Original Article
http://mjiri.iums.ac.ir
Medical Journal of the Islamic Republic of Iran (MJIRI)

Med J Islam Repub Iran. 2017(14 Jan);31.4. https://doi.org/10.18869/mjiri.31.4

Cost-effectiveness of Eplerenone in treatment of cardiovascular diseases: a systematic review

Hossein Mobaraki[1], Saber Azami-Aghdash[2], Ali Sarabi Asiabar[1], Aziz Rezapour[1], Mohammad Hossein Kafaei Mehr[1*], Saeed Emamgolizadeh[3]

Received: 31 Oct 2016 Published: 13 Jan 2017

Abstract

Background: No clear evidence is available on the cost-effectiveness of eplerenone in treatment of cardiovascular diseases. Thus, the present study aimed at systematically reviewing studies that have investigated this issue.

Methods: This systematic review study was conducted in 2016. The required information collected using key Mesh words from the following databases: Google scholar, PubMed, Science Direct, MagIran, SID, Scopus, and hand searching journals and the references of the selected articles. The quality of the selected articles was assessed by the Drummond's checklist.

Results: Nine articles were included from 296 articles found in the literature review. The selected studies have been conducted in 8 countries (The United States, Britain, Australia, Switzerland, France, Spain, the Netherlands, and Canada). In general, the cost-effectiveness of eplerenone was investigated in 31 757 patients with cardiovascular diseases. The average of quality-adjusted life years (QALY) in studies with nonmodeling approach was equal to 0.0908 in Framingham approach, 0.0595 in Saskatchewan approach, and 0.1309 in Worcester approach. The overall average cost of treating cardiovascular diseases with eplerenone was equal to US$6694 in 1year. Cost per additional (QALY) was estimated to be US$9478. Incremental cost-effectiveness ratio was high in the United States compared to European countries. The Average quality of articles was estimated to be 7.4 from 10.

Conclusions: Based on the results of the studies reviewed in the present study, it seems that eplerenone has acceptable cost-effectiveness compared with current treatments, placebo, and similar drugs.

Keywords: Cost-effectiveness, Cardiovascular Disease, Eplerenone, Systematic Review

Cite this article as: Mobaraki H, Azami-Aghdash S, Sarabi Asiabar A, Rezapour A, Kafaei Mehr MH, Emamgolizadeh S. Cost-effectiveness of Eplerenone in treatment of cardiovascular diseases: a systematic review. *Med J Islam Repub Iran.* 2017(14 Jan);31.4. https://doi.org/10.18869/mjiri.31.4

Introduction

Cardiovascular diseases (CVDs) are the main cause of mortality in most high- income counties (HICs) as well as in low- and middle- income countries (LMICs). Moreover, despite the new advanced treatments and the use of sophisticated techniques and surgical interventions, mortality rate due to CVD is very high (1). According to the WHO's report, mortality and disability from CVD and cerebrovascular accident, or stroke involve more than 12 million individuals worldwide annually. WHO also predicts that if the current trends continue, 25% of healthy life years will be lost by 2020 worldwide, with a large share belonging to the LMICs (2). In Iran, CVD is considered as the most common cause of mortality (3).

Aside from deaths due to unprecedented events such as Bam earthquake, the annual number of deaths in Iran has been around 320,203 in 2003. Meanwhile, the first cause of mortality from the view of the number of fatalities was belonged to CVD (72,682 males and 62,068 for females) followed by unintentional accidents as the second cause of mortality in Iran (4).

Therefore, due to lack of resources, especially in the health sector and increased health care expenditures, developing solutions and implementing cost-effective interventions are of prime importance due to the high rate of mortality due to CVD and the high costs of health care services for these disorders (5,6).

Corresponding author to: Mohammad Hossein Kafaei Mehr, m.h_kafa@yahoo.com

[1] Health Management and Economics Research Center, Iran University of Medical Sciences, Tehran, Iran.
[2] Road Traffic Injury Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. Email: saberazami@yahoo.com
[3] Shomal University, Amol, Iran.

↑What is already known about this topic:
Based on a report from Iran, the first cause of mortality from the view of the number of fatalities has belonged to CVD. Despite its high costs, there are evidence proving the effect of eplerenone in treating CVDs.

→What this article adds:
Compared to current treatments for CVD in Iran, our systematic review showed that eplerenone has a far greater impact on reducing the duration of hospitalization, decreasing the mortality rate of the cardiovascular patients, and ensuring the treatment efficacy and safety.

A large part of national health budget and resource planning has already been allocated to non-communicable diseases, and diagnosis and treatment of cardiovascular disorders. Core expenditure relates to medications and drugs. Annually, many medications log in the health care system for the treatment of CVD. Eplerenone is one of the medications which is in the light spot and is medicated by cardiovascular specialists for patients in the recent years (7-10). Many studies have been conducted on the safety and efficacy of eplerenone (11-14). In the recent years, some studies have been designed and conducted to measure the cost-effectiveness of eplerenone in treating CVD (15-18). Although this medicine is produced in HICs extensively is entered from LMICs into the healthcare system.

Due to the high cost of such medications, high expenditures will be imposed on the healthcare system and the community. Thus, the present study aimed at systematically reviewing studies on the cost-effectiveness of eplerenone in treating cardiovascular diseases.

Methods

The adopted approach for systematic review was from "Systematic Review to Support Evidence-Based Medicine" book (19). The data were collected using keywords such as eplerenone, aldosterone antagonists, Inspra, cost-effectiveness, economic, chronic heart failure, heart, and cardiac from the following databases: Google Scholar, PubMed, Scopus, Cochrane, Science Direct, Health Technology Assessment database, MagIran, SID, IranMedex, and hand-searching of journals and selecting articles from resources. In the last step of the literature search, gray literature was also searched and we did contact the experts. The articles conducted during 1990 and 2016 were selected for the review. The process of selecting eligible articles is shown in Diagram 1.

Inclusion criteria were articles in the field of cardiovascular diseases, studies that compared the cost-effectiveness of eplerenone with other medications, and articles that reported at least 1 of the mentioned factors below: gained life years, total costs, and expenditures and cost-effectiveness ratios of treating cardiovascular patients with eplerenone per QALY. All types of observational and interventional studies, except case studies, and published articles in Persian and English which were consistent with the above- mentioned considerations were reviewed in this study. Exclusion criteria were as follow: papers presented at conferences, case reports, and articles that did not have the necessary qualifications.

Quality Assessment of the Selected Articles

According to the Drummond's checklist for assessing the quality of economic evaluations and the agreement between the 2 researchers of this study, quality of the articles was assessed in accordance with the existing standards, and articles that did not meet the necessary qualifications were excluded.

Data Analysis

Selected articles were thoroughly studied and the required data were extracted and summarized using the designed tables. The Endnote X5 (resource management software) was used to organize, read the titles and abstracts, and identify duplicates.

Results

From 296 articles extracted from the references, 9 were related to the objectives of the study and thus included for review.

In general, the cost-effectiveness of eplerenone was investigated in 31 757 patients with cardiovascular diseases. In the 6 reviewed studies, cost-effectiveness of eplerenone was investigated in patients with heart failure after myocardial infarction. In 3 studies, the comparison group included the standard treatment; in 5 studies, placebo was used as the comparison group; in 1 study, spironolactone was used as a comparison group; in 4 of the 9 reviewed studies modeling was used to evaluate cost-effectiveness; in 1 study clinical data were used; and four studies were designed as a clinical trial.

Modeling was used in 4 studies. The discrete event simulation model was used in 2 studies: Markov model in 1 study, and decision analysis model in another study.

In 5 studies, the perspective of health care system was used to evaluate cost-effectiveness. In 3 studies, social perspective and in 1 study perspective of third-party payer were used. In 6 studies, sensitivity analyses were conducted; and probabilistic sensitivity analyses (PSA) was one of the most important methods of sensitivity analyses in these studies.

The discount rate was 3% in 4 studies, 5% in 2, 4% in 1, and 3.5% in 1 study in England. In a study by Li et al., the discount rate was 3.5% for England and 3% for Spain.

In 5 out of 9 reviewed studies, the follow-up period was 1.3 years (16 months). In 1 study, the follow-up period was 7.08 years; follow-up period was 2 years in 1 study, and 10 years in another study; patients were examined for their remaining lifetime in 1 study.

In 2 studies, in which the discrete event simulation model was used, quality- adjusted life years were respectively 1.18, 1.22, and 1.33 (In a study by Li et al., quality-adjusted life years (QALY) was calculated for Britain and Spain). In studies using decision analysis model, the quality-adjusted life years was equal to 0.25. According to a study by Markov model, the quality-adjusted life years +was equal to 0.19.

Another 5 studies which used no modeling as their research method for calculating the quality-adjusted life years, could use 3 approaches based on the average: Framingham, Saskatchewan, and Worcester: the results are shown in Figure 1.

To calculate the total costs of treating cardiovascular patients with eplerenone, 3 studies used Euros, 2 studies used US$, 1 study used Canadian dollars, and 1 study used Australian dollars, and the Swiss Franc was used in another study. Moreover, the total cost was not estimated in 1 study. Distribution of the annual average total cost of treating cardiovascular patients with eplerenone in different currencies is presented in Figure 2.

Although various methods were used to estimate the

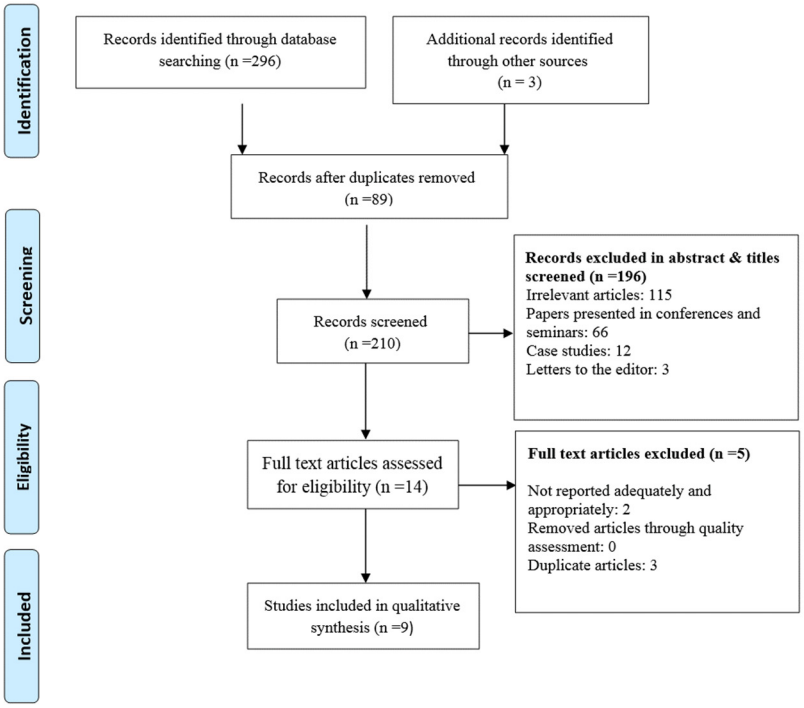

Diagram. 1. Diagram of the process of selecting the articles reviewed studies have been conducted between 2005 and 2016. The studies were performed in 8 countries (The United States, Britain, Australia, Switzerland, France, Spain, the Netherlands, and Canada).

total cost in the articles, the considered factors for calculating the total cost and the exchange rate of the base year varied between the studies. Overall, the total cost was calculated to compare the costs of treatment with eplerenone in different countries. The costs were converted to US$ based on the exchange rate on October 26, 2016.

As observed in Figure 3, costs of treatment with eplerenone were approximately the highest in the United States and Switzerland and the lowest in Britain and Spain. Overall, the average of the total costs was equal to $6694 annually.

However, various methods have been used to estimate the cost per additional QALY. The exchange rate of the base year was different in the articles. Thus, to compare the costs, costs per additional QALY for treatment with eplerenone was calculated in different countries and converted to US$ based on the exchange rate on October 26, 2016. The results are presented in Figure 4 for modeling studies and in Figure 5 for clinical trials and observational studies.

There are some limitations in calculating a specific cost per additional QALY for treatment of patients based on the results of different studies in different situations (Fig. 5). In the present study, the cost per additional QALY for the treatment of cardiovascular patients with eplerenone was estimated to be $9478.

Although the exchange rate of the base year was different, to compare the incremental cost-effectiveness ratios of eplerenone in different countries, costs were calculated and converted to US$ according to the exchange rate on October 26, 2016. As shown in Figure 6, the incremental cost-effectiveness ratio of treating cardiovascular patients with eplerenone was significantly higher in Australia compared to European countries and Canada.

As observed in Figure 7, the incremental cost-effectiveness ratio of treating cardiovascular patients with eplerenone was significantly higher in the United States compared to European countries. Results of quality assessment of the articles based on the Drummond checklist are demonstrated in Table 2. Average of the quality of articles was equal to 7.4 from 10.

Discussion

Eplerenone is one of the medications used for treating patients with heart failure after myocardial infarction, and it can also increase blood pressure. In the recent years, several studies have confirmed the effectiveness of this drug in reducing the mortality rate of cardiovascular patients and decreasing their hospital stay (8, 10, 26).

Few studies have been conducted on the cost-effectiveness of eplerenone in recent years, though robust evidence and information were not available. The current study, which systematically reviewed the results of 9 valid studies, it was found that the results of all the 9 studies approved the cost-effectiveness of this medication compared to the current treatments, the placebo, and similar drugs. The reviewed studies have been conducted between 2005 and 2016 in 8 countries (The United States, Britain, Australia, Switzerland, France, Spain, The Netherlands, and Canada). This indicates that eplerenone has just entered the consumer market recently, and like most other drugs, first it has been exploited on the market of high-income countries.

Cost - effectiveness of eplerenone

Table 1. Information of the articles that studied the cost-effectiveness of eplerenone in the treatment of patients with cardiovascular diseases

Author, year of study	*Study site*	*Purpose of the study*	*Partici-pants (num-ber)*	*Comparison group*	*Study design*	*Decision model*	*Approach of the study*	*Sensitivity analysis*	*the discount rate (percent)*	*Follow-up period*	*QALY*	*Total costs*	*Costs Per each QAYL*	*Incremental cost-effectiveness ratio combined with quality*	*Drummond's Checklist Score of (10)*
1. Thanh et al. 2016 (20)	Canada	Evaluation of the cost-effectiveness of ep-lerenone in patients with heart failure and mild systolic symp-toms	11055	Standard treatment	modeling	Discrete event simu-lation model	Health	Scenario, and proba-bilistic sensitivity analyses (PSA)	3	7.08	1.18	Can$40059	Can$5700	Can$ 6100	8
2.McKenna et al. 2012 (18)	England	Comparing the cost-effectiveness of ep-lerenone with spirono-lactone in patients with heart failure after myocardial infarction	3313	Spironolac-tone	modeling	Decision analysis model	Health	-	3.5	2	0.25	-	£7893	£4457	7
3. Zhang et al. 2010 (16)	America	Evaluation of the cost-effectiveness of ep-lerenone in patients with acute heart Fail-ure after receiving ACE inhibitors and B-blockers	2113	placebo	Observation	3	1.3	-	Based on Framing-ham = 0.1148 Saskatche-wan[2] = 0.0673 Worcester = 0.1504	US$14 563	Based on Framing-ham= US$14926 Saskatche-wan = US$25447 Worcester= US$11393	Based on Framing-ham= 25398 Saskatche-wan= 37664 Worcester= 21326	5	3	1.3
4. De Pouvour-ville et al. 2008 (17)	France	Evaluation of cost-effectiveness in pa-tients with acute heart failure after myocardi-al infarction	3319	Placebo	Trial	5	1.3	Stochastic sensitivity analysis	Based on Framing-ham= −0.0972 Saskatche-wan = −0.0620	£5783.6	Based on Framing-ham= £ 5721 Saskatche-wan = £5721	Based on Framing-ham= £ 9819 Saskatche-wan = £ 15382	7	5	1.3
5. Ademi et al. 2016 (21)	Austral-ia	Comparing the cost-effectiveness of ep-lerenone with current treatments in patients with chronic heart failure and NYHA[4] class 2	1000	Standard treatment	modeling	Markov Model	Health	Determinis-tic sensitivi-ty analysis (DSA), scenario, and PSA	5	10	0.19	$11,848,684	-	$37452	8
6.Weintrau b et al. 2005 (22)	America	Evaluation of the cost-effectiveness of ep-lerenone in myocardial infarction patients with heart failure and left ventricular dysfunction	3319	Placebo	Trial	-	Social	-	3	1.3	Based on Framing-ham= 0.0676 Saskatche-wan = 0.0429 Worcester= 0.0907	$13 494	-	Based on Framing-ham= 29469 Saskatchewan= 43301 Worcester= 23724	9

Cost - effectiveness of eplerenone.

7. Szucs et al. 2006(23)	Swiss	Evaluation of the cost-effectiveness of Eplerenone in myocardial infarction patients with heart failure and left ventricular dysfunction	3319	Placebo	Trial	-	Third party payer	Univariate sensitivity analysis	3	1.3	Based on Framingham= 0.1083 Saskatchewan = 0.0661 Worcester= 0.1518	Swiss Francs16969.78	Framingham= 15,219 Saskatchewan= 23,965 Worcester= 11,337	Framingham= 10145 Saskatchewan= 16178 Worcester= 7693	9
8. Lee et al. 2014 (24)	England and Spain	Evaluation of the cost-effectiveness of eplerenone in patients with systolic heart failure and mild symptoms	1000	Standard treatment	Modeling	Discrete event simulation model	Health	PSA DSA	England=3.5 Spain=3	Lifetime	=England 1.22 =Spain 1.33	England =£18 559 Spain =€23 353	England = £2825 Spain =€4431	England =£3520 Spain =€5532	7
9. Van Genugten et al. 2005 (25)	Netherlands	Evaluation of the cost-effectiveness of eplerenone in myocardial infarction patients with heart failure and left ventricular dysfunction	3319	Placebo	Trial	-	Health	PSA	4	1.3	Based on Framingham= 0.0661	£6035.6	-	Based on Framingham =12147	7

[1]-Peeters A, Mamun AA, Willekens F, et al. A Cardiovascular Life History: A Life Course Analysis of the Original Framingham Heart Study cohort. Eur Heart J 2002; 23: 458-66.
[2]- Downey W, Beck P, McNutt M, et al. Health Databases in Saskatchewan. In: Ttrom BL, Editor. Pharmacoepidemiology. 3rd ed. Chichester: Wiley, 2000: 325-45.
[3]- Goldberg RJ, Yarzebski J, Lessard D, et al. A two-Decade (1975 to 1995) Long Experience in the Incidence, In-Hospital and Long-Term Case-Fatality Rates of Acute Myocardial Infarction: Acommunity-Wide Perspective. J Am Coll Cardiol 1999; 33 (6): 1533-9
New York Heart Association (NYHA).

In 2002, eplerenone was approved by the Food and Drug Administration of America (FDA). Nowadays, this medication is mostly used in high-income countries such as the United States, Canada, and members of the EU (Japan and the European Union) (27).

In this context, these studies were mostly designed and conducted in high-income countries. Thus, these results are not fully applicable in low- and middle-income countries. Therefore, policymakers should benefit from the results of the localized studies in their decision-making.

The results of all the 9 studies approved the cost-effectiveness of this drug compared with the current treatments, the placebo, and similar drugs. One important point was that using eplerenone to treat cardiovascular patients was too costly compared to the comparison groups. However, eplerenone has a far greater impact on reducing the duration of hospitalization, decreasing the mortality rate of the cardiovascular patients, and ensuring efficacy and safety (28-33).

Eplerenone has been estimated to be more cost-effective than comparison groups in general. Therefore, considering the reports of cost-effectiveness of this medication cannot be the only factor to be considered in the decision- making process, and other factors and local conditions of each region should also be considered. One of the most important factors was economic and financial status, health care system of the region, and the country. Moreover, most of the data of these studies were extracted from a base study “EMPHASIS-HF", which was a double-blind, multi-centered clinical trial. In the present study, 6632 patients from 671 centers from 37 countries were registered during 1999 and 2001 and the effectiveness of eplerenone and placebo was evaluated in treating patients with myocardial infarction in this study (34).

Due to the fact that this study had some limitations and shortcomings, using its data and relying on its methodology can distort the application and validity of the results of the other studies. The main objective of this study was to evaluate cost-effectiveness of eplerenone and this factor could have affected the results and conditions of the study.

The results revealed that total costs, cost per additional QALY, and incremental cost-effectiveness ratio were very different in various countries. For example, in a study by Li et al. (2014), which aimed at determining the cost-effectiveness of eplerenone in 2 groups of cardiovascular patients from Britain and Spain, it was found that eplerenone raised QALY up to 1.33 by an increase in direct costs up to 4284 EUR in the English patients and raised QALY up to 1.22 by an increase in direct costs up to 7358 EUR in the Spanish patients, moreover, they found that the cost indicators were higher in Spain than in the UK (24).

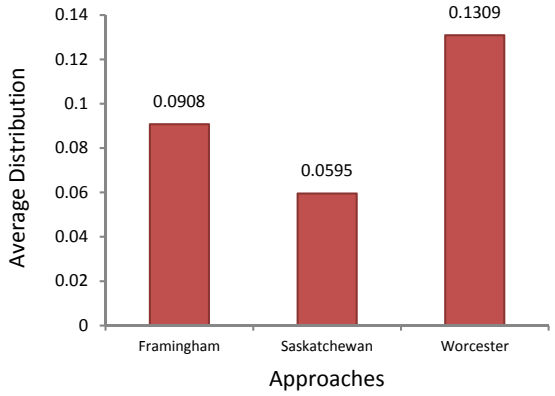

Fig.1. Quality-Adjusted Life Years for patients with cardiovascular diseases who were treated with eplerenone by the 3 following approaches: Framingham, Saskatchewan, and Worcester.

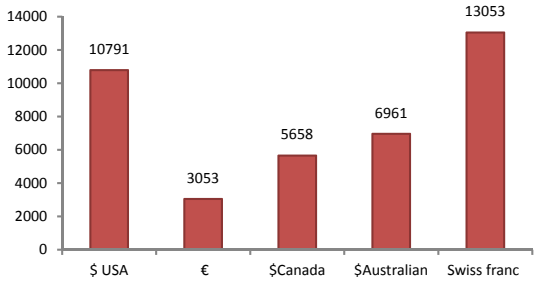

Fig. 2. The total cost of treating cardiovascular patients with eplerenone during 1 year per patient.

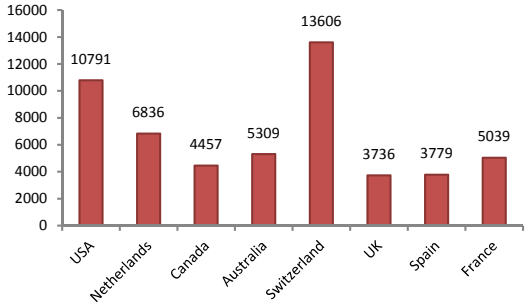

Fig. 3. The total cost of treating cardiovascular patients with eplerenone during one year per patient in different countries (Based on US$ and the exchange rate on October 26, 2016)

This can have various reasons, but it can mainly be due to the price of eplerenone in different countries. General and administrative costs in different countries also play an important role. In general, it seems that costs of using this medicine are higher in the United States and Australia compared to Europe.

What can be deduced from the overall results of the current study is that using eplerenone to treat cardiovascular patients is very costly although it leads to more efficient clinical outcomes. Thus, cost of using this medicine to treat heart failure is approximately $3 per day and to treat hypertension is about $6 per day (27).

These expenses may not seem so high at first glance,

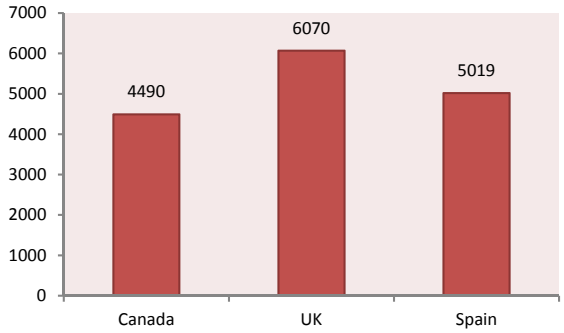

Fig. 4. The cost per extra QALY in the treatment of cardiovascular patients with eplerenone based on modeling studies (Based on US$ and the exchange rate on October 26, 2016)

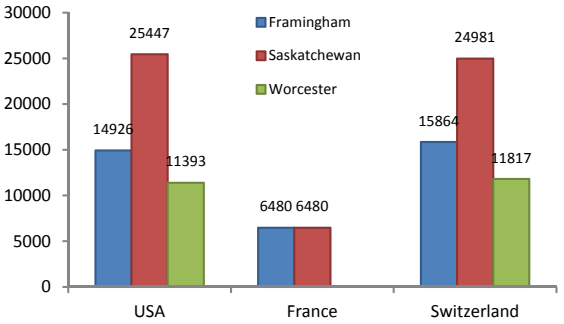

Fig. 5. The cost per extra QALY in the treatment of cardiovascular patients with eplerenone based on clinical trials and observational studies (Based on US$ and the exchange rate on October 26, 2016)

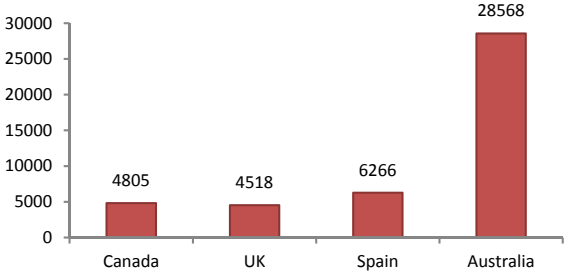

Fig. 6. The cost-effectiveness ratio of the treatment of cardiovascular patients with eplerenone based on modeling studies (Based on US$ and the exchange rates on October 26, 2016)

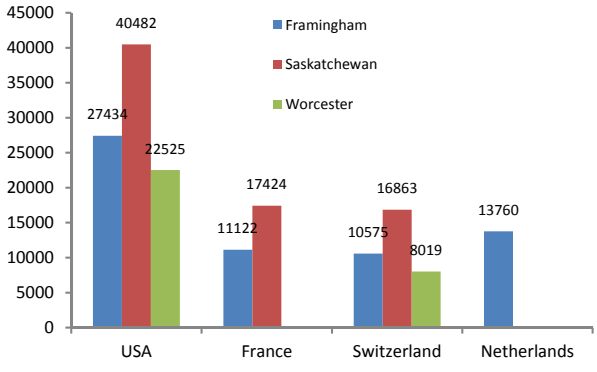

Fig. 7. The cost-effectiveness ratio of the treatment of cardiovascular patients with eplerenone based on clinical trials and observational studies (Based on US$ and the exchange rate on October 26, 2016)

Table 2. Results of quality assessment of the articles on cost-effectiveness of treating cardiovascular patients by eplerenone based on the Drummond Checklist

Row	*Study* / *Criteria*	Thanh et al. 2016	McKenna et al. 2012	Zhang et al. 2010	De Pouvourville et al. 2008	Ademi et al. 2016	Weintraub et al. 2005	Szucs et al.: 2006	Lee et al. 2014	Van Genugten et al: 2005	
1	Are good research questions asked?	√	√	√	√	√	√	√	√		√
2	Is comprehensive description of the competing alternatives offered?	×	×	×	×	×	√	×	×	×	
3	Is there any evidence of effectiveness of the program?	√	√	√	×	×	√	√	√	√	
4	Are all important and relevant costs and consequences identified?	√	√	√	√	√	√	√	√	√	
5	Are all important and relevant costs and consequences measured accurately?	√	√	√	√	√	√	√	√	√	
6	Are all important and relevant costs and consequences valued accurately?	√	√	√	√	√	√	√	√	√	
7	Are costs and outcomes adjusted for different times?	×	√	×	√	√	√	√	×	×	
8	Is an incremental analysis of costs and consequences of the competing alternatives done?	√	√	×	√	√	√	√	√	√	
9	Is the effect of uncertainty (sensitivity analysis) to predict costs and outcomes studied?	√	×	×	√	√	×	√	√	√	
10	Are all the associated issues with the users included in the analysis and presented results?	√	√	√	√	√	√	√	√		√

but treatment of cardiovascular patients usually requires a long period and the total cost would be very high. Also, these costs may be payable for the high-income countries such as the United States and Britain, but most patients in low- and middle-income countries will not be able to pay such prices. Therefore, if policymakers and health care planners decide to use this medicine in their own health care system, they should consider support mechanisms such as insurance.

The results of the quality assessment of reviewed articles indicated that articles had acceptable quality, and one of the main reasons for this could be the fact that the topic of the cost-effectiveness of eplerenone is so new, dominant, and important. This factor encourages the researchers to conduct more accurate articles and publish them in prestigious and high-quality journals. However, the researchers pay less attention to the application and generalization of the findings of the researches based on different users and consumers.

Eplerenone is a newcomer to pharmaceutical market and has not been used in many countries yet. This affects the way it should be used locally in those countries. The results of current research may fall useful while it come to application of related research results for policy making. One of the most important limitations of the present study was the heterogeneity of the results of studies that made the deductive reasoning and conducting quantitative analysis (meta-analysis) impossible. Thus, the explicit and precise estimation of the reported indicators was not possible, so this issue should be considered for using and generalizing the results.

Conclusion

Based on the results of the reviewed studies in this systematic review, it seems that eplerenone has acceptable cost-effectiveness compared to the current treatments, placebo, and similar medications. In this regard, these studies were designed and conducted in high-income countries and in different conditions with low- and middle-income countries; thus, the application of these results in low- and middle-income countries will be limited. Therefore, if policymakers and health care planners decide to use eplerenone in their own health care system, they should design and conduct specialized studies in their own local settings with the help of specialists and experts in health economics.

Acknowledgment

None.

Conflict of Interest: None declared.

References

1. Chung M, Asher R, Yamada D, Eagle K, Podrid P, Kowey P. Arrhythmias after cardiac and non-cardiac surgery. In Cardiac arrhythmia. 2nded. Philadelphia. Lippincott Williams Wilkins. 2001:631-8

2. Yan JH, Pan L, Zhang XM, Sun CX, Cui GH. Lack of efficacy of Tai Chi in improving quality of life in breast cancer survivors: a systematic review and meta-analysis. Asian Pac J Cancer Prev. 2014;15(8):3715-20.

3. Reinhardt UE, Cheng T-m. The world health report 2000-Health systems: improving performance. Bulletin of the World

Health Organization. 2000;78(8):1064-.

4. Nagavi M. The pattern of mortality within 23 provinces of Iran in 2003, Tehran - IRAN: Health Deputy, Iranian Ministry of Health, 2005.

5. Azami S, Tabrizi J, Abdollahi L, Yari Fard Kh, Daemi A, Sadati M, et al. Knowledge and Attitude of Top Managers toward Accreditation; in Tabriz and Ardabil Teaching Hospitals. Health. 2012;3(2):7-15.

6. Rezazadeh E, Hachesu PR, Rezapoor A,Alireza K. Evidence-based medicine: Going beyond improving care provider viewpoints, using and challenges upcoming. J Evid Based Med. 2014 Feb;7(1):26-31.

7. Rezapour A, Ebadifard Azar F, Azami Aghdash S, Tanoomand A, Hosseini Shokouh SM, Yousefzadeh N, et al. Measuring equity in household's health care payments (tehran-iran 2013): Technical points for health policy decision makers. Med J Islam Repub Iran. 2015;29:246

8. Chan PS, Soto G, Jones PG, Nallamothu BK, Zhang Z, Weintraub WS, et al. Patient health status and costs in heart failure: insights from the eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS). Circulation. 2009;119(3):398-407.

9. Mazdaki A, Ghiasvand H, Sarabi Asiabar A, Naghdi S,Aryankhesal A. Economic evaluation of test-and-treat and empirical treatment strategies in the eradication of helicobacter pylori infection; a markov model in an iranian adult population. Med J Islam Repub Iran. 2016;30:327

10. Pinto-Prades JL, Farreras V, de Bobadilla JF. Willingness to pay for a reduction in mortality risk after a myocardial infarction: an application of the contingent valuation method to the case of eplerenone. Eur J Health Econ. 2008;9(1):69-78.

11. Danjuma MI, Mukherjee I, Makaronidis J, Osula S. Converging indications of aldosterone antagonists (spironolactone and eplerenone): a narrative review of safety profiles. Curr Hypertens Rep. 2014;16(2):013-0414.

12. Pelliccia F, Rosano G, Patti G, Volterrani M, Greco C, Gaudio C. Efficacy and safety of mineralocorticoid receptors in mild to moderate arterial hypertension. Int J Cardiol. 2014;24(14):02087-7.

13. Barnes BJ, Howard PA. Eplerenone: a selective aldosterone receptor antagonist for patients with heart failure. Ann Pharmacother. 2005;39(1):68-76.

14. Gupta S, Fugh-Berman AJ, Scialli A. Ethics and eplerenone. J Med Ethics. 2013;39(2):110-4.

15. Ademi Z, Pasupathi K, Krum H, Liew D. Cost effectiveness of eplerenone in patients with chronic heart failure. Am J Cardiovasc Drugs. 2014;14(3):209-16.

16. Zhang Z, Mahoney EM, Kolm P, Spertus J, Caro J, Willke R, et al. Cost effectiveness of eplerenone in patients with heart failure after acute myocardial infarction who were taking both ACE inhibitors and beta-blockers: subanalysis of the EPHESUS. Am J Cardiovasc Drugs. 2010;10(1):55-63.

17. de Pouvourville G, Solesse A, Beillat M. Cost-effectiveness analysis of aldosterone blockade with eplerenone in patients with heart failure after acute myocardial infarction in the French context: the EPHESUS study. Arch Cardiovasc Dis. 2008;101(9):515-21.

18. McKenna C, Walker S, Lorgelly P, Fenwick E, Burch J, Suekarran S, et al. Cost-effectiveness of aldosterone antagonists for the treatment of post-myocardial infarction heart failure. Value Health. 2012;15(3):420-8.

19. S Khan K, Kunz R, Kleijnen J, Antes G. Systematic reviews to support evidence-based medicine. Mazurek Melnyk B, editor.2011.

20. Thanh NX, Ezekowitz JA, Tran DT, Kaul P. Cost Effectiveness of Eplerenone for the Treatment of Systolic Heart Failure with Mild Symptoms in Alberta, Canada. Am J Cardiovasc Drugs. 2016;16(5):365-76.

21. Ademi Z, Pasupathi K, Liew D. Cost-effectiveness of eplerenone compared to usual care in patients with chronic heart failure and nyha class ii symptoms, an Australian perspective. Medicine. 2016;95(18): e3531.

22. Weintraub WS, Zhang Z, Mahoney EM, Kolm P, Spertus JA, Caro J, et al. Cost-effectiveness of eplerenone compared with placebo in patients with myocardial infarction complicated by left ventricular dysfunction and heart failure. Circulation. 2005;111(9):1106-13.

23. Szucs TD, Holm MV, Schwenkglenks M, Zhang Z, Weintraub WS, Burnier M, et al. Cost-effectiveness of eplerenone in patients with left ventricular dysfunction after myocardial infarction--an analysis of the EPHESUS study from a Swiss perspective. Cardiovasc Drugs Ther. 2006;20(3):193-204.

24. Lee D, Wilson K, Akehurst R, Cowie MR, Zannad F, Krum H, et al. Cost-effectiveness of eplerenone in patients with systolic heart failure and mild symptoms. Heart. 2014;100(21):1681-7.

25. van Genugten M, Weintraub W, Zhang Z, Voors A. Cost-effectiveness of eplerenone plus standard treatment compared with standard treatment in patients with myocardial infarction complicated by left ventricular systolic dysfunction and heart failure in the Netherlands. Neth Heart J. 2005;13(11):393-400.

26. Croom KF, Plosker GL. Eplerenone : a pharmacoeconomic review of its use in patients with post-myocardial infarction heart failure. Pharmacoeconomics. 2005;23(10):1057-72.

27. Craft J. Eplerenone (Inspra), a new aldosterone antagonist for the treatment of systemic hypertension and heart failure. Proceedings (Baylor University Medical Center). 2004;17(2):217-20.

28. Rossignol P, Cleland JG, Bhandari S, Tala S, Gustafsson F, Fay R, et al. Determinants and consequences of renal function variations with aldosterone blocker therapy in heart failure patients after myocardial infarction: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study. Circulation. 2012;125(2):271-9.

29. Pelliccia F, Patti G, Rosano G, Greco C, Gaudio C. Efficacy and safety of eplerenone in the management of mild to moderate arterial hypertension: systematic review and meta-analysis. Int J Cardiol. 2014;177(1):219-28.

30. Yano Y, Hoshide S, Tamaki N, Nagata M, Sasaki K, Kanemaru Y, et al. Efficacy of eplerenone added to renin-angiotensin blockade in elderly hypertensive patients: the Jichi-Eplerenone Treatment (JET) study. J Renin Angiotensin Aldosterone Syst. 2011;12(3):340-7.

31. Williams GH, Burgess E, Kolloch RE, Ruilope LM, Niegowska J, Kipnes MS, et al. Efficacy of eplerenone versus enalapril as monotherapy in systemic hypertension. Am J Cardiol. 2004;93(8):990-6.

32. Rossignol P, Menard J, Fay R, Gustafsson F, Pitt B, Zannad F. Eplerenone survival benefits in heart failure patients' post-myocardial infarction are independent from its diuretic and potassium-sparing effects. Insights from an EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) substudy Am J Col Cardiol. 2011;58(19):1958-66.

33. Burgess ED, Lacourciere Y, Ruilope-Urioste LM, Oparil S, Kleiman JH, Krause S, et al. Long-term safety and efficacy of the selective aldosterone blocker eplerenone in patients with es-

sential hypertension. Clin Therapeut. 2003;25(9):2388-404.

34. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. for the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309 -21.