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Original Article

Economic Evaluation of the Drugs Used In Treating Patients with Myocardial Infarction: A Systematic Review

Aziz Rezapour[1], Marziye Hadian[2], Mohammad Ghasemi[3], Sajad Vahedi[4], Abdosaleh Jafari[4*]

[1]Department of Health Economics, School of Health Management and Information Sciences, Iran University of Medical Sciences, Tehran, Iran
[2]Student research committee, Isfahan University of medical sciences, Isfahan, Iran
[3]South Khorasan province health Center, Birjand University of medical sciences, Birjand, Iran
[4]Health Management and Economics Research Center, Iran University of Medical Sciences, Tehran, Iran

Abstract

Introduction: Myocardial infarctions (MI), as one of the outcomes of cardiovascular diseases, are responsible for 20% of deaths, so that every 30 seconds, one person suffers from MI. Various drugs are used to treat myocardial infarction, and we need to have precise information of the cost-effectiveness of these drugs. The aim of this study was to examine economic evaluation of the drugs used for treatment of patients with MI.

Methods: In the present systematic review study, published articles related to economic evaluation of the drugs used for treatment of patients with MI within the time interval between 2000 and 2017 were searched, using electronic databases such as Tufts Medical Center Cost-Effectiveness Analysis Registry ,Cochrane library, NHS Economic Evaluations Database Medline, PubMed, Google scholar, web of science using the following keywords: Cost- effectiveness* OR cost- utility* OR economic evaluation * AND (myocardial infarction *) AND (angiotensin- converting enzyme inhibitor (lisinopril) OR thrombolytic agents (streptokinase, anistreplase or anisoylated plasminogen streptokinase activator complex OR beta blockers (metoprolol, propranolol, atenolol, acebutolol, bisoprolol). Due to heterogeneity in the outcome, we were not able to use meta-analysis. Methodological quality of the structure e of tarticles was examined by Drummond's standard checklist.

Results: Based on the inclusion criteria, the search of databases resulted in 12 articles that fully covered economic evaluation of the drugs used in treating patients with MI. The results of the present study indicated that a streptokinase and t-PA drug for treatment of patients with myocardial infarction was cost-effective. The results showed that most of the studies clearly stated the time horizon of the study and included direct medical costs in their analysis. In addition, the majority of the studies were used the Markov model. The quality-adjusted life years (QALYs) were the main outcome used for measuring the effectiveness.

Conclusion: The results of the present study showed that a thrombolytic agent for treatment of patients with myocardial infarction was cost-effective. The results were relatively varied due to the differences in time horizon and variables used in the models such as efficacy and drug prices. Furthermore, these studies were designed and conducted in high-income countries; thus, the application of these results in low- and middle-income countries will be limited.

Keywords: Economic evaluation, Systematic review, Myocardial Infarction, Drummond's checklist

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***Correspondence to:**
Abdosaleh Jafari,
Health Management and Economics Research Center, Iran University of Medical Sciences, Tehran, Iran
Tel: +98-21-88671615
Fax: +98-21-88671614
Email: abdosaleh.jafari@gmail.com

Introduction

Myocardial infarction is a major cause of mortality, mortality, and rehospitalization throughout the world (1). Statistics have shown that every 33 seconds, one person dies of cardiovascular diseases and it is predicted that 33% of men and 10% of women under the age of 60 have suffered from at least one MI. Overall, myocardial infarction is widely known as one of the most significant outcomes of cardiovascular diseases which alone contribute to 20% of mortalities, such that for every 30 seconds, one person suffers from myocardial infarction and one individual dies of this disorder every minute. 70% of the patients who have suffered from myocardial infarction never fully recover (2). Medical expenditures of myocardial infarction contribute to a great deal to the overall health care expenditures. Patients suffering from myocardial infarction must not only pay the costs for treatment and follow-ups, but if under the coverage of social insurance, certain

unwanted costs are also imposed on the insurance companies due to related ailments and disorders that occur after treatment. A report by Larijani from Iran indicated that the direct expenditure of cardiovascular patients for the year 2000 was 22770 million Rials in the petroleum industry (3). Emamgholipour et al., in their study in Iran, showed that in 2016 the average total cost per patient with cardiovascular disease was $1881.4 and the total costs resulted in 1159.62 $million. Direct costs accounted for 60% and indirect ones for 40% of the total costs (4). Furthermore, studies from Pakistan on medical expenditure of patients suffering from myocardial infarction indicated the average costs of medical drugs and visits in these patients were 2381 Rupees (24 American Dollars) (5). Soe et al., in their study in South Korea, found that the total estimated cost of AMI in 2012 was $1,177,649,323 USD and the majority (52%) of this amount constituted medical costs, followed by productivity losses due to mortality and morbidity (42% of annual cost) (6). One of the most important drug interventions for myocardial infarction patients is the use of certain pharmaceutical products. Amongst these drugs, anticoagulants are the most significant. If EKG submitted during heart pain is "elevation in ST segment", thrombolytic agents (clot-buster drugs) must be prescribed and used within 12 hours after chest pain. The treatment of thrombolytic is initiated by steady injection of streptokinase known as the tissue plasminogen activator followed by intravenous injection of heparin (7). Other drugs used for treating myocardial infarction include beta-blockers (such as metoprolol, atenolol, and propranolol), which are used to decrease the heart load and reduce blood pressure (8, 9). Tsevat et al. showed that the cost-effectiveness of captopril (compared with placebo) after MI ranged from US$3600 to US$60,800 per QALY (US dollar, 1991 prices), depending on the age of the patient and the persistence of treatment benefits (10). Martinez and Ball estimated that the cost-effectiveness of ramipril (compared with placebo) was around £300 per life-year gained (11).

Considering the fact that these drugs must be used by patients in the country where heart stroke is prevalent, it is of upmost importance to have a thorough understanding of the cost-effectiveness of these drugs. Therefore, the aim of this study was to examine the economic evaluation of drugs used for treatment of patients with myocardial infarction.

Methods

Literature Search Strategy

This study is a systematic review on published articles between 2000 and 2017 related to economic evaluation of drugs used by patients suffering from myocardial infarction. The databases used for the present study include:

Tufts Medical Center Cost-Effectiveness Analysis Registry Cochrane library, NHS Economic Evaluation s Database Medline, PubMed, Google scholar, and web of science

The following keywords were used for searching the aforementioned articles:

Cost- effectiveness* OR cost- utility* OR economic evaluation * AND (myocardial infarction *) AND (angiotensin- converting enzyme inhibitor (lisinopril) OR thrombolytic agents (streptokinase, anistreplase or anisoylated plasminogen streptokinase activator complex OR beta blockers (metoprolol, propranolol, atenolol, acebutolol, bisoprolol)).

The articles were included in the review by the following inclusion criteria:

- Articles that had performed full economic evaluation including cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis regarding the drugs used by patients suffering from myocardial infarction
- Original articles published in the English languages
- Articles published during 2000- 2017
- Articles not comparing the drugs used for myocardial infarction with surgical procedures.
- Articles not associated with cardiovascular diseases (such as heart failure, heart surgeries, arrhythmia, etc.)

Quality Assessment of Methodology of the Studies

Methodological quality of articles that met the aforementioned criteria was analyzed by Drummond's standard checklist (Table 1). Questions that assess the design of economic evaluation studies are in terms of the following items: statement of the research question; a comprehensive description of competing alternatives, measurement of effectiveness, appropriate identification, measurement and valuation of the costs and consequences; use of the discount rate, incremental analysis for costs and consequences, examination of the effect of uncertainty in the estimates of costs and consequences, and provision of appropriate interpretation of the results (12). Rezapour et al. (13) used Drummond's checklist for assessing the quality of the published articles in Iranian journals related to economic evaluation in health care programs. All items in the checklist were scored according to their positive, negative, or unclear status. Both first and second authors reviewed the selected articles independently and extracted

Table 1: Drummond's criteria for the quality assessment of economic evaluation studies

Row	Criteria
1	Was the main question of the study asked in an appropriate way?
2	Were the competitor options presented in a comprehensive manner?
3	Were evidences of the effectiveness program presented?
4	Were all significant costs and relevant outcomes identified?
5	Were all significant costs and relevant outcomes properly measured?
6	Were all significant costs and relative outcomes properly valued?
7	Were costs and outcomes adjusted for different time?
8	Were an incremental analysis of the costs and outcomes of competitor options carried out?
9	Were the effects of uncertainty (sensitivity analysis) investigated for all costs and outcomes?
10	Were all problems related to the users of the results of the study investigated during analysis and presentation of results?

the information into predesigned form in the Excel. Any disagreement was solved through subsequent discussion.

Data Analysis

The selected studies were fully reviewed, and the required data were extracted and summarized, using the tables designed. Endnote X5 software was used to organize the studies, read the titles and abstracts, and identify the duplicates.

Results

In the initial search, 200 studies were identified. After screening the studies using the exclusion criteria, 90 studies were selected. Then, through thorough reviews of full texts of the studies, 78 of them were excluded from the study, and finally we selected and assessed the results of 12 studies that carried out a full economic evaluation of the drugs used in myocardial infarction (14-25). Figure 1 presents the results of the systematic review. Also, the results of quality evaluation based on Drummond's checklist are shown in Table 2. Items of the checklist were scored qualitatively as positive (+), negative (-), or not clear (N/A). Results of quality assessment of the article structure indicated that out of 12 reviewed articles, the following articles were incompetent with their respective criteria: 9 articles (75%) had defects regarding result analysis (10^{th} criteria), 6 articles (50%) had flaws regarding identification, measurement, and valuation of the costs and outcomes (4^{th} to 6^{th} criteria), 2 studies (16%) were incompetent regarding the study question and adjustment of the costs and outcomes for different times and sensitivity analysis (the 1^{st},7^{th}, and 9^{th} criteria), and 1 study (8%) had flaws in presenting a comprehensive description of competitor options and incremental analysis of the costs and outcomes of competitor options (the 2^{nd} and 8^{th} criteria). As seen in Table 2, only two studies

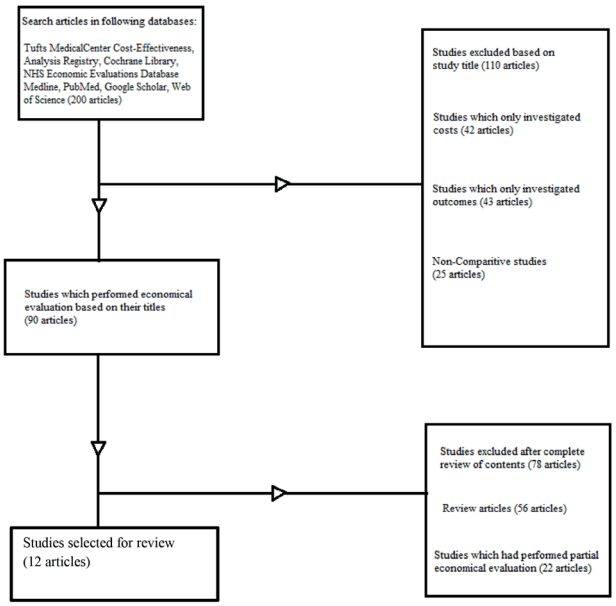

Figure 1: Result of systematic literature search

observed the Drummond's criteria completely. Also, 6 out of 12 articles performed identification, measurement, and valuation of the costs according to the perspective of the study. Table 3 shows the economic features of the reviewed articles. As can be observed from this Table, the number of articles related to cost-effectiveness and cost-utility analysis were 5 and 7, respectively. Amongst the studies that performed cost-utility analysis (studies which used combinational outcomes such as quality-adjusted life year (QALY) or disability-adjusted life year (DALY) to perform evaluation of the outcomes), six studies used the QALY indicator and one used the DALY indicator for measuring effectiveness. On the other hand, amongst the studies that performed cost-effectiveness analysis, 2 had used the survival rate and 3 studies used life years gained (LYG) indicator for measuring the outcomes. Regarding the study design, 5 studies (42%) used the Markov model and 2 used the Markov model and decision tree simultaneously.

Table 2: Qualitative assessment of English articles using Drummond's checklist

No	study	1- Was the main question of the study asked in an appropriate way?	2- Were the competitor options presented in a comprehensive manner?	3- Were evidences of the effectiveness program presented?	4- Were all significant costs and outcomes identified?	5- Were all significant costs and outcomes properly measured?	6- Were all significant costs and relative outcomes properly valuated?	7- Were costs and outcomes adjusted for different times?	8- Were an incremental analysis of the costs and outcomes of competitor options carried out?	9- Were the effects of uncertainty (sensitivity-analysis) investigated for all costs and outcomes?	10- Were all problems related to the users of the results of the study investigated during analysis and presentation of results?
1	Rama (15)	N/A	+	+	N/A	N/A	N/A	-	-	-	N/A
2	Megiddo (14)	+	+	+	+	+	+	+	+	+	N/A
3	Wang (16)	+	+	+	N/A	N/A	N/A	+	+	+	+
4	Welsh (20)	+	+	+	-	N/A	N/A	+	+	+	N/A
5	Taylor (19)	+	+	+	+	+	+	+	+	+	N/A
6	Marcoff (17)	+	+	+	-	N/A	N/A	+	+	+	N/A
7	Scuffham19))	+	+	+	+	+	+	+	+	+	+
8	Araújo (21)	+	+	+	+	+	+	-	+	-	N/A
9	Choudhry (22)	+	+	+	-	N/A	N/A	+	+	+	N/A
10	Maniadakis (24)	+	+	+	+	+	+	+	+	+	-
11	Kent (23)	N/A	N/A	+	N/A	N/A	N/A	+	+	+	N/A
12	Vale (25)	+	+	+	+	+	+	+	+	+	+

With regards to the study perspectives, most studies (5 studies) were performed from the viewpoint of health system and 4 were carried out from the social perspective. Regarding the type of sensitivity analysis for coping with uncertainty in models, 4 studies used one-way and probabilistic methods concurrently, while 2 of them did not perform any sensitivity analysis. In most cases, the lifetime was selected for time horizon and one study used time horizons of less than one year, one year, 10 years, and the remaining lifetime. Regarding the use of discount rate for converting the future outcomes to present values, most studies (4 studies) used the discount rate of 3%, while two of them used discount rates of 5% and 5.3%, respectively. Also, two studies with time horizons of more than one year did not use any adjustment rate at all. The number of articles published on the issue of economic evaluation of myocardial infarction drugs according to the year of publication is shown in Figure 2. This figure indicated the peak number of articles published on economic evaluation of myocardial infarction drugs to be between the years 2008 and 2009.

Discussion

Economic evaluation data are significant tools that can be used by decision- and policy- makers, when allocating resources. Systematic reviews play an important role in investigating the cost-effectiveness of various treatments and medical interventions. In the present study, 12 studies were examined based on the inclusion and exclusion criteria. The reviewed studies have been conducted in the USA (5 studies), Europe (4 studies), Asia (2 studies) and Australia (one study). The results of this review indicated that many articles published on economic evaluation of drugs used in treating myocardial infarction did not meet international standards for performing economical evaluation studies and had major methodological defects, so that only 2 studies met the Drummond's criteria completely. The most common methodological flaws in these articles were related to the 10th Drummond's criteria. Another flaw in the articles was related to perspectives, so that among the studies which did determine the study perspective, many failed to measure the costs according to the approach of the study. For example, in the study performed by Marcoff and Welsh, although the study perspective was selected as society, indirect costs were not measured (17, 20). Regarding the type of models used for analysis, most studies applied the Markov model. Markov model is a technique for presenting and analyzing random procedures during time

Table 3: Economic characteristics of the reviewed articles

Characteristics	Number	Percentage
Type of Economical Evaluation		
cost-effectiveness analysis	5	42
cost-utility analysis	7	58
Study Design		
randomized controlled trial	2	17
observational	1	8
decision tree	2	17
Markov model	5	42
Markov model and decision tree	2	17
Perspective evaluated		
social	4	33
health system	5	42
patient and provider	1	8
Not stated	2	17
Type of Sensitivity Analysis		
one-way	4	33
probabilistic	2	17
one-way and probabilistic	4	33
Not performed	2	17
Time Horizon		
<= 1 year	1	8
1-10 years	3	25
Over 10 years	1	8
lifetime	5	42
less than one year, one year, 10 years, and remaining lifespan	1	8
Not specified	1	8
Type of Outcome		
Disability-Adjusted Life Year (DALY)	1	8
Quality-Adjusted Life Year (QALY)	2	17
Life Years Gained (LYG)	3	25
survival	2	17
QALY and survival	1	8
QALY and LYG	3	25
Discount Rate for Time Horizons of more than 1 Year		
3%	4	33
5%	2	17
5.3%	2	17
Not stated	2	17

intervals. This model is commonly used for simulating the patient progress in a certain time period and is especially used for simulating acute and chronic diseases (26-29). In regards to the type of sensitivity analysis, 4 studies used one-way and probabilistic analysis simultaneously in order to cope with uncertainty, and 4 used one-way sensitivity analysis alone. Sensitivity analysis is a tool which helps the researcher recognize which parameters are the main determinants for the results of economical evaluation (27-31). Regarding the use of threshold value, two studies in Asia used the method introduced by World Health Organization to determine the threshold value. According to the World Health Organization method, if the ICER value of a country is less than 3 times the Gross Domestic Product (GDP) per capita of that country, the intervention is cost-effective (32). Also, two studies from America, one from England and Canada, and one from Australia indicated the threshold value of the cost-effectiveness for each life year as 50, 20, and 70 thousand dollars, respectively. Results also indicated that two studies showed that streptokinase drugs were cost-effective in treating and preventing acute heart failure. Two other studies also indicated that using tissue-plasminogen activator is cost-effective for myocardial infarction patients. One study showed that enoxaparin was more cost-effective compared to heparin. Other studies indicated that for

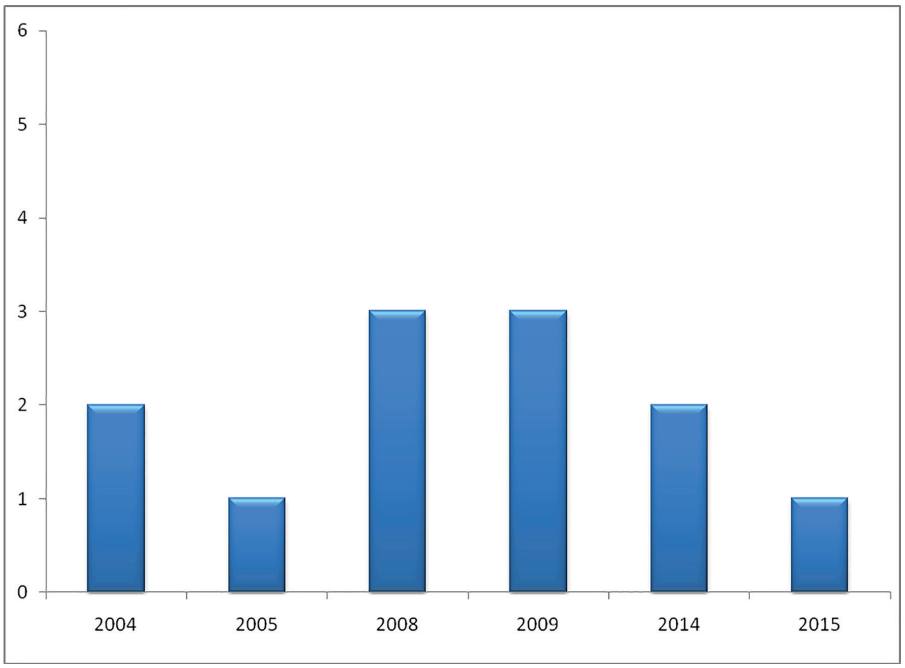

Figure 2: The number of articles published on economic evaluation of myocardial infarction drugs, by year

patients with contraindication for using angiotensin enzyme inhibitor drugs, valsartan was cost-effective after myocardial infarction.

Study Limitation

One of the main limitations of the present study was the heterogeneity of the results of the studies that made conducting quantitative analysis (meta-analysis) impossible. Another limitation of this review was that unpublished studies were not identified by our literature search. These were typical reports from the department of health technology assessment and health economics department, medical schools, reports from pharmaceutical companies and academic thesis.

Conclusion

Based on the results of the reviewed studies in this systematic review, it seems that the streptokinase and tissue-plasminogen activator agents are cost-effective for patients with MI. The results varied for different time horizons and type of parameters used in the models including drug prices and effectiveness. Furthermore, most studies did not examine drugs side-effects which could increase the costs and reduce the effectiveness of a drug. It is suggested that researchers in their future studies should consider several parameters such as drug side effect, use of final outcome instead of intermediate outcome and use of lifetime horizon. In addition, these studies were designed and conducted in high-income countries; thus, the application of these results in low- and middle-income countries will be limited. Therefore, it is suggested if policymakers and health care planners decide to use MI drugs in their health care system, they should design and conduct specialized studies in their own local settings.

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