Original Article

Cost-Effectiveness and Cost–Utility Analysis of the Use of Clopidogrel and Pantoprazole in Comparison with Clopidogrel and Omeprazole for the Secondary Prevention of Myocardial Infarction in Iran

Mohammadreza Amirsadri[1,2], Valiollah Hajhashemi[3], Amir Shahriar Asemi[2]

[1]Health Management and Economics Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

[2]Department of Clinical Pharmacy and Pharmacy Practice, Isfahan University of Medical Sciences, Isfahan, Iran

[3]Department of Pharmacology and Toxicology, and Isfahan Pharmaceutical Sciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

Objective: Gastrointestinal bleeding, a side effect of clopidogrel, is usually prevented by proton-pump inhibitors (PPIs). Due to omeprazole's inhibitory effects on the liver enzyme CYP2C19, its concomitant use with clopidogrel is argued to increase the risk of myocardial infarction (MI) recurrence, as CYP2C19 activates clopidogrel. Pantoprazole as an alternative PPI has shown no inhibitory effect on CYP2C19. This study investigates the cost-effectiveness of concomitant use of clopidogrel and pantoprazole in MI patients compared to the simultaneous use of clopidogrel and omeprazole. **Methods:** We used the Markov-modeling technique with a hypothetical cohort of 1000 acute MI patients aged 55 years using Microsoft Excel 2013 software. The study was done from the payer perspective, and a lifetime horizon with 1-year cycles was considered in the model. Life-years gained (LYG) and quality-adjusted life-years (QALYs) were used to quantify the health effects of these interventions. Two separate scenarios of public tariffs and private tariffs with various discount rates (0%, 3%, and 7.2% discounts (only for costs)) were evaluated, and an incremental cost-effectiveness ratio (ICER) was used to report the results. One-way and probabilistic sensitivity analyses were used to deal with uncertainty. Data were sourced from published literature and tariff book of the Iranian ministry of health. **Findings:** The estimated ICERs were 342 USD/QALY and 236 USD/LYG per patient for the base-case scenario. **Conclusion:** Abiding by the WHO threshold for cost-effectiveness, the concomitant use of pantoprazole and clopidogrel can be considered cost-effective compared to the use of omeprazole and clopidogrel.

KEYWORDS: *Clopidogrel, cost-effectiveness, cost–utility, myocardial infarction, Omeprazole, Pantoprazole*

INTRODUCTION

Cardiovascular diseases are known as the most common causes of death and the most important causes of disability globally and in Iran. Despite rapid advancements in diagnostic methods and therapeutic procedures, one-third of patients with myocardial infarction (MI) die, and two-third of those who survive never fully recover or return to their normal life. These diseases impose a huge financial burden on the health-care system of countries. However, cardiovascular diseases are some of the most preventable noncommunicable diseases in humans.[1,2] Based on clinical studies, the risk of recurrence increases tremendously after the first MI; therefore, it is of utmost importance to prevent probable MI through medications in post-MI treatment. Anticoagulants such as aspirin and clopidogrel are commonly used in post-MI.[3,4] A proton-pump inhibitor (PPI) is usually used together with clopidogrel to prevent its gastrointestinal side effects.[5]

Address for correspondence:
Dr. Mohammadreza Amirsadri,
E-mail: amirsadri@pharm.mui.ac.ir

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Clopidogrel is activated by the liver enzyme CYP2C19. Drugs that inactivate this enzyme can potentially reduce the efficacy of clopidogrel. Consequently, the possible interactions between clopidogrel and some PPIs, particularly omeprazole, have been a concern in many studies.[6,7] Although pantoprazole is from the same drug family as omeprazole, it does not affect the function of CYP2C19, and can reduce the side effects of clopidogrel without reducing its antiplatelet effect.[8,9] Considering the Food and Drug Administration (FDA) warning, the drug interaction between omeprazole and clopidogrel may increase the risk of MI as well as related costs for patients and healthcare organizations.[10] Hence, the present study aimed to investigate the replacement of omeprazole with another PPI that possesses less potential interaction through cost-effectiveness and cost–utility analysis for the first time in Iran.

METHODS

The current study evaluated the effects of the potential interaction between clopidogrel and omeprazole on cost-effectiveness and cost–utility of the therapy compared to pantoprazole clopidogrel cotherapy. Markov-modeling technique with a hypothetical cohort of 1000 acute MI patients aged 55 years was conducted using Microsoft Excel 2013 software. The study was done from the payer perspective, and a lifetime horizon with 1-year cycles was considered in the model. Life-years gained (LYG) and quality-adjusted life-years (QALYs) were used to quantify the health effects of these interventions. Two separate scenarios of

public tariffs and private tariffs with various discount rates (0%, 3%, and 7.2% discounts (only for costs)) were evaluated, and an incremental cost-effectiveness ratio (ICER) was used to report the results. One-way and probabilistic sensitivity analyses (PSA) were used to deal with uncertainty. Data were sourced from published literature and tariff book of the Iranian ministry of health.

Since MI recurrence is relatively higher in the 1st year post-MI and the treatment expenses are substantially higher than that of subsequent years post-MI, separate health states for the 1st year post-MI and following years post-MI were used in this study. In this model, patients may experience a heart attack again after the first heart attack or die due to MI or normal death. If none of these events occur, the patient would be transferred to the next cycle with a history of MI.

Four different health states were considered in the study: nonfatal MI in the 1st year, nonfatal MI following the 1st year, death due to MI, and death for reasons other than MI. Figure 1 demonstrates the Markov diagram.

To measure the cost-effectiveness, QALY and LYG have been employed. Two scenarios with different costs for public tariffs (base-case scenario) and private tariffs were evaluated in the current study. Furthermore, different discount rates including 0% and 3% for effects and 0%, 3%, and 7.2% (according to an Iranian national study) for costs were considered for each scenario.[11] The costs were taken from the health tariffs book compiled in 2019 and the Iranian FDA website.[12,13] Table 1 shows the

Table 1: Data and values used in the model					
	50-59	**60-69**	**70-79**	**80-100**	**Reference**
Transition probability/Age (years)					
First year of nonfatal MI to fatal MI	0.0348	0.7	0.1054	0.127	[14,15]
First year of nonfatal MI to nonfatal MI	0.1152	0.1019	0.0874	0.0711	[16]
Subsequent years of nonfatal MI to nonfatal MI	0.0179	0.0185	0.178	0.016	[16]
Subsequent years of nonfatal MI to fatal MI	0.0092	0.0152	0.0235	0.034	[16,17]
Death for reasons other than MI	0.0073	0.02826	0.12533	0.13925	[18,19]
Relative risks					
Use of omeprazole for nonfatal MI			1.5		[20-22]
Use of omeprazole for fatal MI			1.21		
Use of clopidogrel for MI to the next nonfatal MI			0.42		[23,24]
Use of clopidogrel for MI to fatal MI			0.72		

Total treatment costs (USD)	**Public tariff**		**Private tariff**		**Reference**
	1st year	**2nd year**	**1st year**	**2nd year**	
With omeprazole	815.4		1576.7		[11,12]
With pantoprazole	806.7		1585.4		
Both groups		160.3		196.9	

Utility weights (MI)					
First year			0.76		[25]
Subsequent years			0.88		

MI=Myocardial infraction

data used in the model and their sources. To investigate the uncertainty in the parameters, we used two methods of univariate sensitivity analysis and PSA.

RESULTS

Costs were assessed separately in both omeprazole group and pantoprazole group, each with both private tariffs and public tariffs. The evaluation results are shown in Table 2 in USD. As shown in the table, patients in the intervention group (treated with pantoprazole) paid more than those treated with omeprazole, in all the scenarios. Three different discount rates were considered in the analysis. The highest incremental cost was seen in the base-case (no discounting) scenario ($34), while the least was seen when a discount rate of 7.2% for cost with private tariffs was applied to the model ($17).

Outcomes in both pantoprazole group and omeprazole group were evaluated separately with public tariffs and private tariffs using 0% and 3% discount rates. The results of this evaluation for each patient are shown in Table 2. Again, the highest incremental effects were seen when no discounting was applied to the model, while the incremental effects decreased after discounting at a 3% rate.

ICERs for QALY and LYG were calculated in both public scenario and private scenario using different discount rates [Table 2]. As expected, the highest ICERs ($314 and $213 for QALY and LYG, respectively) were reported for the base-case scenario (no discounting) and the lowest values were estimated when costs and effects were discounted at 7.2% and 3%, respectively.

The univariate sensitivity analysis showed the highest sensitivity to the relative risk of omeprazole effect on fatal MI with clopidogrel [Figure 2a and b] followed by MI treatment cost for both QALY and LYG. The results of the performed PSA with 5000 iterations are presented in Figure 2c and d. These figures represent the robustness of the model. Moreover, the PSA scatter graphs demonstrated a cost-saving intervention in 42% of the iterations, with the use of pantoprazole, while the majority of the points showed a positive incremental effect.

Cost-effectiveness acceptability curves (CEACs) have been widely adopted as a method to represent uncertainty in pharmacoeconomic evaluations.[26]

Figure 3 shows the performed CEAC of the current study.

According to Figure 3, when a person's willingness to pay for each additional QALY unit is greater than the intersection point of the omeprazole and pantoprazole curve ($ 326.5), the probability of the use of pantoprazole for the secondary prevention of MI, being cost-effective, is >50%.

DISCUSSION

The current study showed the cost-effectiveness of pantoprazole compared to omeprazole when used with clopidogrel for the secondary prevention of MI in Iran. Although the costs were higher in the private sector than in the public, the cost difference in the private sector was less. As a result, because the incremental cost is higher in the public sector, the ICER will also be higher.

At a zero discount rate (the base-case scenario), the omeprazole and pantoprazole groups had a QALY
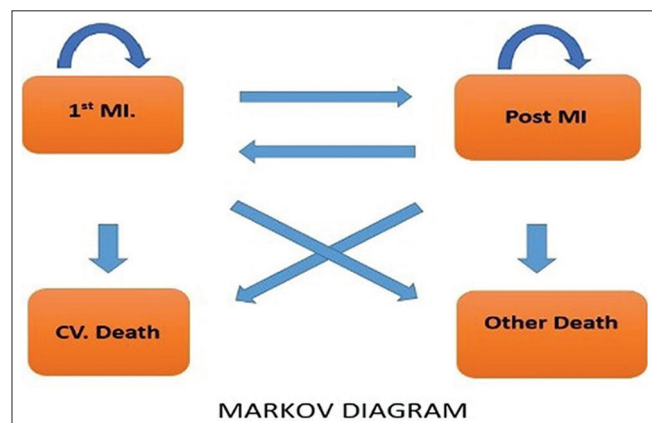

Figure 1: Markov model diagram

Table 2: Costs, effects, and incremental results

Discount rate	Scenarios	Cost (USD/patient)			Effect (per patient)						Incremental result (USD/effect)	
					QALY			LYG				
		OME	PAN	INC	OME	PAN	INC	OME	PAN	INC	ICER for QALY	ICER for LYG
0%	Public	4403	4437	34	13.88	13.99	0.11	20.71	20.87	0.16	314.3	213.2
	Private	6386	6420	34	13.88	13.99	0.11	20.71	20.87	0.16	307.2	208.3
Effects 3%	Public	3414	3441	27	10.01	10.09	0.08	14.82	14.93	0.11	342.3	235.7
	Private	5133	5157	24	10.01	10.93	0.92	14.82	14.93	0.11	313.6	215.9
Costs 7.2%	Public	2654	2674	20	10.01	10.93	0.92	14.82	14.93	0.11	262.5	108.7
	Private	4164	4181	17	10.01	10.93	0.92	14.82	14.93	0.11	222.8	153.4

OME=Omeprazole, PAN=Pantoprazole, INC=Incremental value, QALY=Quality-adjusted life-year, LYG=Life-years gained, ICER=Incremental cost-effectiveness ratio
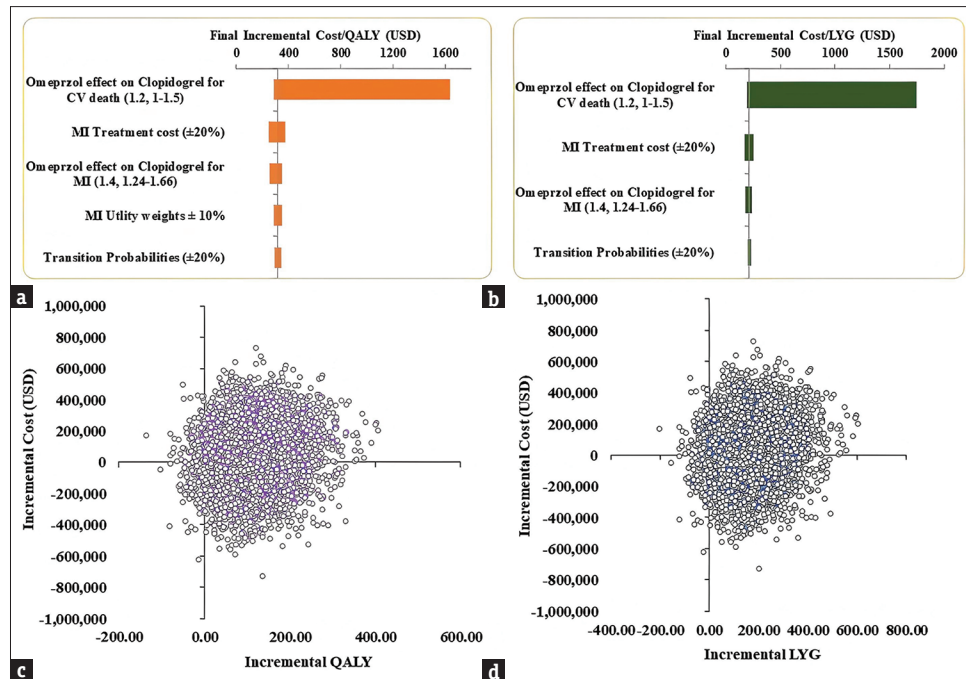
Figure 2: Sensitivity analyses results (the base-case scenario). (a) Tornado chart of univariate sensitivity analysis for quality-adjusted life-year. (b) Tornado chart of univariate sensitivity analysis for life-years gained. (c) Scatter diagram of probabilistic sensitivity analysis for quality-adjusted life-year. (d) Scatter diagram of probabilistic sensitivity analysis for life-years gained
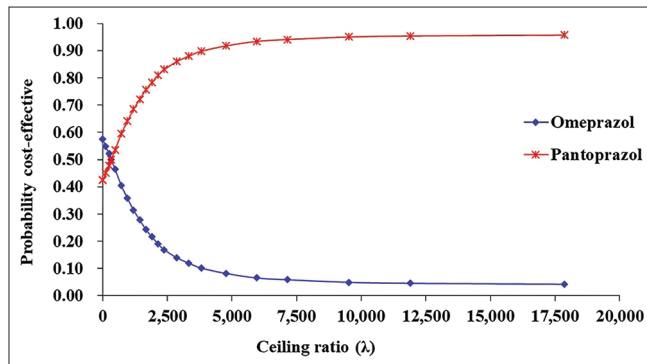
Figure 3: The cost-effectiveness acceptability curve

of 13.88 and 13.99, respectively. This finding shows that pantoprazole in a lifetime period produces 0.1 more QALY for each person. Furthermore, LYG of omeprazole and pantoprazole was 20.71 and 20.87, respectively, with an incremental amount of 0.16 LYG with pantoprazole.

The results of this evaluation demonstrated that the concomitant use of clopidogrel and pantoprazole instead of omeprazole has more ($342) incremental cost per QALY with public tariff when compared to the use of private tariff ($313 per QALY). This was the same when LYG was taken into account ($235 per LYG compared to $215 per LYG, respectively).

Considering the WHO recommendation for considering the gross-domestic production per capita of the country

as a threshold for ICER of QALY ($5550 for Iran 2018), the results show the cost-effectiveness of the use of pantoprazole in comparison with omeprazole.[27]

The univariate sensitivity analysis showed the highest sensitivity of the model to the relative risk of the effect of omeprazole on the fatal MI with clopidogrel. On the other hand, the results of the sensitivity analyses showed a probability of cost saving in 42% of the cases. This implies that the simultaneous use of pantoprazole instead of omeprazole and clopidogrel in 42% of cases has no additional costs and, on the other side, reduces the costs.

The results of the analysis with 5000 iterations of randomly selected input data in the related range and based on the type of statistical distribution of each parameter in the PSA displayed that only <4% of the points are located to the left of the vertical axis. The points on the left side of the vertical axis indicate a negative incremental effect. Therefore, in >96% of the repetitions performed, the beneficial effects of concomitant use of pantoprazole were more significant than the concomitant use of omeprazole.

The high density of the points in the PSA scatter graph represented the robustness of the model.

Although clopidogrel could affect some other health states, for example, stroke, as the focus of this study was on the recurrence of MI, no more health states were included in the model. Furthermore, this study

was performed in the context of Iran. Accordingly, it might not be generalized to other contexts or countries. Although some of the clinical data, used in the current study, sourced from foreign studies, the effect of uncertainty in these parameters was evaluated in the sensitivity analyses.

While many studies related to the interactions of PPIs with platelet inhibitors (mostly aspirin) could be found, however, we could not find any study in which the cost-effectiveness of concomitant use of clopidogrel and omeprazole compared to concurrent use of clopidogrel and pantoprazole has been evaluated, and this study seems to be unique from this point of view.

AUTHORS' CONTRIBUTION

Mohammadreza Amirsadri made design of the study and the model, supervised whole study, contributed in acquisition and reviewing of data and interpretation of the results, and revised the paper critically for important intellectual content. Valiollah Hajhashemi contributed in designing of the study, acquisition and analysis of data, and drafting the article. Amir Shahriar Asemi contributed in acquisition and analysis of data and drafting the article. All authors approved the final version for submission.

Conflicts of interest

There are no conflicts of interest.

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