QATAR UNIVERSITY

COLLEGE OF PHARMACY

ECONOMIC EVALUATION OF THE CYP2C19 GENOTYPE-GUIDED ANTIPLATELET THERAPY COMPARED TO UNIVERSAL USE OF TICAGRELOR OR CLOPIDOGREL IN QATAR

BY

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ABSTRACT

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Title: Economic Evaluation of the CYP2C19 Genotype-Guided Antiplatelet Therapy Compared to the Universal Use of Ticagrelor or Clopidogrel in Qatar

Supervisor of Thesis: Dr. Daoud Al-Badriyeh, PhD.

Background: Clopidogrel requires activation primarily by cytochrome P450 2C19 (CYP2C19). Patients with *CYP2C19* loss-of-function alleles (LOF) are at increased risk of major adverse cardiovascular events. Ticagrelor is a more effective and expensive alternative antiplatelet agent that is unaffected by the *CYP2C19* polymorphism. The main aim of the current thesis is to evaluate the cost-effectiveness of *CYP2C19**2/*3 genotype-guided therapy compared to the universal use of ticagrelor or clopidogrel after a percutaneous coronary intervention (PCI) with acute coronary syndrome (ACS).

With the increasing size of relevant economic literature, another aim of the thesis was to perform a systematic review to answer the question about whether the overall evidence supports the genotype-guided selection of antiplatelet therapy as a cost-effective strategy in post-PCI ACS.

Methods: A two-parts model, including a one-year decision-analytic model and a 20-years follow-up Markov model, was created from the Qatari healthcare provider's perspective, to follow the use of (i) universal clopidogrel, (ii) universal ticagrelor, and (iii) genotype-guided antiplatelet therapy. Outcome measures were the incremental cost-utility ratio (ICUR) and incremental cost-effectiveness ratio (ICER) of genotype-guided therapy. Therapy success was defined as survival without myocardial infarction, stroke, stent thrombosis, cardiovascular death, or the no therapy discontinuation because of adverse events, i.e. major bleeding and dyspnea. Via a Monte Carlo simulation, the model was based on multivariate analysis.

For the systematic review, a literature search of PubMed, Embase, EconLit, and PharmGKB was done to identify all of the economic evaluations related to genotype-guided therapy compared to the universal use of antiplatelets in ACS patients. Quality of Health Economic Studies tool was used for quality assessment.

Results: Genotype-guided therapy was between dominant and cost-effective compared to universal clopidogrel in 100%, over the one-year duration (mean ICER of QAR 22,215 per case of success) and the long-term follow up. Genotype-guided therapy was dominant compared to universal ticagrelor in 60% of the cases over the one-year model, and cost-effective in 96% of the cases over the long term (ICUR of QAR 5,036 per QALY). Universal clopidogrel was dominant in 63% of the cases in the clinical outcomes over the one-year model, and cost-effective in 99% of the cases over the long term (ICUR of QAR 38,650 per QALY). One-way and multivariate sensitivity analyses confirmed the robustness of the study results.

The literature systematic review identified 13 articles. Six studies showed that genotype-guided therapy was cost-effective compared to universal clopidogrel, while five studies showed that it was dominant. One study specified that genotype-guided with ticagrelor is cost-effective only in both *CYP2C19* intermediate and poor metabolizers. Genotype-guided therapy was dominant when compared to universal prasugrel, ticagrelor, or both in five, one, and three studies, respectively. Only two studies reported that universal ticagrelor was cost-effective compared to genotype-guided treatment. All of the included articles had good quality.

Conclusion: *CYP2C19* genotype-guided therapy appears to be the preferred antiplatelet strategy over the universal use of ticagrelor or clopidogrel for post-PCI patients in Qatar. Based on current economic evaluations in the literature, implementing *CYP2C19* genotype-guided therapy is a cost-effective approach in guiding the selection of medication in patients with ACS post-PCI.

DEDICATION

“My Parents”

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This thesis would not have been completed without the support of many people during my studies. I take this opportunity to thank all individuals who generously contributed to the work presented in this thesis:

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ABBRIVATIONS

ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
ADR	Adverse drug reaction
BMS	Bare metal stent
CABG	Coronary artery bypass graft surgery
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
Clo-AM	Clopidogrel active metabolite
CMA	Cost-minimization analysis
CBC	Complete blood count
CMP	Comprehensive metabolic panel
CT	Computed tomography
CVD	Cardiovascular disease
CUA	Cost-utility analysis
CYP450	Cytochrome P450
DAPT	Dual antiplatelet therapy
DECR	Decremental cost-effectiveness ratio
DES	Drug-eluting stent
ECG	Electrocardiograph
ED	Emergency department
ECHO	Echocardiography
FDA	Food and Drug Administration
HbA1C	Hemoglobin A1C
HICs	High-income countries

ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
ICU	Intensive care unit
LMICs	Low-to-middle-income countries
LOF	Loss-of-function
LY	Life-year
MACE	Major adverse cardiovascular events
MRA	Magnetic resonance angiography
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NICE	National Institutional for Health and Clinical Excellence
NSTEMI	Non-ST elevation myocardial infarction
PCI	Percutaneous coronary intervention
PLATO	Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndrome
POC	Point-of-care
QALY	Quality-adjected-life-year
RCT	Randomized clinical trial
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction
UA	Unstable angina
US	United States
WHO	World Health Organization
WTP	Willingness-to-pay threshold

CHAPTER 1: INTRODUCTION

1.1. Cardiovascular disease

The cardiovascular disease (CVD) is a group of diseases that affect the heart and blood vessels. It includes coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism. Mainly, many CVDs are related to atherosclerosis, in which obstruction occurs due to the build-up of plaque on the inner walls of blood vessels, preventing blood supply to the heart or the brain (1). According to the World Health Organization (WHO), CVD is the leading cause of death globally and, in 2016, 17.8 million people died from CVD, accounting for 31% of global mortality (2).

1.2. Acute coronary syndrome

The diagnosis of an acute coronary syndrome (ACS) is applied to patients with probable or definite acute myocardial ischemia and/or infarction that occurs due to an abrupt decrease in the coronary blood flow. ACS is classified according to changes in electrocardiograph (ECG) and detection of abnormal cardiac biomarkers into three types: ST-elevation myocardial infarction (STEMI), Non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA) (3). Although UA and NSTEMI differ in severity, they are largely related conditions with similar pathophysiologic causes and clinical symptoms. The diagnosis of NSTEMI can be distinguished from UA by the degree of the ischemia which results in adequate myocardial damage and the release of detectable quantities of biomarkers of myocardial injury into the blood circulation (i.e., cardiac-specific troponins T or I, creatine kinase myocardial band). Whereas, UA is characterized by the lack of elevation in cardiac biomarkers after the initial onset of ischemic symptoms, the presence of angina even at rest which typically persist for 10-

20 minutes, regardless of the presence or absence of changes in ECG (e.g., ST-segment depression or transient elevation or new T-wave inversion). STEMI is characterized by ST-segment elevation of >1mm above baseline on ECG, or a new- onset left bundle branch block (4).

1.3. Epidemiology and economic burden of ACS

There is a recognized increase in the number of patients with CVD, with the incidence of ACS significantly increasing. At the level of the United States (US), as an example, it is estimated that >780 000 persons will experience ACS every year, and approximately 38% of those will have STEMI (5,6). Data from the Global Burden of Diseases study and multiple registries revealed that the average age of ACS incidence is ten years less in low-to-middle-income (LMICs) countries than in high-income countries (HICs), with the average age in LMICs being approximately 50 years (7–12). A study in Arabian Gulf countries showed that out of the total ACS patients, 45.6% had STEMI and 54.4% had NSTEMI (9). In Qatar, there is no exact data on the spread of ACS, but it was reported in 2013 that cardiovascular disease is the leading cause of mortality and disability from non-communicable diseases, in which the death rate is 8.3 per 100,000 for Qatari males and 4.1 per 100,000 for non-Qatari males (11). Additionally, 27% of the recorded deaths in Qatar were due to cardiovascular disease (13).

The American Heart Association reported that in 2014 and 2015, the direct and indirect costs of CVD and stroke were $351 billion ($214 billion in direct costs and $137.4 billion in lost productivity/mortality) (14). As noted above, ACS has a great impact on household livelihood in LMICs as it affects individuals at a younger age, often when they are economically productive. Households endure an increased burden from both the high costs of treating ACS and loss of productivity (10). However, not

only the LMICs are affected; in Australia, for example, patients with ACS encounter a substantial economic burden as it is associated with excess out-of-pocket cost compared to the national mean cost (15). From the Australian government perspective, it was estimated that ACS cases cost $1,930.2 million in 2017-2018 (16). The costs for medical management, and relevant procedures (*vide infra* in Section 1.5) such as percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) were $34,087, $52,673, and $86,914, respectively (17). A registry in the US showed that the average cost for STEMI was $19327, and for NSTEMI was $18465 (18).

1.4. Early management of ACS

The goals of therapy for the initial management of ACS are to minimize cardiac ischemia and prevent mortality. The initial assessment of ACS should be based on the ECG and cardiac biomarkers results, as well as the careful review of the patient history and physical examination. Nitrates, aspirin, beta-blockers, and oxygen are standard pharmacological therapies that are administered based on the suspicion of ACS at the emergency department (ED) before a definitive diagnosis (19).

1.5. Management of STEMI

Once the diagnosis of STEMI is made, the patient is immediately taken from the ED to the cardiac catheterization laboratory. Patients should undergo coronary angiography and receive reperfusion therapy by either fibrinolysis, PCI, or CABG as soon as possible (20). Fibrinolytic therapy is known as the use of medications to cause lysis of blood clots formed in blood vessels, such as streptokinase, alteplase, and reteplase. PCI is a non-surgical procedure in which a small balloon at the tip of the catheter is inflated with or without a stent replacement to open up blood vessels narrowed by plaque build-up in the heart. Once the artery is opened the balloon is deflated, and the catheter is removed. There are two types of stents either a bare-metal

stent (BMS) or a drug-eluting stent (DES) to open up blood vessels narrowed by plaque build-up in the heart (21). Primary PCI is preferred over fibrinolytic therapy when the expected first medical contact-to-device time is reasonable, and the patient presents to a well-equipped facility with skilled interventional cardiologists and highly trained supporting staff. Compared with fibrinolytic therapy, primary PCI results in higher survival, increased rates of infarct artery patency, and thrombolysis in myocardial infarction (TIMI) 3 flow, as well as lower rates of recurrent ischemia, reinfarction, intracranial hemorrhage, and hospitalization (22). It is recommended that all patients with STEMI undergo primary PCI within 90 minutes of first medical contact at a PCI-capable hospital or within 120 minutes if the patient presents at a facility that is not PCI-capable and a transfer to a PCI-capable hospital is needed (20). PCI, however, commonly causes trauma to the arterial endothelium of the blood vessel, which leads to the activation and aggregation of platelets. Eventually, this can lead to coronary thrombosis. To reduce such risk, patients must receive adjunctive antiplatelet therapies. Dual antiplatelet therapy (DAPT) combining aspirin and a P2Y12 antagonist (i.e., clopidogrel, ticagrelor or prasugrel) is the gold standard regimen after PCI (19).

An alternative procedure to PCI is CABG surgery, which involves grafting arteries or veins from elsewhere in the patient's body to the coronary arteries to bypass atherosclerotic narrowing and improve the blood supply to the coronary circulation supplying the myocardium. Urgent CABG is indicated in STEMI patients with a coronary blockage that is not amenable to PCI who have recurrent ischemia, severe heart failure, or cardiogenic shock (23). Fibrinolytic therapy, on the other hand, is recommended within 30 minutes of arrival to the ED when there is an expected delay in performing primary PCI within 120 minutes of first medical contact (24).

1.6. Management of NSTEMI

In patients with a diagnosis of NSTEMI, it is crucial to use risk stratification tools to differentiate between patients at high versus low risk of having another cardiac event in order to select the appropriate treatment plan. Generally, an early invasive strategy is recommended for patients at medium or high risk, while the early conservative strategy is recommended for those at lower risk (25). The early invasive strategy aims to quickly risk-stratify patients by evaluating their coronary anatomy. Its main advantages are allowing fast and definitive evaluation, early revascularization which prevents any ACS related complications that can occur during medical therapy, and leads to a shorter hospitalization (26,27). The early invasive strategy includes performing invasive coronary angiography, which is followed by PCI or CABG if needed (25). The early conservative strategy aims to avoid the early use of invasive procedures as some patients might be stabilized with medical therapy alone and do not need coronary angiography and revascularization. The early conservative strategy includes administration of heparin product (preferably LMWH or fondaparinux) with or without glycoprotein IIb/IIIa inhibitors (25).

1.7. Dual antiplatelet therapy

The goal of dual antiplatelet therapy is to minimize stent thrombosis as well as recurrent major adverse cardiovascular events (MACE), which is a composite outcome of nonfatal stroke, nonfatal myocardial infarction (MI), and cardiovascular death (28). The optimal duration of DAPT after PCI remains controversial as it is influenced by the patient's risk factors and the type of stent used. European, Canadian, Australian, US, and British guidelines demonstrated that DAPT should be given for a duration of 12 months after placement of either BMS or first-generation DES based on the findings of the CREDO study (29–32). Only clopidogrel and ticagrelor are available in the Qatar

National Formulary. For more than 15 years, clopidogrel has been the gold standard P2Y12 receptor antagonist in Qatar. Ticagrelor was introduced in 2014 to the formulary of Hamad Medical Corporation (HMC), which is the leading healthcare institution in Qatar (33).

1.7.1. Clopidogrel

Clopidogrel is an oral antiplatelet medication that was first manufactured by Sanofi and Bristol-Myer Squibb Pharmaceuticals. It was approved by the U.S. Food and Drug Administration (FDA) in 1997, and its patent continued until 2012 under the trade name Plavix (34,35). It was reported that clopidogrel was the second-highest selling medication globally in 2010, with $9.4 billion in sales (35). In addition, clopidogrel was selected to be among the WHO model list of essential medicines, as it is considered a high priority medicine (34).

As evident from its chemical structure depicted in Figure 1.1, clopidogrel is a second-generation thienopyridine. The active form of clopidogrel selectively and irreversibly binds to P2Y12 adenosine diphosphate receptors (ADP) on platelets. Consequently, it inhibits ADP binding to P2Y12 receptors, activation of the glycoprotein GPIIb/IIIa complex and, eventually, platelet aggregation. The pharmacological effect of clopidogrel lasts for the platelet lifespan (i.e., 7 to 10 days) (36,37).

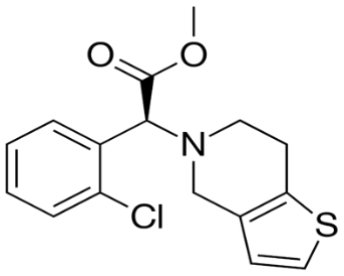


Figure 1.1 The chemical structure of clopidogrel

Clopidogrel is a prodrug that requires hepatic biotransformation to form an active metabolite. Only 15% of clopidogrel dose is converted into the active form by two sequential oxidative steps that involve various cytochrome P450 (CYP450) enzymes, including CYP2C19, CYP2B6, CYP1A2, CYP3A4, and CYP2C9, as shown in Figure 1.2. The remaining 85% undergoes the first-pass metabolism to form inactive metabolites (36). Enzyme kinetics studies illustrated that CYP2C19 (44.9%), CYP1A2 (35.8%), and CYP2B6 (19.4%) contribute to the formation of 2-oxo-clopidogrel, whereas CYP2C19 (20.6%), CYP2B6 (32.9%), CYP3A4 (39.8%), and CYP2C9 (6.79%) contribute to the formation of clopidogrel active metabolite (clop-AM). Therefore, the total contribution of CYP2C19 in the formation of clop-AM is around 50%, which makes it one of the key determinants of the active metabolite concentration (38).

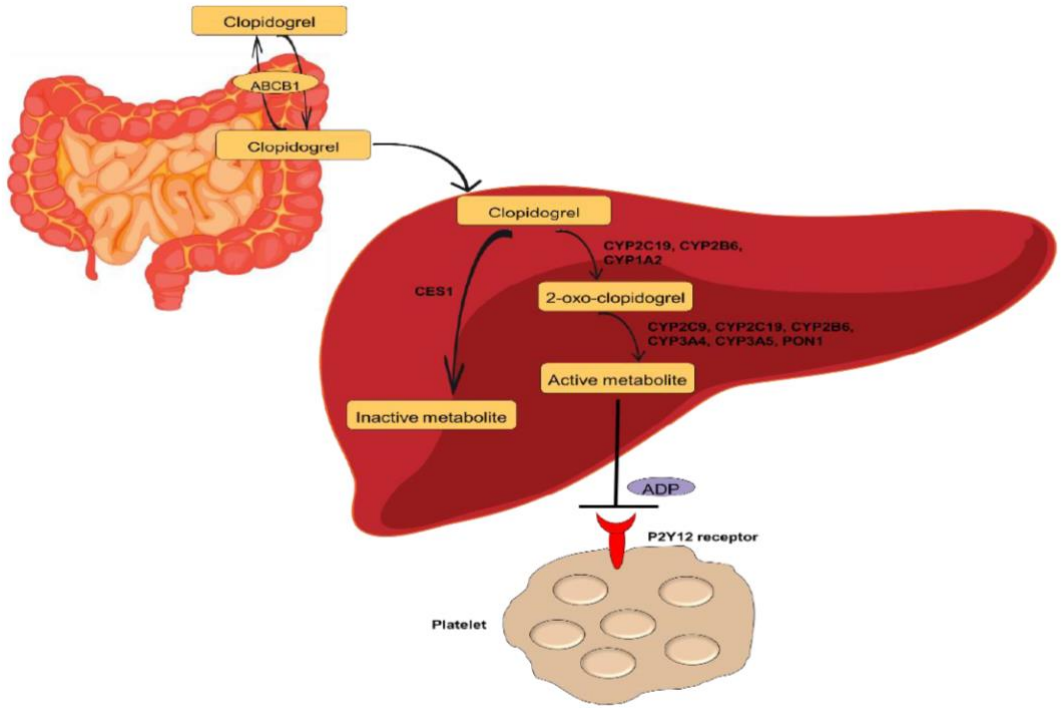


Figure 1.2 Clopidogrel bioactivation

Initially, pharmacogenomic studies investigated the impact of *CYP2C19* loss-of-function (LOF) alleles on clop-AM plasma concentration, and it was shown that the *CYP2C19* LOF alleles carriers have lower plasma concentration of clop-AM compared to the individuals with wild type. Consequently, this can correlate with the extent of platelet inhibition and eventually clinical outcomes (39–41). One-third of patients receiving clopidogrel do not have an adequate response to the therapy. This interpatient variability may negatively affect both the efficacy and safety profile of the drug (42-45).

Genetic polymorphisms in the *CYP2C19* gene is responsible for the inter variability of the response to clopidogrel (45). The wild-type *CYP2C19**1 allele is related to the functional CYP2C19 enzyme (46). The most prevalent *CYP2C19* loss-of-function (LOF) allele is *CYP2C19**2, which creates an aberrant splice site. This defect alters the mRNA reading frame and subsequently results in a non-functional protein (47). The reported *2 allele frequencies are approximately 15%, 15%, and 29–35% in Caucasians, Africans, and Asians, respectively. Other LOF alleles that are less common are *3, *4, *5, *6, *7, and *8, which have frequencies of less than 1%, except for CYP2C*3 that can occur in 2-9% of the Asian population (46). *CYP2C19**3 allele contributes to a premature stop codon at amino acid 212 (47). Contrarily, the increased function allele is *CYP2C19**17 which contributes to the higher *CYP2C19* expression and activity by forming a binding site for the GATA transcription factor family (48). The reported *17 allele frequencies are approximately 21%, 16%, and 3% in Caucasians, Africans, and Asians, respectively (46). On this basis, the FDA has updated the label of clopidogrel to include a warning against its use in *CYP2C19* poor metabolizers (49)

1.7.2. Ticagrelor

Ticagrelor is a newer oral antiplatelet that is marketed by Astra Zeneca Pharmaceuticals in the US as Brilinta and in Europe as Brilique or Possia. It was approved by the FDA in July 2011 and by the European Union in December 2010 (50). The Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndrome (PLATO) trial showed that ticagrelor has higher efficacy compared to clopidogrel in reducing the composite outcome of MACE (i.e., MI, stroke, and cardiovascular death), but it is associated with increased risk of non-procedure-related bleeding (51). Ticagrelor is a non-thienopyridine P2Y12 inhibitor, as shown in Figure 1.3. It binds directly and reversibly to the P2Y12 ADP receptor on platelets; thereby, preventing platelet activation and aggregation (52).

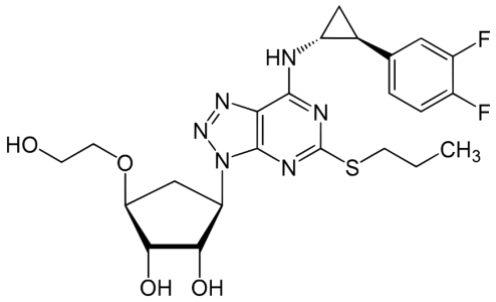


Figure 1.3 The chemical structure of ticagrelor

Ticagrelor does not require biotransformation to an active form, giving it the advantage of a having faster onset of action and being unaffected by *CYP2C19* genetic mutations (53). In the pooled analysis of the ONSET/OFFSET and RESPOND genotype studies, the *CYP2C19* genotype did not influence the antiplatelet activity of ticagrelor as it did clopidogrel (54). A genetic sub-study of the PLATO trial

demonstrated that ticagrelor significantly reduced MACE compared to clopidogrel, irrespective of *CYP2C19* polymorphisms (55). Because ticagrelor is quickly absorbed, it requires twice-daily dosing, unlike clopidogrel, which is administered once daily (53). Ticagrelor can be up to 20 times more expensive than generic clopidogrel since it is still under patency. In addition, it has increased secondary costs due to its higher risk of bleeding complications when compared to clopidogrel (56).

1.8. Pharmacogenomics

Interindividual variability in medication response is an important issue in the current clinical practice, which can greatly impact the efficacy and safety of medications (57). Pharmacogenomics is a field that studies how genetic differences influence the variability in patients' response to medications. Therefore, it enables predicting the medication response based on an individual's genetic make-up. In other words, pharmacogenomics is applied to identify patients with the potential of experiencing a lack of efficacy or having a higher risk of adverse events to medications. Thus, it can be used to guide optimal drug selection and drug dosing for patients to maximize therapeutic outcomes, minimize adverse drug reactions (ADRs), and improve quality of life (58,59).

According to the Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C19* genotype and clopidogrel therapy, individuals are classified based on their *CYP2C19* genotype into (60):

- Ultra-rapid (UR): Have normal or increased activity (~5–30% of patients) with alleles (*1/*17, *17/*17).
- Rapid metabolizer (RM): Carry one *CYP2C19**17 allele with one normal function *CYP2C19**1 allele (*1/*17).

- Extensive (EM): Have the desired normal metabolism (~35–50% of patients) wit alleles (*1/*1).
- Intermediate (IM): Have an intermediate enzyme activity with alleles (*1/*2, *1/*3, *2/*17).
- Poor metabolizers (PM): Have a reduced or deficient activity with alleles (*2/*2, *2/*3, *3/*3).

1.8.1 Genetic testing

Genetic testing requires either a blood sample or buccal swabs (46). Recently, genetic point-of-care (POC) assays for *CYP2C19* were developed for clinical use with many advantages, including high accuracy and reliability (i.e., analytic validity and reliability >97%), a quick turnaround time of genotyping (i.e., results can be available within three hours), minimal training requirements, and portability that enables testing at the patient's bedside. However, the main disadvantage of the genetic POC assay is the higher direct cost (61).

Personalization of antiplatelet therapy in patients undergoing PCI can be achieved by conducting genetic testing for *CYP2C19*, which can help guide the decision between ticagrelor or clopidogrel. In other words, carriers of *CYP2C19*2* or *CYP2C19*3* LOF alleles would receive ticagrelor, and noncarriers would receive clopidogrel (46). The clinical benefit of CYP2C19 genetic testing after PCI was shown in a recent randomized controlled trial (RCT); whereby *CYP2C19* genotype-guided strategy for the selection of oral P2Y12 inhibitor therapy was non-inferior to the universal administration of ticagrelor or prasugrel regarding the thrombotic events and was associated with lower bleeding events at 12 months (62).

1.9. Pharmacoeconomics

Pharmacoeconomics is the field of study that evaluates the costs and consequences of pharmaceutical products and services. Pharmacoeconomics is a description and analysis of the costs of health interventions to the healthcare system and society. It is used as a tool for decision-makers in healthcare sectors as it combines both descriptive and analytical methods to comparatively evaluate alternative health interventions in relation to their costs and outcomes and, ultimately, guide the decision-making process. In addition, it allows clinical decision-makers to prioritize various and competing healthcare services and products for the individual use of interventions and/or inclusion in drug formularies, in order to achieve the efficient utilization of resources. Moreover, pharmacoeconomics allows combining different aspects of the outcomes, accounting for its three-dimensional nature: clinical, economic, and the broader humanistic outcomes, in what is known as the ECHO model (Figure 1.4) (63,64).

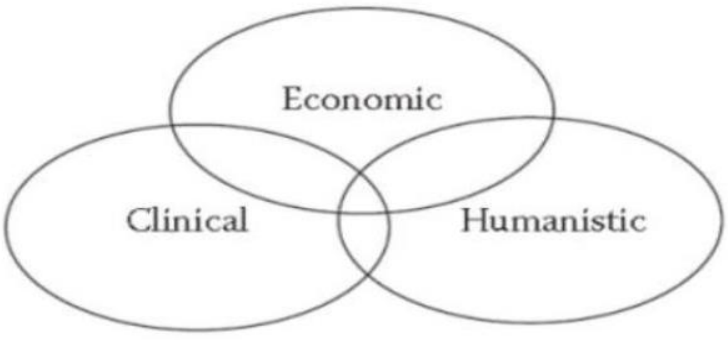


Figure 1.4 The ECHO model

1.9.1. Perspective

In pharmacoeconomics, the ‘perspective’ of the study is a crucial element to differentiate any pharmacoeconomic analysis. The ‘perspective’ is defined as the viewpoint from which (or from whose interest) the analysis is conducted, which determines the input and cost data that should be collected, valued, and included in the analysis. The following are the most common study perspectives (63):

a. Payer perspective: This includes the costs to the third-party plan or the patient or a combination of the patient co-pay and the third-party plan costs. Examples of this perspective include the interest of insurance companies, Medicare, and the Health Maintenance Organization. In a patient perspective, the patient’s out of pocket expenses are estimated.
b. Hospital perspective: This accounts for resources as per their cost to the hospital. It often only includes direct medical costs such as medication acquisition, hospital stay, and medical tests conducted.
c. Societal perspective: This is the broadest and most comprehensive as it considers all costs and effects, including those related to patients such as loss of time, transportation, and travel cost.

1.9.2. Types of cost in pharmacoeconomics

The cost of medical intervention is not its acquisition cost only; rather the actual costs encompass the value of all and any resources consumed during the application of the intervention, including those related to the consequences (65). The key types of costs are direct medical costs, direct nonmedical costs, indirect costs, and intangible costs. Table 1.1 shows examples of each of the cost type (63).

1.9.3. Types of pharmacoeconomic evaluations

There are four basic types of methodologies that are used in pharmacoeconomic evaluations to look at both costs and consequences within the healthcare setting.

Table 1.1 Examples of the four types of costs used in pharmacoeconomic

Type of cost	Example
Direct medical costs	Medication, medication monitoring, medication administration, patient counseling, diagnostic tests, clinic visits, emergency department visits
Direct nonmedical costs	Travel cost to receive health care, nonmedical assistance related to the condition, child care services for children of patients
Non-direct costs	Lost productivity for the patient, lost productivity for the unpaid caregiver
Intangible costs	Pain and suffering, fatigue, anxiety

1.9.3.1. Cost-minimization analysis (CMA)

It is deemed to be the simplest of all pharmacoeconomic evaluations. It compares two or more health interventions that are assumed to have equivalent clinical outcomes and only differ in cost. The use of CMA is limited in the literature because, in practice, clinical outcomes are rarely completely identical. For instance, the ADRs of two different medications used for the same indication may not necessarily be similar. An example of CMA is the comparison of two generic medications for the same indication (63).

1.9.3.2. Cost-effectiveness analysis (CEA)

It is used to compare two or more health interventions with the same type of outcomes, but with a different level of performance, such as two different medications used to reduce blood glucose. In other words, interventions can vary in the level of the outcomes, but the outcomes must be similar in nature. CEA is the most commonly

applied type of pharmacoeconomic evaluations because it only considers outcomes as presented in natural units [e.g., lipoprotein cholesterol (LDL-C), millimeters of mercury (mmHg), and years of life saved] which can be easily accessed and interpreted by practitioners and decision-makers in practices and settings. However, CEA has some disadvantages; firstly, interventions must have similar outcome measures (i.e., similar clinical units). Secondly, humanistic outcomes, including assessment of quality-of-life (QoL), are not considered as evaluations. Finally, interventions have to be compared against one indication at a time, and multiple CEAs will be required if the interventions have several concurrent indications to look at. The results of the CEA are expressed as either the incremental cost-effectiveness ratio (ICER), which expresses the value of money spent to gain one extra natural unit or decremental cost-effectiveness ratio (DCER), which express the value of money saved against one lost natural unit. The ICER is calculated when dominance (better cost and effect with one intervention) does not exist between comparators. When performing a CEA to compare interventions A and B, as illustrated in the cost-effectiveness grid presented in Table 1.2, the ICER will be calculated in the scenarios of having a higher effect but higher cost than the comparator or lower cost but lower effect than the comparator (66).

Table 1.2 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

1.9.3.3. Cost-benefit analysis (CBA)

In contrast to CEA, CBA compares health interventions that have different types of outcomes. This can be achieved by transferring both cost and outcomes into monetary values. Therefore, costs and outcomes are presented as a benefit-to-cost ratio, net cost, or net monetary benefit, where the comparator with the highest net gain (benefit) is preferred. Measuring both costs and benefits in monetary terms have two significant advantages. Firstly, as mentioned above, interventions that have outcomes different in nature can be compared, because all outcomes will be eventually expressed in unified monetary value. Secondly, clinicians and decision-makers can directly determine whether the benefits of an intervention exceed the costs of its implementation. However, the disadvantages of performing CBA is that it is not readily applicable in many clinical situations since there is no standard methodology on how to attribute to money values to specific outcomes and - even when methods are used - they result in subjective estimations, especially regarding non-monetary costs and benefits, such as satisfaction (67).

1.9.3.4. Cost-utility analysis (CUA)

CUA measures cost per an outcome that is based on years of life that are adjusted by 'utility' weights measure (i.e., quality-adjusted life years (QALYs)), which range from utility score 1.0 for 'perfect health' to score 0.0 for 'death'. Thus, CUA does not only consider the extension of life as an outcome of an intervention, but also the quality of that life. QALYs are obtained by multiplying life-years (LYs) by the patients' utility in the year. Similar to CBA, CUA can compare different outcome measures since they are unified as a single measure; QALY in this case. Results of CUA are mostly presented as an incremental cost-utility ratio (ICUR), which is defined as the cost per additional QALY gained. The major disadvantage of CUA is that there is no standard

methodology to measure the utility weights as they are considered subjective estimates. That is why CUA is increasingly deemed as a subset of CEA (67). Just like with when ICER is measured, as explained in Table 1.2, ICUR is only measured in cases where no dominance status exists between comparators.

1.9.4. Decision analysis

Decision analysis is the application of an analytical method to systematically compare different decision options. It allows decision-makers to process available health interventions when comparing them, by identifying the consequences and outcomes of each intervention, estimating the probability of defined outcomes of theirs, analyze the recourse utilization towards each of the outcomes, identify the monetary value of each outcome and, eventually, select the intervention. The visualization of a decision analysis of comparative options and their consequences is best conducted via a decision tree. The decision model (tree) graphically presents the components of the decision problems and relates actions to consequences, displaying choices, and facilitating the calculation of values needed to compare interventions. Creating the decision model is relatively simple as several computer software are available that highly simplify the calculations. Widely known examples of software are Treeage® software (www.treeage.com) and Palisade Risk® (www.palisade.com). Figure 1.5 illustrates the skeleton of a hypothetical decision-analytic model. Currently, in CEA, the focus of decision analysis has extended from comparing decision options in terms of their effect on life and death to comparing the amount of extension in life and on measures of QoL. Life expectancy or QALYs are incorporated in many decision analysis models (66,67).

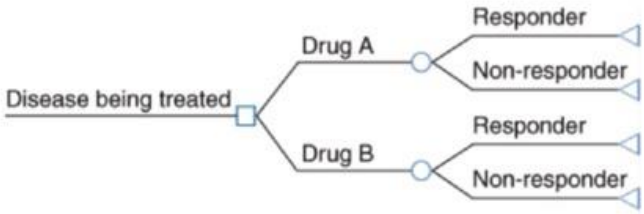


Figure 1.5 Simplified decision tree design

1.9.5. Sensitivity analyses

The pharmacoeconomic analytic modeling is populated with clinical and cost input data that are deterministic and probabilistic in nature. Depending on the data sources and study assumptions, the values of input variables can be associated with uncertainty. In order to ensure the robustness of the economic study's conclusion against such uncertainty, the economic analysis ideally includes sensitivity analyses. Here, a sensitivity analysis is a process in which the baseline values of the main input variables are varied within a range of value uncertainty so that the variations in the outcomes are examined against the baseline study outcomes and value of results (67). The most commonly used types of sensitivity analysis are

a. One-way sensitivity analysis: The value of only one variable is changed in the analysis while the values of other variables are maintained (67).
b. Multivariate sensitivity analysis: Several variables are changed concurrently in the analysis. If applied to the appropriate variables, the multivariate analysis is a better reflection of the real-life parallel uncertainty in inputs (67).
c. The scenario sensitivity analysis: A baseline scenario, about a methodological approach or assumption as an 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 revisited.

1.10. Country profile of Qatar

Qatar is an Arab emirate located in the Gulf region of the Middle East. The recorded population is over 2.7 million, and it is characterized by cultural diversity among residents due to the high percentage of expats (85%) (68).

In 2017, the total gross domestic product (GDP) was approximately United States Dollar (USD) 170.8 billion, accounting for a quarter of the global economy (69). In 2019, the average GDP per capita based on purchasing-power party is projected to remain above Intl$ 134,000 (69); one of the world's highest. In 2014, the total public health expenditure was 34.99% of GDP per capita, and it was reported by the Supreme Council of Heath in 2012 that Qatar spent a total Qatari Riyal (QAR) 15.14 billion on healthcare sector (70,71). In Qatar, the healthcare services are offered through (i) the primary health care centers, which constitute the basic care provided at 21 medical centers, (ii) specialized clinics, (iii) hospitals, and (iv) the private sector which plays an adjunct role in providing health services, mostly through three general hospitals, 131 dental clinics, and 128 clinics for medical services. Qatari patients can receive unlimited free services by government-related institutions. For non-Qatari patients, however, the most necessary healthcare services are fully covered by the governmental insurance, with partial coverage of elective and outpatient services, such as orally prescribed medications (72).

HMC is the main 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. Part of HMC, and in relation to ACS treatment, the only specialized hospital for cardiology and cardiothoracic surgery is the Heart Hospital, with a 116 beds capacity.

CHAPTER 2: REVIEW OF LITERATURE

2.1. Economic studies comparing genotype-guided antiplatelet therapy with ticagrelor versus universal use of ticagrelor or clopidogrel

As discussed in chapter one of the thesis, genotype-guided therapy is used to identify patients with a potential for lack of efficacy or high risk of adverse events to medications. Preemptive identification of *CYP2C19**2 or *3 carrier status might allow personalization of antiplatelet therapy so that the new, more expensive ticagrelor could be selectively prescribed to patients who will not benefit from clopidogrel (those with the *CYP2C19* LOF alleles), while clopidogrel would be prescribed to the rest of the patients. The added value of the genetic testing, however, may not worth the value of money spent on the testing.

There are nine studies in the literature that have sought to evaluate the economic impact of *CYP2C19* genotype-guided antiplatelet therapy versus universal use of ticagrelor or clopidogrel relative to their outcomes in patients with ACS undergoing PCI.

- Genotype-guided therapy with ticagrelor versus universal use of ticagrelor or clopidogrel (n= five studies) (73–77)

In 2011, a CEA was conducted by Crespin et al. in the US (73). They considered the cost of the medications, management of clinical events (i.e., MI, death, dyspnea, and bleeding), genetic test, and subsequent monthly ACS care. The clinical input data of ticagrelor and clopidogrel were obtained from the PLATO trial (51) and a meta-analysis by Mega et al. (43) that assessed the adverse clinical outcomes among patients with *CYP2C19* LOF alleles who were treated with clopidogrel. The study was from the Medicare perspective in the US, and the findings showed that the ICER for universal ticagrelor compared to genotype-guided therapy was USD 42,546 and 10,059 per

QALY at 12 months and 5 years, respectively. Ultimately, prescribing ticagrelor to all patients regardless of their genetic profile increases QALY for ACS patients at a reasonable cost.

Another CEA was conducted in the US in 2019 by Kim et al. (74). The study evaluated costs and cardiovascular adverse events, including death, ischemic stroke, intracranial hemorrhage, and major bleeding. Similar to the study by Crespin et al., the clinical effectiveness data was based on the PLATO trial and a meta-analysis by Mega et al. (43). The study time horizon was one year and a lifetime from the US healthcare sector perspective. It was shown that the use of ticagrelor in both *CYP2C19* intermediate and poor metabolizers (i.e., genotype + liberal ticagrelor) is a cost-effective strategy with an ICER of USD 29,412 per QALY. On the other hand, the use of ticagrelor in *CYP2C19* poor metabolizers only (i.e., genotype + conservative ticagrelor) was not a cost-effective strategy. The ICER for the universal use of ticagrelor was USD 142,456 per QALY.

In a 2013 study in Australia, Sorich et al. included the cost of medications, genetic testing, and MACE (nonfatal MI, fatal MI, nonfatal stroke, fatal stroke) (75). The probability of clinical events was based on the PLATO trial and its genetic sub-study. The study time horizon was one year and a lifetime from the Australian healthcare system perspective. The universal use of ticagrelor was the most cost-effective strategy with an ICER of Australian Dollar (AUD) 23,000 per QALY, while *CYP2C19* genotyping was cost-effective when compared to universal clopidogrel with an ICER of AUD 6,000 per QALY.

A CEA was conducted by Wang et al. in China in 2017, and the clinical data of cardiovascular events were taken from small-scale local observational studies in the Asian populations (76). The cardiovascular events that were included were nonfatal MI,

nonfatal stroke, stent thrombosis, fatal bleeding, and death from vascular or nonvascular causes. The study time horizon was one year and a lifetime from the Asian healthcare provider perspective, thus only the direct medical cost was considered. The findings showed that genotype-guided therapy was dominant compared to universal ticagrelor, but cost-effective when compared to universal clopidogrel with an ICER of USD 2,560 per QALY. Universal ticagrelor was cost-effective compared to universal clopidogrel with an ICER of USD 7,254 per QALY.

Limdi et al. conducted a CEA in 2020 using real-world data to evaluate the clinical and economic impact of universal clopidogrel; universal ticagrelor; *CYP2C19* genotype-guided therapy; nonguided de-escalation strategy (i.e., prescribe universal ticagrelor for the one month after PCI, followed by prescribing universal clopidogrel without genotyping); genotype-guided de-escalation to clopidogrel only in patients without a LOF allele for the remaining 11 months (77). The study time horizon was one-year from the US payer perspective. The primary analysis showed that only genotype-guided therapy was cost-effective with an ICER of USD 42,365 per QALY. The secondary analysis showed that universal clopidogrel and genotype-guided therapy were dominated by the nonguided de-escalation strategy. As well as, compared with the nonguided de-escalation strategy, the genotype-guided de-escalation and universal ticagrelor were not cost-effective with ICER of USD 88,680 and 678,215 per QALY, respectively.

- Genotype-guided therapy with alternative P2Y12 inhibitors (prasugrel and ticagrelor) versus universal use of alternative P2Y12 inhibitors or clopidogrel (n= four studies) (78–81)

In the US in 2014, Kazi et al. sought to assess both clinical and economic aspects of *CYP2C19* genotype-guided therapy compared to the universal administration of

antiplatelets (78). Generally, the data sources were published literature, including the TRITON-TIMI 38, PLATO trials, and Medicare claims. The clinical outcomes were nonfatal MI, revascularization, stent thrombosis, intracranial and extracranial bleeding, and death from any cause. The study time horizon was a lifetime from the US Societal perspective including direct and induced medical costs, but not indirect costs. They explained that they modeled two scenarios due to the uncertainty in the degrees of association between carrier states and thrombotic events and the ability of LOF alleles to discriminate between high- and low-risk patients. The results of the low-discrimination scenario illustrated that genotyping with ticagrelor is a cost-effective strategy with an ICER of USD 30,200 per QALY, while universal ticagrelor had an ICER of USD 52,600 per QALY. In the high-discrimination scenario, genotyping with ticagrelor remained cost-effective with an ICER of USD 24,700 per QALY, while universal ticagrelor had an ICER of USD 104,800 per QALY. They concluded that genotype-guided ticagrelor is a cost-effective strategy after PCI in patients with ACS.

Jang et al. in 2015, conducted a CEA to evaluate *CYP2C19* genotype plus platelet reactivity-guided (PG-PRT) antiplatelet therapy from the perspective of US healthcare providers (79). They included clinical outcomes of MACE (i.e., non-fatal MI, non-fatal stroke, and cardiovascular death), stent thrombosis, and major bleeding. The clinical probabilities were obtained from the TRITON-TIMI 38 trial and its genetic sub-study in addition to the PLATO trial. The study time horizon was one year and a lifetime from the US healthcare provider perspective. PG-PRT was the dominant strategy with the highest QALY gain (7.886 QALYs) and lowest cost (USD 71,887) compared to both universal alternative P2Y12 inhibitors and clopidogrel. Universal alternative P2Y12 inhibitors had an ICER of USD 139,588 per QALY compared to universal clopidogrel.

Another CEA study conducted by Jang et al. in 2016 aimed to compare the

clinical and economic outcomes of genotype-guided antiplatelet therapy (81). The studied clinical outcomes, time horizon, perspective, and sources of data were identical to those in the above-mentioned study by Jang et al. (2015). Genotype-guided therapy was shown to be dominant compared to both universal alternative P2Y12 inhibitors and clopidogrel. Universal alternative P2Y12 inhibitors were cost-effective compared to universal clopidogrel with an ICER of USD 43,683 per QALY.

Jang et al. conducted a CEA in 2017 to examine the cost-effectiveness of *CYP2C19* LOF and gain-of-function allele guided antiplatelet therapy (80). The time horizon, perspective, clinical outcomes, and sources of data were similar to the previous studies published by the same author in 2015 and 2016. Similar patterns were confirmed, whereby the *CYP2C19* LOF guided therapy was dominant (i.e., highest QALY of 7.530 at the lowest cost of USD 76,450) compared to universal alternative P2Y12 inhibitors and clopidogrel. When comparing the two universal arms, the universal alternative P2Y12 inhibitor was cost-effective compared to universal clopidogrel with an ICER of USD 28,542 per QALY.

2.2. Study rationale and research significance

At HMC, the two available antiplatelet medications that are used in ACS patients undergoing PCI are clopidogrel and ticagrelor in addition to aspirin. Both agents are used as first-line with no local comparative evidence for guiding the selection between them. Selection is primarily based on personal experience. No local economic evaluations or evidence on the use of dual antiplatelets in Qatar was ever generated at any level. Given the advantages of ticagrelor (as mentioned in Chapter 1), including having higher efficacy than clopidogrel and being unaffected by *CYP2C19* genetic mutations, it might be suggested that clopidogrel should be replaced by ticagrelor as the first-line option in HMC. This suggestion, however, could be controversial.

Ticagrelor is more expensive than branded clopidogrel (QAR 264 versus QAR 127 per one box, respectively) (82) and is associated with an increased risk of bleeding complications compared to clopidogrel, with the management of which further adds to the secondary cost of ticagrelor. Consequently, it is possible for the value of the added cost of ticagrelor to overtake the value of the clinical benefits that come with it. On the other hand, the personalization of therapy based on the genetic testing for *CYP2C19**2 and *3 genetic variants would be the ideal guide for decision-makers in practices, whereby, *CYP2C19**2 or *3 mutation carriers would receive ticagrelor and *CYP2C19**2 or *3 mutation non-carriers would receive clopidogrel. Nevertheless, the added value of the genetic testing, may not be worth the value of money spent on the testing, as the real cost of genetic testing goes beyond the apparent acquisition cost of the test.

Understanding the trade-off between costs and consequences, comparative economic evaluations of alternative health interventions are performed to guide decisions that best utilize limited resources. While the reported results of the literature economic studies supported the high likelihood of *CYP2C19* genotype-guided antiplatelet therapy to be cost-effective in identifying patients who were at a high risk of adverse cardiovascular events due to CYP2C19 genetic mutations, the studies were not considered to be adequate for local decision-makers in HMC in supporting the use of genotype-guided antiplatelet therapy over the universal use of clopidogrel or ticagrelor as a cost-effective option in Qatar. Several gaps were observed in the literature:

- First, none of the published studies evaluated all relevant clinical outcomes (i.e., MI, stroke, cardiovascular death, stent thrombosis, major bleeding, and dyspnea) in one comprehensive decision-analytic model.

- Second, none of the published studies included discontinuation due to medication ADRs as an outcome in the decision-analytic model, which is identified as of particular interest to HMC practitioners.
- Third, the prevalence of the *CYP2C19* mutation can easily differ in Qatar relative to other international settings, possibly undermining the need for the genotype-guided therapies.
- Fourth, there are no previous economic evaluations of antiplatelet therapies after PCI, whether genotype-guided or not, conducted in relevant settings, in Qatar or regionally.
    - The utilization of resources for patient management under the different therapy outcomes and consequences is largely locally specific. Examining the impact of resource utilization is essential for a better understanding of the impact of *CYP2C19* genetic testing on hospital budgets for decision-makers and practitioners to consider, beyond the acquisition costs. This includes understanding the economic impact of clinicians' handling practices of ADRs and clinical events. Such information can certainly be useful for decision-makers and clinicians alike when considering and revising their protocols and practices in Qatar.
    - This is added to the fact that the unit cost of resources is itself highly variable among different countries and settings and is not generalizable.
- Also important, is the realization that, internationally, and while the available literature supports the paradigm shift from 'one-size-fits-all' treatment to personalized dual antiplatelet use, there are conflicting reports on the economic usefulness of genotype-guided antiplatelet therapy against universal ticagrelor and clopidogrel. The inconsistency in the findings can be related to many factors

that affected the residual benefit and cost of genotype-guided therapy among the different healthcare systems. One important factor is the variations in the modeled clinical outcomes; whereby, as an example, none of the studies in the literature had a comprehensive model that evaluated all relevant clinical outcomes. While positive economic outcomes were reported to the advantage of *CYP2C19* genotype-guided antiplatelet therapy in most of the studies discussed above, the specificity of the local interpretation of a locally generated economic comparative value of the genetic testing cannot be underestimated. As was already implied above, pharmacoeconomic studies are locally specific and not internationally generalizable.

Accordingly, it is only logical that an evaluation of the comparative economic value of *CYP2C19* genotype-guided antiplatelet therapy versus universal clopidogrel and ticagrelor in ACS patients undergoing PCI, that (i) is locally based, and (ii) takes the literature limitations in consideration, will be of significant value to the decision making in the Qatari practices.

On a different note, it is anticipated that there is (and will continue to be) increasing interest in the implementation of genotype-guided antiplatelet therapy as opposed to universal antiplatelets in practices. Here, many economic evaluation studies, specifically over the past five years, were conducted to determine the cost-effectiveness of applying genotype-guided antiplatelet therapy, which come from different perspectives and in relation to different interventions; not only against the universal use of ticagrelor or clopidogrel. The speed and volume of information production create barriers against keeping up to date with potentially contrasting information. In this light, systematic reviews are important in synthesizing a summary of the currently available evidence provided by available primary research in response to a specific question. This

is needed for better guidance of healthcare professionals, managers, researchers, and patients for both decision-making and the guiding and improving future relevant research. Here, within the context applying genotype-guided antiplatelet therapy, and for the settings were no local pieces of evidence are available based on local evaluations, there are no systematic reviews in the literature that provide the initial answer of the question about whether the overall evidence supports the genotype-guided antiplatelet therapy as a cost-effective strategy when compared to the universal use of antiplatelet therapy after PCI in patients with ACS.

2.3. Study Objectives

Phase one: Economic Evaluation of the *CYP2C19* genotype-guided antiplatelet therapy compared to the universal use of ticagrelor or clopidogrel in Qatar.

The objective of this phase was to conduct a comprehensive assessment of the utilization cost of *CYP2C19* genotype-guided antiplatelet therapy versus universal use of clopidogrel or ticagrelor against their outcomes as first-line therapies in patients with ACS undergoing PCI in Qatar. This was conducted through a CEA of *CYP2C19* genetic-guided antiplatelet therapy versus universal use of clopidogrel or ticagrelor and universal use of clopidogrel versus universal use of ticagrelor, from the hospital perspective of the main healthcare provider in Qatar, the HMC.

Phase two: Economic evaluation of *CYP2C19* genotype-guided antiplatelet therapy compared to the universal use of antiplatelets in patients with acute coronary syndrome: A systematic review

This is a systematic review with the objective of generating a summative conclusion of the published economic evaluations of *CYP2C19* genotype-guided antiplatelet therapy in patients with PCI, not just against ticagrelor or clopidogrel, but the antiplatelets in general, including a quality assessment of the published research.

To note, Phase two of the current thesis has been recently published (83): AlMukdad S, Elewa H, Al-Badriyeh D. *Economic Evaluations of CYP2C19 Genotype-Guided Antiplatelet Therapy Compared to the Universal Use of Antiplatelets in Patients with Acute Coronary Syndrome: A Systematic Review*. J Cardiovasc Pharmacol Ther. 2020:1074248420902298

CHAPTER 3: MATERIALS AND METHODS

As per the study objectives, discussed in Section 2.3, the study was conducted over two different phases. The methods for these phases are discussed separately.

3.1. Phase one: Economic evaluation of the *CYP2C19* genotype-guided antiplatelet therapy compared to universal ticagrelor or clopidogrel in Qatar

Following up on the objectives of the thesis, Phase one of the thesis is a CEA analysis of the *CYP2C19* genotype-guided therapy versus universal ticagrelor or clopidogrel in patients with ACS undergoing PCI from the perspective of HMC in the state of Qatar.

3.1.1. One-year model structure

A one-year decision-analytic simulation model was created to follow the use of universal clopidogrel, universal ticagrelor, and genotype-guided antiplatelet therapy and their potential consequences of interest as first-line therapies in patients with ACS undergoing PCI, as demonstrated in Figure 3.1.

A one-year decision-analytic model (Figure 3.1) was developed to simulate the outcomes of three antiplatelet strategies for a hypothetical cohort of patients with ACS undergoing PCI. These strategies were: (i) universal administration of clopidogrel 75mg oral tablet once daily to all patients; (ii) universal administration of ticagrelor 90mg oral tablet twice daily to all patients; and (iii) performance of genetic testing to guide antiplatelet selection, so that *CYP2C19**2 or *3 LOF allele carriers will receive ticagrelor and *CYP2C19**2 or *3 LOF allele non-carriers will receive clopidogrel. The use of ticagrelor in the genotype-guided arm is whenever there was a LOF allele, regardless of whether this was homozygote (2 copies of the LOF allele) or heterozygote (1 copy of the LOF allele). For all treatment strategies, patients received DAPT (either ticagrelor or clopidogrel in combination with aspirin) over a 12 months duration. The

duration of follow up was consistent with the relevant literature in which the 12 months were sufficient for all relevant and essential outcomes to occur (84,85). The model included seven possible outcomes of interest. Patients were exclusively differentiated into a 'success' or a 'failure' outcome health state. Success was defined as survival with no event (without MI, stroke, cardiovascular death, and stent thrombosis), with/without ADRs, in addition to no premature discontinuation due to ADRs. That is, MI, stroke, cardiovascular death, and stent thrombosis were successfully prevented. On the other hand, failure was defined as the occurrence of MI, stroke, cardiovascular death, or stent thrombosis (with/without ADRs), or the discontinuation of the medication due to ADRs. That is, MI, stroke, cardiovascular death, or stent thrombosis were not prevented, or the medication was prematurely discontinued. Cardiovascular death was defined as death due to MI, stroke, acute decompensated heart failure or sudden cardiac death, and stent thrombosis was defined as definite stent thrombosis events according to the Academic Research Consortium criteria. Since only 1.5% of the PLATO trial patients had multiple cardiovascular events (51), it was assumed that within the first 12 months, patients could not experience MI, stroke, or stent thrombosis concurrently. The major bleeding and dyspnea were the ADRs of interest in the current model, including those causing therapy discontinuation, and they could occur regardless of the patient's cardiovascular event state. Major bleeding was defined as non-CABG Thrombolysis in Myocardial Infarction [TIMI] related to major bleeding. Discontinuation was defined as premature discontinuation of therapy because of ADRs after which patients stopped DAPT and continued on aspirin monotherapy lifelong.

The one year and Markov simulation models were based on a multivariate analysis of input data to account for inherent uncertainties in key input data, using Monte Carlo simulation via @Risk-7.6® (Palisade Corporation, NY, US). Monte Carlo

is a systematic technique that enables a simulated cohort of patients by allowing multiple model runs, where in each re-run of the model the baseline value of the uncertain input variable is randomly replaced by a new value of the input that is selected from within a pre-defined uncertainty range that is associated with the input value. About 10,000 iterations of model simulations were conducted, with a triangular type of random input selection.

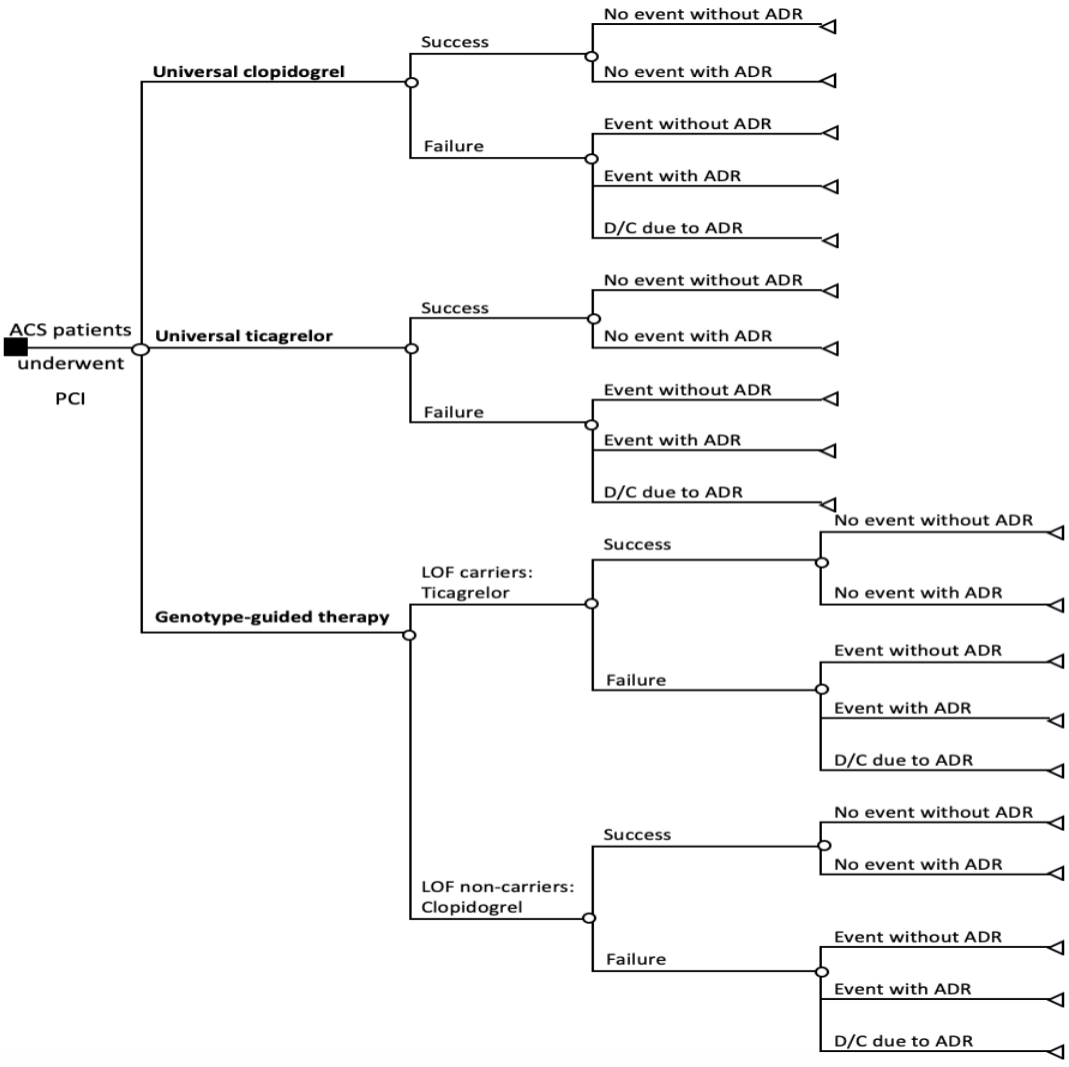


Figure 3.1 One-year economic decision-analytic model of antiplatelet strategies

ACS: Acute coronary syndrome; PCI: Percutaneous coronary intervention; ADR: Adverse drug reaction; LOF: loss-of-function; D/C: Discontinuation

3.1.2. Markov model structure

The life-long Markov model is a logical extension of the short-term decision tree, and it is created to estimate long-term cost and health outcomes. As illustrated in Figure 3.2, all patients are distributed among four terminal states of the initial Markov follow up ('no event', 'post MI', 'post stroke', and 'death'), before being redistributed throughout six mutually exclusive health states in the Markov component of the model. Figure 3.3 demonstrates the possible long-term Markov model transitions among health states, which were mainly adapted from PLATO health economic study, except for stent thrombosis (86). Annual Markov cycles were applied, and the model was run for 20 years, where the cohort of patients progressed through the Markov model according to estimated transition probabilities. The duration of the Markov model (i.e., 20 years) represents the average life expectancy in Qatar (i.e., 80 years) from the baseline population in the PLATO trial (i.e., 60 years) (87). Each health state was assigned a specific cost and a health utility value. Patients' distribution among the terminal states of the first non-Markov year reflected the proportion of patients starting the Markov model in each of the six Markov health states. The exclusive Markov health states are:

- No event: It includes patients who did not experience an MI, stroke, and cardiovascular death in the one-year non-Markov follow-up, regardless of the ADR status. Therefore, patients in the 'no event' state were those who had an ACS in the past 12 months but did not experience MI, stroke, and cardiovascular death since then and before the Markov component. Each year (Markov cycle), patients in the 'no event' state are at risk of non-fatal MI, non-fatal stroke or cardiovascular death and if any of these events take place during a Markov cycle, the patient makes a transition to 'non-fatal MI', 'non-fatal stroke', or 'dead', respectively. Patients

who did not experience any further cardiovascular event remained in the ‘no event’ state.

- Non-fatal MI: It includes patients who had a new non-fatal MI after the first year of non-Markov follow up. The ‘non-fatal MI’ state is known as tunnel state, in which patients could only stay for one cycle once they have MI for the first time during the Markov follow-up. Alive patients after the first MI event in the Markov model (non-fatal MI) made a transition to the "post MI" state. If a patient dies by the non-fatal MI cycle, he/she makes a transition to the ‘dead’ state.
- Non-fatal stroke: It includes patients who had a new non-fatal stroke after the first year of non-Markov follow up. The ‘non-fatal stroke’ state is known as tunnel state, in which patients could only stay for one cycle once they have a stroke for the first time during the Markov follow up. Alive patients after the first stroke event in the Markov model (non-fatal stroke) made a transition to the ‘post stroke’ state. If a patient dies by the non-fatal stroke cycle, he/she makes a transition to the ‘Dead’ state.
- Post MI: It includes patients who had a non-fatal MI in a preceding year during the non-Markov and Markov follow-ups, regardless of the ADR status. Thus, patients who experienced an MI in the one-year decision tree were allocated to this state in the Markov model. Alive patients remained in the ‘post MI’ state, while patients who died made make a transition to the ‘dead’ state.
- Post stroke: It includes patients who had a non-fatal stroke in a preceding year during the non-Markov and Markov follow-ups, regardless of the ADR status. Thus, patients who experienced a stroke in the one-year decision tree were allocated to this state in the Markov model. Alive patients remained in the ‘post stroke’ state, while patients who died made make a transition to the ‘dead’ state.

- Death: It includes patients who had a fatal event (vascular and non-vascular) during any cycle. This state is an 'absorbing' health state in which no further transitions are allowed after the entry into it.

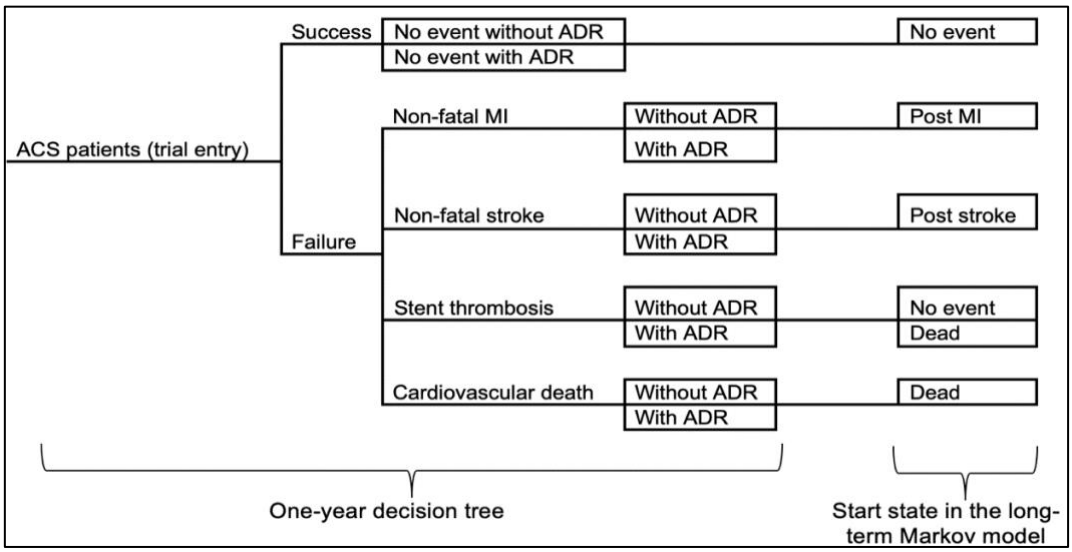


Figure 3.2 Diagrammatic representation of the health status and patient pathways in the decision tree and the start of the Markov model

ACS: Acute coronary syndrome; MI: Myocardial infarction; ADR: Adverse drug reaction

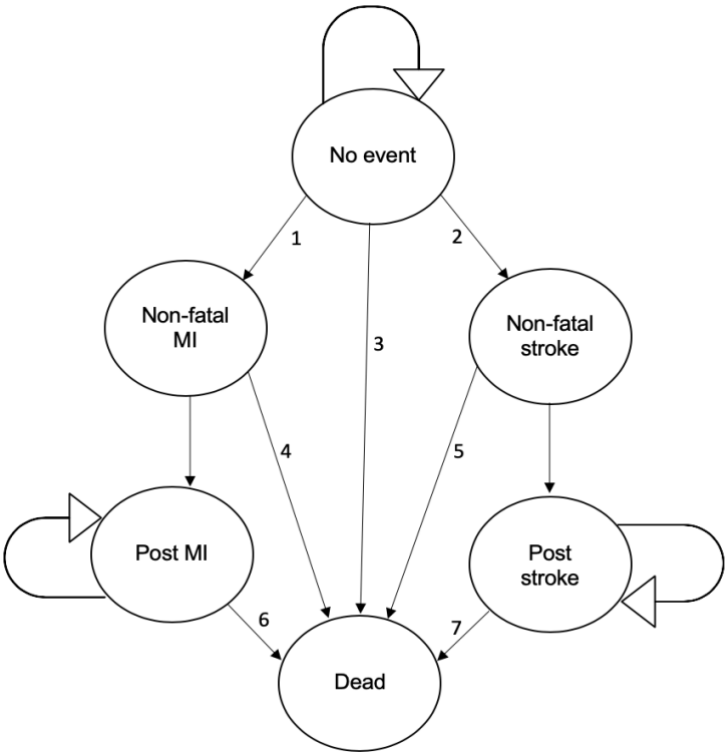


Figure 3.3 Long-term Markov model

Markov model transitions in the figure: (1) Risk of non-fatal myocardial infarction (MI) for patients with no MI or stroke in the one-year decision model. (2) Risk of non-fatal stroke for patients with no MI or stroke in the one-year decision model. (3) Mortality risk for patients with no MI or stroke in the one-year decision model. (4) Mortality risk first year after a non-fatal MI. (5) Mortality risk at the first year after a non-fatal stroke. (6) Mortality risk in the second and subsequent years after a non-fatal MI. (7) Mortality risk in the second and subsequent years after a non-fatal stroke.

It is essential to highlight the key assumptions in the Markov model structure. First, it was assumed that there was no treatment effect after one year as ticagrelor and clopidogrel were both stopped, and patients will continue on aspirin monotherapy only. Thus, medications had no long-term prognostic impact beyond the duration of the therapy (i.e., one year). Second, ADRs (i.e., major bleeding and dyspnea) are not explicitly modeled in the current model structure because ADRs are not prognostic in terms of long-term effects (beyond one year) on survival, quality of life and costs.

Third, it was assumed that there is no explicit modeling of additional cardiovascular events when a non-fatal event has happened in both the one-year non-Markov decision tree and the Markov model. Finally, it was assumed that patients who had stent thrombosis in the one-year non-Markov decision tree make transition only to 'no event' and 'dead' states at the initial Markov follow-up.

3.1.3. Ethics approval

The required ethics approval was obtained via the ethics committee of the Medical Research Centre (MRC) in HMC, Qatar. (See approval letter in Appendix A). As there is no human subject interaction or human subject data in this study (i.e., non-human subject study), the Qatar University Institutional Review Board (QU-IRB) approval was deemed to be not required (Appendix B).

3.1.4. Study perspective

The economic evaluation was performed from a hospital perspective (HMC). Hence, only direct medical costs were taken into consideration, including the cost of drug acquisition, hospitalization, screening and monitoring tests, treatment follow-up, and ADRs management. Only the cost related to DAPT after PCI and ACS management was considered. Indirect, intangible, and non-medical costs, such as patients' travel costs, were not considered in the analysis.

3.1.5. Model input

Input data was mainly extracted from a recent meta-analysis that compared ticagrelor and clopidogrel following PCI in patients with ACS, and from sub-studies of the PLATO RCT (55,88–90). The data were relevant to health state probabilities, based on a 12 months duration, and the ADRs probabilities during therapy. All health outcomes in studies were based on a total duration of 12 months. The PLATO trial is a large prospective, multicenter, international, double-blind, event-driven trial of patients

hospitalized for ACS. It is the largest clinical trial in the literature that provides a head-to-head evaluation between ticagrelor and clopidogrel in patients with ACS. The PLATO Invasive sub-study was used, which compared ticagrelor with clopidogrel in patients with a planned invasive strategy ACS (89). Regarding the treatment regimens in the meta-analysis and RCT, these are identical to what is in the routine practice at HMC in Qatar. Similar to the current project, the studies compared ticagrelor versus clopidogrel for the prevention of cardiovascular events and ADRs.

3.1.5.1. Study model and patients

The meta-analysis by Fan et al. included six RCTs and five observational studies that assessed adult patients with ACS (age from 18 to 90 years) undergoing PCI. A comparison between ticagrelor and clopidogrel as part of DAPT was conducted, and the results of adverse cardiovascular events were reported. The exclusion criteria were patients suffering from cardiogenic shock or receiving oral anticoagulants (88).

The PLATO Invasive Sub-study included a total of 13,408 patients with a planned invasive strategy, in which patients were randomly assigned to receive either ticagrelor (n=6732) (180 mg loading dose followed by 90 mg dose twice a day) or clopidogrel (n=6676) (300–600 mg loading dose followed by 75-100 mg per day) for 12 months (89). The inclusion criteria for patients with NSTEMI were at least two of the following: transient elevation of at least 1 mm in two or more contiguous leads, ST-segment depression, or positive cardiac biomarker. Alternatively, NSTEMI patients were included if they had one of the following risk factors: age ≥60 years, history of MI, ischemic stroke, peripheral artery disease, diabetes mellitus, peripheral artery disease, chronic renal dysfunction, or CABG. Key exclusion criteria were contraindication to clopidogrel, treatment with fibrinolytic drugs within 24 hours before randomization, need for oral anticoagulant drugs, increased risk of bradycardic events,

and concomitant use of strong CYP3A inducers or inhibitors. The baseline characteristics included a median age of 61 years, predominantly male gender (75%), 49% had STEMI, and 51% had NSTEMI and UA. For all patients, early invasive management (i.e., coronary angiography and PCI or CABG, where appropriate) should be anticipated before randomization (89).

The PLATO Genetic Sub-study had voluntary participation for patients and sites, where informed consent was collected apart from the PLATO trial for the purpose of collection and genetic analysis of samples (55). In the PLATO Genetic Sub-study, 10,285 patients provided samples for genetic testing (55). Intermediate metabolizers (i.e., *1/*2 - *8) were 17% in the ticagrelor arm and 18% in the clopidogrel arm, while poor metabolizers (i.e., *2 - *8/ *2 - *8) were 2% for both arms. The patients' baseline characteristics and demographic data and study endpoints were similar and comparable with the PLATO Invasive Sub-study (55).

The mutation prevalence was obtained from a prospective observational study in Qatar (91). The study aimed to determine the prevalence of *CYP2C19*2 and *3* in Arabs. Patients were considered eligible if they are older than 18 years and treated with and stabilized on clopidogrel after a PCI with stent implantation and to be followed for 6 months. Patients were excluded if they had active pathological bleeding, advanced malignancy, platelet count of less than 100 000/ μl, and severe liver dysfunction. A total of 204 patients were included, in which 44 (21.6%) and 4 (2%) were intermediate and poor metabolizers, respectively (91).

The median time to premature cessation due to ADRs was derived from Bern Percutaneous Coronary Intervention Registry that included 1209 patients (92). It was reported that the median duration until dyspnea- and major bleeding-related discontinuation was 36 and 61 days, respectively (92).

3.1.5.2. Model's resource utilization

The management of clinical events was based on clinical practice guidelines (93-97), before confirmed and locally adopted by the study's expert panel. Patterns of resource utilization are in relation to (i) the use of clopidogrel or ticagrelor in addition to aspirin for 12 months, (ii) any required duration of hospitalization, (iii) common diagnostic, screening, and monitoring tests conducted for patients over the 12 months, and (iv) how the cardiovascular events and ADRs are ideally handled when occurring. In cases where several possible resource utilization pathways were possible, the expert panel estimated a probability of distribution among these based on the local HMC experience. Any approach used for the management of an event or an ADR was considered successful. The expert panel confirmation of resource use was conducted over three sessions. The expert panel members involved an interventional cardiologist, a cardiology consultant, specialist senior clinical pharmacists, and an interventional neurologist. All panel members had professional clinical experiences with the study medications, including based on local experiences in the HMC, and answers were discussed until consensus.

3.1.5.2.1. Dosage regimens

According to the DAPT duration and regimen provided by the PLATO Sub-studies, patients received either ticagrelor 90 mg twice daily or clopidogrel 75 mg once daily plus aspirin 75-100 mg once daily for 12 months. These are the same regimens used in HMC, as confirmed by the expert panel.

5.1.5.2.2. Management of clinical events in the non-Markovian one-year model

The management of patients with no events and no ADRs during the first year post-PCI consists of three regular follow-up visits, whereby the following screening tests are performed: electrocardiography (ECG) x3, echocardiography (ECHO) x1,

complete blood count (CBC) x3, comprehensive metabolic panel (CMP) x3, lipid profile x3, and hemoglobin A1C (HBA1C) x3.

The management of MI and stent thrombosis is identical, except that in stent thrombosis, the thrombectomy, instead of placing a new stent, takes place in the majority of cases. All patients with MI or stent thrombosis undergo coronary angiography, then, according to the expert panel, about 70% undergo PCI, and 30% undergo CABG. Around 90% of the patients undergo PCI with a drug-eluting stent. In relation to the CABG procedure, patients should stop clopidogrel or ticagrelor for five days before the procedure, and they will resume it afterward. All patients after MI or stent thrombosis are offered to visit the rehabilitation center, in which they undergo a personalized rehabilitation program for around four months. Additional details related to the management protocol for MI and stent thrombosis are shown in Table 3.1.

The expert panel reported that around 30% of the patients with ischemic stroke undergo both contrast and non-contrast computed tomography (CT) scan. While approximately 85% of the patients undergo brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). Further, they perform neck imaging to approximately 60% of the patients who presented with signs and symptoms of ischemic stroke including, MRI (50%), CT (25%), and carotid ultrasound (25%) to detect atherosclerotic lesions in the neck. It was estimated that only 2% of the patients with ischemic stroke are admitted to the ICU prior to admission to the stroke unit. It was stated that 20% of all patients with ischemic stroke are transferred to the in-patient department of the rehabilitation center, while the remaining are offered to visit the rehabilitation center as outpatients. Alteplase and eptifibatide dose calculations were based on the patient's body weight, thereby an average weight of 80kg for the Qatari population was used (98). Patients who are diagnosed with hemorrhagic stroke should

stop clopidogrel/ticagrelor and continue on aspirin monotherapy for one month. Additional details related to the management of stroke are presented in Table 3.1.

Cardiovascular death included death resulting from an acute MI, stroke, acute decompensated heart failure, or sudden cardiac death. The treatment duration for patients who died during the one-year model was 183 days, assuming that they on average died mid-way throughout the year. Additional details related to the management protocol for cardiovascular death are summarized in Table 3.1.

3.1.5.2.3. Management of ADRs

With regards to major bleeding, the non-CABG TIMI related bleeding criteria was utilized, which is defined as (i) intracranial bleeding, (ii) clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL, and (iii) fatal bleeding (99). Here, the expert panel agreed that gastrointestinal bleeding and intercardinal hemorrhage are the most common and major non-procedure-related bleeding. For patients with gastrointestinal bleeding, clopidogrel or ticagrelor should be stopped, and patients should continue on aspirin monotherapy for approximately seven days. For the intercardinal hemorrhage, just like with the hemorrhagic stroke, patients should stop clopidogrel/ticagrelor and continue on aspirin monotherapy for one month. In relation to dyspnea, and when it is transient, no specific treatment or hospitalization is required, and the medication can be continued without discontinuation. Further details about the management protocol for the ADRs are shown in Table 3.2.

3.1.5.2.4. Management of discontinuation due to ADRs

Premature discontinuation of the medication due to ADRs was defined as the cessation of ticagrelor or clopidogrel and the continuation of aspirin monotherapy.

3.1.5.2.5. Management of post MI and post stroke in Markov model

Post MI and post stroke states represent the prognosis in terms of survival for patients in the second and subsequent years after a non-fatal MI and non-fatal stroke, respectively. The expert panel stated that patients would have regular follow-up visits three times yearly. During the follow-up visits, patients will perform the following tests per year: ECG x3, ECHO x1, CBC x3, CMP x3, lipid profile x3, HbA1C x3.

The expert panel explained that all patients with ACS who underwent PCI should receive a beta-blocker, an angiotensin-converting enzyme (ACE) inhibitor, and a statin as secondary prevention for life-long. Medications for the secondary prevention of ACS are summarized in Table 3.3.

Table 3.1 Protocols for diagnosis and management of the clinical events

Clinical event	Diagnosis	Management and related screening tests	Hospitalization	Rehabilitation services	Follow-up
Myocardial infarction and stent thrombosis	• ECG x1 • ECHO x1 • CBC x1 • CMP x1 • Troponin level x1 • Lipid profile x1 • HbA1C x1 • Chest x-ray	• Coronary angiography • PCI, before the procedure: ○ Aspirin 300mg loading dose + ticagrelor 180mg loading dose • CABG, before the procedure: ○ Serology x1 ○ MRSA/MSSA x1 ○ Thyroid function test x1 ○ TEG x1 ○ CT brain (non-contrast) x1 ○ Carotid doppler x ○ Transesophageal echocardiogram x1 ○ Coagulation profile x1 ○ Activated clotting time x1	• PCI ○ STEMI ward x3 days - Random blood glucose test x3 - Troponin x3 - CMP x3 - ECG x3 • CABG ○ CTICU x1 day ○ HDUD x5 days - CBC x1 - CMP x1 - ECG x6 - Troponin level x1 - Random blood glucose test x1 daily - Heparin 5000 SQ twice daily for 6 days or enoxaparin 40 SQ once daily for 6 days	• Treadmill stress test x2 • CMP x2 • CBC x2 • Uric acid x2 • Vitamin D x2 • HbA1C x2 • lipid profile x2	• PCI and CABG ○ ECG x3 ○ ECHO x1 ○ CBC x3 ○ CMP x3 ○ Lipid profile x3 ○ HBA1C x2

Clinical event	Diagnosis	Management and	Hospitalization	Rehabilitation	Follow-up

		related screening tests		services	
Stroke	• Ischemic stroke ○ CT brain (non-contrast) x1 ○ CT brain (contrast) x1 ○ MRI brain x1 ○ MRA brain x1 ○ Neck ultrasound x1 ○ CT neck (non-contrast) x1 ○ MRI neck x1 ○ Chest x-ray ○ ECHO x1 ○ ECG x1 ○ Troponin x1 ○ CMP x1 ○ CBC x1 ○ Coagulation profile x1 ○ lipid profile x1 ○ HbA1C x1 • Hemorrhagic stroke ○ CT brain (non-contrast) x1 ○ CT brain (contrast) x1 ○ Blood gases x1 ○ ECG x1 ○ Troponin x1 ○ CMP x1 ○ CBC x1 ○ Coagulation profile x1 ○ lipid profile x1 ○ HbA1C x1	• Ischemic stroke ○ Solitaire stent thrombectomy ○ Eptifibatide IV 0.9mg/kg ○ Alteplase 180 mcg/kg followed by 2 mcg/kg/min infusion • Hemorrhagic stroke ○ Mannitol IV 500 mg/kg ○ Labetalol IV 20 mg, followed by 1 mg/min	• Ischemic stroke ○ Stroke unit x5 days ○ General medical ward x3 days ○ ICU x13 days ○ CT brain (non-contrast) x1 ○ Random blood glucose x1 daily • Hemorrhagic stroke ○ ICU x7 days ○ General medical ward x14 days ○ CT brain (non-contrast) x1 ○ CBC x1 daily ○ CMP x1 daily ○ Random blood glucose x1 daily ○ Coagulation profile x3 ○ Intermittent pneumatic compression	• None	• Ischemic stroke ○ ECG x2 ○ lipid profile x2 ○ HbA1C x2 ○ Troponin x1 • Hemorrhagic stroke ○ CT brain (non-contrast) x1 ○ ECG x2 ○ lipid profile x2 ○ HbA1C x2 ○ CBC x2 ○ CMP x2

Clinical event	Diagnosis	Management and related screening tests	Hospitalization	Rehabilitation services	Follow-up

Cardiovascular death	• Due to MI
	  ○ Similar to MI
	• Due to stroke
	  ○ Similar to stroke
	• Due to heart failure
	  ○ ECG x1
	  ○ ECHO x1
	  ○ Chest x-ray x1
	  ○ CBC x1
	  ○ CMP x1
	  ○ HbA1C x1
	  ○ Lipid profile x1
	  ○ Troponin x1
	  ○ Brain natriuretic peptide x1
	• Due to sudden cardiac death
	  ○ ECG x1
	  ○ CBC x1
	  ○ CMP x1
	  ○ Troponin x1
		• Due to MI
		  ○ Similar to MI
		• Due to stroke
		Similar to stroke
		• Due to heart failure
		  ○ Furosemide IV 80mg, followed by 20 mg/hour
		  ○ Isosorbide dinitrate IV 0.0125 mg/min
		• Due to sudden cardiac death
		  ○ None
			• Due to MI
			  ○ Similar to MI
			• Due to stroke
			Similar to stroke
			• Due to heart failure
			  ○ General medical ward x7 days
			  ○ ECG x7
			  ○ ECHO x1
			  ○ CMP x4
			• Due to sudden cardiac death
			  • None
				• None	• None

MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; CBC: Complete blood count; CMP: Comprehensive metabolic panel; HbA1C: Hemoglobin A1C; ECG: Electrocardiography; ECHO: Echocardiography; CT: Computed tomography; MRI: Magnetic resonance imaging; ICU: Intensive care unit; CTICU: Cardiothoracic intensive care unit; HDUD: High-dependency unit; TEG: Thromboelastography; MRSA/MSSA: Methicillin-resistant staphylococcus aureus/ methicillin-susceptible staphylococcus aureus; SQ: Subcutaneous; IV: Intravenous

Table 3.2 Protocols for diagnosis and management of the adverse drug reactions

Type of ADR	Diagnosis	Management	Hospitalization	Follow-up
Major bleeding • Gastrointestinal bleeding • Intracranial hemorrhage	• Gastrointestinal bleeding ○ Endoscopy x1 ○ Stool occult test ○ Coagulation profile x1 ○ CBC x1 ○ CMP x1 ○ ECG x1 ○ lipid profile x1 ○ HBA1C x1 ○ Troponin x1 • Intracranial hemorrhage CT brain (non-contrast) x1 ○ CT brain (contrast) x1 ○ Chest x-ray x1 ○ Blood gases x1 ○ ECHO x1 ○ ECG x1 ○ Troponin x1 ○ CMP x1 ○ CBC x1 ○ Coagulation profile x1 ○ lipid profile x1 ○ HbA1C x1	• Gastrointestinal bleeding ○ Packed RBCs ○ Fresh frozen plasma ○ Packed platelet ○ Esomeprazole 80mg followed by 8mg/hour for 72 hours, then 40mg orally twice daily for 6 weeks ○ Normal saline 0.9% W/V • Intracranial hemorrhage ○ Mannitol IV 500 mg/kg ○ Labetalol IV 20 mg, followed by 1 mg/min	• Gastrointestinal bleeding ○ General medical ward x3 days ○ CBC x1 daily CMP x1 • Intracranial hemorrhage ○ ICU x7 days ○ General medical ward x14 days ○ CT brain (non-contrast) x1 ○ CBC x1 daily ○ CMP x1 daily ○ Random blood glucose x1 daily ○ Coagulation profile x3 ○ Intermittent pneumatic compression	• Gastrointestinal bleeding ○ Endoscopy x1 ○ CBC x2 ○ CMP x2 ○ ECG x2 ○ lipid profile x2 ○ HbA1C x2 • Intracranial hemorrhage ○ CT brain (non-contrast) x1 ○ ECG x2 ○ lipid profile x2 ○ HbA1C x2 ○ CBC x2 ○ CMP x2
Type of ADR	Diagnosis	Management	Hospitalization	Follow-up

Dyspnea	• Chest x-ray x1 • ECG x1	• None	• None	• ECG x2 • ECHO x1 • CBC x2 • CMP x2 • Lipid profile x1 • HbA1C x2
Discontinuation of the medication due to ADR	Similar to dyspnea and major bleeding			

ADR: Adverse drug reaction; CBC: Complete blood count; CMP: Comprehensive metabolic panel; HbA1C: Hemoglobin A1C; ECG: Electrocardiography; ECHO: Echocardiography; CT: Computed tomography; MRI: Magnetic resonance imaging; ICU: Intensive care unit; IV: Intravenous; RBCs: Red blood cells

Table 3.3 Medications for secondary prevention of ACS

Medication	Regimen	Indication
Aspirin	100 mg once daily	Reduce mortality and rates of recurrent coronary heart disease
Metoprolol	25 mg tablet twice daily	Reduce mortality, decrease reinfarction and myocardial ischemia, and ventricular arrhythmias
Carvedilol	25 mg tablet twice daily	
Lisinopril	10 mg tablet once daily	Reduce mortality, decrease reinfarction, and prevent the development of heart failure
Ramipril	5 mg tablet once daily	
Atorvastatin	40 mg tablet once daily	Reduce mortality and rates of recurrent coronary heart disease
Rosuvastatin	20 mg tablet once daily	

3.1.5.3. One-year model outcome probabilities

Data on the event rates of MI, stroke, cardiovascular death, stent thrombosis, and major bleeding for clopidogrel and ticagrelor are available in the PLATO Invasive Sub-study. However, a more recent meta-analysis, by Fan et al. compared ticagrelor to clopidogrel. Hence, while the clopidogrel event rates were obtained from the PLATO, the comparative event rates of ticagrelor were calculated based on the relative performance as was reported by the Fan et al. study (88,89). With a similar trend, the event rate of dyspnea was obtained, based on the PLATO Invasive Sub-study and the more recent meta-analysis by Yang et al. (89,100). The discontinuation due to major bleeding and dyspnea was obtained from the PLATO Bleeding and Dyspnea Sub-studies, respectively (90,101). The probability for the 'no event without ADRs' was the probability of success minus the probability of 'no event with major bleeding' + 'no event with dyspnea'.

Since the PLATO Genetic Sub-study did not report the event rate of the individual MACE outcomes, but only reported a total of MACE events in overall, the probabilistic distribution among the individual MACE outcomes, based on this total of MACE events, was assumed to equal the probabilistic distribution among the individual MACE outcomes in the PLATO Invasive Sub-study. The probabilities of stent

thrombosis and major bleeding were available and directly obtained from the PLATO Genetic Sub-study (55). The probability of dyspnea and premature discontinuation due to ADRs were assumed to not differ among the universal and genotype-guided antiplatelet therapies, which because genetic testing does not affect the outcomes of drugs once given. Additionally, it was assumed that the probabilities ADR distribution, including dyspnea and major bleeding, were identical in all patients with or without events. In the multivariate simulation, a ±5% uncertainty was associated with the probabilities of model health states.

The probabilities of the sub-types of cardiovascular death were derived from PLATO Death Sub-study (102). A similar distribution of the probabilities of death due to MI, stroke, acute decompensated heart failure, and sudden cardiac death between universal antiplatelet strategies and genotype-guided strategy was assumed. In other words, while the probability of overall death varies based on the study intervention, the distribution among the different sub-types of death does not. The same assumption was applied to stroke and its ischemic and hemorrhagic stroke sub-types, major bleeding and its gastrointestinal bleeding and intracranial hemorrhage sub-types, and discontinuation due to major bleeding and its gastrointestinal bleeding and intracranial hemorrhage sub-types. The following is the calculated probabilities of the sub-types of death, stroke, major bleeding, and discontinuation due to major bleeding:

Universal ticagrelor and genotype-guided ticagrelor arms:

Death due to MI: 0.6215

Death due to ischemic stroke: 0.0278

Death due to hemorrhagic stroke: 0.0243

Death due to heart failure: 0.1076

Sudden cardiac death: 0.2188

Ischemic stroke: 0.8182

Hemorrhagic stroke: 0.1818

Gastrointestinal bleeding: 0.8531

Intracranial hemorrhage: 0.1469

Discontinuation of medication due to gastrointestinal bleeding: 0.875

Discontinuation of medication due to intracranial hemorrhage: 0.125

Universal clopidogrel and genotype-guided clopidogrel arms:

Death due to MI: 0.5543

Death due to ischemic stroke: 0.0400

Death due to hemorrhagic stroke: 0.0057

Death due to heart failure: 0.1200

Sudden cardiac death: 0.2800

Ischemic stroke: 0.900

Hemorrhagic stroke: 0.100

Gastrointestinal bleeding: 0.9082

Intracranial hemorrhage: 0.0918

Discontinuation of medication due to gastrointestinal bleeding: 0.750

Discontinuation of medication due to intracranial hemorrhage: 0.250

The clinical outcomes and their probabilities in the one-year decision tree model are summarized in Table 3.4.

Table 3.4 Probability values of the one-year decision model used in the comparison of the antiplatelet strategies

Parameter	Ticagrelor	Clopidogrel	Reference
Clinical probabilities for universal antiplatelets strategy			
Success	0.8309	0.8348	
• No event without adverse drug reaction	0.7741	0.8778	
• No event with major bleeding	0.0458	0.0264	(88,89)
• No event with dyspnea	0.1800	0.0958	(89,109)
Failure	0.1691	0.1652	
• Event without adverse drug reaction	0.6826	0.8415	
○ Myocardial infraction without adverse drug reaction	0.4974	0.4748	(88,89)
○ Stroke without adverse drug reaction	0.0839	0.0719	(88,89)
○ Cardiovascular death without adverse drug reaction	0.2905	0.3094	(88,89)
○ Stent thrombosis without adverse drug reaction	0.1282	0.1439	(88,89)
• Event with adverse drug reaction	0.1282	0.0858	
○ Myocardial infraction with major bleeding	0.1009	0.1024	(88,89)
○ Myocardial infraction with dyspnea	0.3965	0.3724	(88,89,109)
○ Stroke with major bleeding	0.0170	0.0155	(88,89)
○ Stroke with dyspnea	0.0668	0.0564	(88,89,109)
○ Cardiovascular death with major bleeding	0.0590	0.0667	(88,89)
○ Cardiovascular death with dyspnea	0.2316	0.2426	(88,89,109)
○ Stent thrombosis with major bleeding	0.0260	0.0310	(88,89)
○ Stent thrombosis with dyspnea	0.1022	0.1129	(88,89,109)
• Discontinuation of the medication due to adverse drug reaction	0.1892	0.0726	
○ Discontinuation of the medication due to major bleeding	0.2500	0.1667	(90)
○ Discontinuation of the medication due to dyspnea	0.7500	0.8333	(110)

Parameter	Ticagrelor	Clopidogrel	Reference
Clinical probabilities for genotype-guided therapy strategy*			
Success	0.8501	0.8669	
• No event without adverse drug reaction	0.7758	0.8720	
• No event with major bleeding	0.0482	0.0358	(55)
• No event with dyspnea	0.1760	0.0923	(55,89)
Failure	0.1499	0.1331	
• Event without adverse drug reaction	0.6606	0.8189	
○ Myocardial infraction without adverse drug reaction	0.4435	0.4712	(55,89)
○ Stroke without adverse drug reaction	0.0960	0.0789	(55,89)
○ Cardiovascular death without adverse drug reaction	0.2988	0.3122	(55,89)
○ Stent thrombosis without adverse drug reaction	0.1616	0.1376	(55)
• Event without adverse drug reaction	0.1259	0.0909	
○ Myocardial infraction with major bleeding	0.0954	0.1316	(55,89)
○ Myocardial infraction with dyspnea	0.3481	0.3396	(55,89,109)
○ Stroke with major bleeding	0.0207	0.0220	(55,89)
○ Stroke with dyspnea	0.0754	0.0569	(55,89,109)
○ Cardiovascular death with major bleeding	0.0643	0.0872	(55,89)
○ Cardiovascular death with dyspnea	0.2346	0.2250	(55,89,109)
○ Stent thrombosis with major bleeding	0.0348	0.0384	(55,89)
○ Stent thrombosis with dyspnea	0.1269	0.0992	(55,89,109)
• Discontinuation of the medication due to adverse drug reaction	0.2135	0.0902	
○ Discontinuation of the medication due to major bleeding	0.2500	0.1667	(90)
○ Discontinuation of the medication due to dyspnea	0.7500	0.8333	(110)

*In the genotype guided strategy, loss-of-function alleles carriers will receive ticagrelor, and loss-of-function alleles non-carriers will receive clopidogrel

3.1.5.4. Markov model transition probabilities

One of the key assumptions in the Markov model is that no treatment effect is considered in the model as patients are no longer on ticagrelor or clopidogrel. Hence, the transitions probabilities are identical for the universal ticagrelor arm, universal clopidogrel arm, and genotype-guided therapy arm (86). The transition probabilities for 'non-fatal MI' and 'non-fatal stroke' in the 'no event' state were obtained directly from the PLATO Health Economic Sub-study (86). According to the PLATO Health Economic Sub-study, in the Markov model, the probabilities of 'non-fatal MI' and 'non-fatal stroke' to occur at least 12 months post-ACS was constant at 0.019 and 0.003, respectively. The calculations of the transition probabilities for the remaining health states were based on the PLATO Health Economic Sub-study, in which the probability of death is multiplied by a constant value that represents the 'hard ratio over standard mortality' (86). The transition parameters (i.e., hazard ratio over standard mortality) were derived from the PLATO Health Economic Sub-study (86). Consistent with the population in the PLATO trial, and based on Qatar's 2016 standard life tables (87), only the death rate for adults was considered, and the average death rate was calculated based on age and gender (Table 3.5). The average death rate was equal to the probability of death since it was calculated for one year, as shown below:

One-year probability of dying = 0.0263

Annual death rate (r) = $-1/1 \times \ln (1 - 0.0263) = 0.0267$

Annual probability of dying (P) = $1 - e^{-(0.0267)(1)} = 0.0263$

Table 3.5 Death rate by the WHO based on age and gender in Qatar

Age Group	Male	Female	Average death based on gender
20-24 years	0.001	0	0.0005
25-29 years	0.001	0	0.0005
30-34 years	0.001	0	0.0005
35-39 years	0.001	0	0.0005
40-44 years	0.001	0.001	0.0010
45-49 years	0.001	0.001	0.0010
50-54 years	0.003	0.002	0.0025
55-59 years	0.005	0.005	0.0050
60-64 years	0.013	0.012	0.0125
65-69 years	0.025	0.018	0.0215
70-74 years	0.033	0.028	0.0305
75-79 years	0.053	0.045	0.0490
80-84 years	0.089	0.072	0.0805
85+ years	0.173	0.151	0.1620
Total average based on age and gender: Sum of average death based on gender / 14 = 0.368/14 = 0.0263			

The following are the calculated transition probabilities:

Transition from ‘no event’ to ‘dead’: 2 * 0.0263 = 0.0526

Transition from ‘no event’ to ‘non-fatal MI’: 0.019

Transition from ‘no event to ‘non-fatal stroke’: 0.003

Staying in the ‘no event’: 1 – (0.019 + 0.003 + 0.0526) = 0.925

Transition from ‘no-fatal MI’ to ‘dead’: 6 * 0.0263 = 0.1578

Transition from ‘no-fatal MI’ to ‘post MI’: 1 - 0.1578 = 0.8422

Transition from ‘no-fatal stroke’ to ‘dead’: 7.43 * 0.0263 = 0.1954

Transition from ‘no-fatal stroke’ to ‘post stroke’: 1 - 0.1954 = 0.8056

Transition from ‘post MI’ to ‘dead’: 3 * 0.0263 = 0.0789

Staying in the ‘post MI’: 1 - 0.0789 = 0.9211

Transition from ‘post stroke’ to ‘dead’: 3 * 0.0263 = 0.0789

Staying in the ‘post stroke’: 1 - 0.0789 = 0.9211

For stent thrombosis, the four-year mortality rate was obtained from the REAL-ST (Retrospective Multicenter Registry of Stent Thrombosis After First- and Second-Generation DES Implantation) that included 313 patients with definite stent thrombosis. The four years death rate after the index stent thrombosis event was 32% (103). The death rate was converted to annual probability as shown below:

Four-year probability of dying = 0.32

Annual death rate (r) = $-1/4 \times \ln (1 - 0.32) = 0.096$

Annual probability of dying (P) = $1 - e^{-(0.096)(1)} = 0.092$

It was assumed that the patients who experienced stent thrombosis in the one-year decision tree were distributed to ‘dead’ and ‘no event’ states only. Thus, the transition to ‘no event’ state was = 1- 0.092 = 0.908.

The transition matrix for the Markov model is shown in Table 3.6.

Table 3.6 Transition matrix for the Markov model

	End state					
Start state	No event	Non-fatal MI	Non-fatal stroke	Post MI	Post stroke	Dead
No event	0.925	0.019	0.003	0	0	0.053
Non-fatal MI	0	0	0	0.842	0	0.158
Non-fatal stroke	0	0	0	0	0.805	0.195
Post MI	0	0	0	0.921	0	0.079
Post stroke	0	0	0	0	0.921	0.079
Dead	0	0	0	0	0	1

MI: Myocardial infarction

3.1.5.5. Markov model health-related utility values

Patient utility data was required for the CUA, particularly for the Markov model. Because locally derived utility values were not available, the utility construction and assumptions outlined in PLATO Health Economic Sub-study were utilized (86). The study reported the utilities of the 'no event', 'non-fatal MI', 'non-fatal stroke', 'post MI', 'post stroke', and death health states. The long-term quality of life due to a non-fatal cardiovascular event is not widely studied, and there is no evidence that supports the improvement of health-related quality of life over time. Hence, the post MI and post stroke (more than a year form the event) were assumed to have similar utilities to non-fatal MI and non-fatal stroke, respectively (86). The health utility values for health states in the Markov model are summarized in Table 3.7.

Cumulative QALY was calculated by the end of the Markov follow up. This was performed by adding the QALYs for all health states at each cycle, before then adding the total QALYs for all cycles. The calculated cumulative value of QALY by the end of the total follow-up duration was appropriately discounted from the end of the Markov model duration. A 3.5% discount rate was used (104). The discounted QALYs equals: (QALYs before adjustment)/$(1+r)_t$, where "r" is the discount rate (3.5%) and "t" is the number of years in the future where the value occurs (20 years) (105). In the multivariate simulation, a ±10% uncertainty was associated with the utilities of model health state.

Table 3.7 Utility input values

Parameter	Utility value	Reference
No event	0.875	(86)
Myocardial infraction	0.812	(86)
Stroke	0.737	(86)
Post myocardial infraction	0.812	(86)
Post stroke	0.737	(86)
Dead	0	NA

3.1.6. Cost calculations

Cost calculation was expressed in QAR and based on the 2019/20 financial year. As discussed above in Section 3.2.3, only direct medical costs were taken into consideration, under the assumption that patients have completed the full course of therapy, unless they discontinued the medication due to ADRs. All cost data were available for the study. Medication wholesale prices were acquired through the local pharmacy pricing database in HMC, the "MyCare" pricing system, while the costs of hospitalization, procedures, diagnostic and monitoring tests, and management of ADRs were obtained from the department of finance, at HMC.

The acquisition cost of the DAPT was the total cost of clopidogrel or ticagrelor in addition to aspirin for 12 months. The hospitalization cost was based on the in-patient admission due to MI, stroke, cardiovascular death, stent thrombosis, major bleeding, and discontinuation due to ADRs in ACS patients after the primary PCI, taking into consideration the different wards in the hospital. The cost of patient follow-up is the cost of screening and monitoring tests conducted for patients over 12 months. In patients with ADRs, the cost of treating major bleeding and dyspnea was based on the cost of resources utilized in the management of the ADRs. The cost of genetic testing is not available as the genetic test itself is not available in HMC. This was, therefore, input into the study model as an uncertainty range derived from sources available in the

literature (73,74,107). Utilizing this and based on the results of the baseline multivariate model analysis, the price range of the genetic testing at which cost-effectiveness of genotyping is achieved (or not) will be determined.

The cost per patient in the different model pathways (health states) was calculated as the initial therapy cost and any alternative therapies added (if any) to the cost of resources consumed for monitoring and screening tests throughout the duration therapy, including follow up.

a. Cost of a patient without MI, stroke, or stent thrombosis and without ADRs is the sum cost of medication acquisition and follow up.
b. Cost of a patient without MI, stroke, or stent thrombosis and with ADRs is the cost of patients without MI, stroke or stent thrombosis (without ADRs), plus the cost of ADRs management.
c. Cost of a patient with MI, stroke, or stent thrombosis and without ADR is the sum cost of drug acquisition, plus the event management, hospitalization, and screening/monitoring.
d. Cost of a patient with MI, stroke, or stent thrombosis and with ADR is the sum cost of patients with MI, stroke or stent thrombosis (without ADRs), plus the cost of ADRs management.
e. Cost of a dead patient
    - because of a cardiovascular event is the sum cost of drug acquisition, plus the event management, hospitalization, and screening/monitoring.
    - because of a non-cardiovascular event is the sum cost of drug acquisition and follow up.

f. Cost of discontinuation of the medication due to ADRs is the sum cost of drug acquisition for the median time to premature cessation because of ADRs, plus the cost of ADRs management.
g. Cost of a patient in the 'post MI' or 'post stroke' status is the sum of the follow-up and screening tests costs. Here, follow-up and screening tests are identical to those in the no-event status.

As per the decision analysis principles of modeling (67), the overall cost of a study drug based on the non-Markov component of follow-up, including all health states and their uncertainties, is the sum of 'proportional costs' of all the different health states by the end of the non-Markov 12 months follow up. The proportional cost in a health state is the 'cost of the health state' multiplied by the 'probability of the health state'.

The cumulative cost was calculated by the end of the Markov model. This was by adding the costs of all health states in each cycle, before then adding the costs of all cycles. The calculated cumulative cost by the end of the total follow-up duration was appropriately discounted from the end of the Markov model duration. A 3.5% discount rate was used (104). The discounted cost equals: (cost before adjustment)/$(1+r)_t$, where "r" is the discount rate (3.5%) and "t" is the number of years in the future where the value occurs (20 years) (105). In the multivariate simulation of the Markov model, a ±5% uncertainty was associated with the utilities of model health states.

The trade-off between the comparative cost and effectiveness outcomes of study interventions in this model was presented via the ICER (and ICUR). When dominance (higher efficacy and lower cost) is reported in favor of an intervention over another, the relative cost savings were reported. The willingness-to-pay threshold (i.e. cost-effectiveness threshold), against which the ICER is interpreted for whether an intervention is considered cost effective, is not formally available in Qatar. There is no

officially approved cost-effectiveness ratio based on which interventions in the Qatari practice is deemed cost-effective. The WHO's suggestion of using 1-3 times the GDP per capita as the value of the threshold in a country is arbitrary and not based on any methodological justification (107). In this thesis, an estimated value of QAR 550,000 per QALY was used as a threshold. This is adapted from the threshold value of USD 150,000 per QALY, an increasingly accepted higher threshold value in the USA (108), which is also within the range suggested by WHO for Qatar.

3.1.7. Sensitivity analysis

There is a potential uncertainty associated with the models' inputs obtained from the literature. Thus, variations in the values of key variables and assumptions related to deterministic and probabilistic inputs will be analyzed to assess the robustness of the base-case studies' conclusions against any uncertainty. Sensitivity analyses were conducted using one-way and multivariate analyses. One-way sensitivity analyses were conducted on the costs of antiplatelets acquisition (±150% uncertainty). Here, and increasing the generalizability of results to other settings, broad uncertainty ranges were used to enable threshold analyses that determine exact input values where the study conclusion changes. The one-way sensitivity analysis was done using Monte Carlo simulation, utilizing iterations and a type of input distribution that are similar to those performed in the multivariate analyses at the one year and Markov models.

As a follow up to the multivariate model analysis, as discussed earlier, a multivariate uncertainty analysis was conducted on the duration of hospitalization (general medical ward, STEMI ward, coronary care unit, intensive care unit, cardiothoracic intensive care unit, high-dependency unit, and stroke unit) (±30 uncertainty), the proportion of stroke patients performing diagnostic radiation tests [computed tomography (CT) scan, magnetic resonance imaging (MRI), and magnetic

resonance angiography (MRA)] (±30 uncertainty), the proportion of stroke patients hospitalized in the intensive care unit (ICU) and general medical ward (±30 uncertainty), and the proportion of stroke patients receiving Solitaire stent (±30 uncertainty). This was also performed via the Monte Carlo simulation, utilizing iterations and a type of input distribution that are similar to those performed in the multivariate analyses at the one year and Markov models.

3.2. Phase two: Economic evaluation of *CYP2C19* genotype-guided antiplatelet therapy compared to the universal use of antiplatelets in patients with Acute coronary syndrome: A systematic review

(This section of the thesis has been extracted from the following publication:
AlMukdad S, Elewa H, Al-Badriyeh D. *Economic Evaluations of CYP2C19 Genotype-Guided Antiplatelet Therapy Compared to the Universal Use of Antiplatelets in Patients with Acute Coronary Syndrome: A Systematic Review*. J Cardiovasc Pharmacol Ther. 2020:1074248420902298)

3.2.1. Data sources and search

A systematic literature review was performed using four search databases: PubMed, Embase, PharrmGKB, and EconLit, to identify relevant articles. The search strategy followed the PICO format. As an example, within the PubMed database, the population was: acute coronary syndrome, percutaneous coronary intervention; the intervention/comparator was: genotype-guided, genetic guided, genetic diagnostic test, genomic diagnostic test, ticagrelor, prasugrel, clopidogrel, platelet aggregation inhibitors; the outcome was: cost-utility, cost-effectiveness, cost-benefit, costs and cost analysis, economic evaluation. For other databases, a similar search approach was utilized. Keywords were tailored to database-particular indexing terms, e.g. the use of Medical Subject Heading (MeSH) terms. As appropriate, the terms and their substitutes

were combined using Boolean connectors (AND/OR/NOT). PubMed and Embase search terms can be seen in Appendix C. In addition to the electronic search, a manual search of bibliographies and references of identified articles was conducted. The grey literature was also searched using advanced reports, conference proceedings, theses, conference proceedings, and guidelines, as well as searching Google Scholar. A search protocol of the systematic review was registered in PROSPERO (ID#CRD42019133599).

3.2.2. Study population

Included patients were those having ACS and receiving clopidogrel, ticagrelor or prasugrel after PCI. Whereas the excluded patients were those receiving clopidogrel for other indications, such as stroke prevention, peripheral artery disease, or ACS without PCI.

3.2.3. Eligibility criteria

Studies were considered eligible for this review if they were economic evaluation studies comparing genetic testing for ACS patients with PCI, followed by targeted administration of the novel antiplatelets in *CYP2C19* mutation carriers compared to the universal use of antiplatelets. Included comparative studies were restricted to the English language, of human species, and in journal articles with full-text availability. Exclusion criteria included reviews and non-comparative studies. The inclusion and exclusion of articles were conducted by two independent reviewers via the initial screening of titles/abstracts of articles, followed by a screening of the full text. When disagreements occurred, articles were discussed with a third reviewer until consensus. The inclusion of comparative studies was from inception until August 2019.

3.2.4. Outcome Measures

The outcome measure of interest is the observed trends in relation to the

comparative economic outcomes of the *CYP2C19* genotype-guided antiplatelet therapy versus universal use of antiplatelet, including total cost, cost avoidance, and the ICER.

3.2.5. Data extraction and synthesis

A data extraction tool was created, and pilot testing was performed using a sample of three eligible studies. The extracted data were the genetic-guided antiplatelet therapy, antiplatelet therapy used, country, disease states, time horizon, primary and secondary outcomes, the comparative model used, type of cost-effectiveness analysis, the source of clinical and cost data, perspective, cost category, type and outcome of the sensitivity analysis, time adjustment, funding, and summary of findings. Two reviewers independently extracted the data from the included articles, ensuring data reliability and trustworthiness. A consensus was reached whenever differences occurred.

3.2.6. Assessment of quality of studies

The quality of articles was assessed by two independent reviewers, who critically appraised the included articles using the Quality of Health Economic Studies (QHES) tool (110). The QHES tool encompasses 16 questions, in which each question can be given a potential score ranging from ‘0’ to ‘9’, with a total of 100 points adding all questions scores. The findings of the QHES score can be interpreted according to four categories of quality: good (75-100), fair (50-74), poor (25-49), and extremely poor (0-24) (109-111). A third independent reviewer would contribute whenever a disagreement occurs.

Only articles with fair or good methodological quality were included in this review. The systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline, including a 27-item checklist of the essential items to be reported in a systematic review, as relevant (Appendix D) (112).

CHAPTER 4: RESULTS

4.1. Phase one: Economic evaluation of the *CYP2C19* genotype-guided antiplatelet therapy compared to universal ticagrelor or clopidogrel in Qatar

4.1.1. Results of the Multivariate analysis

As discussed in Section 3.1.1, the models was based on a multivariate simulation; the input uncertainty and their distributions are summarized in Table 4.1.

Table 4.1 Input variables and uncertainty distributions used in Monte Carlo simulation in the one year and Markov models

Parameter	Uncertainty distribution	
• Probabilities for universal antiplatelets from the meta-analysis and RCTs (±5%)	Ticagrelor Triangular distribution	Clopidogrel Triangular distribution
○ No event without ADR	0.735, 0.7741, 0.813	0.834, 0.8778, 0.922
○ No event with major bleeding	0.044, 0.0458, 0.048	0.025, 0.0264, 0.028
○ No event with dyspnea	0.171, 0.1800, 0.189	0.091, 0.0958, 0.101
○ MI without ADR	0.473, 0.4974, 0.522	0.451, 0.4748, 0.499
○ Stroke without ADR	0.080, 0.0839, 0.088	0.068, 0.0719, 0.076
○ CV death without ADR	0.276, 0.2905, 0.305	0.294, 0.3094, 0.325
○ ST without ADR	0.122, 0.1282, 0.135	0.137, 0.1439, 0.151
○ MI with major bleeding	0.096, 0.1009, 0.106	0.097, 0.1024, 0.108
○ MI with dyspnea	0.377, 0.3965, 0.416	0.354, 0.3724, 0.391
○ Stroke with major bleeding	0.016, 0.0170, 0.018	0.015, 0.0155, 0.016
○ Stroke with dyspnea	0.063, 0.0668, 0.070	0.054, 0.0564, 0.059
○ CV death with major bleeding	0.056, 0.0590, 0.062	0.063, 0.0667, 0.070
○ CV death with dyspnea	0.220, 0.2316, 0.243	0.230, 0.2426, 0.255
○ ST with major bleeding	0.025, 0.0260, 0.027	0.029, 0.0310, 0.033
○ ST with dyspnea	0.097, 0.1022, 0.107	0.107, 0.1129, 0.118
○ D/C due to major bleeding	0.238, 0.2500, 0.263	0.158, 0.1667, 0.175
○ D/C due to dyspnea	0.713, 0.7500, 0.788	0.792, 0.8333, 0.875
• Probabilities for genotype-guided therapy from RCT (±5%)		
○ No event without ADR	0.737, 0.7758, 0.815	0.828, 0.8720, 0.916
○ No event with major bleeding	0.046, 0.0482, 0.051	0.034, 0.0358, 0.038
○ No event with dyspnea	0.167, 0.1760, 0.185	0.088, 0.0923, 0.097
○ MI without ADR	0.421, 0.4435, 0.466	0.448, 0.4712, 0.495
○ Stroke without ADR	0.091, 0.0960, 0.101	0.075, 0.0789, 0.083
○ CV death without ADR	0.284, 0.2988, 0.314	0.297, 0.3122, 0.328

Parameter	Uncertainty distribution	
○ ST without ADR	0.154, 0.1616, 0.170	0.131, 0.1376, 0.144
○ MI with major bleeding	0.091, 0.0954, 0.100	0.125, 0.1316, 0.138
○ MI with dyspnea	0.331, 0.3481, 0.366	0.323, 0.3396, 0.357
○ Stroke with major bleeding	0.020, 0.0207, 0.022	0.021, 0.0220, 0.023
○ Stroke with dyspnea	0.072, 0.0754, 0.079	0.054, 0.0569, 0.060
○ CV death with major bleeding	0.061, 0.0643, 0.067	0.083, 0.0872, 0.092
○ CV death with dyspnea	0.223, 0.2346, 0.246	0.214, 0.2250, 0.236
○ ST with major bleeding	0.033, 0.0348, 0.037	0.037, 0.0384, 0.040
○ ST with dyspnea	0.121, 0.1269, 0.133	0.094, 0.0992, 0.104
○ D/C due to major bleeding	0.238, 0.2500, 0.263	0.158, 0.1667, 0.175
○ D/C due to dyspnea	0.713, 0.7500, 0.788	0.792, 0.8333, 0.875
• Utility values from RCT (±10%)		
○ No event	0.7875, 0.875, 0.963	
○ Non-fatal MI	0.7308, 0.812, 0.893	
○ Post MI	0.7308, 0.812, 0.893	
○ Non-fatal stroke	0.6633, 0.737, 0.811	
○ Post stroke	0.6633, 0.737, 0.811	
○ Death	0, 0, 0.1	
• Probability for death in Qatar from WHO (±5%)	0.0250, 0.0263, 0.0276	
• Mutation prevalence from local observation study in Qatar (±20%)		
○ *CYP2C19* *2 and *3 carriers	0.1888, 0.236, 0.2832	
○ *CYP2C19* *2 and *3 non-carriers	0.6112, 0.764, 0.9168	
• Cost of genetic test from literature	730, 782, 2555	
• Cost of inpatient rehabilitation* (±100%)	1.00, 1.2, 1.4	

ADR: Adverse drug reaction; MI: Myocardial infarction; CV: Cardiovascular; ST: Stent thrombosis; D/C: Discontinuation; WHO: World Health Organization
* The value was assumed to be 20% higher than the cost of the outpatient rehabilitation

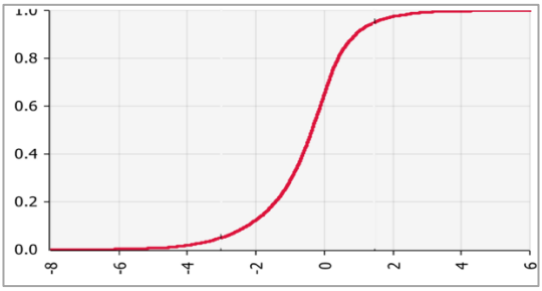
4.1.1.1. QALY outcomes

The discounted cumulative QALYs based on the Markovian follow-up duration with each antiplatelet strategy were calculated, as already discussed in Section 3.1.5, including all health states (Table 4.2).

Table 4.2 Overall QALYs with antiplatelets strategies

Antiplatelet strategy	Cumulative QALY	Discounted QALY
Universal ticagrelor	9.79	4.92
Universal clopidogrel	9.92	4.98
Genotype-guided therapy	10.02	5.04

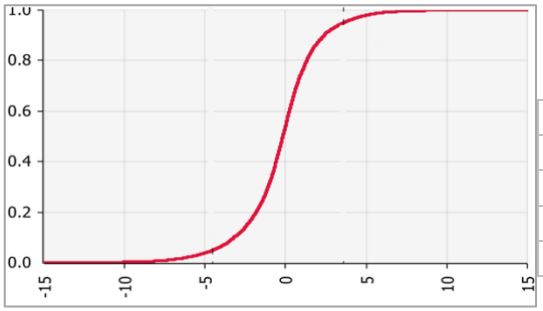
The mean difference in the cumulative QALYs between universal clopidogrel and universal ticagrelor was 0.52 (95% CI, 0.493 - 0.547) in favor of universal clopidogrel. The probability curve of relative QALYs is shown in Figure 4.1.



Minimum	-7.55
Maximum	5.85
Mean	-0.52
Std Dev	1.37
Variations	10,000

Figure 4.1 Probability curve of relative QALYs with universal clopidogrel over universal ticagrelor

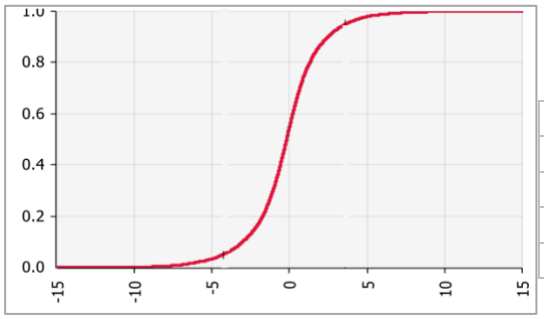
The mean difference in the cumulative QALYs between genotype-guided therapy and universal clopidogrel was 0.29 (95% CI, 0.242 - 0.338) in favor of genotype-guided therapy. The probability curve of relative QALYs is shown in Figure 4.2.



Minimum	-13.41
Maximum	13.19
Mean	-0.29
Std Dev	2.43
Variations	10,000

Figure 4.2 Probability curve of relative QALYs with genotype-guided therapy over universal clopidogrel

The mean difference in the cumulative QALYs between genotype-guided therapy and universal ticagrelor was 0.23 (95% CI, 0.183 - 0.277) in favor of genotype-guided therapy. The probability curve of relative QALYs is shown in Figure 4.3.

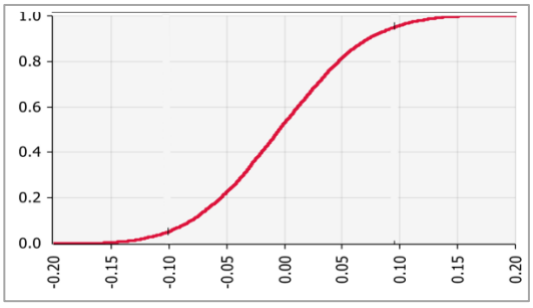


Minimum	-12.14
Maximum	11.30
Mean	-0.23
Std Dev	2.37
Variations	10,000

Figure 4.5 Probability curve of relative QALYs with genotype-guided therapy over universal ticagrelor

4.1.1.2. Clinical outcomes

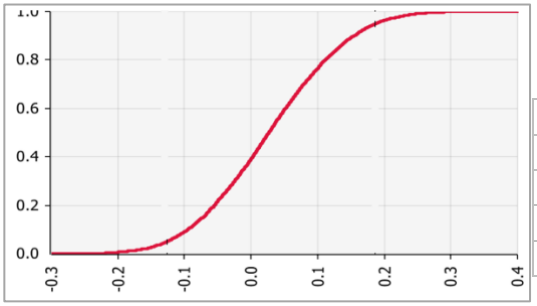
The mean difference in therapy success between universal clopidogrel and universal ticagrelor was 0.003 (95% CI, 0.00182 - 0.00418) in favor of universal clopidogrel. The probability curve of relative success is illustrated in Figure 4.4.



Minimum	-0.18
Maximum	0.20
Mean	-0.003
Std Dev	0.06
Values	10,000

Figure 4.8 Probability curve of relative success with universal clopidogrel over universal ticagrelor

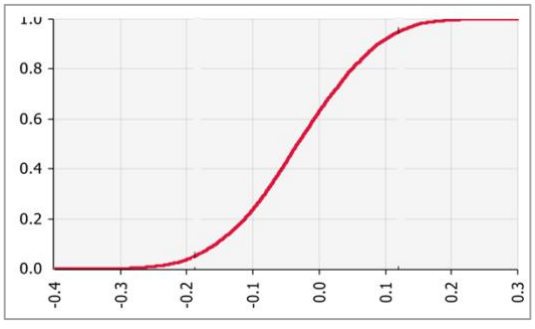
The mean difference in therapy success between genotype-guided therapy and universal clopidogrel was 0.03 (95% CI, 0.0294 - 0.0306) in favor of genotype-guided therapy. The probability curve of relative success is illustrated in Figure 4.5.



Minimum	-0.28
Maximum	0.38
Mean	0.03
Std Dev	0.10
Values	10,000

Figure 4.11 Probability curve of relative success with genotype-guided therapy over universal clopidogrel

The mean difference in therapy success between genotype-guided therapy and universal ticagrelor was 0.03 (95% CI, 0.0282 - 0.0318) in favor of genotype-guided therapy. The probability curve of relative success is illustrated in Figure 4.6.



Minimum	-0.35
Maximum	0.26
Mean	-0.03
Std Dev	0.09
Values	10,000

Figure 4.14 Probability curve of relative success with genotype-guided therapy over universal ticagrelor

4.1.1.3 Economic outcomes

The cost inputs of resources that were included in the model are presented in Table 4.3. According to the published literature, the cost of *CYP2C19* genetic testing was based on an uncertainty range of QAR 730 - 2,555, with a most likely value of QAR 782 (113). To increase the transferability of the genetic test cost, the literature cost was adjusted based on the GDP per capita difference between countries for the year 2019/2020 (69). Generally, the test is performed once only, and the sensitivity and specificity were assumed to be 100%. This approximation was valid as it was shown that both the sensitivity and specificity of the *CYP2C19* genetic test are 99% (114). The cost of all evaluated clinical outcomes based on the one-year non-Markovian follow up is summarized in Table 4.4.

Table 4.3 Cost of resource inputs

Cost category	Cost element	Unit size as per HMC	Cost/ unit (QAR)*
Hospitalization	Bed day in the general medical ward	Per one day	1,621
	Bed day in the STEMI ward		2,334
	Bed day in the intensive care unit		9,580
	Bed day in the cardiothoracic intensive care unit		7,105
	Bed day in the high-dependency unit		2,229
	Bed day in the stroke unit		1,941
Laboratory tests	Comprehensive Metabolic Panel		16
	Complete blood count		43
	Lipid profile test		12
	Thyroid function test (TSH, FT4)		80
	Hemoglobin A1C		22
	Random blood glucose test		8
	Troponin level test		20
	Coagulation profile	Per one test	
	Prothrombin time test		27
	Partial thromboplastin time test		31
	International normalized ratio test		58
	Platelet count test		2
	Arterial blood gas test		70
	Stool occult test		13
	Activated clotting time		14
	Serology		188
	Methicillin-resistant staphylococcus aureus/ methicillin-susceptible staphylococcus aureus		295
	Uric acid level test		8
	Vitamin D level test		233
Screening test	Electrocardiography	*Per one test*	*380*
	Echocardiography		30
	Treadmill stress test		300
	Endoscopy		804
	Magnetic resonance angiography Brain		932
	Magnetic resonance imaging		
	Head/brain		630
	Neck		580
	Computed tomography (contrast)		
	Head/brain		1302
	Neck		593
	Computed tomography (non-contrast)		
	Head/brain		1,020
	Neck		460
	Neck ultrasound (carotid doppler)		210
	Chest x-ray		60
	Thromboelastography		1136

Cost category	Cost element	Unit size as per HMC	Cost/ unit (QAR)*
Procedures	Coronary angiography	Per one procedure	1070
	Percutaneous coronary intervention		
	Bare metal stent		4,350
	Drug eluting stent		18,450
	Coronary artery bypass grafting		20,120
	Solitaire stent thrombectomy		35,000
	Intermittent pneumatic compression*		802
Medications	Aspirin (tablet)	300 mg	0.087
	Aspirin (tablet)	100 mg	0.222
	Ticagrelor (Brilinta®) (tablet)	90 mg	4.399
	Clopidogrel (Plavix ®) (tablet)	75 mg	4.219
	Metoprolol (tablet)	25 mg	0.070
	Carvedilol (tablet)	25 mg	0.365
	Lisinopril (tablet)	10 mg	0.579
	Ramipril (tablet)	5 mg	1.431
	Atorvastatin (tablet)	40 mg	5.870
	Rosuvastatin (tablet)	20 mg	3.792
	Esomeprazole (tablet)	40 mg	3.604
	Eptifibatide (bolus vial)	2mg/ml	102
	Eptifibatide (infusion vial)	0.75 mg/ml	371
	Alteplase (vial)	50 mg	1,523
	Esomeprazole (vial)	40 mg	11
	Mannitol (vial)	200 mg/ml	7
	Normal saline (100 ml bag)	0.9% W/V	8
	labetalol (Ampule)	100 mg/20 ml	14
	Furosemide (Ampule)	20mg/2ml	0.790
	Isosorbide dinitrate (Ampule)	10mg/10ml	7.876
	Heparin (vial)	5000 IU/ml	24
	Enoxaparin (pre-filled syringe)	40 mg/ 0.4 ml	14
	Backed red blood cells	Per unit	214
	Backed platelets*	Per unit	3040
	Fresh frozen plasma	Per unit	71
Genetic test		Per test	782

HMC: Hamad Medical Corporation; QAR: Qatari Riyal
*2019/2020 financial year

Table 4.4 Clinical outcomes and cost of consequences in the one-year decision model

Antiplatelet treatment strategy	Outcome event	Cost (QAR) of health state	Proportional cost (QAR) of health state	Average cost (QAR) per outcome category	Total average cost (QAR) of the antiplatelet strategy
Universal ticagrelor	*Success*			6,096	11,641
	• No event without ADR	6,330	4,072		
	• No event with major bleeding	28,413	1,082		
	• No event with dyspnea	6,297	942		
	Failure				
	• Event without ADR			4,002	
	○ Myocardial infarction without ADR	38,940	2,236		
	○ Stroke without ADR	45,041	436		
	○ Cardiovascular death without ADR	27,512	923		
	○ Stent thrombosis without ADR	27,553	408		
	• Event with ADR			864	
	○ Myocardial infarction with major bleeding	61,848	135		
	○ Myocardial infarction with dyspnea	39,656	341		
	○ Stroke with major bleeding	67,948	25		
	○ Stroke with dyspnea	45,757	66		
	○ Cardiovascular death with major bleeding	50,419	64		
	○ Cardiovascular death with dyspnea	28,228	142		
	○ Stent thrombosis with major bleeding	50,460	28		
	○ Stent thrombosis with dyspnea	28,269	63		
	• Discontinuation of the medication due to ADR			678	
	○ Discontinuation of the medication due to major bleeding	26,258	630		
	○ Discontinuation of the medication due to dyspnea	5,981	48		

Antiplatelet treatment strategy	Outcome event	Cost (QAR) of health state	Proportional cost (QAR) of health state	Average cost (QAR) per outcome category	Total average cost (QAR) of the antiplatelet strategy
Universal clopidogrel	*Success*			4,268	9,506
	• No event without ADR	4,659	3,414		
	• No event with major bleeding	22,002	484		
	• No event with dyspnea	4,626	370		
	Failure				
	• Event without ADR			4,363	
	○ Myocardial infarction without ADR	37,275	2,460		
	○ Stroke without ADR	37,656	377		
	○ Cardiovascular death without ADR	23,464	1,009		
	○ Stent thrombosis without ADR	25,888	517		
	• Event with ADR			508	
	○ Myocardial infarction with major bleeding	55,398	80		
	○ Myocardial infarction with dyspnea	37,991	201		
	○ Stroke with major bleeding	55,780	12		
	○ Stroke with dyspnea	38,372	31		
	○ Cardiovascular death with major bleeding	41,586	39		
	○ Cardiovascular death with dyspnea	24,180	83		
	○ Stent thrombosis with major bleeding	44,011	19		
	○ Stent thrombosis with dyspnea	26,064	43		
	• Discontinuation of the medication due to ADR			366	
	○ Discontinuation of the medication due to major bleeding	35,724	357		
	○ Discontinuation of the medication due to dyspnea	4,474	9		

Antiplatelet treatment strategy	Outcome event	Cost (QAR) of health state	Proportional cost (QAR) of health state	Average cost (QAR) per outcome category	Total average cost (QAR) of the antiplatelet strategy
Genotype-guided ticagrelor	*Success*			1,639	2,804
	• No event without ADR	7,112	1,107		
	• No event with major bleeding	29,195	282		
	• No event with dyspnea	7,079	250		
	Failure				
	• Event without ADR			817	
	○ Myocardial infarction without ADR	39,722	412		
	○ Stroke without ADR	44,927	101		
	○ Cardiovascular death without ADR	28,294	198		
	○ Stent thrombosis without ADR	28,335	107		
	• Event with ADR			180	
	○ Myocardial infarction with major bleeding	62,629	27		
	○ Myocardial infarction with dyspnea	40,438	63		
	○ Stroke with major bleeding	67,835	6		
	○ Stroke with dyspnea	45,644	15		
	○ Cardiovascular death with major bleeding	51,201	15		
	○ Cardiovascular death with dyspnea	29,010	30		
	○ Stent thrombosis with major bleeding	50,702	8		
	○ Stent thrombosis with dyspnea	28,510	16		
	• Discontinuation of the medication due to ADR			167	
	○ Discontinuation of the medication due to major bleeding	27,234	154		
	○ Discontinuation of the medication due to dyspnea	6,763	13		

Antiplatelet treatment strategy	Outcome event	Cost (QAR) of health state	Proportional cost (QAR) of health state	Average cost (QAR) per outcome category	Total average cost (QAR) of the antiplatelet strategy
Genotype-guided clopidogrel	*Success*			4,012	7,327
	• No event without ADR	5,441	3,142		
	• No event with major bleeding	22,783	540		
	• No event with dyspnea	5,408	331		
	Failure				
	• Event without ADR			2,677	
	○ Myocardial infarction without ADR	38,057	1,493		
	○ Stroke without ADR	40,711	268		
	○ Cardiovascular death without ADR	23,464	610		
	○ Stent thrombosis without ADR	26,670	306		
	• Event with ADR			350	
	○ Myocardial infarction with major bleeding	56,179	68		
	○ Myocardial infarction with dyspnea	38,773	122		
	○ Stroke with major bleeding	58,832	12		
	○ Stroke with dyspnea	41,427	22		
	○ Cardiovascular death with major bleeding	42,367	34		
	○ Cardiovascular death with dyspnea	24,962	52		
	○ Stent thrombosis with major bleeding	44,792	16		
	○ Stent thrombosis with dyspnea	27,386	25		
	• Discontinuation of the medication due to ADR			287	
	○ Discontinuation of the medication due to major bleeding	36,506	279		
	○ Discontinuation of the medication due to dyspnea	5,256	8		
Genotype-guided therapy					10,130

ADR: Adverse drug reaction; QAR: Qatari Riyal

Based on the one-year non-Markovian model component, ticagrelor was associated with higher acquisition cost compared to clopidogrel (QAR 3,211 versus 1,540). The costs in relation to other components of therapy were minimally different between the antiplatelet strategies. The cost of hospitalization for the clinical events was the highest, followed by the cost of treatment including medications (i.e., used in the management of the clinical events) and procedures. A summary of the breakdown of the cost components for the antiplatelets strategies is presented in Figure 4.7, and the detailed cost categories for the clinical events are summarized in Table 4.5.

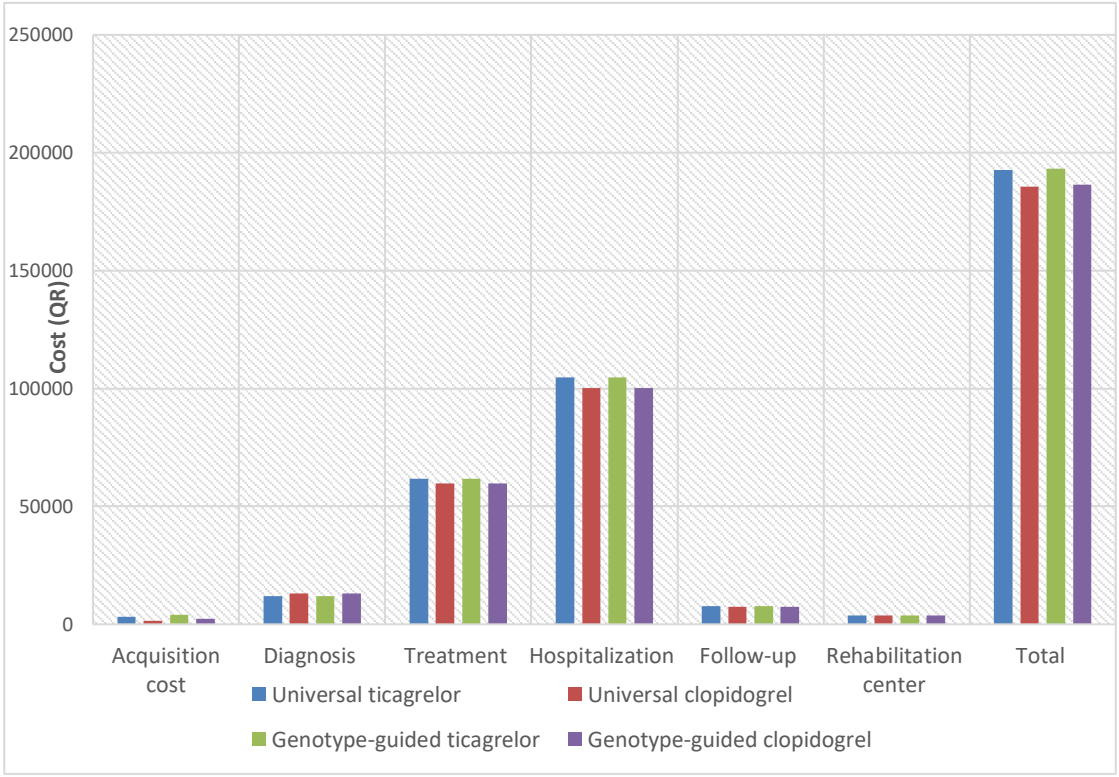


Figure 4.16 Breakdown of cost components for the antiplatelet strategies based on the overall Markov model

Table 4.5 A detailed breakdown of cost components for the antiplatelet strategies, based on the overall Markov model

Clinical outcomes	Ticagrelor (QAR)	Clopidogrel (QAR)	Genotype-guided ticagrelor (QAR)	Genotype-guided clopidogrel (QAR)
• Medication acquisition cost for 12 months | Cost of genetic test	3,211	1,540	782	
• No event without ADR		749		
• Myocardial infarction				
○ Diagnosis	1,653	1,653	1,653	1,653
○ Treatment	19,024	19,024	19,024	19,024
○ Hospitalization	10,700	10,700	10,700	10,700
○ Follow-up	727	727	727	727
○ Rehabilitation center	1,268	1,268	1,268	1,268
○ Total	33,371	33,371	33,371	33,371
• Stent thrombosis				
○ Diagnosis	1,653	1,653	1,653	1,653
○ Treatment	7,096	7,096	19,024	19,024
○ Hospitalization	10,700	10,700	10,700	10,700
○ Follow-up	1,268	1,268	727	727
○ Rehabilitation center	1,268	1,268	1268	1,268
○ Total	21,984	21,984	33,371	33,371
• Stroke				
○ Diagnosis	3,641	3,732	3,641	3,732
○ Treatment	6,248	6,867	6,248	6,867
○ Hospitalization	28,187	21,713	28,187	21,713
○ Follow-up	351	260	351	260
○ Rehabilitation center	1,079	1,187	1,079	1,187
○ Total	39,507	33,758	39,507	33,758
• Cardiovascular death				
○ Diagnosis	1,299	1,199	1,299	1,199
○ Treatment	12,045	10,859	12,045	10,859
○ Hospitalization	10,583	8,453	10,583	8,453
○ Total	23,927	20,511	23,927	20,511
• Major bleeding				
○ Diagnosis	1,341	1,251	1,341	1,251
○ Treatment	2,559	2,720	2,559	2,720
○ Hospitalization	17,926	13,082	17,926	13,082
○ Follow-up	1,081	1,070	1,081	1,070
○ Total	22,907	18,122	22,907	18,122
• Dyspnea				
○ Diagnosis	90	90	90	90
○ Follow-up	626	626	626	626
○ Total	716	716	716	716

Clinical outcomes	Ticagrelor (QAR)	Clopidogrel (QAR)	Genotype-guided ticagrelor (QAR)	Genotype-guided clopidogrel (QAR)
• Discontinuation due to major bleeding				
○ Diagnosis	1,305	1,509	1,305	1,509
○ Treatment	2,623	2,258	2,623	2,258
○ Hospitalization	16,000	26,991	16,000	26,991
○ Follow-up	1,077	1,104	1,077	1,104
Total	21,005	31,863	21,005	31,863
• Discontinuation due to dyspnea				
○ Diagnosis	90			
○ Follow-up	626			
Total	716			
• Post Myocardial infarction	626			
• Post stroke	448			
• Death	24,676	21,260	24,676	21,260

QAR: Qatari Riyal

Based on the overall Markov model, the discounted cumulative cost with each antiplatelet strategy was calculated, as discussed in Section 3.1.5, including all health states (Table 4.6).

Table 4.6 Overall cost with antiplatelets strategies in the Markov model

Antiplatelet strategy	Cumulative cost (QAR)	Discounted cost (QAR)
Universal ticagrelor	270,274	135,760
Universal clopidogrel	275,050	138,231
Genotype-guided therapy	271,414	136,386

4.1.1.3. Cost-effectiveness outcomes

4.1.1.4.1. Universal clopidogrel versus universal ticagrelor

The ICUR of universal clopidogrel versus universal ticagrelor is calculated in the following manner:

- ICUR = (Cost of universal clopidogrel – cost of universal ticagrelor)/ (QALYs of universal clopidogrel – QALYs of universal ticagrelor) = (QAR 133,556 – QAR 131,237)/ (4.82 QALYs – 4.76 QALYs) = 38,650 per QALY

Therefore, universal clopidogrel is cost-effective compared to universal ticagrelor, with higher cost and QALYs. The cost-effectiveness of universal clopidogrel over universal ticagrelor was achieved in 99% of cases.

The tornado analysis of the rank of different study outcomes as per their influence on the study outcome is in Figure 4.8, with the top influencing outcome being the probability of no event without ADR.

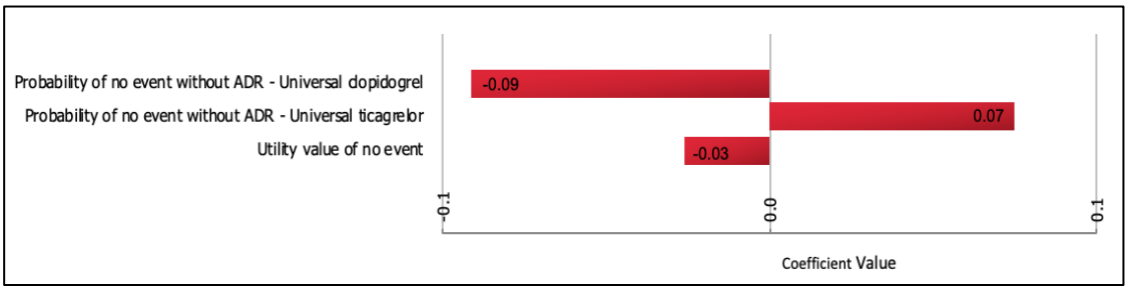


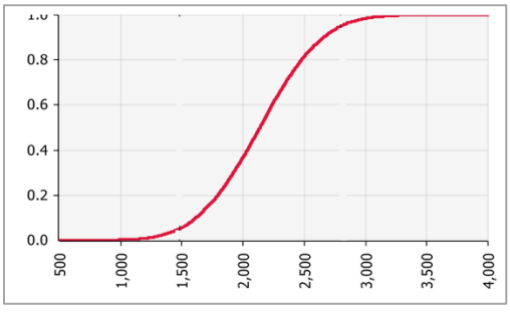
Figure 4.17 Tornado diagram of universal clopidogrel versus universal ticagrelor based on Spearman Rank of the correlation coefficient

The ICER for universal clopidogrel compared to universal ticagrelor was calculated in the following manner:

- ICER = (Cost of universal clopidogrel – cost of universal ticagrelor)/ (Success of universal clopidogrel – success of universal ticagrelor) = (QAR 9,506.22 – QAR 11,640.62)/ (0.8348 – 0.8309) = negative value

Therefore, universal clopidogrel is dominant over universal ticagrelor, with a higher rate of success and a lower cost. This dominance of universal clopidogrel over universal ticagrelor was achieved in 63% of cases; however, it was cost-effective in 30% of the cases. There were only 7% of the cases in which universal clopidogrel was not cost-effective.

Based on the one-year non-Markovian model component, the mean cost-saving was QAR 2,135.81 (95% CI, 2130 - 2140) in favor of universal clopidogrel over universal ticagrelor. The probability curve of universal clopidogrel cost-saving is demonstrated in Figure 4.9.



Minimum	741.90
Maximum	3,513.95
Mean	2,135.81
Std Dev	402.07
Values	10,000

Figure 4.18 Probability curve of cost-saving with universal clopidogrel over universal ticagrelor

The tornado analysis of the rank of different study outcomes as per their influence on the study outcome is in Figure 4.10, with the top influencing outcome being the probability of no event without ADR.

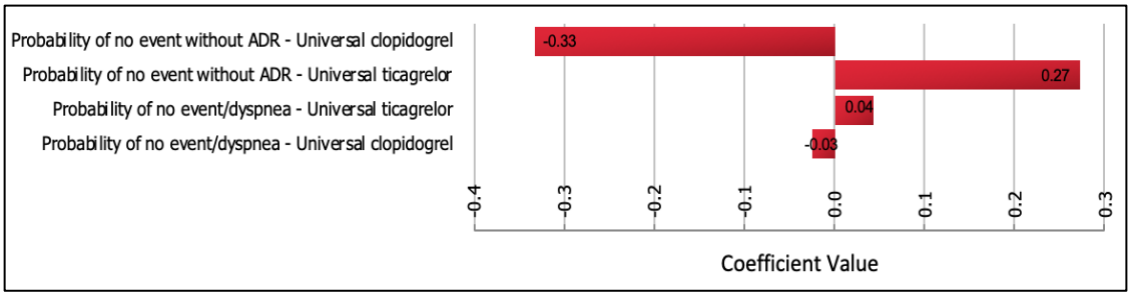


Figure 4.19 Tornado diagram of universal clopidogrel versus universal ticagrelor based on Spearman Rank of the correlation coefficient

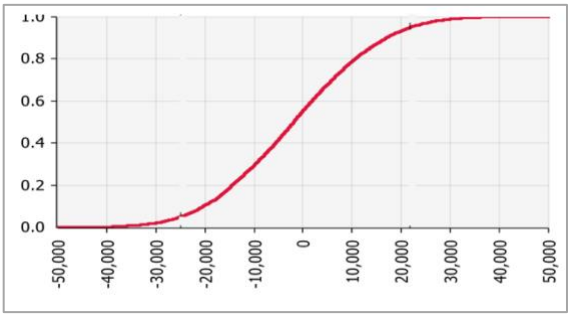
4.1.1.4.2. Genotype-guided therapy versus universal clopidogrel

The ICUR of genotype-guided therapy versus universal clopidogrel is calculated in the following manner:

- ICUR = (Cost of genotype-guided therapy – cost of universal clopidogrel)/ (QALYs of genotype-guided therapy – QALYs of universal clopidogrel) = (QAR 131,791– QAR 133,556)/ (4.87 QALYs – 4.82 QALYs) = negative value

Therefore, genotype-guided therapy is dominant compared to universal clopidogrel, with lower cost and higher QALYs. The dominance of genotype-guided therapy over universal clopidogrel was achieved in 2% of cases. The genotype-guided therapy was cost-effective in 98% of the cases.

Based on the Markov model, the mean cost-saving was QAR 1,813 (95% CI, 1,530 – 2,090) in favor of genotype-guided therapy over universal clopidogrel. The probability curve of genotype-guided therapy cost-saving is depicted in Figure 4.11.



Minimum	-46,323.54
Maximum	49,754.15
Mean	-1,812.74
Std Dev	14,252.46
Variations	10,000

Figure 4.20 Probability curve of cost-saving with genotype-guided therapy over universal clopidogrel

The tornado analysis of the rank of different study outcomes as per their influence on the study outcome is in Figure 4.12, with the top influencing outcome being the utility value of the no event health state.

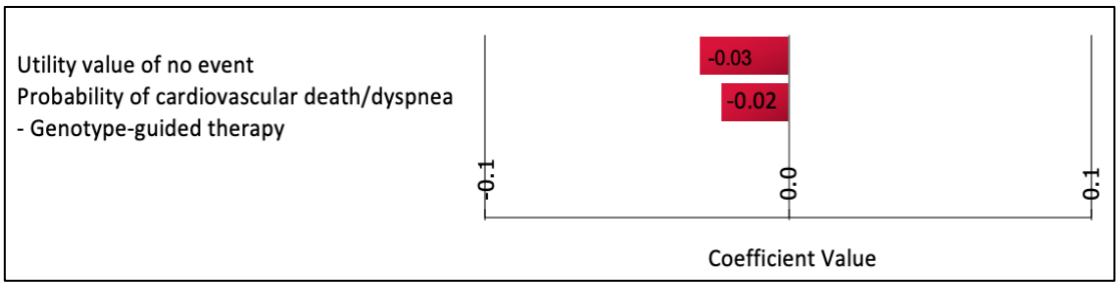


Figure 4.21 Tornado diagram of genotype-guided therapy versus universal clopidogrel based on Spearman Rank of the correlation coefficient

The ICER for genotype-guided therapy compared to universal clopidogrel was calculated in the following manner:

- ICER = (Cost of genotype-guided therapy – cost of universal clopidogrel)/ (Success of genotype-guided therapy – success of universal clopidogrel) = (QAR 10,130.46 – QAR 9,506.22)/ (0.8629 – 0.8348) = 22,215 per case of success

Therefore, genotype-guided therapy is cost-effective over universal clopidogrel, with a higher rate of success and higher cost. This cost-effectiveness of genotype-guided therapy over universal clopidogrel was achieved in 85% of cases. It was dominant in 15% of the cases.

The tornado analysis of the rank of different study outcomes as per their influence on the study outcome is in Figure 4.13, with the top influencing outcome being the probability of *CYP2C19* LOF alleles non-carriers.

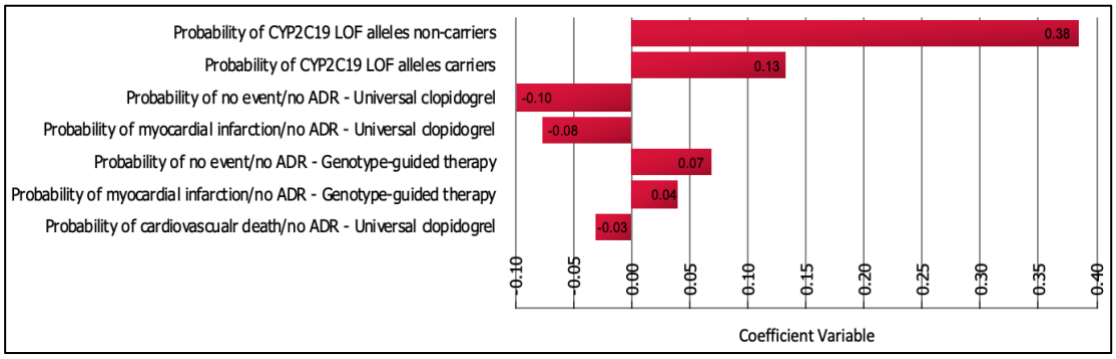


Figure 4.22 Tornado diagram of genotype-guided therapy versus universal clopidogrel based on Spearman Rank of the correlation coefficient

4.1.1.4.3. Genotype-guided therapy versus universal ticagrelor

The ICUR of genotype-guided therapy versus universal ticagrelor is calculated in the following manner:

- ICUR = (Cost of genotype-guided therapy – cost of universal ticagrelor)/ (QALYs of genotype-guided therapy – QALYs of universal ticagrelor) = (QAR 131,791 – QAR 131,237)/ (4.87 QALYs – 4.76 QALYs) = 5,036 per QALY

Therefore, genotype-guided therapy is cost-effective compared to universal ticagrelor, with relatively higher cost and QALYs. The cost-effectiveness of genotype-guided therapy over universal ticagrelor was achieved in 96% of cases. In the remaining 4%, genotype-guided therapy was dominant.

The tornado analysis of the rank of different study outcomes as per their influence on the study outcome is in Figure 4.14, with the top influencing outcome being the probability of *CYP2C19* LOF alleles non-carriers.

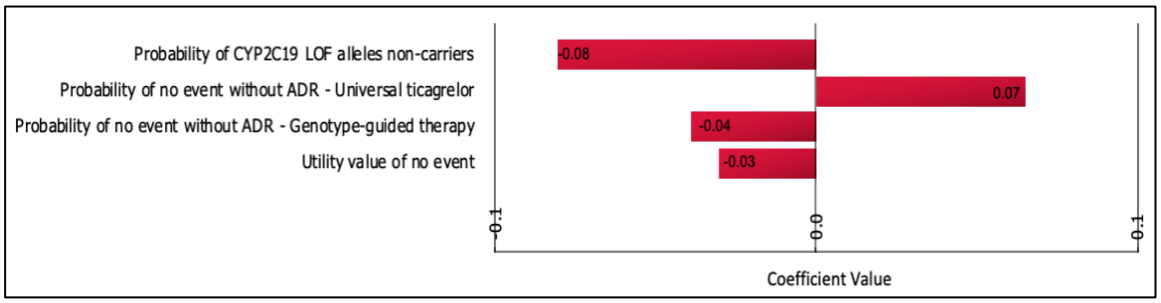


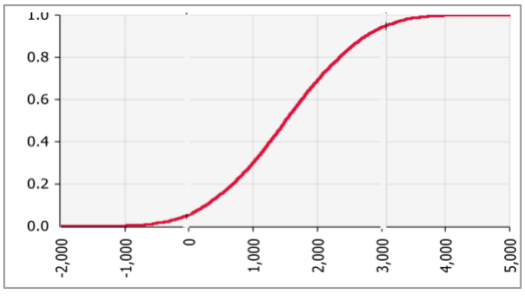
Figure 4.25 Tornado diagram of genotype-guided therapy versus universal ticagrelor based on Spearman Rank of the correlation coefficient

The ICER for genotype-guided therapy compared to universal ticagrelor was calculated in the following manner:

- ICER = (Cost of genotype-guided therapy – cost of universal ticagrelor)/ (Success of genotype-guided therapy – success of universal ticagrelor) = (QAR 10,130.46 – QAR 11,640.62)/ (0.8629 – 0.8309) = negative value

Therefore, genotype-guided therapy is dominant over universal ticagrelor, with a higher rate of success and a lower cost. This dominance of universal clopidogrel over universal ticagrelor was achieved in 60% of cases, and it was cost-effective in 35% of the cases. There were only 5% of the cases in which genotype-guided therapy was not cost-effective.

Based on the one-year model, the mean cost-saving was QAR 1,511.50 (95% CI, 1490 - 1530) in favor of genotype-guided therapy over universal ticagrelor. The probability curve of genotype-guided therapy cost-saving is depicted in Figure 4.9.



Minimum	-1,532.14
Maximum	4,400.88
Mean	1,511.50
Std Dev	945.90
Values	10,000

Figure 4.28 Probability curve of cost-saving with genotype-guided therapy over universal ticagrelor

The tornado analysis of the rank of different study outcomes as per their influence on the study outcome is in Figure 4.16, with the top influencing outcome being the probability of *CYP2C19* LOF alleles non-carriers.

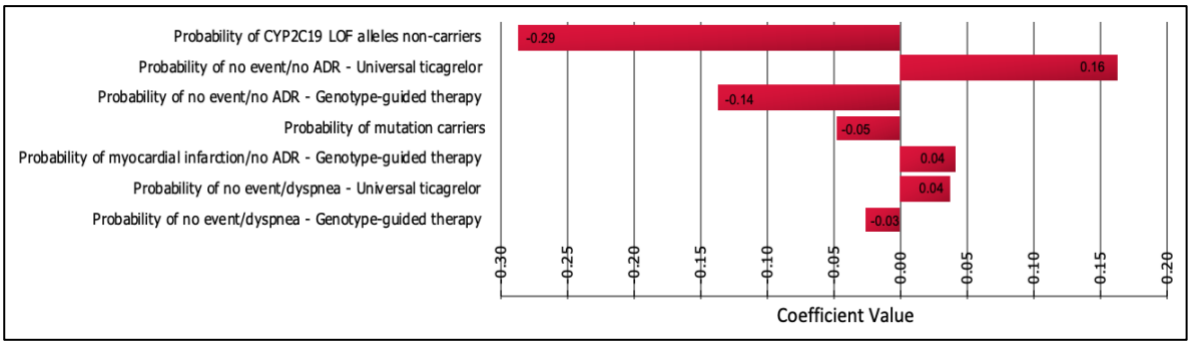


Figure 4.31 Tornado diagram of genotype-guided therapy versus universal ticagrelor based on Spearman Rank of the correlation coefficient

4.1.2. Sensitivity analysis

4.1.2.1 One-way sensitivity analysis

Key variables, the ranges over which they were varied, and their sensitivity analysis outcomes are presented in Table 4.7. Importantly, the superiority of any of the interventions was not sensitive to any uncertainty that was associated with the acquisition costs of ticagrelor and clopidogrel. The probability of being dominant versus cost-effective changed, however. In the one-year analysis, the probability of universal clopidogrel being dominant compared to universal ticagrelor increased from 63% to over 90%, while in the long-term analysis, clopidogrel changed from being 3.5% dominant to 99% cost-effective. For how the genotype-guided therapy compares to universal clopidogrel, the probability of genotype-guided therapy being dominant in

the one-year analysis declined to 0%, to be cost-effective in 99% of the cases. In the long-term analysis, the probability of genotype-guided therapy being dominant compared to universal clopidogrel increased to 99%. For how the genotype-guided therapy compares to universal ticagrelor, the probability of genotype-guided therapy being dominant increased to 90% in the one-year analysis, and in the long-term analysis genotype-guided therapy became cost-effective in 99% of the cases.

4.1.2.2. Multivariate probabilistic sensitivity analysis

The input variables and their uncertainty distributions are presented in Table 4.8. Notably, the study outcomes remained robust against the uncertainty that was associated with hospitalization duration, distribution of patients with ischemic stroke, and performing various radiological imaging and distribution of patients with ischemic stroke.

Table 4.7 Variation range for variables used in one-way sensitivity analyses and main outcomes of interest

Variable	Variation range (QAR)			ICUR of universal clopidogrel and ticagrelor *	ICUR of genotype-guided therapy and universal clopidogrel	ICUR of genotype-guided therapy and universal ticagrelor *	ICER of universal clopidogrel and ticagrelor	ICER of genotype-guided therapy and universal clopidogrel *	ICER of genotype-guided therapy and universal ticagrelor
	Low	Base case	High						
Cost of ticagrelor/ tablet	0	4.399	6.599	49,433 (49,300 – 49,600)	Dominance for genotype-guided therapy	8,046 (7,980 – 8,110)	Dominance for universal clopidogrel	17,865 (17,700 – 18,000)	Dominance for genotype-guided therapy
Cost of clopidogrel/ tablet	0	4.219	6.329	43,227 (43,200 – 43,300)	Dominance for genotype-guided therapy	5,465 (5,430 – 5,500)	Dominance for universal clopidogrel	24,233 (24,200 – 24,300)	Dominance for genotype-guided therapy

QAR: Qatari Riyals; ICUR: Incremental cost-utility ratio; ICER: Incremental cost-effectiveness ratio
* (QAR, 95% Confidence interval)

Table 4.8 Variation range for durations used in multivariate sensitivity analyses, and subsequent changes in outcomes of interests

Input variable	Uncertainty distribution	ICUR of universal clopidogrel and ticagrelor *	ICUR of genotype-guided therapy and universal clopidogrel	ICUR of genotype-guided therapy and universal ticagrelor *	ICER of universal clopidogrel and ticagrelor	ICER of genotype-guided therapy and universal clopidogrel *	ICER of genotype-guided therapy and universal ticagrelor
Hospitalization duration (days) (±30%)		45,172 (45,100 – 45,200)	Dominance for genotype-guided therapy	6,303 (6,300 – 6,310)	Dominance for universal clopidogrel	22,199 (22,200 – 22,200)	Dominance for genotype-guided therapy
• STEMI ward after MI and stent thrombosis	2, 3, 4						
• CTICU after CABG	1, 1, 1						
• HDUD after CABG	4, 5, 7						
• Stroke unit after ischemic stroke	4, 5, 7						
• General medical ward for ischemic stroke	2, 3, 4						
• ICU after ischemic stroke	9, 13, 17						
• ICU after hemorrhagic stroke/intracranial hemorrhage	5, 7, 9						
• General medical ward after hemorrhagic stroke/intracranial hemorrhage	10, 14, 18						
• General medical after gastrointestinal bleeding	2, 3, 4						
• General medical ward after heart failure	5, 7, 9						

Input variable	Uncertainty distribution	ICUR of universal clopidogrel and ticagrelor *	ICUR of genotype-guided therapy and universal clopidogrel	ICUR of genotype-guided therapy and universal ticagrelor *	ICER of universal clopidogrel and ticagrelor	ICER of genotype-guided therapy and universal clopidogrel *	ICER of genotype-guided therapy and universal ticagrelor
Distribution of patients with ischemic stroke and undergoing various radiological imaging (±30%)		45,172 (45,100 – 45,200)	Dominance for genotype-guided therapy	6,303 (6,300 – 6,310)	Dominance for universal clopidogrel	22,199 (22,200 – 22,200)	Dominance for genotype-guided therapy
• Non-contrast brain CT	0.210, 0.3, 0.390						
• Contrast brain CT	0.210, 0.3, 0.390						
• Brain MRI	0.595, 0.85, 1.105						
• Brain MRA	0.595, 0.85, 1.105						
• Neck ultrasound	0.175, 0.25, 0.325						
• Non-contrast neck CT	0.175, 0.25, 0.325						
• Neck MRI	0.350, 0.5, 0.650						
Distribution of patients with ischemic stroke (±30%)		45,260 (45,300 – 45,300)	Dominance for genotype-guided therapy	6,314 (6310 - 6310)	Dominance for universal clopidogrel	22,179 (22,200 – 22,200)	Dominance for genotype-guided therapy
• Patients hospitalized in the ICU	0.140, 0.02, 0.260						
• Patients hospitalized in the general medical ward	0.014, 0.2, 0.026						
• Patients undergoing solitaire stent thrombectomy	0.210, 0.2, 0.390						

HDUD: High-dependency unit; CTICU: Cardiothoracic intensive care unit; ICU: Intensive care unit; MI: Myocardial infarction; CABG: Coronary artery bypass surgery; MRI: Magnetic resonance imaging; CT: Computerized tomography; MRA: Magnetic resonance angiogram; HMC: Hamad Medical Corporation; QAR: Qatari Riyal

* (QAR, 95% Confidence interval)

4.2. Phase two: Economic evaluations of *CYP2C19* genotype-guided antiplatelet therapy compared to the universal use of antiplatelets in patients with acute coronary syndrome: A systematic review

(This section of the thesis has been extracted from the following publication: AlMukdad S, Elewa H, Al-Badriyeh D. *Economic Evaluations of CYP2C19 Genotype-Guided Antiplatelet Therapy Compared to the Universal Use of Antiplatelets in Patients with Acute Coronary Syndrome: A Systematic Review*. J Cardiovasc Pharmacol Ther. 2020:1074248420902298)

4.2.1. Study selection

Out of a total of 204 retrieved articles, 13 articles met the inclusion criteria. The search results are shown in Figure 4.17.

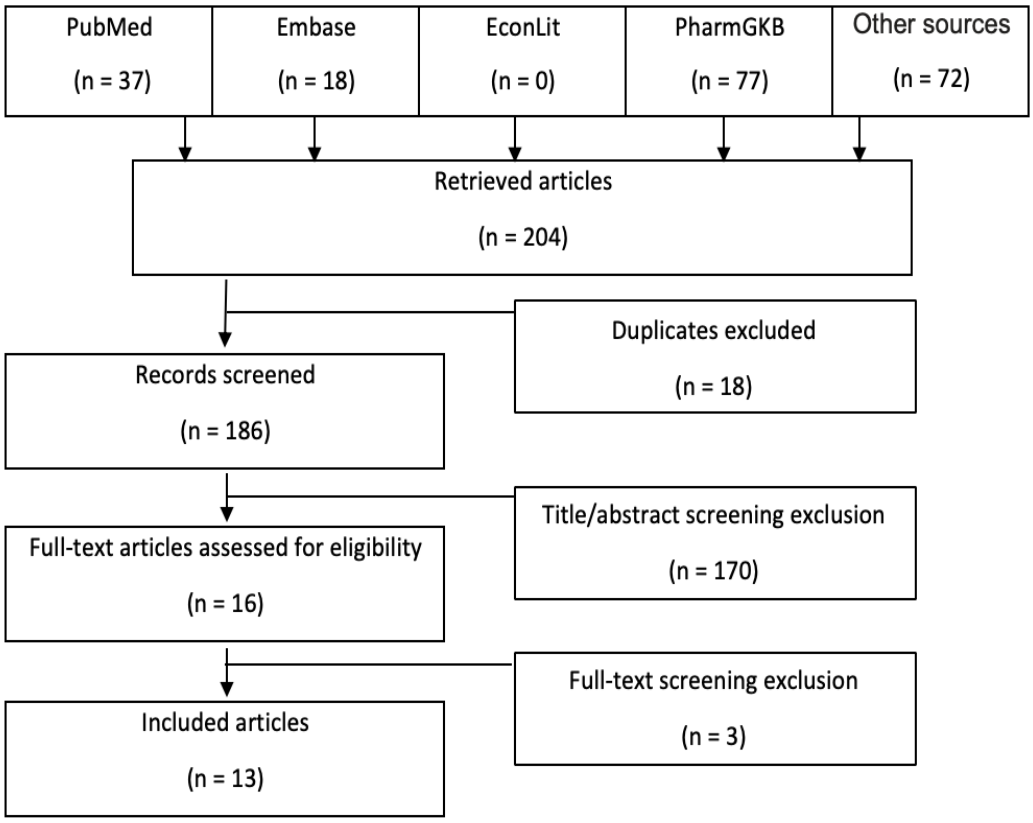


Figure 4.32 Flow diagram of the literature search and selection

4.2.2. Characteristics of the included articles

In patients with ACS undergoing PCI, genotype-guided therapy with prasugrel was compared to universal clopidogrel or prasugrel in five articles (115-119). Genotype-guided therapy with ticagrelor was compared to universal clopidogrel or ticagrelor in four articles (73–76). Four articles evaluated the genotype-guided use of the P2Y12 inhibitors ticagrelor or prasugrel as compared against the universal use of P2Y12 inhibitors, i.e. clopidogrel, ticagrelor, or prasugrel (78–81). In general, key clinical effectiveness data in the majority of the studied comparative models were derived from the two landmark clinical trials of antiplatelet therapy in patients with ACS; the TRITION-TIMI 38 clinical trial (prasugrel versus clopidogrel) and the PLATO clinical trial (ticagrelor versus clopidogrel) (51,120). The most commonly studied LOF allele was *CYP2C19* *2, with others being *3,*4,*5,*6,*7,*8. All the studies considered the use of an alternative to clopidogrel in the genotype-guided arm whenever there was LOF allele, regardless of whether it was homozygote (2 copies of the LOF allele) or heterozygote (1 copy of the LOF allele). Among the 13 included studies, seven were conducted in the US (73,74,78,115,116,118,119), four in China (76,79–81), one in Australia (75), and one in New Zeeland (117). Characteristics of the included studies are summarized in Table 4.9.

Table 4.9 Characteristics of the included articles

Author/ year	Country and underlying disease	Treatment strategy	Type of Model	Time horizon	Cost/ outcome	Economic analysis perspective
Borse et al. (2017) [115]	US, patients with ACS undergoing PCI	Three study arms: Universal clopidogrel or prasugrel versus *CYP2C19* genotype-guided antiplatelet therapy	Decision tree	30 days and 12 months	Cost per avoided MACE or bleeding event	US healthcare payer
Crespin et al. (2011) [73]	US, patients hospitalized for ACS	Two study arms: Universal ticagrelor versus *CYP2C19* genotype-guided antiplatelet therapy	Decision tree and Markov model	12 months and 5 years	Cost per QALY	US third-party payer
Jiang et al. (2017) [81]	China, patients aged 60 years with ACS undergoing PCI	Three study arms: Universal clopidogrel or universal alternative P2Y12 inhibitors (prasugrel or ticagrelor) versus genotype-guided antiplatelet therapy	Decision tree and Markov model	12 months and lifetime	Cost per QALY	US healthcare provider
Jiang et al. (2016) [80]	China, patients aged 60 years with ACS undergoing PCI	Four study arms: Universal clopidogrel or universal alternative P2Y12 inhibitor (prasugrel or ticagrelor) versus platelet reactivity testing-guided therapy versus genotype-guided antiplatelet therapy	Decision tree and Markov model	12 months and lifetime	Cost per QALY	US healthcare provider
Jiang et al. (2015) [79]	China, patients aged 60 years with ACS undergoing PCI	Three study arms: Universal clopidogrel or universal alternative P2Y12 inhibitor (prasugrel or ticagrelor) versus genotype plus platelet reactivity-guided antiplatelet therapy	Decision tree and Markov model	12 months and lifetime	Cost per QALY	US healthcare provider
Kazi et al. (2014) [78]	US, patients aged 65 years with ACS and underwent PCI	Three study arms: Universal clopidogrel or universal alternative P2Y12 inhibitor (prasugrel or ticagrelor) versus genotype-guided antiplatelet therapy	Markov model	Lifetime	Cost per QALY	US societal perspective

Author/ year	Country and underlying disease	Treatment strategy	Type of Model	Time horizon	Cost/ outcome	Economic analysis perspective
Kim et al. (2019) [74]	US, patients with ACS managed with either PCI or medically (without PCI)	Six study arms: Universal clopidogrel; ticagrelor guided by platelet reactivity assay; genotype-guided ticagrelor only in *CYP2C19* poor metabolizers (genotype + conservative ticagrelor); genotype-guided ticagrelor in both *CYP2C19* intermediate and poor metabolizers (genotype + liberal ticagrelor); ticagrelor use only in patients with *CYP2C19* polymorphisms and clopidogrel nonresponse by platelet reactivity assay (genotype + phenotype); and universal ticagrelor	Decision tree and Markov model	12 months and lifetime	Cost per QALY	US healthcare sector
Lala et al. (2013) [116]	US, patients aged 60 years with ACS undergoing PCI	Three study arms: Universal clopidogrel or prasugrel versus genotype-guided antiplatelet therapy	Markov model	15 months and 10 years	Cost per QALY	US payer perspective
Panattoni et al. (2012) [117]	New Zealand, patients aged 45-80 years with ACS and planned PCI	Three study arms: Universal clopidogrel or prasugrel versus genotype-guided antiplatelet therapy	Decision tree	15 months and lifetime	Cost per QALY	New Zealand healthcare system
Patel et al. (2014) [118]	US, patients aged 60 years moderate-to-high risk ACS and planned PCI	Three study arms: Universal clopidogrel or prasugrel versus *CYP2C19* genotype-guided antiplatelet therapy	Decision tree	15 months	Cost per QALY	US healthcare provider
Reese et al (2012) [119]	US, patients with ACS undergoing PCI	Three study arms: Universal clopidogrel or prasugrel versus genotype-guided antiplatelet therapy	Decision tree	15 months	Cost per avoided MACE or bleeding event	US payer perspective

Sorich et al. (2013) [75]	Australia, patients aged 62 years with ACS and underwent PCI	Three study arms: Universal clopidogrel or ticagrelor versus genotype-guided antiplatelet therapy	Decision tree and Markov model	12 months and lifetime	Cost per QALY	Australian healthcare system
Wang et al. (2017) [76]	China, patients aged 60 years underwent PCI after ACS	Three study arms: Universal clopidogrel or ticagrelor versus *CYP2C19* genotype-guided antiplatelet therapy	Decision tree and Markov model	12 months and lifetime	Cost per QALY	Asian healthcare provider

ACS: Acute coronary syndrome; PCI: Percutaneous coronary intervention; MCAE: Major adverse cardiovascular event; QALY: Quality-adjusted life years; US: United States

All included articles applied decision-analytic models (basic decision tree and/or the Markov model) that followed cohorts of patients over follow-up periods of 12 months, 15 months or lifetime of patients. All economic evaluation studies analyzed direct medical costs. A cost-utility analysis was performed in 11 out of 13 studies and the outcome measure used in these studies was cost/ QALY (73-76, 78-81, 116-118). The other two studies conducted a cost-effectiveness analysis and the outcome measure was cost/ avoided cardiovascular or bleeding event (115,119). All studies evaluated the generic clopidogrel and branded ticagrelor or prasugrel at the base case of their analyses. Only four articles reported the genotyping methods, in which Wang et al and Crespin et al. utilized conventional genotyping (73,76), while Kazi et al. and Kim et al. utilized point-of-care genotyping (74,78).

4.2.3. Genotype-guided therapy with prasugrel versus universal use of prasugrel or clopidogrel

4.2.3.1. Clinical and cost outcomes

In the genotype-guided arm, patients with LOF alleles received prasugrel, while patients without LOF alleles received clopidogrel (115-119). All studies reported MACE (i.e. composite of nonfatal stroke, nonfatal MI and CV death), as well as major bleeding as the primary clinical outcome measures. Only Borse et al. and Panattoni et al. reported stent thrombosis in addition to MACE and major bleeding (115,117). The modeled clinical events in the included cost-effectiveness studies were consistent, as all five studies used TRITON-TIMI 38 and genetic sub-studies to obtain the base-case probabilities. Only Panattoni et al used New Zealand's public hospitals' reports in addition to the TRITON-TIMI 38 trial to obtain the clinical effectiveness data (117).

Generally, multiple sources of cost data were used to describe the cost of medications, genetic testing, hospitalization, outpatient visits, and adverse events.

Medicare reimbursement rates and local published data were commonly used among the five articles (115-119). For the purpose of cost adjustment according to time, Lala et al. and Panattoni et al. discounted cost and utilities (116,117), while Patel et al. and Reese et al discounted cost only (118,119).

4.2.3.2. Cost-effectiveness results

Base-case results by Borse et al., Patel et al., Panattoni et al., and Reese et al. showed that genotype-guided treatment was cost-effective compared to universal clopidogrel [ICER/ MACE or bleeding event avoided of USD 50,308; ICER/QALY gained of USD 4,200; New Zealand Dollar (NZD) 24617; and USD 2300, respectively] and dominant when compared to universal prasugrel (115, 117-119). Lala et al. stated that genotype-guided treatment was dominant compared to both universal prasugrel and clopidogrel (116). As illustrated in Table 4.10, all studies performed sensitivity analyses to assess the robustness of the results.

Table 4.10 Base-case and sensitivity analysis results for genotype-guided therapy with prasugrel versus universal use of prasugrel or clopidogrel

Author	Base-case results	Sensitivity analysis results
Borse et al.	The ICER/ MACE or bleeding event avoided for genotype-guided therapy was USD 8525 and 50,308 compared with universal clopidogrel at 30 days and 12 months, respectively The ICER/ MACE or bleeding event avoided for genotype-guided therapy was USD 42,198 at 30 days, but it was dominant at 12 months when compared to universal prasugrel	Probabilistic sensitivity analysis: Genotype-guided therapy was cost-effective over 30 days in 62% of the simulations and over 1 year in 70% of simulations

Author	Base-case results	Sensitivity analysis results
Lala et al.	Genotype-guided therapy was dominant compared to universal clopidogrel and prasugrel	One-way sensitivity analysis: Results were sensitive to the relative risk of thrombotic events in *CYP2C19* LOF alleles carriers and non-carriers of prasugrel versus clopidogrel Probabilistic sensitivity analysis: Genotype-guided therapy was cost-effective in 75% of the simulations
Panattoni et al.	The ICUR/QALY for genotype-guided therapy compared to universal clopidogrel was NZD 24,617 Genotype-guided therapy was dominant compared to universal prasugrel Universal clopidogrel was dominant compared to universal prasugrel	Probabilistic sensitivity analysis: Results were robust across the variations in all input parameters, except the clinical trial event rate
Patel et al.	The ICUR/QALY for genotype-guided therapy compared to universal clopidogrel was USD 4,200 Genotype-guided therapy was dominant compared to universal prasugrel The ICUR/QALY for universal clopidogrel compared to universal prasugrel was USD 227,800	One-way sensitivity analysis: Results were robust against all input variations, expect the relative risk of having MI and stroke between *CYP2C19* loss-of-function alleles carriers and non-carriers Probabilistic sensitivity analysis: Genotype-guided therapy had >70% probability of being the most cost-effective strategy
Reese et al.	Genotype-guided therapy was dominant compared to universal branded clopidogrel and prasugrel The ICER/MACE or bleeding event avoided for genotype-guided therapy compared to universal generic clopidogrel was USD 2,300	Scenario sensitivity analysis: Genotype-guided therapy remained dominant if generic clopidogrel was used Probabilistic sensitivity analysis: 95% certain to avoid one event if the WTP is USD 9,670 (branded clopidogrel) and USD 3700 (generic clopidogrel) when comparing genotype-guided prasugrel and universal clopidogrel. While the thresholds of acceptance increased to USD 225,500 (branded clopidogrel) and USD 55,000 (generic clopidogrel) per event avoided when comparing genotype-guided therapy with universal prasugrel

MACE: Major adverse cardiovascular event; QALY: Quality adjusted life years; ICER: Incremental cost-effectiveness ration; ICUR: Incremental cost-utility ration; USD: United states Dollar; NZD: New Zealand Dollar

4.2.4. Genotype-guided therapy with ticagrelor versus universal use of ticagrelor or clopidogrel

4.2.4.1. Clinical and cost outcomes

In the genotype-guided arm, patients with LOF alleles received ticagrelor, whereas patients without LOF alleles received clopidogrel (73–76). Sorich et al examined MACE, Wang et al. examined MACE as well as stent thrombosis and fatal bleeding, Crespin et al. evaluated MI, bleeding, dyspnea and death, and Kim et al. examined MI, ischemic stroke, intracranial hemorrhage, major bleeding, and death (73–76). Three articles used similar sources of clinical effectiveness events including the PLATO trial and sub-studies (73–75), whereas Crespin et al. and Kim et al. (73,74) used the Medicare program and a meta-analysis by Mega et al. (43), respectively in addition to the PLATO trial (51). On the other hand, Wang et al. relied on local observational studies done in Asian populations (76).

Wang et al described the costs of medications, inpatient, outpatient, and *CYP2C19* genotype testing that were based on public hospital formulary, locally published data and international experience (76). Crespin et al. and Kim et al. presented the cost of resources used after ACS diagnosis, including the cost of the genetic test, medications, ACS events, hospitalization, and subsequent monthly ACS care (73,74). Crespin et al derived the cost data from the Medicare program and sources available in the literature, whereas Kim et al. calculated the cost from the wholesale price available from RedBook, national statistics and previous reports in the literature. Costs and health outcomes were discounted in all articles (73–76).

4.2.4.2. Cost-effectiveness results

Base-case analyses by Wang et al. and Sorich et al. illustrated that genotype-guided treatment with ticagrelor was cost-effective compared to universal clopidogrel (ICER/QALY of USD 2560 and AUD 6000, respectively) (75,76). Wang et al. concluded that the genotype-guided therapy was dominant compared to universal ticagrelor (76). On the contrary, Sorich et al. and Crespin et al. demonstrated that universal ticagrelor was cost-effective compared to genotype-guided treatment with an ICER/QALY of AUD 23,000 and USD 10,059, respectively (73,75). Kim et al. showed that genotype-guided treatment with ticagrelor in both *CYP2C19* intermediate and poor metabolizers (genotype + liberal ticagrelor) was a cost-effective strategy with an ICER/QALY of USD 29,412, whereas genotype-guided treatment with ticagrelor only in *CYP2C19* poor metabolizers (genotype + conservative ticagrelor) was not a cost-effective strategy (74). All studies performed sensitivity analyses, with the results presented in Table 4.11.

Table 4.11 Base-case and sensitivity analysis results for genotype-guided therapy with ticagrelor versus universal use of ticagrelor or clopidogrel

Author	Base-case results	Sensitivity analysis results
Crespin et al.	The ICER/QALY for universal ticagrelor compared to genotype-guided therapy was USD 42,546 and 10,059 at 12 months and 5 years, respectively	One-way sensitivity analysis: Universal ticagrelor remained cost-effective throughout the variation of all model inputs Probabilistic sensitivity analysis: Universal ticagrelor was cost-effective in 97.7% of simulations
Kim et al.	The ICER/QALY for genotype + liberal ticagrelor compared to clopidogrel + phenotype was USD 29,412 Genotype + conservative ticagrelor was not cost-effective due to second-order dominance The ICER/QALY for universal ticagrelor compared to genotype + liberal ticagrelor was USD 142,456	One-way sensitivity analysis: Results were sensitive to the risk ratio of the thrombotic events, bleeding events, and cost of ticagrelor Probabilistic sensitivity analysis: The probability of being cost-effective for the genotype + liberal ticagrelor, universal ticagrelor, and universal clopidogrel strategies were 63%, 33%, and 1%, respectively
Sorich et al.	The ICER/QALY for universal ticagrelor compared to genotype-guided therapy was AUD 22,821 The ICER/QALY for genotype-guided therapy compared to universal clopidogrel was AUD 6000	One-way sensitivity analysis: The hazard ratios for the comparative treatment effect for the *CYP2C19* subgroups were the most influential parameter on the cost-effectiveness of universal ticagrelor Probabilistic sensitivity analysis: Genotype-guided ticagrelor would be a cost-effective strategy if the WTP per QALY was less than AUD 7,000 - 21,000
Wang et al.	The ICER/QALY for genotype-guided therapy compared to universal clopidogrel was USD 2560 Genotype-guided treatment was dominant compared to universal ticagrelor The ICER/QALY for universal ticagrelor compared to universal clopidogrel was USD 7254	One-way sensitivity analysis: Genotype-guided therapy remained cost-effective compared with universal clopidogrel against all variables Probabilistic sensitivity analysis: Genotype-guided therapy was cost-effective in 98.5% of the simulations compared to both universal clopidogrel and ticagrelor

QALY: Quality adjusted life years; ICER: Incremental cost-effectiveness ration; WTP: Willingness-to-pay threshold; USD: United states Dollar; AUD: Australian Dollar

4.2.5. Genotype-guided therapy with alternative P2Y12 inhibitors (prasugrel and ticagrelor) versus universal use of alternative P2Y12 inhibitors or clopidogrel

4.2.5.1. Clinical and cost outcomes

Unlike the studies mentioned above where either prasugrel or ticagrelor is evaluated, four studies assessed both medications in a single study group (78–81). In the genotype-guided group, patients with LOF alleles received either prasugrel or ticagrelor, whereas patients without LOF alleles received clopidogrel. Only one article used both *CYP2C19* genotype plus platelet reactivity-guided antiplatelet therapy as the intervention (79). Jiang et al. (2017), Jiang et al. (2016), and Jiang et al. (2015) evaluated MACE, major bleeding, and stent thrombosis, while Kazi et al. assessed only MACE and bleeding (79–81). Generally, TRITON-TIMI 38 trial, PLATO trial, and meta-analyses were the main sources of clinical effectiveness data in the four articles (78–81).

Cost of clinical outcomes, adverse drug reactions, medications, and genetic testing were estimated from inpatient diagnosis-related group data, retail prices, claims databases and published economic data (78–81). Costs and health outcomes were discounted in all articles (78–81).

4.2.5.2. Cost-effectiveness results

Base-case results illustrated that the genotype-guided treatment was the dominant strategy compared to both universal clopidogrel and P2Y12 inhibitors (79–81). Kazi et al. concluded that genotype-guided therapy with ticagrelor was the most cost-effective strategy (78). Jiang et al. (2017), Jiang et al. (2016), and Jiang et al. (2015) showed that universal use of alternative P2Y12 inhibitors was cost-effective compared to universal clopidogrel with an ICER/QALY of USD 28,542, 43,683, and 139,588, respectively (79–81). In contrast, Kazi et al. explained that universal

clopidogrel was dominant compared to universal prasugrel, while universal ticagrelor was cost-effective compared to the universal clopidogrel with an ICER/QALY of USD 40,300 (78). The four articles performed sensitivity analyses and the results are summarized in Table 4.12.

Table 4.12 Base-case and sensitivity analysis results for genotype-guided therapy with alternative P2Y12 inhibitors (prasugrel and ticagrelor) versus universal use of alternative P2Y12 inhibitors or clopidogrel

Author	Base-case results	Sensitivity analysis results
Jiang et al. (2017)	Genotype-guided therapy was dominant compared to universal clopidogrel and alternative P2Y12 inhibitors The ICER/QALY for universal alternative P2Y12 inhibitors compared to universal clopidogrel was USD 28,542	One-way sensitivity analysis: Results were sensitive to hazard ratio of cardiovascular death Probabilistic sensitivity analysis: Genotype-guided therapy saved cost and QALYs in 99.07% of the simulations
Jiang et al. (2016)	Genotype-guided therapy was dominant compared to the other three arms The ICER/QALY for universal alternative P2Y12 inhibitors compared to universal clopidogrel was USD 43,683	One-way sensitivity analysis: Genotype-guided antiplatelet therapy was the most cost-effective strategy throughout the variation of all model inputs Probabilistic sensitivity analysis: Genotype-guided therapy gained higher QALYs with the lowest cost in 83.22% of the simulations
Jiang et al. (2015)	Genotype plus platelet reactivity-guided therapy was dominant compared to universal clopidogrel and alternative P2Y12 inhibitors	One-way sensitivity analysis: Results were robust against all variables, except for the prevalence of the LOF allele carriers and the percentage of high on-treatment platelet reactivity. Probabilistic sensitivity analysis: Genotype plus platelet reactivity-guided therapy was cost-effective in 96.64% of the simulations
Kazi et al.	The ICER/QALY for genotype-guided ticagrelor was USD 30,200 and 24,700 in low and high discrimination scenarios, respectively	One-way sensitivity analysis: Low-discrimination scenario, results were sensitive to minor variations related to the probability of the thrombotic events, patient's quality of life due to dyspnea, and cost of genetic testing and medications.

The ICER/QALY for universal ticagrelor compared to universal clopidogrel was USD 40,300 Universal use of clopidogrel was dominant compared to universal prasugrel	High-discrimination scenario, results were robust to all variations, except for the cost of genetic testing Probabilistic sensitivity analysis: Low-discrimination scenario, genotype-guided ticagrelor and universal ticagrelor were cost-effective in 39.2% and 42.3% of the simulations. High-discrimination scenario, genotyping with ticagrelor was cost-effective in 63.4% of the simulations

QALY: Quality adjusted life years; ICER: Incremental cost-effectiveness ration; USD: United States Dollar; LOF: Loss-of-function.

Cost outcomes of all studies, adjusted to the USA currency and the 2019/20 financial year, can be seen in Appendix E.

4.2.6. Quality assessment results

All studies were good in quality and none performed poorly. Table 4.13 presents the results of the quality assessment of the included articles using the QHES tool. Detailed QHES results can be seen in Appendix F.

Table 4.13 Quality assessment; QHES tool

Author/ year	Score	Overall assessment
Borse et al. (2017) [115]	80	Good quality
Crespin et al. (2011) [73]	94	Good quality
Jiang et al. (2017) [81]	87	Good quality
Jiang et al. (2016) [80]	93	Good quality
Jiang et al. (2015) [79]	87	Good quality
Kazi et al. (2014) [78]	94	Good quality
Kim et al. (2019) [74]	84	Good quality
Lala et al. (2013) [116]	91.5	Good quality
Panattoni et al. (2012) [117]	79	Good quality
Patel et al. (2014) [118]	90	Good quality
Reese et al. (2012) [119]	87.5	Good quality
Sorich et al. (2013) [75]	84.5	Good quality
Wang et al. (2017) [76]	90	Good quality

CHAPTER 5: DISCUSSION

5.1. Phase one: Economic evaluation of the *CYP2C19* genotype-guided antiplatelet therapy compared to the universal use of ticagrelor or clopidogrel in Qatar

The objective of the first phase of this thesis was to conduct the first economic evaluation in Qatar and the region to compare *CYP2C19* genotype-guided antiplatelet therapy versus universal use of clopidogrel or ticagrelor in patients with ACS undergoing PCI. As indicated earlier in the thesis, clopidogrel and ticagrelor are the only P2Y12 inhibitors available in HMC drug formulary and both can be used as first-line therapy in post-PCI patients.

The results from the comparative one-year non-Markovian cost-effectiveness model in this current research illustrated a difference in the probability of success (i.e., 0.03), in favor of genotype-guided antiplatelet therapy compared to universal clopidogrel. The genotype-guided antiplatelet therapy was cost-effective in 85% of the cases (ICER of mean QAR 22,215 per case of success). Taking the humanistic aspect into consideration, based on the cost-utility analysis, the genotype-guided therapy was between dominant and cost-effective, with an ICUR that is up to 48,321 per QALY, with mean cost-saving of QAR 1,813.

The reported advantage of genotype-guided therapy compared to universal clopidogrel in the current study is supported by the results of other economic evaluations in the literature worldwide. Our findings were similar to prior simulation-based cost-utility analyses, where genotype-guided therapy was the preferred strategy compared to universal clopidogrel. The studies by Jiang et al. (2017), Jiang et al. (2016), and Jiang et al. (2015) indicated a dominance of genotype-guided therapy

compared to universal clopidogrel with cost-saving of USD 476, 1,387, 466, respectively (79–81). Whereas, the studies by Sorich et al., Wang et al., and Limdi et al. demonstrated the cost-effectiveness of genotype-guided therapy compared to universal clopidogrel with ICER of USD 4,702, 2,745, and 42,365 per QALY, respectively (75–77). For a genotype-guided ticagrelor therapy, Kazi et al. also reported cost-effectiveness compared to universal clopidogrel, with an ICER of 28,259 per QALY (78).

The comparison between genotype-guided therapy and universal ticagrelor in the one-year cost-effectiveness model showed that genotype-guided therapy was dominant in 60% of cases, whereby the mean cost-saving was QAR 1,512. With regards to humanistic outcomes, the difference in cumulative QALY was (i.e., 0.23) in favor of genotype-guided antiplatelet therapy compared to universal ticagrelor, and the genotype-guided antiplatelet therapy was cost-effective in 96% of the cases (ICUR of QAR 5,036 per QALY).

Results from the literature that investigated the cost-effectiveness of genotype-guided therapy compared to universal ticagrelor were conflicting. Wang et al. illustrated that genotype-guided therapy was dominant compared to universal ticagrelor with a cost-saving of USD 428. The dominance in this study versus the cost-effectiveness in our study can be explained by the high prevalence of *CYP2C19* LOF carriers (i.e., 51.8%) in the Chinese population. In addition, Wang et al. relied on small-scale clinical trials in Asian populations, instead of the PLATO trial to extract the clinical outcomes (76). Contrary to our results, Sorich et al. and Crespin et al. demonstrated that universal ticagrelor was cost-effective compared to genotype-guided therapy, with ICER of USD 17,885 and 12,066 per QALY, respectively (73,75). The discrepancies in the conclusion between those studies and ours can be

explained by the differences in the included outcomes in models; whereby, Sorich et al. evaluated MI, stroke, and death only, and Crespin et al. evaluated MI, bleeding, dyspnea and death. In our current analysis, however, we performed a much more comprehensive decision-analytic modeling that better reflects all anticipated relevant outcomes in real-life practices. This included MI, stroke, cardiovascular death, stent thrombosis, ADRs (major bleeding and dyspnea), and discontinuation due to ADRs. The overall QALY and cost outcomes are predominantly affected by the type of events considered. Excluding outcomes such as bleeding, dyspnea, or discontinuation of the medication due to ADRs for the decision analysis, will favor ticagrelor over the genotype-guided therapy. It is noteworthy to indicate that costs can extremely vary between healthcare systems given how different resources are utilized, which might also be a leading cause behind the conflicting findings. Important to mention is that the *CYP2C19* LOF mutation prevalence in the studies by Sorich et al. (i.e.,10%) and Crespin et al. (28.35%) was fairly comparable with the current analysis (i.e., 23.6%), also taking into consideration that the sensitivity analyses confirmed robustness against variations in the mutation prevalence as an input. Therefore, the *CYP2C19* LOF mutation prevalence was not an influential factor in the inconsistent results. In our study, the one-way and multivariant sensitivity analyses further confirmed genotype-guided therapy as the favorable option compared to universal clopidogrel and universal ticagrelor.

With regards to the comparison between the two universal strategies, in the one-year model analysis, universal clopidogrel was dominant compared to universal ticagrelor with mean cost-saving of QAR 2,136 in 63% of the cases. In the Markov model, the mean difference in cumulative QALY was (i.e., 0.52) in favor of universal clopidogrel compared to universal ticagrelor, and universal clopidogrel was cost-

effective with an ICUR of QAR 38,650 per QALY in 99% of the cases. The one-way and multivariant sensitivity analyses confirmed the robustness of results.

Only one study in the literature, by Wang et al., compared universal ticagrelor and universal clopidogrel, and this reported contradictory results to ours, where universal ticagrelor was cost-effective compared to universal clopidogrel. Other studies, by Jiang et al. (2017) and Jiang et al. (2016), compared the universal alternative P2Y12 inhibitor with universal clopidogrel, where the universal alternative P2Y12 inhibitor was cost-effective at ICUR of USD 30,038 and 46,953 per QALY, respectively.

Although literature evidence supports the superiority of ticagrelor over clopidogrel in reducing MACE and stent thrombosis in ACS patients (51,88), ticagrelor is associated with a statistically significant higher risk of non-CABG major bleeding, dyspnea, and discontinuation due to ADRs (51,90,101). None of the above economic studies by Wang et al., and Jiang et al. incorporated all these adverse events in the decision-analytic models used, while our study did. It is for this reason that clopidogrel demonstrated a greater clinical and humanistic and, hence, overall economic benefit relative to ticagrelor in our study.

Noteworthy, the published studies evaluated generic clopidogrel, where ticagrelor was at least three times more expensive than generic clopidogrel, and up to 20 times more expensive (73–76). Because in the HMC formulary, it is the branded clopidogrel (Plavix ®) that is being used, the acquisition cost of ticagrelor was only double the cost of clopidogrel in the current model. Shifting to the generic clopidogrel, like in the literature studies, will only further add to the dominance of clopidogrel in the current study.

The breakdown of the cost components for the antiplatelets strategies

indicated that hospitalization costs approximately QAR 100,000 followed by treatment (i.e., medications and procedures used in the management of the clinical events) which costs approximately QAR 60,000. None of the literature studies reported the cost components of an antiplatelet strategy (e.g., cost of hospitalizations, treatment, investigations). Instead, only the overall costs of clinical outcomes were reported. This is considered an additional strength in our study since hospitalization and treatment are the driving cost for an antiplatelet strategy. This further establishes the importance of looking at secondary costs of therapies, in addition to their acquisition costs (18,121,122).

According to the results from the tornado analyses, and in the ICER analysis, the most influential factors on the study outcomes were the probability of 'no event without ADR' and the distribution probability between the *CYP2C19* LOF allele carriers and non-carriers. While the health state 'no event without ADR' is associated with low cost (i.e., QAR 794), it has the highest probability in the one-year model. Similarly, the probability of *CYP2C19* LOF allele carriers over non-carriers is associated with a considerable shift in the overall cost of therapy because of the increase in the use of ticagrelor and the consequences associated with it. In relation to the ICUR analysis, a similar trend was observed in relation to the probability of 'no event without ADR' and the probability of the *CYP2C19* LOF allele carriers. But this was in addition to the ‘utility score’ of the no event state as another influential model input which is also anticipated given the relatively high score value of the utility (i.e., 0.875). In any case, as already discussed, all variations in the model inputs, including the most influential, did not change the conclusion of the study.

The source of the clinical inputs is a strength in the current study. Utilizing sub-studies of the PLATO trial is a strength as the PLATO trial is the largest

international, multicenter, trial that directly compares the efficacy and safety of ticagrelor and clopidogrel. The PLATO invasive sub-study, in particular, was useful in narrowing the model population and making it more relevant to the population of interest in our model (i.e., post-PCI patients). In addition to the PLATO trial, which most prior economic evaluations in the literature relied on, our current study was also the only simulation model that extracts data from a very recent comprehensive meta-analysis, by Fan et al. (88). Relying on the Fan et al. is a strength as it is recently published in 2019, involving six RCTs, including PLATO, and five observational studies that had head-to-head comparisons of ticagrelor and clopidogrel. In addition, this included patients with ACS undergoing PCI, which is identical to the population in the current study. It is important to note that the regimens of study medications in the meta-analysis and the PLATO sub-studies are identical to those in the HMC for the treatment of ACS patients after PCI. Similarly, as already implied above, the baseline characteristics of the patient in the PLATO Sub-studies and the Fan et al. meta-analysis are all comparable to those in the local HMC setting.

Another strength in this study is the decision-analytic model that is more comprehensive than the other models reported in the relevant literature. The model represents all the possible consequences of using DAPT and, hence, an overall cost of resource utilization is more accurately measured, including MI, stroke, cardiovascular death, stent thrombosis, ADRs (dyspnea, major bleeding). This is also the first study that evaluates discontinuation due to ADR as a clinical outcome of the DAPT. Moreover, while all studies in the literature evaluated the long-term cost-utility outcomes of the genotype-guided therapy compared to universal clopidogrel and ticagrelor, the current comparative model is the first to report the short-term cost-effectiveness outcome of therapies (i.e., 12 months follow up), which was based on

the no event status, with/without ADRs, as the success.

It is important to note that the definition of success of therapy was adopted to the local interest by decision-makers at HMC. As already discussed, the therapy outcome of interest, as per local practices, is the absence of MI, stroke, cardiovascular death, and stent thrombosis with/without ADRs (major bleeding and dyspnea). MI, stroke, cardiovascular death, and stent thrombosis were of interest as they are particularly expected to have a significant effect on patient management cost and patient utility. The model was populated with data from different sources available in the literature to account for missing data in each of these individual sources. The probabilities of the clinical events in the decision analytic model were obtained from a meta-analysis that allows more accurate estimation of an effect compared to single studies, due to the increased amount of data and statistical power (123). Also, relying on RCTs that have a well-established methodology comes with high internal validity due to randomization, blinding, and controlling of confounding factors (124). However, relying on meta-analyses and RCTs comes with an important limitation to the economic evaluation, with this being the limited generalizability of the findings to the local setting due to the controlled nature of RCTs with regards to the patient criteria and the possible differences in the patient demographics (125). This translates into inherent uncertainties that are associated with results. Therefore, the simulation model was based at its on a multivariate uncertainty analysis of input data, using the Monte Carlo simulation. This was considered a more meaningful and accurate representation of results, particularly at their case base, unlike in the relevant literature (63–70), where performing the multivariate analysis of input uncertainties was only part of the sensitivity analyses in models. At the one year and Markov models, a simulated cohort of 10,000 patient was used, with uncertainties in a variety of

probabilistic and utility values randomly interacting, just like in real life situation.

Noteworthy, the current study considered the QALY outcome of therapies besides the clinical outcomes. QALY is used to assess the degree of gained benefits from a health intervention in relation to health-related quality of life and survival for the patient, which is especially essential when considering treatments for chronic conditions such as ACS.

Although the outcomes of the current study are robust, they can only be fully confirmed through a follow-up future research that assesses, whether prospectively or retrospectively, the comparative clinical and economic impacts of genotype-guided antiplatelet therapy versus universal clopidogrel and ticagrelor in patients with ACS who underwent PCI at the local Qatari HMC setting. However, this is currently difficult, mostly due to the lack of long-term data in post-PCI patients in HMC, particularly in relation to the lack of local utility data. Therefore, locally specific simulation studies, like the current one, are considered important for decision guidance in local practices. Here, *CYP2C19* genotype-guided antiplatelet therapy has been demonstrated to be at least equally effective to universal clopidogrel and ticagrelor in terms of clinical and humanistic outcomes, including those based on the local Qatari interests and practices, with a considerable anticipated amount of cost-savings. The integration of *CYP2C19* genetic testing for ACS patients who underwent PCI can only be beneficial and will enable the availability of local data that can be then utilized into locally based and relevant head-to-head validation studies among the different antiplatelet strategies in the HMC setting.

5.2. Phase two: Economic evaluation of CYP2C19 genotype-guided antiplatelet therapy compared to the universal use of antiplatelets in patients with Acute coronary syndrome: A systematic review

(This section of the thesis has been extracted from the following publication: AlMukdad S, Elewa H, Al-Badriyeh D. *Economic Evaluations of CYP2C19 Genotype-Guided Antiplatelet Therapy Compared to the Universal Use of Antiplatelets in Patients with Acute Coronary Syndrome: A Systematic Review*. J Cardiovasc Pharmacol Ther. 2020:1074248420902298)

This part of the thesis is the first systematic review that summarizes the cost-effectiveness studies of genotype-guided antiplatelet therapy compared to the universal use of antiplatelet therapy in patients with ACS undergoing PCI. To the best of our knowledge, there are no systematic reviews with similar objectives, comprehensiveness, and scope, specifically focusing on *CYP2C19* genetic testing. In 2016, a systematic review of economic evaluations of pharmacogenetic testing for guiding therapies was reported, but it was not drug specific, nor disease/gene specific, and was focusing primarily on the prevention of adverse drug reactions of therapies. Importantly, that review only included four articles that evaluated clopidogrel, with the most recent being in 2013 (126). The systematic review concluded that high-quality evidence supported the cost-effectiveness of *CYP2C19* genotype-guided antiplatelet therapy (126). Another review of relevance was a 2015 one (127). However, it was narrative in nature and included only seven studies published between 2000 and 2014, where authors did not assess the quality of the retrieved studies (127). The review illustrated that while the genotype-guided use of prasugrel compared to the universal

use of prasugrel or clopidogrel was a cost-effective strategy, results in support of the genotype-guided use of ticagrelor compared to the universal use of ticagrelor or clopidogrel were inconsistent (127).

The choice of antiplatelet therapy after PCI in patients with ACS is complicated. This choice has radical clinical and economic implications and entails a marked trade-off between differences in drug costs, thrombotic events, and major bleeding. The randomized clinical trial by Claassens et al. demonstrated a clinical benefit of *CYP2C19* genotype-guided antiplatelet therapy. After 12 months, *CYP2C19* genotype-guided antiplatelet strategy was non-inferior to the universal administration of oral P2Y12 inhibitor in relation to thrombotic events and was associated with a reduced incidence of bleeding (62). Unlike other studies included in this systematic review, the study done by Crespin et al. estimated the costs and outcomes for a cohort of ACS patients, without specifying if they underwent PCI or not. However, because PCI is an integral part of the management of ACS (128,129), and just in case it took place to a large extent in the ACS population, the study was included in the current review to increase the comprehensiveness of our findings. For the same reason, we included the study by Kim et al., although it considered patients with ACS managed with PCI and those managed medically without PCI.

Six of the included studies showed that genotype-guided antiplatelet therapy was cost-effective when compared to universal clopidogrel (75,76,78,115,117–129), whereas five studies showed that it was dominant (79–81,117). On top of that, genotype-guided antiplatelet therapy was dominant when compared to either universal prasugrel, ticagrelor, or both in five (115–119), one (76), and three studies (79–81), respectively. Kim et al. specified that genotype-guided antiplatelet with ticagrelor is cost-effective in both CYP2C19 intermediate and poor metabolizers, but not in poor

metabolizers only (74). Surprisingly, Sorich et al. and Crespin et al. concluded that universal ticagrelor was cost-effective compared to genotype-guided therapy, which was not in line with our findings from the other studies (73,75). Such an inconsistency can only be explained by the variability in the residual benefit and cost of the intervention among the different healthcare systems as demonstrated by Sorich et al. and Crespin et al. Generally speaking, based on sensitivity analyses results, the variability of outcomes of economic decision models in studies are mostly driven by variability among studies in the relative risk of the thrombotic events between CYP2C19 mutation carriers and non-carriers (74,75,78,80,116–118), in addition to how different are the acquisition costs of the medications (74,78). In relation to why the conclusions of the studies by Sorich et al. and Crespin et al. were particularly in contrast to other studies, a more specific reason would be the variations in the clinical events included in the decision-analytic models used; whereby Sorich et al. evaluated MACE only, excluding stent thrombosis or adverse drug reactions (e.g., bleeding and dyspnea), and Crespin et al. studied MI, death, bleeding, and dyspnea, excluding stent thrombosis and stroke. Such excluded outcomes are particularly associated with high management costs (73,75). Also important, is that the willingness-to-pay thresholds that were used by Sorich et al. and Crespin et al. (USD 20,475-34,125 and USD 50,000, respectively) are at the lower end of the range of what is universality considered acceptable, which may explain the cost-effectiveness of universal ticagrelor.

Here, it is worth noting that whether an ICER indicated cost-effectiveness in a study was based on the local interpretation of the ICER as reported in the study. This is as cost-effectiveness thresholds, based on which ICERs are judged, can vary widely from a country to another, depending on methods and assumptions used in calculations. Cost-effectiveness thresholds can vary from as little as USD 4,419 per QALY in

Thailand to USD 180,653 per QALY in Belgium (95). In the US, over 77% of cost-effectiveness research refers to USD 50,000 or 100,000 per QALY as a suitable threshold. Those values, however, are not well justified, with the former, as an example, stemming from the cost of dialysis in the 1980s (130,131). Currently, however, the range of acceptable threshold value in the US is increasingly up to USD 150,000 per QALY (96).

Although generic ticagrelor and prasugrel are going to be commercially available sometime in the future, we cannot anticipate that the genetic-guided antiplatelet therapy will become less economically attractive. This is as the return to its cost is multifactorial in nature. First, it has been proposed that the cost of genetic testing will be reduced in the future, just like the costs of generic ticagrelor and prasugrel, and it will become part of the routine practice (132,133). In addition, ticagrelor and prasugrel are associated with an increased risk of major bleeding, which has a high cost of management and a significant reduction in the patient's quality of life (78). The secondary costs of therapies are not less important for consideration than the acquisition costs of the therapies. Thus, for an accurate assessment of the impact of introducing generic ticagrelor or clopidogrel to the market, evaluations under future circumstances would ideally be needed in future research.

The results of the included articles were primarily based on clinical outcomes derived from retrospective analyses of the published clinical trials TRITON-TIMI 38 and PLATO, except for the study by Wang et al., in which small scale local observational studies were utilized (76). Although the models relied on the best available sources, none of the articles used an outcome-driven prospective randomized controlled trial. The utilized literature clinical trials, however, are large international in design, with the smallest of which including over 700 sites from 30 countries. This

means that while economic studies in the current review are from different countries, differences in reported outcomes are mostly due to variability in the cost and resource utilization aspects of the therapies, and it is nothing to do with variability in comparative effectiveness or underlying demographic variabilities, such as the level of sickness and the ethnicity of cohorts. All articles used local estimates for cost data such as hospital reports, Medicare reimbursement rates and drug retail pricing, which is appropriate as cost data should be based on the local setting. However, relying on the local healthcare setting might not necessarily reflect the cost-effectiveness of genotype-guided therapy in other countries. The 13 studies used only direct medical costs associated with clinical and adverse outcomes and none used indirect medical cost or intangible cost and, thus, cost-effectiveness results might be underestimated. All of the studies used an appropriate horizon of analysis (≥ 12 months) that allows time for all of the relevant and significant outcomes to be detected (134). Five articles examined the *CYP2C19**2 LOF allele only (73,75,76,116,117), which might limit the generalizability of the results, as it is known that *3 is also a common allele (46).

The results of the quality assessment reflected that all of the studies had a good quality which means that they adhered to most of the QHES items. However, a common element that was not reported in all of the articles was discussing the direction and magnitude of potential biases. In addition, the methodology for data abstraction including the value of health status and other benefits were not completely stated in six articles (75,78,80,115–117). Moreover, the measurement of costs and the methodology for the estimation of quantities and unit costs were not clearly described (78,79,115–117,119). All these poorly executed methodological items are important for the journal editors and researchers to note, not just for the benefit of enhanced quality in future research, but to also enable replication of studies.

This review included only English language articles which may have excluded possible relevant studies; however, no resources to translate non-English articles were available to authors. Despite the comprehensive search that was done, additional studies could have been identified in the literature with the use of additional search engines and/or combinations of search terms. Nevertheless, it is noted that the PubMed and Embase databases encompass almost 80% of the literature, and with the use of EconLit and PharmGKB as well, we believe to have covered a representative sample of literature (135). In addition, the quality assessment did not account for the quality of the journals and their editorial requirements. An additional limitation of the study relates to the fact that out of the 13 included studies, no economic evaluations of genotype-guided antiplatelet therapy have been undertaken in Europe, Africa and the Middle East. Thus, one might assume that the results of the current review might be biased towards the US and Chinese populations. It is important to note, however, that this can only be relevant to changes in the cost of resources among countries and is not in relevance to differences in the clinical performance of interventions. As already discussed above, clinical outcomes in included studies were all, except in one study, primarily extracted from the same literature clinical trials as data sources.

CHAPTER 6: CONCLUSION

The research in the current thesis includes the first cost-utility analytic-modeling of genotype-guided therapy versus universal clopidogrel and ticagrelor in Qatar and the region. Internationally, the model is comprehensive. It is the first to examine all relevant outcomes and related patient direct costs, including ADRs and discontinuation of the medication due to ADRs, and also the first to incorporate an important recent comprehensive meta-analysis of clopidogrel versus ticagrelor as a source of data. In addition, this is the first to report short-term outcome measures (ICER/case of success), in addition to the long-term outcome (ICUR/QALY).

Based on the perspective and limitations in the current study, the *CYP2C19* genotype-guided therapy seems to be a favorable approach for guiding the antiplatelet therapy selection following PCI in Qatar, where ticagrelor is prescribed to *CYP2C19* LOF alleles carrier patients and clopidogrel is prescribed to the *CYP2C19* LOF alleles non-carrier patients. Genotype-guided therapy was between dominant and cost-effective against the universal use of clopidogrel and ticagrelor.

The findings of this research, therefore, are in contrast to the recent practices at the HMC in Qatar, where clopidogrel is administered universally to most of the patients, which is based on the assumption that the genotype-guided therapy is a most expensive approach among the available options.

In relation to the two universal strategies, however, results in the current research support the local practices in HMC, whereby, the universal clopidogrel is the first-line of therapy over ticagrelor. Based on the current study's results, clopidogrel was between dominant and cost effective against ticagrelor, based on the cost-utility

and cost-effectiveness analyses.

Finally, and from the international perspective on the usefulness of the genotype-guided strategy of therapy, including based on the systematic literature review conducted in the thesis, it is concluded that implementing genotype-guided antiplatelet therapy, followed by a targeted administration of ticagrelor or prasugrel in CYP2C19 LOF mutation carriers and clopidogrel in noncarriers, is the most cost-effective approach compared to the universal use of antiplatelets in patients with ACS undergoing PCI.

REFERENCES

1. What is Cardiovascular Disease? American Heart Association. 2017. Available from: https://www.heart.org/en/health-topics/consumer-healthcare/what-is-cardiovascular-disease. (Accessed 14 Jul 2018).
2. Cardiovascular diseases (CVDs). World Health Organization. 2017. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). (Accessed 14 Jul 2018).
3. Simons Michael, Alpert JS. Acute coronary syndrome: Terminology and classification. 2018. Available from: https://0-www.uptodate.com.mylibrary.qu.edu.qa/. (Accessed 15 Jul 2018).
4. Kumar A, Cannon CP. Acute coronary syndromes: Diagnosis and management, part I. Mayo Clin Proc. 2009;84(10):917–38. A
5. Go A, Mozaffarian D, Roger V, Benjamin E, Berry J, Borden WB, et al. Heart disease and stroke statistics: 2013 update: a report from the American Heart Association. Circulation. 2013;127(1): e6–245.
6. Wilson P. Established risk factors and coronary artery disease: The Framingham Study. Am J Hypertens. 1994;7(7 Pt 2):7S-12S.
7. Demirkan B, Ege M, Dogan P, Ipek E, Guray U, Guray Y. Factors influencing the use of ambulance among patients with acute coronary syndrome: Results of two centers in Turkey. Anadolu Kardiyol Derg. 2013;13(6):516–22.
8. Saidi O, Ben Mansour N, O'Flaherty M, Capewell S, Critchley J, Ben Romdhane H. Analyzing recent coronary heart disease mortality trends in Tunisia between 1997 and 2009. PLoS One. 2013;8(5): e63202.

9. Alhabib K, Sulaiman K, Al-Motarreb A, Almahmeed W, Asaad N, Amin H, et al. Baseline characteristics, management practices, and long-term outcomes of Middle Eastern patients in the second Gulf registry of acute coronary events (Gulf RACE-2). Ann Saudi Med. 2012;32(1):9–18.
10. Engelgau M, Karan A, Mahal A. The Economic impact of non-communicable diseases on households in India. Global Health. 2012; 8:9.
11. Supreme Council of Health. Qatar health report 2013. 2014. Available from: https://www.moph.gov.qa/ar/HSF/Documents/Report/Qatar Health Report 2013 (Eng).pdf. (Accessed 21 Jul 2018).
12. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet (London, England). 2012;380(9859):2095–128.
13. World Health Oragnaization. Qatar Mortality Rate. Available from: https://www.who.int/nmh/countries/qat_en.pdf?ua=1. (Accessed 22 Jul 2018).
14. Benjamin E, Muntner P, Alonso A, Bittencourt M, Callaway C, Carson A, et al. Heart disease and stroke statistics—2019 Update: A Report from the American Heart Association. Circulation. 2019;139(10): e56–528.
15. Hyun K, Essue B, Woodward M, Jan S, Brieger D, Chew D, et al. The household economic burden for acute coronary syndrome survivors in Australia. BMC Health Serv Res. 2016;16(1):636.
16. National Heart Foundation of Australia. Economic cost of acute coronary syndrome in Australia: The cost to governments. 2018. Available from: https://www.heartfoundation.org.au/images/uploads/publications/Economic_cost_of_ACS_in_Australia__the_cost_to_governments.pdf. (Accessed 23 Jul 2018).

17. Zhao Z, Winget M. Economic burden of illness of acute coronary syndromes: Medical and productivity costs. BMC Health Serv Res. 2011; 11:35.
18. Cowper P, Knight D, Davidson-Ray L, Peterson E, Wang T, Mark D, et al. Acute and 1-year hospitalization costs for acute myocardial infarction treated with percutaneous coronary intervention: Results from the TRANSLATE-ACS Registry. J Am Heart Assoc. 2019;8(8): e011322.
19. Fox KAA. Management of acute coronary syndromes: An update. Heart J. 2004;90(6):698–706.
20. O'Gara PT, Kushner FG, Ascheim DD, Casey DEJ, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4): e362-425.
21. Heart and Stroke Foundation of Canada. Percutaneous coronary intervention (PCI or angioplasty with stent). 2018. Available from: https://www.heartandstroke.ca/heart/treatments/surgery-and-other-procedures/percutaneous-coronary-intervention (Accessed 28 Jul 2018).
22. Keeley E, Boura J, Grines C. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review of 23 randomised trials. Lancet (London, England). 2003;361(9351):13–20.
23. Caracciolo E, Davis K, Sopko G, Kaiser G, Corley S, Schaff H, et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease. Long-term CASS experience. Circulation. 1995;91(9):2325–34.
24. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more

than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative. Lancet (London, England). 1994;343(8893):311–22.

25. Amsterdam E, Wenger N, Brindis R, CaseyJr D, Ganiats T, HolmesJr D, et al. 2014 AHA/ACC guideline for the management of patients with NSTEMI acute coronary dyndromes. Circulation. 2014;130(25):e344–426.
26. Mehta S, Cannsn C, Fox KAA, Wallentin L, Boden WE, Spacek R, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: A collaborative meta-analysis of randomized trials. JAMA. 2005;293(23):2908–17.
27. Fox KAA, Clayton T, Damman P, Pocock S, de Winter R, Tijssen JGP, et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. J Am Coll Cardiol. 2010;55(22):2435–45.
28. Fanaroff AC, Rao S V. Antiplatelet therapy in percutaneous coronary intervention. Interv Cardiol Clin. 2016;5(2):221–37.
29. Steinhubl S, Berger P, Mann J, Fry ETA, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002;288(19):2411–20.
30. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines: An update of the. Circulation. 2016;134(10): e123-55.
31. Tanguay J, Bell A, Ackman M, Bauer RDC, Cartier R, Chan W, et al. Focused 2012 update of the Canadian Cardiovascular Society guidelines for the use of antiplatelet therapy. Can J Cardiol. 2013;29(11):1334–45.

32. Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol. 2014;64(20):2086–97.
33. Ministry of Public health. Qatar National Formulary (QNF). Available from: http://www.qnf.qa/en/. (Accessed 10 Aug 2018).
34. Patel A, Vidula M, Kishore S, Vedanthan R, Huffman M. Building the case for clopidogrel as a World Health Organization essential medicine. Circ Cardiovasc Qual Outcomes. 2015l;8(4):447–51.
35. Maffrand J. The story of clopidogrel and its predecessor, ticlopidine: Could these major antiplatelet and antithrombotic drugs be discovered and developed today? Comptes Rendus Chim. 2012;15((8)):737–43.
36. Sangkuhl K, Klein TE, Altman RB. Clopidogrel pathway. Pharmacogenet Genomics. 2010;20(7):463–5.
37. Centurion OA. Actual role of platelet glycoprotein IIb/IIIa receptor inhibitors as adjunctive pharmacological therapy to primary angioplasty in acute myocardial infarction: In the light of recent randomized trials and observational studies with bivalirudin. Open Cardiovasc Med J. 2010; 4:135–45.
38. Kazui M, Nishiya Y, Ishizuka T, Hagihara K, Farid NA, Okazaki O, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. Drug Metab Dispos. 2010;38(1):92–9.
39. Brandt JT, Close SL, Iturria SJ, Payne CD, Farid NA, Ernest CS 2nd, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and

pharmacodynamic response to clopidogrel but not prasugrel. J Thromb Haemost. 2007;5(12):2429–36.

40. Brown SA, Pereira N. Pharmacogenomic Impact of CYP2C19 Variation on Clopidogrel Therapy in Precision Cardiovascular Medicine. J Pers Med. 2018;8(1):8.
41. Umemura K, Furuta T, Kondo K. The common gene variants of CYP2C19 affect pharmacokinetics and pharmacodynamics in an active metabolite of clopidogrel in healthy subjects. J Thromb Haemost. 2008;6(8):1439-41.
42. Cattaneo M. Response variability to clopidogrel: is tailored treatment, based on laboratory testing, the right solution? J Thromb Haemost. 2012;10(3):327–36.
43. Mega J, Simon T, Collet J, Anderson J, Antman E, Bliden K, et al. Reduced function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: A meta-analysis. JAMA. 2010;304(16):1821–30.
44. Mega J, Close S, Wiviott S, Shen L, Hockett R, Brandt J, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009;360(4):354–62.
45. Hulot J, Bura A, Villard E, Azizi M, Remones V, Goyenvalle C, et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood. 2006;108(7):2244–7.
46. Scott S, Sangkuhl K, Stein C, Hulot J, Mega J, Roden D, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther. 2013;94(3):317–23.
47. De Morais SM, Wilkinson GR, Blaisdell J, Nakamura K, Meyer UA, Goldstein JA. The major genetic defect responsible for the polymorphism of S-mephenytoin metabolism in humans. J Biol Chem. 1994;269(22):15419–22.
48. Sim SC, Risinger C, Dahl M, Aklillu E, Christensen M, Bertilsson L, et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug

response to proton pump inhibitors and antidepressants. Clin Pharmacol Ther. 2006;79(1):103–13.

49. U.S. Food and Drug Administration. FDA drug safety communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. 2010. Available from: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-reduced-effectiveness-plavix-clopidogrel-patients-who-are-
50. National Institutes of Health. Ticagrelor. 2014. Available from: https://livertox.nih.gov/Ticagrelor.htm#insert. (Accessed 11 Aug 2018).
51. Wallentin L, Becker RC, Budaj A, Cannon C, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045–57.
52. Capodanno D, Dharmashankar K, Angiolillo D. Mechanism of action and clinical development of ticagrelor, a novel platelet ADP P2Y12 receptor antagonist. Expert Rev Cardiovasc Ther. 2010;8(2):151–8.
53. Teng R. Ticagrelor: Pharmacokinetic, pharmacodynamic and pharmacogenetic profile: An update. Clin Pharmacokinet. 2015;54(11):1125–38.
54. Tantry US, Bliden KP, Wei C, Storey RF, Armstrong M, Butler K, et al. First analysis of the relation between CYP2C19 genotype and pharmacodynamics in patients treated with ticagrelor versus clopidogrel: the ONSET/OFFSET and RESPOND genotype studies. Circ Cardiovasc Genet. 2010;3(6):556–66.
55. Wallentin L, James S, Storey R, Armstrong M, Barratt B, Horrow J, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet (London, England). 2010;376(9749):1320–8.

56. Fanari Z, Weiss S, Weintraub W. Cost Effectiveness of antiplatelet and antithrombotic therapy in the setting of acute coronary syndrome: Current perspective and literature review. Am J Cardiovasc Drugs. 2015;15(6):415–27.

57. Ma Q, Lu AYH. Pharmacogenetics, pharmacogenomics, and individualized medicine. Pharmacol Rev. 2011;63(2):437–59.

58. TPA, M SS, Jose A, Chandran L, Zachariah S. Pharmacogenomics: the right drug to the right person. J Clin Med Res. 2009;1(4):191–4.

59. Roden D, Wilke R, Kroemer H, Stein C. Pharmacogenomics: the genetics of variable drug responses. Circulation. 2011;123(15):1661–70.

60. Caudle K, Dunnenberger H, Freimuth R, Peterson J, Burlison J, Whirl-Carrillo M, et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Genet Med. 2017;19(2):215–23.

61. Botomino A, Bruppacher R, Krahenbuhl S, Hersberger K. Change of body weight and lifestyle of persons at risk for diabetes after screening and counselling in pharmacies. Pharm World Sci. 2008;30(3):222–6.

62. Claassens D, Vos GJA, Bergmeijer T, Hermanides R, Van Hof AWJ, Van der Harst P, et al. A Genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. N Engl J Med. 2019;381(17):1621–31.

63. Trask L. Chapter 1. Pharmacoeconomics: principles, methods, and applications. 8th ed. Pharmacotherapy: a pathophysiologic approach. 2011.

64. Drummond M, Sculpher M, Claxton K, et al. Methods for the economic evaluation of healthcare programs. 4th ed. Oxford University Press 2015.

65. Adamiak G. Methods for the economic evaluation of health care programs, 3rd ed. J Epidemiol Community Health. 2006;60(9):822–3.

66. Bootman J; Townsend R. Principles of pharmacoeconomics 1991; Harvey Whitney Books.
67. Kong D. Chapter 3: Economic Evaluations of Health Interventions: Concepts and Values. Book: Progress in Economics Research 2012; V.24.
68. SESRIC, Statistics and Databases: Qatar. 2013. Available from: https://scirp.org/reference/ReferencesPapers.aspx?ReferenceID=1436414. (Accessed 22 Aug 2018).
69. Qatar GDP and Economic Data. Global Finance. 2017. Available from: https://www.gfmag.com/global-data/country-data/qatar-gdp-country-report. (Accessed 22 Aug 2018).
70. Health expenditure, public (% of total health expenditure). Trading Economics. 2014. Available from: https://tradingeconomics.com/qatar/health-expenditure-total-percent-of-gdp-wb-data.html. (Accessed 17 Aug 2018).
71. Qatar National Health Accounts Report. Suprime Council of Health, Qatar. 2012. Available from: https://www.moph.gov.qa/publications/Documents/Health Reports/QNHA 2012 -EN.pdf. (Accessed 22 Aug 2018).
72. National Insurance Scheme, patient information. Hamad Medical Corporation. Available from: https://www.hamad.qa/EN/Patient-Information/National-Insurance-Scheme/Pages/default.aspx. (Accessed 22 Aug 2018).
73. Crespin D, Federspiel J, Biddle A, Jonas D, Rossi J. Ticagrelor versus genotype-driven antiplatelet therapy for secondary prevention after acute coronary syndrome: a cost-effectiveness analysis. Value Heal J Int Soc Pharmacoeconomics Outcomes Res. 2011;14(4):483–91.
74. Kim K, Touchette DR, Cavallari LH, Ardati AK, DiDomenico RJ. Cost-Effectiveness of Strategies to Personalize the Selection of P2Y12 Inhibitors in Patients with Acute Coronary Syndrome. Cardiovasc drugs Ther. 2019;33(5):533-546.

75. Sorich MJ, Horowitz JD, Sorich W, Wiese MD, Pekarsky B, Karnon JD. Cost-effectiveness of using CYP2C19 genotype to guide selection of clopidogrel or ticagrelor in Australia. Pharmacogenomics. 2013;14(16):2013–21.
76. Wang Y, Yan BP, Liew D, Lee VWY. Cost-effectiveness of cytochrome P450 2C19 *2 genotype-guided selection of clopidogrel or ticagrelor in Chinese patients with acute coronary syndrome. Pharmacogenomics J. 2018;18(1):113–20.
77. Limdi NA, Cavallari LH, Lee CR, Hillegass WB, Holmes AM, Skaar TC, et al. Cost-effectiveness of CYP2C19-guided antiplatelet therapy in patients with acute coronary syndrome and percutaneous coronary intervention informed by real-world data. Pharmacogenomics J. 2020
78. Kazi DS, Garber AM, Shah RU, Dudley RA, Mell MW, Rhee C, et al. Cost-effectiveness of genotype-guided and dual antiplatelet therapies in acute coronary syndrome. Ann Intern Med. 2014;160(4):221–32.
79. Jiang M, You JHS. CYP2C19 genotype plus platelet reactivity-guided antiplatelet therapy in acute coronary syndrome patients: a decision analysis. Pharmacogenet Genomics. 2015;25(12):609–17.
80. Jiang M, You JH. Cost-effectiveness analysis of personalized antiplatelet therapy in patients with acute coronary syndrome. Pharmacogenomics. 2016 May;17(7):701–13.
81. Jiang M, You JHS. CYP2C19 LOF and GOF-guided antiplatelet therapy in patients with acute coronary syndrome: A cost-effectiveness analysis. Cardiovasc drugs Ther. 2017;31(1):39–49.
82. Pharmaceutical products. Ministry of Public Health. 2017. Available from: https://www.moph.gov.qa/health-services/Pages/pharmaceutical-products.aspx. (Accessed 15 Sep 2018).

83. AlMukdad S, Elewa H, Al-Badriyeh D. Economic evaluations of CYP2C19 genotype-guided antiplatelet therapy compared to the universal use of antiplatelets in patients with acute coronary syndrome: A systematic review. J Cardiovasc Pharmacol Ther. 2020;1074248420902298.
84. Levine G, Bates E, Bittl J, Brindis R, Fihn S, Fleisher L, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. Circulation. 2016;134(10): e123–55.
85. Yin S-H-L, Xu P, Wang B, Lu Y, Wu Q-Y, Zhou M-L, et al. Duration of dual antiplatelet therapy after percutaneous coronary intervention with drug-eluting stent: systematic review and network meta-analysis. BMJ. 2019;365.
86. Nikolic E, Janzon M, Hauch O, Wallentin L, Henriksson M. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: Results from the PLATO study. Eur Heart J. 2013;34(3):220–8.
87. World Health Organization. Life tables by country: Qatar. 2018. Available from: https://apps.who.int/gho/data/view.main.61320?lang=en. (Accessed 14 Nov 2018).
88. Fan Z-G, Zhang W-L, Xu B, Ji J, Tian N-L, He S-H. Comparisons between ticagrelor and clopidogrel following percutaneous coronary intervention in patients with acute coronary syndrome: A comprehensive meta-analysis. Drug Des Devel Ther. 2019; 13:719–30.
89. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet (London, England). 2010;375(9711):283–93.
90. Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the

PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J. 2011;32(23):2933–44.

91. Ali Z, Bader L, Al-Masri D, Ali M, Arafa S, Arabi A EH. The impact of CYP2C19 genetic mutation and non-genetic factors on the incidence of major adverse cardiovascular events in patients treated with clopidogrel in Qatar. J Thromb Thrombolysis. 2019;74(4):609–609.
92. Zanchin T, Temperli F, Karagiannis A, Zanchin C, Rasanen M, Koskinas KC, et al. Frequency, reasons, and impact of premature ticagrelor discontinuation in patients undergoing coronary revascularization in routine clinical practice: Results from the Bern Percutaneous Coronary Intervention Registry. Circ Cardiovasc Interv. 2018;11(5): e006132.
93. Parodi G, Storey RF. Dyspnoea management in acute coronary syndrome patients treated with ticagrelor. Eur Hear journal Acute Cardiovasc care. 2015;4(6):555–60.
94. O'Gara P, Kushner F, Ascheim D, CaseyJr D, Chung M, de Lemos J, et al. 2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. Circulation. 2013;127(4): e362–425.
95. AdamsJr H, Adams R, Brott T, Del Zoppo G, Furlan A, Goldstein L, et al. Guidelines for the early management of patients with ischemic stroke. Stroke. 2003;34(4):1056–83.
96. Hemphill J, Greenberg S, Anderson C, Becker K, Bendok B, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage. Stroke. 2015;46(7):2032–60.
97. Wilkins T, Khan N, Nabh A, Schade RR. Diagnosis and management of upper gastrointestinal bleeding. Am Fam Physician. 2012 ;85(5):469–76.
98. Qatar biobank report 2016/2017. 2016. Available from: https://www.qatarbiobank.org.qa/app/media/1730. (Accessed 2 Jan 2019).

99. Mehran R, Rao S V, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123(23):2736–47.

100. Wang D, Yang X-H, Zhang J-D, Li R-B, Jia M, Cui X-R. Compared efficacy of clopidogrel and ticagrelor in treating acute coronary syndrome: a meta-analysis. BMC Cardiovasc Disord. 2018;18(1):217.

101. Storey RF, Becker RC, Harrington RA, Husted S, James SK, Cools F, et al. Characterization of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes. Eur Heart J. 2011;32(23):2945–53.

102. Varenhorst C, Alstrom U, Braun OO, Storey RF, Mahaffey KW, Bertilsson M, et al. Causes of mortality with ticagrelor compared with clopidogrel in acute coronary syndromes. Heart. 2014;100(22):1762–9.

103. Garg P, Cohen DJ, Gaziano T, Mauri L. Balancing the risks of restenosis and stent thrombosis in bare-metal versus drug-eluting stents: results of a decision analytic model. J Am Coll Cardiol. 2008;51(19):1844–53.

104. O'Mahony JF, Paulden M. NICE's selective application of differential discounting: ambiguous, inconsistent, and unjustified. Value Heal J Int Soc Pharmacoeconomics Outcomes Res. 2014 Jul;17(5):493–6.

105. Torgerson DJ, Raftery J. Economic notes. Discounting. BMJ. 1999 Oct;319(7214):914–5.

106. Johnson SG, Gruntowicz D, Chua T, Morlock RJ. Financial analysis of CYP2C19 genotyping in patients receiving dual antiplatelet therapy following acute coronary syndrome and percutaneous coronary intervention. J Manag care Spec Pharm. 2015 Jul;21(7):552–7.

107. Cameron D, Ubels J, Norström F. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: A systematic review. Glob Health Action. 2018;11(1):1447828.

108. Institute for Clinical and Economic Review Final Value Assessment Framework for 2017-2019. 2019. Available from: https://icer-review.org/announcements/vaf-update-2017-2019/. (Accessed 2 Dec 2018).

109. Ofman JJ, Sullivan SD, Neumann PJ, Chiou C-F, Henning JM, Wade SW, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm. 2003;9(1):53–61.

110. Al-Badriyeh D, Alameri M, Al-Okka R. Cost-effectiveness research in cancer therapy: a systematic review of literature trends, methods and the influence of funding. BMJ Open. 2017;7(1): e012648.

111. Mishra D, Nair SR. Systematic literature review to evaluate and characterize the health economics and outcomes research studies in India. Perspect Clin Res. 2015;6(1):20–33.

112. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul;6(7): e1000097.

113. Bergmeijer TO, Vos GJ, Claassens DM, Janssen PW, Harms R, Der Heide R van, et al. Feasibility and implementation of CYP2C19 genotyping in patients using antiplatelet therapy. Pharmacogenomics. 2018;19(7):621–8.

114. Ned RM. Genetic testing for CYP450 polymorphisms to predict response to clopidogrel: current evidence and test availability. Application: pharmacogenomics. PLoS Curr. 2010;2: RRN1180.

115. Borse MS, Dong OM, Polasek MJ, Farley JF, Stouffer GA, Lee CR. CYP2C19-guided antiplatelet therapy: a cost-effectiveness analysis of 30-day and 1-year outcomes following percutaneous coronary intervention. Pharmacogenomics. 2017;18(12):1155–66.

116. Lala A, Berger JS, Sharma G, Hochman JS, Scott Braithwaite R, Ladapo JA. Genetic testing in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a cost-effectiveness analysis. J Thromb Haemost. 2013;11(1):81–91.

117. Panattoni L, Brown PM, Te Ao B, Webster M, Gladding P. The cost effectiveness of genetic testing for CYP2C19 variants to guide thienopyridine treatment in patients with acute coronary syndromes: A New Zealand evaluation. Pharmacoeconomics. 2012;30(11):1067–84.

118. Patel V, Lin FJ, Ojo O, Rao S, Yu S, Zhan L, et al. Cost-utility analysis of genotype-guided antiplatelet therapy in patients with moderate-to-high risk acute coronary syndrome and planned percutaneous coronary intervention. Pharm Pract (Granada). 2014;12(3):438.

119. Reese ES, Daniel Mullins C, Beitelshees AL, Onukwugha E. Cost-effectiveness of cytochrome P450 2C19 genotype screening for selection of antiplatelet therapy with clopidogrel or prasugrel. Pharmacotherapy. 2012;32(4):323–32.

120. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20):2001–15.

121. Lastre-Amell G, Suarez-Villa M, Jorge M, María A, Mostapha A. A systematic literature review of treatment costs for patients with Acute Myocardial Infarction. Revista Latinoamericana de Hipertension. 2019;14(2):168-172.

122. R. R. Soekhlal, L. T. Burgers, W. K. Redekop, and S. S. Tam. Treatment costs of acute myocardial infarction in the Netherlands. Neth Heart J. 2013; 21(5): 230–235.

123. Stone DL, Rosopa PJ. The Advantages and limitations of using meta-analysis in human resource management research. Hum Resour Manag Rev. 2017;27(1):1–7.

124. Stanley K. Design of randomized controlled trials. Circulation. 2007;115(9):1164–9.

125. Rothwell PM. Factors that can affect the external validity of randomised controlled trials. PLoS Clin Trials. 2006;1(1): e9.

126. Plumpton CO, Roberts D, Pirmohamed M, Hughes DA. A Systematic review of economic evaluations of pharmacogenetic testing for prevention of adverse drug reactions. Pharmacoeconomics. 2016;34(8):771–93.

127. Jiang M, You JHS. Review of pharmacoeconomic evaluation of genotype-guided antiplatelet therapy. Expert Opin Pharmacother. 2015 ;16(5):771–9.

128. Kim LK, Feldman DN, Swaminathan R V, Minutello RM, Chanin J, Yang DC, et al. Rate of percutaneous coronary intervention for the management of acute coronary syndromes and stable coronary artery disease in the United States (2007 to 2011). Am J Cardiol. 2014;114(7):1003–10.

129. Switaj TL, Christensen SR, Brewer DM. Acute Coronary Syndrome: Current Treatment. Am Fam Physician. 2017;95(4):232–40.

130. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. N Engl J Med. 2014;371(9):796–7.

131. Muurinen JM. Demand for health: a generalized Grossman model. J Health Econ. 1982;1(1):5–28.

132. Wolff ND, Wolff JA. A Commentary on commercial genetic testing and the future of the genetic counseling profession. J Genet Couns. 2018;27(3):521–7.

133. Katsanis SH, Katsanis N. Molecular genetic testing and the future of clinical genomics. Nat Rev Genet. 2013;14(6):415–26.

134. Kikkert WJ, Damman P. Optimal duration of dual antiplatelet therapy for coronary artery disease. Neth Heart J. 2018;26(6):321–33.

135. Falagas ME, Pitsouni EI, Malietzis GA, Pappas G. Comparison of PubMed, Scopus, Web of Science, and Google Scholar: strengths and weaknesses. FASEB J. 2007;22(2):338–42.

APPENDICES

APPENDIX A: Ethics approval letter (ABHATH), Hamad Medical Corporation

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

APPROVAL LETTER

MEDICAL RESEARCH CENTER

HMC, DOHA-QATAR

Dr. Daoud Al-Badriyeh **Date:12th January 2020** **Associate Professor** **Pharmacy** **Medical Research Center - HMC** **Hamad Medical Corporation** **Doha-Qatar**	
Protocol No:	MRC-01-19-390
Study Title:	Cost-Effectiveness of the CYP2C19 Genetic-Guided Antiplatelet Therapy Compared to Universal Use of Ticagrelor or Clopidogrel in Qatar
Team Member List:	Dr. Daoud Al-Badriyeh , Dr. Hazem Fathy Elewa , Dr. Salaheddin Omran Arafa , Ms. Sawsan Ibrahim AlMukdad
The above titled research study has been approved to be conducted in HMC summarized as below:	
Hospitals/ Facilities Approved :	HMC Corporate
Team Member List :	Dr. Daoud Al-Badriyeh , Dr. Hazem Fathy Elewa , Dr. Salaheddin Omran Arafa , Ms. Sawsan Ibrahim AlMukdad
IRB Review Type :	Non Human Subject Research

Following review by the Medical Research Center, the above titled research proposal has been classified as 'non-human subject research'. Please be informed, therefore, that the Medical Research Center has no objection for this study to start/be published.

The study should be in full compliance 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 protocol. When modifications to the initially approved protocol are required, it is the responsibility of the Principal Investigator to ensure that all appropriate reviews and approvals are in place before the study can be allowed to proceed.

Please note that only officially approved versions of the documents should be used at all stages of your research. These documents can be accessed via Abhath.

A final report should be submitted to the Medical Research Center upon completion of the study.

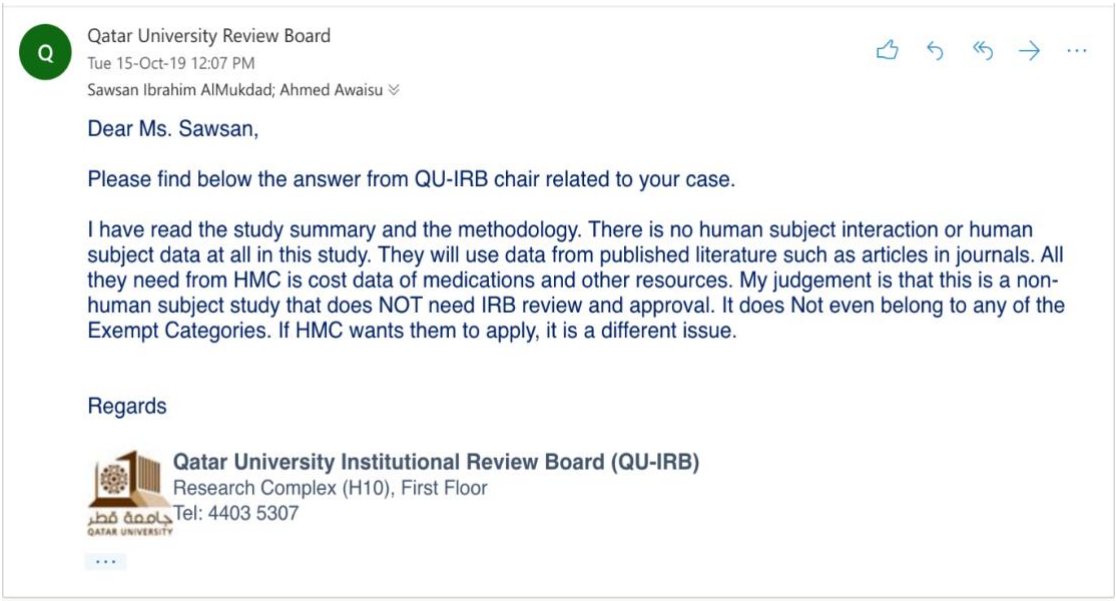
We wish you success and look forward to the outcomes in due course.

Yours sincerely,

Prof. Michael Paul Frenneaux
Chief of Scientific, Academic and Faculty Affairs
Hamad Medical Corporation

Date: 12th January 2020

APPENDIX B: Qatar University ethics approval



Qatar University Review Board
Tue 15-Oct-19 12:07 PM
Sawsan Ibrahim AlMukdad; Ahmed Awaisu

Dear Ms. Sawsan,

Please find below the answer from QU-IRB chair related to your case.

I have read the study summary and the methodology. There is no human subject interaction or human subject data at all in this study. They will use data from published literature such as articles in journals. All they need from HMC is cost data of medications and other resources. My judgement is that this is a non-human subject study that does NOT need IRB review and approval. It does Not even belong to any of the Exempt Categories. If HMC wants them to apply, it is a different issue.

Regards

Qatar University Institutional Review Board (QU-IRB)
Research Complex (H10), First Floor
Tel: 4403 5307

APPENDIX C: Search terms used in Pubmed and Embase databases

PubMed search terms:

("Genetic Testing"[Mesh] OR "Cytochrome P-450 CYP2C19"[Mesh] OR "genotype-guided" OR "genetic guided" OR "genetic diagnostic test" OR "genomic diagnostic test") AND ("Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "cost") AND ("Ticagrelor"[Mesh] OR "Clopidogrel"[Mesh] OR "Prasugrel" OR "Platelet Aggregation Inhibitors"[Mesh] OR "Acute Coronary Syndrome"[Mesh] OR "Percutaneous Coronary Intervention"[Mesh])

Embase search terms:

('genetic screening'/exp OR 'cytochrome p450 2c19'/exp) AND ('cost effectiveness analysis'/exp OR 'cost utility analysis'/exp OR 'cost'/exp) AND ('ticagrelor'/exp OR 'clopidogrel'/exp OR 'prasugrel'/exp OR 'dual antiplatelet therapy'/exp) AND ('acute coronary syndrome'/exp) AND ('percutaneous coronary intervention'/exp) AND [english]/lim AND 'article'/it

APPENDIX D: PRISMA checklist tool

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	29
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	iii,iv,v
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	27,28
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	28
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	44
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	45
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	44
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	44
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	44,45
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	45

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	45
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	46
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	93
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	94-96
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	106
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	98-106
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	115-119

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	119,120
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	121,122
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

APPENDIX E: Literature economic outcomes adjusted to USD and 2019/2020 financial year

Author	Economic outcomes (adjusted to the USD and the financial year 2019/2020)
Borse et al.	The ICER/ MACE or bleeding event avoided for genotype-guided therapy was USD 9,267 and 54,688 compared with universal clopidogrel at 30 days and 12 months, respectively. The ICER/ MACE or bleeding event avoided for genotype-guided therapy was USD 45,8712 at 30 days, but it was dominant at 12 months when compared to universal prasugrel
Crespin et al.	The ICER/QALY for universal ticagrelor compared to genotype-guided therapy was USD 51,036 and 12,066 at 12 months and 5 years, respectively.
Jiang et al. (2017)	Genotype-guided therapy was dominant compared to universal clopidogrel and alternative P2Y12 inhibitors The ICER/QALY for universal alternative P2Y12 inhibitors compared to universal clopidogrel was USD 30,604
Jiang et al. (2016)	Genotype-guided therapy was dominant compared to the other three arms The ICER/QALY for universal alternative P2Y12 inhibitors compared to universal clopidogrel was USD 46,839
Jiang et al. (2015)	Genotype plus platelet reactivity-guided therapy was dominant compared to universal clopidogrel and alternative P2Y12 inhibitors

	The ICER/QALY for universal alternative P2Y12 inhibitors compared to universal clopidogrel was USD 151,560
Kazi et al.	The ICER/QALY for genotype-guided ticagrelor was USD 34,551 and 28,259 in low and high discrimination scenarios, respectively The ICER/QALY for universal ticagrelor compared to universal clopidogrel was USD 46,106 Universal use of clopidogrel was dominant compared to universal prasugrel
Kim et al. (74)(74)(74)(74)	The ICER/QALY for genotype + liberal ticagrelor compared to clopidogrel + phenotype was USD 29,412 Genotype + conservative ticagrelor was not cost-effective due to second-order dominance The ICER/QALY for universal ticagrelor compared to genotype + liberal ticagrelor was USD 142,456
Lala et al.	Genotype-guided therapy was dominant compared to universal clopidogrel and prasugrel
Panattoni et al.	The ICUR/QALY for genotype-guided therapy compared to universal clopidogrel was USD 19,283. Genotype-guided therapy was dominant compared to universal prasugrel Universal clopidogrel was dominant compared to universal prasugrel
Patel et al.	The ICUR/QALY for genotype-guided therapy compared to universal clopidogrel was USD 4,805

	Genotype-guided therapy was dominant compared to universal prasugrel The ICUR/QALY for universal clopidogrel compared to universal prasugrel was USD 260,619
Reese et al.	Genotype-guided therapy was dominant compared to universal branded clopidogrel and prasugrel The ICER/MACE or bleeding event avoided for genotype-guided therapy compared to universal generic clopidogrel was USD 2,631
Sorich et al.	The ICER/QALY for universal ticagrelor compared to genotype-guided therapy was USD 17,885 The ICER/QALY for genotype-guided therapy compared to universal clopidogrel was USD 4,702
Wang et al.	The ICER/QALY for genotype-guided therapy compared to universal clopidogrel was USD 2,745 Genotype-guided treatment was dominant compared to universal ticagrelor The ICER/QALY for universal ticagrelor compared to universal clopidogrel was USD 7,778

USD: United States Dollar; QALY: Quality-adjusted life-years; ICER: Incremental cost-effectiveness ratio; ICUR: Incremental cost-utility ratio

Appendix F: QHES results

Questions		Study				
		Borse et al	Wang at al	Jiang et al (2017)	Jiang et al (2016)	Jiang et al (2015)
1	Was the study objective presented in a clear, specific, and measurable manner?	7	7	7	7	7
2	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	4	4	4	4
3	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?	8	4	8	8	8
4	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	0	1	0	0	1
5	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	9	9	9	9
6	Was incremental analysis performed between alternatives for resources and costs?	6	6	6	6	6
7	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	2.5	5	2.5	5	5
8	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	3.5	7	7	7	7
9	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	4	8	8	8	4
10	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term was justification given for the measures/scales used?	6	6	6	6	6
11	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	7	7	7	7
12	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	8	8	8	8
13	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	7	3.5	7	7
14	Did the author(s) explicitly discuss direction and magnitude of potential biases?	0	0	0	0	0
15	Were the conclusions/recommendations of the study justified and based on the study results?	8	8	8	8	8
16	Was there a statement disclosing the source of funding for the study?	0	3	3	3	0
	Total Points	80	90	87	93	87

Questions		Study				
		Patel et al	Kazi et al	Soirch et al	Lala et al	Panattoni et al
1	Was the study objective presented in a clear, specific, and measurable manner?	7	7	7	7	7
2	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	4	4	4	4
3	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?	8	8	8	8	8
4	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	1	1	1	1
5	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	9	9	9	4.5
6	Was incremental analysis performed between alternatives for resources and costs?	6	6	6	6	6
7	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	5	2.5	2.5	2.5
8	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	7	7	7	7
9	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	4	8	4	8	4
10	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term was justification given for the measures/scales used?	6	6	3	6	6
11	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	7	7	7	7
12	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	8	8	8	4
13	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	7	7	7	7
14	Did the author(s) explicitly discuss direction and magnitude of potential biases?	0	0	0	0	0
15	Were the conclusions/recommendations of the study justified and based on the study results?	8	8	8	8	8
16	Was there a statement disclosing the source of funding for the study?	3	3	3	3	3
	Total Points	90	94	84.5	91.5	79

Questions		Study		
		Reese et al	Crespin et al	Kim at al
1	Was the study objective presented in a clear, specific, and measurable manner?	7	7	7
2	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	4	4
3	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?	8	8	4
4	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	1	1
5	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	9	9
6	Was incremental analysis performed between alternatives for resources and costs?	6	6	6
7	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	2.5	5	5
8	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	7	7
9	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	4	8	8
10	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term was justification given for the measures/scales used?	3	3	6
11	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	7	7
12	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	8	8
13	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	7	7
14	Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	3	0
15	Were the conclusions/recommendations of the study justified and based on the study results?	8	8	8
16	Was there a statement disclosing the source of funding for the study?	0	3	0
	Total Points	87.5	94	84