QATAR UNIVERSITY

COLLEGE OF PHARMACY

CLINICAL AND ECONOMIC IMPACT OF GENETIC AND NON-GENETIC FACTORS ON INR NORMALIZATION IN PRE-OPERATIVE MANAGEMENT OF WARFARIN PATIENTS

BY

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ABSTRACT

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Title: Clinical and Economic Impact of Genetic and Non-genetic Factors on INR Normalization in Pre-Operative Management of Warfarin Patients

Supervisor of Dissertation: Hazem F. Elewa.

The aim of this Ph.D. was to evaluate the periprocedural anticoagulation management of patients receiving warfarin in Qatar clinically and economically. In addition, exploring the clinical and economic impact of genetic and non-genetic factors on INR normalization in pre-operative management of warfarin patients in Arab population.

our review concluded that the clinical decision regarding perioperative warfarin management is a complex aspect of care. Indeed, such an issue would ultimately lead to undesirable variation in care. This would be complicated by the lack of institutional standardized protocols and hence differences in practices, attitudes and periprocedural outcomes.

A local cross-sectional survey on the periprocedural management of warfarin was developed for a better understanding of the current practice, the gap in knowledge and attitude among health care providers in Qatar. It has found that the awareness median (IQR) score was moderate [64.28% (21.43)]. The level of awareness was associated with the practitioner's specialty and degree of education (P= 0.009, 0.011 respectively). Practice leans to overestimate the need for warfarin discontinuation as well as the need for bridging. Participants expressed interest in using genetic tests to guide periprocedural warfarin management [median (IQR) score (out of 10) = 7 (5)].

The results of the mentioned survey were influencer to evaluate the real-world clinical practice of warfarin periprocedural management and investigate the clinical

outcomes associated with warfarin bridging versus non-bridging. This prospective cohort study demonstrated that warfarin was interrupted in 90% of patients, out of them 82% received anticoagulant bridging medication. Minor or low-bleeding risk procedures represented 75% of the performed procedures. The median (IQR) of preoperative warfarin interruption days was 3 (2). No thromboembolic events were observed, while 39.1% of patients experienced bleeding events during the study period. The incidence of overall bleeding and major bleeding were numerically higher for bridging group compared to non-bridging but did not reach statistical significance [(30.6% Vs 22.2%, p= 0.478) and (12.9% Vs 5.6%, p=0.375), respectively].

The results of the above study showed significant limitations that undermine the benefit of bridging and showed that this benefit may not worth the monetary spending and may not achieve cost-effectiveness. To our knowledge, there are no evaluations of the economic value of bridging in the literature. Consequently, a study was conducted to assess the economic consequences of peri-procedural warfarin management of AF patients in Qatar. The economic evaluation of the above practice demonstrated that the mean overall cost of peri-procedural warfarin management per patient was USD 3,260 (QAR 11,900), associated with an overall success rate of 0.752. Based on the cost-effective analysis (CEA), predominant bridging was dominant (lower cost, higher effect) over the predominant non-bridging practice in 62.2% of simulated cases, with a cost-saving of up to USD 2,001 (QAR 7,303) at an average of USD 272 (QAR 993) and was cost-effective in 36.9% of cases.

To optimize the period of preprocedural warfarin interruption to decrease the incidence of bleeding in case of bridging and the incidence of thromboembolism in case of non-bridging, a study was conducted to determine the influence of CYP2C9, *VKORC1, CYP4F2, FII*, and *FVII* genetic polymorphisms and non-genetic factors on

INR decline in a cohort of Arabs undergoing a procedure that requires warfarin interruption and developing an algorithm to tailor the duration of warfarin interruption before the procedure. The study revealed that bridging, INR index and being Sudanese are significant predictors of INR normalization. Moreover, *CYP2C9* and *VKORC1* genetic polymorphisms are influencers to warfarin maintenance weekly dose but none of the genetic factors were associated with the INR decline rate. A more extensive study may be warranted to confirm such findings. Equally important, cost-effective analysis of implementing pharmacogenetics-based algorithm will guide decision-makers to which approach must be subsidized.

To the best of our knowledge, no economic evaluation study investigated the use of pharmacogenetics information in pre-operative warfarin interruption to direct decision-makers. Therefore, a cost-benefit analysis was conducted to examine if the benefits of implementing a genetic-testing in periprocedural warfarin management outweigh the cost. The study showed that the average cost per patient was USD 573.72 (QAR 2,094.07) less with the genetic-guided approach of management compared to the standard of care. This led to an average benefit to cost ratio of 4; whereby, for each USD 1 spent on genetic testing, USD 4 is generated in benefit. This was maintained in 100% of simulated cases.

DEDICATION

To

GOD

My Parents

My Family

All Warfarin Patients.

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Firstly, I want to thank my GOD for giving me the strength, ability, and patience to finish this work in the tiniest possible time.

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CHAPTER 1: INTRODUCTION

1.1 What Is Blood Coagulation?

Blood clotting is an instant process that starts early once an injury occurs to prevent bleeding. The coagulation cascade is initiated via a series of reactions, including the extrinsic (tissue factor) and the intrinsic (contact) pathways, which would eventually converge on a common pathway. The term “extrinsic” is so-called due to the lack of one of the coagulation factors (Factor III, thromboplastin) in the circulating blood. Such a pathway also entails factors IV (calcium) and VII (proconvertin). On the other hand, the components of the intrinsic pathway are entirely contained within the vasculature. These include factors VIII (antihemophilic factor A), IX (Christmas), XI (plasma thromboplastin antecedent), and XII (Hageman). The common pathway of the coagulation cascade includes coagulation factors I (fibrinogen), II (prothrombin), V (prothrombin accelerator), X (Stuart Power), and XIII (fibrin-stabilizing factor) [1]. Table 1.1 demonstrates all the coagulation factors and their roles in the coagulation cascade.

Table 1.1 Coagulation factors

Pathway	Factor number	Factor name
Extrinsic pathway	III	Thromboplastin, tissue factor
	IV	Calcium
	VII	Proconvertin
Intrinsic pathway	VIII	Antihemophilic factor
	IX	Christmas factor
	XI	Plasma thromboplastin antecedent
	XII	Hageman factor

Pathway	Factor number	Factor name
Common pathway	I	Fibrinogen
	II	Prothrombin
	V	Prothrombin accelerator
	X	Stuart (Power)
	XIII	Fibrin-stabilizing factor

1.2 Blood Coagulation Cascade

The clotting cascade starts after vascular injury and tissue factor release, leading to the extrinsic pathway's stimulation. Subsequent thrombin activation would lead to the stimulation of the intrinsic pathway and factor XI activation. Both the extrinsic and intrinsic pathways activate factor Xa in a common pathway. Consequently, the prothrombinase complex is triggered, and hence prothrombin is converted to thrombin. This thrombin could further convert fibrinogen to insoluble fibrin, which would create a fibrin clot (Figure 1.1) [2, 3].

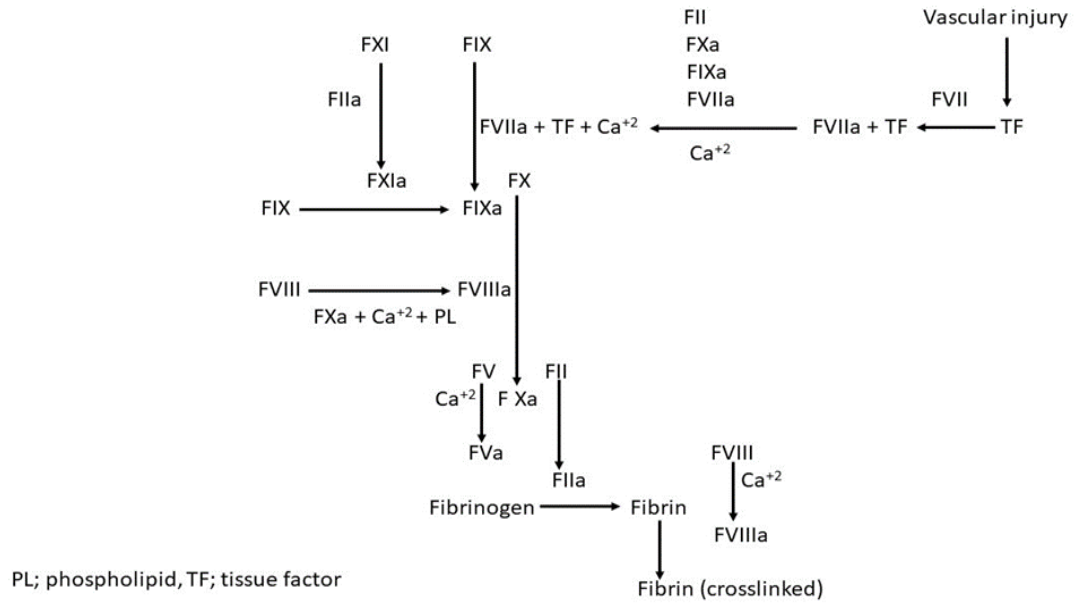


Figure 1.1: Blood coagulation cascade [2, 3]

1.3 What Is Anticoagulation?

Ideally, an anticoagulant (AC) is a blood-thinning agent that prevents or reduces unnecessary blood clotting without causing bleeding. However, an ideal anticoagulant does not exist in clinical practice. During the past decades, various blood thinners have been used clinically to manage venous thromboembolism, including deep vein thrombosis and pulmonary embolism, as well as the thromboembolic complications of cardiac valve replacement or atrial fibrillation [4].

1.4 Classes of Anticoagulants?

The history of antithrombotic agents dates back to 1884 when John Berry Haycraf identified hirudin, a potent thrombin inhibitor, from the secreted saliva of medicinal leeches [5]. However, it was not until the 1930s when unfractionated heparins (UFHs) were tested and became widely used in humans and subsequently, vitamin K antagonists (VKAs), including coumarin and warfarin, were discovered in the 1940s [6, 7]. Owing to their promising specificity and ease of use, both classes remained the mainstay of AC therapy for a long time until the development of low molecular weight heparins (LMWHs) in the 1980s, rendering the treatment process more straightforward by reducing the need to monitor coagulation frequently [8]. Ultra-low molecular heparins (ULMWHs) like fondaparinuxwere then introduced in the 2000s to reduce the risk of heparin-mediated thrombocytopenia and to improve the pharmacokinetic properties of this class [9]. More recently, several ACs have been developed, including direct thrombin inhibitors (DTIs) and indirect and direct Xa inhibitors. In the past decade, the discovery of dabigatran, one of the DTIs, as well as edoxaban, apixaban, and rivaroxaban as factor Xa-inhibitors, represented a new era of ACs available to both the clinicians and patient [10].

1.5 What Is Warfarin?

Coumarins are a group of anticoagulants that interfere with vitamin K; therefore, they

are named VKAs. Coumarins act by inhibiting vitamin K recycling, leading to the depletion of vitamin K-dependent coagulation factors II, VII, IX, and X. Warfarin is the most commonly used coumarin derivative worldwide. In contrast, acenocoumarol and phenprocoumon are commonly prescribed in some European and Asian countries [11].

1.6 History of Warfarin Use

In the 1920s, veterinarians reportedly observed frequent death cases in cattle herds due to uncontrollable internal bleeding in Canada and Northern America. Such hemorrhagic episodes took place after feeding the animals wet and spoiled sweet clover, where the symptoms were apparent on day 15 after ingestion, and death occurred within the following 30-50 days. The cause of such "sweet clover disease" was later identified by Karl Link (1901-1978) and his senior student W. Schoeffel. That is, improperly cured sweet clover hay (*Melilotus alba* and *M. officinalis*) contains dicoumarol (3, 3'-methylene-bis [4-hydroxycoumarin]), which reduces the clotting power in the blood of the ingesting animals. Additionally, in 1939, Link revealed that vitamin K1 could reverse the action of dicoumarol. Subsequently, warfarin (3-a-acetonylbenzyl-4-hydroxycoumarin) was synthesized as a more potent analog of dicoumarol, and it was named from the initials of Wisconsin Alumni Research Foundation. The new product was initially promoted as a rodenticide in 1948, while it was introduced clinically as a useful anticoagulant in 1955 (Coumadin) [1, 6].

1.7 Epidemiology of Warfarin in Qatar

Over the past five decades, warfarin has been widely prescribed for the treatment and prevention of venous thromboembolism in multiple areas worldwide. In Qatar, warfarin prescription accounted for almost 77% of all oral anticoagulants (OACs) in 2015 [12].

1.8 Clinical Indications for Warfarin

The efficacy and safety of warfarin in the treatment and prevention of

thromboembolism have been investigated elsewhere in the literature. Warfarin has demonstrated promising efficacy and safety outcomes in well-designed randomized clinical trials, particularly for patients with atrial fibrillation, venous thrombosis, and mechanical prosthetic heart valves.

1.8.1 Atrial fibrillation

Atrial fibrillation (AF) is a commonly reported type of arrhythmia. The global estimates indicate that AF is prevalent among 1% of the population; however, country-based prevalence is highly variable [13]. Besides, the ethnic disparity is apparent. In the United States, the prevalence of AF is lower among blacks, Asians, and Hispanic populations than white individuals[14, 15]. AF is known to be associated with many complications including thromboembolic complications.

It is estimated that AF patients have 4-5-fold increased risk of stroke due to cardiometabolism compared to those with maintained sinus rhythm [16, 17]. In addition, stroke occurring in the presence of AF is associated with poorer outcomes, including increased disability and mortality [18]. Given the increased prevalence of AF among older adults, stroke prevalence is higher in the older population [14, 15]. Indeed, AF accounts for up to 15% of stroke events, and, more specifically, it is associated with 25% of strokes among individuals aged 80 years.

In AF, the CHA2DS2-VASc Score is the most widely used instrument for predicting thromboembolic risk. The acronym CHA2DS2-VASc stands for congestive heart failure, hypertension, age, diabetes, prior stroke/transient ischemic attack (2 points), artery disorder (peripheral arterial disease, previous myocardial infarction, aortic atheroma), and gender category (female gender). Each risk factor is worth one point, with the exception of age > 75 and stroke/TIA, which are worth two points each. Anticoagulation should be provided to patients with two or more points. Patients with

a single point should be handled with aspirin alone or with complete anticoagulation, depending on the person [19, 20].

1.8.2 Deep venous thrombosis (DVT) and pulmonary embolism (PE)

Venous thromboembolism (VTE) is a condition comprising of blood clots occurring in the veins, causing interrelated conditions; deep venous thrombosis (DVT) and pulmonary embolism (PE). VTE is associated with high morbidity and mortality. New VTE events occur in one individual per 1000 each year, and the incidence increases among those aged 75, reaching up to 5 per 1000 person-years [21]. Notably, VTE occurs among 10-20% of hospitalized patients [22]. At presentation, DVT is prevalent among 42% of patients with VTE, PE among 44%, and the remaining patients usually present with both conditions [23]. In general, the management of patients with DVT or PE using anticoagulant therapies has dual objectives. First, anticoagulation is used to limit thrombus propagation and extension. This would facilitate removing fibrin from the thrombus by the fibrinolytic system, a process that may take up to six weeks. Second, anticoagulants are used to limit the development of additional thrombi [24].

As a consequence, based on patients' clinical conditions, anticoagulation should be continued for ≥ 3 months. Discontinuation of anticoagulants beyond that period should be primarily determined based on the risk of recurrence and, to a lesser extent, on the risk of bleeding and patients' preferences [25-27]. Anticoagulation therapy for VTE has been categorized into short-term, long-term, and extended anticoagulation.

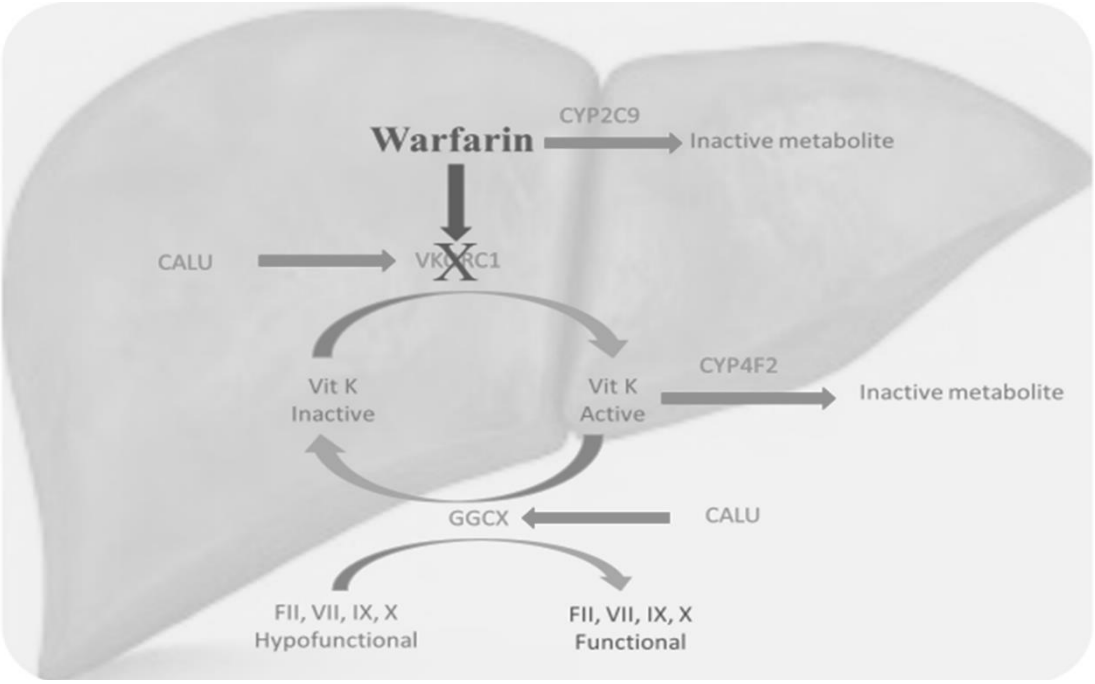
1.8.3 Mechanical heart valve prostheses

In patients with a prosthetic mechanical heart valve (MHV), anticoagulation is necessary to prevent valve thrombosis and systemic embolism. This is because the risk of embolic events and ischemic stroke has been estimated at 4.0 patients per person-years without anticoagulation therapy. In contrast, the risk is lower (1.0 patient per person-years) with oral anticoagulation [28]. Moreover, the risk of valve thrombosis

was 80% lower with using oral anticoagulants compared to no treatment [28]. As such, anticoagulation is crucial in patients with prosthetic valves.

1.9 Pharmacology and Mechanism of Action of Warfarin

Blood coagulation proteins require vitamin K-dependent carboxylation to be biologically active. The posttranslational carboxylation reaction is mediated by the enzyme γ-glutamyl carboxylase (GGCX), which is necessary to activate coagulation factors II, VII, IX, and X. Simultaneously, the reduced vitamin KH2 is oxidized to vitamin K epoxide. The latter should be recycled back by vitamin K epoxide reductase (VOKR) to vitamin KH2. Given the chemical structure similarity between warfarin and vitamin K, warfarin can inhibit the complex subunit 1 of VKOR (VKORC1), leading to blockage of the regeneration of coagulation factors (Figure 1.2) [4].



CALU; calumenin, CYP; Cytochromes P450; GGCX; γ-glutamyl carboxylase, VKORC1; vitamin K epoxide reductase complex subunit 1.

Figure 1.2: Warfarin mechanism of action.

1.9.1 Pharmacokinetics and Metabolism of Warfarin

Warfarin is available as a 50:50 mixture of S and R enantiomers, and the asymmetry of a carbon atom at position 9 gives rise to these two enantiomeric forms. Warfarin is

rapidly and entirely absorbed from the digestive tract. The pharmacological action of S-warfarin is three to five times more potent, and the elimination half-life is generally shorter (24-33 hours) compared to R-warfarin (35-55) [29, 30]. The microsomal monooxygenase mediates the metabolism of R/S warfarin via cytochromes P450 (CYP). More specifically, the CYP2C9 enzyme plays a vital role in S-warfarin metabolism, whereas R-warfarin is metabolized by more than one CYP enzyme (CYP1A2 and CYP3A4). The half-life of racemic warfarin is approximately 36-42 hours [30]. Kidney is responsible for 80% of the excretion, while the remaining is excreted through the liver [30].

1.9.2 Warfarin Pharmacodynamics

Warfarin is a competitive inhibitor of an enzyme responsible for synthesizing multiple coagulation factors, namely VKOR [31]. Such an enzyme was first identified in 1974, and it is encoded by *VKORC1* (chromosome 16). The anticoagulant activity of warfarin is attributable to its ability to interrupt the regeneration of vitamin K hydroquinone (the reduced form of vitamin K) from its epoxide by VKORC1[32]. Of note, warfarin targets the critical step of prothrombin conversion to thrombin. The latter has a half-life of approximately 96 hours. which is one of the main reasons warfarin has a delayed anticoagulant effect. The pharmacological activity in the first 48 hours is exclusively dependent on the reduction of factors VII and IX (the half-lives are 5 and 24 hours, respectively). Therefore, acute anticoagulation using UFH or LMWH is warranted upon starting warfarin therapy to ensure effective anticoagulation with fast onset of action [3].

1.10 International Normalization Ratio (INR)

The prothrombin time test (PT), which assesses the time required for a clot to form, is the mainstay monitoring parameter for warfarin dosing. The result of patient's PT is used to calculate the international normalized ratio (INR) by using the following

formula: $INR = (Patient's\ PT\ \div Control\ PT)^{ISI}$, where ISI refers to the international sensitivity index. This standardization scheme was officially approved by the World Health Organization (WHO) in 1982, and it has subsequently helped in the uniformity of the INR assay across the world. The commercial manufacturers express the used ISI for each particular thromboplastin reagent in a given batch. It is worthy to note that INR levels reflect the levels of three vitamin-K-dependent clotting factors (out of four), including factors II, VII, and X. Furthermore, at the initiation or interruption of warfarin, changes in INR/PT would follow changes in the levels of factors FVII, FX, and finally FII. These changes occur in a sequential pattern due to the variation in the half-lives of such coagulation factors (2-9 hrs, 17-44 hrs, and 60-72 hrs for each factor, respectively) [33]. Thus, normal INR levels would expectedly be attained within five to ten days after warfarin discontinuation and without the administration of vitamin K [34].

1.11 Patient Factors That Influence Warfarin Sensitivity

1.11.1 Age

The pharmacokinetics of warfarin differ among distinct populations. For example, age-related differences in warfarin doses are apparent; it has been shown that warfarin maintenance dose could be reduced by 0.5 to 0.7 mg with each 10-year increase among patients aged 20-90 years [35]. From another perspective, age has been consistently considered an independent predictor of the changes in warfarin dosing requirement in multiple linear regression models [35-37]. Interestingly, elderly patients usually exhibit higher sensitivity and lower dosing requirements than their younger counterparts [38]. More specifically, older adult women require the lowest warfarin doses to achieve the same anticoagulation levels [39]. These observations are explained by the shrinkage of the liver mass and a reduction in the synthesis of vitamin K-dependent clotting factors in elderly patients [40]. Moreover, the affinity of plasma protein binding among older

adults is 15%-25% lower than other age groups, which increases the free warfarin in the bloodstream at the initiation of therapy [41].

1.11.2 BMI

The impact of body size has been on warfarin dosing requirements has been documented elsewhere; however, such effects have been confounded by other variables, such as age, polypharmacy, comorbid diseases, and presence of genetic polymorphisms [38, 41-43]. Therefore, the independent association between the body mass index (BMI) and warfarin maintenance has not been clearly elucidated. The relationship between body mass index (BMI) and warfarin dose seems to be indirect. It may represent an interplay between the two variables and liver size, where the latter increases with an increased BMI. In a recent systematic review [43], (n=32), body weight was not independently associated with VKA doses. However, obese, or morbidly obese patients had required a 30-50% increase in VKA dosing upon therapy initiation than those with lower BMIs.

1.11.3 Alcohol consumption

Alcohol consumption plays a significant role in the anticoagulant activity of warfarin. It has been estimated that the free fraction of warfarin is increased by 3-34% with drinking alcohol [44]. Consuming several drinks in one sitting might increase the anticoagulation activity of warfarin, which might further increase the risk of bleeding. The bleeding potential is augmented due to the alcohol-mediated inhibition of warfarin metabolism by cytochrome P450 enzymes in the liver. Contrastingly, long-term consumption of alcohol induces cytochrome P450, leading to an acceleration of warfarin metabolism. Subsequently, large warfarin doses may be required to obtain the desired anticoagulation effect. Given these varying effects, it is recommended to check the patient's INR once a sudden change in alcohol consumption pattern has occurred, such as stopping alcohol or consuming > 3 drinks a day (binge drinking) [45-47].

1.11.4 Food

Certain types of food and food supplements could be associated with changes in the anticoagulation activity of warfarin. The intake of regular meals has minimal effects on warfarin bioavailability; nonetheless, the anticoagulation activity may be influenced by fluctuations in the consumption of vitamin K-rich foods, such as green leafy vegetables, liver, or other relevant supplements [48-50]. Of note, the impact of vitamin K intake on warfarin sensitivity should be considered upon warfarin initiation and during maintenance. In 2007, Sconce et al. [51], had speculated that vitamin K intake in food is a significant determinant of the anticoagulation outcome. They found that consuming low amounts of vitamin K in food has led to a shorter time in the therapeutic range (TTR), which indicates that INR was controlled over a short period. In a subsequent analysis, the same group revealed that daily supplementation of vitamin K to patients with short TTR had stabilized their anticoagulation control. This was indicated via the significant reduction of the standard deviations of INR (-0.24-0.14 vs. -0.11-0.18; $P<0.001$) and a concomitant increase in the percentage TTR (28%-20% vs. 15%-20%; $P<0.01$) among vitamin K-receiving patients compared to a placebo controlled-group. Based on the observations above, it is necessary to educate patients regarding regular vitamin K consumption daily which would eventually be reflected in anticoagulation control stability, particularly among patients with unstable coagulation outcomes [52-54].

1.11.5 Comorbidities

1.11.5.1 Liver disease

Hepatic diseases are associated with impairment of the production of coagulation factors V, VII, X, as well as prothrombin formation, leading to an increased sensitivity to warfarin [55]. In addition, the relationship between hepatic disease and warfarin sensitivity may be confounded by hypoalbuminemia, reduced vitamin K intake in food,

vitamin K malabsorption, and the disruption of the carboxylation process, which is a crucial step in the synthesis of vitamin K-dependent clotting factors [41].

1.11.5.2 Renal disease

Warfarin is primarily metabolized in the liver and indirectly excreted via the kidney, with a small amount being excreted unchanged. Therefore, the adjustment of warfarin dose in patients with chronic renal failure is not required; however, the 9th edition of American College of Chest Physicians (ACCP) recommended lower warfarin dose for elderly patients with mild to moderate disease of renal function [56, 57]. The risk of bleeding increases in warfarin-receiving patients who have renal insufficiency and those who receive heparin during hemodialysis. Notably, it has been shown that the risk of death is 27% higher among dialysis patients who receive warfarin (HR=1.27, 95% CI=1.18-1.37) [58].

1.11.5.3 Thyroid disease

Although thyroid dysfunction has not been associated with warfarin clearance changes [59], patients with hyperthyroidism are more sensitive to warfarin than those with normal thyroid functions. This might be attributable to the accelerated catabolism of prothrombin and factor VII or the reduction of vitamin K-dependent clotting factor concentrations. Since the concentrations of thyroid hormones can be influenced by the use of antithyroid medications, this has to be accounted for when dosing warfarin in patients with hyperthyroidism. [60]. Conversely, in hypothyroidism, warfarin responsiveness is increased, which necessitates increasing warfarin doses and extensive monitoring of INR, particularly at the time of initiating or adjusting thyroid hormone replacement therapy [41, 60].

1.11.5.4 Drug interactions

Multiple medications interact with warfarin, leading to serious adverse events [6, 61].

Table 1.2: Examples of potential medications that have strong evidence of interaction with warfarin

Level of causation	Potentiation of anticoagulant effect	Inhibition of anticoagulant effect
High probability	Amiodarone	Barbiturates
	Anabolic steroids	Carbamazepine
	Cimetidine	Chlordiazepoxide
	Ciprofloxacin	Cholestyramine
	Citalopram	Etodolac
	Cotrimoxazole	Griseofulvin
	Diltiazem	Mercaptopurine
	Entacapone	Mesalamine
	Erythromycin	Nafcillin
	Fish oil	Ribavirin
	Fluconazole	Rifampin
	Miconazole	Sucralfate
	Omeprazole	Trazodone
	Phenylbutazone	
	Piroxicam	
	Propafenone	
	Propranolol	
	Sertraline	
	Voriconazole	
	Zileuton	

Level of causation	Potentiation of anticoagulant effect	Inhibition of anticoagulant effect
Probable	Acetylsalicylic acid Amoxicillin/clavulanate Azithromycin Celecoxib Clarithromycin Dextropropoxyphene Fluorouracil Fluvastatin Fluvoxamine Interferon Itraconazole Levofloxacin Paracetamol Phenytoin (biphasic with later inhibition) Quinidine Ritonavir Ropinirole Simvastatin Tamoxifen Tetracycline Tramadol Troglitazone	Azathioprine Bosentan Candesartan Dicloxacillin Influenza vaccine Multivitamins (containing vit. K) Raloxifene Ritonavir

Level of causation	Potentiation of anticoagulant effect	Inhibition of anticoagulant effect
Possible	Amoxicillin	Cyclosporine
	Chloramphenicol	Etretinate
	Disopyramide	Sulfasalazine
	Felbamate	Telmisartan
	Gatifloxacin	Terbinafine
	Gemfibrozil	
	Indomethacin	
	Ifosphamide	
	Lovastatin	
	Leflunomide	
	Metolazone	
	Miconazole topical gel	
	Nalidixic acid	
	Norfloxacin	
	Ofloxacin	
	Orlistat	
	Propoxyphene	
	Topical salicylates	
	Saquinavir	
	Terbinafine	
	Ticlopidine	
	Trastuzumab	

(Adapted from Holbrook, 2005 [62])

1.12 Pharmacogenetics and Pharmacogenomics

Over the past decades, clinicians have relied on multiple behavioral, environmental, and genetic determinants to suit treatment to each patient based on his/her condition [63]. The concept of "personalized medicine" was first demonstrated by the Canadian physician Sir William Osler in the late 1800s [64]. Such a concept has undergone a series of modifications to tailor targeted treatments based on personal characteristics.

since the establishment of the Human Genome Project, the reliance on the genetic makeup in new research and clinical fields including pharmacogenomics (PGX) have been established. PGX is an area of personalized medicine which entails investigating the relationship between patients' genomic information and the response of drugs, [64]. The number of described pharmacogenetic associations has grown exponentially over the past few years. Furthermore, more than 2000 genes have been involved in the drug response paradigms in the Pharmacogenomics Knowledge Base (PharmGKB) [63]. The major success areas of PGX have been demonstrated in oncology and cardiovascular medicine. Generally, the relevant studies of PGX had implemented two main approaches to identify drug-gene associations. These included candidate gene identification and genome-wide association (GWA). In candidate gene studies, distinct common variants in a given candidate gene are examined to check their influence on drug response [65]. Conversely, in the GWA approach, variants are screened for in the entire genome. [65].

Notably, before implementing genetic information for further processing in dosing regimens, three major domains should be considered, as indicated by the Evaluation of Genomic Application in Practice and Prevention (EGAPP) initiative [66]. First, analytic validity is an important parameter that entails the capability of a genetic test to quantify the candidate genotype accurately and reliably. This includes the efficacy of such a

measure in the clinical laboratory and representative samples of a given population [66]. Second, the genetic test should precisely and consistently predict the target clinical disorder or phenotype, a property named clinical validity [66]. Finally, clinical utility is the proof of improved patients' clinical outcomes and the added value and benefits of the test to decision making during patient management compared to the established managemental approaches without genetic testing [66].

1.13 Pharmacogenomics in Cardiovascular Diseases

Cardiovascular medications are among the most commonly prescribed medications worldwide. Although many randomized control trials (RCTs) had investigated the efficacy of cardiovascular medications, clinicians have revealed significant variations in the response and adverse events of these drugs. This corroborates the concept of "one shoes does not fit all", in which each patient can exhibit a different response to a given drug dose. Therefore, the administration of a universal drug dose might not be an ideal approach [67]. Essentially, studies investigating the variation in the drug response relied heavily on the genetic variation among patients. Candidate gene studies and GWA investigations have indicated significant associations between specific genetic variants, which are commonly implicated in biological processes, and the variation in the response to particular classes of medications, such as anticoagulants (warfarin), anti-hypertensives (β-blockers and calcium channel blockers), antiplatelet drugs (aspirin and clopidogrel), anti-arrhythmic drugs (digoxin), and statins [67]. Warfarin is an actual example of anticoagulants that have been heavily investigated in PGX studies. GWA and candidate gene studies have revealed specific genetic variants affecting the pharmacodynamics and pharmacokinetics of warfarin, and strongly associated with variations in warfarin dose requirements [67].

1.14 Warfarin Pharmacogenetics

Approximately 40% of variability in warfarin dose-response is mediated by genetic

factors. More specifically, polymorphisms occurring in *CYP2C9, CYP4F2, and VKORC1* genes, and to a lower extent the *GGCX*, *CALU*, *APOE* genes and *EPHX1* (which encodes microsomal epoxide hydrolase 1) have been shown to be associated with warfarin dose requirement) (Figure 1.2) [33, 68]. The effect of *VKORC1, CYP2C9, and CYP4F2* genetic variants, were confirmed in a genome-wide association study [69]. The main genetic determinants are discussed below in detail.

1.14.1 CYP2C9

Warfarin contains a mixture of two active enantiomers: the (R) and (S) enantiomer, where the latter has a five-fold anticoagulation potency than the former [70]. While the enzymes encoded by the *CYP1A2*, *CYP2C19*, and *CYP3A4* genes metabolize the R-enantiomer, the S-enantiomer is metabolized by CYP2C9, and variations in the *CYP2C9* gene can alter its enzymatic activity [32, 68, 71]. Generally, there are 16 genetic variations (on chromosome 10), of which two variant alleles are commonly exhibited in different populations: the *CYP2C9*2* and **3* alleles. The **2* alleles (single nucleotide polymorphisms [SNP] ID: rs1799853, also known as c.430C>T) is found in 5-29% of individuals in the Middle Eastern and North Africa (MENA) region [72]. On the other hand, the **3* allele (SNP ID: rs1057910, known as c.1075A>C) is prevalent in 4.3-27% of the MENA inhabitants. Both allelic variations account for reductions in the enzymatic activity to 12-70% and 5%, respectively [73, 74]. Since the **1* allele is considered the wild-type allele, polymorphisms occurring in the *CYP2C9* gene can be *CYP2C9*1/*1* (wildtype homozygous), *CYP2C9*2/*2*, or *CYP2C9*3/*3* (homozygous), *CYP2C9*1/*2* or *CYP2C9*1/*3* (simple heterozygous) and *CYP2C9*2/*3* (compound heterozygous) [75].

1.14.2 VKORC1

VKORC1 gene is responsible for expressing a small transmembrane protein (VKORC1 enzyme), which reduces vitamin K epoxide to the active form of vitamin K (vitamin

K1). Genetic variation in the *VKORC1* gene is mediated to a large extent by two SNPs on chromosome 16 *(VKORC1*2),* showing a strong linkage disequilibrium (LD). The first allele is on the promoter region (SNP ID: rs9923231, known as c.-1639G > A) The second variant represents a SNP in the first intron (SNP ID: rs9934438, known as 1173C > T [or G>A]) [76]. This variant is relatively common in patients of MENA descent (30-72%) [72]. Overall, the distribution of genotypes in the *VKORC1*2* are G/G or C/C (homozygous for G or C), A/A, or T/T (homozygous for A or T) or G/A or C/T (heterozygous for G or C and A or T) [76]. To date, *VKORC1* variation is the most significant genetic factor that affects warfarin pharmacodynamics, influencing 24% of warfarin dose [77]. Along with *CYP2C9,* they both account for 36% of warfarin response variability [78]. Ultimately, this reduces dosing requirements due to slow metabolism and decreased clearance [77].

1.14.3 CYP4F2

CYP4F2 is a liver enzyme that changes the active form of vitamin K to inactive hydroxy-vitamin K1 to exit from the vitamin K cycle. This stage is considered a counterpart to the *VKORC1* activation stage [79]. One non-synonymous mutation in *CYP4F2* is *CYP4F2*3* (SNP ID: rs2108622, known as c.1297G>A) was shown to have an association with warfarin dose variability [69]. The variant allele (T) is very common across Europeans and is found in 30-42% in the MENA region [72]. Furthermore, studies have shown that *CYP4F2*3* was in LD with an SNP ID: rs2189784 (G>A/ G>C/ G>T), both of which demonstrating a drop in enzyme function [79]. While *CYP4F2* association with warfarin dosing was inconsistent across studies, those that showed significant association indicated that carriers of the A allele must receive an increased dose of warfarin by 8%-11% compared to patients with wild-type genotypes [79].

1.14.4 Coagulation factors

Warfarin inhibits the activation of vitamin K-dependent factors II, VII, IX, and X. As a result, genetic polymorphisms of these factors may affect their regeneration and synthesis rates. Consequently, warfarin dose requirement and the time required for INR normalization can be altered [80].

Significantly, INR normalization is impacted by the half-lives of these coagulation factors, which reflect the interlude between the time of warfarin discontinuation and the clinical changes. Factor II (FII) and Factor VII (FVII) had the most prolonged (42-72 h) and the shortest (4-6 h) half-lives, respectively, whereas the half-life of factor IX (FIX) is 21-30 h and factor X (FX) is 27-48 h [80]. Allelic polymorphisms in these coagulation factors are reviewed below and sorted based on their half-lives.

FVII is activated through its interaction with tissue factor. This complex activates Factor X (FX) [3]. Bertola et al. [81], stated that FVII explains 50% of the individual variation of INR during the first 72 hours after warfarin initiation. Also, the authors indicated a robust correlation between FVII and INR in a higher proportion than that reported between factor II (FII) and INR. Therefore, polymorphism in the gene encoding for FVII could influence warfarin sensitivity variation [82]. Common genetic polymorphisms in *FVII* (affecting its level or its coagulation activity) are -402 A>G/A>T (rs510317), -401 G>T/G>A/G>T (rs510335) and R353Q G>A/G>C/G>T (rs6046) with an average prevalence of >12% among different populations [81]. These are the most frequently impactful coagulation-factor-related polymorphisms on warfarin dose. Previous evidence has revealed that *FVII* variants explain 1.3%-3.4% of warfarin dose variability [83, 84].

FIX is catalyzed by factor XI to FIXa, responsible for the activation of factor X (FX). Notably, factor VIII (FVIII) is required to complete such a step [85]. Multiple allelic variations in the *FIX* gene have been reported, such as the SNPs rs401597 (T>C / T>G)

and rs392959 (T>C), which are intron variants [86]. The other two SNPs showed a reduction in *FIX* affinity to GGCX; one of them causes alanine-to-threonine alteration (Ala-10 Thr, known as 6346 G>A), while the second one is known as 6347C>T and it leads to alanine-to-valine (Ala-10 Val) conversion [87, 88]. The conducted studies did not show any FIX contribution in the prediction of the warfarin maintenance dose [83, 86].

FX is another vitamin-K-dependent coagulation factor activated to FXa by the conjugation of FIXa and FVIIIa, forming the "tenase complex". This would further generate more FXa, which constitute the prothrombinase complex. Such a complex converts large amounts of prothrombin to thrombin [3]. There are four polymorphisms in the *FX* gene's promoter region: A TTGTGA insertion between position -343A and -342G, C/T at -222 position, C/T at -220 position and C/T at -40 position [89]. FX variants account for 2% of the variation in warfarin sensitivity. [90].

FXa activates prothrombin or factor II (FII) to thrombin. The latter acts to convert fibrinogen to fibrin, which forms blood clots at the end of the coagulation cascade [3]. Patients' sensitivity to warfarin is generally affected by two variations in the *FII* gene: SNP ID: rs5896 (also known as 165 T>M) and SNP ID: rs3136516 (also known as 25014 G>A).(18-19*) The rs3136516 polymorphism is reported in 30% of the American population and 10% in Italians [89, 91]. *FII* may explain 1.0%-3.4% of warfarin response dose variability [84, 89].

1.14.5 Polymorphisms in other genes

There are multiple variants of genes involved in the vitamin K cycle, which might impact warfarin dose though their contribution is less significant. APOE is a protein that combines vitamin K to facilitate its transportation to the liver. Therefore, genetic polymorphism of *APOE* may influence the sensitivity to warfarin. There are three

common allelic forms of the *APOE* gene: e2, e3, and e4. There is a consensus in the literature regarding the minimal contribution of the *APOE* genotype, which accounts for <2% of the variability in warfarin dose-response [92, 93]. *APOE* genotype is frequent among MENA region with an estimated MAF of 6.7-7.6% among Egyptians [72].

From another perspective, GGCX is an important enzyme for the posttranslational carboxylation reaction. While *GGCX* gene is affected by multiple variants, the clinical effects of these variants on warfarin dose are small (accounting for 2% of response variability) [92-94]. The same applies for *EPHX1* polymorphisms (rs1877724 and rs1131873) G>A, which might alter the response to warfarin, yet they have little influence on warfarin dose [92, 93].

1.15 Warfarin Pharmacogenetic-Based Dosing

Clinical studies of genotype-guided warfarin dosing aim to tailor patient's warfarin dose at initiation in order to reduce the risk of bleeding and the risk of thromboembolism [95]. These risks are predominantly evident during warfarin initiation [95]. As such, patients would get great benefits from the accurate prediction of their individualized warfarin doses at initiation. This would also help reduce the number of required INR tests and the subsequent dosing adjustments to attain the desired therapeutic INR range [96]. Mutations in the *CYP2C9*2, CYP2C9*3*, and *VKORC1-1639* alleles have been consistently associated with changes in warfarin dosing requirement, while other genetic polymorphisms were somewhat conflicting [97]. Based on three GWA studies, warfarin doses varied with polymorphisms in the *CYP2C9, VKORC1, and CYP4F2* alleles (in some studies), with the major influences implied by *VKORC1* followed by *CYP2C9*, respectively accounting for approximately 35% of warfarin dose variability [98]. Furthermore, about 20% of the individual variations in warfarin dosing have been associated with a combined effect of individual

non-genetic characteristics, including age, nutrition, gender, comorbidities, smoking, and other co-administered medications [99, 100]. The frequencies of alleles responsible for warfarin dose variability among different ethnic groups are demonstrated in Table 1.3.

Several recent studies investigating pharmacogenetic-guided dosing in comparison to clinical-guided dosing have been conducted. In essence, the Clarification of Optimal Anticoagulation through Genetics Trial (COAG) [101], the European Pharmacogenetics of Anticoagulant Therapy Trial (EU-PACT) [102], and Genetics-Informatics Trial (GIFT) [103] are the main landmark trials that attempted to answer this question. The COAG trial was carried out in more than 12 sites in the United States of America (USA), and it compared the effect of a genotype-guided dosing regimen versus a clinical dosing algorithm. In contrast, the EU-PACT trial was conducted in the United Kingdom (UK), and compared the genotyping-guided dosing regimen to a fixed loading dose regimen. In both trials, the primary endpoint was the percentage time within target INR (TTR). The COAG study did not demonstrate any significant difference between the two arms (P=0.91), while the EU-PACT trial revealed that the genetic-guided dosing regimen improved TTR significantly (P<0.001). The difference in outcomes is possibly ascribed to variations in the control arm and the ethnicities of the tested populations and to what extent was the genetic-guided algorithm appropriate for these ethnicities. GIFT, the most recent trial, was published in 2017, and differed primarily from the first 2 by using a composite primary outcome of major bleeding, INR of 4 or greater, venous thromboembolism, or death. The results showed that genotype-guided dosing could reduce at least one of these adverse events (p=0.02) with significant improvements in theTTR (54.7% vs. 51.3%, respectively, p=0.003) compared to the clinically guided group.

Table 1.3: The frequencies of gene alleles responsible for warfarin dose variability among different ethnic groups

Allele	Frequency		
	European Caucasians	**US Hispanics**	**African–Americans**
*CYP2C9*2*	10%	7%	2%
*CYP2C9*3*	6%	5%	1%
*CYP2C9*5*	<1%	<1%	1%
*CYP2C9*6*	<1%	<1%	1%
*CYP2C9*8*	<1%	<1%	6%
*CYP2C9*11*	<1%	<1%	4%
CYP2C9 rs7089580	24%	11%	23%
VKORC1 -1639A	40%	46%	11%
VKORC1 rs61162043	Unknown	Unknown	47%
CYP4F2 433M	23%	22%	9%

(Adapted from Cavalalri, 2012 [104])

1.16 Evidence from Observational Studies in MENA Region

The Middle East and North Africa (MENA) region has a unique strategic location and resources, and it has continually migrating civilizations in and out of its contained countries. Therefore, from a genetic perspective, the MENA populations are heavily admixed with Arab, Caucasian, Asian, and African ancestries. A recent systematic review [72], was conducted including cohort studies and observational cross-sectional investigations, which had assessed the impact of genetic and non-genetic factors on the variability of warfarin dose. The genetic determinants have focused on the genetic variants in *VKORC1* and *CYP2C9* genes, and the prevalence of genetic variants was

evaluated using the minor allele frequency (MAF) of such variants.

Based on the published report in 8 different populations in the MENA region, including individuals from Iran, Egypt, Oman, Sudan, Kuwait, Turkey, Lebanon, and Israel, the *VKORC1* (-1639G>A) variant was most reported across all populations, and the MAF ranged between 30% and 56% among Egyptian and Iranian populations, respectively. Furthermore, other commonly reported variants were the *2 and *3 variants of the *CYP2C9* gene, and the Iranian population has exhibited the highest MAF for CYP2C9*2 (27%). Interestingly, pharmacogenetics studies revealed that *VKORC1* and *CYP2C9* were independently associated with warfarin dose across all MENA populations, with the *VKORC1 (-1639G>A)* variant explaining upto 40% of the variation in warfarin dose. Furthermore, a composite regression model comprising all genetic and non-genetic factors explained 63% of dosing variability in Israeli and Omani patients. However, the genetic variants' performance showed significant heterogeneity among different populations, necessitating conducting future micro-geographically based studies to reveal specific dosing algorithms in each country.

1.16.1 Evidence from Observational Study in Qatar

A recent observational, cross-sectional study [105], was conducted involving 150 warfarin-using patients with a therapeutic INR, which had been achieved for at least three clinic visits. The main objectives included the prevalence of *VKORC1, CYP2C9,* and *CYP4F2* variants and their effects on predicting warfarin dose variability. The results indicated that the MAFs of *VKORC1-1639G>A, CYP2C9*2, CYP2C9*3,* and *CYP4F2*3* were 47%, 12%, 4%, and 43%, respectively. Carriers of any decreased function allele (CYP2C9*2 or *3) had significantly lower warfarin dosing requirements than the patients with the **1/*1* genotype explained 11.8% of the variability of the anticoagulant doses. Moreover, the *VKORC1-1639* was the strongest independent

predictor of warfarin dose, explaining 14.8% of the variability. However, despite its high frequency, the *CYP4F2**3 variant was not associated with warfarin dose. Collectively, the authors found that a dosing algorithm composed of a history of hypertension, heart failure, and smoking and having *VKORC1* and *CYP2C9* variants predicted warfarin dose to a reasonable extent (explaining 40% of dose variability). These findings were limited by the inability to incorporate essential covariates in the regression model, such as the Qatari population's genetic substructure, patient's adherence to warfarin therapy, and dietary vitamin K intake.

1.17 Periprocedural Management of warfarin

The perioperative management of patients receiving OAC therapy is a common clinical dilemma. OAC regimens especially VKA can be continued, interrupted, or replaced with other parenteral ACs, namely "bridging". An initial consideration is that, if possible, the clinician might avoid or delay the procedure until the AC administration is no longer required. If not, the benefits and risks should be thoroughly discussed with the patient, and he/she should be informed about the joint-based decision [106, 107].

Also, clinicians should assess the periprocedural risks of bleeding or thrombosis. For example, patients with VTE are deemed at high risk of thrombosis when they had VTE episodes within the last 3 months or had severe thrombophilia, at moderate risk with VTE episodes within the past 3-12 months, moderate to mild thrombophilia, or active cancer, or low risk when they had VTE within > 1 year without any other apparent risk factors [108]. Besides, thrombotic risk assessment for AF patients, which is the main indication of long-term oral AC therapy, should be based on the annualized stroke risk indicated by the commonly used risk assessment tool-CHA_2DS_2-Vasc score. High scores (≥7) indicate a high thrombotic risk, while scores of 5-6 and 1-4 indicate moderate or low thrombotic risks, respectively [109]. Furthermore, patients with prior thromboembolic events within the past three months, > 3 months, or no prior events are

considered at high, moderate, or low thrombotic risks, respectively [5]. Subsequently, clinicians are required to assess whether there is an evident necessity of OAC interruption to avoid the potential risks, inconvenience, and costs of discontinuation and resumption as well as the need to bridging. Notably, the efficacy and safety of warfarin discontinuation before surgeries are mainly dependent on several domains, which will be addressed below.

1.17.1 Bridging

Clinicians were wrestled for years with the dilemma of how to best manage patients receiving OAC during a therapeutic pause period before and after elective surgeries. In some instances, OAC may be interrupted, and short-term parenteral therapy, using either LMWH or intravenous UFH, may be initiated to reduce the risk of thrombosis or bleeding. Such a clinical scenario is termed “bridging”. Clinicians should firstly obtain INR values 10-14 days before the procedure, to have a clear assessment of patient’s therapeutic level prior to procedural planning. Ideally, for a patient who is receiving warfarin, the interruption starts 3-4 days before the procedure if the INR is subtherapeutic (1.5-1.9), 5 days before the procedure if the INR is normal (2-3), and 7 days (or more) before the procedure if the INR is elevated [110, 111]. Consequently, a therapeutic dose of either LMWH or UFH should be started 36 h following the last dose of warfarin and the INR is remeasured 24 h before the procedure [110-112].

The potential therapeutic benefits of parenteral AC bridging should be assessed versus the putative bleeding risks. However, there is considerable uncertainty regarding this matter. For example, Siegal et al. [113], conducted a meta-analysis of 33 prospective cohort studies and one RCT comprising 7118 bridged and 5160 non-bridged patients receiving VKA therapies for different indications. The authors found no difference in the incidence of thromboembolic events. In contrast, the risk of significant and overall

bleeding was significantly higher in heparin-bridged patients than their non-bridged counterparts. However, the included studies were of low quality, and thus, the interpretation of their outcomes should be taken with caution. More recently, Yong et al. [107], assessed studies conducted between 2005 and 2016 (19 observational studies and six RCTs) for the risks of bleeding or thromboembolic events among 10,313 and 25,631 bridged and non-bridged patients, respectively, who received OAC for varied indications. The authors revealed that heparin bridging led to a significant increase of major, minor, and overall bleeding. At the same time, there was no difference in the risk of thromboembolic events, stroke, or all-cause mortality. The inclusion of many observational studies in the meta-analyses above might limit the statistical significance of these outcomes because patients in control (non-bridged) groups may be at low thromboembolic risks.

Considering specific patients' populations, the risk of bleeding, as well as the risks of myocardial infarction, systemic embolism, hospitalization, or 30-day mortality were also significantly higher in patients receiving bridging therapies (p<0.0001) when compared to non-bridged patients with AF as revealed in a large prospective study of the ORBIT-AF Registry [114]. In such a study, although there was no between-group difference in CHA_2DS_2-Vasc scores (mean 2.4), patients in the bridged group were more likely to have prior mechanical heart valve (MHV) replacements or cerebrovascular events which may pose some risk of selection bias. In the Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial, Douketis and colleagues. [115], randomly assigned 1884 warfarin-receiving patients with AF (mean CHA_2DS_2-Vasc of 2.4) to receive bridging with LMWH or a placebo-controlled bridging perioperatively. They found that bridging was associated with more frequent

incident major bleeding as compared to non-bridging (relative risk [RR]=0.41, 95% confidence interval [CI], 0.20-0.78, *P* = 0.005). Similar findings were reported in a recent meta-analysis of four observational studies and one RCT, showing that the risk of bleeding was significant with bridging in patients with AF (CHA_2DS_2-Vasc =2.34-2.49) who had their OAC therapies temporarily interrupted [116]. Additionally, there was no difference in mortality rates or cerebrovascular accidents.

Among patients with a VTE history, bridging with either LMWH or UFH was investigated versus no bridging in a retrospective analysis of 1178 patients who underwent surgical or invasive diagnostic procedures during which warfarin therapy was discontinued [117]. The risk of bleeding was significantly higher with the bridge therapy than non-bridging (hazard ratio [HR]=17.2, 95% CI, 3.9-75.1). At the same time, there was no difference in the risk of recurrent VTE between both groups. As for patients with MHV, the evidence was relatively scarce. In a retrospective study, Guglielmetti et al.[118], found that more bleeding complications were reported postoperatively among patients who received warfarin with bridging versus warfarin group as evidenced by more frequent pericardial effusions (*P* = 0.02) and reoperation for bleeding (*P* = 0.05). Another case series of 556 patients who were heparin-bridged revealed a rate of 3.6% for major bleeding and 0.9% for 90-day thromboembolism [119].

Focusing on relevant guidelines, the 2012 practice guidelines of ACCP indicated that bridging therapy should be considered in patients with intermediate risk of thromboembolism based on its advantages and disadvantages in each patient as assessed by the risk of thrombosis and the risk of procedural bleeding [108]. For patients with high risk, bridging was recommended in the instance of low risk of procedural bleeding, while it was prohibited for those with low risk of

thromboembolism. However, OAC discontinuation should be avoided for procedures with low bleeding. These guidelines agreed with those of the American Heart Association (AHA), American College of Cardiology (ACC), and Oxford University [120, 121]. Unfortunately, all guidelines are based on low-quality observational studies and considered adopting the bridging therapy as an unanswered question, requiring further large RCTs to resolve the gap. The recommendations were alternatively based on a risk classification scheme, which has been suggested by clinical experts.

The recent BRIDGE RCT [115], has partially clarified and emphasized the association between heparin bridging and increased bleeding risks in patients receiving warfarin . A recent analytical study of the BRIDGE trial using multiple logistic regression analysis showed that baseline bridge therapy is a significant predictor of major bleeding [122]. Therefore, a more recent paper [123] of the ACC recommendations indicated that clinicians should carefully adopt both the need for OAC discontinuation and the bridging process when OAC interruption is needed. The relevant ongoing trials, such as the Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study (clinicaltrials.gov identifier: NCT02228798) and the PERIOP2 study (for the efficacy and safety of LMWH versus placebo bridging among warfarin-receiving patients, clinicaltrials.gov identifier: NCT00432796), would hopefully yield strong recommendations based on well-designed protocols.

Collectively, studies regarding bridging anticoagulation in patients receiving warfarin showed evidence of increased risk of bleeding when bridging has been adopted. Hence, heparin bridging is probably avoidable, which would simplify the process of perioperative management. However, such evidence is based only on one robust RCT and other low-quality observation studies. Also, the distinction of the need to bridge is not investigated in RCTs in specific patients' populations who require anticoagulation

therapy, such as those with MHV. Until further evidence-based clarification, this knowledge gap should be assessed among clinicians regarding their current anticoagulation management practice before and after surgical procedures.

1.17.2 When to interrupt?

Most of the recommendations indicate that warfarin should be stopped five days before surgery, in order to achieve INR of < 1.3 at the time of the procedure to make it safe to proceed with procedures that have more than minimal risk of bleeding. A prospective study assessing preoperative discontinuation of warfarin showed that INR was > 1.5 at the time of surgery in only 7% of patients whose warfarin was interrupted five days before surgery [124]. Also, in a prospective study conducted by Pengo et al. [125], the authors found a mean INR of 1.8 on the day of the operation when patients stopped warfarin five days before surgery. This estimation is based on two evidence-based resources. The first resource is that the rate of synthesis of functional coagulation factors II and X following interruption. Second, the recommended interruption period is sufficient to replenish the essential factor II since the 5-day period corresponds to its double half-life [126]. However, there may be a degree of uncertainty regarding the optimal timing of warfarin interruption before surgeries. The recommendations are still based on expert opinions and may be varied according to surgery type, or individual institutions, patient-related factors. In recent recommendations, although the optimal time was primarily dependent on INR values on the day of surgery, it may be shorter or longer than recommended based on the desired INR, which complicates the clinical issue.

1.17.3 Complications of Warfarin Periprocedural Management

In general, warfarin dose management is a complicated task. Therefore, supra- or sub-therapeutic warfarin anticoagulation is possible, with the former is more predominant than the latter. In the United States, warfarin is the most common cause of drug-related

adverse events that lead to hospitalization among older adults, accounting for approximately one-third of hospital admissions. Furthermore, warfarin-related bleeding has led to more than 21,000 admissions to hospital wards between 2007 and 2009 [104]. Annual rates of major bleeding episodes among warfarin users have been estimated at 1.3%-4.2% per year [54], and 0.4%-2.0% of the episodes of warfarin toxicity required hospitalization, blood transfusion, or surgery [34]. Moreover, re-bleeding has occurred in 1 in every 12 patients after restarting warfarin therapy, and death has taken place in 10% of patients due to the hemorrhagic episodes [127]. The most severe adverse event was intracranial hemorrhage, with an incidence rate of 4 per 1,000 warfarin-receiving patients annually [128]. Besides, almost half of the patients with intracranial hemorrhage have died [129]. Of note, warfarin ranks among the top ten medications that lead to emergency department visits due to drug-related adverse events among the elderly [130]. The risk of bleeding increases, and the risk of over anticoagulation (INR ≥4.0) is 22 times higher among patients aged ≥80 [131]. Besides, focusing on outpatient prescriptions of antiplatelet drugs, the risk for acute bleeding events that necessitate admission to the emergency department was significantly lower among those who had received clopidogrel and aspirin (12 per 10,000 outpatient visits) compared to patients who had received warfarin (25 per 10,000 outpatient visits, RR = 0.49, 95% CI, 0.15-0.83) [132]. Evidence from the United Kingdom has revealed that the rates of bleeding complications ranged between 10% and 24% per year [133]. Based on a systematic review of published reports, it has been shown that warfarin prescription was associated with an increased risk of bleeding independent of other covariates, except for having a history of malignancy or renal disease [134]. Definition of various types of bleeding associated with warfarin use are summarized in Table 1.4.

Based on the preceding observations, it has been reported that the rate of warfarin

prescription is 60-70% lower among AF patients compared to those peers without AF [16]. Early studies carried out among AF patients before the availability of direct OAC (DOACs) showed that only 50% of patients had been managed with warfarin [131]. This indicates that physicians refrained from prescribing warfarin to those populations and, on the other hand, patients were non-adherent to the prescribed medication [135]. In essence, due to safety concerns, about one-quarter of patients aged ≥80 years had stopped warfarin within the first year of treatment [131]. Despite their eligibility for warfarin therapy, high-risk patients had been at an increased risk for stroke if they did not receive warfarin [16].

To overcome the difficulties implied during warfarin therapy, several methods have been suggested to enhance anticoagulation management, including conducting specialized clinics for routine monitoring of anticoagulation, developing specific dosing algorithms and relevant software to augment the efficiency of warfarin dosing, and enhancing patients' adherence to treatment via targeted educational programs [136].

Table 1.4: Clinical definitions of various types of bleeding

Clinical event	Definition	Ref.
Extracranial hemorrhage	Major bleeding that occurs outside the cranium (skull).	[137]
Intracranial hemorrhage	Major bleeding occurs inside the cranium (skull).	[137]
Intracerebral hemorrhage	A dense hematoma within more widespread areas of cerebral contusion.	[138]

Clinical event	Definition	Ref.
Major bleeding	At least one of the following must be satisfied. 1- Symptomatic or clinically overt bleeding that is associated with one or more of: - Transfusion of ≥2 units heterologous packed red blood cells or whole blood - Decrease in hemoglobin level of >20 g/L (>2 g/dL). - Need for reoperation or invasive intervention (e.g., evacuation of wound hematoma). 2- Symptomatic or clinically overt bleeding at a critical anatomic site; bleeding that is intracranial, intraspinal, intraocular (retro-orbital, vitreous, choroidal, or retinal hemorrhage), retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome. 3- Fatal bleeding Bleeding directly contributes to death (e.g., intracranial bleed) or causes clinical deterioration leading to death (e.g., bleeding associated with sepsis or major organ failure).	[139, 140]

Clinical event	Definition	Ref.
Minor bleeding	Symptomatic or clinically overt bleeding that does not satisfy the criteria for major bleeding	[139]
Subarachnoid hemorrhage	The extravasation of blood characterizes it into the CSF.	[138]
Subdural hemorrhage	A collection of blood between the dura and leptomeninges.	[122]

CSF; cerebrospinal fluid.

1.18 Pharmacogenetics-Based Warfarin Interruption

Several genetic and non-genetic factors have been repeatedly contributed to the variability in warfarin dose-response [141, 142]. Focusing on genetic determinants, it was as early as the mid-1990s when Takahashi et al. [143], studied the effect of *CYP2C9* polymorphism on warfarin elimination. Since that time, some articles were published concerning the genetic determinants of warfarin metabolism and clearance, yet more recent evidence has focused on INR normalization, which is more clinically relevant. However, the influence of *CYP2C9, CYP4F2* and *VKORC1* polymorphism on INR normalization has not been studied extensively [143-149]. The main objective of these studies was the assessment of genetic and clinical factors towards warfarin elimination and normalization of INR.

The start when Takajashi et al [143], investigated the effect of *CYP2C9* on warfarin clearance in vivo, and found that only *CY2C9*3* heterozygous, not homozygous mutant affects (S)-warfarin clearance. Later in 2005, Herman et al. performed a genotyping and pharmacokinetic analysis of 188 patients in Slovenia [148]. Based on multiple regression models, the authors found that the *CYP2C9* genotype and age and body

weight, were significantly associated with warfarin dose requirement and that the same variables (except age) were significant predictors of warfarin clearance, explaining 42% of the variability in warfarin dose. After 8 years of last research on the same topic, another work could not find any relationship between the genetics variants of *CYP2C9, CYP4F2* and *VKORC1* and INR normalization (≤1.2) in 30 patients [149]. In Thailand, Chartrungsan et al. [147], sought to explore the proper timing of warfarin discontinuation before surgery and the role of patients' demographic and genetic factors on the timing of interruption. The authors randomized two groups of patients (n=34 in each group) to stop warfarin for either three or five days before surgery. They showed that genetic factors were not associated with INR normalization. Nevertheless, INR normalization was not influenced by possessing the *VKORC1* or *CYP2C9* variants. Such a lack of association may be attributable to recruiting a small number of patients in each group; thus, the sample size might not have sufficient power to indicate significant differences between the randomized arms. Besides, patients' genetic variation was not considered as a covariate in the regression analysis, which might have limited the obtained outcomes.

In the United States, Burmester and colleagues [146] demonstrated similar results. The authors investigated the medical records of patients who had temporarily discontinued warfarin preoperatively, had had two INR values available during the drug discontinuation period, and had their genotypes available for the *CYP2C9*, *VKORC1*, and *CYP4F2* variants. The authors found no significant effects of all the demographic, clinical (history of diabetes, mild liver disease, or heart failure)—genetic variables on the slope of INR decline after warfarin interruption. The study was also limited by the small number of patients included in the analysis (n=89), and the retrospective design might have conferred a lack of significant associations between different variables.

Another major limitation was the small number of patients with rare genotypes (i.e., non-wild *CYP2C9*, which could have contributed to the lack of significant INR decline effects.

In the United Kingdom, in 2015, Abohelaika and co-authors [145] assessed the effect of *CYP2C9* polymorphism and other clinical factors on variability in INR fall among patients who had their warfarin withdrawn before elective surgeries (n=152). Reduced fall rates in INR were independently associated with two *CYP2C9* variant alleles (*CYP2C9*2 or CYP2C9*3*), old age, the number of comorbid conditions, body weight, and low initial INR levels; such variables accounted for 90% of the variability in INR changes. Therefore, the authors recommended the implementation of a genotype-guided protocol for warfarin withdrawal before elective surgeries. Three years later, the same group [144] assessed the influence of *CYP2C9* and *VKORC1* genotypes and patients' clinical variables on warfarin clearance and INR decline following the discontinuation. Among the recruited patients, the time required to attain normal coagulation after warfarin cessation was predominantly dependent on warfarin clearance, which was affected by age and the polymorphism in *CYP2C9*, but not *VKORC1*. These findings might have been limited by the small number of patients with the genotypes *CYP2C9**2*2* (n=6) and *2*3* (n=1), whereas no patients had the **3*3* genotype.

1.19 The Importance of Economic Evaluation in Cardiovascular Management

Ischemic heart disease and stroke are considered the primary cause of morbidity and mortality in Qatar, accounting for 24% of all-cause mortality [150]. As a result, reducing premature mortality from cardiovascular disease has been incorporated as Qatar National Health Strategy (NHS) [151]. Recently, the World Health Organization (WHO) stated that preventive medicine is cost-effective. The majority of health expenditure must be spent on preventable conditions like cardiovascular diseases,

which will remarkably reduce the incidence and prevalence of risk factors [151]. Notably, genetic testing is one of these preventive medicine tools. It predicts how the genetic difference in one or multiple genes can explain the variation in patients' response to medication [152-154]. For such a purpose, Qatar established the first biobank in the Middle East in 2016 and Qatar Genome Project to help identify the genetic mutation in the Qatari population and develop medical treatment and disease prevention plans for the Qatari population health [155]. In other words, Qatar is transforming from a general medicine approach to a personalized approach based on genetic testing, which is still not routinely performed in Qatar. Consequently, there is an urgent need to get insights into the evidence-based cost-effectiveness of genetic testing implementation.

One example of the application of genetic testing in practice is the recommendation implied by the U.S Food and Drug Administration (FDA) to physicians in 2007 to consider genetic testing before warfarin initiation and to modify the label of warfarin (Coumadin, Bristol-Myers Squibb, Princeton, New Jersey) to include this recommendation [57]. Bearing in mind the dramatic increase in warfarin prescription and its potentially severe side effects, the pharmacogenetic-guided algorithm is considered as a promising tool to initiate and stop warfarin more accurately [156]. It has been reported that the identification of the *CYP2C9* and *VKORC1* genetic polymorphism significantly dropped the incidence of bleeding due to an elevated international normalized ratio (INR) after starting maintenance dose by 10.5% [157]. However, pharmacogenetic testing entails a high cost since *CYP2C9* and *VKORC1* genetic screening ranges from United States Dollar (USD) 400-550 in the USA [158]. More evidence of cost-effectiveness is required for the implementation of pharmacogenetic tests in clinical practice.

1.20 Cost-Effectiveness Analysis of Pharmacogenetics-Based Dosing Versus Standard of Care

The cost-effectiveness of the genotyping-guided algorithm in warfarin dosing versus standard dosing has been investigated in different countries worldwide. The first study was performed in 2004 by Joyce H.S. et al. [159] in China, whereas the most recent study was conducted in 2017 by Carlos et al.[160]. During this period, several studies that assess the cost-effectiveness of pharmacogenetic dosing of warfarin against standard dosing were published. A frequently cited investigation was established by Meckley (2010) [161], who developed a Markov model to evaluate the cost-effectiveness of warfarin genetic-guided dosing. The author found a small benefit of applying the pharmacogenetics pathway, and the result is attributable mainly to the cost of genetic testing. The possible driving explanation of this finding is that the study used for clinical input of the model was based on data about patients who initiated warfarin dose as an inpatient, which is not the typical case. Another high-quality study that evaluated the cost-effectiveness of both regimens based on data from the EU-PACT study [162]. Results revealed that that genotype-guided phenprocoumon dosing was cost-effective compared with standard dosing [162]. So far, there is only one systematic review [163], that was published in 2016 and reported the outcome of research studies that assessed the cost-effectiveness of pharmacogenetic-based dosing versus standard dosing or DOAC. The study determined that the genetic-guided pathway was dominant or cost-effective in 60% of the published studies. At the same time, the remaining reviews indicated that the genetic-guided path was not cost-effective. Overall, the results of these studies were controversial because the studies depended on the cost of resources and complications which differ according to the country of the study. Of note, to the best of our knowledge, no cost-effectiveness study investigated the use of pharmacogenetics pathway in interrupting warfarin before elective surgery.

1.21 The Rationale for This Research

In a recent review, Zayed et al. [164] emphasized the need to establish a human genome database for Arab populations to get insights into the molecular basis of genetic diseases, to predict new genetic disorders and drug-drug interactions, and to govern the future of personalized medicine. In Qatar, warfarin prescription represented about 77% of all OACs in 2015 [12]. On the other hand, the consanguine marriage rate is high (35%), which might have influenced the Qatari population's genetic makeup. With the inconclusive results on the effect of genetic factors on the rate of INR decline in warfarin patients undergoing a procedure and the lack of any similar study in the Arab population, we sought to investigate the effects of genetic polymorphisms of the *CYP2C9, VKORC1, CYP4F2, coagulation FII,* and *FVII* genotypes and non-genetic factors on the rate of INR decline followed by economic evaluation of pharmacogenetics-based management. This way, the present study's outcomes might provide significant benefits to estimate the best cutoff time at which warfarin should be discontinued before surgery. Subsequently, the time spent off warfarin will be optimized, and the amount of interim anticoagulation use with LMHW will be best regulated accordingly. This is particularly relevant for patients at a high risk of complications, which might develop due to either early or delayed warfarin interruption.

1.22 Aims of This Research

1. Addressing the gap of warfarin periprocedural management, which is acknowledged by previously published prescribers' questionnaires.
2. Evaluating the current attitude, awareness, and practice among health care providers on warfarin periprocedural management.

3. Evaluating the real-world clinical practice of warfarin periprocedural management and investigate the clinical outcomes associated with warfarin bridging versus non-bridging in Qatar.
4. Performing cost analysis of current warfarin periprocedural management practices, including a cost-effectiveness analysis (CEA) of predominant bridging versus predominant non-bridging practices.
5. Exploring the influence of *CYP2C9, VKORC1, CYP4F2* and coagulation *FII and FVII* genetic polymorphisms and non-genetic factors on INR decline in an Arab population.
6. Assessing the cost and benefit of implementing a pharmacogenetic-guided approach in preprocedural warfarin management.

CHAPTER 2: THE DILEMMA OF PERI-PROCEDURAL WARFARIN MANAGEMENT, A NARRATIVE REVIEW

2.1 Introduction

The perioperative management of patients receiving warfarin therapy is a common clinical dilemma. Warfarin regimens can be continued, interrupted, or replaced with other parenteral anticoagulants (ACs), namely "bridging" [108]. The issue is always complicated with the small overlapping line between thrombotic and bleeding risks. An initial consideration is to avoid or delay the procedure until the warfarin administration is no longer required, if possible. If not, both operation and patient status benefits and risks should be thoroughly considered [108].

Clinicians should assess the periprocedural risks of bleeding or thrombosis. For example, patients with venous thromboembolism (VTE) are deemed at high risk of thrombosis when they had VTE episodes within the last 3 months or had severe thrombophilia. This risk is considered moderate when VTE episodes are within 3-12 months, or in cases with moderate to mild thrombophilia or active cancer. Risk of thrombosis is deemed low in patients with VTE within > 1 year without any other apparent risk factors [108]. On the other hand, thrombotic risk assessment for patients with non-valvular atrial fibrillation (AF) and are at risk of stroke, should be based on CHA2DS2-VASc score. High scores (≥7) indicate a high thrombotic risk, while scores of 5-6 and 1-4 indicate moderate or low thrombotic risks, respectively [165]. Subsequently, clinicians are required to assess whether there is an evident necessity to interrupt warfarin to avoid the potential bleeding risks. If warfarin interruption is deemed necessary, then bridging decision should be made with the consideration of thrombotic/bleeding risks, patient inconvenience, and cost.

The objective of this review is addressing the gap of warfarin periprocedural management which are acknowledged by previously published prescribers' surveys

through a comprehensive assessment of the published surveys on MEDLINE with PubMed interface.

2.2 Review of Surveys Performed on The Periprocedural Management Based on Surgery Type

2.2.1 Patients Undergoing Urological Surgeries

In 1999, a study conducted in the United Kingdom, where a postal survey was sent to urologists and radiologists concerning the practices and attitudes towards warfarin and aspirin use in patients undergoing prostatic biopsies [166]. Among 75% and 65% of responded radiologists and urologists, preferred stopping warfarin three days before biopsies by most of the participants, with a range between 1 and 8 days. Importantly, 52% of the urologists did not indicate the existence of a specific protocol regarding preoperative management of ACs and the same percentage of participants were unaware about cases being postponed owing to patients unexpectedly receiving warfarin. The main finding of the study is that the safe International normalization ratio (INR) level was widespread to proceed with biopsy (1.2-2.0). another online questionnaire was emailed to urologists regarding their practice of warfarin use before and after urological procedures, including minor surgeries, such as circumcision and biopsy, endoscopic procedures, and major surgeries, such as open radical prostatectomy and radical cystectomy [167]. Approximately half of them responded, showing wide variations in their responses. For example, the range of preoperative discontinuation of warfarin was 2-10 days, while no significant differences were noted according to the type of surgery. Heparin bridging was employed by 60% of the urologists. During the postoperative period, urologists restarted warfarin 1-28 days after the procedures with a significant delay of reinitiating after major surgeries (4.38 ± 3.53 days) as compared to endoscopic (3.07 ± 3.52) and minor procedures (2.41 ± 2.31, $P < 0.001$) the authors concluded that procedure grad did not stimulus the warfarin discontinuation

preoperatively, but it influenced its re-initiation. Both studies presented that there is a wide discrepancy in preoperative management strategies for warfarin with many urologists.

2.2.2 Patients Undergoing Cardiovascular Surgeries

The anticoagulation regimens provided to patients undergoing cardiac rhythm device surgery were assessed among device implant physicians via postal questionnaires in Canada [168]. The surveys presented four clinical scenarios to reveal the perceived risks of thromboembolic events based on the existence of Mechanical heart valve (MHV), a history of stroke, AF, and the risk factors (items) of the CHADS2 score. Furthermore, six managemental approaches were offered, including warfarin interruption without bridging, three different protocols of bridging, and ongoing warfarin administration without interruption. Results showed that (83%) of participants chose the ongoing warfarin approach for patients with a low risk of thromboembolism. On the other hand, there were substantial variations regarding high-risk patients; heparin bridging was selected by 38%-72% of respondents, while remaining preferred warfarin continuation. In this study, it is plausible that surgeons tended to pursue the risk of bleeding rather than the risk of thrombosis in the perioperative period since bleeding is rapidly detectable and manageable in such a patient population.

2.2.3 Patients Undergoing Dental Procedures

A sample of general dental practitioners (GDPs) in Wales answered a questionnaire about their practices regarding warfarin peri-procedural management [169]. Only 1% indicated that the patient should stop warfarin before surgeries without consulting other medical practitioners. Notably, 34%, 30%, 10% and 10% of the responders considered normal INR upper limit at 2.5, 3.0, 3.5 and 4.0, respectively. This study showed that the practice of GDPs differed from 2001 recommendation, and a number of them lacked the required knowledge.

Another cross-sectional study conducted among the Michigan Society of Oral and Maxillofacial Surgeons in the United States [170], 188 surveys were distributed to assess practice levels regarding patients receiving AC therapy whom dental procedures of different risks were indicated. Warfarin discontinuation was significantly predominant in high-risk procedures (70.5%) when compared to moderate (48.8%) and low-risk procedures (23.6%, $P < 0.01$). Indeed, these results were relatively surprising since warfarin discontinuation in the low-risk group, which includes 1-5 simple extractions, was indicated even though INR values were maintained at the therapeutic levels (mean=2.68). On the other hand, the practice of dental surgeons regarding moderate- (6-10 simple extractions, one quadrant alveolectomy, and 1 impacted extraction) and high-risk procedures (>10 simple extractions, >2 quadrant alveolectomy, and >2 impacted extraction) are not guided by evident literature investigations. Therefore, it seems that the current attitudes of dental surgeons are affected by the lack of uniformity that exists in the literature. The authors emphasized the need to conduct relevant prospective clinical trials that help create uniform guidelines.

2.2.4 Patients Undergoing Cutaneous Surgeries

The significance of perioperative management of AC in patients undergoing cutaneous surgeries was initially presented in a case series of two patients who experienced postoperative stroke after warfarin discontinuation [171]. Moreover, Kargi et al. [172], revealed that warfarin-receiving patients are at significant risks of persistent bleeding, loss of skin graft, as well as wound hematoma and infection during the procedures although minor surgeries could be performed while taking warfarin with precaution. Therefore, in 2002, Kovich and Otley [173], sent mailed surveys to assess the practice among 168 surgeons of the American College of Mohs Micrographic Surgery and

Cutaneous Oncology. Most of the respondents (80%) employed warfarin interruption, were they discontinued warfarin three days preoperatively and continued it 1-2 days after the procedures. In addition, only 10% of the participants prescribed heparin bridging in the instance of warfarin interruption. These findings were relatively inconsistent with the published recommendations at the time [174], which indicated warfarin continuation during cutaneous surgeries without major risks and, if discontinued, heparin bridging should be considered in high-risk patients. Survey results also showed that only 15% of surgeons measured INR or prothrombin time preoperatively. This observation may be related to the reliance of surgeons on the latest results of the regularly performed laboratory investigations rather than requesting new ones [173].

However, three years later, another survey of surgeons of the same organization showed different results. Kirkorian et al.[175] received completed surveys from 271 physicians (response rate 38%) regarding their practices of patients receiving AC and undergoing Mohs surgery, biopsy, excision, liposuction, and blepharoplasty. Although 62% of the participants indicated that ACs usually leads to marked bleeding during surgeries, 56% and 63% of them never discontinued warfarin and aspirin during the procedures, respectively. In the instance of warfarin interruption, less than half of physicians (42%) discontinue the medication three days preoperatively. Indeed, these results show a significant change in practice levels within a short period as compared to the previous survey, with a remarkable shift toward warfarin continuation. Notwithstanding the agreement between physicians' attitudes and the recommended guidelines at that time [174], the results of this survey underscore the urgent need to set the safe standard through strong recommendations.

More recently, Khadim et al.[176] investigated the practice of members of the British

Association of Plastic Surgeons regarding perioperative AC management of patients undergoing cutaneous surgeries of the head and neck. Among 113 respondents, 43% discontinued warfarin preoperatively, 33% decided based on INR values, while only 18% preferred to continue warfarin. For the INR-dependent group, there was a controversy in decision-making, where warfarin discontinuation was based on INR values over 3, 2.5, and 2 in 36%, 22%, and 36% of participants, respectively. Among warfarin-interrupting respondents, the reasons of interruption were reducing intraoperative bleeding (73%), concerns about hematoma incidence and subsequent skin graft failure (66%). Actually,34% of physicians had already experienced one or more severe complications owing to warfarin interruption. Importantly, 34% of the participants indicated that their practices were based on local departmental policies, while only six respondents preferred to consult clinicians from related specialities regarding changing AC therapies. Overall, these results show significant variability in perioperative practices among plastic surgeons. This was associated with an unexpectedly high incidence of complications and, therefore, standard protocols are needed to address these issues.

2.2.5 Patients Undergoing Ophthalmological Surgeries

Anticoagulation management of ophthalmological procedures was assessed by several studies. An early investigation was conducted in 2000 concerning practice levels of all ophthalmic consultants and oculoplastic specialists in patients undergoing dacryocystorhinostomy, entropion, ectropion, or ptosis procedures in a local region in the United Kingdom (n=62) [177]. At least half of the participants tended to interrupt warfarin, with the least proportions reported cessation before entropion procedures and the highest proportion before dacryocystorhinostomy. Among those physicians, warfarin was stopped at an average of 3 days (range 1-10 days) preoperatively. The

majority of participants (93%) did not consult other relevant specialists about changing AC therapy, although a considerable proportion of them (54%) reported severe complications with either stoppage or continuation of warfarin. Such complications included systemic metabolic episodes, hemorrhagic surgical complications, and mortalities (due to either brachial artery embolism, or cerebrovascular accidents).

Another questionnaire-based study was established among members of the Canadian Society of Cataract and Refractive Surgery to investigate their attitudes towards using warfarin perioperatively [178]. A total of 82 physicians responded (response rate: 74.5%) from different regions in Canada. Approximately one-quarter (23.2%) of physicians discontinued warfarin before surgeries with a range of 3-7 days. Of them, 82.6% resumed warfarin on the first day, and the remainder continued it on the second day postoperatively. The small number of physicians interrupting warfarin may be attributable to the remarkable advances accomplished in cataract surgery, rendering it a minimally invasive procedure. Of note, physicians who employed warfarin interruption had more years of experience and performed surgeries less frequently when compared to their warfarin-continuing counterparts. However, nine patients experienced complication due to warfarin interruption, including cerebrovascular accidents, deep vein thrombosis (DVT), transient ischemic attack, and death (in one patient). In the latter case, the patient stopped warfarin five days before surgery. On the other hand, 15 patients experienced a hemorrhagic complication with warfarin continuation, including peribulbar haemorrhage, retrobulbar haemorrhage, Retrobulbar haemorrhage and hyphemia.

Continuing with cataract surgery, a more extensive study conducted in the United Kingdom showed similar outcomes with lower rates of warfarin discontinuation [179]. Among a total of 535 cataract surgeons participated in the survey, 69.3% were aware

of the existence of warfarin-specific departmental guidelines, and 98% indicated the importance of INR measurement perioperatively. Only 13.2% of participants stopped warfarin preoperatively; most of them did so 2-3 days before surgeries (with a range of 1-14 days). It is worthy to note that warfarin discontinuation was associated with a total of 18 complications, including cerebrovascular events, DVT, arterial embolism, Pulmonary embolism, myocardial infarction, and one reported mortality. Indeed, when compared to the previously mentioned study and other earlier studies [178, 180, 181], this emphasized the gradual decreasing trend in warfarin interruption before cataract surgeries. Although this agreed with the guidelines implied by the Royal College of Ophthalmologists of the United Kingdom (RCOphth) which recommended warfarin continuation to avoid the risk of stroke and death. Importantly, 98% of surgeons adhered to the RCOphth guidelines in terms of the necessity of INR measurement preoperatively. Interestingly, warfarin-interrupting physicians used different periods of interruption before surgeries, which were not explicitly indicated in the relevant guidelines.

Regarding glaucoma surgery, physicians' attitudes and practices were conflicting. In a cross-sectional study in the United Kingdom, Alwitry, et al. [182] received 64 completed surveys (out of 93) from a sample of glaucoma specialists. The authors found that about one-third of surgeons stopped warfarin before surgeries with a mean time of 4 days (range 2-7 days). Of these surgeons, 47.6% consulted a haematologist or a general practitioner regarding warfarin discontinuation, particularly for patients with MHV. Avoiding the risk of haemorrhage (more specifically suprachoroidal haemorrhage) was the main indication of warfarin stoppage. Concerning bridging therapy, heparin bridging was used by 38.1%, 14.1% using heparin bridging depending on the indication of anticoagulation, while the remainder refrained from bridging.

Notably, surgeons showed significant variations in their practices regarding the timing of INR check (ranging between the day of surgery to two weeks before and after surgery) as well as the INR threshold above which surgeries were not performed.

In another study based in Brazil, Balbino, et al. [183] assessed aspects of perioperative management of warfarin among the members of the Brazilian Glaucoma Society (n=52). The majority (82.7%) of respondents interrupted warfarin before surgical procedures; 69.2% of them interrupted warfarin seven days before surgery, and 55.8% resumed it at the evening of the day after the procedure. However, slightly more than half of the participants (51.9%) reported AC-related hemorrhagic complications, including hyphemia, excessive subconjunctival haemorrhage, excessive postoperative bleeding, and a hemorrhagic choroidal detachment. In line with the apparent variations in physicians' practices and the resultant complications, the authors of studies concerning perioperative AC in patients undergoing glaucoma surgeries called for an urgent need of proper guidance to control the risks of thrombosis or bleeding in these populations.

2.2.6 Patients Undergoing Miscellaneous Elective Surgeries

The general clinicians' practices regarding perioperative anticoagulation were investigated in an early study wich conducted by Oh, et al.[184] The authors sent postal and online questionnaire to physicians who frequently involved in making relevant clinical decisions, including four clinical scenarios: two scenarios in patients with established mitral MHV who undergo either major (scenario 1) or minor (scenario 2) surgeries and other two scenarios in patients with established aortic MHV who undergo major (scenario 3) or minor (scenario 4) surgeries. Additionally, the survey contained different preoperative and postoperative options for warfarin use and bridging. In general, the use of low molecular weight heparin (LMWH) was appreciated by most

respondents to all clinical scenarios when warfarin therapy must be interrupted. Although the published guidelines [185, 186] at that time have not indicated the use of perioperative anticoagulation in patients with MHV, there was no clinical consensus as revealed by the obtained responses. However, there was large variability in the preference of LMWH or unfractionated heparin (UFH) in high and low-risk surgeries, indicating a significant uncertainty on the optimal anticoagulation approaches and their association with the lack of proper guidance.

In another cross-sectional study [187], a survey was sent to physicians to assess their practices and attitudes concerning AC therapy in patients with chronic AF who would undergo elective surgeries. Clinical scenarios were classified to low or high risks of stroke. Following warfarin interruption, five options were presented to the physicians, including bridging with full-dose UFH, outpatient full-dose LMWH, low-dose LMWH postoperatively, no bridging, or switching to another AC. Results of patients with low risk of stroke revealed that warfarin interruption preoperatively and resumption after the operation was the most effective approach. In the instance of a high risk of stroke, the responses were highly variable. For example, warfarin interruption, full-dose UFH, and full-dose LWMH were preferred by 54%, 24%, and 20%, respectively before the procedure, while post procedural preferences showed an equal distribution of no bridging and in-hospital administration of full-dose UFH (35% for both). The authors stated that there is an urgent need to unified guidelines based on robust scientific evidence, particularly for the patient at high risk of stroke.

For patients with proximal femoral fractures and long-term warfarin use, the attitudes of the operating surgeons (n=159) were assessed in a cross-sectional study conducted in the United Kingdom [188]. In this study, the majority of respondents (75%) showed that they used either departmental or individual protocols for preoperative reversal as

well as reinitiating of ACs after surgery. Additionally, 70% of them employed a "withhold and wait" approach for warfarin stoppage before surgeries although this approach may be risky since delaying surgeries in patients with hip fracture might lead to deep venous thrombosis, skin breakdown, urinary tract infections and mortality [189]. For hemiarthroplasty, most surgeons aimed for INR of < 2, whereas a proportion of them considered it acceptable to proceed with the procedure with an INR up to 2.5.[188] Of note, only 35% of the respondents in this study considered hemiarthroplasty at the agreed INR of major surgeries (> 1.5). The authors suggested the use of low doses of vitamin K to reverse the therapeutic effects in warfarinized patients, and they underscored the lack of relevant guidelines that might assist in clinical decision making.

In early 2020, a group of researchers in Qatar conducted a survey among all HCPs from different specialties who are managing warfarin peri-procedurally to assess their awareness, attitude and practice towards management of such cases.[190] They found that practitioners' awareness level of warfarin peri-procedural management process is intermediate (64.28%). The main downward driver of this results was low score in 3 areas. Firstly, the awareness of the kind of surgeries that do not need warfarin discontinuation (response rate = 26.2%). Secondly, the awareness concerning the time at which patients must hold warfarin and hold LMWH before surgery (right response rate= 42.2%, 47.1%, respectively). Thirdly, bridging decision was an additional impediment. In bridging decision scenarios, they discovered obvious divergence in answer among departments. The study represented a broad disparity in the clinical practice of warfarin periprocedural management.

2.3 Conclusion

To sum up, the clinical decision regarding perioperative warfarin management is a complex aspect of care. Indeed, such an issue would ultimately lead to undesirable

variation in care. This would be complicated by the lack of institutional standardized protocols and hence differences in practices, attitudes and periprocedural outcomes. As much as possible, there should be a unified protocol followed at the institutional level. Deviation from such protocols should be very well justified by clinical factors.

CHAPTER 3: ASSESSMENT OF THE ATTITUDE, AWARENESS AND PRACTICE OF PERIPROCEDURAL WARFARIN MANAGEMENT AMONG HEALTH CARE PROFESSIONAL IN QATAR. A CROSS SECTIONAL SURVEY

3.1 Introduction

Oral anticoagulants (OAC) have been used for years in the treatment and prevention of thromboembolism [191, 192]. Notably, in Qatar, as well as other parts of the world, warfarin still represents a significant portion of total OAC used [12]. It has been estimated that 10-15% of OAC patients worldwide need to undergo an elective procedure on an annual basis, which may require holding OAC [108].

Periprocedural management of warfarin is a complicated process since it involves multiple steps, each of which must be assessed carefully before making a comprehensive plan. The first step is to decide whether warfarin should be interrupted. While warfarin interruption leads to decreased bleeding risk during and post-procedure, it can also increase the risk of thromboembolism [193]. Second, comes the bridging decision which may be considered to reduce the risk of thromboembolism in patients with moderate to high thromboembolic risk, however, increased risk of bleeding must be put into account [194]. In Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation trial (the BRIDGE Trial),1884 warfarin-receiving patients with atrial fibrillation (AF) (mean CHA2DS2-VASc of 2.4) were randomly assigned to receive bridging with low molecular-weight heparin (LMWH) or a placebo-controlled bridging perioperatively [139]. The study found that bridging was associated with a more frequent incidence of major bleeding compared to non-bridging (relative risk [RR]=0.41, 95% confidence interval [CI], 0.2-0.78, P = 0.005). Furthermore, LMWH did not prevent arterial thromboembolism significantly. Similarly, the outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) trial showed that the composite outcome of systemic embolism or stroke, myocardial infarction,

bleeding, or hospitalization was elevated in the bridging arm significantly [195]. Both studies augment the uncertainty of the need for bridging. Adding to the complexity of the bridging process is that the decision of warfarin interruption according to procedure and patient's bleeding risks are considered another controversy. Most of the guidelines stratify the risk of thromboembolism and procedural bleeding risk into high and low, to facilitate the interruption decision [194]. Unfortunately, these classifications have some drawbacks, such as procedures with a low rate of bleeding, but with severe consequences. Categorizing these procedures as a low bleeding risk instead of a high bleeding risk procedure may be misleading. Moreover, the classification did not consider the level of intermediate bleeding risk category and did not include patients with atrial fibrillation (AF). Besides, there is a disagreement regarding the classification of some procedures such as hip/ knee replacement and prostate biopsy [111].

Collectively, it is evident that the judgment of warfarin holding and periprocedural bridging is not explicit, and decision-makers can be easily misled. This can also create several practices and attitudes among health care professionals. Consequently, a survey on the periprocedural management of warfarin was developed for a better understanding of the current practice, the gap in knowledge and attitude among health care providers in Qatar.

3.2 Methods

3.2.1 Study design and population

This study is an observational prospective cross-sectional self-administered questionnaire survey that aims to understand the practice, awareness, and attitude of health care professionals (HCPs) at Hamad Medical Corporation (HMC), Qatar, toward periprocedural management of warfarin patients.

The study was conducted over six months from July 2019 till January 2020. The participants were among physicians and clinical pharmacists from various departments

involved in the periprocedural management of warfarin. A hard copy of the survey was delivered by one of the investigators. The first page of the survey contained an introductory invitation informing participants about the purpose and objectives of the survey and confirming that the contribution to the survey was voluntary and anonymous. Convenience sampling method was used to approach the participants.

3.2.2 Study setting and ethics approval

The study was performed at Al Wakra Hospital (AWH), Hamad General Hospital (HGH), and Heart Hospital (HH). These Three sites are tertiary hospitals and part of HMC, the most prominent medical institution in Qatar. Ethical approval was obtained from the Institutional Review Board (IRB) of HMC in July 2019 (Protocol# MRC-01-19-57).

3.2.3 Sample size calculation

The sample size was calculated using Roasoft online calculator (www.Roasoft.com) [196], assuming that the HCPs who are involved in warfarin periprocedural management at HMC are 600. To achieve a confidence (power) level of 90% power with a 5% marginal error and taking into consideration 50% response distribution, a sample size of 187 participants was found to be adequate.

3.2.4 Validation and piloting

Content and structure were checked for validity by Three senior faculty members at the College of Pharmacy, Qatar University (one with expertise in pharmacy practice research, and two with cardiovascular clinical practice background). Based on their feedback, modifications were performed. A pilot version was created and disseminated to a random sample of (one internal medicine senior consultant, one cardiology specialist, one general resident physician, and one clinical pharmacist). Respondents reported that the questionnaire was well organized, clear, and with a proper sequence of questions. They also completed the survey within 15-20 minutes, which matched the

stated duration at the invitation page of the survey.

3.2.5 Survey development

The survey was designed after performing a thorough literature review using PubMed, Google Scholar, and EMBASE database in January 2019. The search focused on terms related to the HCP's awareness and practice in warfarin periprocedural management.

The survey consisted of 4 domains. The first domain had 5 questions to assess the attitude of HCPs. The second domain contained 7 questions, and it evaluated the HCP`s practice. The third domain was two case scenarios with 14 questions that assessed the awareness of HCPs. The last domain collected relevant demographic and professional characteristics information of the participants. There was one question with a score ranging from 0 to 10 with one-unit intervals to rate the willingness of HCPs to recommend a genetic test to guide the duration of warfarin discontinuation. The final version of the survey consisted of 31 multiple-choice questions. Survey questions were available only in the English language.

3.2.6 Measured outcome and statistical analysis

All responses were recorded in Excel document and transferred to IBM Statistical Package for Social Science (IBM SPSS 26 software; IBM, New York) for descriptive and inferential statistical analysis. Responses to demographics, professional information practice, and attitude towards periprocedural warfarin management questions, were represented as categorical variables and were expressed in frequencies and percentages. One question was presented as a continuous variable. An awareness score of one point was provided if the participant selected the correct answer for the designated question. For questions with more than one correct answer, a partial score was provided unless the participant selected all the correct answers. The overall score awareness domain was the sum of the scores of all questions under this domain. Percentage Awareness score (PAS) was calculated by dividing the total awareness score

by the maximum possible score and multiplying the result by 100. Since data were non-normally distributed, Mann-Whitney U-test and Kruskal-Wallis H test were used to evaluate the effect of participants' demographics and personal information on PAS which was expressed as median and Interquartile Range (IQR). A Chi-square test was performed to assess the association between different categorical values. Two-tailed *P*-value of <0.05 was considered significant.

3.3 Results

3.3.1 Participants' characteristics

Over six months, a total of 300 questionnaires were distributed, among which 187 questionnaires were collected (62.3% response rate). The plurality of participants (74.4%) were male, and the majority of them (69.3%) had less than 20 years of experience. Responses were received from 150 physicians (80.2%) and 37 clinical pharmacists (19.8%). Most of the physicians (31%) were specialists. A high number of participants (62.3%) were holders of a professional doctor degree such as Medical Doctorate (MD), Pharmacy Doctorate (PharmD), or equivalent degrees (Table 3.1).

Table 3.1: Participants' demographics and professional characteristics

Characteristic	**N (%)**
Years of experience [a=3]	
0-19 years	131 (71.1%)
≥20 years	53 (28.9%)
Gender [a=3]	
Male	137 (74.4%)
Female	47 (25.6%)

Characteristic	N (%)
Highest degree received [a=4]	
Bachelor's degree	29 (15.9%)
Academic degree	40 (21.8%)
Professional doctor degree (MD, Pharm D)	114 (62.3%)
Current position	
Clinical pharmacist	37 (19.8%)
Physicians	150 (80.2%)
Physicians	
Resident	37 (19.8%)
Specialist	58 (31.0%)
Consultant	50 (26.7%)
Physicians' specialty [a=1]	
Internal medicine	52 (34.7%)
Cardiology	20 (13.5%)
Anesthesiology & Surgery	56 (37.7%)
Other	21 (14.1%)

[a] missing response. Other, family medicine, geriatric medicine, general medicine

3.3.2 Awareness of periprocedural warfarin management

The overall median (IQR) of PAS was moderate 64.28% (21.43). Out of 14 awareness questions, the major deficiency was identified in 5 questions [less than 50% of responders chose the right answer(s)]. Firstly, there is the awareness of the type of surgeries that do not require warfarin interruption (right response rate = 26.2%). Also, there is the awareness regarding the time at which patients must stop warfarin and stop LMWH prior to surgery (right response rate= 42.2%, 47.1%, respectively). Furthermore, bridging decision was another obstacle in both case scenarios (right response rate= 38% & 47.6%). In bridging decision scenarios, we found apparent contrast in response among specialties. While 15% of cardiologists agreed on continuing warfarin for patients undergoing cataract or tooth extraction procedure, only 5 % of anesthesia and surgery physicians preferred not to stop warfarin (Table 3.2).

Table 3.2: Survey domains, questions and responses

Attitude Domain	**Respondents (%)**
1. How do you perceive warfarin interruption during periprocedural management based on your clinical experience?	
A. Underused	32 (17.1%)
B. Used appropriately	77 (41.2%)
C. Overused	47 (25.1%)
D. Do not know	31 (16.6%)

Attitude Domain	Respondents (%)
2. How do you perceive heparin bridging use during warfarin interruption in the periprocedural management based on your clinical experience?	
A. Underused	34 (18.2%)
B. Used appropriately	82 (43.9%)
C. Overused	50 (26.7%)
D. Do not know	21 (11,2%)
3. How do you perceive the risk of bleeding when considering bridging with heparin during warfarin periprocedural management? [a=3]	
A. Not important	14 (7.6%)
B. Somewhat important	52 (28.3%)
C. Very important	109 (59.2%)
D. Do not know	9 (4.9%)

Attitude Domain	Respondents (%)
4. How do you perceive the patient burden and cost when considering bridging with heparin during warfarin periprocedural management? [a=2]	
A. Not important	44 (23.8%)
B. Somewhat important	61 (33.0%)
C. Very important	66 (35.7%)
D. Do not know	14 (7.5%)
5. If there is a genetic test which informs you more accurately about the optimal duration of warfarin interruption before z surgery, on a scale of 0-10, how much do you recommend the patient to do this genetic test?	187 (100%)

(Lowest) 0 1 2 3 4 5 6 7 8 9 10 (Highest)

Attitude Domain	Respondents (%)
Practice Domain	
1. On average, how often do you provide care for patients requiring warfarin periprocedural management? [a=5]	
A. 1-2 patients/week	160 (87.9%)
B. 3-5 patients/week	13 (7.1%)
C. 6-8 patients/week	6 (3.3%)
D. More than 8 patients/week	3 (1.7%)
2. Who is typically responsible for warfarin management during the periprocedural period in your unit? [b]	
A. Clinician performing the surgery or procedure	70 (37.6%)
B. Anticoagulation clinic	60 (32.2%)
C. A clinician who prescribed warfarin	71 (38.2%)
D. Other	31 (16.6%)

Attitude Domain	Respondents (%)
2. Which guidelines do you follow for warfarin periprocedural management? [b]	
A. American College of Chest Physician (ACCP)	42 (22.5%)
B. American College of Cardiology (ACC)	64 (34.2%)
C. American Society of Hematology [176]	11 (5.9%)
D. National Institute for Health and Care Excellence (NICE)	22 (11.9%)
E. European Society of Cardiology [197]	26 (13.9%)
F. Clinical Excellence Commission (CEC)	0 (0.0%)
G. HMC's guideline	94 (50.3%)
H. Other [c]	10 (5.3%)

Attitude Domain	Respondents (%)
3. How often do you encounter canceling or postponing a procedure due to elevated INR around the procedure time despite warfarin interruption? [a=3]	
A. Never (0%)	12 (6.5%)
B. Rarely (1-25%)	67 (36.4%)
C. Sometimes (26-75%)	72 (39.1%)
D. Frequently (76-99%)	15 (8.2%)
E. Always (100%)	5 (2.8%)
F. Don’t know	13 (7.0%)

Attitude Domain	Respondents (%)
5.1 How often do you encounter a situation (No warfarin interruption is needed before an elective procedure) for patients requiring periprocedural management of warfarin? [a]	
A. 0-25%	149 (85.2%)
B. 26-50%	14 (8.0%)
C. 51-75%	10 (5.7%)
D. 76-100%	2 (1.1%)
5.2 How often do you encounter situation (Warfarin interruption is needed before the procedure but WITHOUT heparin bridging) for patients requiring periprocedural management of warfarin? [a=13]	
A. 0-25%	72 (41.5%)
B. 26-50%	70 (40.2%)
C. 51-75%	28 (16.0%)
D. 76-100%	4 (2.3%)

Attitude Domain	Respondents (%)
5.3 How often do you encounter situation (Warfarin interruption is needed before the procedure but WITH heparin bridging) for patients requiring periprocedural management of warfarin? a=11	
A. 0-25%	33 (18.8%)
B. 26-50%	41 (23.3%)
C. 51-75%	63 (35.8%)
D. 76-100%	39 (22.1%)
6. Would you check the patient's INR on the day before or the day of the procedure? a=3	
A. For all the patients	153 (83.2%)
B. Only for patients who **DID NOT** have warfarin interrupted before the procedure.	6 (3.3%)
C. Only for patients who **HAD** warfarin interrupted before the procedure.	15 (8.1%)
D. No need to check for the INR before the procedure.	1 (0.5%)
E. Do not know.	9 (4.9%)

Attitude Domain	Respondents (%)
7. On which of the below scales, do you assess this patient's stroke risk? [a=11]	
A. CHA_2DS_2-VAS	125 (67.2%)
B. $CHADS_2$ score	32 (17.2%)
C. Other	1 (0.5%)
D. Do not know	28 (15.1%)
Awareness Domain	
1. Which is the most considerable factor to you during warfarin periprocedural management? [a=3]	
A. Type of surgery	7 (3.8%)
B. Patient`s risk of bleeding	6 (3.3%)
C. Bleeding risk of the procedure	6 (3.3%)
D. Risk of thrombosis	1 (0.6%)

Attitude Domain	Respondents (%)
2. In which of the following procedures/surgeries would you decide to continue warfarin during the procedure time? [b]	
A. Tooth extraction	49 (26.2%)
B. Resection of abdominal aortic aneurysm	10 (5.3%)
C. Cataract	67 (35.8%)
D. Cholecystectomy	10 (5.3%)
E. None of the above	84 (44.9%)
F. Other	8 (4.3%)

Case scenario 1: A 55-year-old female patient currently on warfarin for deep vein thrombosis (DVT) that occurred 10 years ago. Her INR has been within the range lately (most recent INR reading is 2.3) and all her other labs are unremarkable. Patient has also hypertension and hypothyroidism. Patient will have a colonoscopy with possible polypectomy in 10 days.

3. Would you stop warfarin prior to the scheduled colonoscopy?

Attitude Domain	Respondents (%)
A. Yes	146 (78.1%)
B. No	28 (15.0%)
C. Do not know	13 (7.0%)

4. If the patient has to stop warfarin, when do you advise the patient to stop it before the surgery?

A. > -7 days of the surgery	8 (4.3%)
B. -7 to -5 days of the surgery	79 (42.2%)
C. -4 to -3 days of the surgery	77 (41.2%)
D. -2 to -1 days of the surgery	20 (10.7%)
E. Do not know	3 (1.6%)

Attitude Domain	Respondents (%)
5. Would you bridge this patient with heparin? [a=2]	
A. Yes	88 (47.6%)
B. No	89 (48.1%)
C. Do not know	8 (4.3%)
6. Considering that the patient will be bridged with low molecular weight heparin (LMWH), when do you start LMWH before the surgery? [a=8]	
A. -5 days of the surgery	41 (22.9%)
B. -4 days of the surgery	6 (3.3%)
C. -3 days of the surgery	47 (26.3%)
D. -2 days of the surgery	39 (21.8%)
E. -1 day of the surgery	34 (19.0%)
F. Do not know	12 (6.7%)

Attitude Domain	Respondents (%)
7. When do you stop LMWH before the surgery?	
A. -2 days of the surgery	8 (4.3%)
B. -1 day of the surgery	88 (47.1%)
C. On the day of the surgery	87 (46.5%)
D. Do not know	4 (2.1%)
8. What is the safe INR limit for doing the surgery? [a=2]	
A. ≤1.2	16 (8.6%)
B. ≤1.5	146 (79.0%)
C. ≤2	18 (9.7%)
D. Do not know	5 (2.7%)
9. If the patient has to stop warfarin, when do you resume it considering no bleeding post-operatively? [a=3]	
A. The night of or the day following the surgery	110 (59.5%)
B. +2 to +3 days of the surgery	61 (33.4%)

Attitude Domain	Respondents (%)
C. +4 to +5 days of the surgery	1 (0.5%)
D. > +5 days of the surgery	3 (1.7%)
E. Do not know	9 (4.9%)
10. When do you check INR after restarting warfarin? [a=6]	
A. +1 to +2 days	65 (35.5%)
B. +3 to +5 days	102 (55.7%)
C. +5 to +7 days	10 (5.5%)
D. > +7 days	2 (1.1%)
E. Do not know	4 (2.2%)
Case scenario 2: A 75-year-old male patient currently on warfarin for atrial fibrillation. His INR has been within the range lately (most recent INR reading is 2.5) and all his other labs are unremarkable. Patient will have a hip replacement planned in 10 days.	
11. Would you stop warfarin prior to the scheduled hip-replacement? [a=2]	
A. Yes	166 (89.7%)

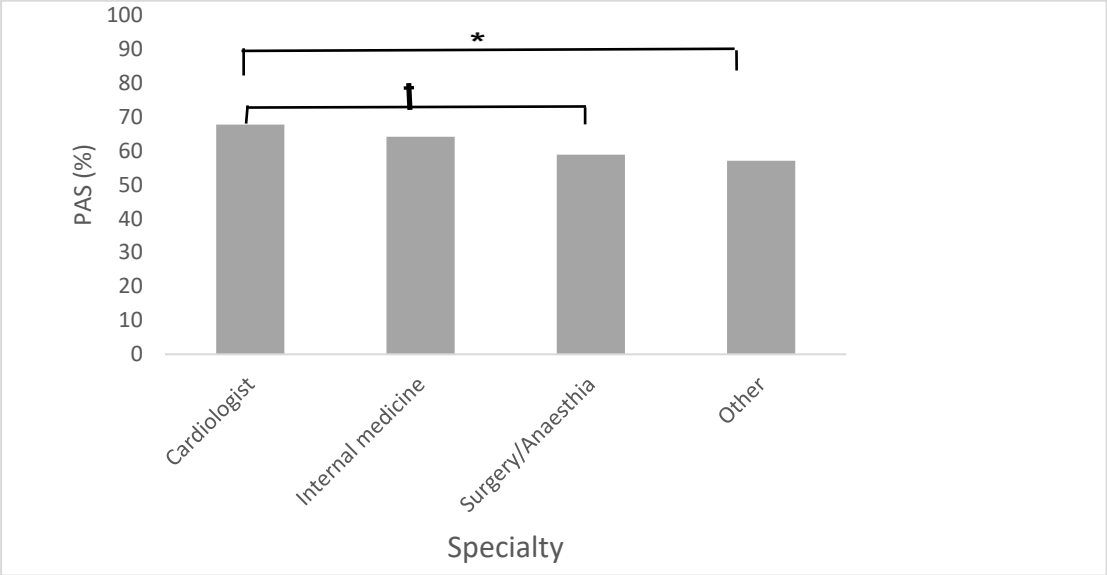
Attitude Domain	Respondents (%)
B. No	4 (2.2%)
C. Do not know	15 (8.1%)
12. If the patient's atrial fibrillation is non-valvular and he has a history of controlled hypertension, diabetes, and gout, would you decide to bridge him before the surgery? **a=2**	
A. Yes	97 (52.4%)
B. No	71 (38.4%)
C. Do not know	17 (9.2%)
13. If you knew that this patient had a history of mechanical mitral valve replacement, would you decide to bridge him before the surgery?	
A. Yes	175 (93.6%)
B. No	3 (1.6%)
C. Do not know	9 (4.8%)

Attitude Domain	Respondents (%)
14. If you knew that this patient had non-valvular atrial fibrillation and history of cardioembolic stroke 2 months ago, would you decide to bridge him before the procedure?	
A. Yes	150 (80.2%)
B. No	19 (10.2%)
C. Do not know	18 (9.6%)

[a] Missing response. [b]Choose all that apply. INR, International Normalization Ratio. [C]Other as identified by responders: American College of Anesthesia, American College of Gastroenterology, American College of Surgeons, American Society of Gastroenterology.

In terms of the effect of demographics and professional information on the participants' awareness, the following were the most significant findings. Participants holding master's or professional degree achieved significantly better median (IQR) PAS, than participants holding a Ph.D. degree [60.71% (18.75), 64.28% (16.07) vs. 50% (17.86), P=0.004, P=0.007 respectively]. Pharmacists showed a significantly superior median (IQR) PAS compared to physicians [75% (20.54) vs. 60.71% (20.54), P=0.001]. As expected, when cardiologists were compared to surgery/anesthesia physicians and other specialties, they attained a significantly higher median (IQR) PAS score [67.85% (24.11) vs. 58.92% (20.98, P=0.036), 57.14% (37.95, P=0.004) respectively]. Similarly, internists got significantly superior median (IQR) PAS score versus other specialties [64.28% (17.86) vs. 57.14% (37.95), P=0.007] (Figure 3.1). Table 3.3 shows

the effect of baseline and professional characteristics on PAS.



Bars represent median percentage of awareness score (PAS) across physicians' specialties. Statistical significance was tested using the Kruskal-Wallis test (P<0.05) followed by post-hoc pairwise comparison. Results are expressed as median (IQR) PAS. PAS, Percentage Awareness Score. *P-Value=0.004; † P-Value=0.036

Figure 3.1: Median PAS across physicians' specialties

Table 3.3: Effect of baseline and professional characteristics on percentage awareness score

Variable	Median PAS (IQR)	*P*-Value*
Years of experience		0.74
0-19 years	60.71 % (19.64)	
≥20 years	64.28% (22.32)	
Gender		0.49
Male	60.71% (25)	
Female	64.28% (16.07)	
Highest degree received		0.011
Bachelor's degree	57.14% (25.57)	0.126[a]
Master's degree	60.71% (18.75)	0.335 [a]

Variable	Median PAS (IQR)	*P*-Value*
Professional doctor degree (MD, Pharm D)	64.28% (16.07)	
Doctorate degree	50% (17.86)	0.007 [a]
Current position		0.001
Clinical pharmacist	75% (21.43)	
Physician	60.71% (20.54)	
Physician Ranking		0.02
Resident	57.14% (28.57)	0.141[b]
Specialist	58.92% (19.64)	0.861[b]
Consultant & Senior consultant	64.28% (17.86)	
Physician specialty		0.009*
Internal medicine	64.28% (17.86)	0.437[c]
Cardiology	67.85% (24.11)	
Anesthesiology & Surgery	58.92% (20.98)	0.036[c]
Other	57.14% (37.95)	0.004[c]

* P value < 0.05 was tested using the Kruskal-Wallis test for the comparison of PAS between the following factors (highest degree, current position, and main specialty), while Mann-Whitney U test was used for the comparison of PAS between following factors (years of experience & gender). PAS, Percentage Awareness Score.

[a] Post-hoc pairwise comparisons of bachelor's, master's and doctorate degree vs. professional doctor degree (MD, Pharm D).

[b] Post-hoc pairwise comparisons of residents' and specialists' Vs. consultants & senior consultants.

[c] Post-hoc pairwise comparisons of anesthesiology/ Surgery physicians and other specialties vs consultants/ senior consultants.

3.3.3 The practice of HCPs in periprocedural warfarin management

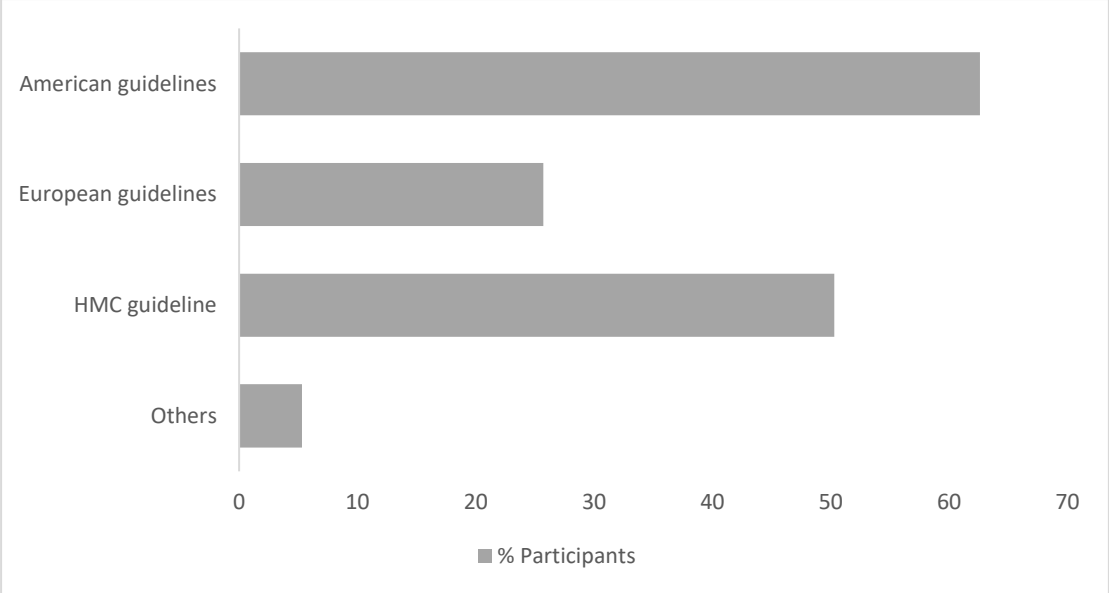
Most of the respondents (87.9%) reported that they deal with 1-2 warfarin patients per week undergoing a procedure. There was a statistically significant association between specialty and who is accounted for the direct management of these cases ($P<0.001$). Half of the cardiologists (50%) indicated that the anticoagulant clinic is responsible for making plans for the patient, while a similar proportion of internal medicine agreed on warfarin prescriber as the main responsible party. In contrast, 37.5% of surgeon and anesthesia physicians declared that clinician performing the procedure is liable to handle these cases.

About a third of the HCP indicated that they encounter a reschedule/ cancellation of the procedure due to elevation in INR some or most of the time.

American guidelines were the most widely used for guidance (62.8%) followed by HMC's guidelines (50.3%), and then the European guidelines (25.8%) (Figure 3.2).

In terms of warfarin interruption, 85.2% of respondents indicated that around 75% of patients need warfarin discontinuation before elective surgery, and that about half of those patients (56.1%) will require bridging.

When the respondents were asked to indicate which criteria are used to assess patient's stroke risk, just under 70% reported that they use the CHA2DS2-VASc score, while fewer (17%) reported the use of $CHADS_2$ score.



Bars represent percentage of participants and the guidelines followed in warfarin periprocedural management.

Other as identified by responders: American College of Anesthesia, American College of Gastroenterology, American College of Surgeons, American Society of Gastroenterology, Clinical Excellence Commission.

Figure. 3.2: Participants use of the different guidelines in warfarin periprocedural management.

3.3.4 Attitude towards periprocedural warfarin management

A chi-square test for association was conducted between demographics and warfarin periprocedural management attitude. Females significantly perceived more than males that warfarin interruption, and heparin bridging are overused (34% vs 22.6%, *P*=0.003, *P*=0.034 respectively). More emphasis on the difference in the attitude of physicians and pharmacists; whereby, more physicians believed that the cost of bridging is very important (38.5%vs 24.3%, *P*=0.042). Participants expressed a good level of interest in using genetic tests to guide periprocedural warfarin management [median (IQR) score (out of 10) = 7 (5)].

3.4 Discussion

In this study, we attempted to assess the attitude, knowledge, and practice of HCPs in Qatar on periprocedural management of warfarin patients undergoing a procedure. The

main finding of the study was that participants' awareness is moderate. In a recent study in Qatar, a similar level of awareness was achieved among HCPs on direct oral anticoagulants (DOACs) [198]. Three areas of knowledge deficiency were the driver of the decline in awareness level in the current study. Firstly, conflicting ability to determine the duration of discontinuation of warfarin prior to the procedure. This is surprising given the fact that a clear recommendation in the 2017 American College of Cardiology (ACC) guideline states that, warfarin should be held 5-7 days before an elective procedure [111]. A second area of deficiency was the inconsistencies between HCPs on who bridge warfarin patient and the duration of preoperative parenteral anticoagulation when a decision to bridge is made. Thirdly, the majority of participants were lacking awareness of the type of procedures that do not require warfarin interruption, such as cataract and tooth extraction due to their low risk of bleeding [199, 200]. Whether the low score achieved in these elements is due to true lack of awareness or judgement from clinical practice and experience is hard to assess. Regardless, we believe that applying inappropriate timing, duration of warfarin interruption or bridging can yield significant risk of bleeding and thromboembolic events. It was also found that cardiologists were the best in continuing warfarin in procedures with low risk of bleeding, while most of the surgeons still stopped warfarin. This is potentially due to the cardiologists' attention to patient's thromboembolic risk, while surgeons give more attention to the procedure's bleeding risk. Results from a survey that evaluated the practice patterns in the Unites States for bridging AC showed that 25% and 45% decided not to interrupt warfarin during dental extraction and cataract surgery, respectively [201]. Bridge or Continue Coumadin for Device Surgery Randomized Controlled trial (BRUISE CONTROL) has shown that maintaining warfarin with an INR of ≤ 3 on the day of the procedure in patients undergoing implantation of

pacemakers or cardioverter defibrillators was associated with significantly less bleeding than warfarin discontinuation along with bridging with heparin (Odds ratio:0.19; $p < 0.001$) [202].

Another critical observation in the survey is that clinical pharmacists had better awareness scores compared to physicians. A possible explanation for this might be that clinical pharmacists have a reasonable knowledge of pharmacokinetics and pharmacology of warfarin, and are frequently involved with warfarin dosing and periprocedural management through anticoagulation clinics and in-patient services [197]. A significant difference was also noted among the physician's specialties, where cardiologists and internalists achieved the highest scores. This result is likely related to these specialties being more involved in the management of warfarin patients.

As expected, HCPs holding professional degrees had a superior awareness than fresh graduate HCPs holding a bachelor's degree. Surprisingly, HCPs with PhD got a lower awareness score than HCPs with a professional degree. It is possible that practical training plays a significant factor in determining the awareness level. We also observed that the position or rank was positively associates with the awareness of periprocedural warfarin management (highest in consultants/senior consultants). While one may expect from recent graduates to have better awareness, extensive clinical practice appears to have a vital role in augmenting awareness levels. These results are also in alignment with the previous survey on DOACs awareness in Qatar [198].

Response to the involvement in periprocedural warfarin management was another interesting finding. The majority of each specialty were biased towards their own practice. For instance, cardiologists, being the specialty running jointly or in close relation to the anticoagulation clinics in Qatar agreed on the anticoagulant service as the main responsible party for periprocedural management. Similarly, surgeons and

anesthesiologists referred to the clinician performing the procedure as the responsible, while internalist referred to the warfarin prescriber as the responsible party. These findings are consistent with data from a recent survey in which respondents distributed the responsibility among cardiologists, surgeons, internists and anticoagulant services to manage warfarin periprocedural (56%, 36%, 28%,and 27%, respectively)[201].

In addition to our main findings above, respondents revealed that warfarin is discontinued in the majority of patients who will undergo elective surgery. This was reflected when most of the participants chose to stop warfarin in cataract and tooth extraction surgeries in separate questions. Similar trends were expressed by participants in this survey and those described by Starks et al.,[188] Krahan et al.,[168] and Balbino et al.[183] (75%, 83%, and 83% interrupted warfarin preoperatively correspondingly). We believe that this clinical practice leans towards fear of bleeding events from warfarin much more than thromboembolic events. However, HCPs in our study stated that almost half of those patients undergoing warfarin discontinuation would require bridging to protect them from thromboembolic events. Both of these practice behaviors (exaggerated discontinuation and bridging) may put the patients at higher risk of thromboembolism and bleeding, respectively. This comes also against the recent expert call to reduce the use of bridging during preoperative management due to the increased risk of bleeding from heparin use [203]. In this report, it was estimated that over 90% of patients receiving warfarin therapy should not receive bridging anticoagulation during periprocedural management. This conclusion was based on accumulating evidence that rated overall and major bleeding significantly higher in bridged rather than non-bridged patients by 2-5 folds while there was no difference in the risk of thromboembolism between both arms [113].

As an area of future research and possible clinical translation we asked HCPs on their

opinion to use a genetic test as a tool to help in personalizing the duration of warfarin interruption before surgery. Remarkably, the survey articulated the interest of HCPs (especially pharmacists) in recommending this tool to their patient in the future. These results are in agreement with Elewa et al [204] findings in 2015, which showed that pharmacists had more willingness and positive attitude towards the application of pharmacogenetics in practice when compared to physicians in Qatar.

A key strength of the current survey is that it investigated different domains (attitude, knowledge, and practice) of various specialties involved in warfarin periprocedural management. On the other hand, this study had some limitations. First, there is a potential for sampling bias since we surveyed a governmental hospital only, i.e. HMC, which could affect the generalizability of the results. Despite a high response rate in this survey (62.3%), some HCPs did not agree to participate possibly due to lack of knowledge or interest which may have had an impact on the generalizability of the results. To overcome that, we intentionally used a paper-based survey instead of an online version to increase the response rate. In addition to the above limitations, survey fatigue, and lack of required time to answer the survey are obstacles that could have affected the response quality. We tried to solve this issue by limiting the number of case scenarios. Moreover, validation of the questionnaire helped to ensure it had appropriate time and clarity. Lastly, and similar to other survey-based studies, our findings may be distinct from what applies in practice.

3.5 Conclusion

This research highlights that HCPs in Qatar have moderate awareness of warfarin periprocedural management with a lack of standardized practice. Practice leans to overestimate the need for warfarin discontinuation due to fear of bleeding risk. Besides, it overestimates the need for bridging to overcome thromboembolic risk. Additionally, HCPs are interested in applying pharmacogenetics to their practice to gage the duration

of warfarin discontinuation. Future work should focus on reassessing practitioners' knowledge after providing well-designed education campaigns.

CHAPTER 4: PERIPROCEDURAL ANTICOAGULATION MANAGEMENT OF PATIENTS RECEIVING WARFARIN IN QATAR: A PROSPECTIVE COHORT STUDY

4.1 Introduction

Need for warfarin interruption prior to elective procedures affects about 250,000 patients annually in the United States of America and Canada alone [106]. Managing warfarin, particularly in the periprocedural period, raises many concerns, primarily how to achieve balance between thromboembolic and bleeding risks. The discontinuation of warfarin may elevate the risk of thromboembolism (TE), while its continuation can boost the risk of bleeding during and/or after the procedure [205, 206]. Another concern is the potential risk of TE when warfarin is interrupted peri procedurally [207]. To balance these risks and overcome these concerns, standard clinical guidance has been put in place when a procedure is scheduled for warfarin patients. Warfarin treatment is typically discontinued if the procedure has more than minimal risk of bleeding. Warfarin is paused 5-7 days prior to the elective procedure to let its anticoagulant effect diminish [208, 209]. The choice of bridging with parenteral anticoagulation therapy (typically with intravenous unfractionated heparin (UFH) or subcutaneous low molecular- weight heparin (LMWH)), for the period of the interruption of warfarin treatment is made if the risk of TE is significant and exceeds the risk of bleeding. The objective of this step is to allow the continuation of the anticoagulation during the transient holding of warfarin. Finally, when hemostasis is secured after the procedure, warfarin is resumed (with bridging if the risk of TE is significant and exceeds the risk of bleeding). The resumption of warfarin needs 5-10 days of treatment to achieve therapeutic anticoagulation [111, 112].

In 2015, 2 major trials reported the clinical outcomes associated with bridging. The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation study (ORBIT-

AF) [114] revealed that anticoagulation disruptions is associated with higher risk for bleeding (Adjusted odds ratio [OR], 3.84 for major bleeding; 95% confidence interval [CI], 2.07-7.14; P<0.0001) and higher risk of adverse events including the composite of myocardial infarction, bleeding, stroke or systemic embolism (Adjusted OR, 1.94; 95% CI, 1.38-2.71; P=0.07). The Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial [139], on the other hand was a large double-blind randomized clinical trial (RCT), comparing bridging anticoagulation versus non-bridging in patients with atrial fibrillation (AF) who interrupted warfarin. The study showed that non-bridging was associated with a significant reduction in major bleeding compared to bridging (relative risk [RR], 0.41; 95% CI, 0.20-0.78; P=0.005). Furthermore, there was no statistical difference in terms of TE events between groups. Unfortunately, these results could not be generalized as the study included AF patients only and predominantly those with low to moderate stroke risk (CHA_2DS_2 score < 3). Both studies compound the uncertainty of the necessity of bridging during the warfarin interruption period.

Current guidelines such as the American College of Chest Physicians (ACCP) endorse an individualized approach to define the need for warfarin bridging based on the patient's anticipated periprocedural bleeding and thromboembolic risk [108]. Nevertheless, these recommendations have weak level of evidence (Level 2C), indicating the absence of high-quality evidence. All the above shows the uncertainty linked with ideal periprocedural warfarin management and the usefulness of bridging therapy, which creates different practices among health care providers (HCPs). The decision of warfarin interruption according to patient's and procedure's bleeding risks is considered another debate.

Our group recently surveyed practitioners in Qatar on their knowledge and practices during the periprocedural management of warfarin and revealed wide variation in the responders' practice [190]. Consequently, this study was designed to evaluate the real-world clinical practice of warfarin periprocedural management and investigate the clinical outcomes associated with warfarin bridging versus non-bridging in Qatar.

4.2 Methods

4.2.1 Study design

The current study is part of an ongoing prospective cohort study that investigates the effect of genetic and non-genetic factors on international normalization ratio (INR) decline in Arabs undergoing warfarin interruption prior to elective surgery. We hereby report the clinical practice of warfarin interruption and the associated clinical outcomes and compare the clinical events in patients undergoing warfarin bridging and those without bridging. The study was performed over 24 months from September 2018 till September 2020.

4.2.2 Study setting and ethics approval

The study was conducted at Al Wakra Hospital (AWH), Hamad General Hospital (HGH), and the Heart Hospital (HH). These three sites are part of Hamad Medical Corporation (HMC), the major medical institution in Qatar. Patients were recruited from anticoagulation, cardiology, anesthesia, or surgery clinics. Ethical approval was obtained from the Institutional Review Board (IRB) of HMC (Protocol# MRC-16415/16) and Qatar University (QU-IRB 1296-FBA/20).

4.2.3 Population

A sample of convenience was used in this study. Inclusion criteria included patients of Arab descent (as confirmed by the reported patient nationality) undergoing elective surgery that requires warfarin discontinuation as per planned clinical decision for 3 days or more; age ≥ 18 years old, and treatment with warfarin for at least one month with a

stable INR for the last two consecutive visits with a minimum one-week interval. A stable INR was defined as INR within ± 0.2 units of the target therapeutic range [210]. Patients were excluded if they had an emergency procedure or minor procedure that required warfarin interruption for 1-2 days; were scheduled for a procedure but did not stop warfarin, received vitamin K, fresh frozen plasma, or Prothrombin complex concentrates (PCC) during the preoperative period; or had major bleeding (MB) within the previous month. The definition of major bleeding was summarized in Table 4.1

Table 4.1: Clinical events definitions

Clinical event	Definition	Ref.
Death	All-cause of death	[139]
Major bleeding	At least one of the following must be satisfied. 1- Symptomatic or clinically overt bleeding that is associated with one or more of: - Transfusion of ≥2 units heterologous packed red blood cells or whole blood - Decrease in hemoglobin level of >20 g/L (>2 g/dL). - Need for reoperation or invasive intervention (e.g., evacuation of wound hematoma). 2- Symptomatic or clinically overt bleeding at a critical anatomic site; bleeding that is intracranial, intraspinal, intraocular (retro-orbital, vitreous, choroidal, or retinal hemorrhage), or retroperitoneal, intraarticular,	[139, 140]

Clinical event	Definition	Ref.
Minor bleeding	Symptomatic or clinically overt bleeding that does not satisfy the criteria for major bleeding	[139]

4.2.4 Data collection

Following subjects' screening and consent, data on patient's demographics, characteristics, and relevant clinical information were collected. A clinical investigator from each facility was responsible for patient recruitment and data collection. All data was then sent to the principal investigator, who was responsible for the maintenance of the study database, data validation, and analyses.

4.2.5 Periprocedural management of warfarin

Periprocedural management of warfarin was according to the treating HCP's decision as there was no unified protocol among the three facilities to instruct on when stop and resume warfarin perioperatively and whether bridging should be applied. The most common practice was to pause warfarin for 5 days before the procedure, then bridge with UFH or LMWH when INR < 2 (typically 3 days prior to the procedure with the last dose 24 hours prior to the procedure for LMWH and 6 hours prior to the procedure for UFH). Following the procedure, warfarin, at the preoperative dose, and UF or LMWH were restarted 12-24 hours post-procedure provided that the patient has normal hemostasis and was stable. Bridging medication was stopped when the INR became therapeutic. Bridging anticoagulation was defined as perioperative use of a therapeutic dose of LMWH (e. g. enoxaparin 1 mg/kg subcutaneously [SC] twice daily, dalteparin sodium 100 IU/Kg SC twice daily) or I.V UFH 18 IU/Kg/hr. before and/or after the procedure.

4.2.6 Categorization of procedures

Procedures were categorized into minor or major according to the same classification used in BRIDGE [139] and RELY- trials [115]. Minor or low-bleeding risk surgery was any surgery lasting for less than 1 hour, otherwise, it was classified as major or high-bleeding risk surgery. Some examples are shown in Table 4.2.

Table 4.2: Examples of minor and major procedures

Minor or low-bleeding risk procedure	Major or high-bleeding risk procedure
Diagnostic test	Intra-abdominal surgery
Endoscopy	Intra-thoracic surgery
Ophthalmic procedure	Internal defibrillator insertion
Dental extraction or procedure	Orthopedic surgery
Dermatological procedure	Resection surgery
Cardiac catheterization procedure	Arterial revascularization

4.2.7 Study outcome

Study outcomes from the time of warfarin interruption until 30 days after the procedure were recorded, with an average total period of 35 ± 2 days. The clinical outcomes were reported through electronic health records and confirmed via follow-up phone calls with the patients. The study outcomes include any major or minor hemorrhage, or TE event like ischemic stroke (IS), systemic embolism (SE), myocardial infarction (MI), deep vein thrombosis (DVT), or pulmonary embolism (PE). The definitions of clinical outcomes were summarized in Table 4.1.

4.2.8 Statistical analyses

For baseline and patient characteristics, continuous data was presented as mean ± SD or median and interquartile range (IQR). Independent Student's t-test and Mann-Whitney U tests were used for comparing means and medians, respectively. Categorical

variables were reported as counts and frequencies. Comparison between categorical data of both bridging and non-bridging groups were performed using the Chi-Square test.

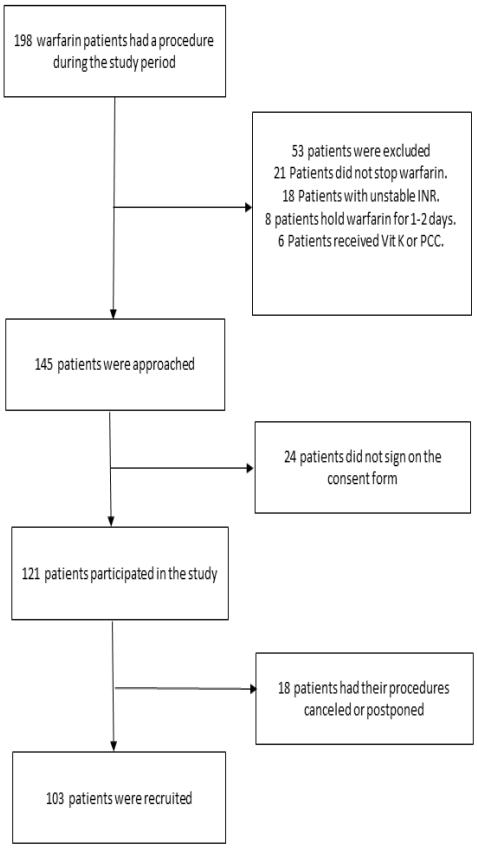
For clinical outcomes and adverse events at 30 days post-procedure, data was expressed as count and frequency. Differences in clinical outcomes between the 2 groups were tested using univariate analysis. Significant differences were further evaluated through multivariate analysis (logistic regression). Logistic regression was also used to determine other factors [body mass index (BMI) (≤25 or >25 kg/m^2), CHF, dyslipidemia, hypertension, and AF conditions, CHA_2DS_2-Vasc score (≤4 or >4 points) as low and moderate/ high, HAS-BLED score (≤ 2 or > 2 points) as low and moderate/high, procedure type (minor or major) vitamin-K intake as low and medium/high and taking high bleeding risk medications] associated with clinical outcomes and was expressed as odds ratio (OR) and 95 % confidence interval (CI). IBM Statistical Package for Social Science (IBM SPSS 26 software; IBM, New York) was used to carry out the statistical analysis. A two-tailed *p*-value of <0.05 was considered significant.

4.3 Results

4.3.1 Patient demographics

One hundred and ninety-eight patients underwent at least one procedure during the study period, but 48% of them were excluded for different reasons (Figure 4.1). One hundred and three patients were recruited from the three healthcare facilities over two years, with an average of 1 patient/week. Bridging was performed in 85 patients (82.5%) while the remaining 18 subjects (17.5%) were in the non-bridging group. Table 4.3 summarizes the patient characteristics. Patients' mean age was 58.7±14.5 years, with a median (IQR) BMI 31.6 (34.5) Kg/m^2; BMI was significantly higher in the bridging compared to the non-bridging group (32.2 vs. 30.1, P= 0.036). About half (56,

53.3%) of the participants were males. The local population (Qatari citizens) represented 40% of the total participants. Fifty-eight patients (56.3%) had AF as their main indication for warfarin. One out of five (20%) of the patients were taking aspirin alone or in combination with clopidogrel. The median (IQR) of CHA_2DS_2-VASc and HAS-BLED were 4 (2) and 2 (2), respectively, and values were not different among the 2 study groups.



INR; international normalization ratio, PCC; Prothrombin Complex Concentrates

Figure 4.1: Diagram of eligible patients' inclusion.

Table 4.3: Clinical and demographics characteristics of patients

Characteristic (N=103)	**Bridging (N=85)**	**Non-bridging (N=18)**	***P*-Value**
Age in years, mean ± SD[i]	58.0 ± 14.7	61.6 ± 13.6	*P* =0.344
BMI in kg/m, median (IQR)[¥]	32.2 (34.5)	30.1 (16.0)	**P*= 0.036
Male gender, no. (%)	46 (54.1)	10 (55.5)	*P*= 0.911
Country of origin, no. (%)			*P*= 0.381
Qatari	33 (38.8)	9 (50.0)	
Non-Qatari	52 (61.2)	9 (50.0)	
Comorbid conditions, no. (%)			
Congestive heart failure (CHF)	12 (14.1)	1 (5.5)	*P*= 0.353
Diabetes mellitus	40 (47.0)	12 (66.6)	*P*= 0.131
Hypertension	49 (57.6)	15 (83.3)	**P*=0.041
Dyslipidemia	37 (43.5)	10 (55.5)	*P*= 0.352
Vitamin-K food intake/ week			*P*=0.907
no. (%)	16 (18.8)	3 (16.6)	
Low	66 (77.6)	14 (77.7)	
Medium	3 (3.5)	1 (5.5)	
High			
Warfarin indication, no. (%)			
AF	44 (51.7)	14 (77.7)	**P*=0.043
Heart valve replacement	37 (43.5)	4 (22.2)	*P*=0.093
VTE	11 (12.9)	4 (22.2)	*P*=0.311
Thrombophilia	7 (8.2)	0	*P*=0.207
Others (LVT, Stroke)	9 (10.5)	1 (5.5)	*P*=0.521

Characteristic (N=103)	Bridging (N=85)	Non-bridging (N=18)	*P*-Value
Concomitant high bleeding-risk medications, no. (%)			
Antiplatelet	26 (30.6%)	5 (27.8%)	*P*=0.83
NSAIDs	5 (5.9%)	3 (16.7%)	*P*=0.120
Risk assessment for AF patients (N=58) ¥	**Bridging (N=44)**	**Non-bridging (N=14)**	
CHA_2DS_2-Vasc, median (IQR)	4 (2)	4 (2)	*P*=0.669
CHA_2DS_2-Vasc ≤ 4, no. (%)	32 (72.7%)	10 (71.4%)	*P*=0.805
HAS-BLED, median (IQR)	2 (2)	2 (2)	*P*=0.953
HAS-BLED ≤ 2, no. (%)	27 (61.4%)	10 (71.4%)	*P*=0.605

All P-value < 0.05 was tested using Chi-square test except ŧ; independent-samples t-test AF, ¥; Mann-Whitney U test. *Significantly different between bridged and non-bridged groups. Atrial fibrillation, BMI; body mass index, COX-2; cyclooxygenase type 2, IQR; interquartile range, LVT; left ventricular thrombosis, NSAIDs; non-steroidal anti-inflammatory drugs, SD; standard deviation. CHA2DS2Vasc refers to congestive heart failure, hypertension, age > 75 years, diabetes and prior stroke or transient ischemic attack, vascular disease, age 65-74 and female gender. HAS-BLED refers to hypertension, abnormal liver or renal function, stroke, bleeding, liable INR, elderly (Age >65), drugs (NSAIDs or aspirin) or alcohol. Vitamin-K was categorized according to the number of portions of vitamin-k food intake/ week as low (1-2 time), medium (3-4 times) and high (5-7 times), one portion equal to one bowl containing approximately 100 gm of food.

4.3.2 Periprocedural warfarin management and the classifications of performed procedures

One hundred and three patients went for a procedure and had warfarin interruption for more than 2 days; the list of complete procedures is categorized and summarized in Table 4.4. Three quarters (75%) of recruited patients had minor or low-bleeding risk

procedures. As expected, minor procedures were more frequent in non-bridging (83.4%) than in the bridging group (75.6%), but the difference was not statistically significant (p=0.178). Dental procedures were the most common (29%) type of minor procedure among bridging and non-bridging groups, whereas resection procedures were the most common major procedure (6.5%).

Periprocedural management variables such as 1st INR reading after warfarin interruption; last INR reading before the procedure; incidence of INR ≥1.5 at the time of procedure; and number of preprocedural warfarin discontinuation days are presented in Table 4.5. There were no statistical differences between bridging and non-bridging groups in these variables.

Table 4.4: List of performed procedures

Procedure	Bridging (N=85)	Non-bridging (N=18)
Minor no. (%)	**64 (75.6%)**	**15 (83.4%)**
Dental procedure no. (%)	24 (28.2%)	6 (33.3%)
Endoscopy no. (%)	13 (15.3%)	5 (27.8%)
Ophthalmology procedure no. (%)	12 (14.1%)	2 (11%)
Valvuloplasty no. (%)	3 (3.6%)	1 (5.6%)
Others no. (%)	12 (12.1%)	1 (5.6%)
Major no. (%)	**21 (24.7%)**	**3 (16.6%)**
Resection no. (%)	6 (7.0%)	1 (5.6%)
CABG no. (%)	5 (5.8%)	2 (11%)
Knee replacement no. (%)	2 (2.3%)	0
MVR no. (%)	2 (2.3%)	0
Gastric sleeve, no. (%)	2 (2.3%)	0

CABG; coronary artery bypass grafting, MVR; mitral valve replacement.

Table 4.5: Periprocedural warfarin management

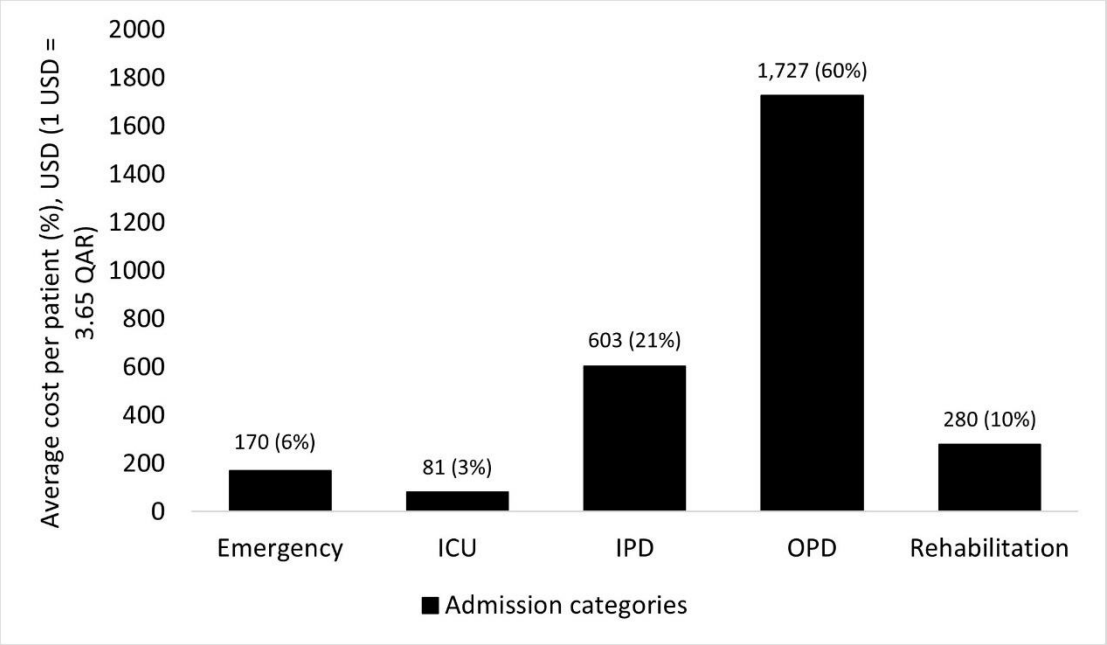
Variable	Bridging (N=85)	Non-bridging (N=18)	*P*-Value
1st INR reading after the interruption median (IQR)	2.1 (0.7)	2.4 (0.8)	*P*= 0.142
last INR reading before the procedure median (IQR)	1.2 (0.9)	1.4 (0.2)	*P*= 0.59
Incidence of INR ≥1.5 at the time of procedure, number (%)	9 (10.5%)	3 (16.6%)	**P*= 0.465
No. of preprocedural warfarin discontinuation days, median (IQR)	3 (2)	3 (2)	*P*= 0.947

* Chi-square test was used, P-value < 0.05 was tested using the Mann-Whitney U test. 1st INR reading was checked on the first day of warfarin discontinuation, last INR was examined on the day or one day before the procedure. INR; international normalization ratio, IQR; interquartile range.

4.3.3 Warfarin periprocedural management clinical outcome

During the 30-day follow-up period following the procedure, there were no thromboembolic events, while 30 (39 %) participants had bleeding events (Figure 2). Eighteen of these events were minor (60%) while the remaining 12 were major (40%). The incidence of overall bleeding was numerically higher in bridging compared to the non-bridging group but did not reach statistical significance (30.6% Vs. 22.2%, p= 0.48). Similarly, postoperative bleeding in the bridging group was more than two-fold higher than bleeding in the non-bridging group (27.1% Vs. 11.1% %, p= 0.241). The

difference did not reach statistical significance likely due to the small sample size. Moreover, bridging was not associated with bleeding events when tested in multivariate analysis after adjustment for other baseline characteristics. Multiple logistic regression however showed low vitamin-K intake to be associated with lower bleeding risk compared to higher vitamin K intake (adjusted OR, 0.1; 95% CI, 0.012 – 0.882; p=0.038), and the use of antiplatelet medications to be associated with MB (OR, 3.7; 95%CI, 1.16 – 12.15, p=0.027). The use of antiplatelet agents also tended to increase overall bleeding, but results were not statistically significant (OR, 2.3; 95%CI, 0.95 – 5.73, *p*=0.064). One death was reported among the participants in the bridging group (Table 4.6).



*others (thoracic bleeding and hemarthrosis), GI; gastrointestinal.

Figure 4.2: Reported hemorrhagic events during periprocedural warfarin management

Table 4.6: Bleeding events from the time of warfarin interruption till 30 days after the procedure

Clinical outcome	Overall (N=103)	Bridging (N=85)	Non-bridging (N=18)	*P*-Value*
Pre-operative				
Overall bleeding, no. (%)	5 (4.9%)	3 (3.5%)	2 (11.1%)	*P*= 0.235
Major bleeding, no. (%)	1 (1.0%)	1 (1.2%)	0	*P*= 0.644
Minor bleeding, no. (%)	4 (3.9%)	2 (2.4%)	2 (11.1%)	*P*= 0.081
Death, no. (%)	0	0	0	
Post-operative				
Overall bleeding, no. (%)	25 (24.3%)	23 (27.1%)	2 (11.1%)	*P*= 0.241
Major bleeding, no. (%)	11 (10.7%)	10 (11.8%)	1 (5.6%)	*P*= 0.338
Minor bleeding, no. (%)	14 (13.6%)	13 (15.3%)	1 (5.6%)	*P*= 0.198
Death, no. (%)	1 (0.97%)	1 (1.1%)	0	
Total observation period				
Overall bleeding, no. (%)	30 (39.1%)	26 (30.6%)	4 (22.2%)	*P*= 0.478
Major bleeding, no. (%)	12 (11.7%)	11 (12.9%)	1 (5.6%)	*P*= 0.375
Minor bleeding, no. (%)	18 (17.5%)	15 (17.6%)	3 (16.7%)	*P*= 0.921
Death, no. (%)	1 (0.97%)	1 (1.1%)	0	*P*= 0.644

******P*-value < 0.05 was tested using Chi-square test to compare the overall bleeding between two groups of bridging and non-bridging.

4.4 Discussion

This study provides insights into the clinical practice of warfarin periprocedural management as well as the procedural characteristics and consequent clinical outcomes

in a Qatari healthcare setting. One of our main findings is that warfarin was interrupted in 90% of patients who had undergone elective surgery. This was consistent with our earlier observation, which showed that HCPs had been interrupting warfarin for more than 75% of cases [190]. This rate of warfarin interruption is even higher than that previously reported in sub-study of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) [211] (63%) and in the ORBIT-AF study [114] (30%). We believe that these results reflect the personal preference of local surgeons, which tends to be more cautious towards intraoperative hemorrhage.

Additionally, the present study underscores the significant use of bridging, which was employed in 82.5% of patients in whom warfarin had been interrupted. This outcome is in line with our previous survey for the HCPs in Qatar who formerly reported the use heparin bridging with an average of 50%-75% of their patients. The proportion of bridging in this study is also significantly higher than those reported in the ORBIT-AF [114] and RE-LY [115] trials (25% and 30%, respectively).

According to the current report, about 25% of performed procedures were major surgeries. This was similar to the finding of Fingar et al. [212], who demonstrated that 29% of procedures performed in the USA in 2003-2012 for warfarin patients were major procedures. Likewise, in the BRIDGE trial [139], major surgeries represented 30% of all the performed operations. Given that more than 75% of the performed procedures in this report were minor, it was surprising to see that warfarin was still interrupted. It was also surprising that bridging was used in more than 80% of patients with major surgery or surgeries with high bleeding risk and despite that TE risk in the cohort was mostly low-moderate based on the CHA_2DS_2-Vasc score (71% had a score ≤ 4). It was noted however, that the frequency of some higher risk TE conditions such

as valvular replacement, thrombophilia and stroke were higher (but not statistically significant) in the bridging arm which justifies the use of bridging in these conditions.

In this study, the median (IQR) of warfarin discontinuation days was 3 (2) days, which was lower than the reported mean ± SD days of interruption in the BRIDGE trial (5.2 ± 1.4) [139]. This could be attributable to the high number of minor operations, which might have required shorter periods to achieve a target INR of <2.

The current study did not show any difference in the incidence of clinical outcomes between bridging and non-bridging groups which is apparently due to the small sample size especially in the non-bridging group (n=18). However, there was a numerical tendency towards increased bleeding risk in majority of bleeding categories in the bridging compared to non-bridging arm. There were also no TE events reported in the study. Increased risk of bleeding with bridging was confirmed in previous studies. In the RE-LY trial [115], the risk of major bleeding among bridged patients was significantly higher than that in non-bridged patients (6.8% vs. 1.6%, P<0.001), and there was no significant impact on ATE (0.5% vs. 0.2%, P = 0.32). The ORBIT-AF trial [114] also revealed a higher bleeding rate when bridging anticoagulation therapy had been implemented during periprocedural warfarin interruption. In the BRIDGE study [139], bridging was correlated with increased bleeding risk, while no additional benefits for ATE prevention could be concluded.

The only deceased case in the present analysis was a 52-year-old female patient using warfarin for stroke prevention status post mitral valve replacement. She underwent a hysteroscopy and polypectomy, and she was bridged. She developed gastrointestinal bleeding 12 days after surgery while she was on postoperative bridging along with warfarin. She died four days after the postoperative hemorrhage.

An overall observation from this study is that the practice followed for warfarin patients

undergoing surgical procedures in Qatar is not in accordance with the most recent clinical evidence guidelines [111, 213]. According to the 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular AF guidelines published by the American College of Cardiology, warfarin should not be discontinued in patients undergoing procedures with minimal to low bleeding risk when these patients don't have risk factors to increase the risk of bleeding [111]. Additionally, the use of bridging in patients with low TE risk (CHA_2DS_2-Vasc score ≤ 4) is not recommended. Similar recommendation is endorsed by the American Society of Hematology 2018 guidelines for patients with VTE that have low to moderate TE risk [213]. These recommendations are based primarily on the overwhelming recent evidence that showed increased bleeding and net harm in patients undergoing bridging with no justifiable reduction in the risk of TE [113-115, 203].

A significant strength of the current research is that it prospectively evaluated the local practice of HCPs and the adverse events of warfarin interruption among patients undergoing surgeries for various warfarin indications and with variable thromboembolic and bleeding risks. However, the study was not without limitations. Importantly, our study lacked the necessary power to detect significant difference between both groups due to the small sample size, particularly in the non-bridging group. Although our study was conducted over a relatively long period (two years) in three hospitals, the slow flow of eligible patients might have contributed to the small sample size. Moreover, patient recruitment might have been affected by the unprecedented situation of the Coronavirus disease 2019 (COVID-19) pandemic, which has resulted in suspending elective surgeries for 6 months. Accordingly, this might have caused a lack of significant differences between bridged and non-bridged patients in clinical outcomes. The small number of major surgeries in our study may partly explain

the lack of TE events, which might be associated with the procedure type and blood pressure variation during the procedure [214, 215]. Lastly, there is a potential for sampling bias since patients were neither randomized to interruption nor to bridging. Based on the mentioned observations, future studies with larger sample sizes are needed to evaluate the clinical benefits of warfarin interruption and bridging in periprocedural management in Qatar. Furthermore, economic analysis may help determining the cost-effectiveness of stopping versus continuing warfarin and bridging against non-bridging in periprocedural management.

4.5 Conclusion

The present study revealed that warfarin is mostly interrupted among patients who undergo elective surgery, and bridging was the primary strategy used by many clinicians. While bridging was numerically associated with increased bleeding events, there is no statistical difference in reported clinical events between bridging and non-bridging strategies.

CHAPTER 5: BRIDGING VERSUS NON-BRIDGING WITH WARFARIN PERI-PROCEDURAL MANAGEMENT: COST AND COST-EFFECTIVENESS ANALYSES

5.1 Introduction

Oral anticoagulants (OAC) have been indicated for decades in the prevention and treatment of thromboembolism [191, 192]. Warfarin represents 70% of OAC in Qatar [12]. Stroke prevention in patients with atrial fibrillation (AF) is among the most prevalent indications for warfarin in Qatar and worldwide [216-220]. Annually, it has been anticipated that 10-15% of OAC patients need to undergo OAC interruption for an elective procedure [108]. Clinicians were wrestled for years with the dilemma of how to manage patients receiving warfarin during a therapeutic pause period before elective surgery procedures. In some instances, warfarin may be interrupted, where anticoagulation with short-term parenteral therapy, using either low molecular weight heparin (LMWH) or intravenous unfractionated heparin (UFH), may be initiated to reduce the risk of thrombosis. Such a clinical scenario is termed “bridging” [12]. Ideally, for a patient receiving warfarin, the interruption starts 3-4 days before the procedure if the International Normalization Ratio (INR) is subtherapeutic (1.5-1.9), 5 days before the procedure if the INR is normal (2-3), and 7 days (or more) before the procedure if the INR is supratherapeutic [108]. Here, a therapeutic dose of either LMWH or UFH should be started 1-3 days following the last dose of warfarin, and the INR is remeasured 24 hours before the procedure [193].

There is, however, considerable uncertainty regarding the potential therapeutic benefits of parenteral anticoagulant (AC) bridging versus the putative bleeding risks. Siegal et al. [113] performed a meta-analysis comprising 7118 bridged and 5160 non-bridged patients receiving vitamin-K antagonist (VKA) therapies. The authors did not find any difference in the incidence of thromboembolic events between both arms. In contrast,

the risk of overall and major bleeding was considerably higher in heparin-bridged patients when compared to their non-bridged counterparts. The recent Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) randomized control trial (RCT) [139] has partially clarified and emphasized an association between heparin bridging and increased bleeding risks in patients receiving warfarin. A recent follow-up multiple logistic regression analysis of the BRIDGE trial showed that baseline bridge therapy is a significant predictor of major bleeding [122].

Significant limitations undermine the benefit of bridging. Bridging anticoagulation raises the risk of hemorrhagic complications, which may surpass the detriment from ischemic stroke, minimizing the overall rate of successful warfarin therapy [221]. Important, estimates of net clinical benefit do not contain costs of care. Even if bridging presents an advantage to wisely selected patients, the benefit may not worth the monetary spending and achieve cost-effectiveness. There are no evaluations of the economic value of bridging in the literature.

This study aimed to evaluate the economic consequences of peri-procedural warfarin management of AF patients in Qatar, including the cost-effectiveness of predominant bridging versus non-bridging strategies in patients who are subjected to peri-procedural warfarin management.

5.2 Methods

This economic analysis was based on a one-year decision-analytic model of cost and effective consequences with peri-procedural warfarin. Clinical model inputs were primarily based on the BRIDGE trial [139], an international, multicenter trial, and the only large study to investigate the bridging versus non-bridging strategies in AF patients during warfarin peri-procedural management.

5.2.1 Study perspective

The economic model was conducted from the hospital perspective, i.e., Hamad Medical Corporation (HMC) in Qatar.

5.2.2 Model structure

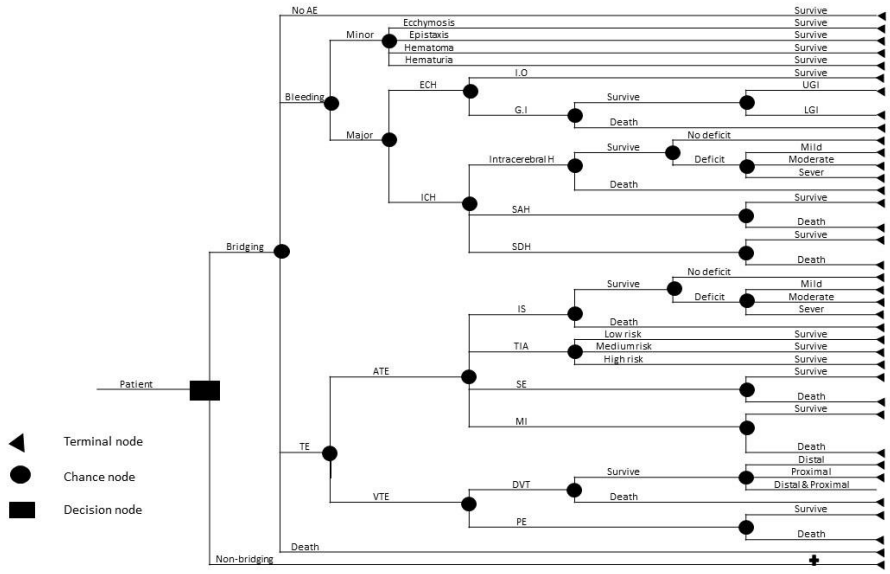
A conventional type of decision-analytic model was used to follow up a hypothetical cohort of AF patients on warfarin as they are undergoing an elective procedure. The model follows up the outcomes of patients based on whether they undergo the bridging versus a non-bridging peri-procedural strategy of management. Bridging versus non-bridging refers to whether heparin (LMWH/UFH) was initiated during warfarin interruption in the peri-procedural management. In HMC, bridging is to start heparin (LMWH/UFH) when warfarin is interrupted for 3-5 days, with a patient INR of < 2. Under either strategy, patients can be in one of four health states of adverse events: no adverse event (AE), bleeding, thromboembolism (TE), and all-cause death. Bleeding can be major bleeding, divided into extracranial hemorrhage (ECH) and Intracranial hemorrhage (ICH), or minor bleeding, including ecchymosis, epistaxis, hematoma, and hematuria. TE can be arterial TE (ATE) or venous TE (VTE). The model's structure of patient pathways is illustrated in Figure 5.1.

The bleeding events were classified as major bleeding and minor bleeding [139]. Minor bleeding was branched into ecchymosis, epistaxis, hematoma, and hematuria [219]. Major bleeding was divided into extracranial hemorrhage (ECH) and intracranial hemorrhage (ICH) [222, 223]. ECH is categorized as intra-ocular (IO) hemorrhage and gastrointestinal (GI) hemorrhage [140], which was classified as survival, with lower GI (LGI) or upper GI (UGI) bleedings, and death [224]. ICH was divided into an intracerebral hemorrhage, subarachnoid hemorrhage (SAH), and subdural hemorrhage (SDH) [138]. Intracerebral hemorrhage and ischemic stroke (IS) were categorized according to the modified Rankin scale (mRS) score to survival without deficit, no

deficit, mild deficit, moderate deficit, severe deficit, and death [225].

Thromboembolism (TE) was classified as arterial TE (ATE) and venous TE (VTE) [139]. ATE was divided into IS, systemic embolism (SE) with survival or death states, and transit ischemic attack (TIA) [139], which was categorized as a low, medium, and high-risk TIA [226]. Myocardial infarction (MI) was added as a subcategory of ATE and was subcategorized into survival and death. VTE was divided into deep venous thrombosis (DVT) and pulmonary embolism (PE) [227]. DVT was categorized into survival with proximal, distal, or proximal and distal DVT, or death [222]. The duration of the model follow up was one year, and a case of success in the current study was defined as survival with no AEs.

An HMC-based expert panel that comprised an internal medicine consultant, a cardiologist, a clinical pharmacist manager of the HMC anticoagulant clinic, and a vascular disease consultant validated the structure of the model and its consequences.



*Death; non-hemorrhagic or non-vascular death.

AE; adverse event, AF; arterial fibrillation, ATE; arterial thromboembolism, DVT; deep vein thrombosis, ECH; extracranial hemorrhage, GI; gastrointestinal, ICH; intracranial hemorrhage, IO; intra-ocular, IS; ischemic stroke, MI; myocardial infarction, PE; pulmonary embolism, SAH; subarachnoid hemorrhage, SDH; subdural hemorrhage, SE; systemic embolism, TE;

thromboembolism, TIA; transient ischemic attack, VTE; venous thromboembolism.

Figure 5.1: Decision-analytic model.

5.2.3 Clinical inputs

All model clinical event rates were retrieved from the published literature. The BRIDGE trial [139] was the primary source of the reported clinical events in the model. The BRIDGE trial is the only source that reports relative event probabilities for bridging versus non-bridging and is robust, including a relatively large population (n=1,804) of AF during warfarin peri-procedural management, reporting the clinical outcomes of a one-month observation period. Notably, the peri-procedural use of warfarin and the bridging practices in the study were consistent with those in the clinical practice at HMC, including in terms of the average number of discontinuation days (3-5 days), the average number of heparin dosing days [3 days before procedure 9 6 doses), and 3 days after the procedure (6 doses)], and the stroke risk score of the AF patients with a mean CHA_2DS_2-Vasc score of 4 as reported in an ongoing local trial in HMC by the same current author group [228]. Obtained from the BRIDGE trial [139], for each of the bridging and non-bridging model pathways, are the probabilities for all main clinical events in the model, which were the no-AE outcome, total bleeding, major and minor bleedings, TE, ATE, ischemic stroke (IS), transient ischemic attack (TIA), systemic embolism (SE), myocardial infarction (MI), VTE, and all-cause (but non-hemorrhagic/vascular) death. Probabilities of further sub-consequences for the outcomes extracted from the BRIDGE trial [139], but were not available in the BRIDGE trial itself, were extracted from other available relevant meta-analysis and comparative clinical studies in the literature that were similar concerning the underlying AF patients, age of patients, the stroke risk score, and the follow-up time for when outcomes were reported. These sub-consequences are minor bleeding sub-types, intra-ocular bleeding (IO), gastrointestinal (GI) hemorrhage, intracerebral hemorrhage,

subarachnoid hemorrhage (SAH) subdural hemorrhage (SDH). Except for ECH and ICH, these sub-consequences were assumed to not differ based on whether patients received bridging or not. Probabilities for ECH and ICH with bridging were available from a study by Hackett et al. [222], where the duration of heparin administration was an average of 3 days, matching the bridging as in the BRIDGE Trial and the HMC practices. The probabilities of ECH and ICH with the non-bridging arm were obtained from the warfarin arm in the RE-LY trial [223], in which the INR level was at sub-therapeutic range when starting warfarin. The model clinical events, their definitions, and sources of data are all summarized in Table 5.1. All reported clinical event rates, from all sources, were consistently reported until one month after warfarin interruption or heparin initiation.

Table 5.1: Clinical events definitions

Clinical event	**Definition**	**Ref.**
Arterial thromboembolism	One or more of the events listed as a stroke, systemic embolism, or acute coronary syndrome (MI- Angina).	[139]
Death	All-cause of death except for death due to vascular or hemorrhage events.	[139]
Deep vein thromboembolism	A combination of a calf trifurcation (Distal vein) or a more proximal vein that was not compressible on ultrasonography or an intraluminal filling defect on venography.	[139, 229]

Clinical event	Definition	Ref.
Distal DVT	Called infrapopliteal, which has no proximal component or pulmonary embolism, also is located below the knee, and is confined to the calf veins (peroneal, posterior, anterior tibial, and muscular veins)	[230]
Proximal DVT	Thrombosis is in the popliteal, femoral, iliac veins, or above.	[230]
Extracranial hemorrhage	Major bleeding that occurs outside the cranium (skull).	[137]
Intracranial hemorrhage	Major bleeding that occurs inside the cranium (skull).	[137]
Intracerebral hemorrhage	A dense hematoma within more widespread areas of cerebral contusion.	[138]
Ischemic stroke	Either criterion must be satisfied: - Any new focal neurologic deficit that persists for >24 hours. - Any new, focal neurologic deficit of any duration and with evidence of acute infarction on CT or MRI of the brain.	[139]

Clinical event	Definition	Ref.
Major bleeding	At least one of the following must be satisfied. 1- Symptomatic or clinically overt bleeding that is associated with one or more of: - Transfusion of ≥2 units heterologous packed red blood cells or whole blood - Decrease in hemoglobin level of >20 g/L (>2 g/dL). - Need for reoperation or invasive intervention (e.g., evacuation of wound hematoma). 2- Symptomatic or clinically overt bleeding at a critical anatomic site; bleeding that is intracranial, intraspinal, intraocular (retro-orbital, vitreous, choroidal, or retinal hemorrhage), retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome. 3- Fatal bleeding Bleeding directly contributes to death (e.g., intracranial bleed) or causes clinical deterioration leading to death (e.g., bleeding associated with sepsis or major organ failure).	[139, 140]

Clinical event	Definition	Ref.
Minor bleeding	Symptomatic or clinically overt bleeding that does not satisfy the criteria for major bleeding	[139]
Myocardial infarction	Typical rise and gradual fall (cardiac troponin) or more rapid rise and fall (creatine kinase-MB) of biochemical markers of myocardial necrosis to at least twice the upper limit of the normal range, with at least one of the following: - Ischemic symptoms. - Development of pathologic Q-waves on the ECG. - ECG changes indicative of ischemia (e.g., ST-segment elevation or depression). - Coronary artery intervention (e.g., coronary angioplasty).	[139]
Pulmonary embolism	Both criteria must be satisfied: 1-Symptoms of thrombosis of the pulmonary arteries (Chest pain) 2- Verified by high-probability ventilation-perfusion lung scan or intraluminal filling defect on CT angiography, intraluminal filling defect pulmonary angiography.	[139, 229]

Clinical event	Definition	Ref.
Subarachnoid hemorrhage	The extravasation of blood characterizes it into the CSF.	[138]
Subdural hemorrhage	A collection of blood between the dura and leptomeninges.	[122]
Transient ischemic attack	Both criteria must be satisfied: 1- Any brief neurologic deficit caused by focal brain or retinal ischemia, with clinical symptoms lasting, typically, for <24 hours. 2- No evidence of acute infarction on CT or MRI of the brain	[139, 231]
Systemic embolism	All three criteria must be satisfied: 1-Symptomatic embolic episode associated with abrupt arterial insufficiency to the upper extremity (10%), lower extremity (60%), or abdominal visceral organ (30%) leads to a sudden loss of end-organ perfusion. 2- Verified by intraoperative or radiologic evidence (e.g., CT angiography) of arterial occlusion. 3-Occurs in the absence of other likely mechanisms (e.g., atherosclerosis)	[139, 232]

CSF; cerebrospinal fluid, CT; Computed tomography, DVT; deep vein thrombosis, ECG; electrocardiogram, MI; myocardial infraction, MRI; Magnetic resonance imaging.

As per local HMC practices, the occurrence probability of bridging versus non-bridging in HMC was obtained from a study by Eljilany et al. [190], where the average percentage of bridging among practitioners managing warfarin peri-procedurally in HMC was reported to be 63%.

Considering the real-life interactions among different concurrent inherent uncertainties in the model input data, the model's analysis at its base case was based on uncertainty analysis of the model event probabilities, using Monte Carlo simulation via @Risk-7.6® (Palisade Corporation, NY, US). Based on 10,000 iterations, a multivariate uncertainty analysis that included variations in all clinical probabilities was conducted, based on 95% confidence interval (CI) uncertainty ranges and a uniform type of distribution for the sampling of probabilities. The Monte Carlo simulation enables the probability of outcome analysis as well as a tornado analysis of clinical outcomes as per their impact on the economic outcome.

Input values and their probabilities in the multivariate analysis of the model are summarized in Table 5.2.

Table 5.2: Model inputs and their uncertainty ranges in Monte Carlo simulation

Variables (%)	**Bridging**			**Non-bridging**		
	Base-case value	**Uncertai-nty Range (95% CI)**	**Ref.**	**Base-case value**	**Uncertainty Range (95% CI)**	**Ref.**
Heparin intervention	63.00	51.00-75.00	[190]	37.00	25.00-49.00	[190]

Variables (%)	Bridging			Non-bridging		
No AE	73.30	63.89-80.99	[139]	85.19	76.93-90.84	[139]
Survive	100.00	96.3-100	[139]	100.00	96.3-100	[139]
Bleeding	24.13	16.80-33.37	[139]	13.29	7.98-21.32	[139]
Minor bleeding	86.57	78.52-91.91	[139]	90.16	82.76-94.59	[139]
Ecchymosis	62.84	53.06-71.67	[219]	62.84	53.06-71.67	[219]
Survive	100.00	96.3-100	[219]	100.00	96.3-100	[219]
Epistaxis	22.62	15.22-31.35	[219]	22.62	15.22-31.35	[219]
Survive	100.00	96.3-100	[219]	100.00	96.3-100	[219]
Hematoma	7.27	3.61-14.09	[219]	7.27	3.61-14.09	[219]
Survive	100.00	96.3-100	[219]	100.00	96.3-100	[219]
Hematuria	7.27	3.61-14.09	[219]	7.27	3.61-14.09	[219]
Survive	100.00	96.3-100	[219]	100.00	96.3-100	[219]

Variables (%)	Bridging			Non-bridging		
Major bleeding	13.43	8.09-21.48	[139]	9.84	5.41-17.24	[139]
ECH	83.33	74.82-89.37	[222]	78.34	69.30-85.28	[223]
IO hemorrhage	13.48	8.13-21.54	[233]	13.48	8.13-21.54	[233]
Survive	100.00	96.3-100	[233]	100.00	96.3-100	[233]
GI bleeding	86.52	78.46-91.87	[233]	86.52	78.46-91.87	[233]
Survive	91.28	84.12-95.39	[224]	91.28	84.12-95.39	[224]
UGI bleeding	49.68	40.08-59.31	[224]	49.68	40.08-59.31	[224]
LGI bleeding	50.32	40.69-59.92	[224]	50.32	40.69-59.92	[224]
Death	8.72	4.61-15.88	[224]	8.72	4.61-15.88	[224]
ICH	16.67	10.63-25.18	[222]	21.66	14.72-30.70	[223]
Intracerebral hemorrhage	63.64	53.87-72.40	[138]	63.64	53.87-72.40	[138]

Variables (%)	Bridging			Non-bridging		
No deficit	27.87	20.04-37.36	[234]	27.87	20.04-37.36	[234]
Deficit	52.46	42.76-61.97	[234]	52.46	42.76-61.97	[234]
Mild deficit	23.44	16.22-32.63	[234]	23.44	16.22-32.63	[234]
Moderate deficit	43.75	34.44-53.53	[234]	43.75	34.44-53.53	[234]
Severe deficit	32.81	24.39-42.5	[234]	32.81	24.39-42.5	[234]
Death	19.67	13.07-28.53	[234]	19.67	13.07-28.53	[234]
SAH	6.06	2.82-13.19	[138]	6.06	2.82-13.19	[138]
Survive	25.00	17.55-34.30	[138]	25.00	17.55-34.30	[138]
Death	75.00	65.70-82.48	[138]	75.00	65.70-82.48	[138]
SDH	30.30	21.72-40.42	[138]	30.30	21.72-40.42	[138]
Survive	75.00	65.70-82.48	[138]	75.00	65.70-82.48	[138]

Variables (%)	Bridging			Non-bridging		
Death	25.00	17.55-34.30	[138]	25.00	17.55-34.30	[138]
TE	2.12	0.6-7.18	[139]	1.20	0.24-5.77	[139]
ATE	89.47	81.93-94.04	[139]	100.00	96.30-100	[139]
IS	17.65	11.42-26.28	[139]	18.18	11.85-26.87	[139]
No deficit	48.18	38.58-57.80	[234]	48.18	38.58-57.80	[138]
Deficit	44.55	35.19-54.31	[234]	44.55	35.19-54.31	[234]
Mild deficit	29.08	21.09-38.62	[234]	29.08	21.09-38.62	[234]
Moderate deficit	48.58	39.02-58.25	[234]	48.58	39.02-58.25	[234]
Severe deficit	22.34	15.92-31.44	[234]	22.34	15.92-31.44	[234]
Death	7.27	3.61-14.09	[234]	7.27	3.61-14.09	[234]
TIA	0.00	0.0-3.70	[139]	18.18	11.85-26.87	[139]
Low risk TIA	13.41	8.07-21.46	[226]	13.41	8.07-21.46	[226]

Variables (%)	Bridging			Non-bridging		
Medium risk TIA	74.39	65.04-81-93	[226]	74.39	65.04-81-93	[226]
High risk TIA	12.20	7.15-20.05	[226]	12.20	7.15-20.05	[226]
SE	0.00	0.0-3.70	[139]	0.00	0.0-3.70	[139]
Survive	75.00	65.70-82.48	[139]	75.00	65.70-82.48	[139]
Death	25.00	17.55-34.30	[139]	25.00	17.55-34.30	[139]
MI	82.35	73.72-88.58	[139]	63.64	53.87-72.40	[139]
Survive	100.00	96.3-100	[139]	71.43	96.3-100	[139]
Death	0.00	0.0-3.70	[139]	28.57	20.64-38.09	[139]
VTE	10.53	5.91-18.07	[139]	0.00	0.0-3.70	[139]
DVT	50.00	40.38-59.62	[139]	0	0.0-3.70	[139]
Survive	92.31	85.93-96.10	[139]	92.31	85.93-96.10	[139]
Distal DVT	33.33	24.89-43.03	[222]	33.33	24.89-43.03	[222]
Proximal DVT	33.33	24.89-43.03	[222]	33.33	24.89-43.03	[222]

Variables (%)	Bridging			Non-bridging		
Distal and proximal DVT	33.33	24.89-43.03	[222]	33.33	24.89-43.03	[222]
Death	7.69	3.90-14.61	[139]	7.69	3.90-14.61	[139]
PE	50.00	40.38-59.62	[139]	0	0.0-3.70	[139]
Survive	89.29	81.71-93.96	[139]	89.29	81.71-93.96	[139]
Death	10.71	6.04-18.26	[139]	10.71	6.04-18.26	[139]
Death*	0.45	0.04-4.50	[139]	0.33	0.02-4.31	[139]

*Death; non-hemorrhagic or non-vascular death, AE; adverse event, AF; Arterial fibrillation, ATE; arterial thromboembolism, CI; confidence interval, DVT; deep vein thrombosis, ECH; extracranial hemorrhage, GI; gastrointestinal, H; hemorrhage, ICH; intracranial hemorrhage, IO; intra-ocular, IS; ischemic stroke, MI; myocardial infarction, PE; pulmonary embolism, SAH; subarachnoid hemorrhage, SDH; subdural hemorrhage, SE; systemic embolism, TE; thromboembolism, TIA; transient ischemic attack, VTE; venous thromboembolism.

5.2.4 Cost calculations

Based on the hospital perspective, only the direct cost of patient management was included in the analysis. The cost of the patient in a model pathway is the cost of the initial warfarin therapy, with/without bridging, added to the cost of clinical events in the pathway.

The patient who interrupts warfarin for any procedural management needs to have the INR checked two times before the procedure and two times after it, noting the need for an out-patient visit with INR test. When there is bridging, a daily dose of 160 mg/day (80 mg BID) of heparin was assumed, based on an average weight of 80 Kg as suggested by the study's expert panel for weight-dependent dose calculations. The standard period of bridging is three days before and after the procedure: twelve doses of heparin per patient. Based on the BRIDGE trial [139] and the ongoing local study by the same group of authors in HMC (HMC study protocol 16415/16), 30% of surgeries are considered major and require pre-operative admission if with bridging, and 70% of the patients perform minor surgeries that require four out-patient clinic visits, regardless of bridging.

The cost of medications was obtained from the drug supply department of HMC. Clinical event costs were based on the finance department of HMC, which were also available as per resource category and admission category, calculated based on a micro-costing approach of involved direct medical resources. Admission cost categories constituted the costs of emergency department (ED), intensive care unit (ICU), in-patient department (IPD), out-patient department (OPD), and rehabilitation department (Rehab), and the medical resource cost categories constituted the costs of outpatient clinic visits, hospitalization, laboratory tests, diagnostic tests, monitoring, and intervention medications, as relevant to the events. All costs were calculated in the 2020-year value of the Qatari Riyal (QAR) and were presented in United States Dollar (USD, USD 1 = QAR 3.65). Due to the short duration of follow up, no cost discounting was performed.

5.2.5 Outcome measures

First, a cost-analysis of the bridging approach in HMC was presented via (i) the average

cost per patient as per current occurrence of bridging versus non-bridging practices (63% versus 37%, respectively) in HMC. The relative overall success rate was also evaluated. Second, the trade-off between the predominant occurrence of bridging in HMC versus a hypothetical predominant occurrence of non-bridging was investigated and presented via an incremental cost-effectiveness ratio (ICER) per case of success. Here, seeing that the current practices in HMC are predominantly based on bridging (63%), the scenario of predominant non-bridging was assumed to be 63% non-bridging versus 37% bridging. If dominance (i.e., lower cost and higher effectiveness) is reported; whereby, an ICER cannot be generated, the relative cost saving was reported. In the current study, the willingness-to-pay (WTP) cost-effectiveness threshold is estimated to be USD 150,000 per case of success.

5.2.6 Sensitivity analysis

Sensitivity analyses were performed to test the robustness of the model to input uncertainty and determine critical determinants of economic outcomes, and to increase the generalizability of results.

For the economic and success impact of bridging practices in HMC, a one-way sensitivity analysis was conducted via introducing uncertainty to the mean 63% probability of occurrence of bridging practices; where, based on the study by Eljilany et al. in HMC [190], an uncertainty range of 51-75% was used for bridging occurrence, with a uniform type of sampling distribution.

In addition to the uncertainty introduced to event probabilities at the base case of the model, a probabilistic sensitivity analysis was conducted by introducing uncertainty to the base case costs of events. No confidence interval was available for event costs, and, therefore, an overestimated ±20% variability was used for the uncertainty range, utilizing a triangular type of sampling distribution.

As with the base case, both one-way and probabilistic sensitivity analyses were performed using the Monte Carlo simulation by @Risk 7.6 (@Risk Software, Palisade Corporation, NY, USA), with 10,000 iterations.

5.3 Results

5.3.1 Cost analysis

Based on the 63% occurrence of bridging (versus non-bridging) in HMC, the overall success rate with warfarin peri-procedural management was 0.752 (95% Cl 0.751, 0.753), with the probability of a success rate illustrated in Figure 5.2. The mean overall cost per patient was USD 3,260 (95% Cl 3,250, 3,270) [QAR 11,900 (95% Cl 11,862, 11,935)] with the probability of the average cost per patient as presented in Figure 5.3. The average cost-effectiveness ratio (ACER) of warfarin interruption per case success was USD 4,335 (95% Cl 4,320, 4,350 [QAR 15,822 (95%Cl 15,768, 15,877)], with the probability of which as can be seen in Figure 5.4. Details of relative success and total costs between bridging and non-bridging are summarized in Table 5.3. In the one-year study model, clinical outcome pathways, their costs, and the calculation of the overall costs of peri-procedural warfarin can be seen in Table 5.4.

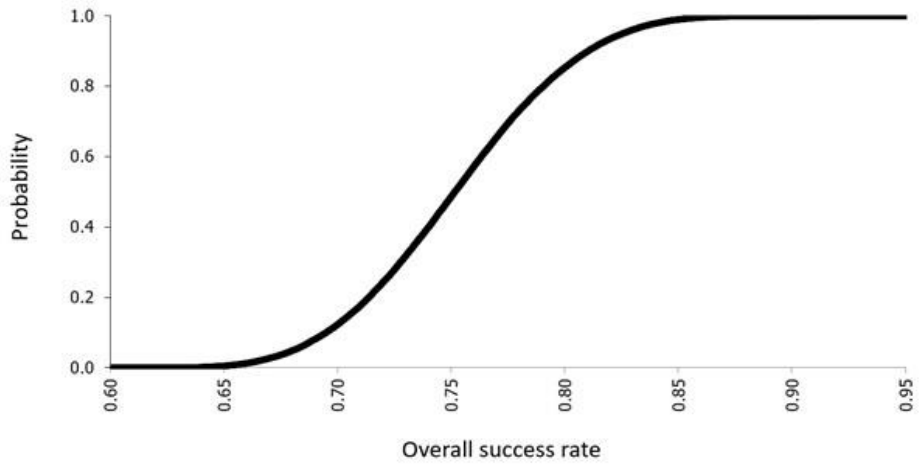
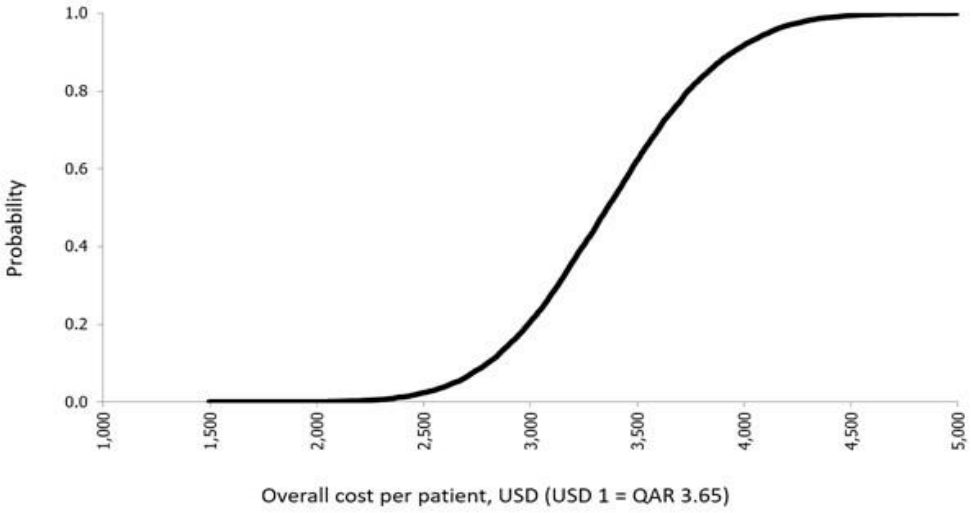
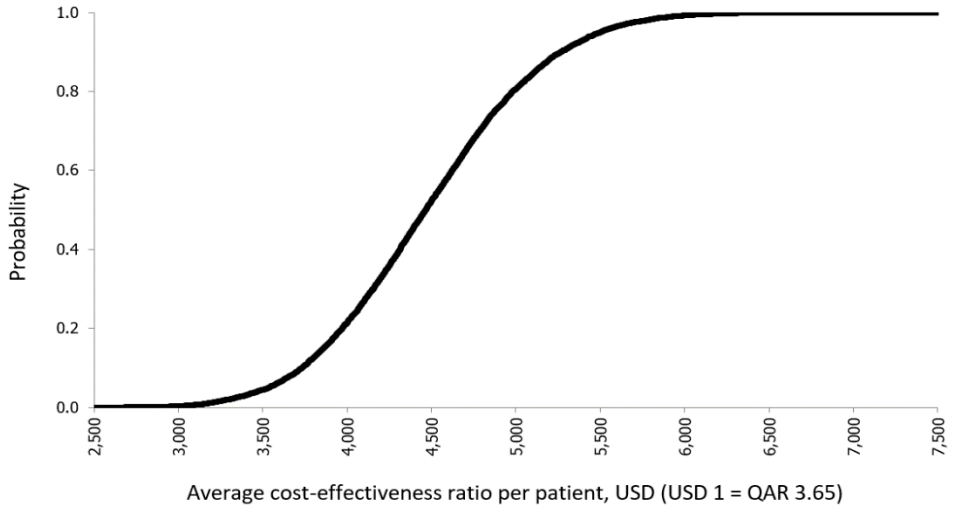


Figure 5.2: Base-case total success probability curve.



USD; United State Dollar, QAR; Qatari Riyal

Figure 5.3: Base-case total cost probability curve.



USD; United State Dollar, QAR; Qatari Riyal

Figure 5.4: Average cost-effectiveness ratio (ACER) per success probability curve.

Table 5.3: Expected cost and effectiveness in base-case analysis

Strategy	Mean effectiveness (95% CI)	Mean cost (USD) (95% CI)	Total mean effectiveness (95% CI)	Total mean cost (USD) (95% CI)	ACER (USD) (95% CI)
Bridging	0.447 (0.446, 0.448)	2,034 (2, 030, 2,040)	0.752 (0.751, 0.753)	3,260 (3,250, 3,270)	4,335 (4,320, 4,350
Non-bridging	0.304 (0.303, 0.305)	1,226 (1,220, 1,230)			

ACER; average cost-effectiveness ratio, CI; confidence interval, USD; United States Dollar (1 USD = 3.65 QAR)

ACER: total cost/total effectiveness, total effectiveness = effectiveness of bridging + effectiveness of non-bridging, total cost = cost of bridging + cost of non-bridging

Table 5.4: Clinical outcomes and their costs at the base-case of the one-year decision model

Strategy	Outcome event			Cost (USD) of outcome	Proportional cost (USD) of outcome ł	Average cost (USD) per outcome category	Total average cost (USD) of the strategy	Total average cost (USD) of the base-case
Bridging	No AE			2,031.63	938.1	938	2,037	3,260
	Bleeding	Minor bleeding	Ecchymosis	3,350.7	279.1	689		
			Epistaxis	2,829.8	85.2			
			Hematoma	3,179.2	30.4			
			Hematuria	4,557.7	44.6			

GI bleeding	IO hemorrhage	2,622.6	6.0
	UGI bleeding	7,261.8	48.4
	LGI bleeding	7,235.8	48.9
	Death	7,235.8	9.2
Intracerebral hemorrhage	No deficit	12,335.3	7.4
	Mild deficit	24,022.4	6.3
	Moderate deficit	36,033.4	18.9
	Severe deficit	58,553.9	22.8
	Death	58,553.9	25.9
SAH	Survive	41,921	2.1

		Death	41,921	6.4	
	SDH	Survive	45,747.9	36.3	
		Death	45,747.9	11.7	
		No deficit	29,435	28.9	
		Mild deficit	40,643.3	7.2	
	IS	Moderate deficit	52,676.1	15.6	
		Severe deficit	75,237.8	10.3	
TE		Death	75,237.8	11.5	404
	TIA	Low risk TIA	6,788	0	
		Medium risk TIA	7,319.9	0	

SE	High risk TIA	7,851.8	0
	Survive	19,138.1	0
	Death	19,138.1	0
MI	Survive	32,174	314.6
	Death	32,174	0
DVT	Distal DVT	9,492	2.0
	Proximal DVT	9,492	2.0
	Distal and proximal DVT	9,492	2.0
	Death	9,492	0.03
PE	Survive	16,183.4	9.0
	Death	16,183.4	1.0

			Death*	2,031.6	5.7	5.7	
			No AE	1,939.7	764.2	764	
Non-bridging	Bleeding	Minor bleeding	Ecchymosis	3,258.8	112.4	292	1,223
			Epistaxis	2,737.9	34.3		
			Hematoma	3,087.3	12.4		
			Hematuria	4,465.8	17.9		
		GI bleeding	IO hemorrhage	2,530.7	39.6		
			UGI bleeding	7,169.9	13.3		
			LGI bleeding	7,143.9	13.4		
			Death	7,143.9	2.5		
			No deficit	12,243.4	2.8		

		Mild deficit	23,930.5	2.4	
	Intracerebral hemorrhage	Moderate deficit	35,941.5	6.8	
		Severe deficit	58,462	8.3	
		Death	58,462	9.5	
	SAH	Survive	41,829.1	0.8	
		Death	41,829.1	2.4	
	SDH	Survive	45,656	5.5	
		Death	45,656	5.5	
TE	IS	No deficit	29,343.1	14.2	164
		Mild deficit	40,551.4	5.3	
		Moderate deficit	52,584.2	11.4	

TIA	Severe deficit	75,145.9	7.5
	Death	75,145.9	5.5
	Low risk TIA	6,696.1	2.4
	Medium risk TIA	7,228	5.4
	High risk TIA	7,759.9	0.95
SE	Survive	19,046.2	0
	Death	19,046.2	0
MI	Survive	32,082.1	79.9
	Death	32,082.1	31.3
DVT	Distal DVT	9,400.1	0

		Proximal DVT	9,400.1	0	
		Distal and proximal DVT	9,400.1	0	
		Death	9,400.14	0	
	PE	Survive	16,091.5	0	
		Death	16,091.5	0	
Death*			1,939.7	2.9	2.9

ŧ Proportional cost = cost of outcome pathway × probability of outcome pathway (Table 5.2). *Death; non-hemorrhagic or non-vascular death. USD; United State Dollar, 1 USD = 3.65 QAR). AE; adverse event, AF; arterial fibrillation, ATE; arterial thromboembolism, DVT; deep vein thrombosis, GI; gastrointestinal, IO; intra-ocular, IS; ischemic stroke, MI; myocardial infarction, PE; pulmonary embolism, SAH; subarachnoid hemorrhage, SDH; subdural hemorrhage, SE; systemic embolism, TE; thromboembolism, TIA; transient ischemic attack, VTE; venous thromboembolism,

At the base case, as per a regression tornado analysis of the strength (size) of the impact of the model clinical outcomes on the overall cost, the TE rate in non-bridging patients is the most influential, followed by the TIA rate in non-bridging patients, and then by total bleeding in bridging patients. The rank of the main model outcomes as per the size of their relationship with the overall cost of warfarin per patient is presented in Figure 5.5.

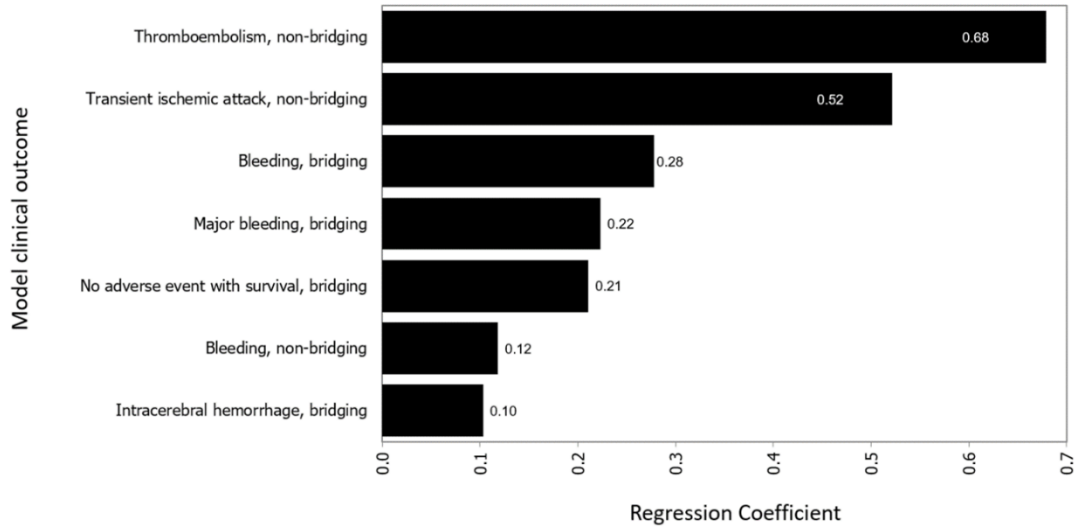
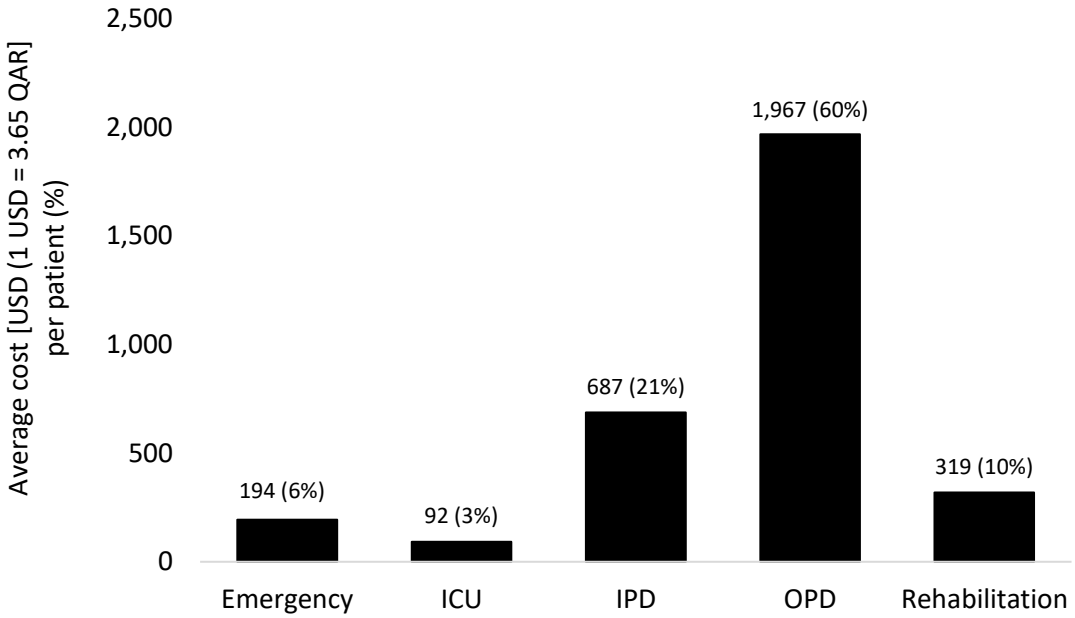


Figure 5.5: Tornado diagram of the base-case total cost based on the regression coefficient.

5.3.2 Event cost per admission category

Out of the overall cost of peri-procedural warfarin per patient, the overall cost of clinical events, excluding the no AE state, as associated with warfarin therapy was USD 1,558 (QAR 5,686) (47.8 %) per patient. Out of which, per patient, USD 1,099 (QAR 4,011) (53.9 %) was associated with bridging versus USD 459 (QAR 1,675) (37.5 %) with non-bridging. The relative contribution of the different admission categories towards the overall events cost per patient is summarized in Appendix 5.6. A case of no AE cost 46.1 % of the total management cost with bridging, and 62.5 % of the total management cost with the non-bridging approach. The AE that costs the most is MI (13.1 %),

followed by ecchymosis (11.9 %) and GI hemorrhage (4.1 %). Unweighted events costs and the details of the contributing admission cost categories are in Table 5.5.



Cost of admission per category contribution in the average cost per patient, ICU; intensive care unit, IPD; in-patient department, OPD; out-patient department.

Figure 5.6: Admission categories contribution in average cost per patient.

Table 5.5: The total cost of managing one patient, including admission categories, with each clinical event of warfarin interruption

Event	Emergency (USD)	ICU (USD)	IPD (USD)	OPD (USD)	Rehabilitation (USD)	Total (USD)
No AE.	0.00	0.00	465.04	1821.40	0.00	2,286.44
Ecchymosis	74.22	0.00	0.00	0.00	0.00	74.35
Hematoma	14.82	0.00	1.95	0.00	0.00	16.78
Hematuria	23.59	0.00	0.00	13.34	0.00	36.94
Epistaxis	0.60	0.00	21.22	0.00	0.00	21.87
Intra-ocular H.	0.16	0.00	0.00	0.00	0.00	0.17
Upper GI H	15.02	10.13	10.52	13.11	0.00	48.79

Event	Emergency (USD)	ICU (USD)	IPD (USD)	OPD (USD)	Rehabilitation (USD)	Total (USD)
GIH Death	2.94	1.87	2.03	2.52	0.00	9.36
No deficit ICH	1.12	0.35	1.46	1.72	4.65	9.30
Mild deficit ICH	0.49	0.16	0.64	0.76	6.70	8.75
Moderate deficit ICH	0.92	0.28	1.20	1.41	21.44	25.27
Severe deficit ICH	0.70	0.22	0.90	1.06	28.63	31.50
ICH Death	0.79	0.25	1.03	1.22	32.71	35.99
SAH	0.08	0.92	0.11	0.15	1.60	2.85
SAH Death	0.24	2.76	0.33	0.44	4.78	8.54
SDH	1.13	15.64	1.95	1.91	22.85	43.48
SDH Death	0.46	6.37	0.80	0.78	9.31	17.72
No deficit IS	4.33	0.75	4.51	5.49	0.00	15.09
Mild deficit IS	0.88	0.15	0.91	1.11	4.02	7.07
Moderate deficit IS	1.46	0.25	1.52	1.85	13.45	18.52
Severe deficit IS	0.67	0.11	0.70	0.84	11.79	14.12
IS death	0.65	0.11	0.68	0.83	11.50	13.78

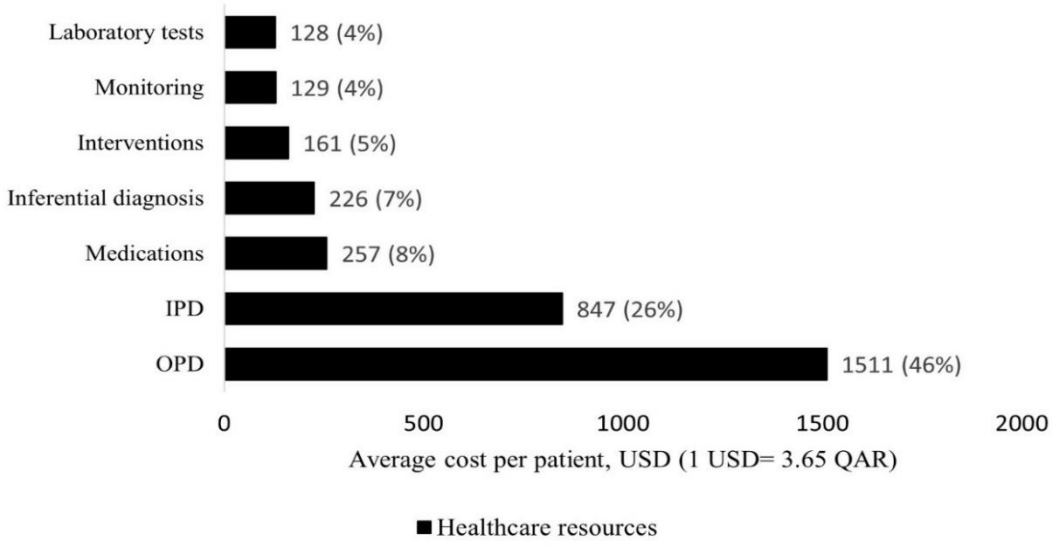
Event	Emergency (USD)	ICU (USD)	IPD (USD)	OPD (USD)	Rehabilitation (USD)	Total (USD)
Low risk TIA	0.58	0.00	0.34	0.71	0.00	1.62
Medium risk TIA	1.16	0.00	1.04	1.42	0.00	3.62
High risk TIA	0.19	0.00	0.23	0.23	0.00	0.65
SE	0.00	0.00	0.00	0.00	0.00	0.00
Death	0.00	0.00	0.00	0.00	0.00	0.00
MI	27.06	39.70	140.73	63.92	137.12	408.54
MI death	1.85	2.70	9.59	4.35	9.33	27.81
Proximal DVT	0.26	0.00	0.30	1.28	0.00	1.85
Distal DVT	0.26	0.00	0.30	1.28	0.00	1.85
Proximal and distal DVT	0.26	0.00	0.30	1.28	0.00	1.85
DVT death	0.00	0.00	0.01	0.02	0.00	0.03
PE	1.27	0.73	3.70	3.39	0.00	9.08
PE death	0.15	0.09	0.44	0.41	0.00	1.09
Death*	0.00	0.00	1.88	7.36	0.00	9.26
Total	194.05	93.05	687.00	1,968.87	319.88	3,263.13

*Death; non-hemorrhagic or non-vascular death. AE; adverse event, DVT; deep vein thrombosis, GI; gastrointestinal, H; hemorrhage, ICH; intracerebral hemorrhage, ICU; intensive care unit,

IPD; in-patient department, IS; ischemic stroke, MI; myocardial infarction, OPD; out-patient department, PE; pulmonary embolism, SAH; subarachnoid hemorrhage, SDH; subdural hemorrhage, SE; systemic embolism, TIA; transient ischemic attack. 1 USD = 3.65 QAR.

5.3.3 Cost per resource category

The resource category that contributed to the overall cost of warfarin peri-procedural management the most was the clinic visits (47%), followed by hospitalization (25%) and then the medications (8%) and inferential diagnosis (7%). Laboratory testing, alternative interventions, and monitoring cost 4-5% each of the total cost per patient. The relative contribution of the different resource categories towards the overall cost of therapy is summarized in Figure 5.7.



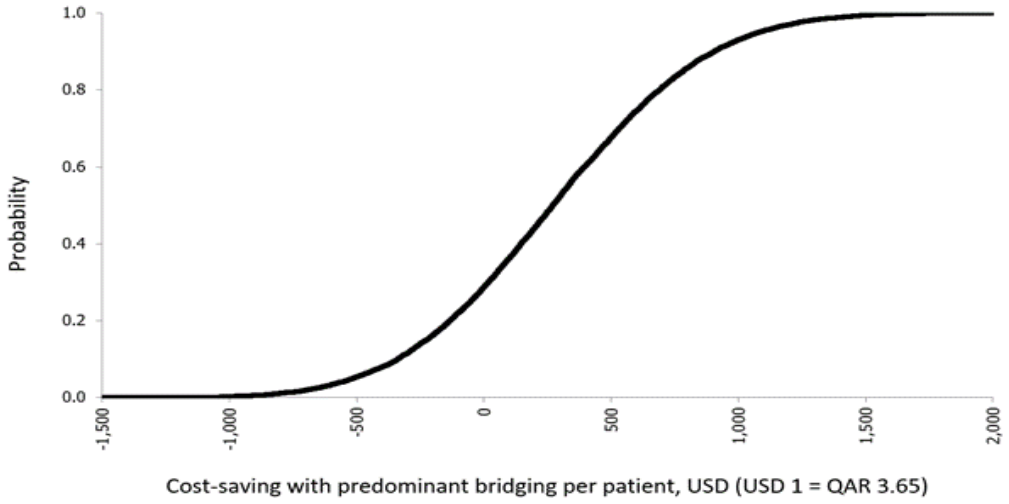
The average cost per patient per health care resources used.
IPD; in-patient department, OPD; out-patient department, USD; United State Dollar.

Figure 5.7: Healthcare resources towards the mean cost per patient of warfarin peri-procedural management

5.3.4 Cost-effectiveness of predominant bridging versus predominant non-bridging

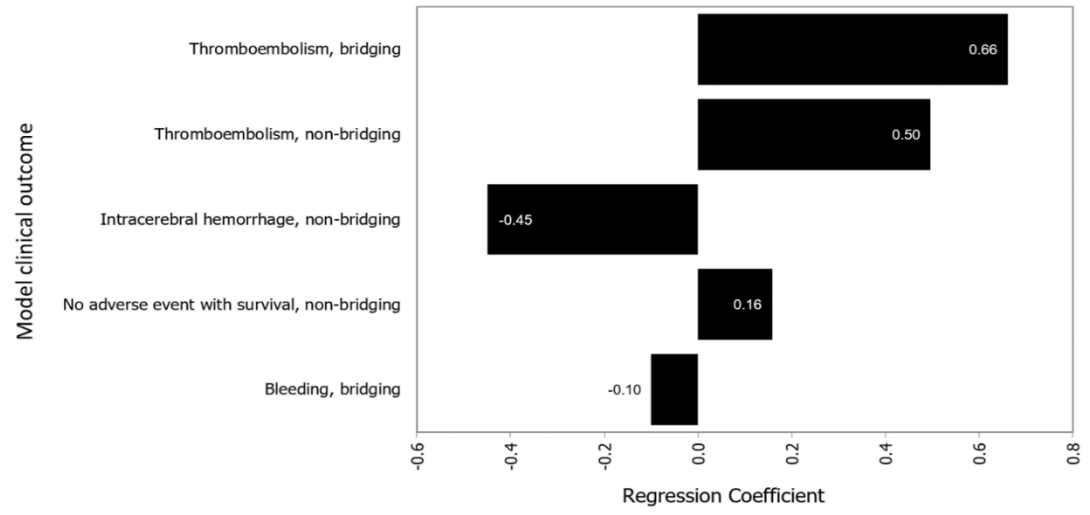
The mean difference in success between 63% bridging and 37% bridging was 14.3 % in favor of the predominant bridging, 0.447 (95% Cl 0.446, 0.448) versus 0.304 (95%

Cl 0.303, 0.305). Taking cost into consideration, the predominant bridging approach was dominant over the predominant non-bridging approach in 62.2 % of simulated cases, with an average cost-saving of USD 272 (QAR 993), with up to a maximum cost saving of USD 2,001 (QAR 7,300) and was cost-effective in 36.9 % of cases. Figure 5.8 presents the probability curve of the cost-saving with the predominant bridging. The regression tornado ranking of model outcomes as per the size of their impact indicated that the rate of TE is the most influential, followed by hemorrhage and then the no AE. The tornado analysis of the regression coefficient can be seen in Figure 5.9.



USD; United State Dollar

Figure 5.8: Cost-saving probability curve with bridging.



ICER; incremental cost-effectiveness ratio

Figure 5.9: Tornado diagram of the base-case ICER based on the regression coefficient.

5.3.5 Sensitivity analysis

5.3.5.1 One-way sensitivity analysis

The base case success and cost associated with warfarin were not sensitive to an uncertainty range of 51-75% when assigned to the occurrence of bridging in HMC. Based on the one-way sensitivity analysis, the resulting mean success was 0.753 (95% Cl 0.752, 0.754), and the mean cost was USD 3,256 (95% Cl 3,240, 3,270) [(QAR 11,884 (95% Cl 11,826, 11,935)]. The probabilities of the success and overall cost based on one-way sensitivity analysis are in Figures 5.10 & 5.11.

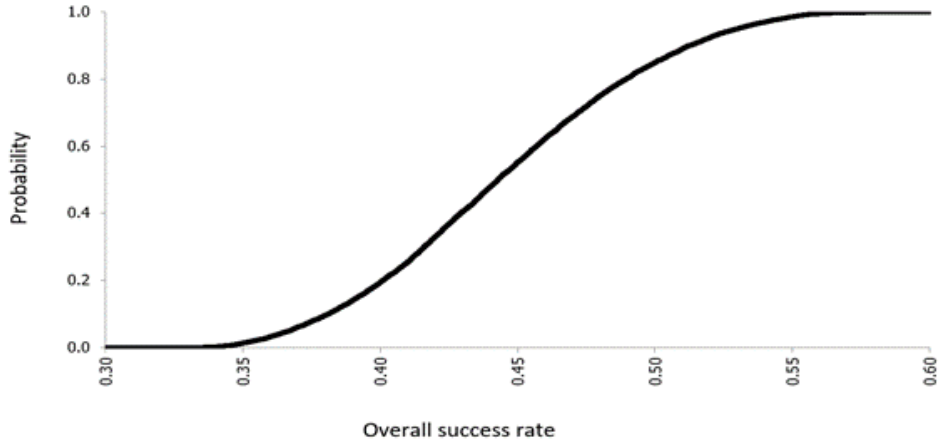
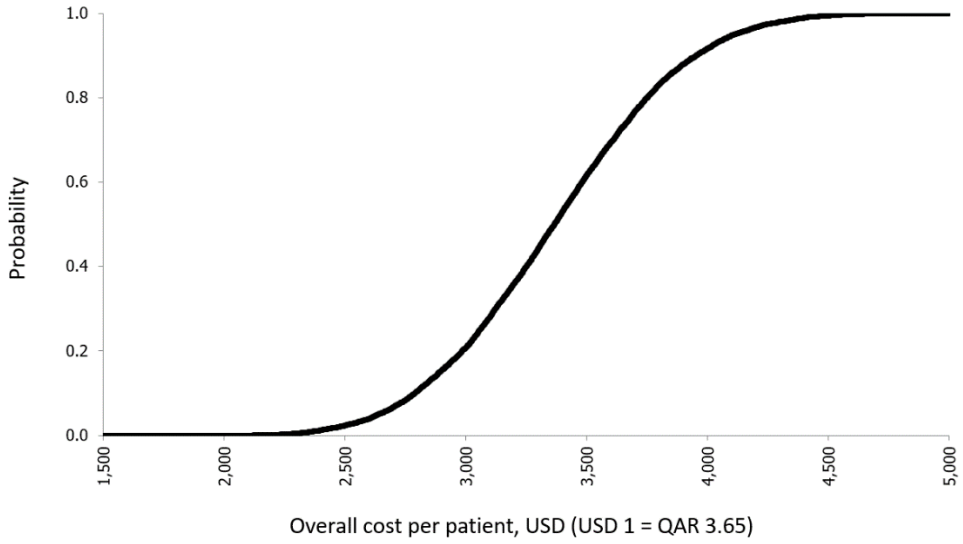


Figure 5.10: Overall success rate per patient probability curves with one-way sensitivity analysis.



USD; United State Dollar

Figure 5.11: Overall cost (USD) per patient probability curves with one-way sensitivity analysis.

5.3.5.2 Probabilistic sensitivity analysis

Adding the event cost uncertainty to the base-case probability uncertainty had no impact on the model outcomes. Event costs and their uncertainty ranges are presented in Table 5.6. The outcomes of the sensitivity analysis, as compared to the base-case analysis, are summarized in Table 5.7 for total success, total cost, and ICER results.

Based on the regression tornado analyses, the rank of outcomes as per their impact on the outcome, as well as the size of the impact, was identical to that at the base case, with no impact of the proposed uncertainty in cost on base-case outcomes. This applied to both the overall cost in the cost-analysis (Figure 5.5) and the cost-saving result of the cost-effectiveness analysis (Figure 5.9).

Table 5.6: Direct cost (USD) of different clinical events and their uncertainty ranges

Event	**Direct cost (USD)**	**Uncertainty range (USD) (-20%, +20%)**	
No AE/death* (bridging)	2,037	1,629.60	2,444.40
No AE /death* (non- bridging)	1,945	1,556.00	2,334.00
Ecchymosis	1,319	1,055.2	1,582.9
Hematoma	1,151	920.80	1,381.20
Hematuria	2,533	2,026.40	3,039.60
Epistaxis	800	640.00	960.00
Intra-ocular H.	593	474.40	711.60
Upper GI H	5,245	4,196.00	6,294.00
Lower GI H	5,218	4,174.40	2,444.40
GIH Death	5,231	4,184.80	6,277.20
No deficit ICH	10,332	8,265.60	12,398.40
Mild deficit ICH	22,051	17,640.80	26,461.20
Moderate deficit ICH	34,095	27,276.00	40,914.00
Severe deficit ICH	56,677	45,341.60	68,012.40
ICH Death	56,677	45,341.60	68,012.40
SAH	37,038	29,630.40	44,445.60
SAH Death	37,038	29,630.40	44,445.60

Event	Direct cost (USD)	Uncertainty range (USD) (-20%, +20%)	
SDH	43,836	35,068.80	52,603.20
SDH Death	43,836	35,068.80	52,603.20
No deficit IS	9,424	7,539.20	11,308.80
Mild deficit IS	21,903	17,522.40	26,283.60
Moderate deficit IS	34,382	27,505.60	41,258.40
Severe deficit IS	57,006	45,604.80	68,407.20
IS death	57,006	45,604.80	68,407.20
Low risk TIA	4,770	3,816.00	5,724.00
Medium risk TIA	5,303	4,242.40	6,363.60
High risk TIA	5,836	4,668.80	7,003.20
SE	17,153	13,722.40	20,583.60
Death	17,153	13,722.40	20,583.60
MI	30,225	24,180.00	36,270.00
MI death	30,225	24,180.00	36,270.00
Proximal DVT	7,481	5,984.80	8,977.20
Distal DVT	7,481	5,984.80	8,977.20
Proximal and distal DVT	7,481	5,984.80	8,977.20
DVT death	7,481	5,984.80	8,977.20
PE	14,191	11,352.80	17,029.20
PE death	14,191	11,352.80	17,029.20

*Death; non-hemorrhagic or non-vascular death. AE; adverse event, DVT; deep vein thrombosis, GI; gastrointestinal, H; hemorrhage, ICH; intracerebral hemorrhage, IS;

ischemic stroke, MI; myocardial infarction, PE; pulmonary embolism, SAH; subarachnoid hemorrhage, SDH; subdural hemorrhage, SE; systemic embolism, TIA; transient ischemic attack. 1 USD = 3.65 QAR.

Table 5.7: Multivariate sensitivity analyses and the subsequent changes in model outcomes

Strategy	Mean total success (95% CI)*	Mean total cost (USD) (95% CI)*	Mean incremental effectiveness in favor of predominant bridging (95% CI)	Mean cost saving in favor of predominant bridging (USD) (95% CI)	ICER
Base-case scenario	0.752 (0.751, 0.753)	3,260 (3,250, 3,270)	0.0442 (0.0434, 0.0445)	272.0 (263, 281)	Dominance
Probabilistic sensitivity analysis	0.753 (0.752, 0.754)	3,256 (3,240, 3,270)	0.0439 (0.0434, 0.0445)	275 (266, 283)	Dominance

*With 63% bridging versus 37% non-bridging. CI; confidence interval, ICER; Incremental cost effectiveness ratio, USD; United States Dollar (1 USD = 3.65 QAR), Dominance; higher effect and lower cost (an ICER cannot be calculated).

5.4 Discussion

This is the most comprehensive follow-up evaluation of the bridging versus non-bridging with peri-operative warfarin management in the literature, including the majority of the possible consequences. As discussed above, the BRIDGE trial is the

only RCT in the literature that compared bridging versus non-bridging with peri-operative warfarin [139], but this did not include some outcomes like; minor bleeding sub-types, IO bleeding, GI hemorrhage, intracerebral hemorrhage, SAH and SDH. Most importantly, this study is also the first literary analysis of the economic consequences of bridging versus non-bridging, which is most important in guiding decision making. The predominant use of bridging in HMC is not based on local guidelines and is influenced by practitioners' experiences and personal opinions. For example, a recent local study that evaluated warfarin peri-procedural management in HMC reported that exaggerated warfarin discontinuation in procedures, such as cataract and dental surgery, was justified by the practitioners' fear of bleeding events. This is when, according to the guidelines [190], such procedures do not require warfarin interruption.

Based on 63% of bridging versus non-bridging in HMC, the overall success (survival with no AEs) was 0.752, mostly associated with the bridging over non-bridging, 0.444 versus 0.307. This was at a cost of USD 3,260 (QAR11,900) per patient, mostly associated with bridging over non-bridging, USD 2,037 (QAR 7,435) versus USD 1,223 (QAR 4,463). The calculated cost and success in HMC were not sensitive to an uncertainty range for bridging occurrence of 51-75%.

Literature studies reported a significant increase in bleeding events with bridging [113, 139, 218, 223], while for the TE events, these were reported not significantly to differ between bridging and non-bridging [139]. The superiority of predominant bridging over predominant non-bridging in the current study, therefore, is in contrast to suggestions in the literature to decrease the use of bridging during warfarin peri-procedural management, mainly due to the elevated risk of bleeding from heparin usage [203]. Here, however, a non-significant clinical benefit does not necessarily correlate

to little economic benefit. Because the TE rate, while non-significant, is higher with the predominant non-bridging than bridging, the reduced cost of TE with predominant bridging was considerably higher, by 25%, than with non-bridging that it overtook the increased cost of bleeding with bridging, as seen in Table 2, to an overall cost saving in favor of bridging. Besides, while 30% of patients with major procedures will require costly hospital admission with bridging, 70% of the current model's performed procedures were minor as already indicated and, hence, did not add to the hospital admission in the predominant bridging study arm. The result that 63% bridging was mostly between cost-saving to cost-effective against 63% non-bridging was not sensitive to a 20% uncertainty in the event costs in the model.

As per both medical resources and type of admission categories, the leading driver of the overall cost of peri-procedural management is the cost of the outpatient clinic visits. This would be the consequence of the cost of the doctor visit, with an average of USD 352 (QAR 1,281) in Qatar, which is higher than that in neighboring countries like Oman, for example, by about 69%, in addition to the frequency of visits during the one year of follow up. Higher frequency of visits to the anticoagulation clinic in particular projects the cost of events such as the VTE.

For the cost of events, stroke has a considerable economic impact on the healthcare system. The average management cost of a patient with severe hemorrhagic stroke is approximately USD 56,677 (QAR 206,871), and a patient with severe ischemic stroke is USD 57,006 (QAR 208,071). Based on HMC practices, these costs are augmented by the severe cases' rehabilitation, representing around 83% of the management plan.

There is no official approved WTP in Qatar. Guiding decision in such cases, the WHO suggested that the value of the threshold in a country can be within 1-3 times the gross domestic product (GDP) per capita in the country [235]. This proposed range, however,

is arbitrary and not based on any methodological justification [235]. Besides, the average 2019 GDP per capita in Qatar was approximately USD 64,781 [236], one of the world's highest. Thus, adopting the WHO recommendations for calculating the WTP will result in a range of too wide values to be directly useful, i.e., USD 64,781-194,343. The current analysis adapted a threshold value of USD 150,000, an increasingly accepted higher threshold value in the literature [237] and, importantly, is also within the range suggested by the WHO for Qatar.

The main limitation of this study is that the model was populated with literature sources instead of local patient data. Literature studies are mostly of Caucasian populations as an example. Also, the BRIDGE trial [139], the primary source of data, which recruited patients with low-intermediate risk of thrombosis (mean CHA_2DS_2 was 2.5), with most patients having CHA_2DS_2 score of <3, may produce results that may not mirror results in high-risk patients. Nevertheless, the literature sources are of top quality. They are relevant to the HMC practices regarding the underlying AF disease and patient age, the warfarin and heparin use, and the stroke risk score. The utilized literature sources are the best sources of evidence available for this study. Noteworthy, the occurrence probability of bridging was locally based. In addition, the base-case study was based on multivariate uncertainty assigned to the study inputs obtained from the literature. This is added to additional levels of sensitivity analyses that were performed, where further uncertainty was introduced to the model, with all confirming the robustness of results against realistic input variability. Another limitation was that this study was conducted from hospital perspective which limited its application on private market. Because the patient's perspective is the main perspective in private market which may includes some indirect cost to the cost analysis.

Results in the current study do not imply that bridging should be universally used with

peri-procedure warfarin. It is recommended that practitioners follow the recent clinical guidelines, which suggest warfarin continuation in minor and low bleeding risk surgeries, to decrease the economic burden of warfarin peri-procedural management. In patients who require to interrupt warfarin; however, with their assessment results regarding favorability of bridging established, warfarin bridging will be more cost-effective than non-bridging.

5.5 Conclusion

Based on the study perspective and assumptions, and as per current practices of bridging versus non-bridging in HMC, the average cost of warfarin peri-procedural management is USD 3,260 (QAR 11,900), associated with a rate of 0.752 for survival with no AEs. Against predominant non-bridging practices, warfarin bridging in AF patients is between cost-saving and cost-effective in 98% of patient cases.

CHAPTER 6: GENETIC AND NON-GENETIC FACTORS IMPACT ON INR NORMALIZATION IN PREPROCEDURAL WARFARIN MANAGEMENT

6.1 Introduction

Warfarin has been the mainstay oral anticoagulant (OAC) prescribed in thromboembolic conditions for several decades [12, 33]. With its challenging narrow therapeutic index, the International Normalized Ratio (INR) is a handy surrogate marker to monitor warfarin's therapeutic effect [238]. In procedures associated with more than minimal bleeding risk, warfarin-receiving patients are expected to stop it 5-7 days before surgery to achieve a baseline INR level and reduce the risk of bleeding during and after the procedure [239]. However, the INR decline varies across patients and may require a shorter or longer warfarin interruption period. Recent studies [124, 217] found that 23% of patients who stopped warfarin reached an INR > 1.2 following 4.7 days of warfarin holding, and 7% reached a preoperative INR > 1.5 after 5 days. Furthermore, Spyropoulos et al. [218] and Pengo et al. [125], found that the mean ± standard deviation (SD) INR was 1.8 ± 0.5 after 5-6 days of warfarin discontinuation.

Mechanistically, warfarin's elimination half-life plays a vital role in INR normalization rate and may at least partly explain this variability [108]. Warfarin is a mixture of two active enantiomers: the (R) and (S) enantiomers, where the latter has five-fold higher anticoagulation potency than the former [70]. Indeed, the S-enantiomer is metabolized by the Cytochrome P450- family 2, subfamily C, member 9 (CYP2C9*)* enzyme [68, 71, 211]. Genetic variants in *CYP2C9* have been widely studied, and it was found that *CYP2C9*2* (rs1799853*)* and *CYP2C9*3* (rs1057910) alleles are the most common variant alleles across different populations including the Middle Eastern and North Africa (MENA) population. [240]. These variants (*CYP2C9*2* and *CYP2C9*3)* account for reductions in the CYP2C9 enzymatic activity to 12-70% and 5%, respectively [73, 74]. The Cytochrome P450- family 4, subfamily F, member 2 (CYP4F2*)* is another liver

enzyme that inactivates the hydroxy-vitamin K1 and may also have an impact on warfarin and the rate of INR normalization [238]. *CYP4F2*3* (rs2108622) is a non-synonymous variant in *the CYP4F2* gene that has been associated with a reduction in the CYP4F2 enzyme activity by 8%-11% and may be associated with warfarin dose increase by 4-12% [239, 241]. *CYP4F2*3* is a commonly occurring mutation in various populations and has a minor allele frequency (MAF) of 30-42% in the MENA region [72]. The most crucial pharmacodynamic target for warfarin is vitamin K epoxide reductase complex subunit 1 (*VKORC1)* enzyme which is inhibited by warfarin leading to the inactivation of vitamin K and its dependent coagulation factors (II, VII, IX, and X) [242]. The most common genetic variation in the *VKORC1* gene is *VKORC1*2* (rs9923231), which is relatively common (30-72%) in patients of MENA descent [72, 211]. A recent local study showed that *VKORC1* and *CYP2C9* variants along with clinical factors can predict warfarin dose variability by 40% [105].

Other than the pharmacokinetic and pharmacodynamic targets for warfarin, coagulation factors regeneration is considered a limiting step in INR decline rate; these factors' genetic polymorphisms may affect their regeneration and synthesis rates and eventually affect the time for INR normalization [80, 108]. The most comment genetic polymorphisms in the genes encoding for factor VII (FVII) is (rs3093229), which has an average prevalence of 22% among diverse populations [243, 244]. Additionally, it has been found that patients' sensitivity to warfarin is generally affected by variations in factor II (*FII)* gene (rs5896) [89, 245]. Its polymorphism is reported in 14% of the American population and 13% of the Italians [89, 91, 245].

Genetic factors that influence INR normalization during preprocedural warfarin interruption have been explored directly and indirectly in previous studies with various ethnic groups [143-149]. Some found that *CYP2C9* is the only genetic player [143, 145,

148], while others failed to find any association between genetic variants and INR decline [144, 146, 147, 149].

To the best of our knowledge, no studies investigated the effect of *CYP2C9, CYP4F2,* and *VKORC1* genetic polymorphism on INR decline in the Arab population. Moreover, coagulations *FII* and *FVII* polymorphisms on INR normalization have not been explored before. This study explores the influence of *CYP2C9, VKORC1, CYP4F2, FII*, and *FVII* genetic polymorphisms and non-genetic factors on INR normalization in the Arab population in preprocedural warfarin management.

6.2 Methods

6.2.1 Study Design and Ethics

This study was designed as an observational prospective cohort study. Ethical approval was obtained from the Institutional Review Board (IRB) of Qatar University (QU) (QU-IRB 1296-FBA/20) and Hamad medical corporation (HMC) (MRC-16415/16).

6.2.2 Study Setting and Timeline

The recruitment started in September 2018 and ended in December 2020. Afterward, genetic and data analyses were conducted in January 2021. Participants were recruited from the anesthesia, anticoagulation, and surgery clinics at Al Wakrah Hospital, Hamad General Hospital, and Heart Hospital, which are all part of HMC, the largest healthcare corporation in Qatar.

6.2.3 Study Population and Enrolment

The study screened warfarin patients of the Arab population (being of any of the League of the Arab States) [246]. The patients reported their nationality verbally, and it was confirmed through the patient's electronic healthcare record (EHR).

Subjects were eligible if he/she was ≥18 years old, on warfarin for ≥ one month with a stable INR for the last two consecutive visits with a minimum one-week interval (a stable INR was defined as INR within ± 0.2 units of the target therapeutic range) [210],

undergoing elective surgery that required warfarin discontinuation for ≥ 3 days. Exclusion criteria were patients on chronic kidney dialysis, suffering from liver cirrhosis, or those who received a pre-operative vitamin K, fresh frozen plasma, or prothrombin complex concentrates.

6.2.4 Data collection and outcome measures

Only subjects who met the inclusion criteria and provided signed informed consent were recruited. Patients were followed for two visits over the last week prior to their procedure. The first visit was a routine visit on the day of warfarin interruption (7-5 days prior to the day of the procedure) to record 1st INR reading. The patient had to attend a second visit on the same day or a day before the surgery, to get 2nd INR reading. DNA sample collection was performed at any of the study visits, where patients were asked to provide either 4 ml of blood in BD Vacutainer® K2E EDTA 7.2 mg glass collection tubes (Ref. No. 368861) or 2 ml of saliva sample single Oragene•DNA® (OG-500) self-collection kit (DNA Genotek™, Canada), according to the manufacturer's instruction.

6.2.5 DNA extraction and genotyping

Blood samples were stored in a -20 C freezer until DNA isolation. Later, genomic DNA was extracted from whole blood as per the manufacturer's protocol and using PureLink® Genomic DNA mini kits, Invitrogen™, in line with the producer standards [247]. On the other hand, saliva sample kits were kept at room temperature until DNA extraction. For the DNA purification from the saliva sample, the PrepIT®•L2P standard protocol was followed [248].

The quality and quantity of the purified DNA were evaluated by Nanodrop 2000c Spectrophotometer (Thermo Fisher Scientific) [249]. Finally, the samples were genotyped for detecting the genetic polymorphisms in the genotypes of *CYP2C9, CYP4F2, VKORC1, and FII* and *FVII* using the real-time Polymerase Chain Reaction

(PCR) QuantStudio™ single nucleotide polymorphism (SNP) genotyping assay manufactured by Applied Biosystems™. All probes were purchased at ThermoFisher Scientific; their context sequences are listed in Table 6.1. Demographics like (age, nationality, gender, weight, height, etc.) and clinical data (concurrent medications, co-morbidities, INR target, etc.) were obtained directly from the patients and their EHR.

Table 6.1: Context sequences of the probes used in genotyping

Genotype	SNP ID*	Context Sequence [VIC/FAM]
*CYP2C9*2*	rs1799853	GATGGGGAAGAGGAGCATTGAGGAC**[C/T]**GTG TTCAAGAGGAAGCCCGCTGCCT
*CYP2C9*3*	rs1057910	TGTGGTGCACGAGGTCCAGAGATAC**[C/A]**TTGA CCTTCTCCCCACCAGCCTGCC
*VKORC1*2*	rs9934438	CCCCGACCTCCCATCCTAGTCCAAG**[A/G]**GTCG ATGATCTCCTGGCACCGGGCA
*CYP4F2*3*	rs2108622	CCCCGCACCTCAGGGTCCGGCCACA**[C/T]**AGCT GGGTTGTGATGGGTTCCGAAA
FII	rs5896	TGCCGCAACCCCGACAGCAGCACCA**[C/T]**GGG ACCCTGGTGCTACACTACAGAC
FVII	rs3093229	ACAACCAAAGTTTTCCTGTGTCCTC**[C/T]**ACAC TCAAGAGTGACTGTGAGGCGG

CYP2C9; cytochrome P450- family 2- subfamily C- member 9, *CYP4F2*; cytochrome P450- family 4- subfamily F- member 2, *FII*; coagulation factor II, *FVII*; coagulation factor VII, *SNP*; single nucleotide polymorphism, *VKORC1*; vitamin K epoxide reductase complex subunit 1.

6.2.6 Study outcome

The primary study outcome is the mean difference in INR drop rate (equals to the

difference between INR readings, divided by the days' interval) between carriers and non-carriers of the genetic variants.

6.2.7 Sample size calculation

The sample size for multiple regression was calculated using http://www.danielsoper.com/statcalc [250]; based on effect size (0.2), 0.8 statistical power, 0.5 alpha level, and 20 predictors, the required sample size was 122 patients. Counting for an anticipated 20% drop-out rate, the sample size was estimated to be 146.

6.2.8 Statistical analysis

Descriptive analysis was used to analyze genetics, demographics, and clinical information. Continuous data were presented as mean ±SD for normally distributed data, the median and interquartile range (IQR) for non-normally distributed data. Categorical variables were described as frequencies and percentages. Independent Student`s t-test and one-way ANOVA test were used for comparing normally distributed continuous data. In contrast, either the Mann-Whitney U test or the Kruskal Wallis test was performed to compare non-normally distributed continuous data. Chi-square- Goodness of Fit was used to ensure that all allele frequencies for the tested genetic variants fit the Hardy- Weinberg equilibrium (HWE). A *P*-value of more than 0.05 indicated that allele frequencies fit HWE. The INR decline rate (slope) was calculated as the ratio between the difference in INR values (delta INR) and the difference in days at which these INR were measured (delta days). Single linear regression (SLR) was performed to assess the impact of genetic, clinical, and demographic factors as a continuous variable on the rate of INR decline; Multiple linear regression (MLR) modeling was used to determine the factors associated with the INR decline and to develop INR normalization model. Logistic regression was used to test the association between genetic and non-genetic factors with an INR of ≤ 1.2 versus > 1.2 on the day before or on the day of the planned surgery. A two-tailed *P*-value of

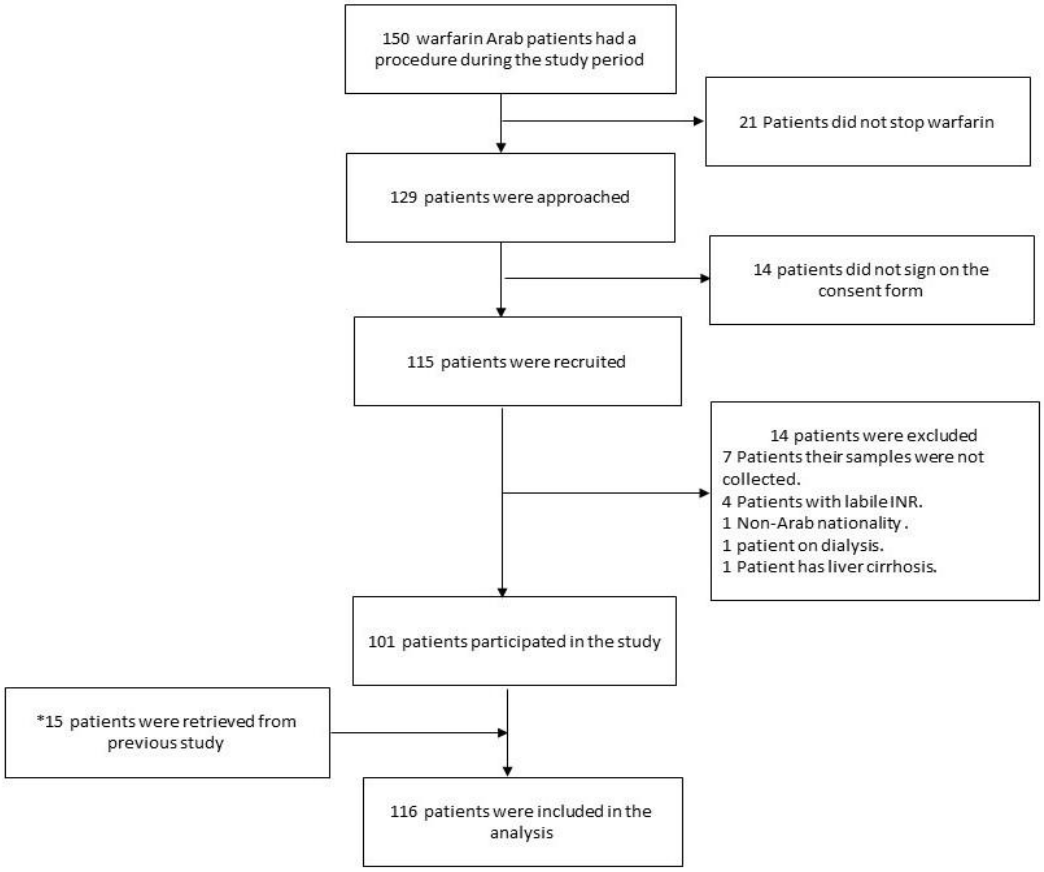
<0.05 was considered significant. IBM SPSS statistics for Windows was used to carry out the statistical analysis.

6.3 Results

6.3.1 Patient Enrollment and Population Characteristics

Out of 129 approached patients, 115 patients were recruited (11% rejection rate). Additional 14 subjects were excluded due to various reasons, as illustrated in Figure 6.1. To expand the sample size, data of 15 eligible patients from previous warfarin research project [105] was integrated into the current analysis to make the total sample size 116. These patients agreed on using their information in future research. The mean ± SD age of the cohort was 66.2 ± 14.4 and were almost equal proportions of both genders [65 (56%) were men]. Table 6.2 shows patients' demographics and characteristics. The majority of the patients (41.4%) were locals (Qataris), and had multiple comorbidities (mean ± SD number of co-morbidities was 4 ± 2.1). Most of the patients (63.8%) had hypertension; besides, half of them (50%) were suffering from diabetes mellitus and/or dyslipidemia. Of the drugs reported as INR and warfarin therapeutic effect inducer, 33 patients were using aspirin, clopidogrel, or both. Seven patients were taking non-steroidal anti-inflammatory drugs (NSAIDs), four were taking amiodarone, one patient was taking metronidazole and another one was on ciprofloxacin. On the other hand, of the drugs stated as a possible reducer of warfarin effect and INR, three patients were on rifampin, one patient was using carbamazepine and one was taking phenytoin.

Most of the participants were taking warfarin for the indication of stroke prevention in atrial fibrillation (AF) or mechanical/ bioprosthetic heart valve replacement [63 (54.3%) and 47 (40.5%), respectively). The mean ± SD INR reading at the time of interruption and day of procedure were (2 ± 0.4 and 1.2 ± 0.13, respectively). Types of performed procedures are summarized in Table 6.3.



(* L. Bader et al. (2020) [105])

Figure 6.1: Flowcharts of patients included in the analysis.

Table 6.2: Patient characteristics

Characteristic	**Cohort (N= 116)**
Age, in years, mean ± SD	66.2 ± 14.4
BMI in kg/m^2, mean ± SD	30.0 ± 5.7
Male gender, no. (%)	65 (56)

Characteristic	**Cohort (N= 116)**
Nationality, no. (%)	
Qatari	48 (41.4)
Egyptian	22 (19.0)
Palestinian	16 (13.8)
Sudanese	10 (8.6)
Others[†]	20 (17.2)
Smoker, no. (%)	14 (12.1)
Amount of vitamin K rich food intake, no. (%) [¥]	
Low	26 (22.4)
Medium	86 (74.1)
High	4.0 (3.4)
Current medical condition, no (%)	
Diabetes mellitus	58 (50.0)
Hypertension	74 (63.8)
Congestive heart failure	13 (11.2)
Cancer	9.0 (7.8)
Dyslipidemia	58 (50.0)
Thyroid's dysfunction	14 (12.0)
Co-morbidities, mean ± SD	4.0 ± 2.1

Characteristic	**Cohort (N= 116)**
Current interacting medications, no. (%)	
Amiodarone	4.0 (3.4)
Metronidazole	1.0 (0.9)
Ciprofloxacin	1.0 (0.9)
Carbamazepine	1.0 (0.9)
Rifampin	3.0 (2.6)
NSAIDs	7.0 (6.0)
PPIs	66 (56.9)
Statins	75 (64.7)
Antiplatelets	33 (28.4)
Warfarin indication, no. (%) *	
AF	63 (54.3)
Mechanical or bioprosthetic heart valve replacement	47 (40.5)
VTE	17 (14.7)
Thrombophilia	6.0 (5.2)
Stroke	15 (12.9)
Others	6 (5.2)
INR target, no. (%)	
2.0-3.0	63 (71.6)
2.5-3.5	22 (19.0)
Others$^{\gamma}$	11 (9.5)

Characteristic	Cohort (N= 116)
Maintenance weekly dose, mean ± SD	29.8 ± 14.0
1st INR reading, mean ± SD	2.0 ± 0.4
2nd INR reading, mean ± SD	1.2 ± 0.13
Difference between INR readings, mean ± SD	0.84 ± 0.38
Days of discontinuation, median (IQR)	5.0 (2.0)
INR decline rate, median (IQR)	0.45 (0.56)
INR <1.5 at time of procedure, no (%)	96 (82.8)
INR ≤1.2 at time of procedure, no (%)	65 (56.1)

[l]Others; According to the League of the Arab States [246]. ¥ amount of Vitamin k rich food intake was defined as low; 1-2 bowl/week, medium; 3-4 bowls/week, high; 5-7 bowls/weeks. *Others; Some patients are taking warfarin for more than one indication. [γ]Others; 2-2.5 /3-3.5 / 3-4, AF; atrial fibrillation, BMI body mass index, INR; international normalization ratio, IQR; interquartile range, NSAIDs; non-steroidal anti-inflammatory drugs, PPI; proton pump inhibitor, SD; standard deviation, VTE; venous thromboembolism.

Table 6.3: List of performed procedures

The procedure, no. (%)	Cohort (N=116)
Minor procedure	**84 (72.5)**
Dental procedure	29 (25.0)
Endoscopy	19 (16.4)
Ophthalmology procedure	15 (12.9)
Valvuloplasty	3.0 (2.6)
CAG	6.0 (5.2)
Others	12 (10.4)

The procedure, no. (%)	Cohort (N=116)
Major procedure	**25 (21.5)**
Resection	7.0 (6.0)
CABG	6.0 (5.2)
Knee replacement	2.0 (1.7)
MVR	2.0 (1.7)
Gastric sleeve	2.0 (1.7)
Others	6.0 (5.2)
None*	**7.0 (6.0)**

* Some procedures were canceled, CAG; coronary angiography, CABG; coronary artery bypass grafting, MVR; mitral valve replacement.

6.3.2 Prevalence of Genetic Variants

MAF was computed to estimate the prevalence of genetic variants. No deviation from Hardy-Weinberg equilibrium (HWE) were detected for any genotype frequencies (Table 6.4). Also, Table 6.5 presents the genotype frequencies.

Table 6.4: Minor allele frequency of genotypes

Genoty -pe	***CYP2C9 *2***	***CYP2C9 *3***	***CYP4F2 *3***	***VKORC1 *2***	***FII (C>T)* (rs5896)**	***FVII (C>T)* (rs3093229)**
SNP ID	rs179985 -3	rs105791 -0	rs21086- 22	rs9923231	rs5896	rs3093229
MAF	0.12	0.08	0.41	0.46	0.09	0.09
P- Value*	0.227	0.105	0.489	0.297	0.259	0.300

* If $P \geq 0.05$ - consistent with HWE. *CYP2C9*; cytochrome P450- family 2- subfamily C- member 9, *CYP4F2*; cytochrome P450- family 4- subfamily F- member 2, *FII*; coagulation factor II, *FVII*; coagulation factor VII, HWE; Hardy-Weinberg equilibrium, MAF; Minor allele frequency, *SNP*; single nucleotide polymorphism, *VKORC1*; vitamin K epoxide reductase complex subunit 1.

Table 6.5: Frequency distribution of different genotypes

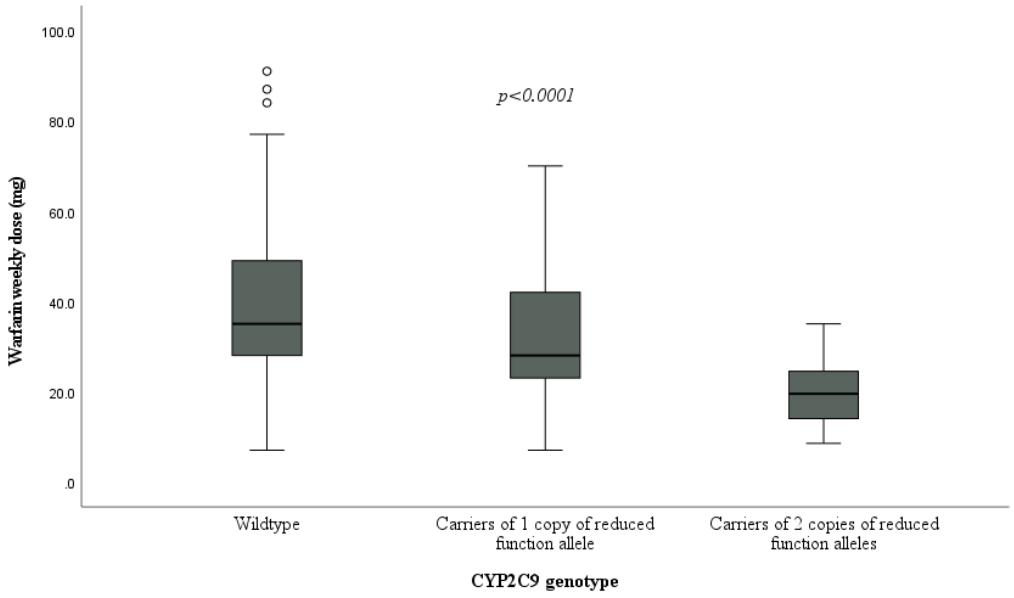
Genotype frequencies no. (%)	**Cohort (N=116)**
*CYP2C9 *2 (C>T)* (rs1799853*)*	
CC	90 (77.6)
CT	22 (19.0)
TT	4.0 (34)
*CYP2C9 *3(A>C)* (rs1057910)	
AA	98 (84.5)
AC	16 (13.8)
CC	2.0 (1.7)
*CYP4F2*3 (C>T)* (rs2108622)	
CC	41 (35.3)
CT	52 (44.8)
TT	23 (19.8)
*VKORC1*2 (C>T)* (rs9923231)	
CC	37 (31.9)
CT	52 (44.8)
TT	27 (23.3)

Genotype frequencies no. (%)	Cohort (N=116)
FII (C>T) (rs5896)	
CC	94 (81.0)
CT	22 (19.0)
TT	0.0 (0.0)
FVII (C>T) (rs3093229)	
CC	96 (82.8)
CT	18 (15.5)
TT	2.0 (1.7)

CYP2C9; cytochrome P450- family 2- subfamily C- member 9, *CYP4F2*; cytochrome P450- family 4- subfamily F- member 2, *FII*; coagulation factor II, *FVII*; coagulation factor VII, *VKORC1*; vitamin K epoxide reductase complex subunit 1.

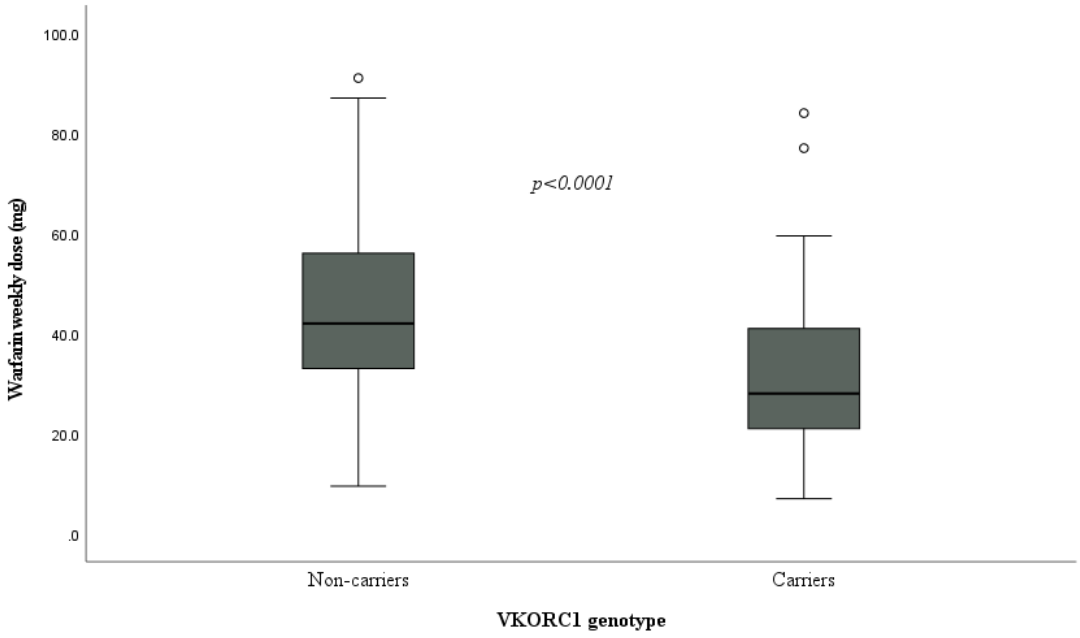
6.3.3 The Effect of Genetic Factors on Weekly Warfarin Maintenance Dose

Warfarin's weekly dose ranged widely from 7.0 mg to 91.0 mg /week. As expected, the results of the univariate non-parametric analysis indicated that carriers of one or two copies of decreased function allele of *CYP2C9 (CYP2C9*2 or *3)* required a lower median (IQR) maintenance dose compared to non-carriers' allele [24.7 (21.1) mg/week vs. 35 (21) mg/week, p =0.001) (Figure 6.2). Similarly, carriers of *VKORC1*2* had a lower median (IQR) maintenance dose compared to the wildtype allele [28 (21) mg/week vs. 42 (23.8) mg/week, p<0.0001) (Figure 6.3).



Kruskal–Wallis test was applied to compare the median warfarin dose between wildtype and carriers of 1 copy or 2 copies of reduced function allele. Boxes represent the median and interquartile range. Lines above and below the boxes represent maximum and minimum values. Mann–Whitney U test was used to compare the median warfarin dose between carriers and noncarriers. *CYP2C9*; cytochrome P450- family 2- subfamily C- member 9.

Figure 6.2: The effect of CYP2C9 variants allele on warfarin weekly maintenance dose.



Mann–Whitney U test was applied to compare the median warfarin dose between carriers and noncarriers. Boxes represent the median and interquartile range. Lines above and below the

boxes represent maximum and minimum values. Mann–Whitney U test was used to compare the median warfarin dose between carriers and noncarriers. *VKORC1*; vitamin K epoxide reductase complex subunit 1.

Figure 6.3: The effect of VKORC1 variants allele on warfarin weekly maintenance dose.

6.3.4 The Effect of Genetic and Non-Genetic Factors on INR Decline Rate

Since the cohort's INR decline rate (slope) was skewed, log transformation was performed before the regression analysis. All variables were tested for association with the log transformation rate of INR decline using univariate linear regression, and the following variables had a *p*-value of <0.2 and thus, were included in the multiple linear regression: cancer status, ciprofloxacin, antiplatelet medication, antibiotics, INR goal, and INR index (INR at visit 1). Stepwise forward selection regression model showed ciprofloxacin, antiplatelet medications, and INR index as the only factors associated with the INR decline rate. Table 6.6 demonstrates that INR decline was steeper (required less time to reach baseline INR) for patients with a higher INR index or who took antiplatelet medications ($p<0.0001$ and $p=0.014$, respectively). In contrast, it was significantly shallower (required more time to reach baseline INR) for those who were using ciprofloxacin ($p=0.001$).

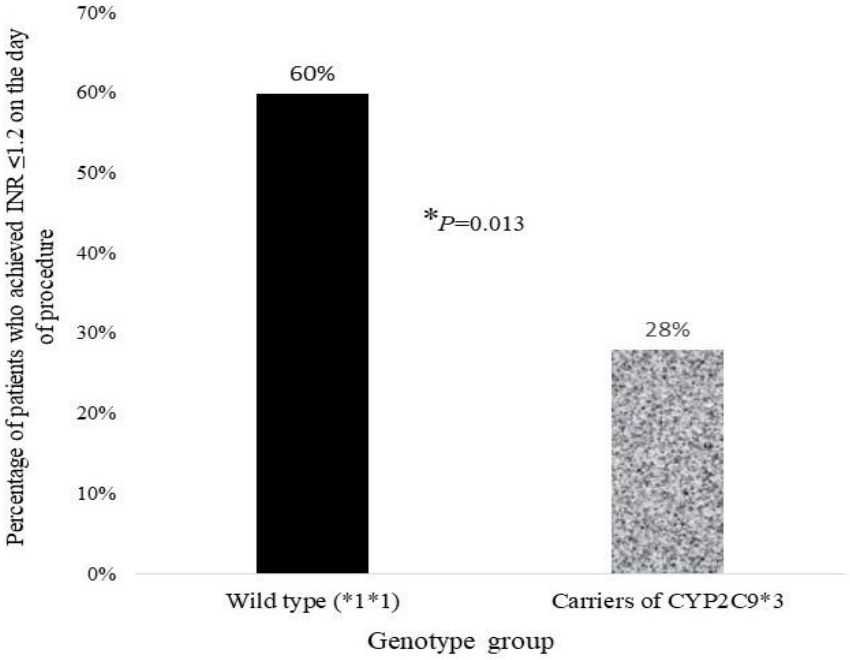
Table 6.6: Multiple linear regression indicating nongenetic factors associated with INR decline rate

Predictor	**Coefficient**	**Standard error**	***p*-value***
Antiplatelet	0.10	0.04	$p=0.014$
Ciprofloxacin	-0.66	0.20	$p=0.001$
INR index	0.31	0.03	$P<0.0001$

*p-value<0.05; is significant. Model adjusted-R^2 =0.435, p-value <0.001

6.3.5 The Effect of Genetic and Non-Genetic Factors on achieving normalized INR (≤1.2)

The proportion of *CYP2C9*3* carriers achieving normalized INR (≤1.2) on the day of surgery was significantly lower than the wildtype allele (28% vs. 60%, *p*=0.013) (Figure 4). Whereas the percentage of *CYP2C9*2* carriers reaching normalized INR (≤1.2) on the day of operation was not different than that of the wildtype allele (63% vs. 60%, *p*=0.80).



* Chi-square test was performed to compare the proportion of carrier of *CYP2C9*3* with INR ≤1.2 to the non-carriers of *CYP2C9*3*, *CYP2C9*; cytochrome P450- family 2- subfamily C- member 9, INR; International Normalized Ratio.

*Figure 6.4: The proportion of individuals with CYP2C9 *3 variant alleles, their INR status before procedure.*

After testing the association between all variables and achieving INR ≤1.2 in univariate analysis, variables with *p*-value <0.2 were added to the binary logistic regression model (Table 7). logistic regression, in both stepwise forward selection and backward elimination, proved that warfarin bridging, INR target, and Sudanese nationality are significant predictors of INR normalization (≤1.2) on the day of the procedure. The

results showed that INR ≤1.2 is most probably to be achieved in the presence of INR goal ≤ 3.5, warfarin bridging and any Arab nationality rather than Sudanese (Table 6.7). Although *CYP2C9*3* genotype was a significant predictor of normalized INR in univariate analysis, it was not significantly associated in the multivariate model (Table 6.8).

Table 6.7: Univariate binary logistic regression displaying genetics and non-genetic influencing INR value of ≤1.2 on the day of the procedure

Predictor	**Odds ratio**	***p*-value***	**95% CI**	
			Lower	**Upper**
Age >65 years	0.52	0.11	0.24	1.16
Weight > 85 kg	1.8	0.12	0.85	3.79
Holding a Sudanese nationality	0.29	0.08	0.07	1.19
Patient with diabetes	0.17	0.13	0.38	3.70
Patient with cancer	0.34	0.15	0.08	1.47
Taking NSAIDs	0.28	0.14	0.05	1.51
Taking drug affecting cardiac action potential[¥]	0.36	0.01	0.15	0.82
Taking Enoxaparin	3.04	0.006	1.42	8.29
Enoxaparin dose is >160 mg	2.65	0.07	0.92	7.63
INR target is ≤3.5	7.02	0.01	1.44	34.15
Having AF	0.36	0.01	0.17	0.79
Having VTE	4.20	0.03	1.14	15.59

Predictor	Odds ratio	*p*-value*	95% CI	
			Lower	Upper
Carrier of reduced function allele of *CYP2C9*3*	0.23	0.01	0.07	0.77
Carrier of reduced function allele of *FVII* genotype	1.91	0.19	0.70	5.57

*p-value<0.05; is significant. ¥; B-blockers, Ca^{+2} channel blockers, K^{+} channel blockers. AF; atrial fibrillation, CI; confidence interval, CYP2C9; cytochrome P450- family 2- subfamily C- member 9, INR; international normalization ratio, NSAIDs; non-steroidal anti-inflammatory drugs, VTE; venous thromboembolism.

Table 6.8: Summary statistics and results from multiple logistic regression analysis

Term	Coefficient	Standard error	Odds ratio	*P*-value*	95% CI	
					Lower	Upper
Constant	-3.86	1.54	0.02	0.013		
Taking Enoxaparin	2.87	1.12	13.5	0.02	1.49	123.3
INR target ≤3.5	2.22	1.23	9.29	0.04	1.02	83.99
Holding a Sudanese nationality	-2.37	1.01	0.09	0.019	0.01	0.67

*p-value<0.05; is significant. CI; confidence interval, INR; international normalization ratio.

6.4 Discussion

This study was set out to identify the genetics, demographics, and clinical factors contributing to the time to normalize INR after the withdrawal of warfarin in periprocedural management in Arab patients. In 2017, Elewa et al. [12] reported that warfarin prescription represented 77% of total OAC use in Qatar, indicating that warfarin is still primarily used despite an increased interest in direct oral anticoagulants. Unfortunately, there is a high inter-and intra-individual variability in warfarin response [218]. This variability is not seen only during warfarin dosing but also during warfarin interruption in periprocedural management. Therefore, it was reasonable to investigate the factors that may affect INR decline after warfarin discontinuation during the preprocedural time.

Previous works evaluating the relation between INR decline and *CYP2C9*, *CYP4F2*, *VKORC1* genetics polymorphism observed inconsistent results. Three studies [146, 147, 149] declined to find any significant genetic predictor of INR decline rate because of their small sample size, which made them not powered enough to detect any difference between carriers and non-carriers of genetics polymorphism. These studies were also limited by the retrospective study design [146] and potential selection bias [147]. Nevertheless, some reported only an impact of *CYP2C9* genetic polymorphic alleles on INR normalization [143, 148]. Since early 2000, it was observed that the *CYP2C9* genetic variant is a significant predictor of the warfarin clearance as an outcome in vivo that may be sound representative of INR decline as an outcome [143, 148]. Abohelaika and his group from the United Kingdom found a significant association between *CYP2C9* genetic polymorphism with INR decline <1.5 in

Caucasians but failed to find any correlation between INR decline rate and warfarin clearance [144, 145]. While our study did not identify any significant genetic polymorphism associated with the INR decline rate, there was a signal that *CYP2C9*3* carriers are less likely to achieve INR≤1.2 at the time of the procedure.

Additionally, the influence of the *CYP2C9*3* allele was more pronounced than of the *CYP2C9*2* allele on time taken to reach INR ≤1.2. This somewhat expected finding could be attributed to the strong inhibitory effect of *CYP2C9*3* on the enzyme activity compared to the effect of *CYP2C9*2* (95% vs. 30%- 88%) [73, 74].

Another finding is that 44% of the participants had INR >1.2, and 17.2% experienced INR ≥1.5 on the day of surgery. A possible explanation for this might be that 72% of performed procedures were minor procedures like dental intervention or endoscopy in which healthcare providers do not prefer a severe drop in INR (≤1.2) during warfarin discontinuation; however, the presence of 17.2% of patients with INR ≥ 1.5 could lead to increasing the cost of preoperative admission, postponing, or canceling planned procedures. This rate was even more than twice what was previously reported [124, 217]. In one of these 2 cited studies, it was found that 23% of patients who stopped warfarin attained an INR > 1.2 and 7% reached a pre-operative INR > 1.5, while the other revealed that 17% of the subjects got INR >1.5 on the day of the procedure.

The results of our study indicate that the prevalence of *CYP2C9*2* and *CYP2C9*3* are (12% and 8%, correspondingly). This accords with an earlier systematic review, which showed that MAF of *CYP2C9*2* and the *CYP2C9*3* in the MENA region ranging between (5%-12.0%) and (4%-10%), respectively among different nationalities in the Arab region [72, 251]. These prevalences are primarily similar to the one previously reported in Qataris and Egyptians, which is logical since these two nationalities represented 60% of the study population [252, 253]. In comparison, *CYP4F2*3* and

*VKORC1*2* are (41% and 46%, respectively) and they were comparable to previous studies done in Egyptians (42% and 46%, respectively) and in Qataris (43% and 47%, respectively) [105, 253]. Looking outside the Arab States, *CYP2C9*2* & *CYP2C9*3* MAF were not much different than prevalence in Europeans (12% & 6.6%) and Turks (13% % 10%). Besides, the MAF of *CYP4F2*3* was closer to South Asians and Turks (36% and 40%) [254]; as well as MAF of *VKORC1*2* was equaling to Latin Americans and Turks (44% and 49%) [105, 255]. The observed similarity between Arabs and Turks in the prevalence of different genotypes could be due to the long history of the Ottoman Empire's occupation, which resulted in many matings, mixing of lineages and transmission of genetic traits between Arabs and Turks [256].

Our study is one of few studies that reported the variant allele frequencies for the polymorphisms of coagulation *FII* and *FVII* genetic variants. In our population, the MAF of *FII (C>T)* (rs5896) and *FVII (C>T)* (rs3093229) were indistinguishable (9%). Regarding the MAF of *FVII,* this frequency was in line with an observation from a previous study in Jordan which revealed that *FVII*'s MAF was 6% [257]. In contrast, this incidence was lower than other populations [258]. Furthermore, the variant allele frequency of *FII* in our results was less than the global population and Europeans (14%).

Another clinically relevant finding was that our results reconfirm the association of *CYP2C9* and *VKORC1* polymorphisms with weekly warfarin dose. It was clear that carriers of wildtype allele of *CYP2C9* or *VKORC1* required a higher mean warfarin dose than carriers of one or two copies of these genes' reduced function alleles. On the other hand, and despite its high prevalence, CYP*4F2*3* did not affect warfarin dose previously shown in studies performed on Egyptian and Qatari populations [105, 253]. The current study's multiple regression analysis showed that antiplatelet and

ciprofloxacin use, and INR index are significant predictors of the INR decline rate. The observed negative relationship between the ciprofloxacin and INR decline rate is likely related to the suppression of vitamin K producing intestinal flora and the CYP inhibition by ciprofloxacin which leads to further deficiency in vitamin K and blunts the INR drop [62]. The significant positive association between the INR index and INR decline rate means that with higher starting INR at the time of interruption, a faster drop in the rate of INR is expected. This was in agreement with the results observed by Abohelaika et al. [145] and Burmester et al. [146]. While the strong positive relation between antiplatelet use and the decline rate is surprising and opposite to what one would expect, it is possible that those patients interrupted the antiplatelets as well during the preprocedural period [132]. Unfortunately, data on the discontinuation of antiplatelet during the periprocedural period was not collected.

There were multiple factors that showed their contribution to reaching normalized INR ≤1.2. Firstly, the lower the INR target (<3.5), the shorter time was to reach INR ≤1.2. Secondly, being a patient of Sudanese nationality was likely to take more time to reach regular INR. The explanation of this could be that Sundanese is the only black race among other participants' races, potentially carriers of other untested common SNPs in blacks like *CYP2C9*5*6*8*11* which decrease CYP2C9 enzyme activity [259].

The uniqueness of this study is in its design and being one of the first studies to report the frequency of *CYP2C9, VKORC1, CYP4F2, FII*, and *FVII* genetic polymorphisms in Arabs. Additionally, it is the first research that investigated the effect of coagulation factors polymorphism on INR normalization. Our study has weaknesses that temper our findings. Notably, the small sample size was likely the leading cause of impeding the necessary power to detect the various significant impact of genetic variants. The small sample size was primarily due to the slow recruitment and low flow of eligible patients.

Moreover, the unprecedented situation of the Coronavirus disease 2019 (COVID-19) pandemic has resulted in suspending elective surgeries for 6 months at our local clinical setting. To lighten this up, we included eligible patients from previous research [105]. Another limitation is that not all participants stopped warfarin for the same period, and they had different INR targets. Nevertheless, our analysis revealed no significant difference between the status of INR ≤1.2 and the INR decline rate (expressed as log slop) which considers the days of interruption and INR index. To develop a complete picture of genetics polymorphism's impact on INR decline rate, an additional more extensive study with patient stratification according to the current results will be needed to eliminate the effect of potential confounders. Equally important, cost-effective analysis of implementing pharmacogenetics-based algorithm will guide decision-makers to which approach must be subsidized.

6.5 Conclusion

This study explored the impact of genetics and non-genetic factors on INR normalization in the Arab population. Index INR and interacting medications were significant predictors of INR decline. Moreover, the study confirmed the effect of *CYP2C9* and *VKORC1* genetics polymorphism and their contribution to warfarin maintenance dose variability. While there was a signal that *CYP2C9*3* variant may contribute to the variability in the INR decline across patients, this requires to be confirmed in future research.

CHAPTER 7: COST BENEFIT ANALYSIS OF GENOTYPE-GUIDED INTERRUPTION DAYS IN WARFARIN PRE-PROCEDURAL MANAGEMENT

7.1 Introduction

The inhibitory effects of warfarin on the biological coagulation factors have grabbed researchers' and clinicians' attention to its use in thromboembolic conditions for multiple decades [33]. Owing to the warfarin's narrow therapeutic index, therefore, the International Normalized Ratio (INR) is a significant marker used to monitor warfarin's therapeutic effect [238]. The INR values are kept within the therapeutic range for long-term warfarin treatments, mitigating the risk of thrombosis/bleeding [260]. While the rate of major hemorrhage is increased with high INR, thromboembolic complications are predominant in patients with low INR values [28]

Up to 10% of all warfarin-receiving patients undergo prearranged surgeries are expected to stop warfarin for reducing the probability of encountering bleeding events during and after the procedures [106]. To achieve a therapeutic INR level at the time of the procedure, most of the recommendations indicate the necessity of warfarin interruption 5-7 days before the procedures [208, 209]. Recent studies [124, 217] found that 23% of patients who stopped warfarin attained INR > 1.2 following 4.7 days of warfarin holding, and 7% reached a pre-operative INR > 1.5 after 5 days of discontinuation of warfarin. Here, very early warfarin cessation may produce thrombosis in patients, and delaying holding warfarin until very late may lead to peri-procedural bleeding [145]. As a result, following the warfarin interruption is necessary for INR to be closely monitored to achieve normalization at the time of the procedure, considering the potential individual variations during this period.

Published research highlighted the effect of many genetic factors on warfarin pharmacokinetic properties [261]. Warfarin contains a mixture of two active enantiomers: the (R) and (S) enantiomer, where the latter has a five-fold anticoagulation

potency over the former [70]. The S-enantiomer is metabolized by the cytochrome P450 2C9 (CYP2C9) encoded enzyme, and variations in the *CYP2C9* gene can alter the enzymatic activity and the time required for warfarin elimination [32, 68, 71]. Genetic factors, thought to be swaying INR normalization during pre-procedural warfarin interruption, have been investigated in several articles in different ethnic groups [143-149]. The *CYP2C9* genetic mutation was the most common polymorphism that can predict the warfarin clearnace, INR normalization or INR decline rate [143-145, 148, 149]. In 2015, Abohelaika et al. succeeded in predicting the INR decline rate in pre-operative warfarin interruption in Caucasians based on *CYP2C9* genetic variation and other clinical and demographics [145]. Later, the same group of researchers accomplished to validate the prediction tool reliability retrospectively [262].

Indeed, genetic testing predicts how the genetic difference in one or multiple genes can explain the variation in patients' response to medication [152-154]. Within the context of pre-operative warfarin, this can be utilized to optimize interruption time before the procedure of minimized risks of thrombosis or bleeding.

While the World Health Organization (WHO) generally stated that preventive medicines are cost-effective, genetic testing is costly and, to the best of our knowledge, there is no literature economic evaluation that investigated the pharmacogenetic-guided algorithm in pre-operative warfarin interruption. Therefore, the current study was to perform a cost-benefit analysis (CBA) of implementing a genetic-testing in per-procedural warfarin management to see whether the genetic testing outcome justifies its cost.

7.2 Methods

The trade-off between the monetary values of the cost and benefit of the pharmacogenetic-guided algorithm (PGX), compared to the standard of care algorithm (SD), was evaluated via a CBA based on a one-year decision-analytic and economic

model, which was primarily based on the Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (The BRIDGE Trial) randomized control trial (RCT) [139], an international multicenter trial, and the only major study to investigate peri-procedural warfarin management.

7.2.1 Study perspective

The cost-benefit analysis (CBA) was conducted from the hospital perspective of Qatar's primary healthcare provider, i.e., Hamad Medical Corporation (HMC).

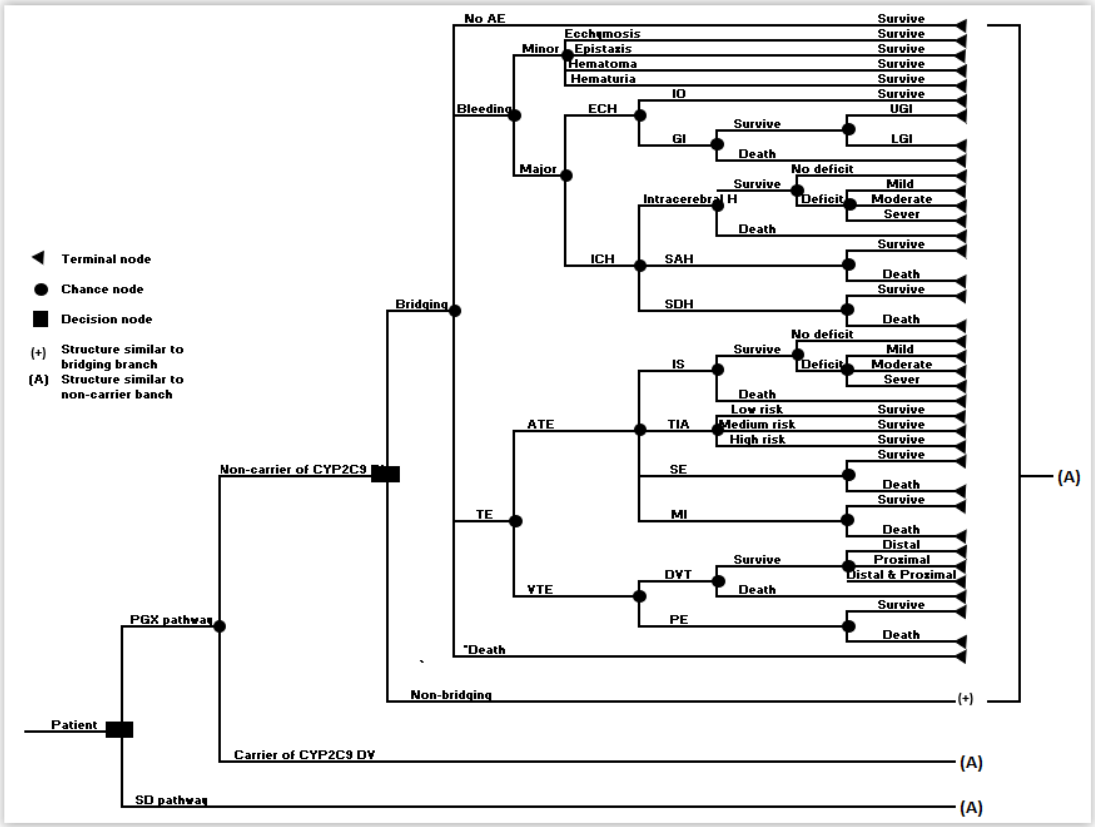
7.2.2 Model structure

A conventional type of a decision-analytic model was used to follow up a hypothetical cohort of patients on warfarin undergoing an elective procedure, based on the implementation of a pharmacogenetic-guided (PGX) approach relative to the existing standard of care (SD) approach for the management of the interruption of warfarin before the procedure.

In the study model, patients will receive the PGX or the SD approach of management. If patients receive the PGX, they will be differentiated based on whether they are carriers of the *CYP2C9* mutation. Afterward, and whether patients are on the SD or the PGX with/without mutation, patients are followed similarly. Patients are differentiated based on whether they receive a bridging preprocedural management strategy. Whether the bridging or the non-bridging strategy being applied, patients are differentiated based on the state of adverse events (AEs) in patients, including four different states: no AE, thromboembolism (TE), bleeding, and non-vascular/non-bleeding death. Bleeding may include minor bleeding, including epistaxis, ecchymosis, hematoma, hematuria, or major bleeding, divided into intracranial hemorrhage (ICH) and extracranial hemorrhage (ECH). TE may be arterial thromboembolism (ATE) or venous thromboembolism (VTE). The duration of the model follow-up was one year.

Bridging refers to the heparin (LMWH/UFH) initiation during warfarin interruption in preprocedural management. In practice, whether a patient is eligible for bridging or not is based on the thromboembolic risk. In HMC, bridging starts with a patient INR of < 2.0. The study model structure is illustrated in Figure 7.1, with detailed follow-up consequences and the literature sources of their probabilities as clarified in the model structure of chapter 5.

The model and its consequences were validated by an HMC-based expert panel that comprised a clinical pharmacist manager at the anticoagulant clinic, a cardiologist, an internal medicine consultant, and a vascular disease consultant.



*Death; non-hemorrhagic or non-vascular death. AE; adverse event, AF; arterial fibrillation, ATE; arterial thromboembolism, DV; double variant, DVT; deep vein thrombosis, ECH; extracranial hemorrhage, GI; gastrointestinal, ICH; intracranial hemorrhage, IO; intra-ocular, IS; ischemic stroke, MI; myocardial infarction, PE; pulmonary embolism, PGX; pharmacogenetic-guided, SAH; subarachnoid hemorrhage, SD; standard of care, SDH; subdural hemorrhage, SE; systemic embolism, TE; thromboembolism, TIA; transient ischemic attack, VTE; venous thromboembolism.

Figure 7.1: Decision-analytic model.

7.2.3 Clinical inputs

7.2.3.1 Standard of care pathway

All model clinical event rates were retrieved from the published literature and our prospective cohort study [228]. The BRIDGE study [139] was the primary source of the clinical events reported in the model. The BRIDGE trial is the only source that reports relative event probabilities for a relatively large population (n=1,804) in peri-procedural warfarin management reporting clinical outcomes based on a one-month observation period. Noteworthy is that the peri-procedural use of warfarin in the BRIDGE study was consistent with that in clinical practice at HMC, including the average number of discontinuation days (3-5 days), the average number of heparin dosing days (3 days before treatment), and the stroke risk score for AF patients with mean CHA_2DS_2-Vasc of 4, as reported by the same group of authors in a published local study at HMC [228]. Obtained from the BRIDGE trial [139], for each of the bridging and non-bridging model pathways, are the probabilities for the major clinical events in the model, which were non-AE outcomes, total hemorrhage, minor and major hemorrhage, TE, ATE, transient ischemic attack (TIA), ischemic stroke (IS), myocardial infarction (MI), systemic embolism (SE), VTE, and non-hemorrhagic or non-vascular death. The probabilities of sub-subsequences for an outcome in the BRIDGE trial [139], which are not available in the BRIDGE study itself, were extracted from other available relevant literature-based comparative clinical studies that were similar concerning underlying patients types, a risk score of stroke, patients age, and follow-up period for reported outcomes. These sub-consequences are minor bleeding, gastrointestinal (GI) bleeding, intraocular hemorrhage (IO), subdural hemorrhage (SAH), intracerebral bleeding, and subdural hemorrhage (SDH), added to their

consequences. Probabilities for ECH and ICH with bridging were available from a study by Hackett et al. [222]. The duration of heparin administration was an average of 3 days, matching the bridging as in the BRIDGE Trial and the HMC practices. Supposedly, the main driver of bleeding in our study was heparin which is the leading cause of hemorrhage in the bridging group. The probabilities of ECH and ICH with the non-bridging arm were obtained from the warfarin arm in the RE-LY trial [223], in which the INR level was at sub-therapeutic range due to starting warfarin recently. Table 5.1 summarizes the model clinical events, their descriptions, and data sources. All reported clinical event rates, from all sources, were consistently reported until one month after warfarin interruption or heparin initiation.

The incidence probability of bridging versus non-bridging in HMC was derived from a recent analysis by Eljilany et al. [228]. According to local HMC clinical practice, bridging was stated to occur in 82.5% of patients with interrupted warfarin, peri-procedurally.

7.2.3.2 Pharmacogenetic-guided pathway

Based on our ongoing research (HMC study protocol 16415/16) [263], the prevalence of carrying *CYP2C9* genetic double variants (either *3*3, *3*2, or *2*2) in our HMC population is 10.3%. Therefore, the probability of any event under the PGX model pathway is calculated as [the prevalence of carrying *CYP2C9* genetic double variants (10.3%) × the event probability under the carriers of genetic variants model pathway] + [the prevalence of non-carrying *CYP2C9* genetic double variants (89.7%) × the event probability under the non-carriers of genetic variants model pathway]. The difference in pre-operative warfarin discontinuation days between carriers and non-carriers was calculated based on the equation reported by Abohelaika et al. [145], which was later validated retrospectively [262]. The equation is that: INR decline by day 5 = 0.9 {INR}

− 0.2 {N. CYP2C9} − 0.2 − [13 {AGE} + 7.4 {W} + 92 {N.COM}]⁄3000. Where INR is index INR, N. *CYP2C9* equal to 1 in the presence of *CYP2C9* double variant or equals to zero in the absence of double variant, AGE is the age in years, W is weight in kg, and N.COM is the number of comorbidities.

The values of the above clinical and demographics predictors were obtained as the mean value from our recent research [228]. As the mean of INR index is 2.0, age is 66.2 years, weight is 85 Kg, and No. of comorbidities is 4.

In case of the absence of *CYP2C9* double variant alleles carriers

INR decline by day 5 = 0.9 × 2 − 0.2 × 0 − 0.2 − [13 × 66.2 + 7.4 × 85 + 92 × 4]⁄3000 = 0.981

INR decline rate = difference in INRs / difference in days

= 0.981 /5 = 0.1962

As the objective of pre-operative warfarin interruption to normalize INR (1.2), so

The difference in days = difference in INRs / INR decline rate

= 0.8 (2.0-1.2) / 0.1962 = 4

As a result, the non-carriers of *CYP2C9* double variant alleles require 4 days after warfarin interruption to normalize INR.

In the case of the presence of *CYP2C9* double variant alleles carriers

INR decline by day 5 = 0.9 × 2 − 0.2 × 1 − 0.2 − [13 × 66.2 + 7.4 × 85 + 92 × 4]⁄3000 = 0.981

INR decline rate = difference in INRs / difference in days

INR decline rate = 0.981 /5 = 0.1562

As the objective of pre-operative warfarin interruption to normalize INR (1.2), so

The difference in days = difference in INRs / INR decline rate

= 0.8 (2.0-1.2) / 0.1562 = 5

As a result, the non-carriers of *CYP2C9* double variant alleles require 5 days after warfarin interruption to normalize the INR.

The calculation above indicates that the non-carriers of genetic polymorphism need 20% fewer days of warfarin interruption compared to carriers of genetic variants. Because of this, the probabilities of AE in non-carriers of *CYP2C9* genetic polymorphism patients were assumed to equal 80% of the probabilities of the AEs in the carriers of *CYP2C9* genetic polymorphism patients. The event probabilities in the patients who are carriers of genetic polymorphism do not differ from the probabilities of the model events in the SD patients because both require the same period of interruption, which is 5 days.

The model analysis at its base-case was based on multivariate uncertainty analysis of the model event probabilities, using Monte Carlo simulation through @Risk-7.6® (Palisade Corporation, NY, US), which was to take into consideration the real-life interactions among different concurrent inherent uncertainties in the model input data. The uncertainty range for any probability input was based on the 95% confidence interval (CI), utilizing a triangular type of distribution sampling within the range. With 5,000 iterations, the Monte Carlo simulation enables an analysis of the probability model outcomes analysis and a tornado regression analysis of the impact of model inputs and the outcome. Table 5.2 summarizes the input values and their probabilities in the study model's multivariate analysis at its base-case.

7.2.4 Cost calculations

As per the principles of decision-analytic modeling, the cost of a management approach per patient is the sum of the proportional costs of all the model pathways generated with the approach. The proportional cost of a pathway is the multiplication of the pathway's cost by the overall probability of the pathway. The probability of the pathway is

calculated as the multiplication of the probabilities of individual consequential outcomes taking place in the pathway.

Based on the hospital perspective, only the direct cost of patient management was included in the analysis. The cost of the patient in a model pathway, and whether patients are on the SD or the PGX with/without mutation, is the cost of the initial warfarin therapy, with/without bridging, added to the clinical cost events in the pathway. The No-AE or non-hemorrhagic/non-vascular death cost was equal to the cost of warfarin interruption management of each pathway.

In the SD pathway, if a patient must stop taking warfarin for elective surgery, the INR should be tested twice before and after the procedure. When bridging is administered, a daily heparin dosage of 160 mg (80 mg BID) was assumed, based on an average weight of 85 kg in Qatar, as per Eljilany et al. [228]. Bridging is given twice per day for three days before the procedure, with each patient receiving six doses of heparin in total. According to the BRIDGE trial [139] and our local research in HMC [228], 30% of operations are deemed major procedures that entail 3 days of pre-operative in-patient department (IPD) admission if bridging is used. In the remaining 70% of patients with minor surgeries, two out-patient (OPD) visits are required, regardless of bridging. The calculation of SD pathway cost is summarized below.

In the PGX model pathway, given that the genetic test can estimate the optimal required number of interruption days, so the cost provided by HMC was recalculated based on the monetary value of resources used with the PGX approach compared by the SD approach as the expert panel of the study. The PGX approach will produce changes in resources used as listed in Table 7.1, including their direct cost and their uncertainty. Also, the new cost of events after adjustment can be seen in Table 7.2.

Clinical event costs were based on the finance department of HMC, as listed in Table

7.3. Also, Table 7.2 shows these relevant resource frequencies and costs with ±20% variability as uncertainty range. A genetic test's cost was based on the HMC cost of sending the patient sample overseas for analysis. Costs were calculated using the 2021 value of the Qatari Riyal (QAR) and presented in US Dollars (USD, 1 USD = QAR 3.65). Since the model follow-up period was not more than 1 year, no discounting of costs was performed.

Table 7.1: Frequencies and direct costs (USD) of various resources used and their uncertainty ranges

Item	**Frequency of resources used**		**Direct cost (USD)**	**Uncertainty range (USD)**	
	Standard of care algorithm	**pharmacogenetic-guided algorithm**		**-20%**	**+20%**
Genetic test	0	1	191.78	230.16	153.42
INR test	2	1	21.91	26.30	17.53
OPD visit	2	1	463.01	555.61	370.41
IPD visit	3	2	669.86	803.83	535.89
Heparin injection 80mg	6	6	7.64	9.16	6.1

INR; international normalization ratio, IPD; in-patient department, OPD; out-patient department. 1 USD = 3.65 QAR.

Table 7.2: Clinical outcomes and the proportional costs, at base-case

Event	Standard of care algorithm		Pharmacogenetic-guided algorithm	
	Probability (95% CI)	**Probabilistic cost (USD)**	**Probability (95% CI)**	**Probabilistic cost (USD)**
No AE	0.7518 (0.7432-0.7602)	943.99	0.7969 (0.7889-0.8047)	582.15
Bleeding	0.2250 (0.2169-0.2333)	740.32	0.1820 (0.1746-0.1897)	574.36
TE	0.0195 (0.017-0.022)	697.73	0.0194 (0.0169-0.0223)	499.91
Death*	0.0043 (0.0032-0.0058)	5.49	0.0035 (0.0025-0.0049	2.65
Total pathway	1.00	2,387.55	1.00	1,659.08

Death; non-hemorrhagic or non-vascular death. AE; adverse event. TE; thromboembolism.

Probabilistic cost of an event = event cost × event probability. 1 USD = 3.65 QAR.

Table 7.3: Direct cost (USD) of various clinical events and their uncertainty ranges

Event	Direct cost (USD)	Uncertainty range (USD) (-20%, +20%)	
No AE/death* (bridging) SD	1,340.81	1,072.65	1,608.97
No AE /death* (non- bridging) SD	893.01	714.41	1071.62
No AE/death* (bridging) PGX	815.74	652.59	987.89
No AE /death* (non- bridging) PGX	367.95	294.36	441.53
Ecchymosis	1,319	1,055.2	1,582.9
Hematoma	1,151	920.80	1,381.20
Hematuria	2,533	2,026.40	3,039.60
Epistaxis	800	640.00	960.00
Intra-ocular H.	593	474.40	711.60
Upper GI H	5,245	4,196.00	6,294.00
Lower GI H	5,218	4,174.40	2,444.40
GIH Death	5,231	4,184.80	6,277.20
No deficit ICH	10,332	8,265.60	12,398.40
Mild deficit ICH	22,051	17,640.80	26,461.20
Moderate deficit ICH	34,095	27,276.00	40,914.00
Severe deficit ICH	56,677	45,341.60	68,012.40
ICH Death	56,677	45,341.60	68,012.40
SAH	37,038	29,630.40	44,445.60
SAH Death	37,038	29,630.40	44,445.60
SDH	43,836	35,068.80	52,603.20
SDH Death	43,836	35,068.80	52,603.20
No deficit IS	9,424	7,539.20	11,308.80

Event	Direct cost (USD)	Uncertainty range (USD) (-20%, +20%)	
Mild deficit IS	21,903	17,522.40	26,283.60
Moderate deficit IS	34,382	27,505.60	41,258.40
Severe deficit IS	57,006	45,604.80	68,407.20
IS death	57,006	45,604.80	68,407.20
Low risk TIA	4,770	3,816.00	5,724.00
Medium risk TIA	5,303	4,242.40	6,363.60
High risk TIA	5,836	4,668.80	7,003.20
SE	17,153	13,722.40	20,583.60
Death	17,153	13,722.40	20,583.60
MI	30,225	24,180.00	36,270.00
MI death	30,225	24,180.00	36,270.00
Proximal DVT	7,481	5,984.80	8,977.20
Distal DVT	7,481	5,984.80	8,977.20
Proximal and distal DVT	7,481	5,984.80	8,977.20
DVT death	7,481	5,984.80	8,977.20
PE	14,191	11,352.80	17,029.20
PE death	14,191	11,352.80	17,029.20

*Death; non-hemorrhagic or non-vascular death. AE; adverse event, ATE; arterial thromboembolism, CI; confidence interval, DVT; deep vein thrombosis, ECH; extracranial hemorrhage, GI; gastrointestinal, H; hemorrhage, ICH; intracranial hemorrhage, IO; intra-ocular, IS; ischemic stroke, MI; myocardial infarction, PE; pulmonary embolism, PGX; pharmacogenomics pathway, SAH; subarachnoid hemorrhage, SD; standard of care pathway, SDH; subdural hemorrhage, SE; systemic embolism, TE; thromboembolism, TIA; transient ischemic attack, VTE; venous thromboembolism. 1 USD = 3.65 QAR.

7.2.5 Cost-benefit analysis

The genetic test's economic benefit was calculated as the cost savings produced because of a decrease in overall patient cost plus the cost of avoided procedure cancelation (because of an elevated INR) using the genetic test. In contrast, the genetic test cost was calculated as the cost of performing the test plus the increase in the overall patient cost because of an increase in resource utilization (if any).

The trade-off between cost and benefit was presented via a cost-benefit ratio. A ratio of < 1 indicates the genetic testing approach as not cost-beneficial and a ratio of > 1 indicates the genetic testing as cost-beneficial.

7.2.6 Sensitivity analysis

Sensitivity analyses were performed to test the model's robustness to input uncertainty and determine critical determinants of economic outcomes and increase the generalizability of results.

A one-way deterministic sensitivity analysis was performed by assigning uncertainty ranges, with a uniform type of sampling distribution, to the mean genetic test, the prevalence of double variant alleles of *CYP2C9*, and relative reduction in days with non-carriers of genetic polymorphism, compared to carriers of genetic variants.

Added to the uncertainty that was introduced to the model event probabilities at its base-case, a probabilistic sensitivity analysis was performed by applying uncertainty to the base-case values of event cost inputs as per Table 7.1 and Table 7.3. Since no confidence intervals for event costs were available, an overestimated 20% variability was used for the uncertainty range, measured using a triangular sampling distribution.

Like in the base-case, both one-way and probabilistic sensitivity tests were conducted with 5,000 iterations, using the Monte Carlo simulation via @Risk 7.6 (Palisade Company, NY, USA).

7.3 Results

7.3.1 Base-case analysis

Based on 10.3% prevalence of *CYP2C9* double genetic variants and, consequently, 20% reduction in pre-operative warfarin interruption period in favor of non-carriers of *CYP2C9* double genetic variants, the rate of not experiencing AE was improved by 0.0451 (95% CI 0.0412-0.0493) in favor of PGX approach, as seen in Table 3. Also resulted was a decrease in the total cost per patient by 30.24%, USD 727.47 (95% CI 726.0-729.0) [QAR 2,626 (95% CI 2649.9-2660.8] in favor of the PGX approach. Add to this the avoided cost of procedure canceling (USD 38.5 per patient), the overall benefit of the PGX approach was USD 765.97 (95% CI 764.0-767.0) [QAR 2,794.11(95% CI 2788.6-2799.5)]. This is while the direct cost of performing the genetic testing was USD 191.78 (95% CI 192-192) [QAR 700.0 (95% CI 700.8-700.8). Therefore, the benefit to cost ratio was 3.99 (95% CI 3.98-4.0), indicating that for each USD 1 invested in the genetic testing, around USD 4 is generated as a return to investment. The increased benefit over cost with the genetic testing was maintained in 100% of the simulated cases. Figure 7.2 represents the probability curve of benefit to cost ratio.

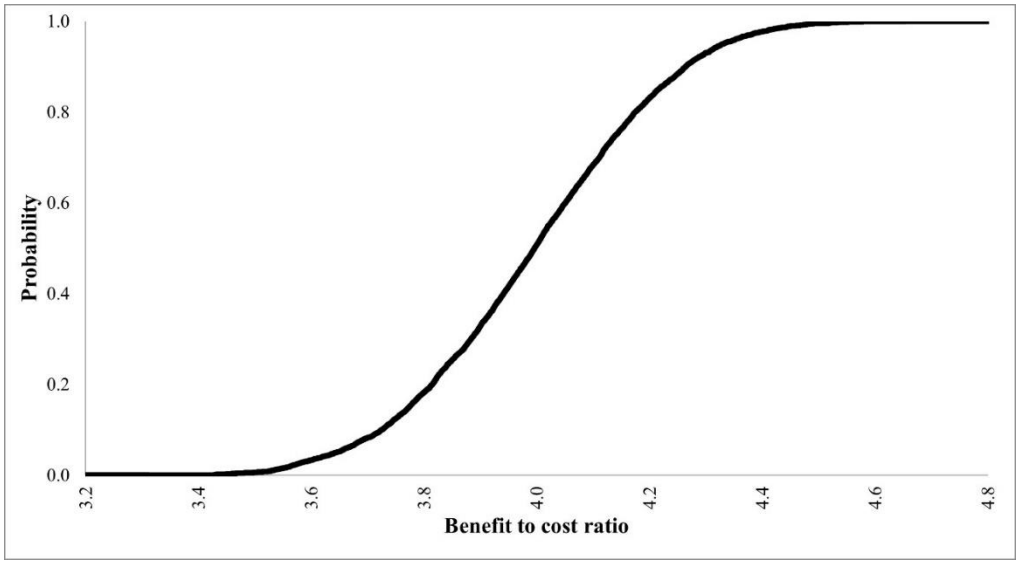
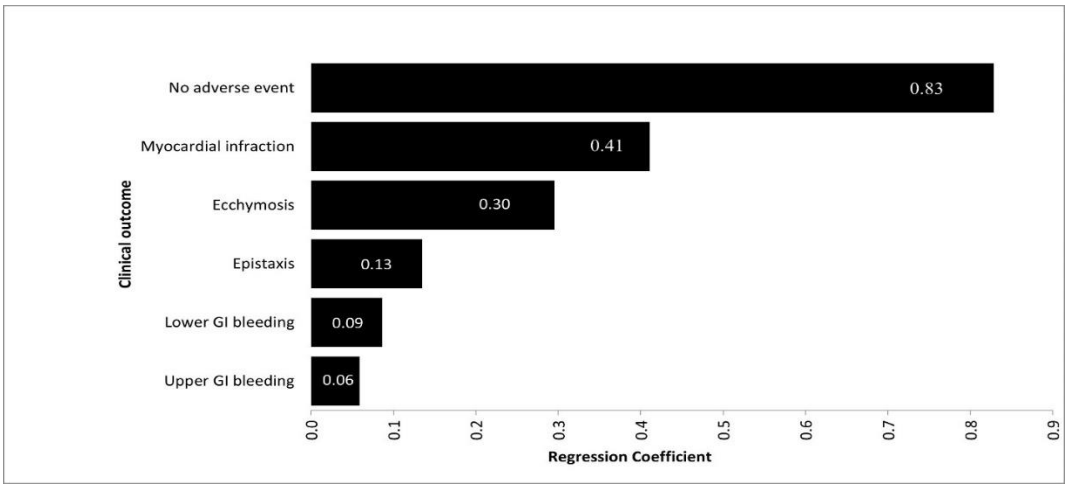


Figure 7.2: Base-case benefit to cost ratio probability curve.

Based on a tornado regression analysis that ranks model inputs as per the strength of their association with the benefit-cost ratio, it demonstrated that no AE rate is the most influential, followed by the rate of MI and then the rate of ecchymosis. Figure 7.3 shows the tornado analysis of the input raking as per the regression coefficient.



GI; gastrointestinal

Figure 7.3: Tornado diagram of the base-case benefit to cost ratio based on the regression coefficient.

7.3.2 Sensitivity analysis

7.3.2.1 One-way sensitivity analysis

The base-case benefit-cost outcome of implementing the PGX approach of management was not affected by the uncertainty assigned to each of the prevalence of *CYP2C9* double genetic variants, genetic test cost, and preoperative warfarin interruption optimization inputs demonstrating the robustness of the model. Table 7.4 shows the benefit, cost, and benefit-to-cost ratio outcomes with each one-way analysis compared to the base-case scenario.

Table 7.4: Outcomes of one-way sensitivity analysis

Outcome	Base-case (95% CI)	SA1 (95% CI)	SA2 (95% CI)	SA3 (95% CI)
Benefit (USD)	765.97 (764.0 -767.0)	754.49 (752.0 -757.0)	765.32 (764.0 – 766.0)	764.58 (763.0 -766.0)
Cost (USD)	191.78 (192.0 – 192.0)	191.78 (192.0 -192.0)	192.13 (192.0 – 193.0)	191.78 (192.0- 192.0)
Benefit-to-cost ratio	3.99 (3.98 - 4.0)	3.93 (3.92 - 3.94)	4.03 (4.02 - 4.04)	3.98 (3.97- 3.99)

SA1, uncertainty of the prevalence of *CYP2C9* double genetic variants, SA2; uncertainty of the genetic test cost, SA3; uncertainty of the pre-operative warfarin interruption optimization ratio. CI; confidence interval. 1 USD = 3.65 QAR.

7.3.2.2 Probabilistic sensitivity analysis

Incorporating the uncertainty in event costs, in addition to the base-case event probability uncertainty, did not reverse how cost-beneficial the genetic testing was. However, it increased it. Table 7.5 summarizes the results of the multivariate sensitivity analysis in comparison to the base-case analysis for the overall benefit, cost, and benefit-cost ratio outcomes. A higher benefit over cost with the genetic testing was also maintained in 100% of the cases, Figure 7.4.

Table 7.5: Multivariate sensitivity analyses and the subsequent changes in model outcomes

Outcome	Base-case (95% CI)	Probabilistic sensitivity analysis (95% CI)
Benefit (USD)	765.97 (764.0 -767.0)	949.81 (946 - 953)
Cost (USD)	191.78 (192.0 – 192.0)	191.78 (192.0 -192.0)
Benefit-to-cost ratio	3.99 (3.98 - 4.0)	4.95 (4.93 - 4.97)

CI; confidence interval. 1 USD = 3.65 QAR.

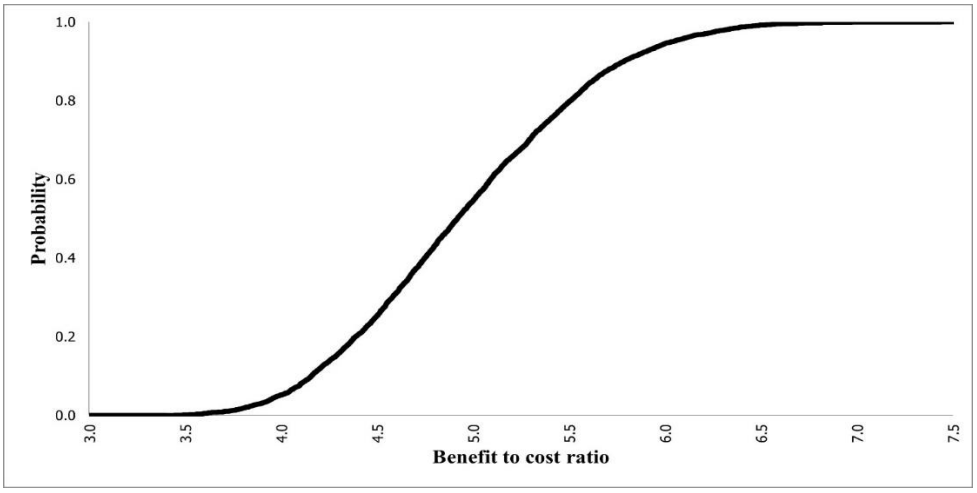
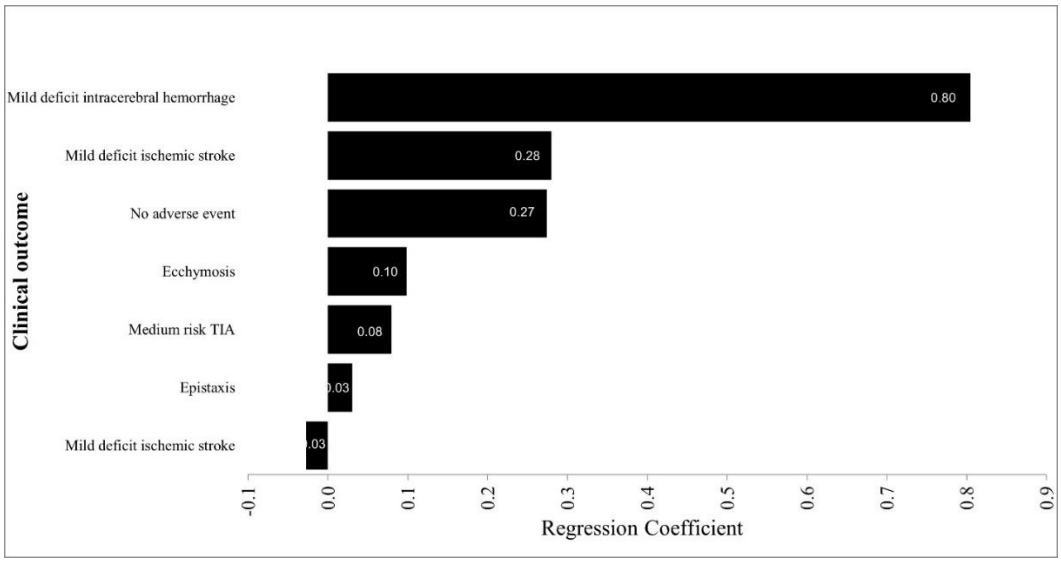


Figure 7.4: Multivariate sensitivity analyses benefit to cost ratio probability curve.

The rank of the model event inputs in terms of the association with model results, as well as the strength of the association (regression coefficient), was not consistent with the status at the base-case. It seems that with the introduced uncertainty in event cost, the most influential model input on model outcomes became the rate of intracerebral stroke, followed by the rate of ischemic stroke before the rate of the no-AEs which was shifted to the third place. The tornado regression analysis of the model inputs

association with the benefit-cost ratio is presented in Figure 7.5.



TIA; transit ischemic attack

Figure 7.5: Tornado diagram of the Multivariate sensitivity analysis based on the regression coefficient.

7.4 Discussion

The present study attempted to evaluate whether implementing a genetic-test-guided strategy for guiding the time of warfarin interruption before procedures is worth its cost. This was via a CBA that assessed the added cost and generated benefit with the PGX approach of pre-procedural management of warfarin, compared to the SD approach.

Since healthcare services are scarce, caution must be exercised when introducing costly, new policies and changes in practices. Judging the benefit of a service based on its cost is ideal in healthcare settings and will guide decision-making, including decisions around the distribution of budgets.

For optimizing warfarin initiation or continuity with genetic testing, several cost-effectiveness studies have been published in the literature, reporting conflicting results [161, 264-268]. However, for the pre-operative interruption of warfarin, no economic evaluations exist. The current project is therefore, the first of its kind internationally.

The principal finding of this analysis was that the average benefit to cost ratio was 4.0,

which indicates that the benefit of implementing PGX is equivalent to 4 times its cost. The cost saving in favor of the PGX strategy, driven by the reduction in cost per patient by USD 573.72 (QAR 2,094.07), is predominantly attributable in this study to around 6% increase in the rate of no-AEs health state (equivalent to a decrease in total rates of AEs) with the PGX compared to the management of events with SD, the management of events with genotype pathway was associated with a drastically lower cost of pre-operative management primarily associated with a lower number of IPD and OPD visits.

The model benefit-cost ratio was robust against proposed changes via the one-way sensitivity analysis, including the variability in the cost of the genetic testing, accounting for potential anticipated changes with the outsourcing process, as well as the prevalence of *CYP2C9* two variant alleles, indicating a model outcome that potentially persists among various ethnic groups. Similarly, with the multi-variate sensitivity, the proposed variability in the cost of events did not also affect the model outcome; add to the base-case uncertainty did not affect the model outcome. On the other hand, we can find that when we added the cost uncertainty to the base-case in probabilities sensitivity analysis, mild deficit hemorrhagic and ischemic stroke became the leading influencer due to their high-ranking management cost [USD 22,051 and 21,903, respectively (QAR 80,486 and 79,945, respectively)

Our results provide compelling evidence for long-term benefits and suggest that this approach appears to be effective in diminishing side effects and the economic burden of warfarin interruption management. However, some limitations are worth noting. Firstly, the current study depended on the BRIDGE trial findings [139], which recruited patients with low-intermediate risk of thrombosis, resulting in different findings in case of application this results on high-risk patients. Here, however, the model inputs in the

model at its base-case were analyzed based on assigned uncertainty analysis, which accounted for potential variability in model probability inputs that may result from less-than-ideal generalizability of patient characteristics in the BRIDGE trial to the Qatari setting. Moreover, the main difference between carriers and non-carriers of genetic variants in the required number of interruption days was calculated based on a retrospectively validated equation. To account for this, nevertheless, we introduced a one-way uncertainty to the calculated relative reduction in the number of days with the non-carriers of genetic variants compared to carriers of the variants, where the robustness of model outcomes was confirmed. All the introduced uncertainty to the model was based on 5000 iterations (simulate cohort sample size) via the Monte Carlo simulation.

Future work should include data from RCTs that specifically compare between the PGX and SD strategies to improve the interruption period as an outcome, where generated prediction calculations can be validated prospectively. Future similar design to the current study also may be conducted to evaluate the cost and benefit of genetic testing on the warfarin dosing as well as the period of warfarin interruption as an aggregated outcome.

7.5 Conclusion

Based on the study assumptions and perspective, and as per current practices in HMC, the average cost per patient was USD 573.72 (QAR 2,094.07) less with the genetic-guided approach of management compared to the standard of care. This led to an average benefit to cost ratio of 4; whereby, for each USD 1 spent on genetic testing, USD 4 is generated in benefit. This was maintained in 100% of simulated cases.

CHAPTER 7: GENERAL DISCUSSION

This research aimed to investigate the local standard warfarin periprocedural management in Qatar to address gaps and the variability in practice. Also, evaluate the clinical and economic impact of the current practice on warfarin periprocedural management and identify the significant genetics and non-genetic factors that can affect INR normalization in preoperative management to be able to personalize this period.

Even though warfarin has been used successfully for over 60 years as an anticoagulant agent for preventing and treating thromboembolic diseases, management challenges exist due to its narrow therapeutic index and wide inter-and intra-individual variability. As a result, it is recommended to monitor INR to ensure sufficient anticoagulation and reduce the risk of adverse effects, including bleeding and TE [269]. The perioperative management of patients receiving warfarin therapy is a common clinical dilemma. Warfarin can be continued, interrupted, or replaced with other parenteral ACs. This issue is even complicated with the small line that existed between thrombotic and bleeding risks. Subsequently, clinicians are required to assess whether there is an evident necessity for warfarin interruption to avoid the potential risks, inconvenience, and costs of discontinuation and resumption, as well as the need to bridging.

We started the work by acknowledging previously published prescribers' surveys by conducting a detailed analysis of the surveys on MEDLINE using the PubMed interface. Following that, we created a multiple-choice questionnaire to determine HCPs' behaviors, skills, and practice about warfarin periprocedural management. We compared our findings to what is internationally accepted.

A prospective cohort study was then conducted to test warfarin periprocedural management's real-world clinical practice and examine clinical results related to warfarin bridging vs. non-bridging in Qatar. Notably, net health outcomes do not

include treatment expenses. Even if bridging provides wise patient benefits, it might not be worth the money and cost-efficiency.

Consequently, based on current practice and local data, cost analysis and cost-effectiveness analysis were performed to assess the economic implications of periprocedural warfarin management of AF patients in Qatar, as well as to compare the cost-effectiveness of bridging versus non-bridging.

An observational prospective cohort study was designed to recruit warfarin patients from the Arab population who were scheduled for an elective procedure to examine the genetic polymorphism that can influence INR normalization. Besides, in a cost-benefit study, the benefit and cost of this pharmacogenetic-guided algorithm are compared to the standard of care.

Our survey's ultimate conclusion is that there is a lack of systematic experience in warfarin periprocedural management. Warfarin is often disrupted locally, and bridging was widely used. Bridging was associated with a higher number of bleeding episodes, but it is also cost-effective in 98 percent of patients. genetic factors did not predict INR normalization before surgery although future studies may be warranted to confirm such findings. When analyzing the cost-benefit of the use of genotyping in preprocedural management from previous studies, the benefits outweighed the costs four times over.

Our narrative analysis showed that the clinical decision about perioperative warfarin management is a complicated aspect of treatment. Most of reported preoperative practice indicated that there is a lack of institutionally structured procedures, as well as variations in processes, behaviors, and periprocedural results. Indeed, such a problem will eventually result in unfavorable variance in treatment. At the institutional stage, a single protocol should be followed as far as possible. Clinical considerations should be sufficient to justify deviation from such protocols.

Our cross-sectional survey results corroborated the preceding inference. The study's key finding was that participants' awareness is moderate. In the current research, three information deficiency areas were the driving force behind the decrease in awareness level. It was, first and foremost, a contradictory ability to assess the length of warfarin discontinuation before the operation. The second area of deficiency was inconsistency among clinicians about who to bridge among warfarin patients and the period of preoperative parenteral anticoagulation when the decision to bridge is made. Third, most participants were unaware of the types of procedures that do not necessitate the interruption of warfarin, such as cataracts and tooth extraction due to their low risk of bleeding.

When we compared the previous survey findings to real, local practice, we discovered that they are both consistent. HCPs have been discontinuing warfarin in more than 75 percent of cases and bridging in 82.5 percent of these cases. The current study found no difference in the incidence of clinical outcomes between the bridging and non-bridging groups, owing to the limited sample size, especially in the non-bridging group (n=18). However, when comparing the bridging arm to the non-bridging arm, there was a numerical bias for increased bleeding risk in most bleeding categories in the bridging arm. Also, no TE events were recorded in the analysis.

The cost of one case of warfarin peri-procedural management was USD 3,260 (QAR11,900) per patient, mainly associated with bridging over non-bridging, USD 2,037 (QAR 7,435) versus USD 1,223 (QAR 4,463), associated with a rate of 0.752 for survival with no AEs. Warfarin bridging in AF patients was cost-saving and cost-effective in 98 percent of patient cases than prevalent non-bridging procedures.

Bridging, INR index, and Sudanese ethnicity are all significant predictors of INR normalization. Furthermore, genetic polymorphisms in CYP2C9 and VKORC1 affect

warfarin maintenance weekly dose.

The cost-benefit analysis of the simulated two scenarios as a pharmacogenetic-guided algorithm based on *CYP2C9* genetic variants and standard of care algorithm in INR normalization preoperatively revealed that the average benefit to cost ratio was 4.0, indicating that the benefit of implementing PGX is equal to four times its cost. The cost savings in favor of the PGX approach in country-specific practice was primarily due to the significantly higher cost of preoperative warfarin management, which is associated with higher costs of OPD and IPD visits, as compared to the current low cost of the single-gene assay. This resulted in a USD 573.72 (QAR 2,094.07) annual cost savings per patient.

Upon completion of the project, some limitations temper our findings. The major limitation was the sample size. The small sample size was primarily due to the slow recruitment and low flow of eligible patients. Moreover, the unprecedented situation of the COVID-19 pandemic has resulted in suspending elective surgeries for six months at our local clinical setting. To lighten this up, we included eligible patients from previous research [105].

Also, the awareness and practice assessment, clinical assessment and economic evaluation were from a governmental hospital perspective, limiting the generalizability of our result to the private market. This happened because around 90% of warfarin patients are followed up in HMC. To overcome this, we performed a probabilistic sensitivity analysis with a cost uncertainty range. The low number of major surgeries was another constrain to detect the TE difference between bridging and non-bridging groups. To eliminate the confounding effect of recruiting patients with various discontinuation periods and INR target on INR normalization, we tested the association between both. However, there was no significant association found. In addition, the

patient's race was not identified. This could be due to the difficulty of race identification among most Arabs because of their mixed races of white and black.

Unfortunately, we had some constraints that limit our economic analysis. Firstly, the model was populated with literature sources instead of local patient data. Literature studies are primarily of Caucasian populations as an example. Also, the BRIDGE trial [139] the primary source of data, which recruited patients with low-intermediate risk of thrombosis (mean CHA2DS2 was 2.5), with most patients having a CHA2DS2 score of <3, may produce results that may not mirror results in high-risk patients. Nevertheless, the literature sources are of top quality. They are relevant to the HMC practices regarding the underlying AF disease and patient age, the warfarin and heparin use, and the stroke risk score. The utilized literature sources are the best sources of evidence available for this study. Noteworthy, the occurrence probability of bridging was locally based. In addition, the base-case study was based on multivariate uncertainty assigned to the study inputs obtained from the literature. This is added to additional levels of sensitivity analyses that were performed, where further uncertainty was introduced to the model, with all confirming the robustness of results against realistic input variability.

Moreover, the main difference between carriers and non-carriers of genetic variants in the required number of interruption days was calculated based on a retrospectively validated equation. To account for this, nevertheless, we introduced a one-way uncertainty to the calculated relative reduction in the number of days with the non-carriers of genetic variants compared to carriers of the variants, where the robustness of model outcomes was confirmed. All the introduced uncertainty to the model was based on 5000-1000 iterations (simulate cohort sample size) via the Monte Carlo simulation.

Lastly, calculation cost analysis based on government perspective allowed the incorporation of direct cost only, which is more attractive to the decision-makers in the government sector.

The future direction of this project could be getting a larger sample size for the INR normalization study to achieve enough power to confirm the impact of genetic variants on INR normalization. After that, we can perform RCT to compare the pharmacogenetic-guided algorithm versus clinical algorithm in warfarin dosing, interruption, and restarting to determine the clinical benefit of implementing genetic testing in the local practice. Then we could use the results as a clinical input for the recalculation of CBA of genetic-guided approach vs. standard of care in our model. This model can be regenerated based on patient perspective which will allow us to include indirect medical and non-medical costs.

Finally, we recommend developing a unified warfarin periprocedural management guideline according to the current practice and increasing adherence to it by putting some incentives. Warfarin interruption and bridging need to be optimized according to the recent guidelines. However, there is a tendency of bleeding with the bridging strategy, but it is more cost-effective. The significance of *CYP2C9* as a predictor for INR normalization needs to be confirmed in futures studies. Implementing *CYP2C9* genotyping into the clinical practice is a cost-effective tool in managing warfarin dosing and discontinuation.

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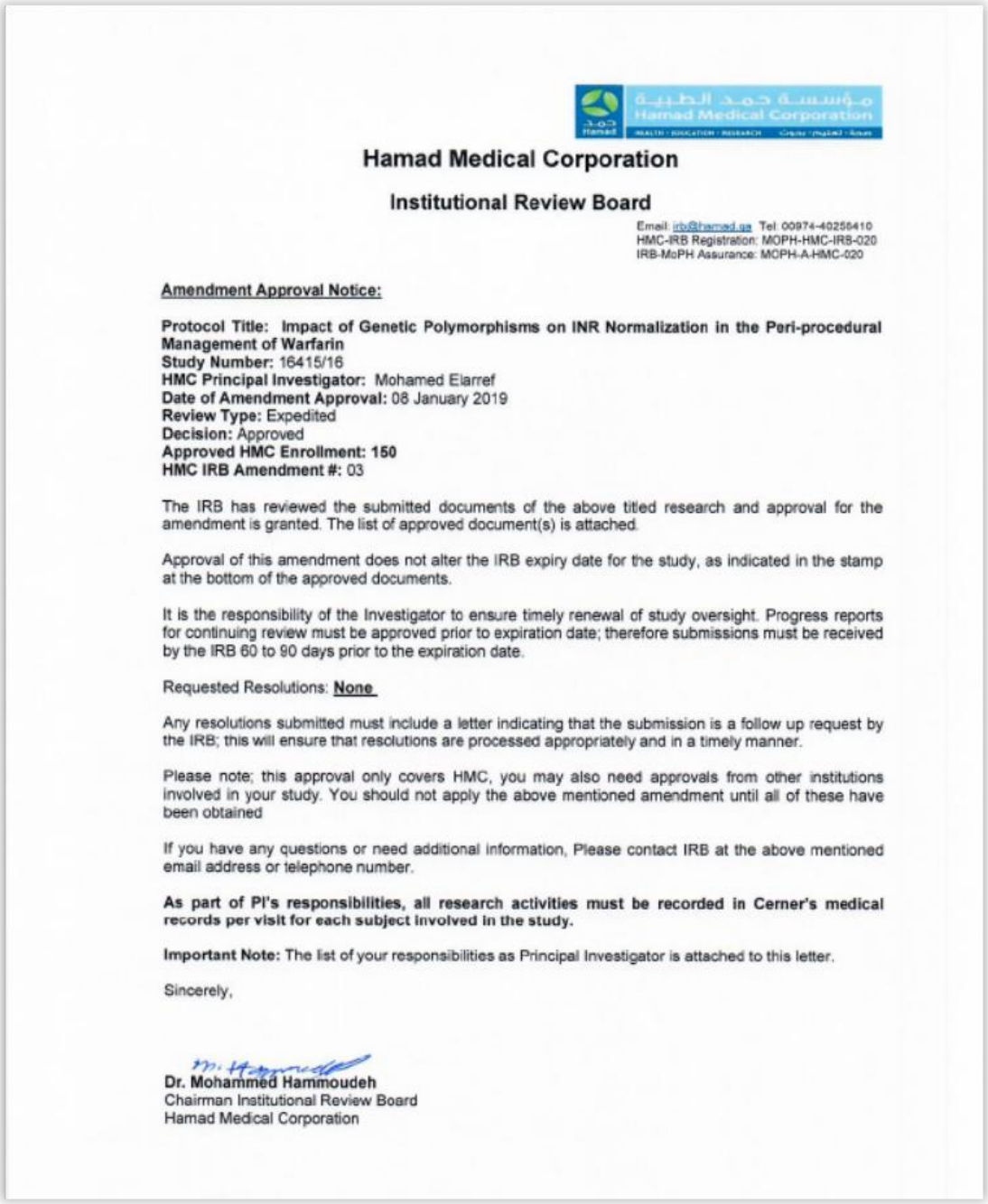
APPENDICS

Appendix A



مؤسسة حمد الطبية
Hamad Medical Corporation

Hamad Medical Corporation

Institutional Review Board

Email: irb@hamad.qa Tel: 00974-40256410
HMC-IRB Registration: MOPH-HMC-IRB-020
IRB-MoPH Assurance: MOPH-A-HMC-020

Amendment Approval Notice:

Protocol Title: Impact of Genetic Polymorphisms on INR Normalization in the Peri-procedural Management of Warfarin
Study Number: 16415/16
HMC Principal Investigator: Mohamed Elarref
Date of Amendment Approval: 08 January 2019
Review Type: Expedited
Decision: Approved
Approved HMC Enrollment: 150
HMC IRB Amendment #: 03

The IRB has reviewed the submitted documents of the above titled research and approval for the amendment is granted. The list of approved document(s) is attached.

Approval of this amendment does not alter the IRB expiry date for the study, as indicated in the stamp at the bottom of the approved documents.

It is the responsibility of the Investigator to ensure timely renewal of study oversight. Progress reports for continuing review must be approved prior to expiration date; therefore submissions must be received by the IRB 60 to 90 days prior to the expiration date.

Requested Resolutions: **None**

Any resolutions submitted must include a letter indicating that the submission is a follow up request by the IRB; this will ensure that resolutions are processed appropriately and in a timely manner.

Please note; this approval only covers HMC, you may also need approvals from other institutions involved in your study. You should not apply the above mentioned amendment until all of these have been obtained

If you have any questions or need additional information, Please contact IRB at the above mentioned email address or telephone number.

As part of PI's responsibilities, all research activities must be recorded in Cerner's medical records per visit for each subject involved in the study.

Important Note: The list of your responsibilities as Principal Investigator is attached to this letter.

Sincerely,

Dr. Mohammed Hammoudeh
Chairman Institutional Review Board
Hamad Medical Corporation

Appendix B

مؤسسة حمد الطبية
Hamad Medical Corporation

Hamad Medical Corporation

Institutional Review Board

Email: irb@hamad.qa Tel: 00974-40256410
HMC-IRB Registration: MOPH-HMC-020
IRB-MoPH Assurance: IRB-A-HMC-2019-0014

Continuing Review Approval Notice:

Protocol Title: Impact of Genetic Polymorphisms on INR Normalization in the Peri-procedural Management of Warfarin
Study Number: 16415/16
HMC Principal Investigator: Mohamed Elarref
Date of HMC-IRB Approval: 30 September 2019
Review Type: Expedited
Decision: Approved for Renewal
Approved HMC Enrollment: 150

The IRB has reviewed the submitted documents of the above titled research and approval to continue the study has been granted. The list of approved document(s) is attached.

IRB oversight expires 12 months from the date of the current expiry date – as indicated in the stamp at the bottom of the approved documents.

It is the responsibility of the Investigator to ensure timely renewal of study oversight. Progress reports for continuing review must be approved prior to expiration date; therefore submissions must be received by the IRB 60 to 90 days prior to the expiration date.

Requested Resolutions: IRB requires PI to ensure that the study file and related records are maintained at their respective facilities at HMC.

Any resolutions submitted must include a letter indicating that the submission is a follow up request by the IRB; this will ensure that resolutions are processed appropriately and in a timely manner.

Please note; this approval only covers HMC, you may also need approvals from other institutions involved in your study. You should not continue your study until all of these have been obtained

If you have any questions or need additional information, Please contact IRB at the above mentioned email address or telephone number.

As part of PI's responsibilities, all research activities must be recorded in Cerner's medical records per visit for each subject involved in the study.

Important Note: The list of your responsibilities as Principal Investigator is attached to this letter.

Sincerely,

M. Hammoudeh

Dr. Mohammed Hammoudeh
Sr Consultant, Rheumatology
Medicine - HMC
001545

Dr. Mohammed Hammoudeh
Chairman Institutional Review Board
Hamad Medical Corporation

Appendix C

Qatar University Institutional Review Board **QU-IRB**
QU-IRB Registration: IRB-QU-2020-006, QU-IRB, Assurance: IRB-A-QU-2019-0009

Full Board Approval April 28th, 2020

Dr. Hazem Elewa
College of Pharmacy
Qatar University
Phone: 4403 5616
Email: hazem.elewa@qu.edu.qa

Dear Dr. Hazem Elewa,

Sub.: Research Ethics Full Board Approval
Project Title: "Clinical and Economic Impact of Genetic and Non-genetic Factors on INR Normalization in Pre-Operative Management of Warfarin Patients"

We would like to inform you that your application along with the supporting documents provided for the above project was discussed in the QU-IRB Full Board meeting of March 26th, 2020. Having met all the requirements, the project is granted Full Board approval for one year effective from April 28th, 2020 to April 27th, 2021

Please note that all approvals are valid for a period of one year and renewals should be sought one month prior to the expiry date to ensure timely processing and continuity. Moreover, any changes/modifications to the original submitted protocol should be reported to the committee to seek approval prior to continuation.

Documents Reviewed: QU-IRB Application Human Subject-V3_Bilingual_april16 INR PGX, 16415_IRB_CR_Approval_Letter_30Sep19,16415_IRB_Amendment05_Approval_Letter_30Sep19, 16415_InformedConsent_Eng-Ara_Oct18_08Pages, 16415 INR PGX protocol signed, 16415_AmendedDataCollectionSheet_Eng_01Page,16415_Interview_BaselineAndDemographic_Ara_01Page, IBC Approval Letter – 2019061, QU-IRB Application Material Check List-warfarin INR final, QU IRB commitment IGX PGX , QU IRB response IGX PGX, QU-IRB Full Board Review notes, responses to IRB queries and updated documents.

Your Research Ethics Full Board Approval number is **QU-IRB 1296-FBA/20.** Kindly state this number in your future correspondence to us pertaining to this project.

Best wishes,
Dr. Ahmed Awaisu
Chairperson, QU-IRB

Institutional Review Board
(IRB)
Office Of Academic Research

Appendix D

Data Collection Form – INR Normalization Pharmacogenetics Study Study number #16415	Patient code ID# Date of consent:

Gender	Age	Weight	Height	Country of Origin	Country of Origin of parents
Male Female					

Social History			
Alcohol intake	No	Yes, No. of cups/week	
Smoking	No	No. of Cigarettes/day	Hours of smoking shisha/day
Vit K rich food intake/week	Low	Normal	High

Medical History	Interacting Medication		Outpatient Medications		
Diabetes	Amiodarone	Phenobarbital	Clopidogrel	Aspirin	Levothyroxine
HTN	Fluconazole	Carbamazepine	Atenolol	Metoprolol	Statins:
CHF	Metronidazole	Rifampin	Digoxin	Diltiazem	PPI:
Cancer	Omeprazole	Sulfamethoxazole	Bisoprolol	Carvedilol	Antibiotic:
Thyroid function	Ciprofloxacin	Trimethoprim	Other Medication:		
Other Medical Conditions:					

Indication(s) for anticoagulation:	AF	PE	DVT/VTE	VR	APLS	Stroke	
Duration of anticoagulation:	Indefinite				Specific		
INR goal:	2-3	2-2.5	2.5-3		2.5-3.5	3-4	
Pre-visit weekly dose:							
Last day warfarin dose was administered:		Time:					

Visit	Visit date	INR	POC/LAB	Time	Type of procedure:			
1					Date of procedure:			
2					Bridging prior to procedure:		Dose/day	
3					Bridging prior to procedure:		Dose/day	

	Minor bleeding	Major bleeding	Thromboembolism	Hospitalization	New meds added or d/c
Pre-operative					
Post-operative					

Genotyping results			
CYP2C9*2	CC	CT	TT
CYP2C9*3	AA	AC	CC
VKORC1 (-1639)	AA	AG	GG
Factor X (-40 C/T)	CC	CT	TT
Factor VII (R353Q)	RR	RQ	QQ

HMC-IRB,16415/16,07Oct19-29Oct19