, ApoE, FXIII, HPA, and fibrinogen. our sample showed heterozygous MTHFR (C677T) was the most commonly prevalent (35.3%) genetic polymorphism \ mutation among the women, followed by heterozygous factor v Leiden and heterozygous MTHFR (A1298C) with the same percentage (32.9%). In comparison, homozygous factor v Leiden represented 5.2% of all samples, and heterozygous prothrombin was 5.9%. other genes including PAI, GPIIIa, HPA, ACE, factor v (H1299A), fibrinogen, FXIII, and APO E were found but have a smaller percentage . Another Palestinian study that observed the association between gene mutation and recurrent miscarriage showed that the MTHFR (C677T) is more prevalent than factor v Leiden which is constituted with our study.

So, this over screening which includes who is asked to do the test and what genes are included in the panel was responsible for increasing thrombophilia mutation among pregnant women. 61.3% of women who did the thrombophilia panel in our sample have other mutations rather than factor v Leiden and prothrombin. universal thrombophilia screening is not recommended and recommendations for which clinical subgroups should undergo screening vary nationally and internationally (84)

Regarding fibrinogen and HPA genes, a study done in Gaza in 2014 showed that the prevalence of RPL in the Gaza Strip is not significantly correlated with frequent polymorphisms in Integrin beta-3 (PLA1/A2) (HPA) or β-fibrinogen (455 G>A). This nonsignificant relationship suggests that there is no real risk of RPL in this cohort from the examined SNPs. Therefore, while screening for hereditary thrombophilia in the Gaza Strip, it is not advised to take these two polymorphisms into account (104). Other study also showed there is no significant association was observed between *GPIIIa* polymorphism and recurrent pregnancy loss (RPL) (105).

Methylenetetrahydrofolate reductase (*MTHFR*) is a major regulatory enzyme in the metabolism of homocysteine that catalyzes the reduction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, C677T and A1298C mutations are the two most common mutations within the MTHFR gene. Although MTHFR C677T and A1298C mutations' involvement in RPL is still up for controversy and not fully understood. In Korean women, the MTHFR gene polymorphisms C677T and

A1298C are not linked to idiopathic RPL, indicating that they may not be vulnerable allelic variations or deficiencies that result in RPL (106). According to the Indian study findings, there is no correlation between PE and RPL risk and the MTHFR gene (A1298C). There is a notable correlation between the derived allele and (C677T) (107).

In September 2020, a Turkish study revealed that there is insufficient evidence to support the use of LMWH to prevent adverse perinatal outcomes in MTHFR polymorphism-related thrombophilia worldwide. Empirical therapy using prophylactic doses of LMWH is becoming trending in Turkish clinical practice, and they showed that enoxaparin is not required to improve pregnancy outcomes in cases of homozygous and heterozygous MTHFR polymorphism-related pregnancy loss (108). They also suggested that folic acid is sufficient in these cases, as stated by international guidelines for both preventing adverse outcomes of MTHFR polymorphisms and reducing neural tube defects.

As we mentioned, the extensive test of thrombophilia gene mutations during pregnancy commonly termed “over-screening”, sparked controversy regarding its necessity, efficacy, and associated risks (84). Many implications are related to over-screening of thrombophilia, 1st one is the lack of clear clinical advantages, routine thrombophilia mutation for all pregnant women is not fully supported by current data (109, 110). in many cases, as we mentioned, the thrombophilia gene mutation does not necessitate lead to maternal or fetal complications. 2nd one is psychological and financial issues. excessive stress caused by over-screening for women who test positive mutations but may not develop any pregnancy problems, and the cost of genetic testing and long-term enoxaparin treatment can cause an economic burden on patients themselves and the Ministry of Health without any clear benefits. if patients are insured, the burden on MOH, and if not insured, the burden on patients themselves and the cost of these tests and treatments are expensive.

So, without clear clinical indications, there are more implications and disadvantages than advantages to over-screening thrombophilia gene mutation during pregnancy. The screening is more beneficial for high-risk groups (multiple miscarriages, history of VTE) to avoid unnecessary anxiety, economic burden, and unwarranted medical intervention (enoxaparin). More studies are needed to improve criteria for screening and treatments throughout pregnancy.

Other hypothesis that may also play a role in increasing thrombophilia mutation in pregnancy are including covid 19 and using oral contraceptives. According to many studies, the global use of OCP was highly increasing (111), and the use of combined oral contraceptives (COCs) has been linked to a higher risk of venous thromboembolism (VTE), with a greater incidence observed among women who have inherited thrombophilia. According to current WHO guidelines, there is an unacceptable danger to the health of women who have genetic thrombophilia (antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden, and prothrombin mutation). (112).

Regarding covid 19 and thrombophilia, when compared to moderate COVID-19 instances, heterozygous mutations for all the genes under study were substantially more common in adults and children with severe COVID-19. Furthermore, patients with severe illness have been observed to exhibit higher activity in factor V. The association between factor V Leiden mutation carriers and digital vein thrombosis in COVID-19 patients demonstrated significant inflammation caused by the virus, which in turn led to endothelial dysfunction and thrombosis (113). Similarly, it was discovered that a mutation in the prothrombin gene was linked to a higher risk of thrombosis in related to covid 19 (114). Severe COVID-19 and inherited thrombophilia are clearly related; patients with thrombophilia had considerably higher D-dimer values than those without discernible genetic thrombophilia, the FV gene mutation carries the highest risk of getting a severe (115).

Our results showed that there was an increasing trend in abortions and in vitro fertilization pregnancy over the study period (p-value = 0.002), the increasing trends in abortion and IVF were related to increasing trends of thrombophilia mutation as we mentioned above. 79.8% of pregnant women who were prescribed enoxaparin during pregnancy had an abortion, 11.6% had an IVF pregnancy and the rest was distributed to have a vascular disease such as varicose vein, HTN, lupus anticoagulant and ischemic stroke. both abortion and IVF populations were prescribed enoxaparin in related to thrombophilia gene status. The women who had multiparity were more likely to have abortions, which makes sense. The women who had multiparity would not have a fertility problem, so they do not need to IVF, but may have abortion due to activate

asymptomatic thrombophilic mutation over years by factors such as covid 19 and using OCP which are mentioned above.

Previous studies showed the relation between gene mutation and infertility that including MTHFR C677T, factor v Leiden, PAI -1 4G\5G and I\D ACE (55) (56) (57), that in comparison to normal women, women who had recurrent IVF failures had a higher prevalence of hereditary thrombophilia and the MTHFR C677T mutation and the Factor V Leiden mutation were substantially more common in the group of IVF failure cases, the exact mechanism by which thrombophilia affects IVF failure is yet undetermined, but we have a possible mechanism such as the thrombosis of maternal arteries, which lowers intervillous space perfusion and results in IVF failure, may be a contributing factor. Nevertheless, additional processes could also be at play, such as chorionic or decidual artery injury or a decrease in trophoblast invasiveness (116). The PAI-1 4G/5G polymorphism is a possible screening factor that may be used to target some cases of female infertility that are not explained. The 4G allele is associated with this, and it may be the result of improper implantation, but the exact mechanism is still controversial (117), Through the fibrinolytic pathway, the renin-angiotensin-aldosterone system (RAAS) either directly or indirectly causes preeclampsia and thrombophilia, which in turn induces RPL or infertility. The ACE gene I/D polymorphism is the common link in these pathways; however, the underlying mechanisms of this relationship are still unknown (118). our findings show that the women who had homozygous MTHFR (A1298C), I/D ACE, 4/5G PAI, and 1a/1a HPA polymorphisms/mutations were more likely to have in vitro fertilization pregnancy, so my explanation for the difference between our study results and what is found in the literature is due to the small sample studied (just 20 IVF case (11.6%)), so we need more studies in this field to investigate it.

LMWH (enoxaparin) dose that mainly used in thrombophilic pregnant women was a prophylactic dose which mainly used once daily and calculated by the body weight, so the most common used dose was 40. Our study showed that a high percentage of the women (31.8%) received enoxaparin at a dose of 80 mg and were ordered to divide the dose because of the unavailability of 40 mg doses in the health care centers, which have many clinical consequences. Reusing enoxaparin injections carries several risks, such as infection, blunts needle and incorrect dosage, and maybe lead to bacterial

contamination, so resulting localized infection (119). on the other hand, these reusing also could cause under or over dose, because enoxaparin syringe is prefilled with a specific dose, when it is divided, it results in improper dosing which leads to either subtherapeutic anticoagulation or excessive dosing which might lead to increasing the risk of bleeding. in addition to, reusing enoxaparin injections could cause blunts needle which cause pain and tissue damage.

During pregnancy, low-dose aspirin has been used, mostly in order to prevent the onset of preeclampsia (120). In the Hypertension in Pregnancy Group's Report, the American College of Obstetricians and Gynecologists advised women who had a history of early-onset preeclampsia and preterm delivery at less than 34 0/7 weeks of gestation, or who had more than one previous pregnancy complicated by preeclampsia, to start taking daily low-dose aspirin starting in the late first trimester, Women who have more than one of many intermediate risk factors for preeclampsia should think about low-dose aspirin prophylaxis. The presence of one or more high-risk variables (preeclampsia history, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes, and chronic hypertension) defines women at risk of preeclampsia. Current research does not support the use of prophylactic low-dose aspirin for the prevention of early pregnancy loss, fetal growth restriction, stillbirth, or premature birth in the absence of significant risk factors for preeclampsia (121).

But, Our data showed high percentage of thrombophilic pregnant women (78.6%) taking aspirin of anti-platelet dose in combination with anticoagulant (enoxaparin), 8% of them have a history of fetal death, 2.3% has history of preeclampsia, 4% has HTN, 1.1% has vascular disease, 1.7 % has previous neonatal death,2.3 has preterm birth and 1.1% has GDM, the rest of percentage has no any past medical histories or comorbidities rather than abortions. This high percentage (78.6), which does not much consistent with what is found in literature, refers to what the obstetric specialists think that they have to prevent any chance of complications related to thrombophilia mutation especially preeclampsia, fetal death and placental abruption. Preeclampsia is one of the major causes of maternal and fetal morbidity and mortality, one of the studies reported that the prevalence of 67% of some forms of thrombophilia in patients with severe preeclampsia versus 20% in controls (122).

As we mentioned above, one of the main use of ASA in pregnancy was to prevent or manage preeclampsia and gestational HTN, our data represented that the women who had homozygous MTHFR (A1298C) were less likely to received acetylsalicylic acid (p value (0.043) as shown in , this result could explained with the Pakistani study that observe that there is a significant correlation between the polymorphism of MTHFR (A1298C) and reduced susceptibility toward preeclampsia and also it play a preventive role against the development of preeclampsia (123), other meta-analysis suggest that the MTHFR (C677T) rather than MTHFR (A1298C), polymorphism maybe associated with HTN and GHTN (124), so these studies support the finding related to MTHFR (A1298C) and using ASA that observed in our data.

The live birth percentage of thrombophilic pregnant women which was prescribed enoxaparin in this study was 87.3 which is compatible with previous studies with a live birth percentage 86% (125), the rest of the data 12.7% have unsuccessful pregnancies because multi factor could cause miscarriage rather than thrombophilia mutation such as chromosomal, endocrine and anatomical abnormalities.

The women who had multiparity were significantly older than the women who had a single birth (32.9 ± 4.9 vs 26.5 ± 5.0 years, p-value < 0.001), which is make sense.

The second group in which there is an increased of prescribed enoxaparin over the study period are post-partum women, either post caesarean and post vaginal delivery . According to previous studies, there is estimated that 1 to 2 cases of venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary thromboembolism, occur for each 1,000 deliveries.1-3 Compared to their non-pregnant counterparts, pregnant and postpartum patients are four to five times more likely to have VTE.3-5 Venous thromboembolism has significantly contributed to maternal morbidity and death, accounting for 9% to 10% of maternal mortality during the past 20 years (126). A hypercoagulable state, increased venous stasis, compression of the inferior vena cava and pelvic veins as the gravid uterus enlarges, decreased mobility, and other physiological changes of pregnancy increase the risk of VTE even in the absence of other risk factors, but pregnant patients are still at high risk for VTE during pregnancy and the postpartum period (3). The risk of VTE is increased by certain pregnancy problems and comorbidities, such as cesarean delivery, especially if postpartum hemorrhage or a puerperal infection are present. medical conditions like diabetes,

obesity, sickle cell disease, hypertension, heart disease, and systemic lupus erythematosus, as well as obstetric issues such multiple pregnancies and preeclampsia (126).

The American College of Chest Physicians, the Royal College of Obstetricians and Gynecologists (RCOG), the Society for Maternal-Fetal Medicine, the American College of Obstetricians and Gynecologists (ACOG), and advise applying these risk indicators in a risk-stratified manner to direct the proper use of postpartum chemoprophylaxis. These recommendations are based on observational data and expert opinion because there weren't any randomized clinical research discussing the proper prophylactic anticoagulation for postpartum patients (82) . According to RCOG guidelines, there are a risk factors that make decision about to use or do not use thromboprophylaxis (mainly enoxaparin) of the post-partum population and this guideline has classified the post-partum women into 3 groups, high, intermediate and low risk based on the risk factors, detailed RCOG guidelines**.**

Chi-square/Fisher's exact tests showed that the patients who had hypertension, diabetes mellitus, diabetic foot ulcer, vascular disease, and chronic kidney disease were less likely to be prescribed enoxaparin compared to the patients who did not have these diseases. 55% of post cs women who have prescribed enoxaparin and 93% of post-vaginal delivery women who were prescribed enoxaparin are have no any past medical histories, comorbidities or past surgical histories, which is responsible for increased prescribed enoxaparin. The increased prescribing enoxaparin post-partum in low risk patient or patients with no medical comorbidities may be lead to increase adverse effect with no increased benefit of VTE prophylaxis and this information was confined by the US study that was conducted in 2024 (compare the frequency of post-partum bleeding complications and VTE between the original protocol and the more selective protocol) , which showed that using a risk-stratified protocol for enoxaparin use (like RCOG OR ACOG) was linked to a two-fold higher risk of wound hematomas (0.7% vs. 0.4%; adjusted odds ratio [OR], 2.34; 95% CI, 1.54-3.57), as well as higher odds of unintended surgery and blood transfusions without a noticeable reduction in VTE (0.1% vs. 0.1%; OR, 1.0; 95% CI, 0.5-2.1), while Using an a more selective risk-stratified approach of post-partum thromboprophylaxis for VTE was linked to a decrease in any wound hematoma (0.7%vs0.3%;adjusted odds ratio[OR],0.38;95%CI,0.21-0.67),

specifically due to a lower rate of superficial wound hematomas (0.6%vs0.3%;aOR,0.43;95%CI, 0.24-0.75). There was no significant increase in VTE or individual types of VTE (0.1% vs 0.1%; aOR,0.40;95%CI,0.12-1.36) (71). (82)

Other studies also conducted this topic like Ferresetal and Kotaska, according to a study by Ferresetal that found a significantly higher rate of wound separation (6.8% vs. 3.6%) in patients receiving chemoprophylaxis after the implementation of an institutional practice guideline for postoperative thromboprophylaxis in 2509 patients undergoing cesarean sections and there was not a significant difference in VTE or thromboembolism between patients receiving and not receiving prophylactic anticoagulation (83). The advice for increased use of postpartum chemoprophylaxis was further questioned in a more recent publication by Kotaska. These authors concluded that while postpartum chemotherapy is recommended for patients who are at a high risk of developing postpartum VTE, doctors should exercise caution in lower-risk populations because there is insufficient information about the benefits and potential risks (127).

Also, Dr Cochrane's challenge has a practical and ethical basis. The drug cost for 7 days of enoxaparin is approximately £22 in the UK and $100 in the USA, yielding a drug cost to prevent one VTE between £80,000 and $400,000, not including the costs of administration and treating complications. Ethically, the probability of net harm from LMWH for most postpartum women makes it difficult to justify offering it outside a research trial. Dr Cochrane asserted that the net benefit of new therapies be proven in adequately powered RCTs before dissemination and Cochrane reviewers have concluded: ‘There is insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the early postnatal period. Large-scale, high-quality randomized trials of currently used interventions are warranted. Instead, guidelines recommend a costly, unproven, potentially harmful therapy in large numbers of birthing women. Without a power calculation, ethics approval, systematic measurement of benefit and harm, or truly informed patient consent, the specialty has embarked on an enormous uncontrolled experiment.

T-tests showed that the patients who were prescribed enoxaparin were significantly younger than those who were not prescribed enoxaparin (39.4 ± 18.0 vs. 50.1 ± 19.4, p-value = 0.021), this is because the majority of patients who taken enoxaparin are pregnant women or post-partum women.

In our opinion, more validation is required, preferably in a group of women who did not receive postpartum thromboprophylaxis and have no, low, or intermediate VTE risk factors. Finally, further research is needed to better understand patient experience and associated preferences and values in order to inform clinical practice recommendations and postpartum thromboprophylaxis research.

One of the most common drugs used in cardiovascular diseases is aspirin (ASA). It is used in the obstetric population for many comorbidities mentioned. Our study showed a decrease of ASA uses between 2020 – 2021 and then an increase was witnessed **.** I guess the reason for the decreasing use in 2020 – 2021 is that the patients with critical conditions who have taken or needed to be prescribed ASA were referred to other hospitals rather than the hospitals included in our study due to the COVID-19 pandemic.

4.2 strength of the study

The strength of our thesis about the trend of anticoagulant use is the ability to provide brilliant observations of the prescribing pattern and clinical practice changes. Evaluating trends of anticoagulants is useful for public health and clinical decision-making, our study focuses on the shifts and increased use of anticoagulants such as the growing preference for DOAC over warfarin and enoxaparin increasing use among the obstetric population.

Our data was based on hospitals and healthcare centers data that represent real-world data, so it reflects actual patterns of prescribing and gives a picture of how anticoagulant use across different patient populations and healthcare settings, these findings can directly influence clinical settings and future practice.

Evaluating the trend of anticoagulant use in our study was on over time, so we can identify when newer agents replacing warfarin. All of these provide a broad framework for understanding and evaluating the impact of oral anticoagulants in clinical practice.

4.3 limitations of the study

Even though our thesis can provide valuable insights, however, several limitations should be mentioned. First, it should be taken into consideration that many private hospitals were not included in our sample and these hospitals may provide large databases, second, some patients stop taking their medications if they experience side effects such as bleeding and go to the doctors private clinics not to the hospital where the drugs were prescribed, third, the pattern of anticoagulants discontinuation, interruption, and switching were very complex, therefore it would be difficult to adequately adjust for the effect of these on clinical events and these changes or patients follow up almost done in private clinics as we mentioned, this will lead to missing data, fourth, we use electronic health record and these may have missing data (incomplete patients record or missing follow up data), fifth, during the five years study period, many changes occurred such as clinical guidelines, drugs availability, drug cost and specialist preference, which all influence the pattern of anticoagulants prescription, sixth, given the retrospective nature of the study, we were unable to evaluate causality or fully address confounding .

Finally, exposure to anticoagulants was assessed based on prescribing, not actual consumption, which may lead to exposure misclassification.

4.4 Conclusion

There has been a rapid increase in the prescribing of anticoagulants, over the last five years in the West Bank. In this retrospective cohort study, we observed a substantial shift in the use of OAC over the study period, with DOAC becoming overwhelmingly preferred over warfarin, largely due to their improved safety profile, fewer dietary restrictions, and no need for routine monitoring, rivaroxaban has emerged as preferred NOAC.

Regarding enoxaparin, there was observed increasing use in pregnant women with thrombophilia mutations due to an increasing number of women who have a thrombophilia gene mutation and postpartum women (post cesarean and post vaginally), using enoxaparin postpartum without any indications could cause a side effect without increasing the VTE prophylaxis.

In conclusion, with the potential to improve patient outcomes, the changing patterns in anticoagulant use are suggestive of a more significant shift in the treatment of thromboembolism disorder, nevertheless, to maximize anticoagulant treatment for patients, continued investigations and monitoring are required.

4.5 Recommendations

Future studies are warranted considering a change in the anticoagulant use on a larger scale as well as the rationale and influence factors on anticoagulant use and more studies are needed to explore other genetics modifiers of thrombophilia mutation and may explore the contractor observed concerning the points. More studies are needed to improve criteria for screening of thrombophilia gene mutations and treatments throughout pregnancy.

Specific studies also need to be done in the field of using enoxaparin postpartum to compare the side effects and efficacy of VTE prophylaxis in the low-risk patients' group. To evaluate the long-term safety and efficacy of oral anticoagulants in a variety of groups, more studies should concentrate on real-world data, to record uncommon adverse occurrences and guide clinical practice, this involves carrying out large observational studies and post-marketing surveillance.

We need multidisciplinary collaboration, to ensure an effective and well-coordinated approach to an anticoagulant medication, pharmacists, doctors, and specialists should work together more, in particular, pharmacists may be quite helpful in managing dose changes and keep looking for possible drug interactions. Future research should also focus on long-term outcomes associations with enoxaparin and OAC and cost-effectiveness.

List of Abbreviations

Abbreviation	Meaning
VTE	venous thromboembolism
DVT	deep vein thrombosis
PE	pulmonary embolism
AF	atrial fibrillation
DOACs	direct oral anticoagulants
NOACs	novel oral anticoagulants
VKA	vitamin K antagonist
FVL	factor v Leiden
MTHFR	Methylenetetrahydrofolate reductase
ACE	angiotensin-converting enzyme
PAI	plasminogen activator inhibitor
HPA	human plasminogen activator
GPIIIa	glycoprotein IIIa
APOE	apolipoprotein E

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Appendices

Appendix A

An-Najah National University Institutional Review Board (IRB) approval

An-Najah National University
Faculty of Medicine & Health Sciences
Institutional Review Board

جامعة النجاح الوطنية
كلية الطب وعلوم الصحة
لجنة اخلاقيات البحث العلمي

Ref: Mas. April. 2023/20

IRB Approval Letter

Title of Research:

Trends of anticoagulant prescription in different hospitals in the West Bank of Palestine: A retrospective study

Submitted by:
Sajeda Makhamra

Supervisor:
Ramzi Shawahna, Suhaib Hattab

Approved:
30th April, 2023

Your Study Title "**Trends of anticoagulant prescription in different hospitals in the West Bank ofPalestine: A retrospective stud**"reviewed by An-Najah National University IRB committee and was approved on 30th April, 2023

Hasan Fitian, MD

IRB Committee Chairman

IRB

Appendix B

Palestinian Ministry of Health approval

State of Palestine
Ministry of Health
Education in Health and Scientific
Research Unit

دولة فلسطين
وزارة الصحة
وحدة التعليم الصحي
والبحث العلمي

Ref.: .....
Date:.....

الرقم: ٢٠٢١/٣٤٩/٥٤٤
التاريخ: ٢٠٢١/٠٦/٢٠

عطوفة الوكيل المساعد المدير التنفيذي لمجمع فلسطين الطبي المحترم،،،
عطوفة الوكيل المساعد لشؤون الصحة العامة وصحة الاسرة المحترم،،،
عطوفة الوكيل المساعد لشؤون المستشفيات والطوارئ المحترم،،،
تحية واحترام،،

الموضوع: تسهيل مهمة بحث

يرجى تسهيل مهمة الطالبة ساجدة مخامرة، طالبة ماجستير علم الادوية- جامعة النجاح، في عمل بحث بعنوان:

اتجاهات وصف الأدوية المضادة للتخثر في المستشفيات المختلفة في الضفة الغربية من فلسطين: دراسة بأثر رجعي "

حيث ستقوم الطالبة بجمع معلومات من ملفات المرضى، وذلك في:

- مستشفى رفيديا- مستشفى عالية - مستشفى يطا - مستشفى دورا
- مستشفى المحتسب - مستشفى بيت جالا - مستشفى حلحول
- مجمع فلسطين الطبي
- مديريات الصحة في محافظات: الخليل – بيت لحم – رام الله – نابلس – يطا - دورا
- مجمع فلسطين الطبي

على ان يتم الالتزام بأساليب وأخلاقيات البحث العلمي، وعدم التعرض للمعلومات الشخصية للمرضى.
على ان يتم تزويد الوزارة بنسخة PDF من نتائج البحث، التعهد بعدم النشر لحين الحصول على موافقة الوزارة على نتائج البحث.

مع التحية،،

د. عبد الله القواسمي
رئيس وحدة التعليم الصحي والبحث العلمي

نسخة: النائب الاكاديمي المحترم/ جامعة النجاح

Telfax. 09-2333901 scientificresearch.de[illegible]il.com تلفاكس: 09-2333901

Appendix C

Tables of the study

Table C1

Place of patient residence

Place of residence		
Yatta	2938	57.4
Hebron	986	19.3
as-Samu	471	9.2
Dura	182	3.6
Halhul	131	2.6
ad-Dhahiriya	67	1.3
Bani Na'im	59	1.2
Tarqumiyah	53	1.0
Ithna	46	0.9
Fawwar	42	0.8
Sa'ir	37	0.7
Bethlehem	22	0.4
Beit Ummar	21	0.4
Beit Ula	10	0.2
Gaza	9	0.2
Surif	9	0.2
Ramallah	7	0.1
Beit Kahil	7	0.1
Arroub	5	0.1
Nuba	5	0.1
Beit Fajjar	3	0.06
Jericho	3	0.06
Nablus	2	0.04
Taffouh	2	0.04
Jerusalem	2	0.04
Deir Dibwan	1	0.02
Qalqilya	1	0.02

Table C2

Association between prescribing apixaban and variables of the patients

		Apixaban				
		No		Yes		
Variable	Category	n	%	n	%	p-value
Sex	Male	922	18.0	27	0.5	< 0.001
	Female	4145	80.9	27	0.5	
Age (years)	< 18	70	1.4	0	0.0	< 0.001
	18-30	2069	40.4	2	0.0	
	30-50	1688	33.0	6	0.1	
	50-65	641	12.5	18	0.4	
	≥ 65	599	11.7	28	0.5	
Year	2019	716	14.0	0	0.0	< 0.001
	2020	902	17.6	2	0.0	
	2021	939	18.3	9	0.2	
	2022	1134	22.1	19	0.4	
	2023	1376	26.9	24	0.5	
Diabetes mellitus	No	4302	84.0	34	0.7	< 0.001
	Yes	7. 65	14.9	20	0.4	
Hypertension	No	4200	82.0	28	0.5	< 0.001
	Yes	867	16.9	26	0.5	
Smoking	No	4895	95.6	48	0.9	0.010
	Yes	172	3.4	6	0.1	
Stroke	No	4848	94.7	45	0.9	0.001
	Yes	219	4.3	9	0.2	
Vascular disease	No	4582	89.5	34	0.7	< 0.001
	Yes	485	9.5	20	0.4	
Atrial fibrillation	No	5052	98.7	41	0.8	< 0.001
	Yes	15	0.3	13	0.3	
Deep venous thrombosis	No	5030	98.2	45	0.9	< 0.001
	Yes	37	0.7	9	0.2	
Pulmonary embolism	No	5060	98.8	51	1.0	< 0.001
	Yes	7	0.1	3	0.1	
Pregnancy	No	4719	92.1	54	1.1	0.050
	Yes	348	6.8	0	0.0	
Post a Cesarean section	No	2610	51.0	54	1.1	< 0.001
	Yes	2457	48.0	0	0.0	
Postpartum	No	4611	90.0	54	1.1	0.013
	Yes	456	8.9	0	0.0	
Orthopedic surgery	No	4712	92.0	45	0.9	0.013
	Yes	355	6.9	9	0.2	
Thrombophilia positive	No	4740	92.6	54	1.1	0.048
	Yes	327	6.4	0	0.0	
Heart failure	No	4904	95.8	43	0.8	< 0.001

	Yes	163	3.2	11	0.2	
Symptoms of heart attack	No	4503	87.9	42	0.8	0.010
	Yes	564	11.0	12	0.2	
Chronic kidney disease	No	4949	96.6	47	0.9	< 0.001
	Yes	118	2.3	7	0.1	
Chest pain	No	4935	96.4	49	1.0	0.014
	Yes	132	2.6	5	0.1	
Noncardiac chest pain	No	4935	96.4	49	1.0	0.014
	Yes	132	2.6	5	0.1	
Being discharged on proton pump inhibitors	No	5011	97.9	51	1.0	0.024
	Yes	56	1.1	3	0.1	
Acetylsalicylic acid	No	4524	88.3	32	0.6	< 0.001
	Yes	543	10.6	22	0.4	

Table C3

Prescription of anticoagulants and antiplatelet

Medication	n	%
Anticoagulant		
Injectable		
Enoxaparin	5106	99.7
Heparin	114	2.2
Oral		
Rivaroxaban	128	2.5
Apixaban	54	1.1
Warfarin	18	0.4
Dabigatran	3	0.1
Antiplatelet		
Acetylsalicylic acid	565	11.0

Table C4

Causes of death

Cause of death	n	%
Cardiopulmonary arrest	91	1.8
Sepsis/septic shock	29	0.6
Stroke	6	0.1
COVID-19	4	0.1

Table C5

Prevalence of genetic polymorphism and mutation related to enzyme, protein, and other factors affecting blood coagulation

#	Genetic polymorphisms and mutations	N	%
	1. MTHFR (Methylenetetrahydrofolate Reductase)		
	C677T Mutation:		
1	Heterozygous MTHFR (C677T)	61	35.3
2	Homozygous MTHFR (C677T)	19	11.0
	A1298C Mutation:		
3	Heterozygous MTHFR (A1298C)	57	32.9
4	Homozygous MTHFR (A1298C)	21	12.1
	Unspecified Mutation:		
5	Homozygous MTHFR	3	1.7
6	Heterozygous MTHFR	12	6.9
	2. ACE (Angiotensin-Converting Enzyme)		
	Insertion/Deletion Polymorphism:		
7	D/D ACE	25	14.5
8	I/D ACE	27	15.6
9	I/I ACE	7	4.0
	3. PAI (Plasminogen Activator Inhibitor)		
	4G/5G Polymorphism:		
10	4/5G PAI	3	1.7
11	5G PAI	3	1.7
12	5G/4G PAI	3	1.7
13	4G/5G PAI	5	2.9
14	4G/4G PAI	2	1.2
	Unspecified Type:		
15	Heterozygous PAI	55	31.8
16	Homozygous PAI	23	13.3
	4. Factor V (Leiden)		
	Leiden Mutations:		
17	Heterozygous FV Leiden	57	32.9
18	Homozygous FV Leiden	9	5.2
	Other Variants:		
19	Heterozygous FV (H1299A)	11	6.4
20	Heterozygous FV (H1299R)	14	8.1
	5. Fibrinogen		
	Variants:		
21	Heterozygous fibrinogen	47	27.2
	6. GPIIIa (Glycoprotein IIIa)		
	Polymorphisms:		
22	Heterozygous GPIIIa	28	16.2
23	Homozygous GPIIIa	5	2.9
24	1a/1a GPIIIa	3	1.7
	7. HPA (human plasminogen activator)		

	Polymorphisms:		
25	1a/1a HPA	48	27.7
26	1a/1b HPA	16	9.2
27	1b/1b HPA	3	1.7
28	1a HPA	6	3.5
29	1b HPA	1	0.6
30	Ia/Ib HPA	1	0.6
31	Homozygous HPA	1	0.6
32	Heterozygous HPA	3	1.7
	8. FXIII (Factor XIII)		
	Variants:		
33	Homozygous FXIII	2	1.2
34	Heterozygous FXIII	33	19.1
	9. Prothrombin		
	Mutations:		
35	Heterozygous prothrombin	12	6.9
36	Homozygous prothrombin	1	0.6
37	Prothrombin (above normal range)	1	0.6
	10. APOE (Apolipoprotein E)		
	Genotypes:		
38	E3/E3 APO E	2	1.2
39	E4/E4 APO E	1	0.6
40	E3/E4 APO E	1	0.6
	11. Protein C Deficiency		
	Deficiency:		
41	Protein C deficiency	1	0.6
42	Heterozygous 5-methyltetrahydrofolate-homocysteine methyltransferase reductase	18	10.4
43	Homozygous 5-methyltetrahydrofolate-homocysteine methyltransferase reductase	6	3.5
44	Heterozygous Angiotensin converting enzyme	31	17.9
45	Homozygous Angiotensin converting enzyme	16	9.2
46	5/5G Plasminogen activator inhibitor-1	3	1.7
47	Homozygous fibrinogen	3	1.7
48	1/D Angiotensin converting enzyme	1	0.6
49	Human plasminogen activator (1a/1a)	1	0.6
50	Heterozygous factor Viii	2	1.2
51	Factor v Leiden	1	0.6
52	I//D Angiotensin converting enzyme	1	0.6
53	a/a human plasminogen activator	1	0.6
54	Heterozygous FXIII	1	0.6
55	D/I Angiotensin converting enzyme	3	1.7
56	Factor v low	1	0.6
	Has FV Leiden or prothrombin mutations		
	No	106	61.3
	Yes	67	38.7

Table C6

Association between prescribing rivaroxaban and variables of the patients

		Rivaroxaban				
		No		Yes		
Variable	Category	n	%	n	%	p-value
Sex	Male	870	17.0	79	1.5	< 0.001
	Female	4123	80.5	49	1.0	
Age (years)	< 18	69	1.3	1	0.0	< 0.001
	18-30	2063	40.3	8	0.2	
	30-50	1661	32.4	33	0.6	
	50-65	628	12.3	31	0.6	
	≥ 65	572	11.2	55	1.1	
Year	2019	709	13.8	7	0.1	< 0.001
	2020	895	17.5	9	0.2	
	2021	908	17.7	40	0.8	
	2022	1139	22.2	14	0.3	
	2023	1342	26.2	58	1.1	
Diabetes mellitus	No	4257	83.1	79	1.5	< 0.001
	Yes	736	14.4	49	1.0	
Hyperlipidemia	No	4928	96.2	123	2.4	< 0.001
	Yes	65	1.3	5	0.1	
Hypertension	No	4151	81.1	77	1.5	< 0.001
	Yes	842	16.4	51	1.0	
Smoking	No	4826	94.2	117	2.3	0.005
	Yes	167	3.3	11	0.2	
Stroke	No	4780	93.3	113	2.2	< 0.001
	Yes	213	4.2	15	0.3	
Vascular disease	No	4539	88.6	77	1.5	< 0.001
	Yes	454	8.9	51	1.0	
Atrial fibrillation	No	4972	97.1	121	2.4	< 0.001
	Yes	21	0.4	7	0.1	
Deep venous thrombosis	No	4961	96.9	114	2.2	< 0.001
	Yes	32	0.6	14	0.3	
Pulmonary embolism	No	4987	97.4	124	2.4	< 0.001
	Yes	6	0.1	4	0.1	
Pregnancy	No	4645	90.7	128	2.5	< 0.001
	Yes	348	6.8	0	0.0	
Post a Cesarean section	No	2537	49.5	127	2.5	< 0.001
	Yes	2456	48.0	1	0.0	
Postpartum	No	4537	88.6	128	2.5	< 0.001
	Yes	456	8.9	0	0.0	
Orthopedic surgery	No	4666	91.1	91	1.8	< 0.001
	Yes	327	6.4	37	0.7	
Fracture	No	4839	94.5	99	1.9	< 0.001

	Yes	154	3.0	29	0.6	
Thrombophilia positive	No	4667	91.1	127	2.5	0.003
	Yes	326	6.4	1	0.0	
Heart failure	No	4831	94.3	116	2.3	0.001
	Yes	162	3.2	12	0.2	
Pneumonia	No	4828	94.3	94	1.8	< 0.001
	Yes	165	3.2	34	0.7	
Chronic kidney disease	No	4877	95.2	119	2.3	0.004
	Yes	116	2.3	9	0.2	
Chest pain	No	4865	95.0	119	2.3	0.007
	Yes	128	2.5	9	0.2	
Noncardiac chest pain	No	4865	95.0	119	2.3	0.007
	Yes	128	2.5	9	0.2	
Being discharged on proton pump inhibitors	No	4939	96.4	123	2.4	0.015
	Yes	54	1.1	5	0.1	
Acetylsalicylic acid	No	4466	87.2	90	1.8	< 0.001
	Yes	527	10.3	38	0.7	
Death	No	4870	95.1	121	2.4	0.043
	Yes	123	2.4	7	0.1	

Table C7

Association between prescribing acetylsalicylic acid and variables of the patients

		Acetylsalicylic acid				
		No		Yes		
Variable	Category	n	%	n	%	p-value
Sex	Male	755	14.7	194	3.8	< 0.001
	Female	3801	74.2	371	7.2	
Age (years)	< 18	69	1.3	1	0.0	< 0.001
	18-30	1969	38.4	102	2.0	
	30-50	1568	30.6	126	2.5	
	50-65	513	10.0	146	2.9	
	≥ 65	437	8.5	190	3.7	
Year	2019	601	11.7	115	2.2	< 0.001
	2020	835	16.3	69	1.3	
	2021	872	17.0	76	1.5	
	2022	1013	19.8	140	2.7	
	2023	1235	24.1	165	3.2	
Diabetes mellitus	No	4001	78.1	335	6.5	< 0.001
	Yes	555	10.8	230	4.5	
Diabetic foot ulcer	No	4480	87.5	541	10.6	< 0.001
	Yes	76	1.5	24	0.5	
Hyperlipidemia	No	4505	88.0	546	10.7	< 0.001
	Yes	51	1.0	19	0.4	
Hypertension	No	3949	77.1	279	5.4	< 0.001

	Yes	607	11.9	286	5.6	
Smoking	No	4419	86.3	524	10.2	< 0.001
	Yes	137	2.7	41	0.8	
Stroke	No	4404	86.0	489	9.5	< 0.001
	Yes	152	3.0	76	1.5	
Vascular disease	No	4256	83.1	360	7.0	< 0.001
	Yes	300	5.9	205	4.0	
Atrial fibrillation	No	4542	88.7	551	10.8	< 0.001
	Yes	14	0.3	14	0.3	
Pulmonary embolism	No	4550	88.8	561	11.0	0.018
	Yes	6	0.1	4	0.1	
Abortion	No	4514	88.1	502	9.8	< 0.001
	Yes	42	0.8	63	1.2	
Pregnancy	No	4371	85.4	402	7.9	< 0.001
	Yes	185	3.6	163	3.2	
In vitro fertilization pregnancy	No	4492	87.7	546	10.7	0.001
	Yes	64	1.2	19	0.4	
Post a Cesarean section	No	2132	41.6	532	10.4	< 0.001
	Yes	2424	47.3	33	0.6	
Postpartum	No	4108	80.2	557	10.9	< 0.001
	Yes	448	8.7	8	0.2	
Symptoms of heart attack	No	4102	80.1	443	8.7	< 0.001
	Yes	454	8.9	122	2.4	
Thrombophilia positive	No	4389	85.7	405	7.9	< 0.001
	Yes	167	3.3	160	3.1	
Heart failure	No	4459	87.1	488	9.5	< 0.001
	Yes	97	1.9	77	1.5	
Pneumonia	No	4397	85.9	525	10.3	< 0.001
	Yes	159	3.1	40	0.8	
Chronic kidney disease	No	4469	87.3	527	10.3	< 0.001
	Yes	87	1.7	38	0.7	
Hysterectomy	No	4460	87.1	563	11.0	0.004
	Yes	96	1.9	2	0.0	
Chest pain	No	4453	87.0	531	10.4	< 0.001
	Yes	103	2.0	34	0.7	
Noncardiac chest pain	No	4453	87.0	531	10.4	< 0.001
	Yes	103	2.0	34	0.7	
Received cardiac catheterization	No	4199	82.0	472	9.2	< 0.001
	Yes	357	7.0	93	1.8	
Unsuccessful pregnancy	No	4551	88.9	548	10.7	< 0.001
	Yes	5	0.1	17	0.3	
Death	No	4457	87.0	534	10.4	< 0.001
	Yes	99	1.9	31	0.6	

Table C8

Association between the use of aspirin and genetic polymorphisms\ mutations

		Acetylsalicylic acid				
		No		Yes		
Variable	Category	n	%	n	%	p-value
Homozygous MTHFR (A1298C)	No	28	16.2	124	71.7	0.020
	Yes	9	5.2	12	6.9	

Appendix D

Data Collection Form

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V
							Diagnosis														
Participant	Gender	Age	File Number	Patient Address	health centre Name	Year	Strock	MI	DVT	PE	after General Surgery	prgrency	AF	orthope-dic diorder	bedridden (rest)	PVD(peripheral vascular disease)	post partum	post cesssir-an	others	notes	thrombophilia screening

W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO	AP	AQ	AR	AS
comorbidities													score variables									
cerebral infarction	HF	vascular dieses	CKD	Liver Damage	Bleeding	alcoholism	HTN	DM	Dialysis	hyperlipidemia	others or (PSH , PMH)	concomitant drugs	CHF	HTN	age >75	DM	sex category (female)	vascular disease (MI, aortic plaque)	age 65-74	prior TIA or strock	CHADS2-VASc Score	rivaroxan

AS	AT	AU	AV	AW	AX	AY	AZ	BA	BB	BC	BD	BE	BF	BG	BH	BI	BJ	BK	BL	BM	BN	BO
anti coagulant type									Route of adminstiration								blood coagulation test				allergy	smoking
rivaroxiban	apixiban	warfarin	dabigatran	heparin	deltaparin	tinzaparin	enoxaparin	anti coagulant dose	SC	IV	ORAL	anti cogulant duration	dosage regimen of anti coagulant	time to initiate anti coagulant	anti platlet therapy	anti platlet therapy Notes	INR	PT	dimer	Aptt		

BP	BQ	BR	BS	BT	BU	BV
patient outcomes						
live	dead	side effect	effectivness	NOTES	gene mutation in thrombophilia panel	body wt

جـامعـــة النجاح الوطنية

كليـــة الدراســـات العليـــا

اتجاهات وصف الأدوية المضادة للتخثر في المستشفيات المختلفة في الضفة الغربية من فلسطين: دراسة بأثر رجعي

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إشراف

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د. صهيب حطاب

قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجة الماجستير في علم الأدوية، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس– فلسطين.

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الملخص

الخلفية: اليوم، تعد أمراض القلب والأوعية الدموية والأحداث الخثارية السبب الرئيسي للوفاة في جميع أنحاء العالم. تزداد شعبية مضادات التخثر في الوقاية من وعلاج الأحداث الخثارية المرتبطة بالرجفان الأذيني والانسداد الوريدي والخثار الوريدي العميق والانسداد الرئوي. في أقسام العظام، تُستخدم مضادات التخثر بشكل متكرر في جراحة العظام مثل استبدال مفصل الورك وكسور العظام كوقاية من الانسداد الخثاري. في أمراض النساء، تُستخدم مضادات التخثر بشكل شائع لدى النساء الحوامل المعرضات لخطر الإصابة بالجلطة أو اللاتي يعانين من حالات إجهاض متعددة بسبب الجلطة.

الاهداف: أجريت هذه الدراسة لتقييم اتجاهات وصف مضادات التخثر الفموية والحقنية في المستشفيات الفلسطينية المختلفة وتصور الاتجاهات المتزايدة أو المتناقصة في وصف مضادات التخثر الفموية والحقنية في المستشفيات الفلسطينية المختلفة.

المنهجية: تم جمع بيانات الوصفات الطبية لمضادات التخثر، بما في ذلك الأشكال القابلة للحقن والفموية، بأثر رجعي من قواعد بيانات ابن سينا و dhis من 2019–2023 في الخليل في الضفة الغربية. تم إجراء مقارنات على نمط استخدام مضادات التخثر بناءً على المؤشرات والسنوات.

النتائج: تم تسجيل 5121 مريضًا في الدراسة بأثر رجعي. كان متوسط العمر (39.4 ± 18.0 سنة). كانت غالبية المرضى من الإناث (81.5٪). كانت هناك أنماط متزايدة في العدد الإجمالي لوصفات مضادات التخثر. تم زيادة وصفات مضادات التخثر الفموية الجديدة (ريفاروكسابان وأبيكسابان ودابيجاتران) بشكل كبير منذ عام 2020 بقيمة p <0.001 لريفاروكسابان وأبيكسابان، بينما انخفضت وصفات الوارفارين. تم وصف عقار ريفاروكسابان لـ 63% من مستخدمي مضادات التخثر الفموية، و26.6% أبيكسابان و8.8% وارفارين. وفيما يتعلق بمضادات التخثر القابلة للحقن، كان استخدام الهيبارين مستمرًا طوال فترة الدراسة بينما زاد وصف إينوكسابارين خاصة في السكان الذين يعانون من أمراض النساء والتوليد. وزاد استخدام إينوكسابارين في السكان بعد الولادة من 11.2% في عام 2019 إلى 22.9% في عام 2023 ومن 11% إلى 24.4% في النساء الحوامل المصابات بطفرات التخثر.

الاستنتاجات: تشير النتائج الرئيسية إلى ارتفاع كبير في وصف مضادات التخثر الفموية الجديدة، ويرجع ذلك في الغالب إلى ملفها الحركي الدوائي والديناميكي الدوائي المواتي، وسهولة الاستخدام، وقلة الحاجة إلى المراقبة مقارنة بالعلاجات القديمة. فضلاً عن ارتفاع ملحوظ في وصف عقار إينوكسابارين للنساء الحوامل وبعد الولادة. مع إمكانية تحسين نتائج المرضى، فإن الأنماط المتغيرة في استخدام مضادات التخثر تشير إلى تحول أكثر أهمية في علاج اضطراب الانصمام الخثاري. ومع ذلك، لتحقيق أقصى استفادة من علاج مضادات التخثر للمرضى، هناك حاجة إلى تحقيقات مستمرة.

الكلمات المفتاحية: اتجاه الوصفات الطبية، الوارفارين، مضادات التخثر غير الستيرويدية، إينوكسابارين، الخثار.