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Cost Effectiveness Analysis Rivaroxaban Plus Aspirin versus Aspirin alone in Treatment Cardiovascular Diseases: A Systematic Review

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Abstract

Background: Cardiovascular diseases (CVDs) are one of the chronic diseases and the leading cause of death worldwide. More people die from CVDs worldwide than from any other cause each year. The effects of CVDs are not limited to mortality and morbidity but also have important health and economic outcomes.

Methods: This was a systematic review that evaluated the economic evaluation of rivaroxaban plus aspirin compared with aspirin alone for the treatment of CVDs. The present study reviewed articles that performed a complete economic evaluation, including cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis related to the economic evaluation of rivaroxaban compared to enoxaparin for knee replacement patients during the years 2007 and 2023. In order to find relevant studies, databases including Pubmed, Web of Science, Embase, Scopus, Economic Evaluations Database, and Proquest were searched. Inclusion criteria included Studies that carried out a complete economic evaluation including cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis in relation to the economic evaluation of rivaroxaban plus aspirin compared to aspirin alone for CVD patients, economic evaluation studies carried out using decision analysis models based on the economic evaluation approach, full-text studies, English studies, and were studies published between 2007 and 2023. Exclusion criteria also included partial economic evaluation (such as effectiveness evaluation, cost evaluation, and quality of life evaluation), studies of low methodological quality based on the CHEERS checklist, non-English studies and all protocols, conference abstracts, and letters-to-the-editor

Results: After searching various databases, all retrieved articles were entered into EndNote software, and duplicates were removed. The remaining studies were reviewed independently by two relevant researchers. At this stage, preferred reporting items for systematic reviews (PRISMA) were used to retrieve the final articles. Out of 1048 studies, nine studies met the inclusion criteria. The economic evaluation studies included in the present study were conducted between 2018 and 2023. Cost-effectiveness analysis (CEA) was used in all studies.

Conclusion: The findings of the present study showed that rivaroxaban plus aspirin is more cost-effective than aspirin alone in the patient with CVDs, But to generalize the results to other countries of the world, more studies are needed

Keywords: Cost-Benefit Analysis, Rivaroxaban, Aspirin, Cardiovascular Disease

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↑What is "already known" in this topic:
Cardiovascular diseases are the first cause of death in the world. In other words, more people around the world die from cardiovascular diseases than any other cause. About three-quarters of deaths from heart diseases occur in countries with a low or middle economic level. Most cardiovascular diseases are preventable, and due to risk factors such as smoking, improper diet, obesity and overweight, inactivity, and alcohol consumption, the mortality rate of these diseases can be reduced.

→What this article adds:
Rivaroxaban plus aspirin is more cost-effective than aspirin alone in patient with CVDs. Among these studies, only one study mentioned indirect costs, while these costs can play a major role in increasing the costs of the disease.The generalization of economic evaluation studies should be done with caution due to the limitations of these studies.

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Introduction

Cardiovascular diseases (CVDs), such as ischemic heart disease and stroke, are the principal causes of death and one of the leading causes of disability in high-income countries (1, 2). Individuals with coronary artery disease (CAD) or peripheral artery disease (PAD) constitute a large proportion of patients at high risk of atherothrombotic cardiovascular events and death (3).

Cardiovascular diseases (CVDs) impose a serious burden on healthcare systems, both in epidemiological and economic terms, with a mortality rate ranging from 481 to 680 deaths per 100,000 people in Eastern Europe, North Asia, the Middle East, and parts of Africa (4). CVDs can lead to disability, greatly affect the productivity of the active labor force, and result in reduced gross domestic product (GDP) and national income (2). In 2017, CVDs were the main cause of life years lost (LYs) (5, 6). It is estimated that the global cost generated by CVDs will increase from $863 billion in 2012 to $1044 billion in 2030 (i.e., cost per capita of $125) (7).

In these populations, the role of antiplatelet therapy with aspirin as an anchor strategy for secondary cardiovascular prevention is largely recognized, with a 19% lower risk of major adverse cardiovascular events (MACE) and a 9% lower risk of cardiovascular death than placebo (3).

Rivaroxaban is a selective direct Factor Xa inhibitor that has been shown to be effective for the prevention and treatment of venous thromboembolism (VTE) and the prevention of stroke or systemic embolism in patients with atrial fibrillation in several large randomized controlled trials. Rivaroxaban 2.5 mg or 5 mg twice daily(bid)also reduced the risk of non-fatal and fatal cardiovascular (CV) events in patients with recent acute coronary syndrome (8).

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial demonstrated that rivaroxaban 2.5 mg twice daily in combination with aspirin 100 mg once daily was more effective than aspirin 100 mg once daily for the prevention of cardiovascular (CV) death and stroke, or MI in patients with stable coronary artery disease (CAD) or peripheral artery disease (PAD), whereas rivaroxaban (5 mg twice-daily without aspirin) was not beneficial .The use of a combination of rivaroxaban 2.5 mg BID with aspirin significantly improves outcomes in patients and understanding the potential cost implications of this secondary prevention strategy will be important for many health providers and decision-makers (9).

Although new anticoagulants such as rivaroxaban can reduce the burden of disease, adding new and expensive drugs to patients' treatment regimens may impose a special financial and health burden on patients and the health system. To decide whether to use this combination for cardiovascular patients, it is necessary to determine its effectiveness (quality of life and survival of patients) and cost. Therefore, the economic evaluation of these drugs can play an important role in informing decision-makers, providing targeted interventions and producing scientific evidence for policy decisions, and ultimately ensuring better cost management, efficiency, and optimal allocation of limited financial resources of the health system. Therefore, the aim of the present study is to investigate the cost-effectiveness analysis of rivaroxaban plus aspirin versus aspirin alone in the treatment of cardiovascular diseases.

Methods

This was a systematic review that evaluated the economic evaluation of rivaroxaban plus aspirin versus aspirin alone in the treatment of Cardiovascular disease patients. The present study reviewed articles that performed a complete economic evaluation including cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis related to the economic evaluation of rivaroxaban compared to enoxaparin for knee replacement patients during the years 2007 to 2023. Given that rivaroxaban was patented in 2007 and approved for medical use in the United States in 2011, the study period from 2007 to 2023 was chosen. In order to find relevant studies, databases including Pubmed, Web of Science, Embase, Scopus, Economic Evaluations Database, and Proquest were searched. The search strategy was designed by combining keywords. To search for relevant articles, search keywords, synonyms and their combination with OR and AND operators were used to increase search sensitivity. The search strategy for the PubMed database is as follows:

(“Cost benefit analysis” [Title/Abstract] OR “Cost effectiveness” [Title/Abstract] OR “Economic evaluation” [Title/ Abstract] OR “Cost utility” [Title/Abstract] AND (“Cardiovascular Disease” [Title/Abstract] OR “angiocardiopathy” [Title/Abstract] OR “angiocardiovascular disease” [Title/ Abstract]) AND (“Rivaroxaban” [Title/Abstract]) AND (“Aspirin” [Title/Abstract])

Inclusion and exclusion criteria

Inclusion criteria included: Studies that carried out a complete economic evaluation, including cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis in relation to the economic evaluation of rivaroxaban plus aspirin compared to aspirin alone for CVD patients, economic evaluation studies carried out using decision analysis models based on the economic evaluation approach, full-text studies, English studies, and were studies published between 2007 and 2023.

Exclusion criteria also included partial economic evaluation (such as effectiveness evaluation, cost evaluation, and quality of life evaluation), studies of low methodological quality based on the CHEERS checklist, non-English studies and all protocols, conference abstracts, and letters to editor.

Quality assessment of the methodology of the studies

The quality of the studies was assessed using the consolidated health economic evaluation reporting standards (CHEERS) checklist. This checklist includes 5 questions with 24 criteria that examine the quality of each economic evaluation study in terms of title and abstract / introduction and problem statement / methodology / findings / and discussion and conclusion in each country. The results of the quality assessment of the studies are presented based on the

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CHEERS checklist.

Data analysis

After searching various databases, all retrieved articles were entered into EndNote software, and duplicates were removed. The remaining studies were reviewed independently by two relevant researchers. At this stage, preferred reporting items for systematic reviews (PRISMA) were used to retrieve the final articles. In the first stage, the title and abstract of the studies were examined and the relevant items were selected according to the inclusion and exclusion criteria. In the next stage, if the selected full-text studies were carefully reviewed and the eligible studies were selected. The studies were reviewed by a third researcher in case of disagreement between the two researchers in each of these stages. For each study entered in the final stage, a spreadsheet was created in Excel, in which the basic information about the study, including author name, year of publication, country of origin, study population, cost-effectiveness, intervention, comparator, cost calculation basis, effectiveness calculation basis, and cost-effectiveness / cost saving, were entered.

Results

According to the initial search in the above-mentioned databases, 1048 articles were entered into the Endnote software. This figure was reduced to 750 articles after deleting duplicates. These articles were reviewed for the title, of which 681 were deleted, and 69 underwent abstract review in the next stage. Abstracts of 69 articles were reviewed and 19 articles were included in the study. The full text of these 19 studies was reviewed, of which 9 were selected based on inclusion and exclusion criteria for a more detailed review (Figure 1). A new and relevant study was not found while reviewing the references of the final articles.

Quality assessment

The CHEERS checklist was used to assess the quality of these nine studies. To avoid bias when assessing the quality of articles, the researcher was unaware of the basic information of the article, such as the author's name, country, and year of publication.

The results of the quality assessment of studies were acceptable, and no study was excluded based on quality criteria.The report quality of the five studies was evaluated using a 24-item CHEERS checklist and scores 1 (✓) and 0 (x) were respectively assigned for the cases that were fully observed and not observed. four articles were rated "excellent quality" with a score above 85% (Table 1).

Basic characteristics of the studies

After quality assessment, the data of the articles were extracted using the data extraction form (Table 2).

The economic evaluation studies included in the present study were conducted between 2018 and 2022. One of the reasons for the novelty of the articles is the identification and introduction of the combination of rivaroxaban and aspirin in recent years. Among the selected economic evaluation studies, two studies were conducted in 2018 (10, 11),

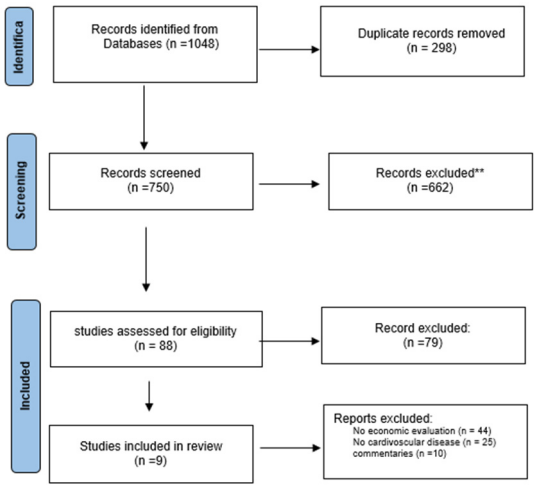

Figure 1. Results of the systematic literature search

four studies in 2020 (8, 12-14), one study in 2021 (15), and two studies in 2022 (9, 16). Among them, two were conducted in Australia (10, 11), one in England, Taiwan, Finland, Italian, Netherlands, and chinses (8, 12-15, 17). A study was conducted jointly in Canada, France and Germany (9). Cost-effectiveness analysis (CEA) was used in all studies. The perspective of eight studies was based on healthcare. Perspective was one of the society studies (16). Since these two drugs are used for different CVDs, a column called the disease type was added to the data table. In four of the nine studies, CVD was mentioned in general (10, 12, 13, 16) and carotid artery disease and peripheral artery disease were considered in the other five studies (8, 11, 14-15, 9). In all intervention studies, rivaroxaban plus aspirin was compared with aspirin alone. In economic evaluations, it is necessary to specify the time period both for the review and follow-up of the intervention and the outcomes and subsequent costs. The time period was not the same for all studies.

In these studies, time periods included 20 years, 15 years, 10 years, and 3 months. In four studies, the time horizon was lifetime (8, 14-16, 9). Markov model was used in all studies.

Indirect costs, including lost productivity, were calculated only in one study (12). In other studies, treatment costs, periodic treatment costs, drug costs, and general direct costs were calculated. Life years gained (LYGs) and quality-adjusted life (QALY) were two parameters in determining the effectiveness of studies. QALY was used in three studies to determine effectiveness (15,9,16). Discount rates varied in the studies. The discount rate was 3.5%, 3%, and 3.5-5% in studies, respectively. The threshold value was expressed in all studies. Sensitivity analysis was performed in all studies.

In all studies, rivaroxaban plus aspirin was more expensive than aspirin alone but more effective.

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Table 1. Quality Assessment

Author	Title	Abstract	Background	Population characteristic	Setting and location	Perspective	Comparators described	Time horizon	Discount rate	Outcomes and relevance	Measurement of effectiveness	Preference based outcomes	Estimating resources and costs	Currency, date	Model choice described	Assumptions	Analysis methods	Parameters of values	Incremental costs	sensitivity analyses	Heterogeneity explained	Findings and limitations	Funding source	Potential conflict of interest	Total	Percent satisfied
Zanfina Ademi	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	#	✓	×	✓	×	✓	✓	✓	✓	#	✓	×	×	19	79%
Ella Zomer	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	×	✓	✓	✓	✓	#	✓	✓	×	20.5	85%
Martin R. Cowie	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	#	✓	×	✓	×	✓	✓	✓	✓	#	×	✓	✓	20	83%
Mei-Chuan Lee	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	#	✓	✓	✓	22.5	93%
Erkki Soini/	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	×	✓	✓	✓	✓	✓	✓	×	×	20	83%
Pietro Ferrara	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	22	91%
Andre Lamy	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	#	✓	✓	✓	×	✓	✓	✓	✓	#	✓	×	×	19	79%
Tianyu Feng	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	#	✓	×	×	20.5	85%

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Table 2. Description of basic characteristics

Author/Year	Country	Diseases	intervention	Com-para-tor	perspective	Model	Time	COST	Health outcome
Zanfina Ademi/2018 (10)	Australia	cardiovascular disease	rivaroxaban plus aspirin	Aspi-rin	Australian healthcare perspective	Markov model	20 year	Direct cost	QALY, YoLS
Ella Zomer/2018 (11)	Australia	peripheral or carotid artery disease	rivaroxaban plus aspirin	Aspi-rin	Australian healthcare perspective	Markov model	20 year	Direct cost	QALY, YoLS
Petersohn/2020 (13)	Netherland	cardiovascular disease	rivaroxaban plus aspirin	Aspi-rin	Dutch societal perspective	Markov model	3 months	Direct and Indirect cost	QALY, YoLS
Martin R. Cowie/2020 (8)	UK	chronic coronary artery disease or peripheral artery dis-ease	rivaroxaban plus aspirin	Aspi-rin	UK National Health System perspective	Markov model	lifetime	Direct cost	QALY, LYS
Mei-Chuan Lee/2020 (13)	Taiwan	chronic cardiovascular diseases	rivaroxaban plus aspirin	Aspi-rin	Taiwan national payer's perspective	Markov model	15 year	Direct cost	QALY, LYS
Erkki Soini/2020 (14)	Finland	chronic coronary syndrome (CCS) or symptomatic pe-ripheral artery disease (PAD) in	rivaroxaban plus aspirin	Aspi-rin	public payer	Markov model	lifetime	Direct cost	QALY, LYG
Pietro Ferrara/2021 (16)	Italy	Coronary and Peripheral Artery Diseases	rivaroxaban plus aspirin	Aspi-rin	Italian National Healthcare Service	Markov model	lifetime	Direct cost	QALY
Andre Lamy/2022 (10) (9)	Canada, France and Germany	stable coronary artery disease (CAD) or peripheral artery disease (PAD)	rivaroxaban plus aspirin	Aspi-rin	-	Markov model	lifetime	Direct cost	QALY
Tianyu Feng/2022 (16)	China	Cardiovascular Disease	rivaroxaban plus aspirin	Aspi-rin	Chinese healthcare system.	Markov model	2 & 5 years	Direct cost	QALY

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Table 3. Description of cost-effectiveness study characteristics

			Total Cost		Total cost (USD 2022 PPP)		QALY		LYS/LE/ YoLS						
First Author	Country	Study design	A	B	A	B	A	B	A	B	ICER	ICER (USD 2022 PPP)	Discount (cost effect)	threshold	Sensitivity analysis
Zanfia Ademi	Australia	Cost effectiveness	AUD$ 67630903	AUD$ 55574557	$ 45966431	$3777214	7382	6996	9529	9013	ICER of AUD$ 23,560 YoLS and AUD$ 31,436 QALY	ICER of $ 16012 YoLS and $ 21365 QALY	5%	AUD$ 50000	Yes
Ella Zomer	Australia	Cost effectiveness	AUD$ 62945575	AUD$ 6087472	$ 42781973	$4137448	6273	6017	8224	7970	ICER of AUD$ 27037 YoLS and AUD$ 31,436 QALY	ICER of 18376 YoLS and 21365 QALY	5%	AUD$ 50000	Yes
Petersohn	Nether-land	Cost effectiveness	£109,941	£99,807	$ 122650	$111344	8.089	7.773	12.13	11.69	£ 32,035 per QALY	35738 per QALY	1.5%	£ 50000	Yes
MartinR. Cowie	UK	Cost effectiveness	£13947	£8126	$14875	$8667	9.7	9.3	12.0	11.6	£ 16360 per QALY / £ 14380 per life years	$17449 per QALY / £ $15337per life years	3.5%	£ 30000	Yes
Mei-Chuan Lee	Taiwan	Cost effetiveness	$ 469,834	$ 430,608	$ 469834	$430608	16.47	16.00	31.83	30.6	$ 83,459 per QALY / $ 33,526 per life years	$ 83,459 per QALY / $ 33,526 per life years	10%	25456 and 76368	Yes
Erkki Soini	Finland	Cost effectiveness	`€41788	€38547	$44571	$41114	10.3	9.9	12.99	12.52	€ 8031per QALY gained and € 6834 per LYG	$ 8565 per QALY gained and $ 7289 per LYG	3%	€ 25254	Yes

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Table 3. Continued

First Author	Country	Study design	Total Cost A	Total Cost B	Total cost (USD 2022 PPP) A	Total cost (USD 2022 PPP) B	QALY A	QALY B	LYS/LE A	LYS/LE B	ICER	ICER(USD 2022 PPP)	Discount(cost effect)	threshold	Sensitivity analysis
Pietro Ferrara	Italy	Cost effectiveness	€ 18643	€ 12858	$19884	$13714	9.62	9.27	-	-	ICER of €16522 per QALY	ICER of $ 17622 per QALY	3.5%	€40000	Yes
Andre Lamy	Canada, France and Germany	Cost effectiveness	Canada$49041/France $44062 / Germany $41285	Canada $44424 /France $32406/ Germany $29276	Canada$49041/France $44062 / Germany $41285	Canada $44424 /France $32406/ Germany $29276	1.17	1.17	-	-	ICER for canada $3946/for france $9962/ for germany $10264	ICER for canada $3946/for france $9962/ for germany $10264	3%	$ 25000	Yes
Tianyu Feng	China	Cost effectiveness	$ 4818	$ 253.3	$ 4818	$ 2533	11.7	11.4	-	-	$ 15045	$ 15045	3%	$ 11000	Yes

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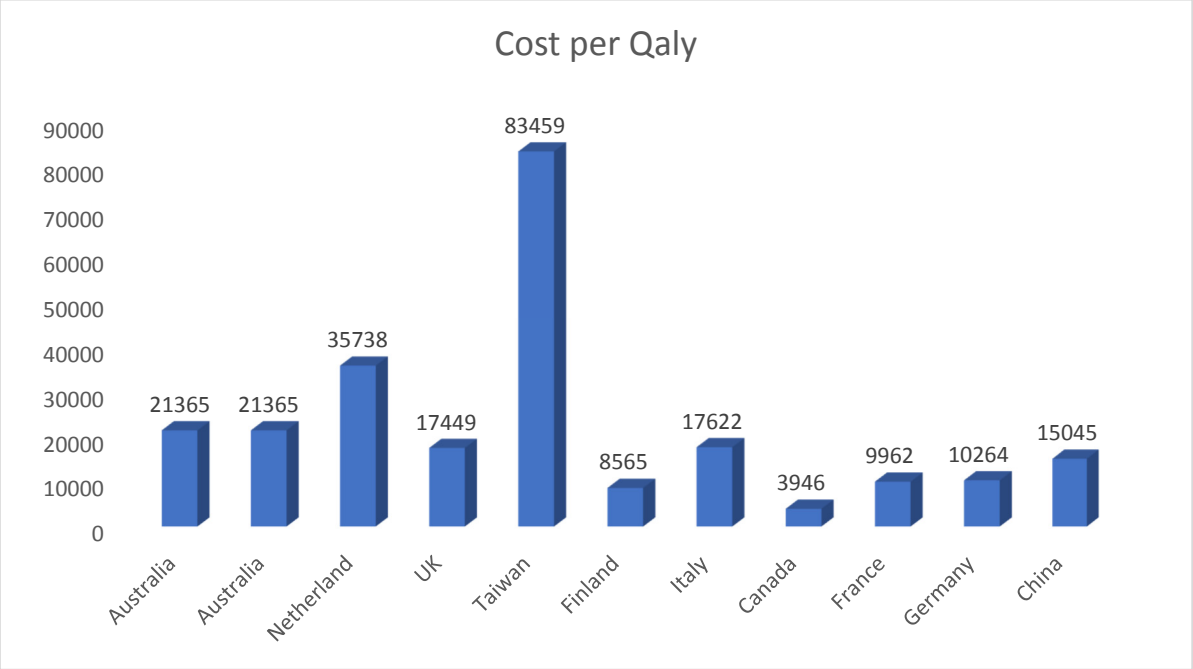

Figure 2. The cost per QALY (USD 2022 PPP)

LYGs and QALY were longer in all studies in the case of rivaroxaban plus aspirin together than aspirin alone. The cost per QALY was specified in all studies (Table 3).

The highest and lowest cost-effectiveness rates were reported in Taiwan and Canada at 83459$ and 3946$, respectively (Figure 2). In all studies, rivaroxaban plus aspirin was more cost-effective than aspirin alone.

Discussion

Ischemic cardiovascular disease with progressive atherosclerosis and acute thrombotic complications is the most common cause of morbidity and mortality worldwide (17).

Economic evaluation including cost-effectiveness with determination, calculating and comparing costs and benefits of health and treatment interventions help health systempolicymakers to apply health and treatment interventions at high benefit or higher effectiveness (18).

Clinical trials of cardiovascular outcomes of anticoagulant drug strategies indicate that there was a 24% reduction in the composite of cardiovascular (CV) death, stroke, or myocardial infarction as well as an 18% reduction in overall mortality rate among individuals with CAD or PAD who had optimal secondary prevention therapies, namely rivaroxaban (2.5 mg/twice daily) plus aspirin (100 mg/ once a day) compared to aspirin alone (100 mg) (19). Rivaroxaban is a specific active factor X inhibitor with excellent bioavailability and a half-life of approximately three hours, which not only releases factor Xa inhibitors but also inhibits prothrombinase and factor Xa activities with clots (20). Nowadays, in addition to paying attention to the pharmacological value and clinical effectiveness of drugs, their economic aspects and cost-effectiveness in comparison with existing alternative and conventional drugs are being considered (21, 22). The present study evaluated the cost-effectiveness of rivaroxaban plus aspirin compared with aspirin alone in reducing g the clinical outcomes of CVDs (including progressive coronary atherosclerosis, acute thrombotic complications, CAD, PAD or other conditions) based on various health economic assessment studies. All studies have been conducted in developed countries such as Australia, Taiwan, Italy, and the Netherlands. On the other hand, these studies have been conducted in recent years (2018 to 2022) following the publication of the results of a COMPASS trial (23), indicating the infancy of the subject matter.

In five separate health economic assessment studies, a similar Australian research team in 2018 evaluated the cost-effectiveness of rivaroxaban plus aspirin compared to aspirin alone in reducing clinical adverse outcomes in patients with PAD or CAD and people with stable coronary artery disease (8, 10, 11, 14-9). Both studies used the cost perspective of the provider in Australia and the willingness-to-pay (WTP) with a payment threshold of 50,000 per QALY. The results showed that the rivaroxaban plus aspirin strategy was more cost-effective than aspirin alone in preventing recurrent cardiovascular events in both groups of patients. The present study also reviewed a study conducted in Italy using the perspective of the provider and taking into account the WTP or the threshold value of 40,000 euros per QALY. The results of this study are consistent with previous studies and reported that rivaroxaban plus aspirin was more cost-effective than aspirin alone in preventing recurrent cardiovascular events in patients with CAD or PAD (13). On the other hand, Peterson et al. (2020) used a social perspective in their study in the Netherlands. They reported that lifelong use of rivaroxaban plus aspirin, with WTP and the threshold value of 50,000 euros per QALY, improves

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health outcomes in people with PAD, especially those with other underlying diseases and is a cost-effective intervention. However, they found that combination drug intervention was not cost-effective in older patients as well as CAD people (15).

Although Lee et al. set a relatively higher level of WTP and threshold compared to other studies 76,000 dollars), their study provided no evidence of the cost-effectiveness of the rivaroxaban + aspirin strategy as compared to aspirin alone for prophylactic purposes in patients with stable coronary artery disease. However, there was evidence of the cost-effectiveness of this combination in patients with CAD (13). One of the strengths of the studies reviewed in this review was that the selected studies benefited from the relatively more comprehensive costing perspectives of the provider and the social perspective and were relatively similar in terms of lifetime horizon, threshold values, and WTP, which facilitate the comparison of their results. On the other hand, the weakness of the present study is the limited number of studies and the infancy of the subject matter. On the other hand, as referred to earlier, the clinical data of all five selected studies have been extracted only from one clinical trial in 2017 (19) and their population is the same in this respect. There may be some biases in this clinical trial that have led to economic evaluation studies. It is suggested to carry out future economic evaluation studies based on the clinical data of newer trials that have examined the long-term outcomes of using a combination drug strategy or based on a set of clinical trial studies through meta-analysis.

Conclusion

The findings of the present study showed that rivaroxaban plus aspirin is more cost-effective than aspirin alone in the patient with CVDs.

Limitation

In this study, it was tried to avoid any bias by conducting a comprehensive and systematic search. However, the failure to follow a standard cost detection approach in the selected studies reduced the consistency of the reported results; hence, it might prevent the analysis of the reported results on the basis of different dimensions.

Authors' Contributions

A senior researcher OR led and coordinated all aspects of the review, including but not limited to preparation of the literature search, screening of relevant material, extraction, and analysis of data, interpreting the results of the meta-analytic procedures, investigating bias, and preparing the final report. Two researchers AR, LE conducted independent duplicate screening and data extraction. Disagreements be resolved through discussion and consensus. A two-step process be used to select studies. First, the project coordinator NA and AR and Two researchers OR and LE screened citation titles, abstracts, and keywords and classified each citation as "include," "exclude," "unclear," or "duplicate." Next, the full-text reports for citations classified as "include" and "unclear" will be read in full, and a final decision on inclusion or exclusion was made using a standardized form outlining the inclusion and exclusion criteria.

Ethical Considerations

This study was supported by the School of Pharmacy,Mashhad University of Medical Sciences (with ethical code IR.MUMS.PHARMACY.REC.1402.025).

Acknowledgment

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Conflict of Interests

The authors declare that they have no competing interests.

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