QATAR UNIVERSITY

COLLEGE OF PHARMACY

MULTI-CRITERIA DECISION ANALYTIC MODEL FOR THE COMPARATIVE FORMULARY INCLUSION OF DIRECT ORAL ANTICOAGULANT IN QATAR

BY

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ABSTRACT

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Title: Multi-criteria Decision Analytic Model for The Comparative Formulary Inclusion of Direct Oral Anticoagulants In Qatar

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Aim: The formulary inclusion of direct oral anticoagulant (DOACs) in the government hospital health services in Qatar is not comparative or restricted. Requests to include a DOAC in the formulary are typically accepted if evidence of efficacy and tolerability is presented. There are no literature reports of a DOAC scoring model that is based on comparatively weighted multiple indications and no reports of DOAC selection in Qatar or the Middle East. This study aims to compare first-line use of the DOACs that are available in Qatar.

Methods: A comparative, evidence-based multicriteria decision analysis (MCDA) model was constructed to follow the multiple indications and criteria of DOACs. Literature and best evidence informed and guided the selection criteria of DOACs, oversees and confirmed by a specialized expert panel. Input from the relevant local practitioner population steered the relative weighting of selection criteria. The base case MCDA model was based on multivariate uncertainty analysis to account for inherent input uncertainty. Comparatively scored DOACs, exceeding a defined score threshold, were recommended for formulary selection. The model comprised main criteria and sub-criteria. The criteria of most weight in differential selection were determined. Out of all available DOACs, inside and outside Qatar, the top-scoring DOACs were suggested as formulary options, followed by others for nonformulary use. About the DOACs available in Qatar, and based on the outcomes of the MCDA model, the DOAC that is best suited for first-line use at current HMC practices will be determined.

Results: The selection criteria included 10 main criteria and 28 sub-criteria. Main criteria according to their weight from highest to lowest are; clinical efficacy, safety, dosage frequency, drug interaction, availability of a specific and approved reversal agent, ease of switching during treatment, regimen flexibility, special population requirements, pharmacokinetics properties, and administration as a crushed tablet. DOACs total achieved performance mean scores were as follow: apixaban 711.8 (95% CI 711.5 – 712.1), rivaroxaban 699.6 (95% CI, 699.4 – 699.9), edoxaban 658.7 (95% CI, 658.4 – 658.9), and dabigatran 569.6, (95% CI 569.4 – 569.8). Based on one-way sensitivity analysis, excluding dosage frequency did not change DOACs ranking. However, DOACs recommendations changed to only apixaban being recommended as a formulary option, while dabigatran, rivaroxaban, and edoxaban are recommended to be excluded from the formulary. Excluding availability of a specific and approved reversal agent, however, resulted in edoxaban being ranked first with mean score of 737.2 (95% CI, 736.9 - 737.5), followed by apixaban 677.2 (95% CI,676.9 - 677.5), rivaroxaban 663.5 (95% CI, 663.2 - 663.8), and dabigatran 518.1 (95% CI, 517.9 - 518.3). As a result, both edoxaban and apixaban were recommended as formulary option, and rivaroxaban as non-formulary option, and dabigatran is recommended to be excluded from the formulary. Both multivariate and scenario sensitivity analysis did not change the results of the base-case analysis.

Conclusion: When incorporating and investigating the input of all key relative criteria of DOACs from relevant local practitioners in the MCDA model, apixaban was ranked the highest followed by rivaroxaban, edoxaban, and lastly dabigatran. Thus, apixaban and rivaroxaban were recommended as formulary options, edoxaban for non-formulary use, and dabigatran was rejected.

Implication: The implementation of a locally developed DOACs-specific comparative

MCDA scoring model, will help assess any future DOAC, against locally available DOACs, for the purpose of making decisions about formulary inclusion. Results of the study will help in determining the best of the Qatari available DOACs for first-line use, based on evidence-based clinical, safety and economic data

DEDICATION

To all people who believed in me

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ABBREVIATIONS

CVD	Cardiovascular disease
VTE	Venous thromboembolism
DVT	Deep vein thrombosis
PE	Pulmonary embolism
AF	Atrial fibrillation
NVAF	Non-valvular atrial fibrillation
MI	Myocardial infarction
US	United States
USD	United State dollar
ICH	Intracranial hemorrhage
IS	Ischemic stroke
HS	Hemorrhagic stroke
TKA	Total knee arthroplasty
THR	Total hip replacement
LMWH	Low molecular-weight heparin
DOACs	Direct oral anticoagulants
OAs	Oral anticoagulants
INR	International normalized ratio
ISI	International sensitivity index
SE	Systematic embolism
NOACs	Novel oral anticoagulants
TSOACs	Target specific oral anticoagulant
P-gb	Permeability-glycoprotein

CYP3A4	Cytochrome P450 3A4
PO	Oral
HR	Hazard ratio
CI	Confidence interval
UFH	Unfractionated heparin
CMA	Cost-minimization analysis
CEA	Cost-effectiveness analysis
ACER	Average cost-effectiveness ratio
CER	Cost-effectiveness ratio
ICER	Incremental cost-effectiveness ratio
CUA	Cost-utility analysis
QoL	Quality of life
QALYs	Quality-adjusted life years
ICUR	Incremental cost-utility ratio
CBA	Cost benefit analysis
MCDA	Multi-criteria decision analysis
EMA	European Medicines Agency
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
GDP	Gross domestic product
HMC	Hamad Medical Corporation
ACS	Acute coronary syndrome
HH	Heart hospital
Ppy	Per patient year
IRB	Institutional review board
MRC	Medical research center

ASHP	American society of health-system pharmacists
FDA	Food and drug administration
RCTs	Randomized control trials
HR	Hazard ratio
GFR	Glomerular filtration rate
HD	Hemodialysis
Pgb	P-glycoprotein
HGH	Hamad general hospital
AWH	Al wakra hospital
GI	Gastrointestinal
MPR	Medication possession ratio

Chapter One: INTRODUCTION

1.1 Cardiovascular disease

Cardiovascular disease (CVD) is a group of conditions that affect the heart and blood vessels. It includes coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, and venous thromboembolism (VTE) (1,2). Acute events of CVD include strokes, ischemic heart disease, deep vein thrombosis (DVT), and pulmonary embolism (PE), which are caused by the occlusion of blood vessels within the brain, heart, leg veins, and lungs, respectively. This blockage is due to the build-up fatty deposits within blood vessels' inner walls, which leads to thrombus formation in the arteries supplying the heart and the brain. Alternatively, thrombus may not involve plaque formation, and be mediated primarily through impairment in the coagulation cascade, such as in DVT, PE, and certain forms of ischemic stroke (IS). CVD is considered to be the leading cause of death in the state of Qatar, as well as globally (1,2). In 2016, approximately 17.9 million people died from CVD, which accounts for 31% of the total deaths globally, and it was documented that the majority of the deaths occurred in low- and middle-income countries. Patients who are at high risk of developing CVD (i.e., history of hypertension, hyperlipidemia, and diabetes) or who have an established risk of CVD require early detection and management through proper counseling and medications (3).

1.2 Atrial Fibrillation

Atrial fibrillation (AF) is another type of CVD, and is defined as supraventricular tachyarrhythmia in which the blood flow from the atriums to the ventricles varies from beat to beat, and the heart cannot pump blood to the rest of the body efficiently. It has been reported that AF is one of the most common types of

arrhythmias, with a prevalence of 1% in the general population (4). AF can be either valvular AF, which is responsible for the highest risk of stroke and is caused by congenital heart diseases or structural changes in the mitral valve, or non-valvular AF (NVAF). NVAF is caused by other factors such as hyperthyroidism, heart stimulants (i.e., caffeine, alcohol, tobacco), lung diseases (pneumonia), stress, and hypertension (5). Over the past several decades, several studies have reported a positive association between AF and stroke, and have illustrated that AF is associated with a five-fold increase in the risk of developing a stroke. Also, AF is associated with an increased risk of developing other severe cardiovascular complications, such as heart failure and increased mortality in patients with myocardial infarction (MI) (6–8). Consequently, anticoagulation therapy is the cornerstone in the management of patients with AF to prevent the risk of future embolic events.

In the United States (US), epidemiologic studies suggest that approximately 5.3 million patients have AF, and 795,000 patients have a new or recurrent stroke annually (9). Moreover, in 2014, AF was reported to be the primary diagnosis in 454,000 of the total hospitalizations in the US. AF occurrence is related to aging, and it was estimated that by the age of 85, one in every ten would have AF (10).

1.2.1 Economic burden of stroke

In US healthcare programs funded by the Government, approximately 780,000 cases of all types of stroke occurred in 2008 (11). The total estimated cost of stroke was USD 65.5 billion, where direct and indirect cost accounted for USD 43.9 billion (67%) and USD 21.6 billion (33%), respectively (12). The mean cost of four years of hospitalization according to 5% random sample of 1997 medicare beneficiaries after stroke index in patients aged ≥ 65 was USD 48,327, USD 38,023, and USD 39,396 for subarachnoid hemorrhage, intracranial hemorrhage (ICH), and IS, respectively,

whereas the four years' survival-adjusted mean cost was USD 60,177, USD 50,015, and USD 49,996 for subarachnoid hemorrhage, ICH, and IS, respectively (13). During the first post-discharge year of stroke survivors during 2001-2005, the total cost per stroke patient was USD 17,081/year, according to Medicare reimbursement rates (14).

Notably, the total cost of stroke is derived mainly by adverse events related to medication. In AF patients, anticoagulation therapy is associated with an increased risk of bleeding. In a study of a health claims database from 2002-2005 in the US, among the 127,135 AF patients, 11,266 patients had bleeding event. From these bleeding events, 87.4% were minor bleedings, 10.8% were major bleedings, and 1.8% ICH. Over one year followup, major bleeding and ICH total adjusted increamental costs were USD 88,775 and USD 258,968, respectively (15). Another study showed that among 2,345 patients treated with warfarin, 126 developed bleeding, and the cost of hospitalization due to bleeding events was USD 10,819 (16). A study of 119,764 patients who were taking warfarin for stroke prevention showed that major bleeding and hemorrhagic stroke (HS) costs were USD 39,943 and USD 60,123, respectively, while the cost for patients with no major events was USD 15,718 (17).

1.3 Venous thromboembolism

VTE refers to the formation of thrombus within deep veins of the leg, causing DVT. This thrombus can embolize to the lungs, causing a PE. Both DVT and PE are referred to as VTE. In the US, VTE is ranked as the third leading vascular diagnostic disease after MI and stroke, affecting around 300,000 to 600,000 of the population annually (18,19). After the age of 60, the incidence of VTE rises dramatically for both genders, particularly the rate of PE (20). Based on a 5025 Worcester population-based analysis, VTE incidents increased from 73 cases per 100,000 capita in 1985 to 133 cases per 100,000 capita in 2009, driven primarily by the increase in PE cases (21).

Furthermore, the discharge rate from the hospital due to primary or secondary PE increased from 126,546 to 229,637 cases, while fatality rates decreased from 12.3 to 8.2 % (22). The reduced PE fatality rates and the increased incidence may be explained by the enhanced detection of small pulmonary emboli and the improved sensitivity of diagnostic imaging. Moreover, the rise in the number of patients with chronic indwelling central venous catheters, internal cardiac defibrillators, and permanent pacemakers has led to an increase in the frequency of VTE in the upper extremity. The Surgeon General of the US estimated that PE accounts for 100,000–180,000 deaths annually, and among hospitalized patients, PE is recognized as the leading preventable cause of death (23). The estimate of mortality rate in hospitalized patients with acute PE is 7%, and this rises exponentially up to 32% in patients with hemodynamic instability (24).

The annual age- and sex-adjusted rate of recurrent VTE declined from 39 to 19 per 100,000 between 1985 and 2003, and increased again in 2009 to 35 (21). Following the completion of anticoagulation therapy, patients with idiopathic (unprovoked) VTE were at higher risk of recurrent events compared with patients for whom provoking factors had been identified (25,26). Over ten years of unprovoked VTE, the rate of recurrent VTE ranged from 30% to 50%; however, these events occurred in 20% of patients after a provoked event over ten years (25,26).

Furthermore, immobility is considered to be one of the most common causes of VTE, especially in hospitalized patients who undergo orthopedic surgery, such as total knee arthroplasty (TKA) or total hip replacement (THR). The incidence rate of symptomatic VTE in the 35 days following orthopedic surgery was 4.3% in patients who did not receive VTE prophylaxis (27). Thus, VTE pharmacological prophylaxis is recommended in current clinical guidelines for patients undergoing TKA and THR

surgeries (27). The pharmacological prophylaxis includes warfarin, low molecular-weight heparin (LMWH), fondaparinux, and direct oral anticoagulants (DOACs).

Similar to AF, oral anticoagulants (OAs) and antithrombotic medications are considered the cornerstone for the prevention of future thromboembolic events in patients with VTE.

1.3.1 Economic burden of VTE

The benefits of disease prevention can be projected by using cost estimates (28). Each year in the US, VTE causes 500,000 hospitalizations and more than 100,000 deaths with total medical costs estimates of USD 5–10 billion (29–31). VTE's total economic burden, which includes costs associated with premature death, is around USD 69 billion every year (32,33).

1.4 Anticoagulation medications

An ideal anticoagulant would allow normal response to vascular injury and would have a low risk of bleeding. The role of anticoagulant medications is to inhibit the activity of coagulation factors, including specific targets in the coagulation cascade. Theoretically, this could be accomplished by preserving the TF-VIIa initiation phase of the clotting mechanism. However, no novel drug with these characteristics exists, and all anticoagulant and fibrinolytic drugs are associated with bleeding risk as their primary side effect (34).

1.4.1 Warfarin and other coumarin anticoagulants

Coumarin anticoagulant clinical use began with the discovery of an anticoagulant substance in spoiled sweet clover silage that caused hemorrhage in cattle. In 1950, warfarin, which is a congener of dicumarol, was introduced under the brand name of Coumadin as a human antithrombotic medication (35). The mechanism of action of coumarin anticoagulant involves blockade of the γ-carboxylation of

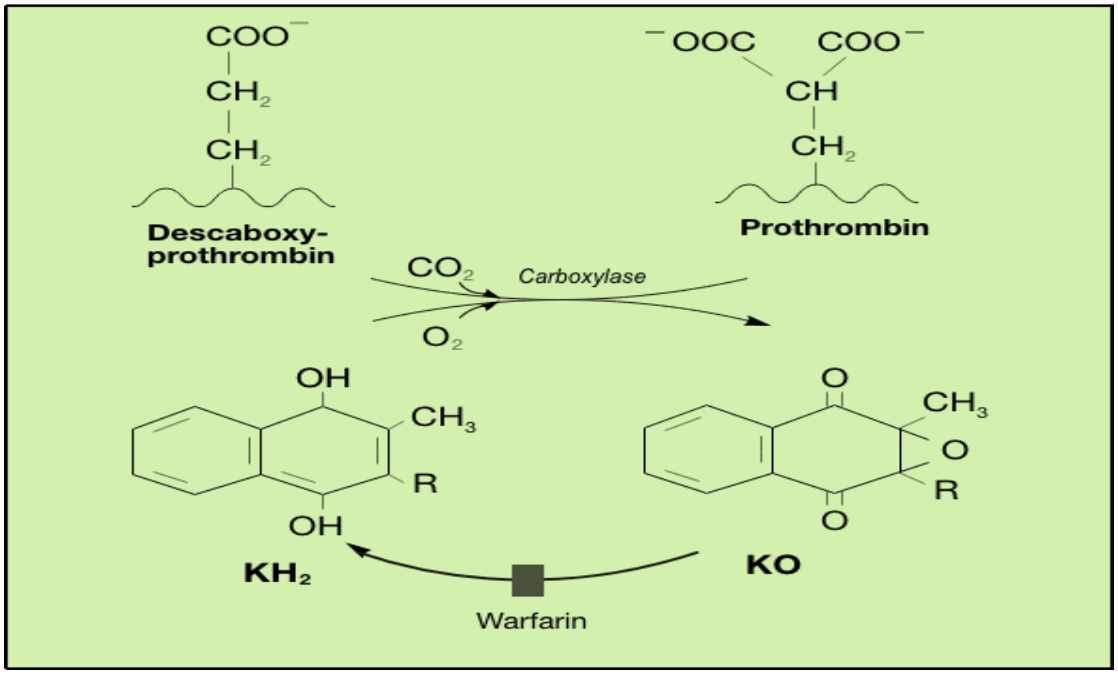

Figure 1-1: Vitamin K cycle

prothrombin, several glutamate residues, factors VII, IX, and X, and proteins C and S, which leads to incomplete and biologically inactive coagulation factors (Figure 1-1). The carboxylation reaction of the protein is coupled with vitamin K oxidation, and vitamin K must be reduced to reactivate it. Warfarin prevents the reduction of vitamin K, thus inhibiting the carboxylation reaction (36). Warfarin is prepared as a sodium salt with almost 100% bioavailability after oral administration. Upon systematic absorption, over 99% of racemic warfarin is bound to albumin plasma protein, which may explain its long half-life in plasma (i.e., 36 hours) and its decreased volume of distribution.

The warfarin therapeutic range is defined in terms of the international normalized ratio (INR). The INR is the ratio of prothrombin time (measured prothrombin time/normal prothrombin time mean in the lab)ISI. The international sensitivity index (ISI) is dependent on the instruments and reagents used. In the context of the treatment or prophylaxis of thrombotic events, the recommended range of the

INR value is 2–3. In some patients who have artificial heart valves or who are at increased risk of developing thrombosis due to other underlying medical conditions, the recommended INR range is 2.5–3.5.

In addition, warfarin can interact with a broad range of medications, food, and disease states, which can be categorized into pharmacodynamic and pharmacokinetic interactions. Pharmacokinetic refers to how the body processes the drug, which is mainly mediated by enzyme inhibition or induction and reduced binding to plasma proteins, such as drug-drug and drug-food interactions. Potential drug–drug interactions with warfarin are summarized in Table 1-1. Additionally, warfarin can interact with many common foods and drinks that are rich in Vitamin K that would counteract the action of warfarin, thus increasing the risk of thrombus formation. These foods and drinks include green leafy vegetables, black licorice, grapefruit, cranberry juice, and alcohol. Pharmacodynamic, on the other hand, refers to how the drug affects the body, such as its synergistic effect (hepatic disease, impaired homeostasis, and reduced clotting factor synthesis), competitive antagonism (vitamin K), and an altered physiologic control loop for vitamin K.

Furthermore, warfarin has been the gold standard and the only anticoagulant for several decades. However, it has many drawbacks, such as a narrow therapeutic window, patient adherence, physician's reluctance to prescribe it due to frequent INR measurements and clinic visits, drug–drug, and drug–food interactions (37). Consequently, less than half of the patients who should be on anticoagulation treatment are prescribed warfarin (less than a third for older patients). Furthermore, among patients who were prescribed warfarin and were adherent to treatment, less than a third maintained targeted therapeutic INR (38,39). Ultimately, traditional treatment with

Table 1-1: Pharmacokinetic and pharmacodynamic interactions with warfarin

Increased Protohemin Time		**Decreased Protohemin Time**	
Pharmacokinetic	**Pharmacodynamic**	**Pharmacokinetic**	**Pharmacodynamic**
Amiodarone	**Drugs**	Barbiturates	**Drugs**
Cimetidine	Aspirin (high doses)	Cholestyramine	Diuretics
Disulfiram	Cephalosporins, third generation	Rifampin	Vitamin K
Metronidazole	Heparin		**Body factors**
Fluconazole	**Body factors**		Hereditary resistance
Phenylbutazone	Hepatic disease		Hypothyroidism
Sulfinpyrazone	Hyperthyroidism		
Trimethoprim-sulfamethoxazole			

warfarin may not minimize the risk of IS and systematic embolism (SE) in patients with AF and VTE (40). Therefore, efforts have been made to find alternatives to warfarin by targeting other factors in the coagulation cascade.

1.4.2 Direct oral anticoagulants

DOACs have changed the landscape of anticoagulation medications, and these novel medications are increasingly replacing conventional treatment with warfarin in the majority of patients requiring oral anticoagulants (OAs) (41). DOACs showed comparable efficacy and a significantly superior safety profile, especially for bleeding risk, compared with warfarin and other anticoagulants (42–77).

DOACs include dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban. Rivaroxaban, apixaban, edoxaban, and betrixaban, inhibit factor Xa, which is the common factor that gets activated in both intrinsic and extrinsic pathways of clot

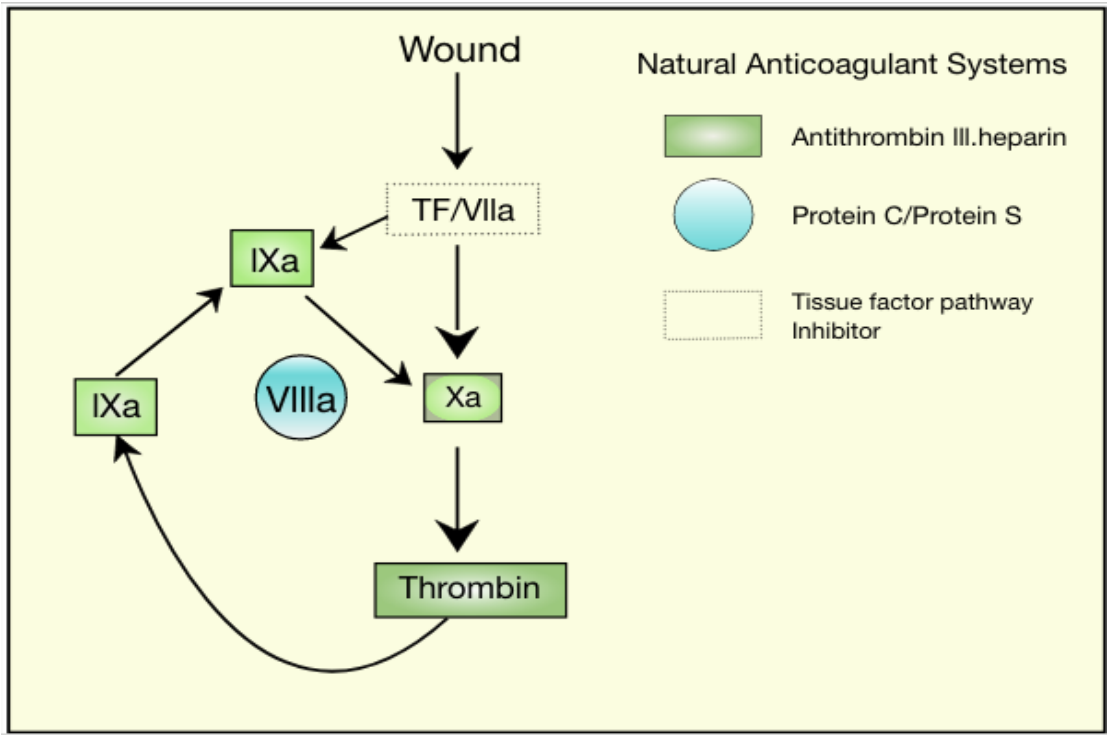

Figure 1-2: A model of blood coagulation

formation. Dabigatran, however, directly inhibits thrombin, which is involved in the conversion of fibrinogen into fibrin, resulting in the inhibition of the tight fibrin clot formation (78,79) (Figure 1-2). The nomenclature of DOACs has sometimes been referred to as novel oral anticoagulants (NOACs) or target-specific oral anticoagulants (TSOACs).

While DOACs share many characteristics, there are significant differences between them, which may favor one versus the others. For instance, the half-life of the medications varies, where the half-life of dabigatran is 12–17 hours, rivaroxaban 6–9 hours, apixaban 8–15 hours, edoxaban 6–11 hours, and betrixaban 19–27 hours. Further, the percentage of renal elimination differs significantly among DOACs, such that dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban have is 80, 66, 25, 35, and 5, respectively. Moreover, the bioavailability percentages for dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban are 3–7, 80, 50, 62, and 34%,

respectively. Furthermore, only rivaroxaban, apixaban, and edoxaban can be crushed except for dabigatran, which cannot be crushed. Concerning administration with food, only rivaroxaban and betrixaban should be taken with food (80).

All DOACs should not be used with permeability-glycoprotein (P-gb) inducers (e.g., carbamazepine, rifampin) (Figure 1-2). Rivaroxaban should be avoided in P-gb potent inhibitors (e.g., amiodarone, carvedilol, dronedarone, quinidine, and verapamil), while dose reduction is recommended for the remaining DOACs. Dabigatran, edoxaban, and betrixaban are not affected by either Cytochrome P450 3A4 (CYP3A4) inducers (e.g., carbamazepine, phenytoin, and rifampin) or inhibitors (e.g., clarithromycin, ketoconazole itraconazole, and voriconazole). Apixaban dose should be reduced to 2.5 mg daily with CYP3A4 inhibitors, and it should be avoided with CYP3A4 inducers, while rivaroxaban should be avoided with both CYP3A4 inducers and inhibitors (81,82).

The recommended dosing regimens of DOACs are listed below:

- Dabigatran:
    - VTE prophylaxis: 110 mg orally (PO) on the first day, followed by 220 mg PO daily for 28–35 days
    - VTE treatment, reduction in the risk of recurrent VTE, and stroke prevention in NVAF patients: 150 mg PO twice daily
- Rivaroxaban:
    - VTE prophylaxis and reduction in the risk of recurrent VTE: 10 mg PO daily
    - VTE treatment: 15 mg PO twice daily the first 21 days, followed by 20 mg daily
    - Stroke prevention in NVAF patients: 20 mg PO daily

- Apixaban:
    - VTE prophylaxis and reduction in the risk of recurrent VTE: 2.5 mg PO twice daily
    - VTE treatment: 10 mg PO twice daily for the first seven days, followed by 5 mg PO twice daily
    - Stroke prevention in NVAF patients: 5 mg PO twice daily
- Edoxaban:
    - VTE treatment and stroke prevention in NVAF patients: 60 mg PO

In a similar trend, there are also differences between DOACs in relation to safety and efficacy (42,83). For example, Graham et al. compared the risk of bleeding, stroke, and mortality in elderly patients treated with dabigatran or rivaroxaban for NVAF in a retrospective cohort study (84). The study showed that rivaroxaban was associated with a statistically significant increase in ICH compared with dabigatran, with a hazard ratio (HR) of 1.71 (95% confidence interval (CI), 1.35–2.17), and in major extracranial bleeding compared with dabigatran (HR = 1.32; 95% CI, 1.21–1.45) and apixaban (HR = 2.70; 95% CI, 2.38–3.05), and death compared with dabigatran (HR = 1.12 95% CI, 1.01–1.24) and apixaban (HR = 1.23; 95% CI, 1.09–1.38). Dabigatran was associated with increased risk of major extracranial hemorrhage (HR = 2.04; 95% CI, 1.78–2.32) and decreased risk of ICH (HR = 0.70; 95% CI, 0.53–0.94) compared with apixaban (84).

1.4.3 Indirect and direct thrombin inhibitors

Indirect thrombin inhibitors exert their anti-thrombotic effect by interacting with a protein named antithrombin from which they were named. Three medication classes belong to this group; unfractionated heparin (UFH), LMWH, and the pentasaccharide synthetic drug fondaparinux. These drugs enhance the inactivation of

factor Xa via binding to antithrombin (85,86). These medications can only be administered through parenteral injections, which makes them inconvenient for many patients requiring anticoagulants in ambulatory settings.

In contrast to the indirect thrombin inhibitors, direct thrombin inhibitors exert their antithrombotic effect through binding to thrombin active sites directly, which inhibits the downstream effect of thrombin. Medications belonging to this group are hirudin and bivalirudin, which bind to thrombin active sites as well as the substrate recognition site, argatroban and melagatran, which bind only to thrombin active sites (86).

1.5 Economic evaluation of health interventions

Currently, both decision-makers and physicians have a wide range of effective and safe medications and interventions to include in the formulary or to prescribe. However, the utilization of such new interventions is linked to high expenditure compared with older ones, which is driven in part by the increasing demand for more efficacious and safe medications. In addition to this, the increasing production cost of innovative drugs and techniques plays a crucial role in the rapid increment in the cost of newer medications that are available.

The relative returns of expensive medications and interventions in healthcare systems must be examined and inspected carefully and thoroughly, given their high associated cost. The increased economic burden of preventative and therapeutic interventions to prevent or reduce a particular illness requires resource allocation. In recognition of this, it is valuable to scrutinize the efficiency of substituting alternative interventions that have been made available, if the total and maximal efficiency can be achieved from the expended input resources. From an economic point of view, therapeutic intervention cost is the overall cost of that intervention, which includes the

cost of all resources utilized through the application of that intervention, and not just intervention cost. In any healthcare system, the goal is to achieve all desired outcomes of any health intervention efficiently, while preventing resources scarcity and eventually incapacity, which necessitate making decisions regarding the different options available.

Pharmacoeconomics, which is a branch of health economics, is concerned with the efficient utilization of pharmaceuticals by linking inputs and outputs, such as costs and consequences, in order to reduce spending (87). However, that is not the main aim of pharmacoeconomics. The main objective of pharmacoeconomics in any given case is generating data regarding the optimal utilization of limited resources, which can yield the maximum value for money for both patients and society in general, and health care payers.

1.5.1 Types of cost in economic evaluation

In economic evaluations, the costs usually used for any intervention or medication can be categorized into two main categories: direct and indirect medical costs.

- Direct cost: Refers to the cost of the utilized resources concerning a disease state or health intervention, which can be further classified into:
    - Direct medical costs: Comprises a defined health intervention or medical service, such as medication acquisition and follow-up cost, hospitalization, and health interventions in any hospital setting (screening tests, lab tests).
    - Direct non-medical cost: Comprises the non-medical costs associated with a disease, for example, costs related to travel, transportation, accommodation, and child support service during illness.

- Indirect cost: Refers to costs due to loss of productivity of patients associated with a disease state or health intervention, such as absenteeism from work due to disease.

There are other types of costs less frequently used in economic evaluation, such as opportunity cost, fixed cost, variable cost, intangible cost, and marginal cost. A summary of each of them is listed below in Table 1-2.

Table 1-2: Other types of cost in economic evaluation

Type of cost	Summary
Opportunity cost	Gained by using the resource in an alternative intervention
Fixed cost	Even if the output of production varies, it remains unchanged
Variable cost	When the output of production varies, it varies too
Intangible cost	Difficult to measure (nonphysical), such as pain
Marginal cost	Change of total cost to produce a significant change in output

1.5.2 Types of the economic evaluation of health interventions

Economic evaluation within the healthcare setting consists primarily of four methodologies (Table 1-3). All methods share the same measurement of cost, which is monetary value; however, they differ in the way the analysis and comparison of health outcomes are conducted (88–94).

Table 1-3: Health economic evaluation analysis types

Methodology	Cost measurement unit	Outcome measurement unit
Cost-minimization analysis	Monetary units	Assumed to be equivalent
Cost-effectiveness analysis	Monetary units	Natural units (life-years, death, blood sugar level)
Cost-benefit analysis	Monetary units	Monetary units
Cost-utility analysis	Monetary units	Quality-adjusted life years or other utilities

1.5.2.1 Cost-minimization analysis

Cost-minimization analysis (CMA) is used when two or more interventions are compared, knowing that alternative interventions demonstrate equivalent clinical effectiveness and differ only in their cost only. The cost parameter may include preparation, acquisition, or administration cost, and the therapeutic equivalence parameter includes adverse drug reactions, complications, and therapy duration. An ideal scenario for using CMA is the comparison between different generic alternatives with similar consequences. The drawbacks of CMA include its core assumption that alternatives have the same clinical effectiveness, which in turn limit its application to interventions.

1.5.2.2 Cost-effectiveness analysis

Alternative healthcare interventions may vary in their clinical outcomes. For instance, medication A may reduce the symptoms of a particular disease of interest faster than medication B in patients with similar conditions. In such scenarios, a decision can be made based on the relative alternative option cost for each particular outcome achieved. This analysis is known as cost-effectiveness analysis (CEA), and it

is considered to be the most common economic appraisal tool used today. CEA can answer questions similar to “Among two or more different health intervention alternatives, which one is considered the best to achieve a specific health outcome?” The ability of CEA to easily quantify health outcomes makes it a powerful tool for both decision-makers and prescribers, compared with the outcomes of other economic evaluation tools, such as cost-benefit and cost-utility analysis (CUA).

Furthermore, in clinical trials and daily clinical practice, these outcomes are regularly collected, whereby both decision-makers and prescribers are accustomed to their definitions and how to measure and estimate them. However, CEA comprises two main limitations. First, CEA fails to capture more than one dimension of any health outcome under investigation. As an example, if disease-free survival is the outcome of interest, CEA does not take into consideration the quality of the patient's life. Second, alternative interventions with diverse types of outcomes cannot be compared in CEA. As an example, when comparing outcomes between two different clinical services where the first involves a hypertension clinic, and the other is a diabetic clinic, the outcomes for each clinic differs from the other (e.g., blood pressure control in the hypertension clinic compared with the blood glucose level in the diabetic clinic). Moreover, if there are significant differences in the primary outcome of different alternatives (e.g., complications, side effects, interactions between various diseases), it is still challenging to merge these differences in one single effectiveness measure to be used in CEA.

The average cost-effectiveness ratio (ACER) or cost-effectiveness ratio (CER), and the incremental cost-effectiveness ratio (ICER) are part of CEA, in which the effect and cost of both interventions are combined. ACER is the total cost of the intervention divided by the therapeutic outcome of that intervention. ACER allows the identification

of the less expensive alternative clinical option by decision-makers; however, it does not allow the calculation of the additional cost linked to a particular intervention when it is compared with a less expensive one. Figure 1-3 represents the ACER equation. In contrast, ICER is a ratio of the differences in cost and clinical effectiveness of the two interventions. ICER can be calculated by dividing the cost difference between the two interventions by their clinical effectiveness difference, as shown in Figure 1-4.

$$\text{ACER} = \frac{\text{health care costs}}{\text{clinical outcome}}$$

Figure 1-3: Average cost-effectiveness ratio equation

$$\text{ICER} = \frac{\text{cost}_A - \text{cost}_B}{\text{effect}_A - \text{effect}_B}$$

Figure 1-4: Incremental cost-effectiveness ratio equation

When conducting a CEA to compare two interventions (intervention A and B, as represented in the cost-effectiveness grid presented in Table 1-4) in the scenarios of dominant, semi-dominant, or dominated strategy, and ICER. An intervention is deemed to be dominant when it has low cost and high effect, while it is considered to be dominated when it has a high cost with low effect, and ICER is reported when an intervention has either high cost and high effect or low cost and low effect compared with other alternatives.

Table 1-4: Cost-effectiveness grid

A versus B	Higher effect	Same effect	Lower effect
Higher cost	ICER	B is semi-dominant	B is dominant
Same cost	A is semi-dominant		B is semi-dominant
Lower cost	A is dominant	A is semi-dominant	ICER

ICER: Incremental cost-effectiveness ratio

1.5.2.3 Cost-utility analysis

CUA and CEA share the same fundamental concept of being useful for comparing interventions with different outcomes and costs; however, they differ in terms of the outcome measurement unit. In CUA, the outcomes are measured in terms of utilities related to health, such as a patient's well-being or satisfaction, compared with the clinical or natural units used in CEA. CUA can also measure a patient's quality of life (QoL), in addition to clinical outcomes (e.g., lives saved). This distinctive characteristic of CUA is achieved through what is known as quality-adjusted life years (QALYs). QALYs is an adjustment of the life years gained from a particular intervention by the quality of each life-year, where one alternative is compared with another. In other words, the equivalent of a healthy year or the overall health status or QALYs related health is the measured outcome in CUA. The utility is a measurement scale of the satisfaction of the patient concerning his well-being, with the worst-case scenario (e.g., death) represented by "0," a full and healthy life represented by "1," and morbidity represented by scores between "0" and "1." Similar to CEA, we can apply the incremental cost ratio concept to CUA through the incremental cost-utility ratio (ICUR). The ICUR is used to measure the incremental cost with each additional QALY

gained by the patient.

CUA comprises many advantages, including the ability to compare different alternatives with different types of outcomes, and the ability to combine both mortality and morbidity into a single standard unit. Furthermore, the morbidity of varying disease statuses can be determined in the long term by conducting utility adjustments over the years. Nonetheless, CUA has its disadvantages, such as the difficulty associated with utility measurement, and the lack of consensus in the literature for that matter, and the methods used to measure utilities. These methods include standard gamble and time tradeoff methods along with the rating scale method.

1.5.3 Decision analysis

Decision analysis is a tool that is used to compare and evaluate different decision alternatives of relative value in a systematic and quantitate manner (95). It can help both decision-makers and healthcare providers to distinguish between available alternatives when confronting a decision, predict the outcomes and consequences of each alternative, evaluate the probability of an outcome, and choose the decision alternative while taking into consideration all other factors.

To evaluate different health alternatives economically and clinically in a decision analysis model, a decision model (decision tree) is structured. In the decision tree, the decision problem components are constructed graphically by displaying alternatives to facilitate the linking between actions and consequences, and the calculation of needed values to compare between alternatives (96).

Decision tree structuring is an almost straightforward process, with software such as Treeage® and Palisade's @ Risk® to facilitate the process. Primarily, decision tree construction occurs according to several conventions, which allow the building of a decision tree from left to right. The skeleton of the decision tree comprises nodes,

branches, and outcomes. There are two types of nodes: decision nodes, which are presented by squares, and chance nodes, which are presented by circles. Triangles or rectangles represent the outcomes in the decision tree. Figure 1-5 depicts a hypothetical skeleton of a decision tree that contains nodes, branches, and labels for different outcomes. Decision nodes illustrate the different possible pathways of any decision that can be made by the decision-maker. Meanwhile, chance nodes illustrate the various events that can happen outside of the decision-maker's control. The sum of the probabilities of the events at any chance node must equal one (Figure 1-5). In the decision tree, outcomes are the results of the final events, and they may comprise life or death, health or disability, or any other benefits or risks of a particular intervention. Furthermore, outcomes are measured in terms of QALYs or life expectancy, and as discussed above, QALYs estimation relies on utility measurement. Table 1-5 represents a spreadsheet of the calculations of a decision tree.

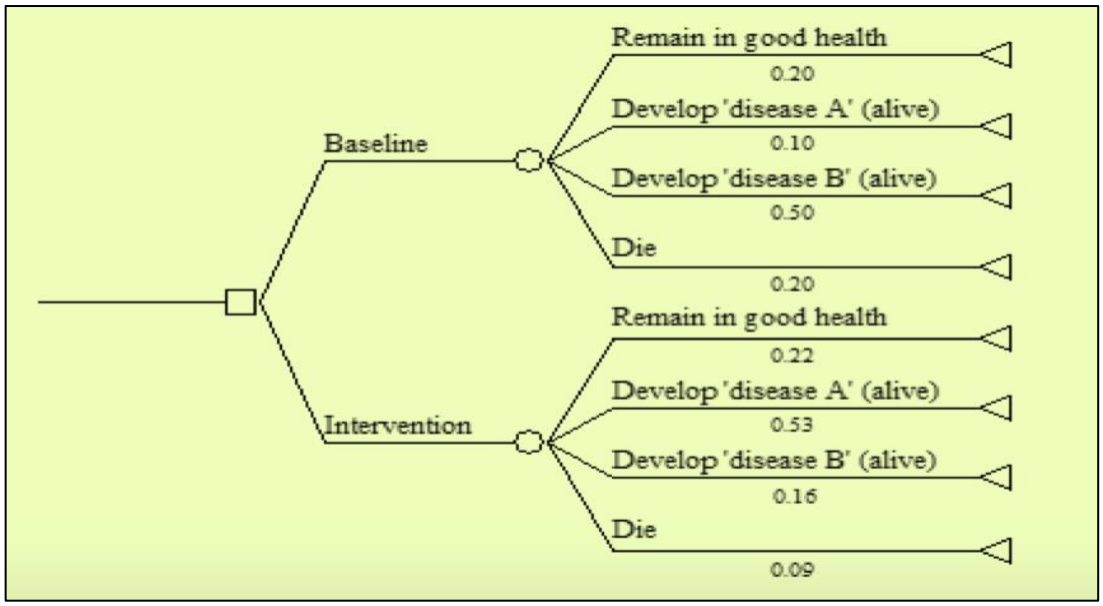

Figure 1-5: Hypothetical skeleton of a decision tree

1.5.4 Sensitivity analyses

The pharmacoeconomic analytic model is populated with clinical and economic input data that are deterministic or probabilistic in nature. Depending on the data sources and study assumptions, the values of the input variables can be considered uncertain. To ensure robustness in the conclusion of the economic study against such uncertainty, the economic analysis includes sensitivity analyses (87,96–100). Here, sensitivity analysis is a process whereby the value of the main uncertain study input variables are varied within a range of uncertainty assigned to the baseline value of the input, so that the consequential variation in the study outcomes can be

Table 1-5: Spreadsheet of the calculations of a decision tree

Outcome	Cost	Probability	Cost x Probability
Remain in good heath	$ 800	0.2	$ 160
Develop disease A	$ 900	0.1	$ 500
Develop disease B	$ 1000	0.5	$ 160
Die	$ 800	0.2	$ 910
Total for placebo		1	
Intervention			
Remain in good heath	$ 700	0.22	$ 154
Develop disease A	$ 800	0.53	$ 424
Develop disease B	$ 900	0.16	$ 144
Die	$ 700	0.09	$ 63
Total for intervention		1	$ 785

investigated against the baseline study conclusion and the value of the results (87,96–100). The following are the most common types of sensitivity analysis.

1.5.4.1 One-way sensitivity analysis

In one-way sensitivity analysis, the value of only one model input is changed in an analysis, while maintaining all remaining inputs as they are. One-way sensitivity analysis is the most common in literature as it is the easiest to conduct.

1.5.4.2 Multivariate sensitivity analysis

Multivariate sensitivity analysis is similar to the one-way analysis, except that variation concurrently takes place in two or more input values in an analysis. If implemented with the appropriate inputs, multivariate analysis gives a better reflection of the real-life parallel uncertainty in inputs, but it is less commonly conducted in the literature because it is more challenging to undertake and interpret than the one-way analysis.

1.5.4.3 Scenario sensitivity analysis

The sensitivity analysis scenario is an analysis where a baseline scenario, concerning a methodological approach or assumption for example, is entirely replaced by a different scenario before the study model is re-run. Here, it is not the value of the input variable that is varied, but the nature or existence of the input that is changed. The analysis threshold is also called the "break-even point," which is an analysis to identify the point at which a study conclusion changes as a result of varying the value of the input of interest. It is conducted as part of the one-way and multivariate analyses of uncertainty.

1.5.5 Healthcare systems and economic evaluation

In general, a healthcare system in any country faces many challenges in employing robust, evidence-based policies when making decisions related to funding,

covering, or reimbursing medical technologies or interventions. In the past, CEA was promoted by technology assessment agencies as the primary decision aid for assessing competing claims in healthcare systems with restricted resources. ICER is the recommended metric to describe cost-effectiveness and is considered the most commonly used analysis in governments that compare the costs of alternative ways to obtain similar kinds of outputs (101). Cost-benefit analysis (CBA) is another widely used method in health and safety, and less common in other areas, in which a group of essential outcomes is explicitly measured in money terms.

The cost-effectiveness threshold determines the judgment surrounding the money value, which for any healthcare system represents the opportunity cost of choosing one alternative over another. CEA is an essential component regarding informing resource-constrained healthcare systems. However, CEA has its limitations because it does not take into consideration other relevant criteria, such as incidence rate, prevalence rate, disease severity, the affected population group, the availability of alternative options, the strength and quality of available evidence, the pharmacokinetic and pharmacodynamic characteristics, dosing frequency, and special population requirements (102).

1.6 Multi-criteria decision analysis

Multi-criteria decision analysis (MCDA) is a modeling technique that can cover CEA limitations while maintaining its advantages. MCDA can capture treatment performance through different criteria, and sum up the results of these criteria in an overall numerical score estimate of treatment value (103). It also takes into consideration the comparative significance (weight) of the score estimates (104). MCDA use has been increased in healthcare settings because of its capability to support the assessment of treatments. The latest reviews demonstrate that for drug benefit-risk

assessment, MCDA may be the proper methodology (105–107). European Medicines Agency (EMA) declared MCDA benefit-risk methodology to be "the most relevant tool" for drug benefit-risk assessment (108). Furthermore, a dedicated task force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) provides guidance for MCDA utilization in treatment assessment (109,110). MCDA methodology have been used successfully for comparison and ranking between cardiovascular drug classes, such as antiplatelet drugs and statins (103,111).

MCDA represents a set of methods that may be useful when decision-makers consider multiple criteria in prioritizing setting activities. It can aid in decisions that help stakeholders outline complicated value trade-offs, consistently and transparently, thus resulting in fairer decision-making. MCDA can make explicit the applied criteria and their relative importance; thus, it is a process that combines value judgment with objective measurement while managing subjectivity (112). To enable these goals, the methodologies and theories that support MCDA must permit the technical and non-technical elements of decision-making; they need to comprise advanced quantitative algorithms while also providing structure to a decision-making process. All of which help in promoting both the transparency and replicability of policy decisions (112).

1.7 Qatar country profile

Qatar is an Arab emirate located in the Gulf region of the Middle East, with a population of around 2.84 million. It is well known for cultural variability among residents due to the high percentage of expats (i.e., 85%). The total gross domestic product (GDP) of Qatar was approximately USD 152.50 billion in 2016, accounting for 0.25% of the world economy. It reflects an average GDP per capita of $66,415, which is equivalent to 526% of the world's average GDP per capita. Interestingly, in 2014, the total public health expenditure was reported to be 34.99% of the GDP per capita (113).

In the health sector in Qatar, which is under the umbrella of the Ministry of Public Health, the healthcare services are provided through (1) primary health care centers, constituting the basic care provided at 21 medical centers, (2) specialized clinics, (3) hospitals, and (4) the private sector that plays an adjunct role in providing health services, mostly through three general hospitals, 131 dental clinics, and 128 clinics for different medical services. Unlimited free services are provided to all Qatari nationals through all government-related sectors. For non-Qatari residents, most essential healthcare services are fully covered by the government insurance policy, with only partial coverage of elective and outpatient services, such as orally prescribed medications (114).

The first government hospital in Qatar, known as Al-Rumailah, opened in 1957. This hospital subsequently became part of a larger medical organization upon the establishment of Hamad Medical Corporation (HMC) by a royal decree in 1979. Since then, the health sector in Qatar has grown exponentially. HMC is the primary provider of secondary and tertiary healthcare in Qatar, and it is one of the preeminent hospital providers in the Middle East. HMC is in charge of nine hospitals, as well as the National Ambulance Service and home and residential care services. In relation to acute coronary syndrome (ACS) treatment, the only specialized hospital for cardiology and cardiothoracic surgery is the Heart Hospital (HH), which is part of HMC and has a capacity of 116 beds (115).

1.7.1 Drug selection in HMC

Decisions related to healthcare are considered to be complex processes that require facing trade-offs between different and sometimes conflicting objectives. For such reasons, individuals or decision-making committees in any healthcare system confront some difficulties when processing and systematically assessing related

information. The inclusion of DOACs into the HMC formulary is controlled by the evidence of efficacy and tolerability, cost, and supply chain alternatives in a country where most medications are imported. If a request is approved, the new medications are added to the formulary as first-line alternatives for prescribers to choose between them, rather than replacing other medications in the formulary.

These loose restrictions on formulary practices in HMC are well-acknowledged as a waste of available resources. Although the income per capita in Qatar is considered to be one of the highest worldwide, annual healthcare sector governmental funding increases by 18%, accommodating a yearly increase in the size of the population by approximately 15%. Thus, there is increasing pressure to maximize health care investments, and this is where the advantages of MCDA arise.

As discussed earlier, MCDA enables the incorporation of different clinically relevant criteria, such as pharmacokinetic and pharmacodynamic properties, tolerability, adherence, and social value, in a single numerical measure between alternatives, while taking into account the relative importance (weight) of each criterion and sub-criterion. Furthermore, MCDA is a score-based method for ensuring that alternatives (e.g., DOACs) are being assessed in a uniform way, as they should be.

Overall, when it comes to decision-making for either formulary inclusion or prescribing, the MCDA method has the power to add clarity to different clinically relevant criteria and their relative importance, and provides a comprehensive framework with which to asses and evaluate other alternative interventions. Moreover, MCDA can result in a systematic stepwise process for the formulary inclusion of different interventions while maintaining a transparent, consistent, and accountable method for decision-makers in the public sector.

1.8 Selection among DOACs

OAs are prescribed widely for stroke prevention in NVAF patients, and for acute VTE treatment and extended prevention of recurrent VTE. Additionally, it is considered a therapeutic alternative for VTE prophylaxis, especially in post total hip or knee replacement surgeries. OAs include the gold standard vitamin K antagonist (e.g., warfarin) and DOACs (e.g., dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban).

The CEA DOACs, along with their cost per the QALY framework are well understood, and both allow for an evaluation from a precise pharmacoeconomic point of view (116–118). However, the non-clinical characteristics of DOACs vary considerably, including pharmacokinetic and pharmacodynamic properties, availability of reversal agents for their effects in the case of bleeding, and administration frequency (119). Those non-clinical characteristics are not considered in traditional pharmacoeconomic analysis.

First, traditional CEA is considered the cornerstone of formulary inclusion. CEA allows the measurement of differences in cost and effect between alternatives for one intervention at a time. However, this does not reflect the practice in real life, as many clinical indications may exist in different settings; thus, CEA is not an ideal method. Second, the efficacy and safety of interventions are the bases for practice guidelines. However, these guidelines do not take into consideration other clinically relevant criteria, for which individual DOACs may have different levels of strength. Third, in HMC, there is no structured stepwise method to follow when the pharmacy and therapeutic committees review particular criteria to judge a medication; thus, the formulary inclusion process can be arbitrary. Therefore, the formulary decision can be influenced by conflicting interests, limited personal experience, and/or industry sponsor

marketing.

1.9 Synopsis of thesis rationale and objectives

This thesis is designed to generate a comprehensive MCDA measurement of the total benefits of DOACs for different indications. We included an evaluation of the value of DOACs for all patient populations who are candidates for DOAC treatment, which makes the results valuable for informing both formulary and prescription decisions. Four DOACs were compared (dabigatran, rivaroxaban, apixaban, edoxaban), rendering their dosing recommendations for VTE treatment and prophylaxis, and stroke prevention in patients with NVAF worldwide.

The objective of this thesis is to generate a comprehensive MCDA measurement of the total benefits and risks of DOACs for their approved indications. These indications are: stroke prevention in NVAF patients, VTE acute treatment, extended prevention of recurrent VTE, primary prevention of VTE in high-risk hospitalized patients, and after total hip or knee replacement surgeries. DOACs compared in the MCDA model include dabigatran, rivaroxaban, apixaban, edoxaban.

The resulting contribution of this thesis is twofold. First, this is the first MCDA to compare DOACs with all of their approved indications over a wide range of criteria and sub-criteria that fulfill the requirements of the MCDA model [5,6]. The second contribution is the adoption of a weighting methodology based on ranking, which allows the prioritization of criteria based on their impact on patients prescribed DOACs from the prescriber's point of view.

Chapter Two: A LITERATURE REVIEW

The mainstay anticoagulants before 2010 were warfarin, heparin, LMWH, and fondaparinux (120). In 2010, dabigatran was introduced to the market as the first DOAC followed by rivaroxaban, apixaban, edoxaban, and betrixaban. Since then, the anticoagulation landscape has gradually changed. As discussed in **Chapter One**, DOACs comprise several advantages compared with the gold standard anticoagulant, warfarin, including a fixed dosing regimen, reduced drug–drug and food-drug interactions, and no need for regular monitoring of the INR. However, DOACs are associated with an increased risk of gastrointestinal adverse drug events (dabigatran and rivaroxaban), lack of easily monitored surrogate markers, and a higher acquisition cost (121). DOACs are currently used for stroke prevention in NVAF patients, VTE acute treatment, extended prevention of recurrent VTE, and secondary prevention of VTE in high-risk hospitalized patients and after total hip or knee replacement surgeries.

2.1 Economic evaluation of OAs for stroke prevention

Different anticoagulated medications have been used for stroke prevention in patients with NVAF such as warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban. An economic evaluation study by Gage et al. (1995) compared warfarin and aspirin (122). A lifelong Markov model was used, and the probabilities of the clinical outcomes were derived from published clinical trials (123–126). Results showed that treatment with warfarin dominates aspirin (less expensive and more effective), with an ICER of USD 8000 per QALY in high-risk stroke patients with one additional risk factor for stroke, and USD 370,000 per QALY without additional risk factors for stroke (122). The authors concluded that in patients with NVAF and one or more risk factors, treatment with warfarin is cost effective.

A CEA was conducted by Freeman et al. (2011) in the US to evaluate the clinical and economic impact of dabigatran compared with warfarin in NVAF patients with moderate-to-high risk for stroke (127). A lifelong Markov model was used, and the probabilities of the clinical outcomes were obtained from the RE-LY trial (43). The results illustrated that dabigatran 110 mg and 150 mg were more cost effective compared with warfarin, with ICERs of USD 51,229 per QALY and USD 45,372 per QALY, respectively (127).

Another CEA was conducted by Shah et al. (2011) to compare between dabigatran 150 mg, dabigatran 110 mg, aspirin, warfarin, and dual therapy (aspirin and clopidogrel) for stroke prevention in AF patients (128). The marginal cost per QALY in the base case analysis for dabigatran 110 mg and dabigatran 150 mg against warfarin was USD 150,000 per QALY and USD 86,000 per QALY, respectively. Compared with aspirin, dabigatran 110 mg, dabigatran 150 mg twice daily, warfarin, and dual therapy, the marginal cost per QALY was USD 66,000 and USD 50,000, USD 12,500, and USD 99,000, respectively (128). The author concluded that in AF patients with an average major bleeding risk of 3% per year, the cost-effective treatment relied on the risk of stroke. Aspirin was cost-effective in patients with low stroke risk, warfarin was cost-effective in patients with a moderate risk of stroke, and dabigatran 150 mg twice daily was cost-effective in patients at high risk of stroke. Both dabigatran 110 mg and dual therapy were not cost-effective.

A third CEA by Kamel et al. (2012) aimed to compare both the cost QALYs between dabigatran 150 mg twice daily and warfarin treatments in NVAF patients with a history of stroke or transient ischemic stroke (129). From the base-case analysis, dabigatran costs USD 9,000 with 0.36 additional QALYs and an ICER of USD 25,000. The authors concluded that treatment with dabigatran 150 mg twice daily was cost-

effective compared with warfarin in NVAF patients with a prior history of stroke or TIA (129).

In the US, Lee et al. (2012) sought to assess both clinical and economic aspects of rivaroxaban and adjusted-dose warfarin for stroke prevention in NVAF patients (130). A lifelong Markov model was used, and the probabilities of the clinical outcomes were derived from the ROCKET-AF trial (54). Results showed that patients treated with rivaroxaban lived a 10.03 average QALYs with USD 94,456 lifetime treatment cost, compared with 9.81 QALYs and 88,544 lifetime treatment cost treatment with warfarin. The rivaroxaban ICER was USD 27,498/QALY. The authors concluded that treatment with rivaroxaban might be cost-effective compared with dose-adjusted treatment with warfarin for stroke prevention in NVAF patients.

Another CEA by Kim et al. (2019) in Korea was conducted to evaluate the cost and effect of rivaroxaban compared with warfarin (131). A Markov model was performed, and it was based on data from the Korean Health Insurance Database. Results showed that patients treated with rivaroxaban lived an average of 11.8 QALYs with a lifetime cost of USD 20,886, compared with 11.4 QALYs and a USD 17,151 lifetime treatment cost with warfarin. Rivaroxaban was cost-effective compared with warfarin, with an ICER of $9,707/QALY.

Lee et al. (2012) conducted a CEA to evaluate apixaban compared with aspirin in AF patients at high risk of stroke and low risk of bleeding (132). One-year simulation and lifelong Markov models were constructed relying on clinical outcome probabilities from the AVERROES trial (133). The one-year base-case results illustrated that the cost per patient was USD 3,454, with 0.96 QALYs gained for apixaban, compared with a USD 1,805 cost per patient and 0.96 QALYs gained for aspirin. In the Markov model, the cost per patient was USD 44,232, with 6.87 QALYs gained in the apixaban group,

and USD 50,066 with 6.51 QALYs gained for the aspirin group.

Another CEA conducted by Lee et al. (2012) aimed to compare the clinical and economic outcomes of apixaban versus warfarin. Clinical outcome probabilities were obtained from the ARISTOTLE trial (72). In the base-case analysis, the total cost per patient was USD 86,007, with 11.6 QALYs gained for apixaban, compared with a total cost per patient of USD 94,941 and 10.69 QALYs gained for warfarin. The authors demonstrated that treatment with apixaban was dominant compared to warfarin (134).

A study by Deitelzweig et al. (2012) in the US aimed to assess the medical cost reduction of apixaban, dabigatran, and rivaroxaban compared with warfarin (excluding drug acquisition costs). Over the one-year analysis, treatment with apixaban instead of warfarin was associated with the highest medical cost reduction of USD -485, compared with USD -179 for dabigatran and USD -89 for rivaroxaban (135).

Magnuson et al. (2015) conducted a CEA in the US to evaluate edoxaban versus warfarin for stroke prevention in patients with NVAF (136). A lifelong Markov model was constructed based on clinical outcome probabilities from the ENGAGE AF-TIMI trial (73). Edoxaban was associated with an incremental lifetime cost of USD 16,384 and 0.44 QALYs. Edoxaban was cost-effective compared with warfarin, with an ICER of USD 36,862 per QALY (136).

In another study by Miller et al. (2016) in the US, edoxaban (60 mg/30 mg dose-reduced) was compared with rivaroxaban (20 mg/15 mg dose-reduced) in NVAF patients with moderate to high risk of stroke (137). A lifelong Markov model was used with probabilities derived from the ENGAGE AF-TIMI and ROCKET-AF trials. Results showed that edoxaban (60 mg or 30 mg reduced dose) once-daily treatment was cost-effective and cost-saving compared with rivaroxaban in NVAF patients with a moderate-to-high risk of developing stroke (137).

2.2 Economic evaluation of OAs for the treatment of VTE

In terms of DOACs' cost-effectiveness and cost-benefit for VTE treatment, numerous studies and systematic reviews have compared them with warfarin (116,138–145). In general, all studies used clinical trials that compared DOACs versus warfarin as primary sources of clinical input data. These trials were for dabigatran (RE-COVER, RE-COVER II, and RE-MED) (47,74,75), rivaroxaban (EINSTEIN, EINSTEIN-DVT, EINSTEIN-PE) (54,76,77), apixaban (AMPLIFY, AMPLIFY-EXT) (45,146), and edoxaban (Hokusai-VTE) (46).

Amin et al. (2014, 2015, 2016) concluded in each of their three studies that variations in both VTE and major bleeding had the highest impact on medical cost differences in terms of total medical cost differences and avoidance between DOACs, standard therapy, and placebo (147–149). Al-Saleh et al. (2017) reported that fatality rates in the short run and pharmaceutical care were the highest determinants of uncertainty in the conducted analysis (150). Quon et al. (2014) concluded that both major and clinically relevant non-major bleeding events were the main drivers for apixaban being the cost-effective choice among other DOACs (151). Lanitis et al. (2016) reported that apixaban would not be considered a dominant choice when the differential price between other DOACs and apixaban was increased, and when the relative risk of recurrent VTE was reduced for rivaroxaban versus apixaban from the baseline 1.08 to 0.69 (152).

The measures used to assess the cost effectiveness of DOACs were not the same between the different studies. The majority of studies (n=4) mainly used the cost per QALY measure, including the total cost calculations (150–153). Jurgin et al. (2016) reported that dabigatran for 6-month therapy was dominant when compared with 3-, 6-, and 12-month treatment with rivaroxaban in a cohort of 10,000 patients (153).

The dominance of dabigatran over rivaroxaban (having lower cost and higher QALY) was consistent in VTE treatment, extended anticoagulation, and index DVT and PE treatment. A similar trend was observed in their study evaluating the VTE treatment and extended anticoagulation indication and for index DVT and PE treatment over 6 months of therapy among a cohort of 10,000 patients for both dabigatran and rivaroxaban, where dabigatran also dominates rivaroxaban in all these settings. In a 6 month evaluation of VTE treatment over a patient's lifetime, Lanitis et al. (2016) reported apixaban to be dominant over both rivaroxaban and LMWH/dabigatran, with total costs of £4,696, £4,731, and £4,792 for each, respectively. Apixaban did not dominate LMWH/warfarin, with apixaban costing £2,520 over the latter per QALY.

Overall, the per-patient treatment, administration, and monitoring costs were lower for apixaban by £11 and £45 than for rivaroxaban and LMWH/dabigatran, respectively. In a study by Quon et al. (2014), the total lifetime costs per patient with up to 18 months of DOACs or 6 months of enoxaparin/warfarin were reported. Apixaban had lower costs and longer survival or higher QALYs than enoxaparin/warfarin, rivaroxaban, and dabigatran. Al Saleh et al. (2017) reported the comparative cost/QALY among the therapies LMWH/VKA, LMWH/dabigatran, rivaroxaban, and apixaban, with apixaban dominating other DOACs with an ICER of $84.08 relative to LMWH/VKA. Furthermore, at a discount rate of 0%, apixaban dominates other strategies, and with a 3% discount rate, apixaban dominates other DOACs with an ICER of $36.79 relative to LMWH/VKA. In a different analysis of 3 months of therapy and for a lifetime duration of anticoagulation therapy, apixaban dominated other DOACs with an ICER relative to LMWH/VKA of $7,379.66 and $174,614.23, respectively. However, over 12 months of therapy, apixaban dominated all other treatments.

Two studies reported annual total medical cost avoidance as the primary measure (147,148). Amin et al. (2015) reported the annual total medical cost avoidance associated with DOAC use compared with a placebo as $2,794, $2,948, $4,249, and $4,244 per patient year (ppy) for VTE patients treated with dabigatran, rivaroxaban, apixaban 2.5 mg, apixaban 5 mg, respectively, with the highest cost avoidance associated with apixaban 2.5 mg, followed by apixaban 5 mg. They also observed a similar trend in a different study (2016), where they reported annual total medical cost avoidance for VTE treatment with DOACs versus warfarin ppy as follows: USD 572, USD 2,971, USD 4,440, and USD 1,957 with dabigatran, rivaroxaban, apixaban, and edoxaban, respectively. Reporting the total medical cost differences as the outcome measure in a third study, Amin et al. (2014) reported that the use of DOACs in comparison with standard therapy was associated with overall medical cost differences of USD 146, USD 482, USD 918, and USD 344 for VTE patients treated with dabigatran, rivaroxaban, apixaban, and edoxaban, respectively, with the highest cost differences associated with apixaban. When treatment duration was normalized, the annual total medical cost differences were USD 153, USD 454, USD 1108, and USD 261 for a patient with VTE treated with dabigatran, rivaroxaban, apixaban, and edoxaban, respectively, also with the highest cost differences associated with apixaban.

2.3 Economic evaluation of OAs for the prevention of VTE after TKA and THR

A systematic review conducted by Brockbank et al. (2017) aimed to assess the economic evaluation of DOACs for VTE prevention after TKA and THR, and included 16 relevant studies (138). The study concluded that DOACs are always dominant compared to LMWH. The difference in the incremental QALYs was generally small, with no clinical significance. However, compared with LMWH, the reduced cost of

drug administration of DOACs was the driving factor for DOACs being more cost-effective than LMWH. Studies that used a short duration of drug administration generally resulted in DOACs not being a cost-effective choice. When DOACs were compared against each other, dabigatran was the least cost-effective choice, while rivaroxaban was the most cost-effective choice, and apixaban was in between. The cost savings of both rivaroxaban and apixaban were derived from the improved prevention of VTE compared with dabigatran, which was more pertinent (138).

2.4 Multi-criteria decision analysis among OAs

The process of choosing the most appropriate OAs to use for stroke prevention in NVAF patients is difficult because of the different treatment options available, which vary in their clinical effects and other non-clinical characteristics. The MCDA model has been used effectively in several studies to evaluate multiple conflicting criteria in the decision-making process regarding the use of the most appropriate OAs in NVAF patients. Jason et al. (2015) reported the net clinical benefit of DOACs (dabigatran, rivaroxaban, apixaban) and warfarin for the prevention of stroke in NVAF patients (154). Two main criteria were used in the MCDA model, which were risk criteria and benefit assessment criteria. The benefit assessment criteria included the prevention of ischemic stroke and systematic embolism, while the risk assessment included both ICH and extracranial bleeding. These two criteria were assessed in four different scenarios: (1) general population, (2) high-risk stroke patients, (3) primary prevention of stroke, and (4) secondary prevention of stroke. The study concluded that dabigatran 150 mg had the highest performance score (0.529) in the general population scenario, followed by rivaroxaban (0.462), apixaban (0.426), and lastly warfarin (0.191). In the primary prevention scenario, dabigatran 150 mg also had the highest performance score, while dabigatran 110 mg had the highest performance score in the secondary prevention

scenario compared with rivaroxaban, apixaban, and warfarin. Apixaban had the highest performance score (0.686) in the high-risk stroke patients compared with dabigatran 150 mg (0.462), dabigatran 110 mg (0.392), rivaroxaban (0.271), and warfarin (0.116).

Jose et al. (2018) assessed the benefit, risk, and cost of DOACs and warfarin for stroke prevention in AF patients using the MCDA model (155). The benefit criteria included both a reduction in stroke and all-cause mortality, while the risk criteria included ICH and GI hemorrhage, minor bleeding, and MI. The cost criteria included clinical events from a payer perspective, and along with event probabilities, both were derived from a study by Harrington et al. (117). The weight of each criterion was based on expert opinion using a scale from 1–100. The relative weight for each criterion was 40.4, 51.1, and 8.5 for benefit, risk, and cost, respectively. They concluded that apixaban had the highest score of 33, followed by dabigatran with 25, warfarin 18, and finally rivaroxaban with a score of 14 (155).

Tommi et al. (2017) compared DOACs and warfarin for stroke prevention in NVAF patients using the MCDA model (156). Two criteria were evaluated in the model: the clinical events and other criteria. The clinical events criteria included ischemic stroke, systemic embolism, MI, ICH (excluding HS), HS, GI hemorrhage, other major bleeding, nonmajor bleeding, and dyspepsia. The other criteria include real-world evidence, interaction with food, administration frequency, and the availability of treatment reversal agents. They concluded that dabigatran was the best DOAC, with an overall value of 0.69, followed by apixaban 0.65, edoxaban, rivaroxaban, and lastly, warfarin with an overall score of 0.43 (156).

Nevertheless, OAs evaluation in previous MCDA studies focused only on a limited number of criteria in treatment performance, and incorporated only a subset of available DOACs, while mortality rates were double counted (154–158).

Chapter Three: METHODOLOGY

3.1 Development of the MCDA

The MCDA method in this thesis progressed through eight sequential stages (159), which took place within the years 2018 and 2019. All the HMC study sites, institutional review board (IRB), and medical research center approvals were obtained as appropriate (Appendix 1).

To oversee the undergoing of the different MCDA method stages, including in relation to data analysis and interpretation, a specialized expert panel was constituted. The panel consisted of a health economist, pharmacy and therapeutic committee member, hematologist, clinical pharmacist specialist, anticoagulation clinical pharmacist, internist, and cardiology consultant, adding to seven panel members in total. The practitioner panel members are currently HMC based, with expert-level personal experiences and knowledge in relation to the use of DOACs, including those used in HMC. The panel did not provide study inputs, but only confirmed the appropriateness of how the different aspects of the MCDA method were carried out, vide infra. The questioning approach of the panel members was via face-to-face meetings. The group meeting format is an efficient and suitable method of communication since it is less time consuming compared to other relevant methods, such as the Delphi method, which demands that a revised set of questions are to be frequently recirculating among the same members until agreement. Furthermore, decisions made through meetings are transparent, do not require written and communication skills, and do not require maintaining the confidentiality of members.

3.1.1 The decision problem (stage one)

In this thesis, the decision problem was a sorting type of problem, in which MCDA creates an assignment of alternatives to categories in a predefined order. The

alternatives are the DOACs, and the sorting problem objective is to assign each of the DOACs to one of three categories: formulary, non-formulary, and rejected.

3.1.2 Alternatives in the decision problem (stage two)

The included DOACs are those currently available in the HMC formulary (i.e. dabigatran, rivaroxaban, and recently apixaban), and those that are not still available (i.e. edoxaban). All DOACs are analyzed as per their proprietary formats.

3.1.3 Establishing the DOACs selection criteria (stage three)

Based on relevant published literature (160–164), including formulary management guidelines and the American Society of Health-System Pharmacists (ASHP) guidelines that contain elements of drug evaluation (165), a draft list of the selection criteria regarding the use of DOACs was created. A list that was eventually confirmed via a series of meetings and discussions that were conducted with the expert panel of the study. A selection criterion is a targeted characteristic, against which the DOAC's ability to achieve the characteristic is evaluated as part of making the decision about the selection of the DOAC. The selection criteria list comprises main as well as sub-type criteria.

3.1.4 Measurement of target achievement, i.e. level of performance (stage four)

Following the development of the selection criteria, a comparison between DOACs against each main and sub-criterion of the selection criteria was made. The basis of this comparison was the level at which each DOAC comparatively achieved (or satisfied) each of the targeted main criteria and sub-criteria. Important, is that this comparision was evidence based, before was also confirmed by the expert panel. The full available weight score of each selection criterion, to reflect the significance of the criterion, is determined in the later stages of the methods.

The main criterion of clinical efficacy has several sub-criteria that reflected the approved indications that DOACs possibly had in a major market such as Food and Drug Administration (FDA) or EMA, also taking in consideration any off label use based on well designed and high-quality randomized control trials (RCTs) or sub-group analysis of pivotal trials or case reports. Measurement of a DOAC's achievement (or performance) level against each indication was quantified by assigning to the DOAC the full criterion weight score (i.e. 100% of the criterion weight score to be later determined in stage 5) available for the indication if the DOAC had an official approval (FDA, EMA) for that clinical indication. A 0.5 and zero proportion of the full criterion weight score was assigned to DOACs if there is medium-/high-quality RCT in support of off label use, and if there is no official approval or low-quality RCT or neither, respectively.

For the safety main criteria, the measurement of DOACs performance level against the lack of individual adverse events (sub-criteria) was derived from a network meta-analysis, by López-López et al (2017), of DOACs trials for stroke prevention in NVAF patients, where safety outcomes are reported in terms of HR for each DOAC in comparison to warfarin (143). The HR was then inverted (1/HR) in order to measure the performance of DOACs in terms of their benefits. The calcuated relative fraction reflected the comparative ability of DOACs, out of 1, in preventing an adverse event of interest. The López-López et al study provided safety data of DOACs as it analyzed them for the prevention of stroke in AF with the objective of comparing the efficacy, safety, and cost effectiveness of DOACs. The study was deemed to be a best source of comparative safety data as it included 23 published RCTs with 94,656 patients to evaluate the use of DOACs, VKA, and antiplatelet drugs for stroke prevention in AF patients. Out of the 23 included RCTs, 13 were comparing between a DOAC and

warfarin. It was assumed that the safety data for DOACs based on this meta-analysis is sufficient to reflect the overall safety of DOAC use. This is based on the fact that stroke prevention in NVAF is the first, common, and main indication for all DOACs, and requires life-time treatment which would reflect and represent an estimate of all possible adverse events concerning the use of DOACs. HS data was obtained from another systematic review and meta-analysis, by Al mutairi et al (2017, of DOACs trials for stroke prevention in NVAF patients, where safety outcomes are reported in terms of HR for each DOAC in comparison to warfarin (166). The study was deemed to be the best source of comparative safety data of HS as it included six published RCTs to evaluate the use of DOACs for stroke prevention in AF patients. In regards to gastrointestinal (GI) side effects, excluding GI bleeding, data were obtained manually from each of the DOACs' pivotal trials from www.clinicaltrials.gov (dabigatran; NCT00262600, rivaroxaban; NCT00403767, apixaban; NCT00412984, edoxaban; NCT00781391). The GI related side effects of interest were serious and non-serious dyspepsia, diarrhea, abdominal pain, and constipation.

Regarding regimen flexibility as a main criterion, this comprised two sub-criteria of interest, which are 'the lack of need of bridging at initiation' and the 'lack of need for complicated regimen at initiation'. How a DOAC performed gainst a sub-criterion was calculated based on its performance under each of different categories in relevance to the sub-criterion. If a DOAC fulfills the category requirement, it was assigned a score of one, and zero score if it does not. The sum of the final categories' performance scores was converted to a score out of one (full weight of the sub-criterion) that reflected the performance of the DOAC against the sub-crriterion in overall. For example, a DOAC with four approved indications will have its 'the lack of need of bridging at initiation' sub-criteria including four categories, and if the DOAC does not

require bridging at initiation in three indications, it will score three out of four. Then, this will be converted into a score out of one (3/4 = 0.75). The overall performance of the DOAC against the 'the lack of need for bridging at initiation' sub-criterion is, therefore, a 0.75 proportion of the full available score of the sub-criteria. The drug information section from the UpToDate database, by Wolters Kluwer (www.uptodate.com), was used to evaluate the DOACs regimen flexibility, as confirmed by the panel (167–170).

A similar approach was followed regarding the special population requirements as another main criterion, which included 'lack of need for dose adjustment based on renal function', 'lack of need for dose adjustment in impaired liver function', and the 'availability of evidence-based dose adjustment in elderly' sub-criteria. For the dose adjustment based on renal function sub-criterion, the overall performance score was calculated according to the fulfillment of six categories, based on the glomerular filtration rate (GFR); > 95, 50-95, 30-50, 15-30, >15, and hemodialysis (HD), which was for two main indications; stroke prevention in NVAF patients and VTE treatment. Those two indications comprise the majority of the dosage regimens of DOACs, thus, we assumed they would be sufficient to measure DOACs performance in regard to the lack of need for dose adjustment based on renal function sub-criterion. The performance against each category was based on the performance under two sub-categories; if the DOAC can be used and if no dose adjustment is required. If the DOAC fulfills the sub-category, it was assigned a score of one, and zero if it does not. Eventually, based on the two sub-categories assessments, under each of the six categories, and for both the main indications of interest, a DOAC received a cumulative score out of 24. This final score is then converted to a score out of one, which reflected the full available performance score weight of the 'dose adjustment based on renal function' sub-

criterion. The dose adjustment in the liver impairment sub-criterion was calculated according to the Child-Pugh classification of liver impairment. Performance weight score of the sub-criteria was based on performance against three categories; Child-Pugh classes A, B, and C. A DOAC was assigned a category score of one, 0.5, and zero, if it can be used without dose adjustment, if it requires dose adjustment or need to be monitored, and if it is contraindicated or not recommended to use, respectively, with total possible score of three. The final score is then converted to a proportion out of the full available performance weight score of the sub-criterion. Furthermore, the panel reviewed available evidence for each DOAC for use in elderly patients and based on the number, strength, and quality of evidence, full or zero performance weight scores was assigned to DOACs, accordingly. The drug information section from the UpToDate database, by Wolters Kluwer (www.uptodate.com), was used to evaluate the DOACs used based on renal function and in liver impairment, as confirmed by the panel (167–170).

Ease of switching between different anticoagulants was also a main criterion of interest in the MCDA model. These switching patterns included switching from DOAC to DOAC, warfarin/anticoagulant to DOAC, and DOAC to warfarin/anticoagulant. Full criterion performance weight score was assigned to DOACs that do not require any other anticoagulant medication or require at least one anticoagulant medication during the switching process, and a zero criterion score was assigned if the DOAC requires two or more other anticoagulant medications during the switching, as confirmed by the panel of experts. The drug information section from the UpToDate database, by Wolters Kluwer (www.uptodate.com), was used to evaluate the DOACs ease of switching, as confirmed by the panel. (167–170).

Pharmacokinetic properties as a main criterion were based on the interaction between DOACs and CYP3A4 and P-glycoprotein (Pgb) enzymes, either as inducers or inhibitors of these enzymes, with a total of four sub-criteria. A DOAC was assigned a performance weight score 1, or 0.75, 0.25, or zero of it, if it does not interact with the enzymes, if it requires therapy monitoring, if it requires dosage modification, and if it should be avoided, respectively. The drug information section from the UpToDate database, by Wolters Kluwer (www.uptodate.com), was used to evaluate the DOACs drug interaction, as confirmed by the panel (167–170).

The performance against main criteria with no sub-criteria, which involved the dosage frequency, availability of approved reversal agent, administration as a crushed tablet, and pharmacokinetic properties, was measured by assigning a DOAC the full available weight score (100% of it) or zero of it, based on whether the DOAC fulfilled the selection criteria or not, respectively. The drug information section from the UpToDate database, by Wolters Kluwer (www.uptodate.com), was used to evaluate these criteria, as confirmed by the panel (167–170).

3.1.5 Scoring and weighting the target achievement level (i.e. the available score weight for a criterion) (stage five)

The purpose of the scoring method is to allow comparable target accomplishment measures for distinctive goal criteria, using the score estimate as a measure involving a multidimensional evaluation of alternate options (171). In other words, this is to develop the full available score weight for each of the criteria, against which the performance of the DOACs was assessed as discussed in the above stage four of the method. This constituted asking HMC practitioners to score the importance of each main and sub-criterion and then calculating the available full score weight for each.

3.1.5.1 Survey questionnaire

Throughout a number of meetings with the expert panel, target criteria were drafted to build up a scoring model that includes main and sub-criteria. To ensure face and content validity, the survey was reviewed by academics in pharmacy practice at the college of pharmacy, Qatar University. After that, the survey was piloted by a group (n=20) of clinical pharmacists, internists and cardiologists. The piloting group was asked to make comments on clarity, organization and content of the questionnaire. Taking into consideration these comments and discussing them with the panel members, the scoring questionnaire was re-drafted into a final version that was distributed electronically via SurveyMonkey, and by hand. Survey questionnaire IRB approval by HMC and research info sheet can be seen in Appendix 2. Moreover, the survey questionnaire draft can be seen in Appendix 3.

The target population of the survey questionnaire included specialist and consultant physicians in the emergency, internal medicine, cardiology, pharmacy, and orthopedic surgery departments at three HMC sites; Hamad general hospital (HGH), Al Wakra hospital (AWH), and heart hospital (HH). A list of the exact targeted individuals were provided by relevant administrative departments at the sites. The respondents were asked to rank pre-identified main criteria according to how important each criterion is for them to consider when prescribing or selecting DOACs, with '1' as most important. Following the ranking of the main criteria, respondents were asked to rank the importance of each sub-criteria of the main criteria as having high, medium, low, or no importance level as part of the relevant main criteria. Respondents' anonymity and confidentiality were insured since answers were fully unidentified except for specialty, department, and hospital.

3.1.5.2 Target criteria weighting

Target criteria weighting objective is to calculate the extent to which a criterion defined score contributes to the measurement of the final score of a DOAC, based on the principles of developing MCDA models (171,172). For every criterion and sub-criterion, and based on the scores of main criteria and sub-criteria provided by the questionnaire respondents, comparative scores were calculated from 1000 points for the ease of handling as follows: relative weight of a main criterion = (mean score response of the main criterion / sum of means for all main criteria) * 1000. Sub-criterion relative weight was obtained from a similar approach: relative weight of a sub-criterion = (mean score response of the sub-criterion / sum of means of all sub-criteria in the relevant main criterion) * (relative weight of the main criterion).

Eventually, a pharmacotherapeutic scoring model was finalized, comprising the selection criteria list with relative weight for each (i.e. the available score against which the performance of DOACs was assessed in stage four). Based on the calculation methods of relative criterion, it is essential to emphasize that changing the score values of the different levels of criterion importance (e.g. 2 to 12 instead of 1 to 11) has no effect on the results of the study. Regardless of the different scores values used, the important is to maintain equal differences among the different score values used to reflect the levels of importance.

3.1.6 Aggregation of measurement results (stage six)

The aggregation of sum weights was used in the MCDA model of this thesis. The DOAC final score comprised the sum of weighted scores of all target criteria that the DOAC achieved.

In order to account for possible variations and uncertainty in the scores that are provided by individuals, the base case of the model was run through a multivariate

analysis; whereby, the Monte Carlo simulation was used to run the MCDA model while assigning an uncertainty range to each of inputs that are deemed to be most uncertain. The Monte Carlo simulation is a technique that enables re-running the model several times, wherein in each re-run, the value of an input is randomly sampled from a predefined uncertainty range of input values. In the current model, the random sampling of input values from uncertainty ranges was happening for all uncertain inputs in the model simultaneously, to simulate real-life interactions among uncertainties of inputs.

The Monte Carlo simulation was conducted via @RISK 5.5 (Palisade Corp, Ithaca, New York). The predefined inputs range of the base-case model multivariate uncertainty in this model was set at ±2 survey responses in relevance to each of the criteria. The Monte Carlo simulation was based on 1000 iterations, with a triangular type of distribution of how random values were selected from the uncertainty range of an input.

3.1.7 DOAC selection (stage seven)

According to the pharmacotherapeutic total selection scores, the expert panel ranked DOACs. DOACs were then sorted to be recommended for formulary inclusion that includes only DOACs that score 95% of the highest scoring DOAC. DOACs with a total score of 90%, but less than 95%, of the highest DOAC scoring will also be considered, however, as a non-formulary alternative. The remaining DOACs, with lesser than 90% of the highest scoring DOAC, did not progress. These different indicators of the formulary categories distribution was based on published literature (164,173).

3.1.8 Sensitivity analysis (stage eight)

While high statistical confidence was associated with the weighting of the scores in the model, given the high response rate (see Results section of the thesis),

sensitivity analyses were conducted to further investigate the robustness of the study's conclusions.

3.1.8.1 One-way sensitivity analyses

One-way sensitivity analysis is conducted to assess the sensitivity of the study conclusion to main model inputs of interest, one input at a time. In the current model, the two main criteria of dosage frequency and the availability of an approved reversal agent were weighted highly by practitioners, while the performance of DOACs against them vried considerably. The stand-alone influence of each of these two main criteria on the final pharmacotherapy rank of DOACs was, therefore, of particular interest. In the one-way sensitivity analysis, the MCDA model was re-run twice, with each of the two main criteria removed from considerations in each separate run. When doing so, in each run, the available weight for each remaining main and sub-criteria in the model was adjusted accordingly.

3.1.8.2 Multivariate sensitivity analyses

A multivariate sensitivity analysis was conducted in this thesis. This is to investigate the sensitivity of the model outcome to several model inputs while maintaining real-life interaction among the uncertainties of the inputs. Safety probabilities were derived from a meta-analysis that used data from DOACs pivotal trials with DOACs being compared against warfarin. Such probabilities contain uncertainty since they are not derived from head-to-head comparisons between DOACs. Uncertainty in the performance of DOACs against the lack of drug interactions and the need for dose adjustment in special populations (i.e. renal and hepatic impairment patients) were also considered of interest. Many drugs can affect both CYP 450 and Pgb enzymes at the same time, and there is no clear cut or solid evidence for the use of DOACs in the renal and hepatic impaired patients. In the current mode,

therefore, a multivariate sensitivity analysis was conducted by assigning ±10% variability to all safety, drug interactions, and the need for special population dose adjustments DOACs performance scores in the model.

The Monte Carlo simulation was used for the purpose of the multivariate sensitivity analysis, with iterations and a type of value selection distribution that are identical to those performed at the base-case model.

3.1.8.3 Scenario sensitivity analysis

As already indicated above, the probabilities of DOACs performance in relation to the safety profile were obtained from a meta-analysis, by López-López et al (2017), which derived data from DOACs pivotal trials with DOACs being compared against warfarin. Results from this, therefore, is not based on head-to-head data of DOACs.

As a scenario analysis in the current model, the comparative MCDA of DOACs was re-performed but with replacing the study, by López-López et al (2017), with the meta-analysis by Douros et al (2019) (174). While, unlike the former, the latter meta-analysis only included three of the model's DOACs (dabigatran, rivaroxaban, and apixaban), and the included studies were observational cohort studies, and reported safety results based on head-to-head studies of DOACs. To note, the meta-analysis by Douros et al (2019) included only results in relation to major bleeding, ICH, HS, and GI bleeding adverse events. It did not include results in relation to GI related side effects. Thus, these adverse events (GI-related adverse effects excluding GI bleeding and minor bleeding) which were identified as sub-criteria in our base-case model were not included in the scenario sensitivity analysis.

Chapter Four: RESULTS

4.1 Selection criteria results

The list of selection criteria was developed based on literature review and validated by the expert panel through several meetings (80,154–156,175–182). The final selection criteria comprised 10 main criteria and 28 sub-criteria. The main criteria were:

1) Administration of the medication as crushed tablets
2) Availability of a specific and approved reversal agent
3) Clinical efficacy (e.g., stroke prevention, recurrent VTE)
4) Dosage frequency (e.g., once or twice daily)
5) Drug interaction (e.g., CYP3A4 and/or Pgp inducers/inhibitors)
6) Ease of switching during treatment (e.g., from warfarin/parental to DOAC)
7) Pharmacokinetics properties (e.g., administration flexibility in regard to food)
8) Regimen flexibility (e.g., lack of need for bridging at initiation)
9) Safety (e.g., hemorrhagic stroke, gastrointestinal hemorrhage etc...)
10) Special population requirements (i.e., dose adjustment in elderly).

The administration as a crushed tablet, availability of a specific and approved reversal agent, dosage frequency, and pharmacokinetics properties main criteria did not have any sub-criteria. Further details related to the identified criteria and sub-criteria are summarized in Table 4-1.

Table 4-1: Selection criteria and sub-criteria

Criterion	Sub-criterion
Administration as a crushed tablet	N/A
Availability of reversal agent	N/A
Clinical efficacy	Cancer-associated thrombosis Extended prevention of recurrent VTE HIT Prevention of VTE post TKA/THR Recurrent VTE in APLAS Recurrent VTE in other thrombophilia conditions Secondary prevention of myocardial infarction Secondary prevention of stroke in patients with NVAF and PCI Stroke prevention in NVAF Treatment of VTE including DVT and PE
Dosage Frequency	Once vs twice-daily dosing
Drug Interaction	Lack of CYP3A4 inducers Lack of CYP3A4 inhibitors Lack of Pgp inducers Lack of Pgp inhibitors
Ease of switching	From DOACs to DOACs From DOACs to warfarin/parenteral From warfarin/parenteral to DOACs
Pharmacokinetic properties	Administration flexibility in regard to food
Regimen Flexibility	Lack of need for bridging at initiation Lack of need for complicated regimen at initiation
Safety	GI bleeding GI-related side effects excluding GI bleeding HS ICH excluding HS Other major bleedings Minor bleeding
Special population	Availability of evidence-based dose adjustment in elderly Dose adjustment based on renal function Dose adjustment in impaired liver function

APLAS: Antiphospholipid antibody syndrome; DOACs: Direct oral anticoagulants; GI: Gastrointestinal; HIT: Heparin induced thrombocytopenia; VTE: Venous thromboembolism; PE: Pulmonary embolism; DVT: Deep vein thrombosis; NVAF: non-valvular atrial fibrillation; PCI: Percutaneous coronary intervention; CYP3A4: Cytochrome P450 3A4; Pgb: P-glycoprotein; HS: Hemorrhagic stroke; ICH: Intracranial hemorrhage.

4.2 Survey questionnaire results

As mentioned in **Section 3.1.5.1**, the survey was piloted by a group (n=20) of clinical pharmacists, internists and cardiologists. The piloting period was from May 2019, to June 2019. Over a five-months period (from June 2019 to December 2019), 152 surveys were collected and included in the final analysis. Table 4-2 outlines the participants' characteristics. We had 106 (69.74%) of the respondents who were DOACs prescribers, and 46 (30.26%) who were clinicians and clinical pharmacists making recommendations about DOACs. The majority of the respondents were from HGH (52.63%), 36.18% from HH, and 11.19% from AWH. Out of the respondents, 32.24% were cardiologists, 28.95% were internists, 14.47% were clinical pharmacists, and 11.84% were emergency department physicians. According to these responses, criteria were weighted.

Table 4-2: Survey questionnaire respondents' characteristics

Respondent category	Number/total	Percentage (%)
Respondents role in DOAC management	152/152	100%
DOACs prescribers	106/152	69.74%
Make recommendations about DOACs	46/152	30.26%
Respondents workplace	152/152	100%
Hamad General Hospital	80/152	52.63%
Heart Hospital	55/152	36.18%
Al Wakra Hospital	17/152	11.19%
Respondents specialty	152/152	100%
Cardiologists	49/152	32.24%
Internists	44/152	28.95%
Clinical pharmacists	22/152	14.47%
Emergency department physicians	18/152	11.84%
Orthopedics	9/152	5.92%
Surgeons	5/152	3.29%
Others	5/152	3.29%

DOACs: Direct oral anticoagulants

4.2.1 Base-case model analysis results of the selection criteria

As discussed in Section 3.1.9, the base-case model was based on a multivariate simulation; whereby, main and sub-criteria base-case survey responses varied by ±2 responses. An example of implemented uncertainty ranges of criteria survey responses can be seen in Table 4-3.

Table 4-3: Sub-criteria base-case model inputs with uncertainty ranges in the multivariate analysis

Inputs of the sub-criteria importance responses from high, medium, low, not important (±2 responses)				
Criteria / Sub-criteria	**High importance**	**Medium importance**	**Low importance**	**Not important**
Clinical efficacy				
Cancer-associated thrombosis	61,63,65	58,60,62	21,23,25	4,6,8
Extended prevention of recurrent VTE	76,78,80	56,58,60	10,12,14	2,4,6
Heparin induced thrombocytopenia (HIT)	53,55,57	71,73,75	16,18,20	4,6,8
Prevention of VTE post-hip and knee replacement	55,57,59	65,67,69	23,25,27	0,1,3
Recurrent VTE in antiphospholipid antibody syndrome (APLAS)	75,77,79	47,49,51	16,18,20	6,8,10
Recurrent VTE in other thrombophilia conditions	66,68,70	62,64,66	13,15,17	3,5,7
Secondary prevention of Myocardial infarction (MI)	37,39,41	60,62,64	28,30,32	19,21,23
Secondary prevention of stroke in patients with NVAF and PCI	75,77,79	48,50,52	19,21,23	2,4,6
Stroke prevention in non-valvular atrial fibrillation (NVAF)	107,109,111	29,31,33	8,10,12	0,2,4
Treatment of venous thromboembolism (VTE) including DVT and PE	103,105,107	39,41,43	4,6,8	0,0,2
Drug Interaction				
Lack of CYP3A4 inducers	59,61,63	70,72,74	16,18,20	0,1,3
Lack of CYP3A4 inhibitors	63,65,67	70,72,74	13,15,17	0,0,2
Lack of Pgp inducers	54,56,58	71,73,75	20,22,24	0,1,3
Lack of Pgp inhibitors	67,69,71	68,70,72	9,11,13	0,2,4

Ease of Switching				
From DOACs to DOACs	38,40,42	80,82,84	22,24,26	4,6,8
From DOACs to warfarin/parenteral	42,44,46	84,86,88	16,18,20	2,4,6
From warfarin/parenteral to DOACs	54,56,58	73,75,77	15,17,19	2,4,6
Regimen Flexibility				
Lack of need for bridging at initiation	60,62,64	75,77,79	10,12,14	0,1,3
Lack of need for complicated regimen at initiation	60,62,64	75,77,79	10,12,14	0,1,3
Safety				
GI bleeding	128,130,132	18,20,22	0,2,4	0,0,2
GI related side effects excluding GI bleeding	69,71,73	64,66,68	10,12,14	1,3,5
HS	131,133,135	16,18,20	0,1,3	0,0,2
ICH excluding HS	128,130,132	19,21,23	0,1,3	0,0,2
Minor bleeding	29,31,33	79,81,83	36,38,40	0,2,4
Other major bleeding	78,80,82	62,64,66	6,8,10	0,0,2
Special population requirement				
Availability of evidence-based dose adjustment in elderly	97,99,101	45,47,49	4,6,8	0.0.2
Lack of need for dose adjustment based on renal function	92,94,96	52,54,56	2,4,8	0,0,2
Lack of need for dose adjustment in patients with impaired liver function	86,88,90	54,56,58	6,8,10	0,0,2

VTE: Venous thromboembolism; HIT: Heparin induced thrombocytopenia; TKA: Total knee arthroplasty; THR: Total hip replacement; APLAS: Antiphospholipid antibody syndrome; MI: Myocardial infarction; NVAF: Non-valvular atrial fibrillation; PCI: Percutaneous coronary intervention; DVT: Deep vein thrombosis; PE: Pulmonary embolism; CYP3A4; Cytochrome P450 3A4; Pgb; P-glycoprotein; DOACs: Direct oral anticoagulants; GI: Gastrointestinal; HS: Hemorrhagic stroke; ICH: Intracranial hemorrhage

Base-case model analysis of the main criteria results is presented in Figure 4-1 according to their mean weight score from highest to lowest.

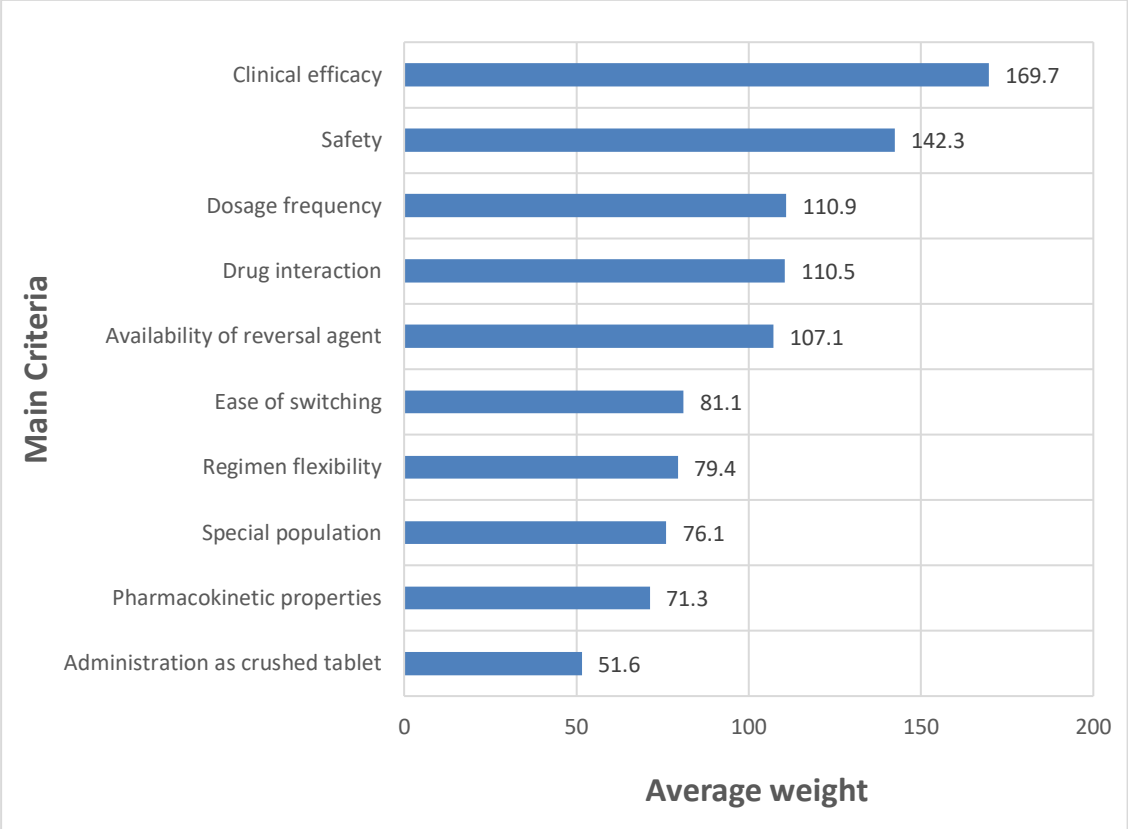

Figure 4-1: Base-case model mean weight scores of the main criteria

4.2.2 Base-case model analysis results of the sub-criteria

DOACs had ten indications of interest as sub-criteria of the clinical efficacy main criterion, with a total criterion mean weight of '169.7'. The ten clinical indications and their mean score weights are presented in Table 4-4.

Table 4-4: Clinical efficacy sub-criteria and their score weight

Sub-criterion	Mean score weight
Treatment of VTE including DVT and PE	18.9
Stroke prevention in NVAF	18.7
Extended prevention of recurrent VTE	17.5
Secondary prevention of stroke in patients with NVAF and PCI	17.2
Recurrent VTE in APLAS	17
Recurrent VTE in other thrombophilia conditions	17
Cancer-associated thrombosis	16.5
Prevention of VTE post-hip and knee replacement	16.4
Heparin induced thrombocytopenia	16.4
Secondary prevention of MI	14.4

VTE: Venous thromboembolism; DVT: Deep vein thrombosis; PE: Pulmonary embolism; NVAF: Non-valvular atrial fibrillation; PCI: Percutaneous coronary intervention; APLAS: Antiphospholipid antibody syndrome; MI: Myocardial infarction.

The safety main criterion of DOACs included six adverse events of interest as sub-criteria with a total weight of ‘142.3’. The six adverse events and their mean score weights are presented in Table 4-5.

Drug interactions of DOACs as a main criterion included four interactions of interest as sub-criteria with an overall weight of ‘110.5’. The four drug interactions of DOACs and their mean score weights are presented in Table 4-6.

The DOACs ease of switching main criterion included three switching patterns of interest as sub-criteria with an overall weight of '81.1’. The three switching patterns of DOACs and their mean score weights are presented in Table 4-7.

Table 4-5: Safety sub-criteria and their score weight

Sub-criterion	Mean score weight
HS	25.80
ICH excluding HS	25.70
GI bleeding	25.60
Other major bleeding	23.20
GI related side effects excluding GI bleeding	22.30
Minor bleeding	19.50

HS: Hemorrhagic stroke; ICH: Intracranial Hemorrhage; GI: Gastrointestinal

Table 4-6: Drug interactions sub-criteria and their score weight

Sub-criterion	Mean score weight
Lack of CYP3A4 inducers	27.4
Lack of CYP3A4 inhibitors	27.9
Lack of Pgp inducers	26.9
Lack of Pgp inhibitors	28.2

CYP3A4: Cytochrome P450 3A4; Pgb: P-glycoprotein

Table 4-7: Ease of switching sub-criteria and their score weight

Sub-criterion	Mean score weight
From DOACs to DOACs	26.3
From DOACs to warfarin/parenteral	27.1
From warfarin/parenteral to DOACs	27.8

DOACs; Direct oral anticoagulants

The regimen flexibility main criteria included the lack of need for complicated regimen at initiation and the lack of need for bridging at initiation as two sub-criteria with an overall weight of '79.3'. The two regimen flexibility sub-criteria of DOACs and their mean score weights are presented in Table 4-8.

Table 4-8: Regimen flexibility sub-criteria and their score weight

Sub-criterion	Mean score weight
Lack of need for complicated regimen at initiation	39.6
Lack of need for bridging at initiation	39.6

The special population requirements as a main criterion had an overall weight of '76.1'. The three special populations sub-criteria of DOACs and their mean score weights are presented in Table 4-9.

Table 4-9: Special population requirements sub-criteria and their score weight

Sub-criterion	Mean score weight
Availability of evidence-based dose adjustment in elderly	25.6
Dose adjustment based on renal function	25.5
Dose adjustment in impaired liver function	25

The main criteria, with no sub-criteria, of administration as a crushed tablet, availability of a specific and approved reversal agent, dosage frequency, and pharmacokinetic properties had overall mean weights of '51.6', '107.1', '110.9', and '71.3', respectively.

4.3 DOACs performance against each sub-criterion of the main criteria

DOACs performance against each sub-criterion of the main criteria results are summarized in Table 4-10.

4.4 DOACs performance score against each sub-criterion of the main criteria

DOACs performance scores against each sub- and main criterion of the selection criteria results are summarized in Table 4-11.

4.5 Comparison between DOACs against main criteria

The MCDA model allows the comparison between different DOACs for each main criterion; whereby, the overall scores of each of dabigatran, rivaroxaban, apixaban, and edoxaban against each main criteria are illustrated in Figure 4-2.

Table 4-10: DOACs performance against each sub-criterion of the main criteria

Criterion	Dabigatran score	Rivaroxaban score	Apixaban score	Edoxaban score
Administration as crushed tablet	0	1	1	1
Availability of reversal agent	1	1	1	0
Clinical efficacy				
Cancer-associated thrombosis	0.5	0.5	0.5	0.5
Extended prevention of recurrent VTE	1	1	1	0
HIT	0.5	0.5	0.5	0
Prevention of VTE post TKA/THR	1	1	1	1
Recurrent VTE in APLAS	0	0	0	0
Recurrent VTE in other thrombophilia conditions	0	0	0	0
Secondary prevention of MI	0	0.5	0	0
Secondary prevention of stroke in patients with NVAF and PCI	0.5	0.5	0.5	0.5
Stroke prevention in NVAF	1	1	1	1
Treatment of VTE including DVT and PE	1	1	1	1
Dosage Frequency				
Once vs twice daily dosing	0	1	0	1
Drug Interaction				
Lack of CYP3A4 inducers	0	0	0	0.75
Lack of CYP3A4 inhibitors	0.25	0	0.75	0.75
Lack of Pgp inducers	0.25	0	0	0.75
Lack of Pgp inhibitors	0.25	0.75	0.75	0.75

Ease of switching				
From DOACs to DOACs	1	1	1	1
From DOACs to warfarin/parenteral	0.75	0.75	0.75	1
From warfarin/parenteral to DOACs	1	1	1	1
Pharmacokinetic properties				
Administration flexibility in regard to food	1	0	1	1
Regimen Flexibility				
Lack of need for bridging at initiation	0	1	1	0
Lack of need for complicated regimen at initiation	0.625	0.75	0.75	1
Safety				
GI bleeding	0.397	0.405	0.529	0.450
GI related side effects excluding GI bleeding	0.894	0.944	0.937	0.930
HS	0.775	0.556	0.662	0.699
ICH excluding HS	0.714	0.606	0.704	0.685
Other major bleeding	0.391	0.493	0.599	0.543
Minor bleeding	0.515	0.493	0.585	0.562
Special population				
Availability of evidence-based dose adjustment in elderly	1	1	1	1
Dose adjustment based on renal function	0.542	0.458	1	0.417
Dose adjustment in impaired liver function	0.5	0.33	0.5	0.5

VTE: Venous thromboembolism; HIT: Heparin induced thrombocytopenia; TKA: Total knee arthroplasty; THR: Total hip replacement; APLAS: Antiphospholipid antibody syndrome; MI: Myocardial infarction; NVAF: Non-valvular atrial fibrillation; PCI: Percutaneous coronary intervention; DVT: Deep vein thrombosis; PE: Pulmonary embolism; CYP3A4; Cytochrome P450 3A4; Pgb; P-glycoprotein; DOACs: Direct oral anticoagulants; GI: Gastrointestinal; HS: Hemorrhagic stroke; ICH: Intracranial hemorrhage

Table 4-11: DOACs performance scores against each sub- and main criterion of the selection criteria

Criterion	Mean* available score weight	Dabigatran score	Rivaroxaban score	Apixaban score	Edoxaban score
Administration as crushed tablet	51.6	0	51.6	51.6	51.6
Availability of reversal agent	107	107	107	107	0
Clinical efficacy	169.7				
Cancer-associated thrombosis	16.5	8.2	8.2	8.2	8.2
Extended prevention of recurrent VTE	17.5	17.5	17.5	17.5	0
HIT	16.4	8.2	8.2	8.2	0
Prevention of VTE post TKA/THR	16.4	16.4	16.4	16.4	16.4
Recurrent VTE in APLAS	16.9	0	0	0	0
Recurrent VTE in other thrombophilia conditions	16.9	0	0	0	0
Secondary prevention of MI	14.4	0	7.2	0	0
Secondary prevention of stroke in patients with NVAF and PCI	17.1	8.6	8.6	8.6	8.6
Stroke prevention in NVAF	18.7	18.7	18.7	18.7	18.7
Treatment of VTE including DVT and PE	18.8	18.8	18.8	18.8	18.8
Dosage Frequency	110.9				
Once vs twice-daily dosing	110.9	0	110.9	0	110.9
Drug Interaction	110				
Lack of CYP3A4 inducers	27.4	0	0	0	20.6
Lack of CYP3A4 inhibitors	27.9	7.0	0	21.0	7.0
Lack of Pgp inducers	26.9	6.7	0	0	20.2
Lack of Pgp inhibitors	28.2	7.0	21.1	21.1	7

Ease of switching	81.1				
From DOACs to DOACs	26.3	26.3	26.3	26.3	26.3
From DOACs to warfarin/parenteral	27.1	20.3	20.3	20.3	27.1
From warfarin/parenteral to DOACs	27.8	27.8	27.8	27.8	27.8
Pharmacokinetic properties	71.3				
Administration flexibility in regard to food	71.3	71.3	0	71.3	71.3
Regimen Flexibility	79.4				
Lack of need for bridging at initiation	39.7	0	39.7	39.7	0
Lack of need for complicated regimen at initiation	39.7	24.8	29.8	29.8	39.7
Safety	142.3				
GI bleeding	25.6	19.2	19.6	25.7	21.8
GI related side effects excluding GI bleeding	22.4	21.2	22.4	22.2	22.0
HS	25.8	25.8	18.5	22.1	23.3
ICH excluding HS	25.7	25.7	21.8	25.3	24.6
Other major bleeding	23.2	20.4	19.5	23.2	23.3
Minor bleeding	19.5	12.8	16.1	29.5	17.7
Special population	76.0				
Availability of evidence-based dose adjustment in elderly	25.6	25.6	25.6	25.6	25.6
Dose adjustment based on renal function	25.5	13.8	11.7	25.5	10.6
Dose adjustment in impaired liver function	25.0	12.5	8.3	12.5	12.5

*Based on the base-case ±2 survey responses uncertainty, this is the mean value of input in the multivariate analysis at base case

VTE: Venous thromboembolism; HIT: Heparin induced thrombocytopenia; TKA: Total knee arthroplasty; THR: Total hip replacement; APLAS: Antiphospholipid antibody syndrome; MI: Myocardial infarction; NVAF: Non-valvular atrial fibrillation; PCI: Percutaneous coronary intervention; DVT: Deep vein thrombosis; PE: Pulmonary embolism; CYP3A4; Cytochrome P450 3A4; Pgb; P-glycoprotein; DOACs: Direct oral anticoagulants; GI: Gastrointestinal; HS: Hemorrhagic stroke; ICH: Intracranial hemrrhage

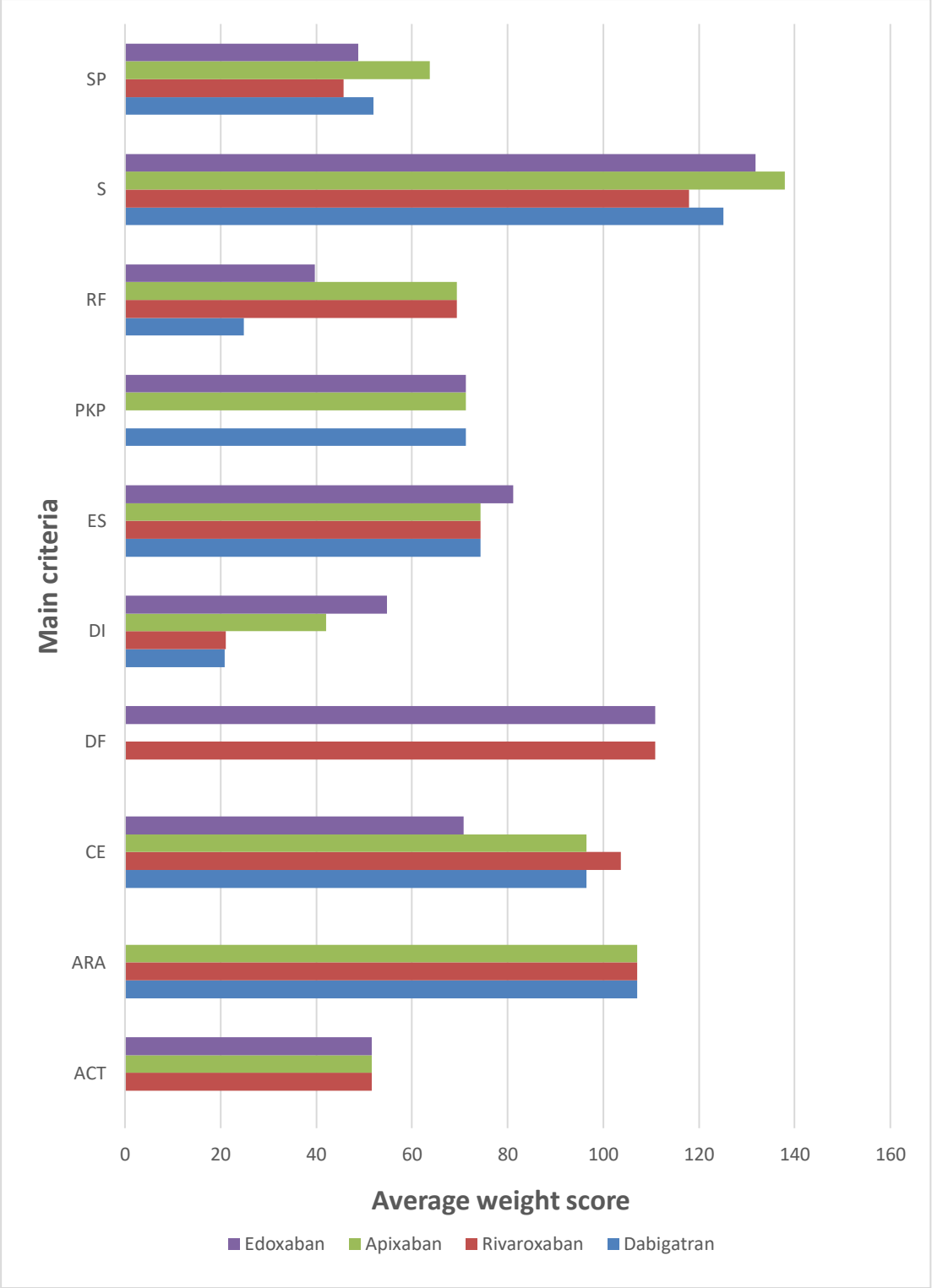

Figure 4-2: DOACs scores against the main criteria

ACT: Administration as crushed tablet; ARA: Availability of reversal agent; CE: Clinical efficacy; DF: Dosage frequency; DI: Drug interaction; ES: Ease of switching; PKP: Pharmacokinetic properties; RF: Regimen flexibility; S: Safety; SP: Special population.

4.6 Selection of DOACs

Apixaban ranked first in regard to the selection criteria, with a total score of '711.8' (95% CI, 711.5 – 712.1), followed by rivaroxaban '699.6' (95% CI, 699.35 – 699.9), edoxaban '658.7' (95% CI, 658.4 – 658.9), and finally dabigatran '569.6' (95% CI, 569.4 – 569.8). This is summarized in Figure 4-3, with the overall DOAC score varying between zero (the worst possible treatment performance) and 1000 (the best possible treatment performance). Accordingly, apixaban and rivaroxaban were recommended as first-line formulary options, edoxaban was recommended as a non-formulary option, and dabigatran was recommended to be excluded from the formulary.

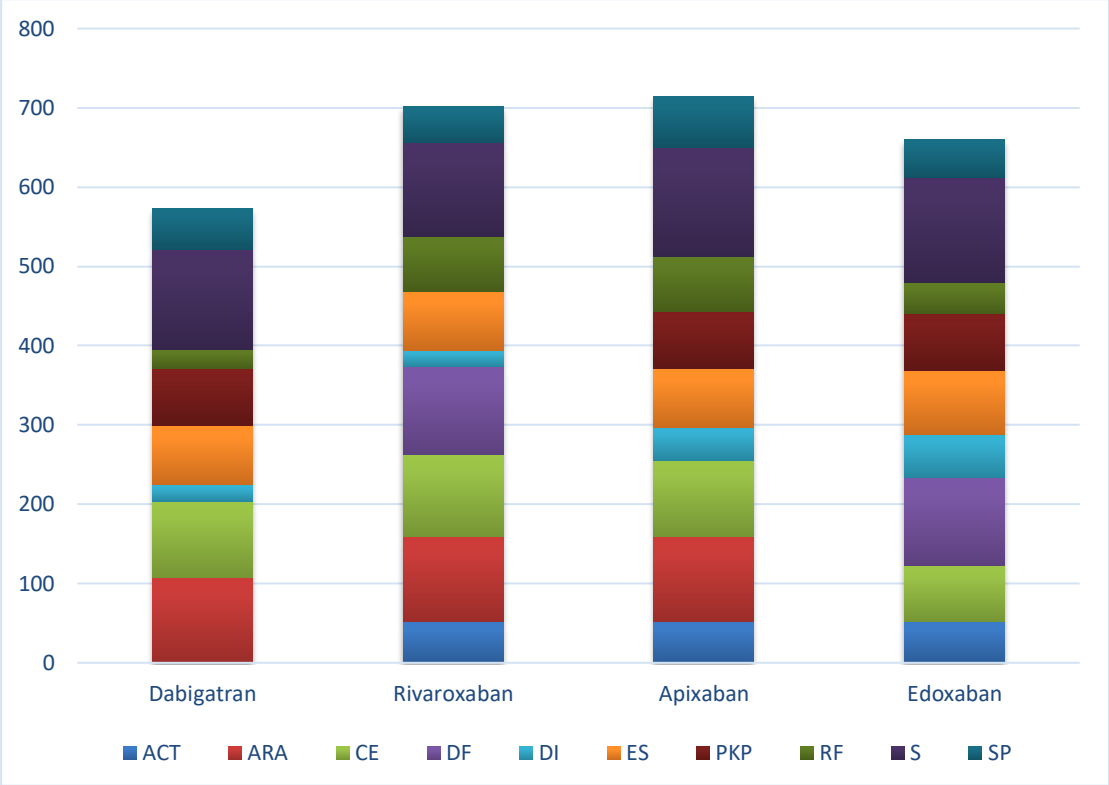

Figure 4-3: Base-case model criteria contribution to an overall DOAC score

ACT: Administration as a crushed tablet; ARA: Availability of reversal agent; CE: Clinical efficacy; DF: Dosage frequency; DI: Drug interaction; ES: Ease of switching; PKP: Pharmacokinetic properties; RF: Regimen flexibility; S: Safety; SP: Special population.

4.7 Sensitivity analysis

4.7.1 One-way sensitivity analysis

Based on the one-way sensitivity analysis, each of the dosage frequency and the availability of approved reversal agent main criteria had a differential impact on the rank of DOACs. The ranking changed after excluding the dosage frequency criterion where apixaban and rivaroxaban remain being ranked first and second, respectively, and dabigatran changed from being ranked fourth to the third, and edoxaban from being ranked third to fourth. As a result, DOACs formulary inclusion recommendations changed to apixaban still being recommended as formulary option, while other DOACs changed to being recommended to be excluded from the formulary. The ranking also changed when excluding the availability of the approved reversal agent criterion, to edoxaban being ranked first, followed by apixaban, rivaroxaban, and lastly dabigatran. As a result, DOACs formulary inclusion recommendations changed to edoxaban being recommended as a formulary option, and both rivaroxaban and apixaban being recommended as non-formulary options, while dabigatran is still recommended to be excluded from the formulary. The results of the one-way sensitivity analysis regarding DOACs ranking and formulary inclusion recommendations compared to base-case line results are summarized in Table 4-12.

Table 4-12: Results of the one-way sensitivity analysis regarding DOACs ranking and formulary inclusion recommendations

Criterion	Dabigatran (95% CI) (Ranking) (Formulary inclusion recommendation)	Rivaroxaban (95% CI) (Ranking) (Formulary inclusion recommendation)	Apixaban (95% CI) (Ranking) (Formulary inclusion recommendation)	Edoxaban (95% CI) (Ranking) (Formulary inclusion recommendation)
Base case	569.6 (569.377 - 569.823) (Fourth) (Excluded)	699.6 (699.346 - 699.854) (Second) (Formulary)	711.8 (711.54 - 712.06) (First) (Formulary)	658.7 (658.446 - 658.954) (Third) (Non-formulary)
Exclusion of dosage frequency	640 (639.740 - 640.260) (Third) (Excluded)	662.1 (661.840 - 662.360) (Second) (Excluded)	799.9 (799.596 - 800.204) (First) (Formulary)	616.3 (616.040 - 616.560) (Fourth) (Excluded)
Exclusion of availability of approved reversal agent	518.1 (517.877 - 518.323) (Fourth) (Excluded)	663.5 (663.227 - 663.773) (Third) (Non-formulary)	677.2 (676.921 - 677.479) (Second) (Non-formulary)	737.2 (736.902 - 737.498) (First) (Formulary)

4.7.2 Multivariate sensitivity analysis

Based on the multivariate sensitivity analysis, DOACs maintained high probabilities to maintain their rank at base-case model, where apixaban remains being ranked first, followed by rivaroxaban, edoxaban, and lastly dabigatran. Ranking probabilities of DOACs are summarized in Figure 4-4.

The DOACs also had high probabilities to maintain their formulary inclusion categorization as a base-case model, with apixaban and rivaroxaban being recommended as a formulary option, and edoxaban being recommended as non-formulary options, while dabigatran is recommended to be excluded from the formulary. The results of the multivariate sensitivity analysis regarding DOACs ranking and formulary inclusion recommendations compared to base-case results are summarized in Table 4-13.

4.7.3 Scenario sensitivity analysis

Based on the scenario analysis performed, the ranking of apixaban, rivaroxaban and dabigatran did not change, with apixaban maintaining the first rank, followed by rivaroxaban and dabigatran. Apixaban was still recommended as a formulary option. However, rivaroxaban changed to being recommended as non-formulary option, while dabigatran was recommended to be excluded from the formulary. As mentioned in **section 3.1.8.3**, edoxaban was excluded from the scenario sensitivity analysis. The results of the scenario sensitivity analysis regarding DOACs ranking and formulary inclusion recommendations compared to base-case results are summarized in Table 4-14.

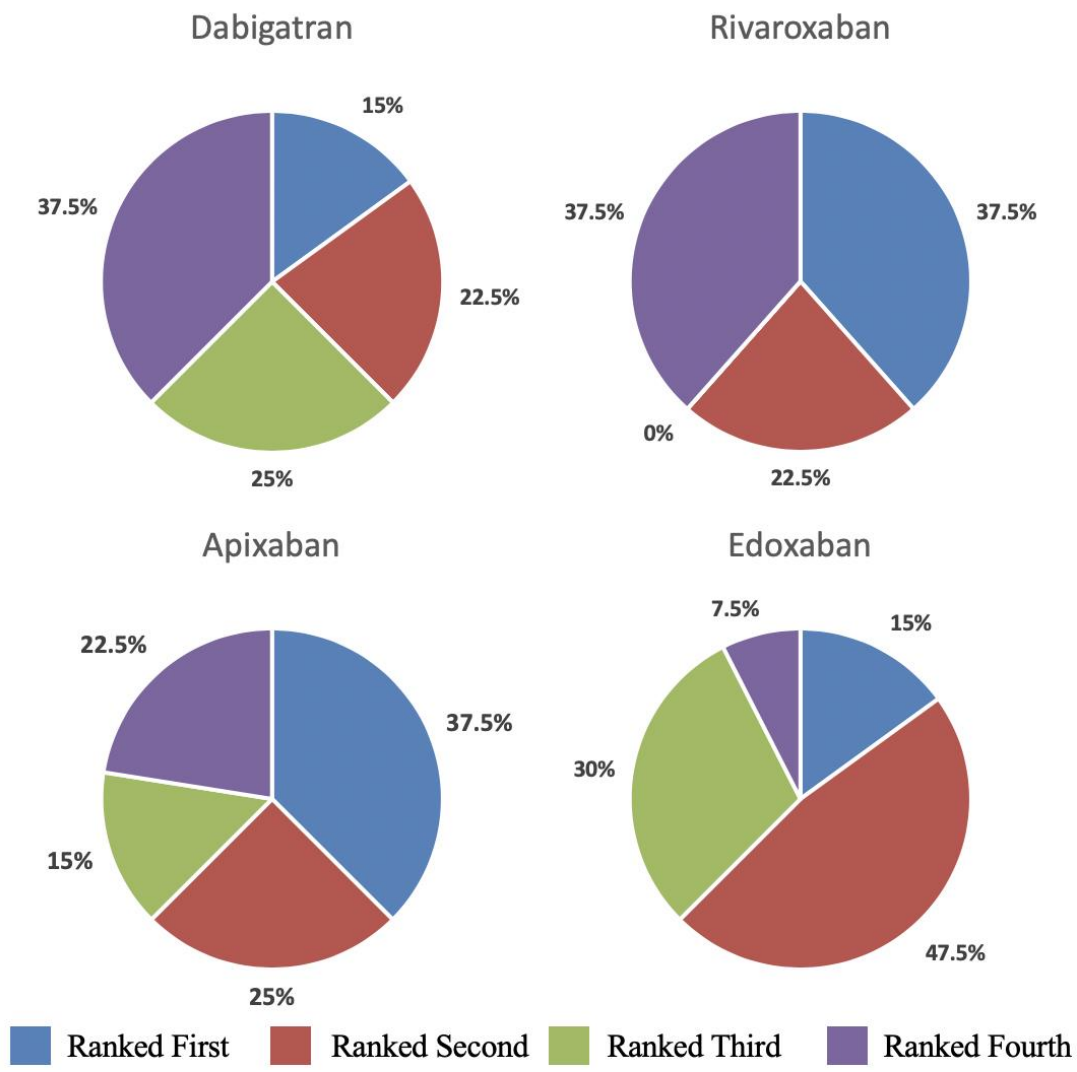

Figure 4-4: Multivariate sensitivity analysis ranking probabilities

Table 4-13: Results of the multivariate sensitivity analysis regarding DOACs ranking and formulary inclusion recommendations

Criterion	Dabigatran (95% CI) (Ranking) (Formulary inclusion recommendations)	Rivaroxaban (95% CI) (Ranking) (Formulary inclusion recommendations)	Apixaban (95% CI) (Ranking) (Formulary inclusion recommendations)	Edoxaban (95% CI) (Ranking) (Formulary inclusion recommendations)
Base case	569.6 (569.377 - 569.823) (Fourth) (Excluded)	699.6 (699.346 - 699.854) (Second) (Formulary)	711.8 (711.54 - 712.06) (First) (Formulary)	658.7 (658.446 - 658.954) (Third) (Non-formulary)
Multivariate sensitivity analysis	571.1 (558.283 - 583.917) (Fourth) (Excluded)	695.7 (674.286 - 717.114) (Second) (Formulary)	709.4 (691.978 - 726.822) (First) (Formulary)	659.2 (658.791 - 659.609) (Third) (Non-formulary)

Table 4-14: Results of the scenario sensitivity analysis regarding DOACs ranking and formulary inclusion recommendations

Criterion	Dabigatran (95% CI) (Ranking) (Formulary inclusion recommendations)	Rivaroxaban (95% CI) (Ranking) (Formulary inclusion recommendations)	Apixaban (95% CI) (Ranking) (Formulary inclusion recommendations)	Edoxaban (95% CI) (Ranking) (Formulary inclusion recommendations)
Base case	569.6 (569.377 - 569.823) (Fourth) (Excluded)	699.6 (699.346 - 699.854) (Second) (Formulary)	711.8 (711.54 - 712.06) (First) (Formulary)	658.7 (658.446 - 658.954) (Third) (Non-formulary)
Alternative source of safety data	555.9 (555.677 -556.123) (Third) (Excluded)	642.7 (642.452 - 642.948) (Second) (Non-formulary)	702.5 (702.240 - 702.760) (First) (Formulary)	Excluded from the analysis

Chapter Five: DISCUSSION

The objective of this thesis was to generate the first comprehensive MCDA measurement of the total benefits and risks of DOACs for their approved indications in Qatar and the region. The included indications, as recommended by recent published clinical practice guidelines, were stroke prevention in NVAF patients, VTE acute treatment, extended prevention of recurrent VTE, and secondary prevention of VTE in high-risk hospitalized patients and after total hip or knee replacement surgeries (183–189). The included DOACs in the MCDA model were dabigatran, rivaroxaban, apixaban, and edoxaban. Nevertheless, none of the guidelines recommended one DOAC over another for any of the above indications, nor recommended what DOAC should be included in the formulary. In practice, the selection is based on personal experience and preference.

HMC is the primary provider for healthcare services in Qatar, and the inclusion of medications in the formulary is evaluated and determined through a hospital-based pharmacy and therapeutic committee. The current practice at HMC involving the use of DOACs is neither supported nor justified by evidence. Dabigatran is the most commonly used DOAC, and rivaroxaban is the least commonly used due to its safety concerns (190–192). Moreover, apixaban was recently added to the formulary, and edoxaban is not available in Qatar.

The current MCDA model demonstrated that apixaban should be recommended as a formulary option, rivaroxaban and edoxaban as non-formulary options, while dabigatran should be excluded from the formulary. These recommendations were for all DOAC approved indications of stroke prevention in NVAF patients, VTE acute treatment, extended prevention of recurrent VTE, and primary prevention of VTE in high-risk hospitalized patients and after total hip or knee replacement surgeries. From

the selection criteria, apixaban scored the highest for safety and special population criteria. Moreover, apixaban shared the highest score for administration as a crushed tablet, availability of approved reversal agent, pharmacokinetic properties, and regimen flexibility criteria. Furthermore, apixaban has one limitation in regards to the dosage frequency criterion, where it shares a score of zero with dabigatran, which represents the only criterion where apixaban scored the lowest score. Accordingly, the apixaban performance score regarding the selection criteria is 711.8 ± 0.260 (±0.04%).

Likewise, the rivaroxaban overall performance score regarding the selection criteria is 699.6 ± 0.254 (±0.04%), which is found within 95% of the apixaban score; thus, it was recommended as a formulary option. Although rivaroxaban scored the lowest in pharmacokinetic properties, safety, and special population criteria, it is due to rivaroxaban's advantageous characteristics that it was recommended as a formulary option. These advantageous characteristics are related to the efficacy criteria, where it has an additional EMA approval for the secondary prevention of MI, the ability to be administered as a crushed tablet, availability of approved reversal agent, regimen flexibility, and once-daily dosage frequency. These characteristics allow rivaroxaban to score the highest for the clinical efficacy criterion, and share the highest score for administration as a crushed tablet, availability of approved reversal agent, and dosage frequency criteria.

On the other hand, the edoxaban performance score regarding the selection criteria was 658.7 ±0.254 (±0.04%), which is found within 90% of the apixaban score; thus, it was recommended as a non-formulary option. Edoxaban is a promising DOAC agent that covers the drawbacks of both apixaban and rivaroxaban. Unlike apixaban, edoxaban can be administered once daily, and compared with rivaroxaban, edoxaban has a better safety profile, pharmacokinetic properties, and special population criteria.

Moreover, edoxaban scored the highest in the ease of switching and drug interaction criteria, and shared the highest score for administration as a crushed tablet and dosage frequency. Furthermore, edoxaban had the second-highest score in regard to the safety criterion. However, it was due to edoxaban's lack of approved reversal agent and fewer approved clinical indications and off-label uses that it scored the lowest in the availability of approved reversal agent and clinical efficacy criteria. As a result of this, when the availability of approved reversal agents was excluded from the selection criteria, edoxaban scored the highest and was recommended as a formulary option along with apixaban in our one-way sensitivity analysis.

Dabigatran's performance score regarding the selection criteria was 569.6 ±0.223 (±0.04%), which was not found within either 95% or 90% of the apixaban score; thus, it was recommended that it should be excluded from the formulary. Dabigatran's only advantageous characteristic was the availability of approved reversal agents and administration flexibility. However, dabigatran scored the lowest or shared the lowest score for many other criteria, such as administration as a crushed tablet, clinical efficacy, dosage frequency, drug interactions, ease of switching, and regimen flexibility.

The identified criteria were considered to be the most relevant regarding the prescribing of DOACs. Clinical efficacy criterion scored the highest of the selection criteria, especially because DOACs are steadily replacing warfarin as alternative anticoagulants for various indications. Our model included different disease states, where DOACs could be used either with FDA/EMA approval or off-label indications. Currently, most DOACs are officially approval for stroke prevention in NVAF patients, VTE acute treatment, extended prevention of recurrent VTE, and secondary prevention of VTE in high-risk hospitalized patients and after total hip or knee replacement

surgeries. Moreover, evidence-based for the use of DOACs in other indications are increasing (i.e., rivaroxaban additional EMA approval for use, as in ACS), coupled with the use of DOACs outside the setting of clinical trials (i.e., use of DOACs in HIT and other thrombophilia conditions). In terms of the CVD indications of DOACs, we included MI secondary prevention in NVAF patients undergoing PCI. Currently, expert consensus recommends triple therapy (OAs, aspirin, clopidogrel) for a short period of 1–6 months based on bleeding risk, followed by dual therapy (OAs and either aspirin or clopidogrel) for a period of 12 months after an ACS event, instead of OAs alone (193). DOACs showed no inferiority when used in low doses for stroke prevention in NAVF patients undergoing PCI compared with warfarin, and therefore they could be considered as alternative options to warfarin (193–195).

Regarding VTE treatment, there are many grey areas concerning the use of DOACs, such as VTE treatment in cancer and thrombophilia patients. While DOACs might be considered an appealing alternative to LMWH for this patient population, current evidence recommends LMWH as an initial VTE treatment in patients with cancer (196). However, DOAC pivotal trials for VTE treatment included a small percentage of active cancer patients of 5.2%, 3.1%, and 2.5% in the EINSTEIN (rivaroxaban), AMPLIFY (apixaban), and HOKUSAI-VTE (edoxaban) pivotal trials, respectively (44,46,197). With regard to the use of OAs for VTE treatment in APLAS syndrome, warfarin is considered to be the mainstay treatment (198). DOAC efficacy for use in APLAS syndrome is still uncertain, and current evidence suggests that rivaroxaban could be an effective and safe treatment alternative for patients with APLAS syndrome and a history of VTE (199).

Nonetheless, a recent systematic review evaluating the use of DOACs in 122 patients with APLAS syndrome addressed the risk of recurrent thrombosis that

occurred in 15.6%, and the authors concluded that further RCTs were required to establish safety and efficacy concerns regarding DOAC use in APLAS syndrome patients (200). Concerning the use of DOACs in HIT, several studies evaluated their use for the treatment of acute HIT as an initial therapy in hemodynamically stable patients, or as secondary to parenteral anticoagulant therapy (201–203). Although DOACs do not have official approval for use in HIT, they are currently used as off label for this indication (167–170). To summarize, this model comprises all approved DOAC indications along with other off-label uses that cover all potential aspects of clinical efficacy. In our model, rivaroxaban scored the highest for clinical efficacy criterion, and this can be explained by its additional EMA approval for use in the secondary prevention of MI. In contrast, edoxaban scored the lowest, which was anticipated because it was recently introduced to the market and has fewer FDA approved indications than other DOACs (167–170).

Safety criteria were the second most important of the selection criteria. The current model included the most important and severe adverse events related to the use of DOACs (190–192,204,205). Prescribers ranked HS, ICH, and GI bleeding as the most significant adverse events related to the use of DOACs, followed by other types of major bleeding, GI-related side effects excluding GI bleeding, and lastly, minor bleeding. This ranking was appropriate as it considered the seriousness and severity of adverse events that reflect real-life practice (204,206). Apixaban was ranked as the safest DOAC, which has been confirmed by several studies in the literature (190–192,205). In a large observational study (ARISTOPHANES) of 162,707 NVAF patients that compared between DOACs, apixaban was associated with a lower risk of stroke, systematic embolism, major bleeding, and a composite outcome of stroke, systematic embolism, and major bleeding (191). On the other hand, rivaroxaban was

ranked as the least safe DOAC, and this has also been demonstrated by multiple studies in the literature (190–192,205). In a systematic review and meta-analysis of 25 RCTs and 24 non-RCTs of 897,748 NVAF patients evaluating the safety and efficacy of DOACs, rivaroxaban was associated with increased risk for major bleeding in elderly patients (192).

Interestingly, the dosage frequency was ranked third in the selection criteria, which can be translated to prescribers' experiences with adherence to anticoagulation medications. Although DOACs have a higher adherence rate compared with warfarin, accounting for the dosing frequency may have a high impact on adherence by patients (207,208). For the majority of the indications, both rivaroxaban and edoxaban were given once daily, while dabigatran and apixaban required twice-daily dosing. This was emphasized via the results of the one-way sensitivity analysis, which indicated that only apixaban should be included in the formulary, and that the other DOACs should be excluded from the formulary when removing the dosage frequency from the model. A study used a French national healthcare database to examine the one-year dabigatran and rivaroxaban adherence rates in patients with nonvalvular atrial fibrillation. The results illustrated that the adherence rate was 53.3% and 59.9% in patients receiving dabigatran and rivaroxaban, respectively (209). Another recent study used medical and pharmacy claims to evaluate adherence to DOACs in patients with AF by calculating medication possession ratio (MPR). Surprisingly, the study results conflicted with the current analysis, although the difference in the adherence rate was not statistically significant ($P = 0.075$), apixaban had the highest rate of adherence, with mean MPRs of 0.91, 0.93, and 0.95 for rivaroxaban, dabigatran, and apixaban, respectively (210).

The fourth-ranked criterion was the drug interactions, which could lead to either safety or efficacy failure (211–215). Prescribers indirectly related the drug interactions

of DOACs to safety concerns, which might, in turn, explain the high ranking of the drug interactions, because safety was ranked second (216). Edoxaban had the lowest rate of drug interaction followed by apixaban, rivaroxaban, and lastly, dabigatran. Another criterion that could be linked to the safety criteria was the availability of approved reversal agent, which was ranked fifth in the selection criteria. As DOACs are being used to an increasing extent in clinical practice, the need for effective and approved reversal agents has increased, especially for controlling life-threatening bleeding or to counteract the effects of DOACs for urgent interventions (e.g., surgeries or procedures) (217). Currently, idarucizumab (praxbin) have an FDA approval as reversal agents for dabigatran, and andexanet alfa (andexxa) have an FDA approval as reversal agents for rivaroxaban and apixaban (218–220). However, edoxaban does not have an approved reversal agent, which may negatively impact its use in clinical practice. This was evident in our one-way sensitivity analysis, where excluding the availability of approved reversal agent from the model resulted in edoxaban being ranked first, followed by apixaban, rivaroxaban, and lastly, dabigatran. Thus, both edoxaban and apixaban should be recommended as formulary options, rivaroxaban as non-formulary, and dabigatran should be excluded from the formulary.

The switching patterns between anticoagulant and regimen flexibility ranked sixth and seventh, respectively, in the selection criteria. Almost all DOACs have similar guidelines concerning switching between different anticoagulants, which sometimes requires bridging with LMWH or concomitant use of DOACs and warfarin until INR is within the therapeutic range. One difference that favors edoxaban when switching from DOAC to warfarin/parentral, is that its dose can be reduced by 50% while a patient is taking warfarin, until INR reaches the therapeutic range, unlike other DOACs that require bridging with parenteral anticoagulant until INR reaches a therapeutic range. In

contrast, DOACs have some differences related to regimen flexibility in terms of bridging with parenteral anticoagulant before the DOACs are begun, and the need for complicated regimens at initiation. When dabigatran and edoxaban are prescribed for VTE treatment, they must be bridged with a parenteral anticoagulant for five days before initiation. However, in terms of the lack of complicated regimen requirements, edoxaban does not require dosage changes compared with other DOACs. Overall, rivaroxaban and apixaban are associated with simple prescription regimens compared with dabigatran and edoxaban.

Surprisingly, special population requirements ranked eighth in the selection criteria, which include dose adjustment in patients with renal or liver impairment and the level of evidence for the dose adjustment of DOACs in elderly patients. Almost one-third of patients with NVAF suffer from chronic kidney disease, which can increase the risk of bleeding, stroke, and systematic embolism (221–224). Reduced renal function is associated with the accumulation of DOACs, which requires dose adjustment, routine monitoring of serum creatinine, and assessment of the creatinine clearance of the DOACs (225). Although the renal excretion percentage of dabigatran, rivaroxaban, edoxaban, and apixaban are 80%, 66%, 35%, and 25%, respectively, however, apixaban is considered the safest DOAC to use in patients with renal impairment, and edoxaban is the least safest DOAC (80,167–170). In regard to liver impairment patients, DOACs share a very similar profile, except for rivaroxaban, which lacks enough evidence to be used in Child-Pugh class B patients (167–170).

Pharmacokinetic properties in regard to drug–food interactions of DOACs ranked ninth in the selection criteria, which is logical as DOACs are known to have minimal drug–food interactions. Administration as crushed tablet was ranked the tenth criterion. Although DOAC administration as a crushed tablet is an important aspect for

prescribers to take into consideration when prescribing medications to elderly patients due to swallowing disorders (226–229), it was ranked the least important in the model due to the relative trade-off with other important criteria, including efficacy and safety.

Previous MCDA studies have focused primarily on stroke prevention in NVAF patients, without taking into consideration other important and FDA-approved indications. Nevertheless, OA evaluation in previous MCDA studies have focused only on a limited number of criteria in treatment performance, which incorporated only a subset of the available DOACs and double-counted mortality rates (154,157,158).

Tommi et al. (2017) compared DOACs versus VKA for stroke prevention in NVAF patients using an MCDA model that included two main criteria: clinical event criteria that consisted of nine sub-criteria, and other criteria that consisted of four sub-criteria, adding to a total of 13 sub-criteria. Those clinical event sub-criteria were somehow similar to the ones used in our model under safety criteria, including IS, SE, MI, ICH excluding HS, GI bleeding, other major bleeding, non-major bleeding, and dyspepsia. The other criteria were also somehow similar to the ones used in our model, which consisted of four sub-criteria: administration frequency, interaction with food, real-world evidence, and reversal agent availability. The study showed that dabigatran had the highest score, followed by apixaban, edoxaban, rivaroxaban, and lastly, warfarin. The criteria used in the model were identified through a literature search and clinical judgment of expert clinicians in the field, which was an approach similar to the one used in this thesis. However, there are several limitations to their analysis. First, the ranking of the criteria was based on HR obtained from clinical trials, and as mentioned earlier, there were variations in the population baseline characteristics, that did not reflect the real-world population. Thus the method used to rank the criteria is not considered reliable. Second, their model lacked other important criteria, such as

renal function, hepatic impairment, the administration flexibility of DOACs, other approved and off-label indications, pharmacokinetic interactions, and ease of switching between OAs.

In contrast, our model used the clinical judgment of several healthcare providers from different specialties to ensure the generalizability of the ranking process. During the time of their analysis, apixaban did not have an approved reversal agent, which resulted in dabigatran scoring the highest among the DOACs. However, Andexxa received FDA approval in May 2018 as a reversal agent for both apixaban and rivaroxaban, and this was taken into consideration in our analysis, contributing to apixaban scoring the highest in the current study (219).

In another study by Jose et al. (2018) assessed the benefit, risk, and cost of OAs (dabigatran, rivaroxaban, apixaban, and warfarin) for AF by using MCDA. In this study, Jose and his colleagues used only three main criteria and six sub-criteria. These criteria consisted only of clinical efficacy, safety, and cost as their primary source for assessing OAs. Similar to the approach followed by Tommi and his colleagues, they relied on three expert panel clinical judgments (vascular neurologist, cardiologist, and internist) to assess the weights of these criteria using a 0–100 scale. OA achievement probabilities were obtained from a CEA conducted by Harrington and his colleagues (117). They did not take into consideration other important criteria as did our model, and to a lesser extent, as did the study by Tommi and his colleagues. In a similar approach, Jason and his colleagues quantitively compared the safety and efficacy of DOACs (dabigatran, rivaroxaban, and apixaban) and VKA for stroke prevention by using MCDA model. They included only the two criteria of efficacy and safety in their model, with a total of four sub-criteria under four different scenarios. They relied on health utilities derived from the literature to assess the weights of the criteria. Similar

to the previous MCDA studies, many other important criteria were not taken into consideration. From the survey results we obtained, those other than safety and efficacy criteria scored a high weight when healthcare providers were asked about them—highlighting the importance of including them in such an analysis to assess DOACs comprehensively.

The main results validity of rigorous model-based evaluation depends on both the quality of data and the assumptions required to derive the functional forms of the model. MCDA models are vulnerable to uncertainty, especially with performance measurements and weight inputs. The sensitivity analysis indicated that our study conclusion is generally robust and generalizable. The selection criterion that affected the study recommendations for first-line use the most was the availability of reversal agent, whereby excluding the availability of reversal agent resulted in edoxaban being recommended as a formulary option, and both apixaban and rivaroxaban being recommended as non-formulary. This was followed by dosage frequency, which resulted in apixaban still being recommended as a formulary option, while other DOACs were recommended to be excluded from the formulary. In the multivariate sensitivity analysis, an investigation of the sensitivity of the model outcome to the model inputs of the safety, special population, and drug interaction criteria did not result in any change in the formulary inclusion recommendations. The scenario where DOAC performance data in regard to safety criteria were derived from another meta-analysis of head-to-head observational cohort studies did not result in any change in the formulary inclusion recommendations.

Our MCDA model comprises many strong points. Firstly, this is the first MCDA model that compares DOACs for different indications across multiple criteria, accounting for the local prescriber's perspective of the relative importance of different

criteria in Qatar and the Middle East. Our MCDA model has the ability to capture both treatment performance through different criteria and sum up the results of these criteria in an overall numerical score estimate of treatment value (103). MCDA represents a useful tool for decision-makers, as it allows them to consider multiple criteria in prioritizing setting activities, and it helps in outlining complicated value trade-offs, consistently and transparently, which in turns leads to fairer decision-making. Moreover, the MCDA model used in this thesis followed the checklist of ISPOR recommendations for good MCDA practice guidelines (Appendix 4) (110). Secondly, the model was built based on a clear description of the decision problem, which included the classification of the assessed DOACs in one of the three categories: formulary, non-formulary, and rejected. The decision problem was also validated by an HMC practitioners expert panel, who had considerable experience and knowledge concerning DOAC use. The method used to identify criteria was based on a literature review of the most relevant criteria regarding the use of DOACs, as well as the clinical judgment of the panel members. Thirdly, our MCDA model is a useful tool that can be used to assess future DOACs, such as betrixaban. Fourthly, DOAC prescribers in HMC are of diverse cultures, scientific backgrounds, and ethnicities, which gives generalizability to our survey questionnaire criteria and sub-criteria weighting. Furthermore, we included prescribers from different specialties to account for all possible behaviors regarding the use of DOACs. Lastly, our sensitivity analysis results outlined the sensitivity of the model to changes in the criteria. The resulting changes in the rankings and formulary recommendations in the one-way sensitivity analysis proved the generalizability of our model in regard to DOACs against various criteria.

This thesis comprises several limitations. Firstly, the main and sub-criteria weighing was based on the results of the survey questionnaire. Survey-based studies

are vulnerable to many limitations, such as false answers by responders, differences between understanding the questions and interpreting them (face and content validity), difficulties in conveying emotions and feelings, difficulty im understanding and analyzing certain questions, especially the main criteria ranking questions, the hidden agendas of respondents, and responses of an unconscious nature. These limitations also applied to the expert panel members who reviewed and evaluated the survey draft, survey responses, measurement of the DOAC achievement levels, and final results. However, we obtained a large response from various specialities and hospital sites that would cover individual biases. Furthermore, by using a survey-based weighting method, we ensured that the results reflected real practice, which had not been done in any previous DOACs MCDA studies. Secondly, some sub-criteria overlapped with the same main criterion and other criteria. An example of this overlap can manifest in the drug interaction criterion, where many drugs can act as both inducers or inhibitors of both CYP 450 and Pgb enzymes, thus making it difficult to differentiate between the performance achievement level of DOACs. In our analysis, we relied on specific drugs that were most associated with single interaction with these enzymes, which minimizes such overlapping. Thirdly, some criteria needed to be judged by the panel members, such as quality and strength of evidence regarding dose adjustment in the elderly from the literature, which may have introduced some bias. Nevertheless, in our analysis, the DOACs achieved a full available score regarding this sub-criterion because there was clear evidence from multiple literature sources, thus the performance achievement level of the DOACs was not affected. Fourthly, when calculating DOAC performance against the clinical safety criterion, and although data were obtained from top sources such as network meta-analysis, there was some overlap between some of the safety sub-criteria, such as HS and ICH, excluding HS. The network meta-analysis did not report ICH

alone and excluded HS; thus, the HR obtained might have been overestimated or underestimated for some DOACs, especially the ones associated with a high risk of bleeding. Also, regarding GI side effects, data was obtained manually from pivotal trials of DOACs compared with warfarin from www.clinicaltrials.gov, which might have been different from the published trials. We only took into consideration serious and non-serious cases of dyspepsia, diarrhea, abdominal pain, constipation. These adverse events may not represent all GI side effects, and they also may overlap each other, thus duplicating the number of events. However, in our multivariate sensitivity analysis, we took into consideration such variabilities, and we also used another source of safety data in the scenario sensitivity analysis, all of which did not change the results of our base-case analysis. Fifthly, our model did not include cost as a criterion, which is considered important in an MCDA model. However, the DOACs had similar acquisition cost. Future studies should incorporate the costs of DOACs in regards to patients and institutions, taking into consideration the costs associated with treatment failure. Sixthly, we used the percentages range of 95%, 90-95%, and less than 90% of the highest score to guide DOACs formulary inclusion recommendations. We relied on evidence from the literature for these percentages range and futher validate them with the expert panel. However, both literature evidences and the expert panel are located in Qatar, which might makes these recommendations invalid elsewhere.

Chapter Six: CONCLUSION

Up to our knowledge, there are no literature reports of a DOAC scoring model that is based on comparatively weighting multiple indications of stroke prevention in NVAF patients, VTE acute treatment, extended prevention of recurrent VTE, and primary prevention of VTE in high-risk hospitalized patients and after total hip or knee replacement surgeries. In addition, there have been no previous reports of DOAC selection in Qatar or the Middle East. Our MCDA model analysis has shown the possibility of making a credible and comprehensive comparative evaluation of the overall value of DOACs After incorporating and investigating the input of all key relevant criteria of DOACs from relevant local practitioners in the MCDA model, apixaban was ranked the highest, followed by rivaroxaban, edoxaban, and lastly, dabigatran. Given the above, our evaluation suggests there would be an advantage in redefining the formulary inclusion of DOACs. Our recommendations include considering apixaban and rivaroxaban as formulary options, edoxaban as a non-formulary option, and excluding dabigatran from the formulary.

The implementation of a locally developed DOAC-specific comparative MCDA scoring model will help assess any future DOAC against locally available DOACs for the purpose of making decisions about formulary inclusion. The results of this study will help in determining the best available DOACs for first-line use in Qatar based on evidence-based clinical, safety, and other essential criteria.

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APPENDIXES

Appendix 1: IRB, MRC, HMC sites approval letters

(Hamad General Hospital (HGH) Medical Director Approval Form		
Initial Information		
Title of Study	Multi-criteria Decision Analytic Model for the Comparative Formulary Inclusion of Direct Oral Anticoagulants in Qatar	
Principal Investigator Name	Dr. Daoud Al-Badriyeh	
HMC Investigators	Dr. A/Latif Mohd. Al Khal , Dr. Abdul Moqeeth Mohammed , Dr. Daoud Al-Badriyeh , Dr. Hazem Fathy Elewa , Mr. Ahmed Sobhy Hassan Ghonim Mahfouz , Mr. Mohammad Ibrahim Al Mukdad	
Contact Details	Phone No: 0097444035591	Email Id: daoud.a@qu.edu.qa

Site Details	
Type of Request	New Study Application
Project type	Social, Public and Behavioural Surveys
Is there any prospective recruitment of patients to study, collection of samples or data from human subjects?	No
Departments Used	Medicine,Pharmacy
Summary of Tasks to be undertaken at this Hospital	Online Survey among staff ,data collection, Online Survey, Member for the Expert Panel.
Other Hospitals to be used in this study	Al Wakra Hospital (AWH),Heart Hospital (HH),Qatar University
Is the Scheme of Delegation list complete and signed?	Yes

ClinicalGovernance	Reviews
Hospital Governance	
The hospital is satisfied with the clinical governance arrangements for this project	Yes
The HRO confirms that the clinical governance has been completed and signed by the relevant departments as per sites listed in the study protocol	Yes
Does the objective of this study comply with the Hospital policies	Yes
The hospital has the Capacity & Capability to deliver this study.	Yes

Approval
Recommendation: Approved **Medical Director?s Name:** Dr. Yousuf Khalid Al Maslamani **Medical Director?s signature:** **Date: 10/01/2019**   

APPROVAL LETTER
MEDICAL RESEARCH CENTER
HMC, DOHA-QATAR

Dr. Abdul Moqeeth Mohammed **Corp. No. 043905** **Consultant** **Department of Medicine** **HGH- HMC**	**Date: 19 February 2019**
Protocol No.	MRC-01-18-249
Study Title:	Multi-criteria Decision Analytic Model for the Comparative Formulary Inclusion of Direct Oral Anticoagulants in Qatar
Hospitals/ Facilities Approved:	Al Wakra Hospital (AWH),Hamad General Hospital (HGH),Heart Hospital (HH)
Team Member List:	Dr. A/Latif Mohd. Al Khal , Dr. Abdul Moqeeth Mohammed , Dr. Daoud Al-Badriyeh , Dr. Hazem Fathy Elewa , Mr. Ahmed Sobhy Hassan Ghonim Mahfouz , Mr. Mohammad Ibrahim Al Mukdad
Review Type:	Expedited
Decision:	Approved

The Medical Research Center has reviewed and approved the request for this research study to be conducted in the HMC on condition that continual approval, including approval renewals, from the HMC Institutional Review Board (IRB), as per the IRB terms.

This study must be fully compliant with all the relevant sections of the 'Rules and Regulations for Research' at HMC and the Medical Research Center should be notified immediately of any proposed changes to the study protocol. Wherever amendments to the initial protocol are deemed necessary, it is the responsibility of the Principal Investigator to ensure that appropriate reviews and renewed approvals are in place before the study will be allowed to proceed.

Please note that only official, stamped versions of the approved documentation are to be utilized at any stage in the conduct of this study and follow the validity dates as mentioned in the IRB stamped documents. The research team must ensure that progress on the study is appropriately recorded in ABHATH, the online research system of the Medical Research Center.

We wish you success in this research and await the outcomes in due course.

Yours sincerely,

Ms. Emma Pendleton
Assistant Director Business Development and Research
Medical Research Center- HMC

Date:19 February 2019

مؤسسة حمد الطبية
Hamad Medical Corporation
HEALTH · EDUCATION · RESEARCH صحة · تعليم · بحوث

AMENDMENT APPROVAL LETTER
MEDICAL RESEARCH CENTER
HMC, DOHA-QATAR

Dr. Abdul Moqeeth Mohammed **Consultant** **Department of Medicine** **HGH- HMC**	**Date: 26 May 2019**
Protocol No.	MRC-01-18-249 (Amendment - 01)
Study Title:	Multi-criteria Decision Analytic Model for the Comparative Formulary Inclusion of Direct Oral Anticoagulants in Qatar
Hospitals/ Facilities Approved:	Al Wakra Hospital (AWH),Hamad General Hospital (HGH),Heart Hospital (HH)
Team Member List:	Dr. A/Latif Mohd. Al Khal , Dr. Abdul Moqeeth Mohammed , Dr. Daoud Al-Badriyeh , Dr. Hazem Fathy Elewa , Mr. Ahmed Sobhy Hassan Ghonim Mahfouz , Mr. Mohammad Ibrahim Al Mukdad
Subject:	Amendment Approval Letter 01

The Medical Research Center hereby acknowledges the Amendment Approval Notice #01 from the IRB dated 20 May 2019. Please be informed that your request for amendment have been reviewed and approved.

This study must be fully compliant with all the relevant sections of the `Rules and Regulations for Research` at HMC and the Medical Research Center should be notified immediately of any proposed changes to the study protocol. Wherever amendments to the approved protocol are deemed necessary, it is the responsibility of the Principal Investigator to ensure that appropriate reviews and renewed approvals are in place before the study will be allowed to proceed.

Please note that only official, stamped versions of the IRB approved documentation are to be utilized at any stage in the conduct of this study and follow the validity dates as mentioned in the IRB stamped documents. The research team must ensure that progress on the study is appropriately recorded in ABHATH, the online research system of the Medical Research Center.

We wish you success in this research and await the outcomes in due course.

Yours sincerely,

Ms. Emma Pendleton
Assistant Director Business Development and Research
Medical Research Center- Hamad Medical Corporation

Medical Research Centre
Hamad Medical Corporation - Doha - Qatar
Hamad

Date:26 May 2019

AMENDMENT APPROVAL LETTER
MEDICAL RESEARCH CENTER
HMC, DOHA-QATAR

Dr. Abdul Moqeeth Mohammed **Consultant** **Department of Medicine** **HGH- HMC**	**Date: 07 October 2019**
Protocol No.	MRC-01-18-249
Study Title:	Multi-criteria Decision Analytic Model for the Comparative Formulary Inclusion of Direct Oral Anticoagulants in Qatar
Team Member List:	Dr. A/Latif Mohd. Al Khal , Dr. Abdul Moqeeth Mohammed , Dr. Daoud Al-Badriyeh , Dr. Hazem Fathy Elewa , Mr. Ahmed Sobhy Hassan Ghonim Mahfouz , Mr. Mohammad Ibrahim Al Mukdad
Subject:	Amendment Approval Letter #02

The Medical Research Center hereby acknowledges the Amendment Approval Notice #02 from the IRB dated on 30 September 2019.Please note that your request for amendment have been reviewed and approved.

The requested amendments do not affect the review status of this study and are hence approved based on the justifications provided.This study must be fully compliant with all the relevant sections of the `Rules and Regulations for Research` at HMC and the Medical Research Center should be notified immediately of any proposed changes to the study protocol. Wherever amendments to the initial protocol are deemed necessary, it is the responsibility of the Principal Investigator to ensure that appropriate reviews and renewed approvals are in place before the study will be allowed to proceed.

Please note that only official, stamped versions of the IRB approved documentation are to be utilized at any stage in the conduct of this study and follow the validity dates as mentioned in the IRB stamped documents. The research team must ensure that progress on the study is appropriately recorded in ABHATH, the online research system of the Medical Research Center.

We wish you success in this research and await the outcomes in due course.

Yours sincerely,

Ms. Emma Pendleton
Assistant Director Business Development and Research
Medical Research Center- Hamad Medical Corporation

Date:07 October 2019

INSTITUTIONAL REVIEW BOARD
HAMAD MEDICAL CORPORATION
DOHA-QATAR

Abdul Moqeeth Mohammed **Consultant, Medicine** **Hamad Medical Corporation** **Doha-Qatar**	**Email: irb@hamad.qa Tel: 00974-40256410** **HMC-IRB Registration: MoPH-HMC-IRB-020** **IRB-MoPH Assurance: MOPH-A-HMC-020**

APPROVAL NOTICE

Protocol No. :	MRC-01-18-249
Protocol Title :	Multi-criteria Decision Analytic Model for the Comparative Formulary Inclusion of Direct Oral Anticoagulants in Qatar
QNRF/Other Reference Number :	NA
Date of HMC-IRB Approval :	05 February 2019
Date of Letter Issued :	07 February 2019
Review Type :	Expedited
Decision :	Approved
Approved HMC Enrollment :	300 Patients Survey - All practitioners/clinicians (involved in prescribing anticoagulants) in HGH, HH and Wakra Hospital
NPRP Grant Holder :	NA

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

IRB oversight expires 12 months from the date of approval indicated above. 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 start 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.

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

Sincerely,

Chairman of Institutional Review Board: _____

Date: _____

Signature:

List of Approved Documents:

DOCUMENTTYPE	DOCUMENTNAME	LANGUAGE	NOOFPAGES	VERSIONNO
Research Protocol	MRC-01-18-249_ResearchProtocol_V1.0_07-FEB-19_16Pages_443439.8_07-FEB-19_16Pages_443439.pdf	English	16	V1.0
Research Info Sheet	MRC-01-18-249_ResearchInfoSheet_Eng_V1.0_07-FEB-19_1Pages_444288.7_07-FEB-19_1Pages_444288.pdf	English	1	V1.0
Data Collection Sheet	MRC-01-18-249_DataCollectionSheet_Eng_07-FEB-19_5Pages_453932.pdf	English	5	V1.0
Other/Supporting document	MRC-01-18-249_Selection criteria.pdf	English	1	V1.0
Other/Supporting document	Exper Panel Invitation.pdf	English	2	V1.0
Group Discussion/ Script	MRC-01-18-249_GroupDiscussion/Script_Eng_V1.0_07-FEB-19_1Pages_642009.2_07-FEB-19_1Pages_642009.pdf	English	1	V1.0

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

Responsibilities of the Principal Investigator:

As the Principal Investigator of this research project, you are ultimately responsible for:

- Protecting the rights, safety and welfare of research subjects
- Following the IRB-approved protocol (application and any materials submitted with it; e.g. only research team members designated to obtain consent on the scheme of delegation should only do so and no other personnel)
- Maintaining confidentiality of the subjects by not sharing Patient Identifiable Information outside HMC Facility
- Maintaining privacy of the subjects by performing research related procedures on subjects in private settings
- Reporting serious adverse events and serious unanticipated problems to the HMC-IRB and the other relevant compliance entities of HMC within 24 Hours of knowing about it
    - "Serious Adverse Event" (SAE) is any adverse event temporally associated with the subject's participation in research (whether or not considered related to the subject's participation in the research) that meets any of the following criteria:
    - results in death;
    - is life-threatening (places the subject at immediate risk of death from the event as it occurred);
    - requires inpatient hospitalization or prolongation of existing hospitalization;
    - results in a persistent or significant disability/incapacity;
    - results in a congenital anomaly/birth defect; or
    - any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

- Keeping the source documents (i.e. Cerner's medical records) updated regarding the enrollment of the patient , the MRC study number and study related procedures for each subject involved in the study

- Using only HMC-IRB stamped documents at HMC facilities while conducting the research. Those documents might have other institution's IRB stamp if applicable
- Following the requirements of HMC HRP policies, especially with regard to obtaining prior approval of changes to the research, reporting events or new information, progress reports before the expiry of the IRB approval by 60-90 days and final reports.
- Making sure that no study procedures should be conducted after the expiry date of the ethical (IRB) approval
- The conduct of the study team with regards to all of the above

Sincerely,

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

Signature:

Dr. Mohammed Hammoudeh

Chairman Institutional Review Board

Hamad Medical Corporation

Appendix 2: Survey questionnaire IRB approval and research info sheet

مؤسسة حمد الطبية
Hamad Medical Corporation
HEALTH · EDUCATION · RESEARCH صحة · تعليم · بحوث

INSTITUTIONAL REVIEW BOARD

HAMAD MEDICAL CORPORATION
DOHA-QATAR

Abdul Moqeeth Mohammed **Consultant Medicine** **Hamad Medical Corporation** **Doha-Qatar**	**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 :	Multi-criteria Decision Analytic Model for the Comparative Formulary Inclusion of Direct Oral Anticoagulants in Qatar
Study Number :	MRC-01-18-249
JIRB Number :	NA
QNRF Number :	NA
HMC Principal Investigator:	Abdul Moqeeth Mohammed
Date of Amendment Approval :	20 May 2019
Review Type :	Expedited
Decision :	Approved
Approved HMC Enrollment :	**300 Patients** **Survey - All Practitioners/ Clinicians (involved in prescribing anticoagulants) in HGH, HH and Wakra Hospital**
HMC IRB Amendment# :	01
NPRP Grant Holder:	NA

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.

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

مؤسسة حمد الطبية
Hamad Medical Corporation
HEALTH · EDUCATION · RESEARCH صحة · تعليم · بحوث

Sincerely,

Chairman of Institutional Review Board: **Dr. Mohammed Hammoudeh**

Date: 21st May 2019

Signature:

List of Approved Documents:

DOCUMENTTYPE	DOCUMENTNAME	LANGUAGE	NOOFPAGES	VERSIONNO
Other/Supporting document	selectioncriteria.pdf	English	1	V1.0
Questionnaire/ Survey	MRC-01-18-249_Questionnaire/Survey_Eng_V1.0_21-MAY-19_8Pages_1031756.1_16-MAY-19_8Pages_1031756.pdf	English	8	V1.0

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Institutional Review Board

Email: irb@hamad.qa Tel: 00974-40256410

HMC-IRB Registration: MoPH-HMC-IRB-020

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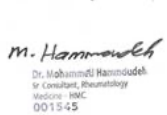
Responsibilities of the Principal Investigator:

As the Principal Investigator of this research project, you are ultimately responsible for:

- Protecting the rights, safety and welfare of research subjects
- Following the IRB-approved protocol (application and any materials submitted with it; e.g. only research team members designated to obtain consent on the scheme of delegation should only do so and no other personnel)
- Maintaining confidentiality of the subjects by not sharing Patient Identifiable Information outside HMC Facility
- Maintaining privacy of the subjects by performing research related procedures on subjects in private settings
- Reporting serious adverse events and serious unanticipated problems to the HMC-IRB and the other relevant compliance entities of HMC within 24 hours of knowing about it
    - "Serious Adverse Event" (SAE) is any adverse event temporally associated with the subject's participation in research (whether or not considered related to the subject's participation in the research) that meets any of the following criteria:
        - results in death;
        - is life-threatening (places the subject at immediate risk of death from the event as it occurred);
        - requires inpatient hospitalization or prolongation of existing hospitalization;
        - results in a persistent or significant disability/incapacity;
        - results in a congenital anomaly/birth defect; or
        - any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition
- Keeping the source documents (i.e. Cerner's medical records) updated regarding the enrollment of the patient , the MRC study number and study related procedures for each subject involved in the study
- Using only HMC-IRB stamped documents at HMC facilities while conducting the research. Those documents might have other institution's IRB stamp if applicable
- Enrolling only the approved sample size which will include all the withdrawn and lost to follow up subjects. Over recruitment, without prior approval is considered as protocol deviation.
- Following the requirements of HMC HRP policies, especially with regard to obtaining prior approval of changes to the research, reporting events or new information, progress reports before the expiry of the IRB approval by 60-90 days and final reports.
- Making sure that no study procedures should be conducted after the expiry date of the ethical (IRB) approval.
- The conduct of the study team with regards to all of the above.

Sincerely,



Signature:

Dr. Mohammed Hammoudeh

RESEARCH INFORMATION SHEET

Dear Participant:

You are invited to participate in Project title:

"Multi-criteria Decision Analytic Model for the Comparative Formulary Inclusion of Direct Oral Anticoagulants in Qatar**"**

Name of HMC Co-Investigator: Dr. Abdul Moqeeth Mohammed, Hamad Medical Corporation

The Medical Department at Hamad Medical Corporation is conducting this research to determine the best of the Qatari available DOACs for first-line use, based on evidence-based clinical, safety and economic data

The study will include all medical staff (Internal physicians, cardiologist, clinical pharmacists) at Hamad General Hospital, Al Wakra Hospital and Heart Hospital.

You are invited to take part in an anonymous questionnaire. This should take around 5-10 minutes to complete.
Your participation in the questionnaire is completely voluntary. If you choose to complete the questionnaire then completion is considered approval of participation. You can stop participating at any time and we will not hold it against you.

There is no risk to participating in this study. Your choice to participate or not will not affect your employment status; and your immediate supervisors/managers will not know your participation answers.

There are no direct benefits to you by taking part in the research. However, your participation may assist in creating a locally specific screening tool for the inclusion of DOAC in the HMC drug formulary.

No financial compensation for your participation

This research has been funded by Hamad Medical Corporation.

Your participation is anonymous, and all information will be kept confidential.
You have the right of knowing the results of this study at the end of it.
The total estimation for this study is two years.

If you have questions or concerns, or if you think the research has hurt you, talk to the HMC research team at:
Dr. Abdullatif Al-Khal, HMC (aalkhal@hmc.org.qa)
Dr. Abdul Moqeeth Mohammed, HMC (amohammed42@hamad.qa)
Dr. Daoud Al-Badriyeh, Qatar University (daoud.a@qu.edu.qu),
Dr. Hazem Fathy Elewa, Qatar University (hazem.elewa@qu.edu.qa)
Tel: (+ 974) 4403 5616 / 4403 5591, Fax: (+974) 4403 5551

If you have questions about your rights as a volunteer, or you want to talk to someone outside the research team, please contact:

- HMC Medical Research Centre at 4439 2440 or research@hamad.qa

Appendix 3: Survey questionnaire draft

Dear Participant:

You are invited to participate in Project title:

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If you have questions or concerns, or if you think the research has hurt you, talk to the HMC research team at:

Dr. Abdullatif Al-Khal, HMC (aalkhal@hmc.qa)
Dr. Abdul Moqeeth Mohammed, HMC (amohammed42@hamad.qa)
Dr. Ahmed Sobhy Hassan Ghonim Mahfouz, HMC (amahfouz1@hamad.qa)

If you have questions about your rights as a volunteer, or you want to talk to someone outside the research team, please contact: HMC – IRB at irb@hamad.qa

MRC-01-18-249 Validity: 30 09 2019 – 04 02 2020 E-stamped 01 Oct 2010

1. Are you a health-care provider involved in DOACs prescribing or making recommendations about DOAC?

- ☐ DOAC prescriber
- ☐ Make recommendations about DOAC
- ☐ No, I'm not a DOAC prescriber nor making recommendations about DOACs

2. Which hospital do you work for?

- ☐ Hamad General Hospital (HGH)
- ☐ Al Wakra Hospital (AWH)
- ☐ Heart Hospital (HH)
- ☐ Other: please specify ……

3. Which department do you work under?

- ☐ Cardiology department
- ☐ Emergency department
- ☐ Internal medicine department
- ☐ Pharmacy department
- ☐ Other: please specify ……
- ☐ Critical care department
- ☐ Hematology department
- ☐ Orthopedic department
- ☐ Surgery department

4. Rank the following 10 main selection criteria according to their importance to YOU when choosing one DOAC drug to prescribe/select among the DOACs drug class

(Rank from '1' as most important, to '10' as least important)

Rank	Main Selection Criteria
	Administration as crushed tablet
	Availability of a specific and approved reversal agent
	Clinical efficacy (e.g., stroke prevention, recurrent VTE etc...)
	Dosage frequency (e.g., once or twice daily)
	Drug interaction (e.g., CYP3A4 and/or Pgp inducers/inhibitors)
	Ease of switching during treatment (e.g., from warfarin/parental to DOAC)
	Pharmacokinetics properties (e.g., administration flexibility in regard to food)
	Regimen flexibility (e.g., lack of need for bridging at initiation)
	Safety (e.g., hemorrhagic stroke, gastrointestinal hemorrhage etc...)
	Special population requirements (i.e., dose adjustment in elderly)

5. Based on your clinical practice at HMC, how important is each of the following indicators when choosing a DOAC drug to prescribe/select among the DOACs drug class?

Indicator	High importance	Medium Importance	Low importance	Not Important
Administration as a crushed tablet				
Availability of a specific and approved reversal agent				
Clinical efficacy				
Cancer-associated thrombosis				
Extended prevention of recurrent VTE				
Heparin induced thrombocytopenia (HIT)				
Prevention of VTE post-hip and knee replacement				
Recurrent VTE in antiphospholipid antibody syndrome (APLAS)				
Recurrent VTE in other thrombophilia conditions (e.g. protein C deficiency, protein S deficiency, factor V Leiden)				
Secondary prevention of Myocardial infarction (MI)				
Secondary prevention of stroke in patients with NVAF and post-percutaneous coronary intervention (PCI)				
Stroke prevention in non-valvular atrial fibrillation (NVAF)				
Treatment of venous thromboembolism (VTE) including DVT and PE				
Dosage frequency indicator				
Once vs twice daily dosing				
Drug interaction indicators				
Lack of CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampin, or St John's wort)				
Lack of CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole itraconazole, or voriconazole)				
Lack of Pgp inducers (e.g. carbamazepine, rifampin)				
Lack of Pgp inhibitors (e.g. amiodarone, carvedilol, dronedarone, quinidine and verapamil)				
Ease of switching				
From DOACs to DOACs				
From DOACs to warfarin/parenteral				
From warfarin/parenteral to DOACs				

We thank you again for your time and effort. Your assistance in creating a scoring system for the DOACs formulary inclusion in HMC is very much appreciated.

As noted above, the collected data is anonymous and cannot be traced to an individual.

Yours sincerely,

HMC team

Appendix 4: ISPOR MCDA Good Practice Guidelines Checklist

MCDA Step	Recommendation	Implementation Brief Summary
1. Defining the decision problem	a. Develop a clear description of the decision problem b. Validate and report the decision problem	Determine whether the objective is to rank or value alternatives; whether the decision is one-off or whether a reusable model is required; consider alternatives; stakeholders; and decision constraints, such as budgets.
2. Selecting and structuring criteria	a. Report and justify the methods used to identify criteria b. Report and justify the criteria definitions c. Validate and report the criteria and the value tree	Criteria can be identified in documents describing previous decisions; evaluations to support related decisions; studies of stakeholders' priorities; and treatment guidelines. Effective criteria are marked by completeness, nonredundancy, nonoverlap, and preference independence. Individual criteria should be unambiguous, comprehensive, direct, operational, and understandable.
3. Measuring performance	a. Report and justify the sources used to measure performance b. Validate and report the performance matrix	The method for measuring performance should conform to the broad principles of evidence-based medicine and to local methods guidelines. Often such guidelines will recommend analysis of trial data or network meta-analysis to generate evidence on performance. When such data are not available, expert opinion should be used to fill the data gap.
4. Scoring alternatives	a. Report and justify the methods used for scoring b. Validate and report scores	The objective of scoring is to capture stakeholders' strength of preferences for changes in the performance within a criterion. The selection of the scoring method will depend on a number of characteristics of the decision problem. The full report includes a typology of scoring and weighting methods.
5. Weighting criteria	a. Report and justify the methods used for weighting b. Validate and report weights	The objective of weighting is to capture stakeholders' preferences between criteria. The selection of weighting methods should be made with consideration for the cognitive burden on stakeholders, level of precision required, theoretical foundations, and stakeholder heterogeneity.
6. Calculating aggregate scores	a. Report and justify the aggregation function used b. Validate and report results of the aggregation	The objective of aggregation is to combine scores and weights in a way that is consistent with stakeholders' preferences. The most commonly applied aggregation formula in health care MCDAs is the additive model.
7. Dealing with uncertainty	a. Report sources of uncertainty b. Report and justify the uncertainty analysis	The types of uncertainty that may impact the results of an MCDA should be reported, including imprecise or incomplete model inputs, variability in model inputs, quality of evidence, and structural uncertainty. Two broad approaches to considering the impact on uncertainty are available (ie, including uncertainty as a criterion in the MCDA and sensitivity analysis).
8. Reporting and examining the findings	a. Report the MCDA method and findings b. Examine the MCDA findings	The inputs/outputs of an MCDA can be communicated by the use of several tabular and graphical formats. In the end, MCDA is intended to serve as a tool to help decision makers reach a decision—their decision, not the tool's decision. This can be facilitated by presenting the MCDA model to decision makers and allowing them to explore the results and their sensitivity to inputs.