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Original Article

Cost-Effectiveness Comparison between Ticagrelor and Clopidogrel in Acute Coronary Syndrome in Iran

Amir Hashemi-Meshkini, PhD[1], Amirmohammad Tajik, PharmD[2], Nayyereh Ayati, PhD[1], Shekoufeh Nikfar, PhD[1,3], Reza Koochak, PharmD[4], Saeed Yaghoubifard, PhD[1], Azam Abbasi, MA[5], Mehdi Varmaghani, PhD[6*]

[1]*Department of Pharmacoeconomics and Pharmaceutical Administration, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.*
[2]*School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.*
[3]*Evidence-Based Evaluation of Cost-Effectiveness and Clinical Outcomes Group, Pharmaceutical Sciences Research Center (PSRC), and the Pharmaceutical Management and Economics Research Center (PMERC), the Institute of Pharmaceutical Sciences (TIPS), Tehran University of Medical Sciences, Tehran, Iran.*
[4]*Promethean BioPharma Limited, Sydney, Australia.*
[5]*Department of Management Sciences and Health Economics, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran.*
[6]*Social Determinants of Health Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.*

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Abstract

Background: *The present study aimed to determine the cost-effectiveness of ticagrelor compared with clopidogrel in Iranian patients with acute coronary syndrome (ACS).*

Methods: *A 1-year decision tree model combined with a 20-year Markov transition model was used to simulate the long-term cost and effectiveness of both ticagrelor and clopidogrel in Iran based on an Iranian payer's perspective. Clinical efficacy data were extracted from the PLATO trial and other published studies. Costs were estimated based on local prices in public sectors. Deterministic and probabilistic sensitivity analyses were used to test the robustness of base-case results over the uncertainties of model inputs. All calculations, analyses, and modeling were done in TreeAge 2011 and Microsoft Excel 2013.*

Results: *Compared with clopidogrel, the treatment of Iranian ACS patients with ticagrelor for 20 years resulted in an additional cost of US$ 2.39 in a hypothetical cohort of 1000 patients. However, ticagrelor led to 7.2 quality-adjusted life-years (QALYs) gained per 1000 hypothetical patients. Accordingly, the estimated incremental cost-effectiveness ratio for this analysis was US$ 332.032 per 1 QALY gained.*

Conclusion: *Ticagrelor was a cost-effective antiplatelet medicine compared with clopidogrel in Iranian patients with ACS. This could help Iran's policymakers to allocate resources more efficiently to ACS.*

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Keywords: *Acute coronary syndrome; Ticagrelor; Clopidogrel; Cost-effectiveness analysis*

[*]**Corresponding Author:** ***Mehdi Varmaghani,*** *Associate Professor of Pharmacoeconomics and Pharmaceutical Administration, Department of Health Economics and Management, School of Health, Social Determinants of Health Research Center, Basic Sciences Research Institute, Mashhad University of Medical Sciences, Shahid Fakouri Blvd, Mashhad, Iran. 91778-99191. Tel: +98 51 38049. Fax: +98 51 38713638. E-mail: VarmaghaniM@mums.ac.ir.*

Introduction

Acute coronary syndrome (ACS) refers to acute myocardial ischemia or injury from coronary plaque rupture, thrombosis, or stenosis progression. It includes ST-elevation myocardial infarction (STEMI), non–ST-elevation myocardial infarction (NSTEMI), and unstable angina, distinguished by the underlying pathophysiology, severity of symptoms, release of biomarkers, and therapeutic approaches.[1] ACS is a significant cause of mortality, morbidity, and loss of disability-adjusted life years (DALYs), especially in low and middle-income countries due to recent economic growth and lifestyle transformation.[2-4] According to the American Heart Association, 1 MI attack per 44 seconds occurs in the United States. Within 1 year after the first attack, 18.0% of men and 23.0% of women older than 40 lose their life.[5,6] The average age of disease onset in the United States is 68 years, and 30.0% of patients are elderly. Generally, ACS is more prevalent among men, with a men-to-women ratio of 3:2.[7]

The average age of patients with ACS in Iran is 55.1 years, with men accounting for almost two-thirds of the cases.[8] Cardiovascular diseases comprise 46.0% of all deaths and between 20.0% and 23.0% of the disease burden.[9] According to a local study in Iran, the economic burden of cardiovascular diseases in Iran was 6700 billion Iranian rials, primarily due to expensive therapeutic procedures, hospitalization, and productivity loss.[10] Although we found no published data for Iran, ACS is responsible for US$ 6194±315.00 healthcare expenditures and US$ 5266 productivity losses per patient annually in the United States.[11]

Over the past decades, ACS management has dramatically improved treatment and prevention. Significant work has been done to enhance ACS survival and lower bleeding events.[10,12] Antiplatelet therapy constitutes the cornerstone of ACS management.[6,13] Clopidogrel is a P2Y12 platelet receptor antagonist widely used for a long time, either as monotherapy or in combination with aspirin.[14-16] Nonetheless, its use has limitations: higher risk of ischemic vascular complications[17,18] and hypo-responsiveness to its therapeutic effects in some patients.[19-21] Ticagrelor is a newer and United States Food and Drug Administration (FDA)-approved option from this class. Clinical evidence reported by the European Medicines Agency indicates that ticagrelor is a more effective treatment than clopidogrel. International guidelines have also adopted ticagrelor for the secondary prevention of ACS.[23,24] Nevertheless, the daily cost of treatment is higher with ticagrelor than with clopidogrel. Economic evaluation studies are performed to determine whether the added benefit outweighs the added cost. Indeed, many investigations have compared the cost-effectiveness between ticagrelor and clopidogrel in different countries,[25-27] yet transferability concerns around the cost-effectiveness analysis limit such evaluations to assist decisions in the Iran context.[28] Accordingly, the present study aimed to determine the cost-effectiveness of ticagrelor in comparison with clopidogrel in Iranian patients with ACS.

Methods

The current study consists of a 2-part model. First, a 1-year decision tree model was employed to estimate relevant costs and efficacy outcomes in each treatment strategy for the first year when patients received either clopidogrel or ticagrelor. In the second part, a Markov model in Microsoft Excel 2013 and TreeAge 2011 was utilized to simulate a cohort of 1000 ACS patients at an average age of 62 years and extrapolate long-term health and cost outcomes. Clinical efficacy and safety data were extracted from international evidence due to the need for local data. Still, the present study drew upon local costs based on official tariffs in public sectors.

The characteristics of our hypothetical cohort were assumed to be the same as patients with ACS in the PLATO trial with or without ST-segment elevation or unstable angina. The mean age of the patients in the PLATO study was 62 years, and 25.0% were women. These characteristics were comparable with Iranian patients with ACS, whose mean age was 60.5 years and 62.9 years in the NSTEMI and STEMI groups, respectively. Additionally, 27.0% of the patients were female according to the registry data of Iran heart hospitals.[29]

Patients with ACS could receive ticagrelor (180.0 mg as the loading dose and 90.0 mg BID afterward) or clopidogrel (300 mg as the loading dose in the medical approach or 600 mg in candidates for percutaneous coronary intervention, followed by 75 mg once daily). Both medicines were assumed to be used only for 1 year.

In this decision tree model, at the end of the 1-year treatment, patients with ACS could develop into 1 of 4 health states: “no event”, “post-MI”, “post-stroke”, and “death”, (Figure 1 A).

The results of the PLATO trial were used to extract the clinical efficacy and safety data of ticagrelor and clopidogrel in patients with ACS, given that it was a head-to-head design.[30]

A Markov model (Figure 1 B) was applied to simulate the long-term medical and cost consequences of each treatment for the remaining years of life. This model encompassed 6 states: “no event”, “nonfatal MI”, “nonfatal stroke”, “post-MI”, “post-stroke”, and “death”. Therefore, hypothetical patients falling into each of the 4 states of the 1-year decision tree model were transferred to the first cycle of the Markov model. The processes of the Markov model lasted for 1 year, and the model’s time horizon was 20.0 years. Since it was assumed that patients received either clopidogrel or ticagrelor only in the first year, the probabilities of transition

in the Markov model were identical in both groups.[31] The determinant factor was, thus, the distribution of patients in each state after 1 year of the decision tree model (the input of the Markov model). The same approach has been adopted by other cost-effectiveness studies.[32-37] In the case of mortality in the Markov model, the 2019 life table of Iran was used to develop an age-dependent mortality risk adjusted by the hazard ratio (HR) of death in each of the states of "no event", "nonfatal MI", "nonfatal stroke", "post-MI", and "post-stroke".[37] More details pertaining to the probabilities of the decision tree and Markov models are provided in Table 1.

The current study included only direct medical costs based on the payer's perspective. For the estimation of the cost incurred by each treatment strategy, the local cost of procedures and care for each event was included in the analysis. Since the prices of pharmaceutical products are almost the same in all centers in Iran, they were extracted from the Iran FDA's list of pharmaceutical costs. Medical tariffs of the public sector were used based on patient discharge documents collected from 5 general hospitals after they were double-checked with the latest officially published tariff list. According to these data, the cost per care package was estimated for the different model states (Table 1). An annual discount rate of 7.2% was considered to include the value of time preferences in costs.

The results of the analysis were reported based on the incremental cost-effectiveness ratio (ICER). The effectiveness measurement was according to quality-adjusted life-years (QALYs), and the costs were calculated

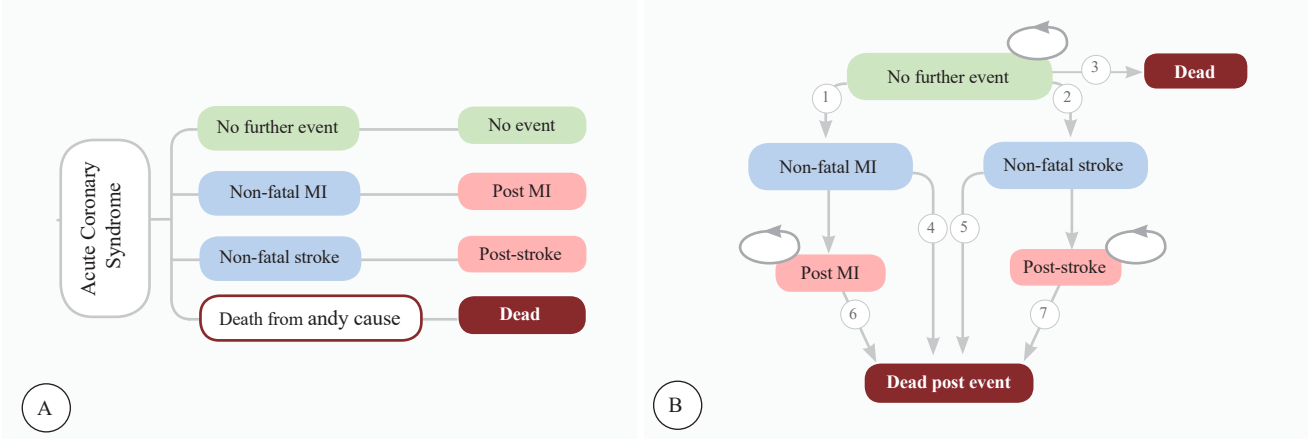

Figure 1. The image depicts the decision tree model (A) and the Markov model (B) for patients with acute coronary syndrome.
MI, Myocardial infarction

Table1. Utilities, transition probabilities, and RR to adjusted mortality

Parameter	Clopidogrel	Ticagrelor	Reference
Utility			37
No event	0.8763	0.8732	
MI	0.8136	0.8106	
Stroke	0.7379	0.7349	
Death	0.2503	0.2473	
No event	0.8763	0.8732	
No event	0.8763	0.8732	
MI	0.8136	0.8106	
Stroke	0.7379	0.7349	
Death	0.2503	0.2473	
Transitional Probabilities Used in the 1-Year Decision Tree Model and the Long-term Markov Model			31
Health state	Clopidogrel	Ticagrelor	
No event	0.875	0.895	
MI	0.058	0.050	
Stroke	0.009	0.010	
Death	0.059	0.046	
RR to Adjusted Mortality			37
RR of death in nonfatal MI	5.84	NA	
RR of death in nonfatal stroke	7.43	NA	
RR of death post-stroke	2.07	NA	
RR of death post-MI	2.21	NA	

NA, Not available; RR, Relative risk; MI, Myocardial infarction

in 2022 US dollars (exchange rate: US$ 1=249 359 Iranian rials). For the assessment of the cost-effectiveness of healthcare interventions in Iran, a cost-effectiveness analysis threshold of US$ 1604 was used based on the latest announced acceptable cost-effectiveness analysis threshold by the Health Technology Assessment Committee of the Iran FDA.

The impact of the uncertainties of the model inputs on the final results of the study was addressed using deterministic and probabilistic sensitivity analyses. For the deterministic sensitivity analysis, ±5% variations in some necessary information (eg, the average cost of MI care, average cost of stroke care, prices of ticagrelor and clopidogrel, and probability of MI, stroke, and death in the first year) were assigned. For the probabilistic sensitivity analysis, a Monte Carlo simulation was employed with 5000 iterations to produce a scatter plot and acceptability curve.

Results

Compared with clopidogrel, ticagrelor raised the treatment cost of our hypothetical cohort of 1000 patients with ACS by only US$ 2.39 within 20 years of simulation (US$ 2.39 per patient). On the other hand, ticagrelor gained 7.2 QALYs (0.0072 QALYs per patient). Accordingly, the estimated ICER for this analysis was US$ 332.032 per QALY gained, which means that ticagrelor is very cost-effective in Iran. The results of the cost-effectiveness model in the base-case analysis with different time horizons are provided in Table 2.

The results of the probabilistic sensitivity analysis showed

Table 2. Costs of health states-lifetime in the Markov model

Medical Cost Item	Average Cost*	Medical Cost Item	Average Cost*
Medicines Costs		Post-MI	
Clopidogrel	0.47	Hospitalizations	207.2
Ticagrelor	0.67	Examinations	13.8
Disease costs per cycle		Imaging modalities	6.6
No Event		Stroke	
Hospitalizations	89.7	Hospitalizations	461.2
Examinations	4	Examinations	24.40
Imaging modalities	2.9	Imaging modalities	11.7
MI		Post-stroke	
Hospitalizations	496.1	Hospitalizations	169.3
Examinations	45.3	Examinations	14.2
Imaging modalities	28.6	Imaging modalities	7.8

MI, Myocardial infarction

Table 3. Model parameters used in the probabilistic sensitivity analysis

Parameter	Base-Case Value	Range		Distribution	Reference
Utility					37
No event	0.8763	a= 28004.078	b= 5254.922	Beta	
MI	0.8136	a= 1341.11861	b= 5254.922	Beta	
Stroke	0.7379	a= 1467.80073	b= 620.10927	Beta	
Post-MI	0.821	a= 83.55494391	b= 18.21721676	Beta	
Post-stroke	0.703	a= 101,64825	b= 42.94385526	Beta	
Cost					Direct Medical Cost
No event					
Hospitalizations	89.7	SD: 18.3		Gamma	
MI					
Hospitalizations	496.1	SD: 113.1		Gamma	
Post-MI					
Hospitalizations	207.2	SD: 80.8		Gamma	
Stroke					
Hospitalizations	461.2	SD: 236.1		Gamma	
Post-stroke					
Hospitalizations	169.3	SD: 15.1		Gamma	

NA, Not available; RR, Relative risk; MI, Myocardial infarction

Table 4. Results of the cost-effectiveness study in different time-horizon scenarios

Time Horizon	Strategy	Cost per Patient	Incremental Cost	QALY per Patient	Incremental Effectiveness	ICER
1 year	Ticagrelor	135.5	10.29	0. 7338	0.0134	762.556
	Clopidogrel	145.8		0. 7203		
5 years	Ticagrelor	101.7	7.72	0.6481	0.0119	647.168
	Clopidogrel	109.4		0.6361		
10 years	Ticagrelor	70.9	5.32	0.5532	0.0101	522.937
	Clopidogrel	76.2		0.5430		
20 years (base case)	Ticagrelor	33.1	2.39	0.3904	0.0072	332.032
	Clopidogrel	35.5		0.3832		

QALY, Quality-adjusted life-year; ICER, Incremental cost-effectiveness ratio

that ticagrelor was cost-effective, with an acceptable threshold of US$ 1604 (Figure 2) (Table3).

Most simulated ICERs indicated QALYs gained and incremental costs by ticagrelor compared with clopidogrel. The cost-effectiveness acceptability curve (Figure 3) (Table 4) also indicated that at a threshold of over US$ 882, ticagrelor was a cost-effective treatment in Iran.

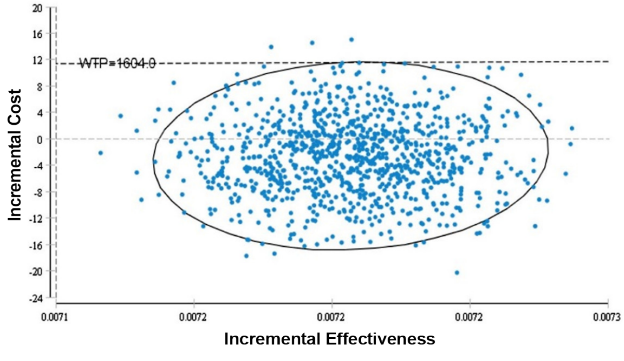

Figure 2. The image illustrates the incremental cost-effectiveness scatter plot for ticagrelor versus clopidogrel.

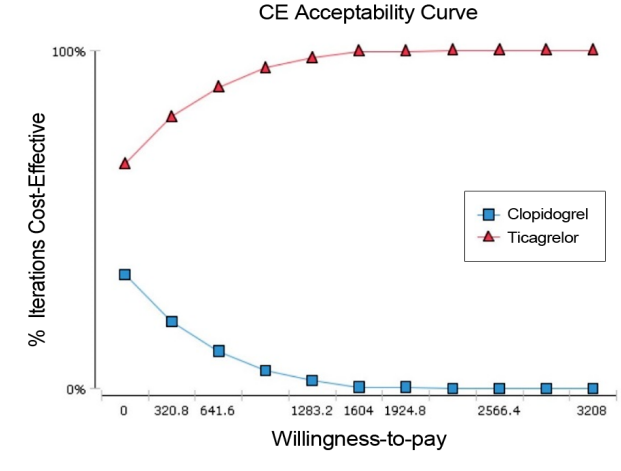

Figure 3. The image presents the Monte Carlo simulation acceptability curve.

Discussion

The present economic evaluation suggested that ticagrelor was a cost-effective strategy compared with clopidogrel for the secondary prevention of ACS in Iran. The findings of our study are consistent with similar studies on ticagrelor and clopidogrel in various countries.[31-35,38-42] Our economic evaluations revealed that despite its price, ticagrelor significantly reduced patient mortality, and its ICER fell below the conventional threshold values; consequently, it was more cost-effective than clopidogrel. Zyryanov et al[25] conducted a budget-impact analysis using the PLATO trial data and reported that clopidogrel-based antiplatelet therapy was a cheaper alternative. Still, ticagrelor-based antiplatelet therapy is more successful in resource savings in patients with ACS undergoing coronary artery bypass graft surgery.

Economic evaluations based on the payer's perspective from Chile and Thailand using the PLATO trial data have reported that ticagrelor is more cost-effective than generic clopidogrel.[35,40] Chiming with our study, Pawęska et al[31] used the 1-year decision tree model and the Markov model to investigate the cost-effectiveness of ticagrelor based on the PLATO trial, with the difference that they also drew upon the category of life years gained. We did not investigate this category because of our sharper focus on proving the effectiveness and assessing costs incurred by patients. To demonstrate efficacy, we directed our attention toward the QALY category. However, the results of these 2 studies are in line with each other. In Germany, Tiedel et al[33] compared cost-effectiveness between ticagrelor and clopidogrel in different brands. The difference between their investigation and ours is that Tiedel and colleagues measured the cost-effectiveness of ticagrelor and clopidogrel in patients with ACS taking aspirin by default simultaneously. Nonetheless, aspirin consumption made no tangible differences between our results insofar as both studies indicated that ticagrelor was more effective than clopidogrel, despite its higher cost

(albeit within the cost threshold).

The methodology of most studies comparing cost-effectiveness between ticagrelor and clopidogrel is based on a combination of a 1-year decision tree model and a lifetime Markov model. In most cases, the utilization of either of these medicines is limited to only 1 year. However, the experience of each event (eg, MI, stroke, and stent thrombosis) in the first year could impact the probability of re-experiencing those events in consequent years. Hence, pharmacoeconomic studies have followed the hypothetical cohort for a longer period, most of them for a lifetime.

We did not include indirect costs due to the perspective of the study, which could be considered a limitation. Cardiovascular diseases and events such as MI and stroke cause hospitalization, render patients bedridden for an extended period, and lead to considerable productivity loss. Given the superiority of ticagrelor in MI and death avoidance, had we included productivity loss in our analysis, this medication could have proven much more potent than clopidogrel. We utilized public sector tariffs for each service. Nevertheless, such urgent situations usually prompt most patients, especially in large cities, to seek help at private hospitals because public hospitals might be distant or occupied. There are some other limitations in this study's structure of the Markov model. For instance, the Markov model assumes no transition from MI to MI (re-MI), stroke to stroke (re-stroke), or post-MI to MI and post-stroke. Still, other studies have also accepted this limitation to avoid more complexity in the model, considering that no good sources exist for extracting transitional probabilities. We also did not include the cost and effect of CYP2C19 genetic testing before treatment with either clopidogrel or ticagrelor.

The current study is the first economic evaluation of ticagrelor and clopidogrel in Iranian patients with ACS. Since ticagrelor is not covered by any health insurance in Iran, the results of this study could be regarded as evidence by reimbursement bodies in the decision-making process. Based on our results, although ticagrelor can increase the cost of drug acquisition, it can compensate for it by diminishing other expenses on the strength of its impact on stroke and MI rates in 1-year and long-term time horizons. Hence, health insurance organizations should assess all these aspects to manage their budget with these 2 treatment options.

Conclusion

In the present study, ticagrelor was a cost-effective antiplatelet medicine compared with clopidogrel in Iranian patients with ACS. This could help Iran's policymakers to allocate resources to ACS more efficiently.

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