# Cost-Benefit Analysis of Genotype-Guided Interruption Days in Warfarin Pre-Procedural Management

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**Abstract: Warfarin is commonly used in thromboembolic conditions. Warfarin interruption represents a significant challenge in pre-operative warfarin management as it is associated with major consequences. Genetics polymorphism demonstrated to be a significant predictor of the required days of warfarin interruption. This study sought to assess the economic benefit of implementing a pharmacogenetic-guided approach in the preprocedural warfarin management. From the hospital's perspective, a cost-benefit analysis was conducted based on a 1-year decision-analytic follow-up model of the economic implications of using a pharmacogenetic algorithm vs standard of care in preoperative warfarin management in the Hamad Medical Corporation, Qatar. The benefit of the interventional algorithm was based on estimated reduction in the probabilities of clinical events and their cost, added to the avoided cost because of canceled procedures. The cost of the algorithm was the cost of the genotyping assay. The model event probability inputs were**

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**extracted from major literature clinical trials, and the setting-specifc and cost inputs were locally obtained. The model was based on a multivariate analysis at its base case. As per 10.3% prevalence of genetic variants, 82% bridging, and a calculated 20% optimization in the preparative period of warfarin management, the benefit to cost ratio was 4.0 in favor genotype-guided approach. This positive benefit to cost ratio was maintained in 100% of the simulated study cases. Sensitivity analyses confirmed the robustness and generalizability of the study conclusion. A pharmacogenetic- guided pre-operative warfarin interruption management is a cost-beneficial approach in the Qatari practice. (Curr Probl Cardiol 2022;00:101128.)**

## Introduction

The inhibitory effects of warfarin on the biological coagulation factors have grabbed researchers' and clinicians' attention to its use in thromboembolic conditions for multiple decades.[1] Owing to the warfarin's narrow therapeutic index, therefore, the International Normalized Ratio (INR) is a significant marker used to monitor warfarin's therapeutic effect.[2] The INR values are kept within the therapeutic range for long term warfarin treatments, mitigating the risk of thrombosis/bleeding.[3] While the rate of major hemorrhage is increased with high INR, thromboembolic complications are predominant in patients with low INR values.[4]

Up to 10% of all warfarin-receiving patients undergo prearranged surgeries and are expected to stop warfarin for reducing the probability of encountering bleeding events during and after the procedures.[5] To achieve a therapeutic INR level at the time of the procedure, most of the recommendations indicate the necessity of warfarin interruption 5-7 days before the procedures.[6,7] Recent studies[8,9] found that 23% of patients who stopped warfarin attained INR $>$ 1.2 following 4.7 days of warfarin holding, and 7% reached a pre-operative INR $>$ 1.5 after 5 days of discontinuation of warfarin. Here, very early warfarin cessation may produce thrombosis in patients, and delaying holding warfarin until very late may lead to peri-procedural bleeding.[10] As a result, following the warfarin interruption is necessary for INR to be closely monitored to achieve normalization at the time of the procedure, considering the potential individual variations during this period.

Published research highlighted the effect of many genetic factors on warfarin pharmacokinetic properties.[11] Warfarin contains a mixture of 2 active enantiomers: the (R) and (S) enantiomer, where the latter has a five-fold anticoagulation potency over the former.[12] The S-enantiomer is metabolized by the cytochrome P450 2C9 (CYP2C9) encoded enzyme, and variations in the *CYP2C9* gene can alter the enzymatic activity and the time required for warfarin elimination.[13-15] Genetic factors, thought to be swaying INR normalization during pre-procedural warfarin interruption, have been investigated in several articles in different ethnic groups.[10,16-21] The *CYP2C9* genetic mutation was the most common polymorphism that can predict the warfarin clearance, INR normalization, or INR decline rate.[10,16,19-21] In 2015, Abohelaika et al. succeeded in predicting the INR decline rate in pre-operative warfarin interruption in Caucasians based on *CYP2C9* genetic variation and other clinical and demographics.[10] Later, the same group of researchers validated the prediction tool reliability retrospectively.[22]

Indeed, genetic testing predicts how the genetic difference in one or multiple genes will affect the patients' response to medication.[23-25] Within the context of pre-operative warfarin, this can be utilized to optimize interruption time before the procedure to minimize risks of thrombosis or bleeding.

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

## Materials And Methods

The trade-off between the monetary values of the cost and benefit of the pharmacogenetic-guided algorithm (PGX), compared to the standard of care algorithm (SD), was evaluated via a CBA based on a 1-year decision-analytic and economic model, which was primarily based on the Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (The BRIDGE Trial) randomized control trial (RCT),[26] an international multicenter trial, and the only major study to investigate peri-procedural warfarin management.

## Study Perspective

The CBA was conducted from the hospital perspective of the main secondary and tertiary healthcare provider in Qatar, that is Hamad Medical Corporation (HMC).

## Model Structure

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

In the study model, patients will receive the PGX or the SD approach of management. If patients receive the PGX, they will be differentiated based on whether they are carriers of the *CYP2C9* mutation. Afterward, and whether patients are on the SD or the PGX with/without mutation, patients are followed similarly. Patients are differentiated based on whether they receive a bridging preprocedural management strategy. Whether the bridging or the non-bridging strategy is being applied, patients are differentiated based on the state of adverse events (AEs) in patients, including 4 different states: no AE, thromboembolism (TE), bleeding, and non-vascular/non-bleeding death. Bleeding may include minor bleeding, including epistaxis, ecchymosis, hematoma, hematuria, or major bleeding, divided into intracranial hemorrhage (ICH) and extracranial hemorrhage (ECH). TE may be arterial thromboembolism (ATE) or venous thromboembolism (VTE). The duration of the model follow-up was one year.

Bridging refers to the heparin (LMWH/UFH) initiation during warfarin interruption in preprocedural management. In practice, whether a patient is eligible for bridging or not is based on the thromboembolic risk. In HMC, bridging starts with a patient INR of $< 2.0$. The study model structure is illustrated in Figure 1, with detailed follow-up consequences and the literature sources of their probabilities as clarified in Appendix 1.

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

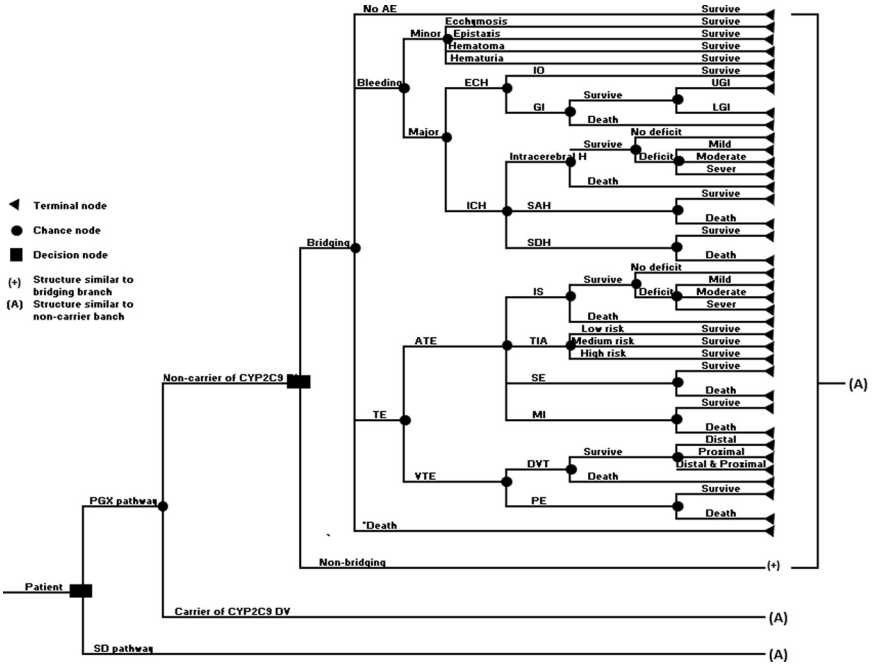


**FIG 1.** Decision-analytic model.

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

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

## Clinical Inputs

***Standard of Care Pathway.*** All model clinical event rates were retrieved from the published literature and a recent local prospective cohort study at HMC by Eljilany et al.[27] The BRIDGE study[26] was the primary source of the clinical events reported in the model. The BRIDGE trial is the only source that reports relative event probabilities for a relatively large population (n = 1,804) in peri-procedural warfarin management reporting clinical outcomes based on a one-month observation period. Noteworthy is that the peri-procedural use of warfarin in the BRIDGE study was consistent with that in clinical practice at HMC, including the average number of discontinuation days (5 days), the average number of heparin dosing days (3 days before treatment), and the stroke risk score for AF patients with mean $CHA_2DS_2$-Vasc of 4, as reported in a published local study at HMC.[27] Obtained from the BRIDGE trial,[26] for each of the bridging and non-bridging model pathways, are the probabilities for the major clinical events in the model, which were non-AE outcomes, total hemorrhage, minor and major hemorrhage, TE, ATE, transient ischemic attack (TIA), ischemic stroke (IS), myocardial infarction (MI), systemic embolism (SE), VTE, and non-hemorrhagic or non-vascular death. The probabilities of sub-cosequences for an outcome in the BRIDGE trial,[26] which are not available in the BRIDGE study itself, were extracted from other available relevant literature-based comparative clinical studies that were similar concerning underlying patients types, a risk score of stroke, patients age, and follow-up period for reported outcomes. These sub-consequences are minor bleeding, gastrointestinal (GI) bleeding, intraocular hemorrhage (IO), subdural hemorrhage (SAH), intracerebral bleeding, and subdural hemorrhage (SDH), added to their consequences. Probabilities for ECH and ICH with bridging were available from a study by Hackett et al.[28] The duration of heparin administration was an average of 3 days, matching the bridging as in the BRIDGE Trial and the HMC practices. Supposedly, the main driver of bleeding in our study was heparin which is the leading cause of hemorrhage in the bridging group. The probabilities of ECH and ICH with the non-bridging arm were obtained from the warfarin arm in the RE-LY trial,[29] in which the INR level was at sub-therapeutic range due to starting warfarin recently. Appendix 2 summarizes the model clinical events, their descriptions, and data sources. All reported clinical event rates, from all sources, were consistently reported until one month after warfarin interruption or heparin initiation.

The incidence probability of bridging vs non-bridging in HMC was derived from a recent analysis by Eljilany et al.[27] According to local HMC clinical practice, bridging was stated to occur in 82.5% of patients with interrupted warfarin, peri-procedurally.

***Pharmacogenetic-Guided Pathway.*** Based on a recent HMC-based publication.[30], the prevalence of carrying *CYP2C9* genetic double variants (either *3*3, *3*2, or *2*2) in our HMC population is 10.3%. Therefore, the probability of any event under the PGX model pathway is calculated as [the prevalence of carrying *CYP2C9* genetic double variants (10.3%) × the event probability under the carriers of genetic variants model pathway] + [the prevalence of non-carrying *CYP2C9* genetic double variants (89.7%) × the event probability under the non-carriers of genetic variants model pathway]. The difference in pre-operative warfarin discontinuation days between carriers and non-carriers was calculated based on the equation reported by Abohelaika et al.,[10] which was validated.[22] The equation is that: INR decline by day $5 = 0.9\ \{\text{INR}\} - 0.2\ \{\text{N. CYP2C9}\} - 0.2 - [13\ \{\text{AGE}\} + 7.4\ \{\text{W}\} + 92\ \{\text{N.COM}\}]\ /3000$. Where INR is index INR, N. *CYP2C9* equal to 1 in the presence of *CYP2C9* double variant or equals to zero in the absence of double variant, AGE is the age in years, W is weight in kg, and N.COM is the number of comorbidities. The calculation in Appendix 3 indicates that carriers of *CYP2C9* genetic polymorphism require 5 days as SD pathway. However, the non-carriers of genetic polymorphism need 20% fewer days of warfarin interruption compared to carriers of genetic variants. Because of this, the probabilities of AEs in non-carriers of *CYP2C9* genetic polymorphism patients were assumed to equal 80% of the probabilities of the AEs in the carriers of *CYP2C9* genetic polymorphism patients. The event probabilities in the patients who are carriers of genetic polymorphism do not differ from the probabilities of the model events in the SD patients because both require the same period of interruption, which is 5 days.

The model analysis at its base case was based on multivariate uncertainty analysis of the model event probabilities, using Monte Carlo simulation via @Risk-7.6 (Palisade Corporation, NY, US), which was to take into consideration the real-life interactions among different concurrent inherent uncertainties in the model input data. The uncertainty range for any probability input was based on the 95% confidence interval (CI), utilizing a triangular type of distribution sampling within the range. With 5000 iterations, the Monte Carlo simulation enables an analysis of the probability of model outcomes and a tornado regression analysis of the impact of model inputs on the outcome.

Table1 summarizes the input values and their probabilities in the study model's multivariate analysis at its base case.

## Cost Calculations

As per the principles of decision-analytic modeling, the cost of a management approach per patient is the sum of the proportional costs of all the model pathways generated with the approach. The proportional cost of a pathway is the multiplication of the pathway's cost by the overall probability of the pathway. The probability of the pathway is calculated as the multiplication of the probabilities of individual consequential outcomes taking place in the pathway.

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

In the SD pathway, if a patient must stop taking warfarin for elective surgery, the INR should be tested twice before and after the procedure. When bridging is administered, a daily heparin dosage of 160-mg (80-mg BID) was assumed, based on an average weight of 85 kg in Qatar, as per Eljilany et al.[27] Bridging is given twice per day for 3 days before the procedure, with each patient receiving 6 doses of heparin in total. According to the BRIDGE trial[26] and our local research in HMC,[27] 30% of operations are deemed major procedures that entail 3 days of pre-operative inpatient department (IPD) admission if bridging is used. In the remaining 70% of patients with minor surgeries, 2 out-patient (OPD) visits are required, regardless of bridging. The calculation of SD pathway cost is summarized below.

In the PGX model pathway, given that the genetic test can estimate the optimal required number of interruption days, the cost of the PGX pathway provided by HMC was recalculated based on how the use of resources changes with the PGX approach, relative to the SD approach, which was guided by the expert panel of the study. The PGX approach will produce changes in resources used as listed in Table 2, including their direct cost and their uncertainty. Also, the new cost of events after adjustment can be seen in Table 3.

**TABLE 1.** Model inputs and their uncertainty ranges in Monte Carlo simulation

| Variables | Bridging | | | Non-bridging | | |
|---|---|---|---|---|---|---|
| | Base-case value | Uncertainty range (95% CI) | Ref. | Base-case value | Uncertainty range (95% CI) | Ref. |
| Heparin intervention (%) | 82.52 | 73.92-88.78 | 30 | 17.48 | 11.22-26.08 | 30 |
| No AE (%) | 73.30 | 63.89-80.99 | 26 | 85.19 | 76.93-90.84 | 26 |
| Survive (%) | 100.00 | 96.3-100 | 26 | 100.00 | 96.3-100 | 26 |
| Bleeding (%) | 24.13 | 16.80-33.37 | 26 | 13.29 | 7.98-21.32 | 26 |
| Minor bleeding (%) | 86.57 | 78.52-91.91 | 26 | 90.16 | 82.76-94.59 | 26 |
| Ecchymosis (%) | 62.84 | 53.06-71.67 | 31 | 62.84 | 53.06-71.67 | 31 |
| Survive (%) | 100.00 | 96.3-100 | 31 | 100.00 | 96.3-100 | 31 |
| Epistaxis (%) | 22.62 | 15.22-31.35 | 31 | 22.62 | 15.22-31.35 | 31 |
| Survive (%) | 100.00 | 96.3-100 | 31 | 100.00 | 96.3-100 | 31 |
| Hematoma (%) | 7.27 | 3.61-14.09 | 31 | 7.27 | 3.61-14.09 | 31 |
| Survive (%) | 100.00 | 96.3-100 | 31 | 100.00 | 96.3-100 | 31 |
| Hematuria (%) | 7.27 | 3.61-14.09 | 31 | 7.27 | 3.61-14.09 | 31 |
| Survive (%) | 100.00 | 96.3-100 | 31 | 100.00 | 96.3-100 | 31 |
| Major bleeding (%) | 13.43 | 8.09-21.48 | 26 | 9.84 | 5.41-17.24 | 26 |
| ECH (%) | 83.33 | 74.82-89.37 | 28 | 78.34 | 69.30-85.28 | 29 |
| IO hemorrhage (%) | 13.48 | 8.13-21.54 | 32 | 13.48 | 8.13-21.54 | 32 |
| Survive (%) | 100.00 | 96.3-100 | 32 | 100.00 | 96.3-100 | 32 |
| GI bleeding (%) | 86.52 | 78.46-91.87 | 32 | 86.52 | 78.46-91.87 | 32 |
| Survive (%) | 91.28 | 84.12-95.39 | 33 | 91.28 | 84.12-95.39 | 33 |
| UGI bleeding (%) | 49.68 | 40.08-59.31 | 33 | 49.68 | 40.08-59.31 | 33 |
| LGI bleeding (%) | 50.32 | 40.69-59.92 | 33 | 50.32 | 40.69-59.92 | 33 |
| Death (%) | 8.72 | 4.61-15.88 | 33 | 8.72 | 4.61-15.88 | 33 |
| ICH (%) | 16.67 | 10.63-25.18 | 28 | 21.66 | 14.72-30.70 | 29 |
| Intracerebral hemorrhage (%) | 63.64 | 53.87-72.40 | 34 | 63.64 | 53.87-72.40 | 34 |
| No deficit (%) | 27.87 | 20.04-37.36 | 35 | 27.87 | 20.04-37.36 | 35 |

(*continued on next page*)

**TABLE 1.** (*continued*)

| Variables | Bridging | | | Non-bridging | | |
|---|---|---|---|---|---|---|
| | Base-case value | Uncertainty range (95% CI) | Ref. | Base-case value | Uncertainty range (95% CI) | Ref. |
| Deficit (%) | 52.46 | 42.76-61.97 | 35 | 52.46 | 42.76-61.97 | 35 |
| Mild deficit (%) | 23.44 | 16.22-32.63 | 35 | 23.44 | 16.22-32.63 | 35 |
| Moderate deficit (%) | 43.75 | 34.44-53.53 | 35 | 43.75 | 34.44-53.53 | 35 |
| Severe deficit (%) | 32.81 | 24.39-42.5 | 35 | 32.81 | 24.39-42.5 | 35 |
| Death (%) | 19.67 | 13.07-28.53 | 35 | 19.67 | 13.07-28.53 | 35 |
| SAH (%) | 6.06 | 2.82-13.19 | 34 | 6.06 | 2.82-13.19 | 34 |
| Survive (%) | 25.00 | 17.55-34.30 | 34 | 25.00 | 17.55-34.30 | 34 |
| Death (%) | 75.00 | 65.70-82.48 | 34 | 75.00 | 65.70-82.48 | 34 |
| SDH (%) | 30.30 | 21.72-40.42 | 34 | 30.30 | 21.72-40.42 | 34 |
| Survive (%) | 75.00 | 65.70-82.48 | 34 | 75.00 | 65.70-82.48 | 34 |
| Death (%) | 25.00 | 17.55-34.30 | 34 | 25.00 | 17.55-34.30 | 34 |
| TE (%) | 2.12 | 0.6-7.18 | 26 | 1.20 | 0.24-5.77 | 26 |
| ATE (%) | 89.47 | 81.93-94.04 | 26 | 100.00 | 96.30-100 | 26 |
| IS (%) | 17.65 | 11.42-26.28 | 26 | 18.18 | 11.85-26.87 | 26 |
| No deficit (%) | 48.18 | 38.58-57.80 | 35 | 48.18 | 38.58-57.80 | 34 |
| Deficit (%) | 44.55 | 35.19-54.31 | 35 | 44.55 | 35.19-54.31 | 35 |
| Mild deficit (%) | 29.08 | 21.09-38.62 | 35 | 29.08 | 21.09-38.62 | 35 |
| Moderate deficit (%) | 48.58 | 39.02-58.25 | 35 | 48.58 | 39.02-58.25 | 35 |
| Severe deficit (%) | 22.34 | 15.92-31.44 | 35 | 22.34 | 15.92-31.44 | 35 |
| Death (%) | 7.27 | 3.61-14.09 | 35 | 7.27 | 3.61-14.09 | 35 |
| TIA (%) | 0.00 | 0.0-3.70 | 26 | 18.18 | 11.85-26.87 | 26 |
| Low risk TIA (%) | 13.41 | 8.07-21.46 | 36 | 13.41 | 8.07-21.46 | 36 |
| Medium risk TIA (%) | 74.39 | 65.04-81-93 | 36 | 74.39 | 65.04-81-93 | 36 |
| High risk TIA (%) | 12.20 | 7.15-20.05 | 36 | 12.20 | 7.15-20.05 | 36 |
| SE (%) | 0.00 | 0.0-3.70 | 26 | 0.00 | 0.0-3.70 | 26 |

(*continued on next page*)

**TABLE 1.** (*continued*)

| Variables | Bridging | | | Non-bridging | | |
|---|---|---|---|---|---|---|
| | Base-case value | Uncertainty range (95% CI) | Ref. | Base-case value | Uncertainty range (95% CI) | Ref. |
| Survive (%) | 75.00 | 65.70-82.48 | 26 | 75.00 | 65.70-82.48 | 26 |
| Death (%) | 25.00 | 17.55-34.30 | 26 | 25.00 | 17.55-34.30 | 26 |
| MI (%) | 82.35 | 73.72-88.58 | 26 | 63.64 | 53.87-72.40 | 26 |
| Survive (%) | 100.00 | 96.3-100 | 26 | 71.43 | 96.3-100 | 26 |
| Death (%) | 0.00 | 0.0-3.70 | 26 | 28.57 | 20.64-38.09 | 26 |
| VTE (%) | 10.53 | 5.91-18.07 | 26 | 0.00 | 0.0-3.70 | 26 |
| DVT (%) | 50.00 | 40.38-59.62 | 26 | 0 | 0.0-3.70 | 26 |
| Survive (%) | 92.31 | 85.93-96.10 | 26 | 92.31 | 85.93-96.10 | 26 |
| Distal DVT (%) | 33.33 | 24.89-43.03 | 28 | 33.33 | 24.89-43.03 | 28 |
| Proximal DVT (%) | 33.33 | 24.89-43.03 | 28 | 33.33 | 24.89-43.03 | 28 |
| Distal and proximal DVT (%) | 33.33 | 24.89-43.03 | 28 | 33.33 | 24.89-43.03 | 28 |
| Death (%) | 7.69 | 3.90-14.61 | 26 | 7.69 | 3.90-14.61 | 26 |
| PE (%) | 50.00 | 40.38-59.62 | 26 | 0 | 0.0-3.70 | 26 |
| Survive (%) | 89.29 | 81.71-93.96 | 26 | 89.29 | 81.71-93.96 | 26 |
| Death (%) | 10.71 | 6.04-18.26 | 26 | 10.71 | 6.04-18.26 | 26 |
| Death (%) * | 0.45 | 0.04-4.50 | 26 | 0.33 | 0.02-4.31 | 26 |

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

**TABLE 2.** Frequencies and direct costs (USD) of various resources used and their uncertainty ranges

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

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

Clinical event costs were based on the finance department of HMC, as listed in Table 4. The cost of PGX pathway was based on revising the use of resources as indicated in Table 2. Also, Table 2 shows the genetic test's cost that was based on the HMC cost of sending the patient sample overseas for analysis. Costs were calculated using the 2021 value of the Qatari Riyal (QAR) and presented in US Dollars (USD, 1 USD = QAR 3.65). Since the model's follow-up period was not more than one year, no discounting of costs was performed.

## *Cost-Benefit Analysis*

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

**TABLE 3.** Clinical outcomes and the proportional costs, at base-case

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

Death, non-hemorrhagic or non-vascular death; AE, adverse event; TE, thromboembolism. Probabilistic cost of an event = event cost × event probability. 1 USD = 3.65 QAR.

**TABLE 4.** Direct cost (USD) of various clinical events and their uncertainty ranges

| Event | Direct cost (USD) | Uncertainty range (USD) (-20%, +20%) | |
|---|---|---|---|
| No AE/death* (bridging) SD | 1,340.81 | 1,072.65 | 1,608.97 |
| No AE /death* (non- bridging) SD | 893.01 | 714.41 | 1071.62 |
| No AE/death* (bridging) PGX | 815.74 | 652.59 | 987.89 |
| No AE /death* (non- bridging) PGX | 367.95 | 294.36 | 441.53 |
| Ecchymosis | 1,319 | 1,055.2 | 1,582.9 |
| Hematoma | 1,151 | 920.80 | 1,381.20 |
| Hematuria | 2,533 | 2,026.40 | 3,039.60 |
| Epistaxis | 800 | 640.00 | 960.00 |
| Intra-ocular H. | 593 | 474.40 | 711.60 |
| Upper GI H | 5,245 | 4,196.00 | 6,294.00 |
| Lower GI H | 5,218 | 4,174.40 | 2,444.40 |
| GIH Death | 5,231 | 4,184.80 | 6,277.20 |
| No deficit ICH | 10,332 | 8,265.60 | 12,398.40 |
| Mild deficit ICH | 22,051 | 17,640.80 | 26,461.20 |
| Moderate deficit ICH | 34,095 | 27,276.00 | 40,914.00 |
| Severe deficit ICH | 56,677 | 45,341.60 | 68,012.40 |
| ICH Death | 56,677 | 45,341.60 | 68,012.40 |
| SAH | 37,038 | 29,630.40 | 44,445.60 |
| SAH Death | 37,038 | 29,630.40 | 44,445.60 |
| SDH | 43,836 | 35,068.80 | 52,603.20 |
| SDH Death | 43,836 | 35,068.80 | 52,603.20 |
| No deficit IS | 9,424 | 7,539.20 | 11,308.80 |
| Mild deficit IS | 21,903 | 17,522.40 | 26,283.60 |
| Moderate deficit IS | 34,382 | 27,505.60 | 41,258.40 |
| Severe deficit IS | 57,006 | 45,604.80 | 68,407.20 |
| IS death | 57,006 | 45,604.80 | 68,407.20 |
| Low risk TIA | 4,770 | 3,816.00 | 5,724.00 |
| Medium risk TIA | 5,303 | 4,242.40 | 6,363.60 |
| High risk TIA | 5,836 | 4,668.80 | 7,003.20 |
| SE | 17,153 | 13,722.40 | 20,583.60 |
| Death | 17,153 | 13,722.40 | 20,583.60 |
| MI | 30,225 | 24,180.00 | 36,270.00 |
| MI death | 30,225 | 24,180.00 | 36,270.00 |
| Proximal DVT | 7,481 | 5,984.80 | 8,977.20 |
| Distal DVT | 7,481 | 5,984.80 | 8,977.20 |
| Proximal and distal DVT | 7,481 | 5,984.80 | 8,977.20 |
| DVT death | 7,481 | 5,984.80 | 8,977.20 |
| PE | 14,191 | 11,352.80 | 17,029.20 |
| PE death | 14,191 | 11,352.80 | 17,029.20 |

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

cost of performing the test plus the increase in the overall patient cost because of an increase in resource utilization, if any.

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

### *Sensitivity Analysis*

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

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

Added to the uncertainty that was introduced to the model event probabilities at its base case, a probabilistic sensitivity analysis was performed by applying uncertainty to the base-case values of event cost inputs as seen in Table 2 and Table 4; whereby, given that no confidence intervals for event costs were available, an overestimated 20% variability was used for the uncertainty ranges, measured using a triangular type of sampling distribution.

Like in the base case, both one-way and probabilistic sensitivity tests were conducted with 5000 iterations, using the Monte Carlo simulation via @Risk 7.6 (Palisade Company, NY, USA).

## Results

### *Base-Case Analysis*

Based on 10.3% prevalence of *CYP2C9* double genetic variants and, consequently, 20% reduction in pre-operative warfarin interruption period in favor of non-carriers of *CYP2C9* double genetic variants, the rate of not experiencing AE was improved by 0.0451 (95% CI 0.0412-0.0493) in favor of PGX approach, as seen in Table 3. Also resulted was a decrease in the total cost per patient by 30.24%, USD 727.47 (95% CI 726.0-729.0) [QAR 2,626 (95% CI 2649.9-2660.8] in favor of the PGX approach. Add to this the avoided cost of procedure canceling (USD 38.5 per patient), the overall benefit of the PGX approach was USD 765.97 (95% CI 764.0-767.0) [QAR 2,794.11(95% CI 2788.6-2799.5)]. This is

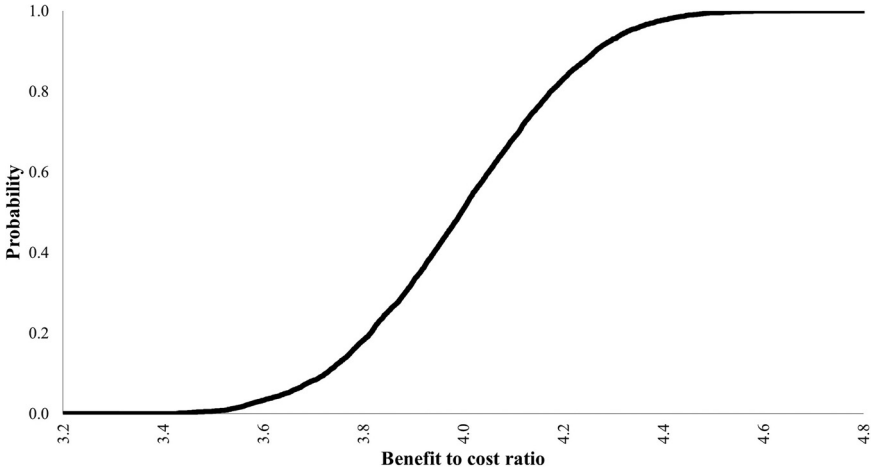


**FIG 2.** Base-case benefit to cost ratio probability curve.

while the direct cost of performing the genetic testing was USD 191.78 (95% CI 192-192) [QAR 700.0 (95% CI 700.8-700.8). Therefore, the benefit to cost ratio was 3.99 (95% CI 3.98-4.0), indicating that for each USD 1 invested in the genetic testing, around USD 4 is generated as a return to investment. Important, is that the increased benefit over cost with the genetic testing was maintained in 100% of the simulated cases at base case. Figure 2 presents the probability curve of the benefit to cost ratio.

Based on a tornado regression analysis that ranks model inputs as per the strength of their association with the benefit-cost ratio outcome, it is demonstrated that the no-AE rate is the most influential, followed by the rate of MI and then the rate of ecchymosis. Figure 3 shows the tornado analysis of the input raking as per the regression coefficient.

## *Sensitivity Analysis*

***One-Way Sensitivity Analysis.*** The base-case benefit-cost outcome of implementing the PGX approach of management was not affected by the uncertainty assigned to each of the prevalence of *CYP2C9* double genetic variants, genetic test cost, and pre-operative warfarin interruption optimization model inputs, demonstrating the robustness of the model. Table 5 shows the benefit, cost, and benefit-to-cost ratio outcomes with each one-way analysis compared to the base-case scenario.

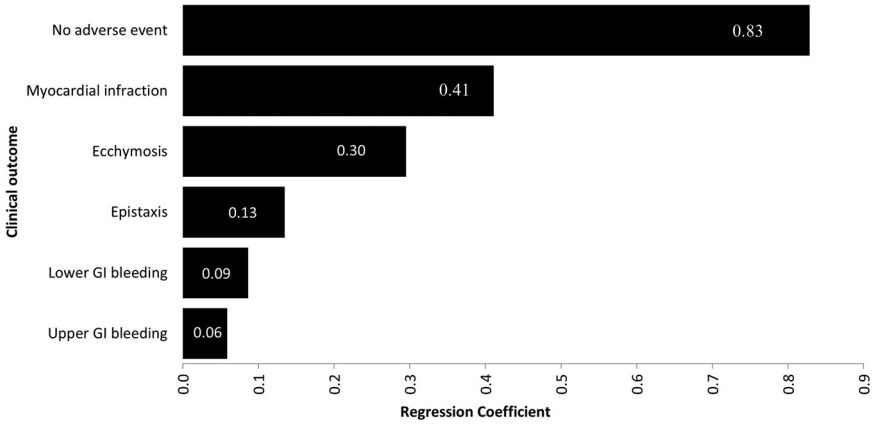


**FIG 3.** Tornado diagram of the base-case benefit to cost ratio based on the regression coefficient. GI; gastrointestinal.

***Probabilistic Sensitivity Analysis.*** Incorporating the uncertainty in event costs, in addition to the base-case uncertainty in event probabilities, did not reverse how cost-beneficial the genetic testing was. It, in fact, increased it. Table 6 summarizes the results of the multivariate sensitivity analysis in comparison to the base-case analysis for the overall benefit, cost, and benefit-cost ratio outcomes. A higher benefit over cost with the genetic testing was also maintained in 100% of the cases, Figure 4.

The rank of the model event inputs in terms of the association with model results, as well as the strength of the association (regression coefficient), was not consistent with the status at the base case. It seems that with the introduced uncertainty in event cost, the most influential model input on model outcomes became the rate of intracerebral stroke, followed by the rate of ischemic stroke, before the rate of the no-AEs. The tornado regression analysis of the model inputs association with the benefit-cost ratio is presented in Figure 5.

**TABLE 5.** Outcomes of one-way sensitivity analysis

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

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

**TABLE 6.** Multivariate sensitivity analyses and the subsequent changes in model outcomes

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

CI, confidence interval. 1 USD = 3.65 QAR.

## Discussion

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

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

For optimizing warfarin initiation or continuity with genetic testing, several cost-effectiveness studies have been published in the literature, reporting conflicting results.[31-36] However, for the pre-operative interruption of warfarin, no economic evaluations exist.

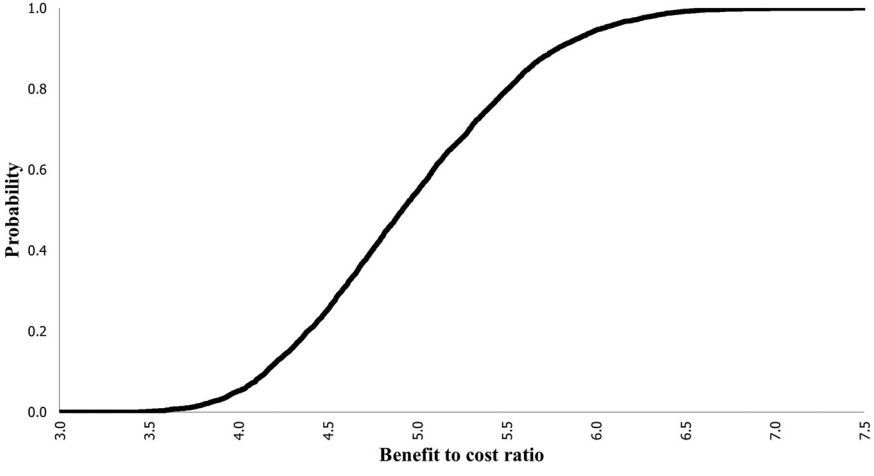


**FIG 4.** Multivariate sensitivity analyses benefit to cost ratio probability curve.

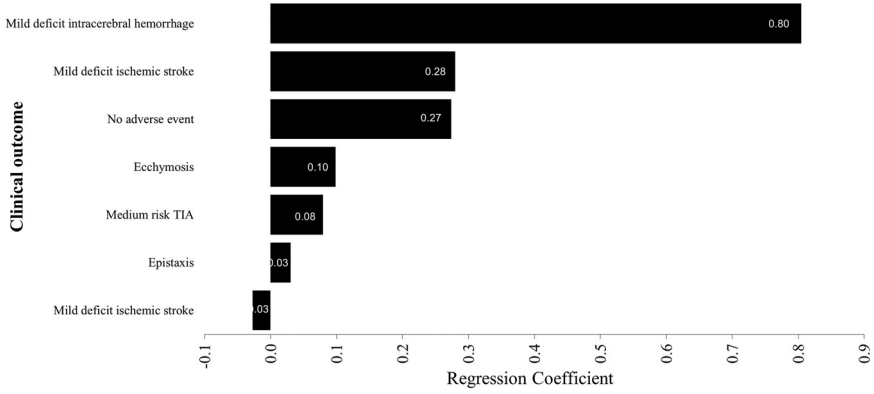


**FIG 5.** Tornado diagram of the multivariate sensitivity analysis based on the regression coefficient. TIA; transit ischemic attack.

The principal finding of this analysis was that the average benefit to cost ratio was 4.0, which indicates that the benefit of implementing PGX is equivalent to 4 times its cost. The economic benefit in favor of the PGX strategy, driven by the reduction in cost per patient by USD 573.72 (QAR 2,094.07), is predominantly attributable in this study to around 6% increase in the rate of no-AEs health state (equivalent to a decrease in total rates of AEs) with the PGX compared to the management of events with SD. Added to that the management of events with genotype pathway was associated with a drastically lower cost of pre-operative management primarily associated with a lower number of IPD and OPD visits.

The model benefit-cost ratio was robust against proposed changes the cost of the genetic testing, accounting for potential anticipated changes with the outsourcing process, as well as against the prevalence of *CYP2C9* two variant alleles, indicating a model outcome that potentially persists among various ethnic groups. Similarly, with the multivariate sensitivity, the proposed variability in the cost of events did not affect the model outcome. On the other hand, we can find that when we added the cost uncertainty to the base-case uncertainty in event probabilities, the mild deficit hemorrhagic and ischemic stroke became the leading influencers due to their relatively high management cost.

Our results provide compelling evidence for long-term benefits and suggest that this approach appears to be effective in diminishing side effects and the economic burden of warfarin interruption management. However, some study limitations are worth noting. First, there is the relaying on literature clinical trials for probability data, instead of local data, which may limit the local relevance. However, evidence about the

event probabilities as effects of interruption days in warfarin pre-procedural management, including with the genotype-guided, among the local Qatari population is lacking, whereby relying on international, relevant clinical trials is justified and is best practice in health economics, pending evidence of robustness via sensitivity analyses. Also a limitation is that the current study depended on the BRIDGE trial findings,[26] where recruited patients have low-intermediate risk of thrombosis, which may limit generalizability to setting of high-risk patients. Here, however, the model inputs in the model at its base case were analyzed based on assigned uncertainty analysis, which accounted for potential variability in model probability inputs that may result from less-than-ideal generalizability of patient characteristics in the BRIDGE trial to the Qatari setting. Another limitation is that the main difference between carriers and non-carriers of genetic variants in the required number of interruption days was calculated based on a retrospectively validated equation. To account for this, nevertheless, we introduced a one-way uncertainty to the calculated relative reduction in the number of days with the non-carriers of genetic variants compared to carriers of the variants, where the robustness of model outcomes was confirmed.

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

## Conclusion

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

## Acknowledgments

None

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2022.101128.

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