Bridging vs Non-Bridging with Warfarin Peri-Procedural Management: Cost and Cost-Effectiveness Analyses

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Abstract: The warfarin peri-procedural management in Qatar is predominantly based on bridging (63%), compared to non-bridging. This study sought to perform a first-time cost analysis of current warfarin peri-procedural management practices, including a cost-effectiveness analysis (CEA) of predominant bridging vs predominant non-bridging practices. From the hospital perspective, a one-year decision-analytic model followed the cost and success consequences of the peri-procedural warfarin in a hypothetical cohort of 10,000 atrial fibrillation patients. Success was defined as survival with no adverse events. Outcome measures were the cost and success consequences of the 63% bridging (vs not-bridging) practice in the study setting, ie, Hamad Medical Corporation, Qatar, and the incremental cost-effectiveness ratio (ICER, cost/success) of the warfarin therapy

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when predominantly bridging based vs when predominantly non-bridging based. The model was based on Monte Carlo simulation, and sensitivity analyses were performed to confirm the robustness of the study conclusions. As per 63% bridging practices, the mean overall cost of peri-procedural warfarin management per patient was USD 3,260 (QAR 11,900), associated with an overall success rate of 0.752. Based on the CEA, predominant bridging was dominant (lower cost, higher effect) over the predominant non-bridging practice in 62.2% of simulated cases, with a cost-saving of up to USD 2,001 (QAR 7,303) at an average of USD 272 (QAR 993) and was cost-effective in 36.9% of cases. Being between cost-saving and cost-effective, compared to predominant non-bridging practices, the predominant use of bridging with warfarin seems to be a favorable strategy in atrial fibrillation patients. (Curr Probl Cardiol 2021;46:100839.)

Introduction

Oral anticoagulants (OAC) have been indicated for decades in the prevention and treatment of thromboembolism.[1,2] Warfarin represents 70% of OAC in Qatar.[3] Stroke prevention in patients with atrial fibrillation (AF) is among the most prevalent indications for warfarin in Qatar and worldwide.[4-8] Annually, it has been anticipated that 10%-15% of OAC patients need to undergo OAC interruption for an elective procedure.[9] Clinicians were wrestled for years with the dilemma of how to manage patients receiving warfarin during a therapeutic pause period before elective surgery procedures. In some instances, warfarin may be interrupted, where anticoagulation with short-term parenteral therapy, using either low molecular weight heparin (LMWH) or intravenous unfractionated heparin (UFH), may be initiated to reduce the risk of thrombosis. Such a clinical scenario is termed “bridging”.[3] Ideally, for a patient receiving warfarin, the interruption starts 3-4 days before the procedure if the International Normalization Ratio (INR) is subtherapeutic (1.5-1.9), 5 days before the procedure if the INR is normal (2-3), and 7 days (or more) before the procedure if the INR is supratherapeutic.[9] Here, a therapeutic dose of either LMWH or UFH should be started 1-3 days following the last dose of warfarin, and the INR is remeasured 24 hours before the procedure.[10]

There is, however, considerable uncertainty regarding the potential therapeutic benefits of parenteral anticoagulant bridging vs the putative bleeding risks. Siegal et al.[11] performed a meta-analysis comprising 7,118 bridged and 5,160 non-bridged patients receiving vitamin-K antagonist therapies. The authors did not find any difference in the incidence of thromboembolic events between both arms. In contrast, the risk of overall and major bleeding was considerably higher in heparin-bridged patients when compared to their non-bridged counterparts. The recent Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) randomized control trial (RCT)[12] has partially clarified and emphasized an association between heparin bridging and increased bleeding risks in patients receiving warfarin. A recent follow-up multiple logistic regression analysis of the BRIDGE trial showed that baseline bridge therapy is a significant predictor of major bleeding.[13]

Significant limitations undermine the benefit of bridging. Bridging anticoagulation raises the risk of hemorrhagic complications, which may surpass the detriment from ischemic stroke, minimizing the overall rate of successful warfarin therapy.[14] Important, estimates of net clinical benefit do not contain costs of care. Even if bridging presents an advantage to wisely selected patients, the benefit may not worth the monetary spending and achieve cost-effectiveness. There are no evaluations of the economic value of bridging in the literature.

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

Materials and Methods

This economic analysis was based on a one-year decision-analytic model of cost and effect consequences with peri-procedural warfarin. Clinical model inputs were primarily based on the BRIDGE trial,[12] an international, multicenter trial, and the only large study to investigate the bridging vs non-bridging strategies in AF patients during warfarin peri-procedural management.

Study Perspective

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

Model Structure

A conventional type of decision-analytic model was used to follow up a hypothetical cohort of AF patients on warfarin as they are undergoing an elective procedure. The model follows up the outcomes of patients based on whether they undergo the bridging vs a non-bridging peri-procedural strategy of management. Bridging vs non-bridging refers to whether heparin (LMWH/UFH) was initiated during warfarin interruption in the peri-procedural management. In HMC, bridging is to start heparin (LMWH/UFH) when warfarin is interrupted for 3-5 days, with a patient INR of < 2. Under either strategy, patients can be in one of four health states of adverse events (AEs): no adverse event (AE), bleeding, thromboembolism (TE), and all-cause death. Bleeding can be major bleeding, divided into extracranial hemorrhage (ECH) and intracranial hemorrhage (ICH), or minor bleeding, including ecchymosis, epistaxis, hematoma, and hematuria. TE can be arterial TE (ATE) or venous TE (VTE). The model's structure of patient pathways is illustrated in Figure 1, and detailed follow-up consequences, and the literature references are clarified in Appendix 1. The duration of the model follow up was one year, and a case of success in the current study was defined as survival with no AEs.

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

Clinical Inputs

All model clinical event rates were retrieved from the published literature. The BRIDGE trial,[12] was the primary source of the reported clinical events in the model. The BRIDGE trial is the only source that reports relative event probabilities for bridging vs non-bridging and is robust, including a relatively large population (n=1,804) of AF during warfarin peri-procedural management, reporting the clinical outcomes of a one-month observation period. Notably, the peri-procedural use of warfarin and the bridging practices in the study were consistent with those in the clinical practice at HMC, including in terms of the average number of discontinuation days (3-5 days), the average number of heparin dosing days (3 days before procedure [6 doses], and 3 days after the procedure [6 doses]), and the stroke risk score of the AF patients with a mean CHA_2DS_2-Vasc score of 4 as reported in an ongoing local trial in HMC by the same current author group (HMC study protocol 16415/16). Obtained from the BRIDGE trial,[12] for each of the bridging and non-

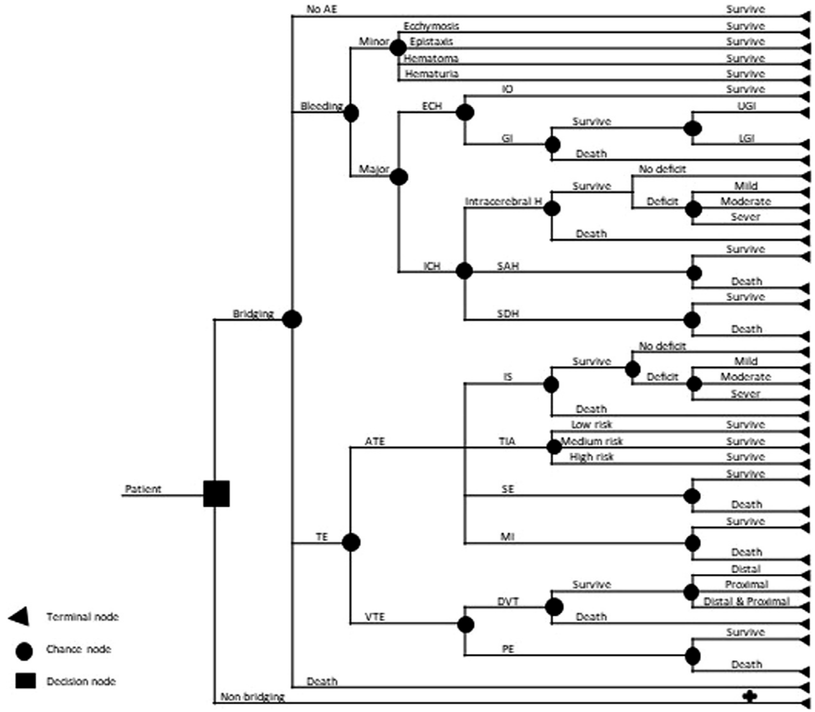

FIG 1. Decision-analytic model. *Death; non-hemorrhagic or non-vascular death. AE; adverse event, AF; arterial fibrillation, ATE; arterial thromboembolism, DVT; deep vein thrombosis, ECH; extracranial hemorrhage, GI; gastrointestinal, ICH; intracranial hemorrhage, IO; intra-ocular, IS; ischemic stroke, MI; myocardial infarction, PE; pulmonary embolism, SAH; subarachnoid hemorrhage, SDH; subdural hemorrhage, SE; systemic embolism, TE; thromboembolism, TIA; transient ischemic attack, VTE; venous thromboembolism.

bridging model pathways, are the probabilities for all main clinical events in the model, which were the no-AE outcome, total bleeding, major and minor bleedings, TE, ATE, ischemic stroke, transient ischemic attack, systemic embolism, myocardial infarction, VTE, and all-cause (but non-hemorrhagic/vascular) death. Probabilities of further sub-consequences for the outcomes extracted from the BRIDGE trial[12] but were not available in the BRIDGE trial itself, were extracted from other available relevant meta-analysis and comparative clinical studies in the literature that were similar concerning the underlying AF patients, age of patients, the stroke risk score, and the follow-up time for when outcomes were reported. These sub-consequences are minor bleeding sub-types, intra-ocular bleeding, gastrointestinal (GI) hemorrhage, intracerebral hemorrhage, subarachnoid hemorrhage (SAH) subdural hemorrhage (SDH). Except for ECH and ICH, these sub-consequences were assumed to not differ based on whether patients received bridging or not. Probabilities for ECH and ICH with bridging were available from a study by Hackett et al.,[15] where the duration of heparin administration was an average of 3 days, matching the bridging as in the BRIDGE trial and the HMC practices. The probabilities of ECH and ICH with the non-bridging arm were obtained from the warfarin arm in the RE-LY trial,[16] in which the INR level was at sub-therapeutic range when starting warfarin. The model clinical events, their definitions, and sources of data are all summarized in Appendix 2. All reported clinical event rates, from all sources, were consistently reported until one month after warfarin interruption or heparin initiation.

As per local HMC practices, the occurrence probability of bridging vs non-bridging in HMC was obtained from a study by Eljilany et al.,[17] where the average percentage of bridging among practitioners managing warfarin peri-procedurally in HMC was reported to be 63%.

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

Input values and their probabilities in the multivariate analysis of the model are summarized in Appendix 3.

Cost Calculations

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

The patient who interrupts warfarin for any procedural management needs to have the INR checked two times before the procedure and two times after it, noting the need for an out-patient visit with INR test. When there is bridging, a daily dose of 160 mg/day (80 mg BID) of heparin was assumed, based on an average weight of 80 Kg as suggested by the study's expert panel for weight-dependent dose calculations. The standard period of bridging is three days before and after the procedure: twelve doses of heparin per patient. Based on the BRIDGE trial[12] and the ongoing local study by the same group of authors in HMC (HMC study protocol 16415/16), 30% of surgeries are considered major and require pre-operative admission if with bridging, and 70% of the patients perform minor surgeries that require four out-patient clinic visits, regardless of bridging.

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

Outcome Measures

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

Sensitivity Analysis

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

For the economic and success impact of bridging practices in HMC, a one-way sensitivity analysis was conducted via introducing uncertainty to the mean 63% probability of occurrence of bridging practices; where, based on the study by Eljilany et al. in HMC,[17] an uncertainty range of 51%-75% was used for bridging occurrence, with a uniform type of sampling distribution.

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

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

Results

Cost Analysis

Based on the 63% occurrence of bridging (vs non-bridging) in HMC, the overall success rate with warfarin peri-procedural management was 0.752 (95% Cl 0.751, 0.753), with the probability of a success rate illustrated in Figure 2. The mean overall cost per patient was USD 3,260 (95% Cl 3,250, 3,270) [QAR 11,900 (95% Cl 11,862, 11,935)] with the probability of the average cost per patient as presented in Figure 3. The

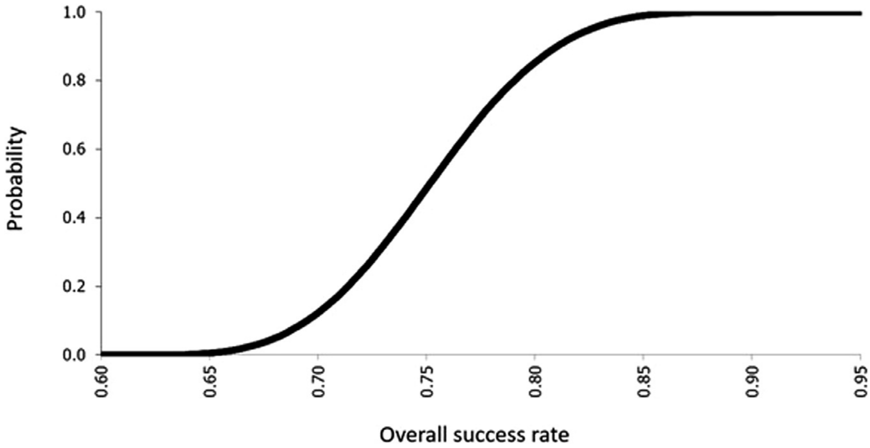

FIG 2. Base-case total success probability curve.

average cost-effectiveness ratio (ACER) of warfarin interruption per case success was USD 4,335 (95% Cl 4,320, 4,350 [QAR 15,822 (95%Cl 15,768, 15,877)], with the probability of which as can be seen in Appendix 4. Details of relative success and total costs between bridging and non-bridging are summarized in Table 1. In the one-year study model, clinical outcome pathways, their costs, and the calculation of the overall costs of peri-procedural warfarin can be seen in Table 2.

At the base case, as per a regression tornado analysis of the strength (size) of the impact of the model clinical outcomes on the overall cost, the TE rate in non-bridging patients is the most influential, followed by

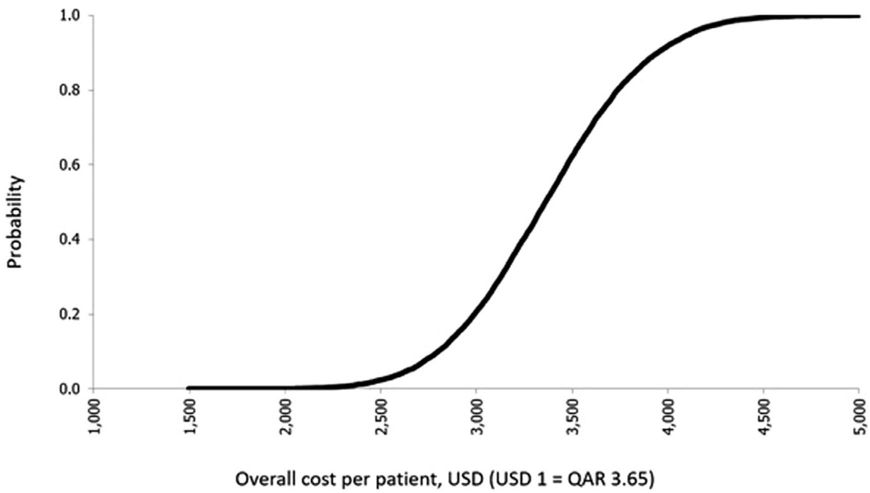

FIG 3. Base-case total cost probability curve. USD; United State Dollar

TABLE 1. Expected cost and effectiveness in base-case analysis

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

ACER; average cost-effectiveness ratio, CI; confidence interval, USD; United States Dollar (1 USD = 3.65 QAR)
ACER: total cost/total effectiveness, total effectiveness = effectiveness of bridging + effectiveness of non-bridging, total cost = cost of bridging + cost of non-bridging

the transient ischemic attack rate in non-bridging patients, and then by total bleeding in bridging patients. The rank of the main model outcomes as per the size of their relationship with the overall cost of warfarin per patient is presented in Appendix 5.

Event Cost Per Admission Category

Out of the overall cost of peri-procedural warfarin per patient, the overall cost of clinical events, excluding the no AE state, as associated with warfarin therapy was USD 1,558 (QAR 5,686) (47.8 %) per patient. Out of which, per patient, USD 1,099 (QAR 4,011) (53.9 %) was associated with bridging vs USD 459 (QAR 1,675) (37.5 %) with non-bridging. The relative contribution of the different admission categories towards the overall events cost per patient is summarized in Appendix 6. A case of no AE costs 46.1 % of the total management cost with bridging, and 62.5 % of the total management cost with the non-bridging approach. The AE that costs the most is MI (13.1 %), followed by ecchymosis (11.9 %) and GI hemorrhage (4.1 %). Unweighted events costs and the details of the contributing admission cost categories are in Appendix 7.

Cost Per Resource Category

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

Table 2. Clinical outcomes and their costs at the base-case of the one-year decision model

Strategy	Outcome event			Cost (USD) of outcome	Proportional cost (USD) of outcome	Average cost (USD) per outcome category	Total average cost (USD) of the strategy	Total average cost (USD) of the base-case
Bridging	No AE			2,031.63	938.1	938	2,037	3,260
	Bleeding	Minor bleeding	Ecchymosis	3,350.7	279.1	689		
			Epistaxis	2,829.8	85.2			
			Hematoma	3,179.2	30.4			
			Hematuria	4,557.7	44.6			
			IO bleeding	2,622.6	6.0			
		GI bleeding	UGI bleeding	7,261.8	48.4			
			LGI bleeding	7,235.8	48.9			
			Death	7,235.8	9.2			
		Intracerebral hemorrhage	No deficit	12,335.3	7.4			
			Mild deficit	24,022.4	6.3			
			Moderate deficit	36,033.4	18.9			
			Severe deficit	58,553.9	22.8			
			Death	58,553.9	25.9			
		SAH	Survive	41,921	2.1			
			Death	41,921	6.4			
		SDH	Survive	45,747.9	36.3			
			Death	45,747.9	11.7			
	TE	IS	No deficit	29,435	28.9	404		
			Mild deficit	40,643.3	7.2			
			Moderate deficit	52,676.1	15.6			
			Severe deficit	75,237.8	10.3			
			Death	75,237.8	11.5			
		TIA	Low risk TIA	6,788	0			
			Medium risk TIA	7,319.9	0			
			High risk TIA	7,851.8	0			
		SE	Survive	19,138.1	0			
			Death	19,138.1	0			
		MI	Survive	32,174	314.6			
			Death	32,174	0			
		DVT	Distal DVT	9,492	2.0			
			Proximal DVT	9,492	2.0			

(*continued on next page*)

Table 2. (*continued*)

Strategy	Outcome event			Cost (USD) of outcome	Proportional cost (USD) of outcome	Average cost (USD) per outcome category	Total average cost (USD) of the strategy	Total average cost (USD) of the base-case
			Death / Distal and proximal DVT	9,492	2.03 / 0.03			
		PE	Survive	16,183.4	9.0			
			Death	16,183.4	1.0			
	Death*			2,031.6	5.7	5.7		
Non-bridging	No AE			1,939.7	764.2	764	1,223	
	Bleeding	Minor bleeding	Ecchymosis	3,258.8	112.4	292		
			Epistaxis	2,737.9	34.3			
			Hematoma	3,087.3	12.4			
			Hematuria	4,465.8	17.9			
			IO bleeding	2,530.7	39.6			
		GI bleeding	UGI bleeding	7,169.9	13.3			
			LGI bleeding	7,143.9	13.4			
			Death	7,143.9	2.5			
		Intracerebral hemorrhage	No deficit	12,243.4	2.8			
			Mild deficit	23,930.5	2.4			
			Moderate deficit	35,941.5	6.8			
			Severe deficit	58,462	8.3			
			Death	58,462	9.5			
		SAH	Survive	41,829.1	0.8			
			Death	41,829.1	2.4			
		SDH	Survive	45,656	5.5			
			Death	45,656	5.5			
	TE	IS	No deficit	29,343.1	14.2	164		
			Mild deficit	40,551.4	5.3			
			Moderate deficit	52,584.2	11.4			
			Severe deficit	75,145.9	7.5			
			Death	75,145.9	5.5			
		TIA	Low risk TIA	6,696.1	2.4			
			Medium risk TIA	7,228	5.4			
			High risk TIA	7,759.9	0.95			
		SE	Survive	19,046.2	0			
			Death	19,046.2	0			

(*continued on next page*)

Table 2. (*continued*)

Strategy	Outcome event			Cost (USD) of outcome	Proportional cost (USD) of outcome	Average cost (USD) per outcome category	Total average cost (USD) of the strategy	Total average cost (USD) of the base-case
		MI	Survive	32,082.1	79.9			
			Death	32,082.1	31.3			
		DVT	Distal DVT	9,400.1	0			
			Proximal DVT	9,400.1	0			
			Distal and proximal DVT	9,400.1	0			
			Death	9,400.14	0			
		PE	Survive	16,091.5	0			
			Death	16,091.5	0			
	Death*			1,939.7	2.9	2.9		

Proportional cost = cost of outcome pathway × probability of outcome pathway (Online Resource 3).
*Death; non-hemorrhagic or non-vascular death.AE; adverse event, AF; arterial fibrillation, ATE; arterial thromboembolism, DVT; deep vein thrombosis, GI; gastrointestinal, IO; intra-ocular, IS; ischemic stroke, MI; myocardial infarction, PE; pulmonary embolism, SAH; subarachnoid hemorrhage, SDH; subdural hemorrhage, SE; systemic embolism, TE; thromboembolism, TIA; transient ischemic attack, VTE; venous thromboembolism, USD; United State Dollar, 1 USD = 3.65 QAR).

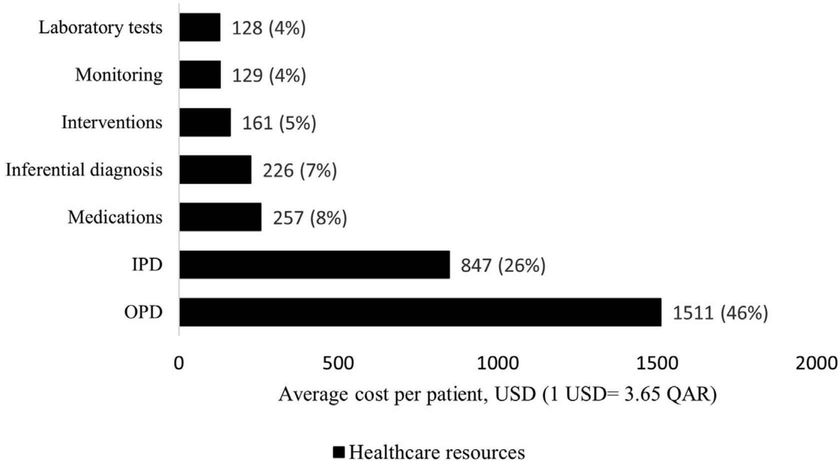

FIG 4. Healthcare resources towards the mean cost per patient of warfarin peri-procedural management. The average cost per patient per health care resources used, IPD; in-patient department, OPD; out-patient department, USD; United State Dollar.

contribution of the different resource categories towards the overall cost of therapy is summarized in Figure 4.

Cost-Effectiveness of Predominant Bridging vs Predominant Non-Bridging

The mean difference in success between 63% bridging and 37% bridging was 14.3 % in favor of the predominant bridging, 0.447 (95% Cl 0.446, 0.448) vs 0.304 (95% Cl 0.303, 0.305). Taking cost into consideration, the predominant bridging approach was dominant over the predominant non-bridging approach in 62.2 % of simulated cases, with an average cost-saving of USD 272 (QAR 993), with up to a maximum cost saving of USD 2,001 (QAR 7,300) and was cost-effective in 36.9 % of cases. Figure 5 presents the probability curve of the cost-saving with the predominant bridging. The regression tornado ranking of model outcomes as per the size of their impact indicated that the rate of TE is the most influential, followed by hemorrhage and then the no AE. The tornado analysis of the regression coefficient can be seen in Appendix 8.

Sensitivity Analysis

One-Way Sensitivity Analysis. The base-case success and cost associated with warfarin were not sensitive to an uncertainty range of 51%-

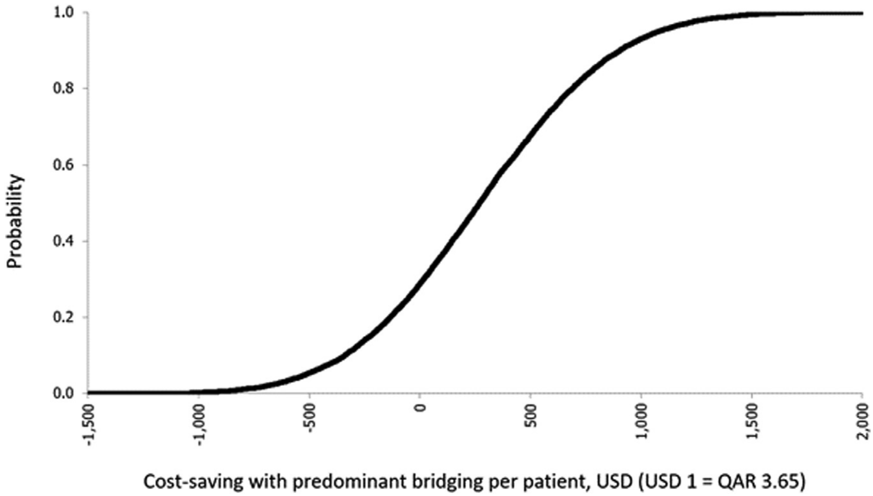

FIG 5. Cost-saving probability curve with bridging. USD; United State Dollar.

75% when assigned to the occurrence of bridging in HMC. Based on the one-way sensitivity analysis, the resulting mean success was 0.753 (95% Cl 0.752, 0.754), and the mean cost was USD 3,256 (95% Cl 3,240, 3,270) (QAR 11,884 [95% Cl 11,826, 11,935]). The probabilities of the success and overall cost based on one-way sensitivity analysis are in Appendix 9.

Probabilistic Sensitivity Analysis. Adding the event cost uncertainty to the base-case probability uncertainty had no impact on the model outcomes. Event costs and their uncertainty ranges are presented in Appendix 10. The outcomes of the sensitivity analysis, as compared to the base-case analysis, are summarized in Table 3 for total success, total cost, and ICER results. Based on the regression tornado analyses, the rank of outcomes as per their impact on the outcome, as well as the size of the impact, were identical to that at the base case, with no impact of the proposed uncertainty in cost on base-case outcomes. This applied to both the overall cost in the cost-analysis (Appendix 5) and the cost-saving result of the cost-effectiveness analysis (Appendix 8).

Discussion

This is the most comprehensive follow-up evaluation of the bridging vs non-bridging with peri-operative warfarin management in the

TABLE 3. Multivariate sensitivity analyses and the subsequent changes in model outcomes

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

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

literature, including the majority of the possible consequences. As discussed above, the BRIDGE trial is the only RCT in the literature that compared bridging vs non-bridging with peri-operative warfarin,[12] but this did not include some outcomes like; minor bleeding sub-types, IO bleeding, GI hemorrhage, intracerebral hemorrhage, SAH and SDH. Most importantly, this study is also the first literature analysis of the economic consequences of bridging vs non-bridging, which is most important in guiding decision making. The predominant use of bridging in HMC is not based on local guidelines and is influenced by practitioners' experiences and personal opinions. For example, a recent local study that evaluated warfarin peri-procedural management in HMC reported that exaggerated warfarin discontinuation in procedures, such as cataract and dental surgery, was justified by the practitioners' fear of bleeding events. This is when, according to the guidelines,[17] such procedures do not require warfarin interruption.

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

Literature studies reported a significant increase in bleeding events with bridging,[6,11,12,16] while for the TE events, these were reported to not significantly differ between bridging and non-bridging.[12] The superiority of predominant bridging over predominant non-bridging in the current study, therefore, is in contrast to suggestions in the literature to decrease the use of bridging during warfarin peri-procedural management, mainly due to the elevated risk of bleeding from heparin usage.[18] Here, however, a non-significant clinical benefit does not necessarily correlate to little economic benefit. Because the TE rate, while non-significant, is higher with the predominant non-bridging than bridging, the reduced cost of TE with predominant bridging was considerably higher, by 25%, than with non-bridging that it overtook the increased cost of bleeding with bridging, as seen in Table 2, to an overall cost saving in favor of bridging. Besides, while 30% of patients with major procedures will require costly hospital admission with bridging, 70% of the current model's performed procedures were minor as already indicated and, hence, did not add to the hospital admission in the predominant bridging study arm. The result that 63% bridging was mostly between cost-saving to cost-effective against 63% non-bridging was not sensitive to a 20% uncertainty in the event costs in the model.

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

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

There is no official approved WTP in Qatar. Guiding decision in such cases, the WHO suggested that the value of the threshold in a country can be within 1-3 times the gross domestic product (GDP) per capita in the country.[19] This proposed range, however, is arbitrary and not based on any methodological justification.[19] Besides, the average 2019 GDP per capita in Qatar was approximately USD 64,781,[20] one of the world's highest. Thus, adopting the WHO recommendations for calculating the WTP will result in a range of too wide values to be directly useful, ie, USD 64,781-194,343. The current analysis adapted a threshold value of USD 150,000, an increasingly accepted higher threshold value in the literature[21] and, importantly, is also within the range suggested by the WHO for Qatar.

The main limitation of this study is that the model was populated with literature sources instead of local patient data. Literature studies are mostly of Caucasian populations as an example. Also, the BRIDGE trial,[12] the primary source of data, which recruited patients with low-intermediate risk of thrombosis (mean CHA_2DS_2 was 2.5), with most patients having CHA_2DS_2 score of <3, may produce results that may not mirror results in high-risk patients. Nevertheless, the literature sources are of top quality. They are relevant to the HMC practices regarding the underlying AF disease and patient age, the warfarin and heparin use, and the stroke risk score. The utilized literature sources are the best sources of evidence available for this study. Noteworthy, the occurrence probability of bridging was locally based. In addition, the base-case study was based on multivariate uncertainty assigned to the study inputs obtained from the literature. This is added to additional levels of sensitivity analyses that were performed, where further uncertainty was introduced to the model, with all confirming the robustness of results against realistic input variability.

Results in the current study do not imply that bridging should be universally used with peri-procedure warfarin. It is recommended that practitioners follow the recent clinical guidelines, which suggest warfarin continuation in minor and low bleeding risk surgeries, to decrease the economic burden of warfarin peri-procedural management. In patients who require to interrupt warfarin; however, with their assessment results regarding favorability of bridging established, warfarin bridging will be more cost-effective than non-bridging.

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

Ethics Approval

Ethical approval was obtained from the Institutional Review Board (IRB) of HMC (Protocol# MRC-16415/16) and Qatar University (QU-IRB 1296-FBA/20).

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Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2021.100839.

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