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Original Article

Cost-effectiveness evaluation of aspirin in primary prevention of myocardial infarction amongst males with average cardiovascular risk in Iran

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Abstract

Aspirin is one of the certified medicines commonly used for the secondary prevention of myocardial infarction (MI). Aspirin side effects and gastrointestinal bleeding, in particular, have arisen debates on its use for the primary prevention of MI. The present research evaluates the cost-effectiveness of the use of aspirin in the primary prevention of MI among Iranian men with average cardiovascular disease (CVD) risk, using Markov modeling technique. The incremental cost-effectiveness ratios (ICERs) estimated to be 864 USA dollars (USD) per quality-adjusted life years (QALY) gained and 782 USD per life years gained (LYG) for each patient in the base-case scenario (public tariffs and no discounting). This research proves cost-effectiveness of the use of aspirin in the primary prevention of MI in targeted population, since the assessed ICERs are quite under the recommended threshold by WHO which is one gross domestic product (GDP) per capita ($5315.1 for Iran in 2015).

Keywords: Aspirin; Primary prevention; Cardiovascular diseases; Markov chain; Cost-effectiveness

INTRODUCTION

Cardiovascular disease (CVD) is experiencing an upward trend among fatal factors from its 1990 ranking of fifth place to the first in 2020. The CVD-related death rate will also rise from 25% to 40% in the same year (1).

By 2030, CVD will continue to be the leading cause of death in the Middle East (2). Beyranvand, *et al.* estimated that nearly 50% of deaths in Iran happened due to CVDs (3). CVDs impose different direct and indirect costs to society including morbidity, disability and mortality. More than 80% of the global burden of CVDs occurs in the developing or undeveloped countries (4).

Approximately, one-fourth of potential years that are lost and one-tenth of total healthcare expenses in Iran are related to CVDs (3).

Myocardial infarction (MI) is one of the most important and frequent cardiovascular conditions. Even though the rate of fatality due to coronary heart disease (CHD) has experienced a decline over the course of past four years, it is still responsible for one-third of all death toll reported for men at the age of 35 and more in Europe (5) and one-fifth of all death reported in the United States in 2014 (6).

Although aspirin is categorized as one of the main certified medicines to be taken for the secondary prevention of MI, debates around its use for the primary prevention of MI are still arising, bearing in mind the side effects of aspirin and especially its impacts on gastrointestinal system (7,8). Using aspirin in high-risk people (with a 10-year CVD risk of 20% or more) is advised in medical guidelines, however, the important point is lack of consensus on the use of aspirin in medical guidelines for those at moderate risk of CVD (15 % CVD risk in 10 years) and the appropriateness of using aspirin in these individuals is under question (9,10). Men aged 45 or older would cover most men at a moderate CVD risk (11,12).

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This study, for the first time, evaluated the cost-effectiveness and cost-utility of the use of aspirin for the primary prevention of MI in men with a 10-year CVD risk of 15% from payer's perspective in Iran.

MATERIALS AND METHODS

The population of this study was a hypothetical cohort of men above 45 years of age with a moderate CVD risk of 15% in 10 years period. A semi-Markov model was used to estimate the cost-effectiveness and cost-utility of the use of aspirin 80 mg compared to no-drug therapy. Life years gained (LYG) for cost-effectiveness analysis (CEA) and quality-adjusted life years (QALY) for cost-utility analysis (CUA) are the two main measured outputs. In this study, the first year after a new MI and the years following it have been assumed as separated health states (also called Markov states). This is due to the higher risk of reoccurrence of MI as well as greater imposed costs in the first year after MI compared to the subsequent years (13). Similarly, separated health states have been considered for gastrointestinal-bleeding (GIB).

The model assumes a hypothetical cohort of individuals (Iranian men above 45 years) with no previous MI or GIB. People in the intervention group would receive aspirin for the primary prevention of MI, while no strategy has been considered for the primary prevention in the no-intervention group. This procedure continues to the age of 100 or death (although, not all the cohort die before 100, however majority of them would die before the age of 100). The length of each Markov cycle was considered to be one year. This can capture most of the probable transitions and attributed costs of MI and is consistent with much other published literature regarding the modelling of CVD (14,15). Fig. 1 shows different health states and permitted transfers used in the model.

Occurrence of GIB in the group which was taking aspirin for the primary prevention led to removal of aspirin with no substitution, however; these patients were treated using treatment protocol for GIB.

A healthy individual is exposed to any of the related presented health states in the model or may remain healthy in the following years. Treatment strategies differ according to different health states. A person with an experience of MI would receive prescribed aspirin 80 mg and atorvastatin 10 mg for the secondary prevention in both intervention and no-drug groups. If he had experienced GIB too, clopidogrel was substituted with aspirin in order to continue secondary prevention procedure. Clopidogrel may impose fewer side effects, particularly GIB, compared to aspirin in such patients (16).

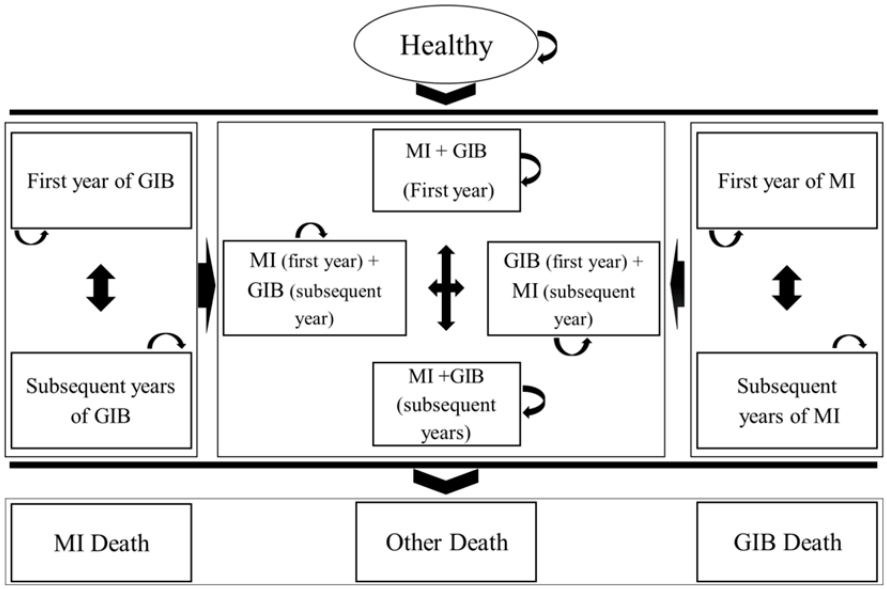

Fig. 1. The semi-Markov model. (GIB) gastrointestinal bleeding; (MI) myocardial infarction; other death, death because of causes except MI and GIB.

To consider the time preference, discounting process is taken into account. Different scenarios for discounting rates have been codified in this model, based on WHO's recommendations as well as domestic studies. WHO suggests considering the rate of 3% for both effects and costs (17), while a domestic study estimated a discount rate of 7.2% for costs in Iran (18). A third scenario with no discounting also was performed in this study based on the international society for pharmacoeconomics and outcome research (ISPOR) recommendation. Also two different scenarios were performed in this study based on the probability of occurrence of the first MI. In the base-case scenario a 10-year CVD risk of 15% was taken into account while in the second scenario the reported probability of MI occurrence for the related age and gender was sourced from a domestic study (ICS, Isfahan cohort study) (19).

As the risk of CVD rises with age, to consider this, an annual increase of CVD risk of 0.03% was used in the model (20). Considering the differences between private and public tariffs in Iran, the model has taken these different sectors into account. Tables 1 and 2 show the parameters used in the model. The probability used for mortality with GIB was considered to be 4% for ages ≤ 60 and 10% for ages > 60, respectively (35). To consider the impact of aging on individual's health (obviously, as a person ages, his health-related quality of life diminishes) age-specific utility weights were also applied to the model. These utility weights sourced from the Ward, *et al.* study in 2007 (20). Table 3 names other utility weights required for calculating QALY.

From payers' view, direct costs which were considered in this study are as follows: admission and hospitalization charges, laboratory and para-clinical test expenses, medication costs and specialist's tariffs (physician visit).

Table 1. Relative risks used in the model.

	Aspirin		**Clopidogrel**	
	Relative risk	**Reference**	**Relative risk**	**Reference**
Health to non-fatal MI	0.68	21	-	-
Health to fatal MI	0.87	22	-	-
Post-MI to non-fatal MI	0.72	23	0.68	23, 26
Post-MI to fatal MI	0.85	24	0.78	24, 26
MI to non-fatal MI	0.44	23	0.42	23, 26
MI to fatal MI	0.78	24	0.72	24, 26
GIB	1.8	25	1.67	25
GI re-bleeding (history of GIB)	3.1	-	-	27

MI, myocardial infarction; GIB, gastrointestinal bleeding.

Table 2. Transition probabilities of Markov states applied in model.

TP/age	**45-49**	**50-54**	**55-59**	**60-64**	**65-69**	**70-74**	**75-79**	**80-84**	**85-100**	**Ref.**
MI to MI	0.128	0.128	0.115	0.115	0.102	0.102	0.087	0.087	0.071	20
MI to FMI	0.022	0.035	0.035	0.070	0.070	0.105	0.105	0.127	0.127	28, 29, 30, 31
Post-MI to MI	0.016	0.016	0.018	0.018	0.019	0.019	0.018	0.018	0.016	20
Post-MI to FMI	0.005	0.005	0.009	0.009	0.015	0.015	0.024	0.024	0.034	20, 32
To other death	0.003	0.004	0.006	0.008	0.013	0.021	0.043	0.070	0.149	33, 34
Healthy to MI (SS)	0.003	0.003	0.004	0.004	0.009	0.009	0.006	0.006	0.006	19
Healthy to FMI (SS)	0.002	0.002	0.005	0.005	0.008	0.008	0.008	0.008	0.008	19
Healthy to NFGIB	31.46×10^{-5}	31.46×10^{-5}	31.46×10^{-5}	$31.46 \times *10^{-5}$	31.46×10^{-5}	31.46×10^{-5}	31.46×10^{-5}	31.46×10^{-5}	31.46×10^{-5}	34

MI, non-fatal myocardial infarction; FMI, fatal myocardial infarction; Post-MI, subsequent years of myocardial infarction; SS, second scenario; TP, transition probabilities; NFGIB, non-fatal gastrointestinal bleeding.

Table 3. Utility weights used in the model.

	Utility weight	**References**
First year of MI	0.76	20
Post - MI	0.88	36
First year of GIB	0.98	37

MI, non-fatal myocardial infarction; GIB, gastrointestinal bleeding.

Currency exchange rate is determined as 30256 Iranian Rials for each USA dollars (USD) in this model, according to the central bank of Iran report (38). Data from Amirsadri, *et al.* study was used to estimate the costs of treatment charges for MI and GIB (39). Also, information for 200 GIB patients from Isfahan's Al-Zahra Hospital was adopted to estimate the related costs. Tables 4 and 5 show the treatment tariffs used in the model.

One-way and probabilistic sensitivity analyses (PSA) were included in the proposed model, as well. The latest edition of Tariff Book of Health Services was used to determine the expenses for hospitalization, clinical and para-clinical laboratory tests (40).

Table 4. Myocardial infarction treatment tariffs.

		Private tariff				Public tariff				
		MI (first year)		Post MI			MI (first year)		Post MI	
	UC	NU	Total cost	NU	Total cost	UC	NU	Total cost	NU	Total cost
CCU hospitalization (per day)	235	2	471.	-	-	83.1	2	166.	-	-
General care units hospitalization fee (per day)	184	2	368.	-	-	65.2	2	130.	-	-
Consultant visit fee	9.90	7	69.4	2	19.8	3.80	7	26.6	2	7.60
General practitioner visit fee	6.30	3	18.8	4	25.1	3.00	3	9.10	4	12.2
Para-clinical examinations										
Electro-cardiography	6.60	9	59.5	2	13.2	2.90	9	26.2	2	5.80
Echo-cardiography	72.7	1	72.7	-	-	32.0	1	32.0	-	-
Exercise tolerance test	37.7	1	37.7	-	-	16.6	1	16.6	-	-
Medical laboratory tests										
Lab. patient admission fee	0.87	3	2.59	2	1.73	0.42	3	1.20	2	0.80
Lab. service fee	0.66	3	2.00	2	1.33	0.00	3	0.00	2	0.00
CBC Diff	1.80	3	5.39	2	3.59	0.66	3	2.00	2	1.33
BUN	0.80	3	2.40	2	1.60	0.37	3	1.10	2	0.73
Cr	0.96	3	2.89	2	1.93	0.47	3	1.40	2	0.93
Na	1.16	3	3.49	2	2.33	0.53	3	1.60	2	1.06
K	1.16	3	3.49	2	2.33	0.53	3	1.60	2	1.06
BS	0.87	3	2.59	2	1.73	0.42	3	1.20	2	0.80
TG	1.40	3	4.19	2	2.79	0.63	3	1.90	2	1.26
Cholesterol	1.00	3	3.00	2	2.00	0.47	3	1.40	2	0.93
PT INR	1.63	1	1.63	-	-	0.83	1	0.83	-	-
PTT	1.63	1	1.63	-	-	0.83	1	0.83	-	-
Troponin	7.89	2	15.8	-	-	2.40	2	4.80	-	-
LDH	3.86	1	3.86	-	-	1.66	1	1.66	-	-
CPK	4.79	1	4.79	-	-	2.23	1	2.23	-	-
SGOT	1.30	3	3.89	2	2.62	0.57	3	1.70	2	1.13
SGPT	1.30	3	3.89	2	2.65	0.57	3	1.70	2	1.13
ESR	0.50	1	0.50	-	-	0.23	1	0.23	-	-
Pharmaceuticals										
ASA 80	0.03	365	9.650	365	9.65	0.03	365	9.650	365	9.65
Clopidogrel	0.32	365	115.4	365	115.4	0.32	365	115.4	365	115.38
Metoprolol	0.01	365	5.100	365	5.10	0.01	365	5.100	365	5.10
Enoxaparin	4.66	1	4.660	-	-	4.66	1	4.660	-	-
Atorvastatin	0.03	365	10.69	-	-	0.03	365	10.70	-	-
Ranitidine	0.02	30	0.650	-	-	0.02	30	0.650	-	-
Oxazepam	0.01	4	0.040	-	-	0.01	4	0.040	-	-
Captopril 25	0.01	4	0.050			0.01	4	0.050		
Streptokinase	22.39	1	22.29	-	-	22.3	1	22.30	-	-
Drug dispensing fee	0.53	6	3.190	6	3.19	0.18	6	1.060	6	1.06
Total			1336.84		218.07	-	-	603.49	-	167.95

UC, unit cost; NU, number of units.

Table 5. Gastrointestinal bleeding treatment tariffs.

	GIB (private tariff)			GIB (public tariff)		
	Unit cost ($)	**Number of units**	**Total cost ($)**	**Unit cost($)**	**Number of units**	**Total cost**
Emergency ward hospitalization (per day)	102.4	1	102.5	35.80	1	35.80
Gastroenterology ward hospitalization (per day)	143.4	5	717.2	53.70	5	268.5
Consultant visit fee	9.910	5	49.60	3.800	5	19.02
General practitioner visit fee	6.280	1	6.280	3.040	1	3.040
Para-clinical examinations						
Endoscopy	238.0	1	238.0	238.0	1	238.0
Echocardiography	97.17	1	97.17	97.17	1	97.17
Blood transfusion	16.53	2	33.05	16.53	2	33.05
Medical laboratory tests						
Lab. patient admission fee	0.400	1	0.400	0.400	1	0.400
Lab. service fee	0.670	1	0.670	0.000	1	0.000
CBC Diff	0.670	2	1.330	0.670	2	1.330
BUN	0.800	6	4.800	0.370	6	2.200
Cr	0.960	6	5.800	0.470	6	2.800
Na	1.160	6	6.990	0.530	6	3.190
K	1.160	6	6.990	0.530	6	3.190
BS	0.870	2	1.730	0.400	2	0.800
Amylase	2.910	1	2.910	0.630	1	0.630
AST	1.300	1	1.300	0.570	1	0.570
ALP	1.300	1	1.300	0.570	1	0.570
PT INR	1.630	6	9.780	0.830	6	4.990
PTT	1.630	6	9.780	0.830	6	4.990
Troponin	7.900	1	7.900	2.380	1	2.380
Bilirubin/Total	2.010	1	2.010	0.930	1	0.930
Ca	1.300	1	1.300	0.570	1	0.570
CRP	11.50	1	11.50	5.550	1	5.550
Organic phosphorus	1.130	1	1.130	0.470	1	0.470
Lipase	2.210	1	2.210	1.350	1	1.350
Mg	1.620	1	1.620	0.830	1	0.830
Venus blood gas	6.540	1	6.540	2.710	1	2.710
HCT/HMG	1.790	12	21.45	0.670	12	7.940
Pharmaceuticals						
Pantoprazole 40 mg vial	3.960	5	19.82	3.960	5	19.820
Pantoprazole 40 mg tab	0.120	14	1.630	0.120	14	1.630
Drug dispensing fee	0.530	1	0.530	0.180	1	0.180
Medical devices						
Ward medical devices	-	-	48.35	-	-	48.35
Total	-	-	1423.57	-	-	812.95

GIB, gastrointestinal bleeding.

Table 6. Results of the performed scenarios. The results are reported per patient.

		Cost (USD/patient)				Effect (per patient)				Incremental results (USD/effect)			
		Public tariffs		**Private tariffs**		**QALY**		**LYG**		**ICER for QALY**		**ICER for LYG**	
Discount rate	Scenario	NDT	ASA	NDT	ASA	NDT	ASA	NDT	ASA	Pub.	Prv.	Pub.	Prv.
0%	Base-case	214.8	472.3	435.9	633.8	18.2	18.50	24.10	24.40	864.3	664.3	781.5	600.6
	SS	259.8	497.1	530.5	695.3	17.6	18.00	23.40	23.80	678.1	471.0	608.5	422.7
3%	Base-case	110.1	275.4	226.8	360.7	9.3	9.400	12.20	12.30	1308.6	1059.8	1234.8	1000
	SS	127.4	285.1	263.8	385.0	9.1	9.300	12.00	12.10	1051.6	807.7	986.0	757.2
7.2% for costs &	Base-case	54.20	160.3	114.0	204.2	9.3	9.400	12.20	12.30	840.4	713.6	793.0	673.3
3% for effects	SS	58.40	162.8	123.5	210.5	9.1	9.300	12.00	12.10	695.5	580.0	652.1	543.8

ASA, aspirin; NDT, no drug therapy; SS, second scenario; QALY, quality-adjusted life years; LYG, life years gained; ICER, incremental cost-effectiveness ratios.

RESULTS

The outcomes of all executed scenarios are included in Table 6. The Tornado charts of one-way sensitivity analysis results with the evaluated parameters and their variability spectrum are presented in Figs. 2 and 3.

It has been shown in the tornado charts that the conclusions were, to a great extent, sensitive to the fluctuation in the price of aspirin, the risk of CVD during a period of ten years and the relative risk of being transferred from a healthy situation to non-fatal MI with aspirin.

The scatter plots of the performed PSA are demonstrated in Figs. 4 and 5. The estimated points are located at the upper right corner of the cost-effectiveness plane, representing a more effective and also costlier intervention compared to no-drug therapy. The more the points concentrate; the more the robustness of the performed model.

As per PSA results, the average estimated ICERs are $882 (95%CI: 564.24–1272.02) and $794 (95%CI: 520.88–1122.86) for QALY and LYG, respectively.

The cost-effectiveness acceptability curve (CEAC) shows the uncertainty that is assessed in cost-effectiveness (41,42). The CEAC of aspirin therapy against the state of having no medication can be seen in Fig. 6.

The CEAC curve illustrates that once willingness to pay per QALY is more than 868 USD, the cost-effectiveness of aspirin therapy gains a higher probability than no drug therapy.

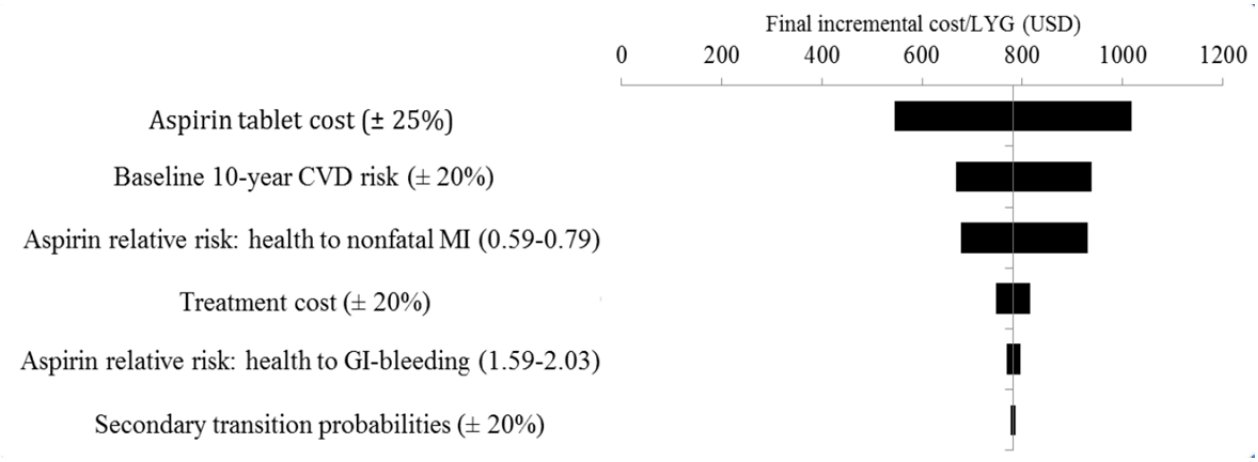

Fig. 2. One-way sensitivity analysis of incremental cost/LYG (public tariffs). (LYG) life years gained.

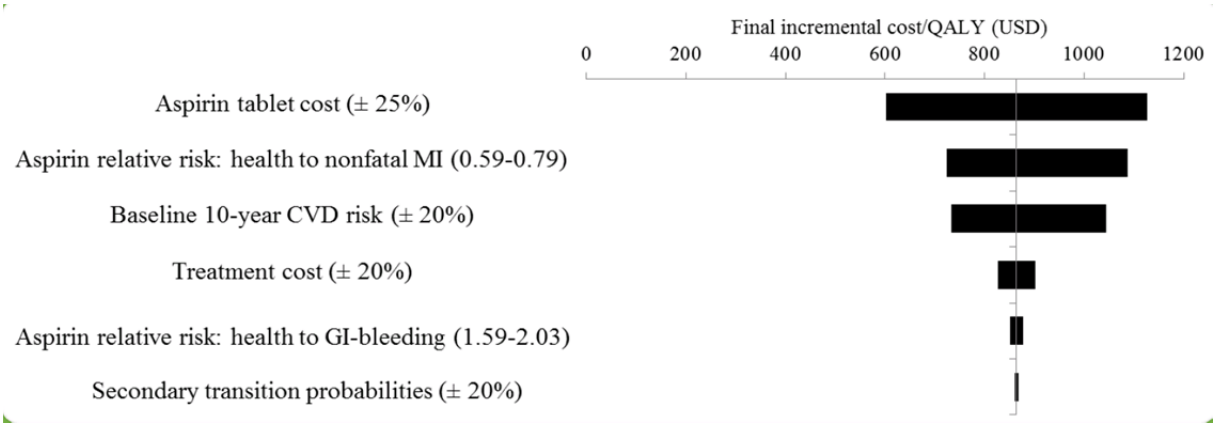

Fig. 3. One-way sensitivity analysis of incremental cost/QALY (public tariffs). (QALY) quality-adjusted-life-years.

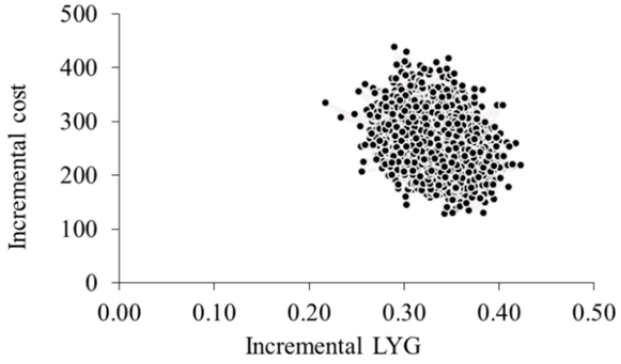

Fig. 4. Probabilistic sensitivity analyses scatter plot of incremental cost/LYG ratio (public tariffs). (LYG) life years gained.

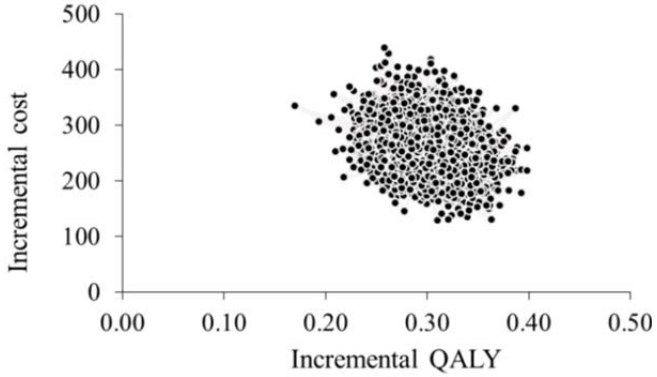

Fig. 5. Probabilistic sensitivity analyses scatter plot of Incremental cost/QALY ratio (public tariffs). (QALY) quality-adjusted life years.

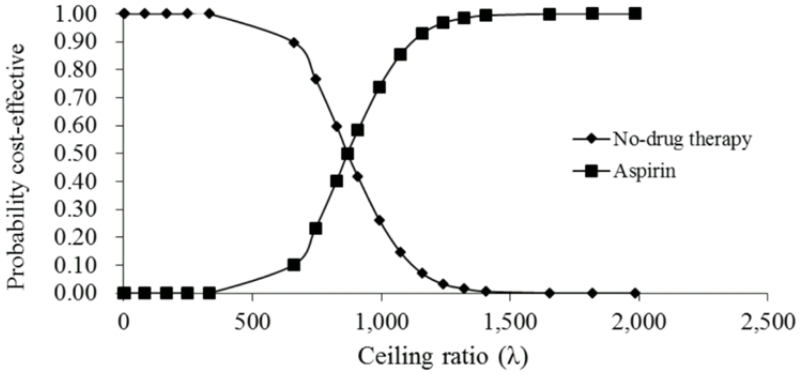

Fig. 6. Cost-effectiveness acceptability curve plot of aspirin therapy versus no medication.

DISCUSSION

MI is one of the main causes of death and disability in both developed and developing countries. Although the use of aspirin for the primary prevention of CVD in people at higher risks (around 20% CVD risk within 10 years) is recommended, however the use of this medicine in people at lower risks is controversial (11).

This research is conducted to examine the cost-effectiveness of the use of aspirin for the primary prevention of MI among men of 45 years of age that possess an average (15%) risk of developing MI over a course of 10 years in Iran. The authors believe that this is the first study in the field has been done in Iran.

The current study revealed that low dose of aspirin, costs $864 per QALY ($664 with

private tariff) and $782 per LYG ($600 with private tariff) for the primary prevention of MI in 45-year-old men with moderate CVD risk (15% absolute risk of CVD over the course of 10 years) in comparison with the group that did not take any medication. As the estimated ICERs are less than the recommended threshold introduced by WHO, based on the gross domestic product (GDP) per capita (the amount of GDP per capita for Iran was reported to be $5315.1 in 2015 (43)) this intervention could be considered as a highly cost-effective strategy.

Results from various designed scenarios in this study illustrate incremental expenses of no more than $1308.6 per patient (the base-case scenario with public tariffs and a discount rate of 3% for both effects and costs) for each unit outcome (either QALY or LYG). This represents that the assessed intervention proved to be highly cost-effective in all the performed scenarios, considering the recommended threshold by WHO. Although the absolute amount of costs were lower with public tariffs, however due to the greater difference between the costs of the intervention and no-intervention groups, the estimated incremental costs were higher when compared to private tariffs scenarios.

Outcomes were shown to be strong by executing sensitivity analyses; however the results were particularly sensitive to the price of aspirin, the risk of CVD during a period of ten years and the relative risk of being transferred from a healthy situation to non-fatal MI with aspirin. So, the price of aspirin tablet is of particular importance in making the decision. The achieved 95% confidence intervals in the performed PSA showed to be well below the considered threshold. The CEAC curve demonstrates a higher probability for the cost-effectiveness of aspirin therapy compared to no-drug therapy for willingness to pay amounts of more than 868 USD per each QALY gained. This seems to be a reasonable willingness to pay when the reported GDP for Iran is taken into account.

Although some research has been conducted in other countries on the application of aspirin for the prevention of CVD, their data is not comparable to ours as a result of remarkable differences. These differences include target population (the reason to select the aimed population explained in the introduction), applied discount rates (considering the domestic studies as well as the international guidelines), different costs (surely considered costs are dependent on the context of the study), and different health states (the focus of this study was MI in men due to its great probability in Iran). Two of the most similar studies to ours were as follows: a study by Grieving, *et al.* in which the cost-effectiveness of the use of aspirin for the primary prevention of CVD among different categories of age and gender was evaluated. In this study the authors concluded that the use of aspirin is cost-effective for the primary prevention in men with average CVD risk who aged 55 to 75 years (44). The second study is the Pignone, *et al*. study in which the authors proved cost-effectiveness of the use of aspirin for the primary prevention of CVD in men above 45 years with 10-year CVD risk of more than 7.5%, compared to no-drug therapy (45).

This research only brings into account the direct expenses undertaken by the payers and did not assessed the indirect expenses of the intervention, because it didn't concern a social perspective. The outcomes that are estimated in this research are a result of employing age-related probabilities and compound health states at the expense of making the model more complex. Other determining factors such as hypertension, other CVDs and diabetes also play important roles which were not dealt with in this research. Although the effect of aspirin on the occurrence of haemorrhagic stroke is not unimportant, due to the use of compound health states and age-dependent probabilities (a semi-Markov model instead of a simple Markov model with constant probabilities), considering more health states could soon make the model cumbersome. Consequently, only the effect of aspirin on GI system was taken into account as the major side effect of aspirin.

CONCLUSION

Considering the estimated results of this study, the use of low dose aspirin for the

primary prevention of MI among Iranian men with an average risk of CVD can be considered as a highly cost-effective intervention compared to no-drug therapy. The outcomes of this research might be useful for healthcare policy makers to develop national strategies and to rationally plan health services for the prevention of MI, particularly in Iran.

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