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Short- and long-term cost-effectiveness analysis of CYP2C19 genotype-guided therapy, universal clopidogrel, versus universal ticagrelor in post-percutaneous coronary intervention patients in Qatar

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ABSTRACT

Background: Patients having *CYP2C19* loss-of-function alleles and receiving clopidogrel are at higher risk of adverse cardiovascular outcomes. Ticagrelor is an effective antiplatelet that is unaffected by the *CYP2C19* polymorphism. The main aim of the current research is to evaluate the cost-effectiveness among *CYP2C19* genotype-guided therapy, universal ticagrelor, and universal clopidogrel after a percutaneous coronary intervention (PCI).

Methods: A two-part decision-analytic model, including a one-year model and a 20-year follow-up Markov model, was created to follow the use of (i) universal clopidogrel, (ii) universal ticagrelor, and (iii) genotype-guided antiplatelet therapy. Outcome measures were the incremental cost-effectiveness ratio (ICER, cost/success) and incremental cost-utility ratio (ICUR, cost/quality-adjusted life years [QALY]). Therapy success was defined as survival without myocardial infarction, stroke, cardiovascular death, stent thrombosis, and no therapy discontinuation because of adverse events, i.e. major bleeding and dyspnea. The model was based on a multivariate analysis, and a sensitivity analysis confirmed the robustness of the model outcomes, including against variations in drug acquisition costs.

Results: Against universal clopidogrel, genotype-guided therapy was cost-effective over the one-year duration (ICER, USD 6102 /success), and dominant over the long-term. Genotype-guided therapy was dominant against universal ticagrelor over the one-year duration, and cost-effective over the long term (ICUR, USD 1383 /QALY). Universal clopidogrel was dominant over ticagrelor for the short term, and cost-effective over the long-term (ICUR, USD 10,616 /QALY).

Conclusion: CYP2C19 genotype-guided therapy appears to be the preferred antiplatelet strategy, followed by universal clopidogrel, and then universal ticagrelor for post-PCI patients in Qatar.

1. Introduction

Dual antiplatelet therapy (DAPT), through the use of a P2Y12 inhibitor, i.e. ticagrelor, prasugrel, or clopidogrel, along with aspirin, is the mainstay secondary prevention treatment of acute coronary syndrome (ACS), particularly in patients undergoing percutaneous coronary intervention (PCI) [1]. Clopidogrel is a prodrug that requires hepatic activation by cytochrome P450 (CYP), primarily CYP2C19 [2,3]. The *2 and *3 alleles are among the most common genetic variants, as reported in various populations, that are associated with CYP2C19 loss of enzymatic function [4]. Studies have shown that patients who are having *CYP2C19* loss-of-function (LOF) alleles are at higher risk of major adverse cardiovascular events (MACE), i.e. myocardial infarction (MI), stroke, and cardiovascular death, mostly explained by the impairment in the formation of clopidogrel active metabolites in *CYP2C19* LOF allele carriers [5–7].

On the other hand, ticagrelor is relatively a newer oral antiplatelet. Compared to clopidogrel, ticagrelor has a higher efficacy in reducing the composite outcome of MACE, as well as stent thrombosis, but at the expense of having a higher risk of major bleeding and dyspnea [8]. Since ticagrelor does not require biotransformation to an active form, it is not affected by *CYP2C19* polymorphism and has less interpatient variability [9,10].

Personalization of antiplatelet therapy in post-PCI patients can be achieved by conducting genetic testing for *CYP2C19*, which can help guide the selection between ticagrelor and clopidogrel [4,11,12].

At Hamad Medical Corporation (HMC), the main public healthcare provider in Qatar, incorporating 12 secondary and tertiary hospitals,

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the two available P2Y12 inhibitors are clopidogrel and ticagrelor, with both being available for first-line use. Although various literature studies examined the cost-effectiveness of *CYP2C19* genotype-guided therapy; whereby, a paradigm shift from 'one-size-fits-all' treatment to personalized antiplatelet use was generally supported [13–17], several gaps were identified. None of the reported economic models in the literature comprehensively included all relevant clinical outcomes. Additionally, there are conflicting reports on the economic usefulness of *CYP2C19* genotype-guided therapy against universal ticagrelor [13–17]. In an Australian based study, for example, *CYP2C19* genotype-guided therapy was not cost-effective [16]. Moreover, the prevalence of the *CYP2C19* LOF alleles varies according to the local populations, where no study included Middle Eastern patients. Furthermore, none of the studies assessed the short-term versus long-term cost-effectiveness outcomes among the different comparative therapeutic strategies. Consequently, the current study sought to comprehensively assess the utilization cost of *CYP2C19* genotype-guided antiplatelet therapy, universal use of clopidogrel, and ticagrelor against their outcomes as first-line therapies in patients with ACS who underwent PCI in Qatar.

2. Materials and methods

This is a pharmacoeconomics analysis that is based on a two-component decision-analytic model; a short-term one-year model of cost-effectiveness analysis (CEA), followed by a long-term Markov model of cost-utility analysis (CUA). Clinical model inputs were mainly extracted from published substudies of the Platelet Inhibition and Patient Outcomes (PLATO) trial, which is the largest, international, multicenter trial that directly compared the efficacy and safety of ticagrelor and clopidogrel. Results of the substudies of the PLATO were reported in relation to planned invasive strategies, genetic polymorphisms, bleeding complications, and characterization of dyspnea [8,18–21]. In addition to the PLATO trial, meta-analyses were utilized, primarily including a recent study by Fan et al. that pool analyzed six randomized controlled trials (RCTs) and five observational studies that had head-to-head comparisons of ticagrelor and clopidogrel after a PCI in patients with ACS [22].

2.1. Study perspective

The economic modeling was performed from a hospital perspective (i.e. HMC).

2.2. One-year CEA model structure

A one-year decision-analytic model was created to follow up on the outcomes of three antiplatelet strategies for a hypothetical cohort of post-PCI patients with ACS, as demonstrated in Fig. 1A. These strategies were: (i) universal administration of clopidogrel 75 mg oral tablet once daily to all patients; (ii) universal administration of ticagrelor 90 mg oral tablet twice daily to all patients; and (iii) 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. For all treatment strategies, patients received DAPT over a 12-month duration. In the genotype-guided arm, the LOF allele was considered regardless of whether patients were intermediate metabolizers, i.e. intermediate enzyme activity such as *1/*2, *1/*3, *2/*17, or poor metabolizers, i.e. reduced or deficient enzyme activity such as *2/*2, *2/*3, *3/*3.

Patients were exclusively differentiated into a 'success' or a 'failure' outcome health state. Success was defined as survival with no event (i.e. without MI, stroke, cardiovascular death, or stent thrombosis), with/without ADRs (no premature discontinuation due to ADRs); i.e. MI, stroke, cardiovascular death, and stent thrombosis were successfully prevented. 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; i.e. MI, stroke, cardiovascular death, or stent thrombosis were not prevented, or the medication was prematurely discontinued. Since only 1.5% of the patients included in the PLATO trial had multiple cardiovascular events [8], it was assumed that during the one year, patients could not have 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-coronary artery bypass grafting (CABG) Thrombolysis in Myocardial Infarction (TIMI) related to major bleeding [23]. Discontinuation was defined as premature discontinuation of therapy because of ADRs after which patients stopped DAPT and continued on aspirin monotherapy lifelong.

2.3. Long-term Markov model structure

By the end of the short-term follow up, patients were distributed among four terminal states, i.e. 'no event', 'post MI', 'post stroke', and 'death', before being redistributed among six mutually exclusive health states throughout the Markov component of the model. The six Markov health states are 'no event', 'non-fatal MI', 'non-fatal stroke', 'post MI', 'post stroke', and 'death'. The possible long-term Markov model transitions among health states are illustrated in Fig. 1B. Annual Markov cycles were applied, and the model was run for 20 years.

Key assumptions in the Markov model structure were that, first, there was no treatment effect after the one-year short-term model as ticagrelor and clopidogrel were both stopped, and patients continued on aspirin monotherapy only [24]. Second, ADRs (i.e. major bleeding and dyspnea) are not explicitly modeled in the Markov model structure because ADRs are not prognostic in terms of long-term effects (beyond the one-year model follow up) on survival, quality of life, and costs [24]. Finally, it was assumed that patients, who had stent thrombosis by the end of the one-year non-Markov model, only made transition to the 'no event' and 'dead' states in the Markov follow-up.

2.4. Clinical and utility model input

Data on the event rates of MI, stroke, cardiovascular death, stent thrombosis, major bleeding, and dyspnea for universal ticagrelor and clopidogrel are available in the PLATO invasive substudy [19]. A meta-analysis by Fan et al. provided more recent data about the events. This however was only of the odds ratio with ticagrelor over clopidogrel [22]. Hence, while the universal clopidogrel event rates were obtained from the PLATO invasive substudy, the comparative event rates of universal ticagrelor were calculated based on the relative performance as was reported by the Fan et al. study [19,22]. With a similar trend, the event rate of dyspnea was obtained, based on the PLATO invasive substudy and a more recent meta-analysis by Wang et al. [19,25]. The discontinuation due to major bleeding and dyspnea was obtained from the PLATO bleeding and dyspnea substudies, respectively [18,20]. The probability for the 'no event without ADRs' was the probability of success minus the probability of 'no event with major bleeding' plus 'no event with dyspnea.'

The probabilities of the clinical outcomes in the genotype-guided therapy arm were obtained from the PLATO genetic substudy [21]. The probabilities of dyspnea and premature discontinuation due to ADRs were assumed to not differ among the universal and genotype-guided antiplatelet therapies because genetic testing does not affect the outcomes of drugs once given [26,27]. Additionally, it was assumed that the probabilities of ADR distribution, including dyspnea and major bleeding, were identical in all patients with or without events. The local prevalence of *CYP2C19* LOF alleles in Qatar was obtained from Ali et al. based on a recent study in the same patients [28].

Patient utility data was required for the long-term Markov cost-utility analysis. As locally based utility values were not available, the utility data in the PLATO health economic substudy was utilized [24].

To account for real-life interactions among different concurrent inherent uncertainties in key input data, the analysis of clinical and utility input values in the study's two-component model was based on a multivariate analysis, using Monte Carlo simulation via @Risk-7.6® (Palisade Corporation, NY, US). Based on 10,000 iterations, a multivariate sensitivity analysis that included variations in all clinical probabilities, utility values, and mutation probability. This was based on 95% CI uncertainty range and a trigen type of distribution for the probabilities. For the utility values, where CI was not available, ±10% variation with a triangular distribution was used. Trigen and Triangular distributions were, therefore, respectively used as relevant.

The calculations of the transition probabilities for the health states in the Markov model were based on the PLATO health economic substudy, in which the probability of death is multiplied by a constant value that represents the 'hazard ratio over standard mortality' (Appendix 1) [24,29].

Input values and their probabilities, including *CYP2C19* LOF alleles prevalence, in the multivariate analysis of the model are summarized in Table 1. The transition matrix for the Markov model is shown in Table 2.

2.5. Cost calculations

Given the study perspective, only the costs of direct medical resources in patient management were taken into consideration. Resources and how they are used were based on published clinical practice guidelines, adapted to the local perspective according to the available clinical guidelines at HMC [30–34]. The cost per patient in the different model pathways (health states) was calculated as the initial therapy cost added to the cost of hospitalization, resources consumed for monitoring, and screening tests throughout the duration therapy, including follow up.

All unit costs of resources were initially obtained in Qatari Riyal (QAR) based on the 2019/20 financial year, and then converted to United States Dollar (USD) for result presentation, USD 1 = QAR 3.65. The unit cost of resources that were included in the model and their sources are presented in Appendix 2.

2.6. Outcomes measures

The trade-off between the comparative costs and outcomes of study interventions in modeling was presented via the incremental cost-effectiveness ratio (ICER) per case of success, and the incremental cost-utility ratio (ICUR) per quality-adjusted life year (QALY). Both of the cumulative long-term cost and QALY sums in the Markov model were discounted at 3.5% annually [35]. When dominance (i.e. lower cost and higher effectiveness) is reported in favor of an intervention over another, the relative cost saving was reported. The willingness-to-pay threshold (WTP), against which cost-effectiveness is judged, is not formally available in Qatar. Consistent with literature and the World Health Organization (WHO), however, an estimated value of USD 150,000 was used [36–38].

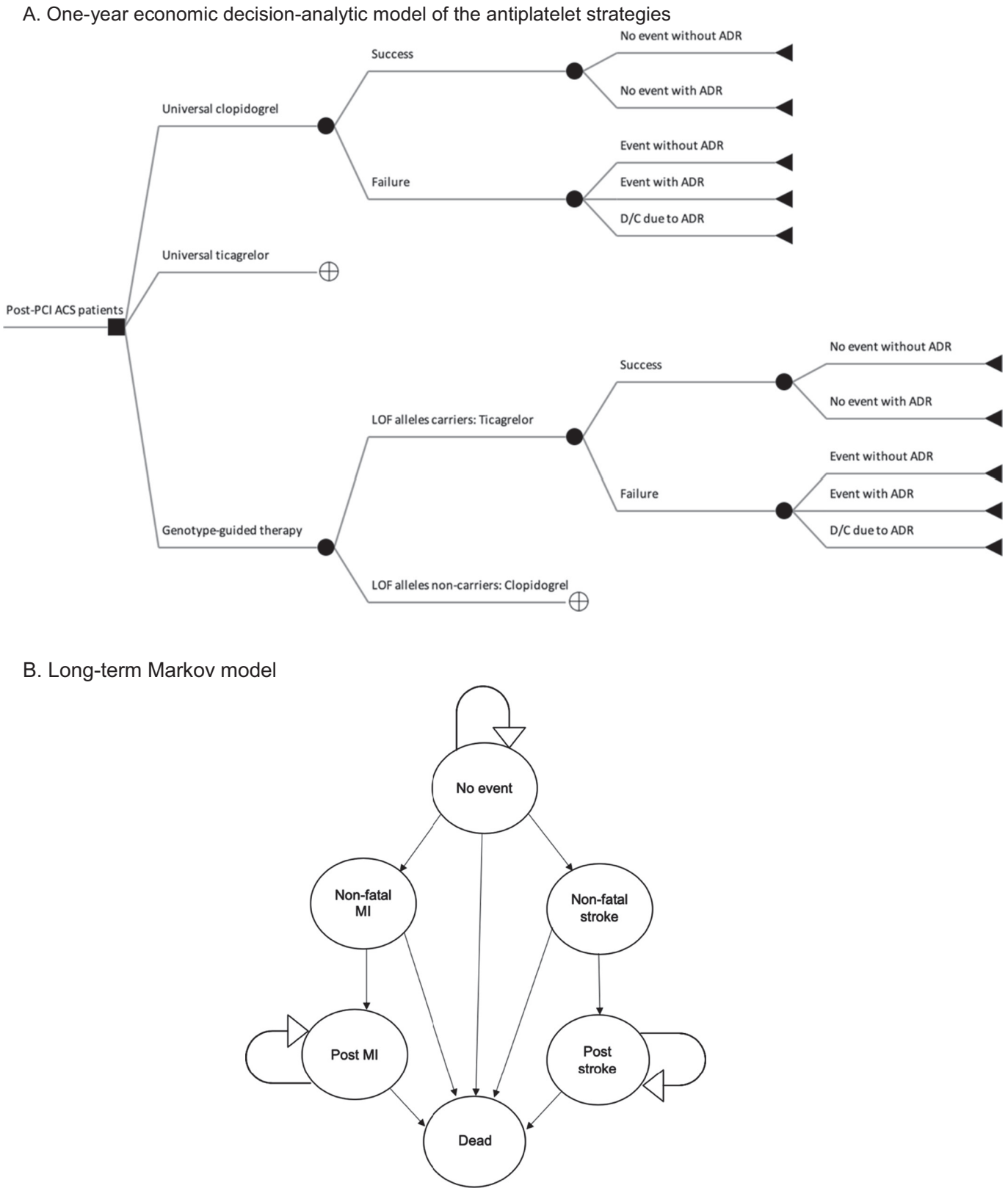

Fig. 1. Decision-analytic models of the antiplatelet strategies: A. One-year economic decision-analytic model of the antiplatelet strategies, and B. Long-term Markov model. ⊕ Follow up model pathways are as above. *ACS* acute coronary syndrome, *ADR* adverse drug reaction, *D/C* discontinuation, *LOF* loss-of-function, *PCI* percutaneous coronary intervention, *MI* myocardial infarction.

2.7. Sensitivity analyses

Accounting for variability in acquisition costs with the availability of cheaper generics, a one-way sensitivity analysis was conducted for the costs of antiplatelets acquisition; whereby, increasing the generalizability of results, a broad uncertainty range of 0–150% was used, with a uniform type of distribution. Multivariate sensitivity analysis was performed by assigning uncertainty to the proportion of patients with stroke performing diagnostic radiation tests, the proportion of hospitalized patients with stroke in the

Table 1
Input variables and uncertainty distributions used in the multivariate analysis of the models.

Parameter	Uncertainty distribution (trigen/triangular[a] distribution)		Reference
Clinical probabilities for universal antiplatelets in short-term model	**Ticagrelor**	**Clopidogrel**	
Success			
o No event without ADR	0.741, 0.831, 0.897	0.753, 0.835, 0.905	
o No event with major bleeding	0.675, 0.774, 0.848	0.799, 0.878, 0.936	
o No event with dyspnea	0.016, 0.046, 0.112	0.006, 0.026, 0.085	[19,22]
Failure	0.110, 0.180, 0.269	0.049, 0.096, 0.176	[19,25]
• Event without adverse drug reaction	0.102, 0.169, 0.258	0.102, 0.165, 0.258	
o MI without ADR	0.579, 0.683, 0.769	0.719, 0.812, 0.881	[19,22]
o Stroke without ADR	0.398, 0.497, 0.601	0.379, 0.475, 0.582	[19,22]
o Cardiovascular death without ADR	0.035, 0.084, 0.151	0.028, 0.072, 0.138	[19,22]
o Stent thrombosis without ADR	0.203, 0.291, 0.389	0.221, 0.309, 0.410	[19,22]
• Event with adverse drug reaction	0.071, 0.128, 0.212	0.078, 0.144, 0.223	
o MI with major bleeding	0.071, 0.128, 0.212	0.042, 0.086, 0.164	[19,22]
o MI with dyspnea	0.049, 0.101, 0.176	0.049, 0.102, 0.176	[19,25]
o Stroke with major bleeding	0.303, 0.397, 0.502	0.275, 0.372, 0.472	[19,22]
o Stroke with dyspnea	0.002, 0.017, 0.070	0.002, 0.016, 0.070	[19,25]
o Cardiovascular death with major bleeding	0.028, 0.067, 0.138	0.022, 0.056, 0.126	[19,22]
o Cardiovascular death with dyspnea	0.022, 0.059, 0.126	0.028, 0.067, 0.138	[19,25]
o Stent thrombosis with major bleeding	0.151, 0.232, 0.324	0.160, 0.243, 0.335	[19,22]
o Stent thrombosis with dyspnea	0.006, 0.026, 0.085	0.006, 0.031, 0.085	[19,25]
• Discontinuation due to ADR	0.049, 0.102, 0.176	0.056, 0.113, 0.188	
o Discontinuation due to major bleeding	0.118, 0.189, 0.280	0.028, 0.073, 0.138	[18]
o Discontinuation due to dyspnea	0.168, 0.250, 0.346	0.102, 0.167, 0.258	[20]
Clinical probabilities for genotype-guided therapy in short-term model	0.653, 0.750, 0.831	0.741, 0.833, 0.897	
Success			
o No event without ADR	0.764, 0.850, 0.913	0.788, 0.867, 0.928	
o No event with major bleeding	0.686, 0.776, 0.856	0.788, 0.867, 0.928	
o No event with dyspnea	0.016, 0.048, 0.112	0.011, 0.036, 0.099	[21]
Failure	0.110, 0.176, 0.269	0.042, 0.092, 0.164	[19,21]
• Event without adverse drug reaction	0.086, 0.150, 0.235	0.071, 0.133, 0.212	
o MI without ADR	0.558, 0.661, 0.751	0.730, 0.819, 0.889	
o Stroke without ADR	0.340, 0.444, 0.542	0.369, 0.471, 0.572	[19,21]
o Cardiovascular death without ADR	0.049, 0.096, 0.176	0.035, 0.079, 0.151	[19,21]
o Stent thrombosis without ADR	0.212, 0.299, 0.399	0.221, 0.312, 0.410	[19,21]
• Event with adverse drug reaction	0.094, 0.162, 0.246	0.078, 0.138, 0.223	[21]
o MI with major bleeding	0.071, 0.126, 0.212	0.042, 0.091, 0.164	
o MI with dyspnea	0.049, 0.095, 0.176	0.071, 0.132, 0.212	[19,21]
o Stroke with major bleeding	0.257, 0.348, 0.451	0.248, 0.340, 0.441	[19,21,25]
o Stroke with dyspnea	0.002, 0.021, 0.070	0.002, 0.022, 0.070	[19,21]
o Cardiovascular death with major bleeding	0.035, 0.075, 0.151	0.022, 0.057, 0.126	[19,21,25]
o Cardiovascular death with dyspnea	0.022, 0.064, 0.126	0.042, 0.087, 0.164	[19,21]
o Stent thrombosis with major bleeding	0.160, 0.235, 0.335	0.151, 0.225, 0.324	[19,21,25]
o Stent thrombosis with dyspnea	0.011, 0.035, 0.099	0.011, 0.038, 0.099	[19,21]
• Discontinuation due to ADR	0.071, 0.127, 0.212	0.049, 0.099, 0.176	[19,21,25]
o Discontinuation due to major bleeding	0.134, 0.214, 0.302	0.042, 0.090, 0.164	
o Discontinuation due to dyspnea	0.168, 0.250, 0.346	0.102, 0.167, 0.258	[18]
• **Utility values in Markov model**	0.653, 0.750, 0.831	0.741, 0.833, 0.897	[20]
o No event	0.7875, 0.875, 0.963		[24]
o Non-fatal MI	0.7308, 0.812, 0.893		
o Post MI	0.7308, 0.812, 0.893		
o Non-fatal stroke	0.6633, 0.737, 0.811		
o Post stroke	0.6633, 0.737, 0.811		
o Death	0, 0, 0.1		
• **Probability for death in Qatar that was used to calculate the transition probabilities for Markov model**	0.0261, 0.0263, 0.0265		[29]
• **Prevalence of *CYP2C19* genetic polymorphism in Qatar**[b]			[28]
o *CYP2C19* *2 and *3 carriers	0.148, 0.201, 0.262		
o *CYP2C19* *2 and *3 non-carriers	0.737, 0.799, 0.851		

ADR adverse drug reaction, *MI* myocardial infarction.
[a] Trigen distribution was used for all values except for utility values where triangular distribution was used.
[b] The minor allele frequencies for *CYP2C19* *2 and *3 were 0.18 and 0.02, respectively.

intensive care unit versus general medical ward, and the proportion of patients with stroke receiving solitaire stent. These inputs, which were utilized in the cost calculation of resource use, were particularly of interest because they were obtained from internal unpublished reports and, hence, were associated with a relative high uncertainty. No confidence interval (CI) was available and, hence, overestimated ±30% was used for uncertainty range, with triangular distribution. Both one-way and multivariate sensitive analyses were performed by Monte Carlo simulation via @Risk-7.6® (Palisade Corporation, NY, US) with 10,000 iterations.

3. Results

Based on the one-year non-Markov model, clinical outcomes, their costs, and the overall costs of treatment strategies are summarized in Appendix 3. Based on the Markov model, the discounted cumulative cost and QALY with each antiplatelet strategy are as in Appendix 4.

Table 2
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.
Markov health states are: No event (Included patients who did not experience MI, stroke, and cardiovascular death in the one-year non-Markov follow-up, regardless of the ADR status); Non-fatal MI (Included patients who had a new non-fatal MI after the first year of non-Markov follow up, regardless of the ADR status); Non-fatal stroke (Included patients who had a new non-fatal stroke after the first year of non-Markov follow up, regardless of the ADR status); Post MI (Included patients who had a non-fatal MI in a preceding year during the non-Markov and Markov follow-ups); Post stroke (Included patients who had a non-fatal stroke in a preceding year during the non-Markov and Markov follow-ups); Death (Included patients who had an all-cause mortality event).

The ICER and ICUR among all antiplatelets strategies are summarized in Table 3.

3.1. Genotype-guided therapy versus universal ticagrelor

In the one-year non-Markovian model, 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. Genotype-guided therapy was dominant over universal ticagrelor in 60% of cases with a mean cost-saving of USD 415 (95% CI: 409–420), and it was cost-effective in 35% of the cases with an ICER of up to USD 72,072 per case of success. The tornado analysis of the rank of different study outcomes as per their influence on the study conclusion demonstrated that the top influencing model outcome is the probability of *CYP2C19* LOF alleles non-carriers.

In the Markov model, 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. Genotype-guided therapy was cost-effective in 96% of cases compared to universal ticagrelor, with a mean ICUR of USD 1383 per QALY. The top influencing outcome on the study result is the probability of *CYP2C19* LOF alleles non-carriers.

Probability curves of success, cost, and QALY as well as the tornado analyses for genotype-guided therapy versus universal ticagrelor are in Appendix 5.

3.2. Genotype-guided therapy versus universal clopidogrel

In the one-year non-Markovian model, 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. Genotype-guided therapy was cost-effective over universal clopidogrel in 85% of cases, with a mean ICER of USD 6102 per case of success, and it was dominant in 15% of the cases. The outcome that influenced the model result the most is the probability of *CYP2C19* LOF alleles non-carriers.

In the Markov model, 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. Genotype-guided therapy was dominant compared to universal clopidogrel with a mean cost-saving of USD 498 (95% CI: 420–574). Genotype-guided therapy was between dominant and cost-effective in 100%. The top influencing outcome on the model's result is the utility value of the no event health state.

Probability curves of success, cost, and QALY as well as the tornado analyses for genotype-guided therapy versus universal clopidogrel are in Appendix 6.

3.3. Universal clopidogrel versus universal ticagrelor

In the one-year non-Markovian model, 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. Universal clopidogrel was dominant over universal ticagrelor with the mean cost-saving of USD 587 (95% CI: 585–588). This dominance was achieved in 63% of cases, and universal clopidogrel was cost-effective in 30% of the cases with an ICER of up to USD 132,976 per case of success. The model's outcome was affected the most by the probability of no event without ADRs.

In the Markov model, the mean difference in the cumulative QALYs was 0.52 (95% CI: 0.493–0.547) in favor of universal clopidogrel. Universal clopidogrel was cost-effective compared to universal ticagrelor. The cost-effectiveness of universal clopidogrel was achieved in 99% of cases, with a mean ICUR of USD 10,616 per case of success. The outcome that influenced the result of the model the most is the probability of no event without ADRs.

Probability curves of success, cost, and QALY as well as the tornado analyses for universal ticagrelor versus universal clopidogrel are in Appendix 7.

3.4. Sensitivity analyses

3.4.1. One-way sensitivity analyses

The model outcomes are robust, whereby, the superiority of an antiplatelet strategy versus another was not sensitive to any uncertainty that was associated with the acquisition costs of ticagrelor and clopidogrel. What changed was only the probability of a treatment strategy being dominant versus cost-effective. Acquisition costs, uncertainty distributions, and the outcomes of the one-sensitivity analysis are in Appendix 8.

Table 3
Results of the multivariate analyses among antiplatelet strategies.

	One-year model			*Markov model*		
Strategy	Cost (USD)	Effectiveness (Success)	ICER	Cost (USD)	Effectiveness (QALYs)	ICUR
Genotype-guided therapy compared to universal ticagrelor						
Universal ticagrelor	3197	0.8309	Negative value	36,047	4.76	1383 per QALY
Genotype-guided therapy	2783	0.8629		36,199	4.87	
Genotype-guided therapy compared to universal clopidogrel						
Universal clopidogrel	2611	0.8348	6102 per case of success	36,684	4.82	Negative value
Genotype-guided therapy	2783	0.8629		36,199	4.87	
Universal clopidogrel compared to universal ticagrelor						
Universal clopidogrel	2611	0.8348	Negative value	36,684	4.82	10,616 per QALY
Universal ticagrelor	3197	0.8309		36,047	4.76	

ICER incremental cost-effectiveness ratio, *ICUR* incremental cost-utility ratio, *QALY* quality-adjusted life year, *USD* United States Dollar.

3.4.2. Multivariate sensitivity analyses

The model outcomes are robust, where the advantage of a treatment strategy over another remained robust against the multivariate uncertainty in the sensitivity analysis, with only the probability of a treatment strategy being dominant versus cost-effective changing. Model inputs, their uncertainty distributions, and the outcomes of the multivariate sensitivity analysis are in Appendix 9.

4. Discussion

The current study is the first economic evaluation in the Middle East and North African region to compare *CYP2C19* genotype-guided antiplatelet therapy, universal clopidogrel, and ticagrelor post-PCI in patients with ACS. The study findings showed that genotype-guided therapy was between dominant and cost-effective compared to universal ticagrelor and clopidogrel over the one-year duration and the long-term follow up. Whereas universal clopidogrel was between dominant and cost-effective compared to universal ticagrelor over the one-year model and the long term.

The decision-analytic model is more comprehensive than other relevant models reported in the literature [39]. The model depicts all the possible consequences of using DAPT and, hence, an overall cost of resource utilization is more accurately measured [39]. It is also the first study that evaluates discontinuation due to ADR as a clinical outcome of DAPT use. While all studies in the literature evaluated the long-term cost-utility outcomes of the genotype-guided therapy [13–17], the current comparative model is the first model to report the short-term cost-effectiveness outcome of therapies. This is important as the DAPT is not a lifelong therapy and evidence of an abrupt performance from the clinical perspective will only enable better guidance in the decision-making process. In addition to the PLATO substudies, which most prior economic evaluations in the literature relied upon [13,14,16,17], the current study was also the only simulation model that extracted data from recent comprehensive meta-analyses, including that by Fan et al. [22,25]. Further, this is the first simulation model that was based on a multivariate uncertainty analysis of input data, using the Monte Carlo simulation. This was considered a more real-life and accurate representation of results, particularly at their case base, unlike in the relevant literature [13–17], where performing the multivariate analysis of input uncertainties was only part of the sensitivity analyses in models. Furthermore, the current analysis is the first to utilize the micro-costing approach, which is a most accurate estimation of resource use and economic impact.

Results from the literature that investigated the cost-effectiveness of genotype-guided therapy compared to universal ticagrelor were conflicting. Wang et al. reported the dominance of the genotype-guided therapy [17], which can be explained by the high prevalence of *CYP2C19* LOF carriers (51.8%) in the Chinese population [17]. Contrary to our results, Sorich et al. and Crespin et al. showed that universal ticagrelor was cost-effective compared to genotype-guided therapy [13,16], which can be explained by the differences in the included outcomes in the models; whereby, Sorich et al. evaluated MI, stroke, and death, and Crespin et al. evaluated MI, bleeding, dyspnea and death. In our current analysis, however, we performed a more comprehensive decision-analytic modeling that better reflects all anticipated relevant outcomes in real-life practices. It is noteworthy to indicate that costs can immensely vary between healthcare systems, given how different resources are utilized, which might also be a leading cause behind the conflicting findings. Furthermore, Sorich et al. and Crespin et al. utilized WTP thresholds that are at the lower end of the range of what is universally considered acceptable (USD 20,475–34,125 and USD 50,000, respectively), which may explain the cost-effectiveness of universal ticagrelor [13,16]. 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 [15–17,40–43].

With regards to the comparison between the two universal strategies, 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 [17]. Although literature evidence supports the superiority of ticagrelor over clopidogrel in reducing MACE and stent thrombosis in patients with ACS [8,22], ticagrelor is associated with a statistically significant higher risk of major bleeding, dyspnea, and discontinuation due to ADRs [8,18,20]. None of the above economic studies incorporated all these adverse events in the decision-analytic models used, while our study did. For this reason, clopidogrel demonstrated a greater clinical and humanistic and, hence, overall economic benefit relative to ticagrelor in the current analysis.

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. This is expected as, while the health state 'no event without ADR' was associated with low cost (i.e. USD 218), it had the highest probability in the one-year model. Similarly, the probability of *CYP2C19* LOF allele carriers over non-carriers was 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 addition to the 'utility score' of the 'no event' health 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.

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 [37]. This proposed range, however, is arbitrary and not based on any methodological justification [36]. In addition, the average 2019 GDP per capita in Qatar was approximately USD 64,781 [44]; one of the world's highest. Thus, adopting the WHO recommendations for calculating the WTP will result in a range of values that is too large to be directly implemented, i.e. USD 64,781–194,343. The current analysis adapted a threshold value of USD 150,000, an increasingly accepted higher threshold value in the literature [38] and, importantly, is also within the range suggested by the WHO for Qatar.

Notwithstanding the fact that generic ticagrelor is going to be commercially available in the market in the future, genotype-guided antiplatelet therapy cannot be expected to be less economically attractive due to several reasons. First, it has been suggested that the cost of genetic testing will decrease in the future, similar to the cost of generic ticagrelor as it will be part of the routine clinical practice [45,46]. Second, the high risk of ticagrelor to cause major bleeding and dyspnea will further add to its secondary cost, regardless of its patency status. Third, and most importantly, is that we accounted for the significant decrease in the acquisition cost of ticagrelor via the one-way sensitivity analysis and the study conclusion did not change.

The limitation of the current study is that the model was based on simulated data from literature sources rather than local patient cases or medical records. However, the literature sources used are of top quality and, importantly, are relevant to the local setting; whereby, the regimens of study medications in the meta-analyses and the PLATO substudies are identical to those in the HMC for the treatment of ACS patients after PCI. Likewise, the baseline characteristics of the patients in the PLATO substudies and meta-analyses are all comparable to those in the local HMC setting. Nevertheless, it must be acknowledged that the majority of the population in the PLATO trial was Caucasian, which is generally different from the local Qatari population, despite the latter being mostly of expats. Given the lack of local data, however, the utilized literature sources are the best sources of evidence that are available. Importantly, the prevalence of *CYP2C19* LOF alleles was locally specific and based in Qatar. In addition, the model analysis, including

at base case, was conducted based on an uncertainty analysis; whereby, the outcome probabilities that are obtained from literature were associated with respective uncertainty ranges for analysis, confirming the robustness of the literature data and increasing its generalizability. Although utility values can vary across different settings, it is highly associated with the socioeconomic status of the country [47,48]. Here, our utility data was obtained from an international and multicenter study that is done mostly in industrialized countries [24], which have a comparable quality of life to the Qatari setting; being one the richest countries in the world with the highest gross domestic income per capita [44].

In conclusion, based on the study perspective and assumptions, and regardless of the acquisition costs of clopidogrel and ticagrelor, *CYP2C19* genotype-guided therapy remained at least a cost-effective antiplatelet strategy compared to either universal use of clopidogrel or ticagrelor over the short-term and long-term evaluations, and the universal clopidogrel was dominant and cost-effective compared to universal ticagrelor in the short-term and long-term analyses, respectively.

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Author Contribution Statement

Al-Badriyeh D conceived the study design. Al-Badriyeh D and Almukdad S performed data collection, data analysis, and interpreted results. Almukdad S wrote the first manuscript draft. Elewa H and Arafa S contributed to data collection and result interpretation. All authors reviewed the manuscript drafts critically, and read and approved the final manuscript.

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.01.044.

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