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Cost-effectiveness and budget impact analysis of rivaroxaban with or without aspirin compared to aspirin alone in patients with coronary and peripheral artery diseases in Iran

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Abstract

Background Low-dose aspirin and rivaroxaban are the cornerstone treatment for cardiovascular prevention in patients with peripheral artery disease (PAD) and/or stable coronary artery disease (SCAD). The combination of rivaroxaban with aspirin imposes a synergistic effect on the inhibition of factor-induced platelet aggregation. The present work aimed at comparing the cost-utility and cost-effectiveness of rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban alone (5 mg twice daily) with aspirin alone in patients with peripheral artery disease (PAD) or coronary artery disease (CAD) and related subgroups.

Methods This pharmacoeconomic study was performed based on the insurance organization and utilized a state-transition decision Markov model. From the COMPASS trial, Clinical efficacy and Clinical events were collected. Health outcomes and cost were assessed over a 20-year time horizon (lifetime). The direct costs of medical services were included in the analysis. The results were stated based on Incremental Cost-Utility (ICUR) and Incremental Cost Effectiveness Ratio (ICER). Uncertainty was assessed utilizing deterministic and probabilistic sensitivity analyses. Discount rates of .058 and .03 were included for cost and effectiveness data, respectively. The budget impact based on the Markov model was estimated as the financial burden resulting from the insurance coverage of rivaroxaban.

Results In the total of CAD and PAD patients, treatment with rivaroxaban plus aspirin and rivaroxaban alone were more expensive than the aspirin alone, but also more effective, resulting in ICUR being $4594/QALY and $13601/QALY respectively, and for ICER being $3348/LYG and $9901/LYG. In PAD patients rivaroxaban plus aspirin had higher effectiveness than aspirin alone that ICUR and ICER being $11929/QALY and $9896/LYG respectively. In CAD patients, treatment with rivaroxaban plus aspirin was expensive and less effective than aspirin alone. The estimated annual budget impact was $28,253,135 for the rivaroxaban plus aspirin and $292,593,909 for the rivaroxaban alone in the total of CAD and PAD patients.

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Conclusions This study showed that rivaroxaban plus aspirin is a cost-effective alternative in PAD and total of CAD and PAD patients. In CAD patients, rivaroxaban plus aspirin and rivaroxaban alone were not cost-effective.

Keywords Cost-effectiveness, Cost-utility, CAD, PAD, Rivaroxaban, Aspirin

Background

Atherosclerosis is one of the leading causes of morbidity and mortality in most countries [1]. Peripheral artery disease (PAD), and Chronic coronary artery disease (CAD) result from atherosclerosis and occur by a buildup of plaque in the arteries. Atherosclerosis leads to coronary artery disease (CAD) by restricting blood flow to the heart, or peripheral artery disease (PAD), resulting in blockage and stenosis of noncerebral and noncoronary arteries, which impact the arteries of the lower limbs. The patients with PAD or CAD impose a substantial risk of atherothrombotic events, ischemic stroke (IS), and myocardial infarction (MI). PAD and CAD are reported to affect about 13% and 7.2% of people aged greater than 50 years [2]. The prevalence of CAD and PAD disease in patients over 40 years old in the Iranian population is reported to be 21.8% and 9.8%, respectively [3, 4]. Both lead to a considerable economic burden on the health system and society [5].

Risk reduction with antiplatelet and anticoagulant therapies are cornerstones in preventing ischemic and cardiovascular limb events. Treatment strategies for PAD have involved mainly statins and proper antithrombotic medications [6]. Acetylsalicylic acid (aspirin) alone denotes the standard of care for preventing atherothrombotic events in the patients with chronic PAD or CAD. Despite the wide range of usage, aspirin, which is effective in preventing atherothrombotic events in patients with chronic PAD or CAD, related vascular events risk is still high [7–9].

Novel anticoagulant drugs, such as Rivaroxaban were recommended to prevent and manage atherothrombotic events, such as stroke, venous thromboembolism (VTE), as well as systemic embolism events in atrial fibrillation in patients with CAD and PAD. In many studies, rivaroxaban, a selective direct Factor Xa inhibitor, has been recommended to treat stroke and venous thromboembolism (VTE) in patients with atrial fibrillation [10–12]. The outcomes of "the Cardiovascular Outcomes for People utilizing Anti-Coagulation Strategies (COMPASS)" trial within the 23 months observation indicated that rivaroxaban 2.5 mg daily twice plus aspirin had a positive effect of preventing atherothrombotic events in adult patients with PAD or CAD at higher risk of ischemic events compared with other treatment strategies [13, 14]. Besides, Fitchett et al. reported a relative risk reduction in ischemic stroke (IS), cardiovascular death, or myocardial infarction (MI), and all-cause death by 20% [15].

Based on a health economics analysis, various therapeutic approaches have different costs for long-term management and initial treatments. Although there are few cost-effective strategies for rivaroxaban plus aspirin in PAD and CAD patients [6, 16, 17]. The cost-effectiveness of Rivaroxaban compared with aspirin has not yet been determined in Iran. Because of high medical expenditure of rivaroxaban in Iran, adding an expensive new drug to the treatment regimen may put a significant financial burden on the patients and society. Thus, this paper aimed to approximate the costs, quality-adjusted life-years (QALYs), as well as cost-effectiveness of aspirin 100 mg alone with vs. Rivaroxaban 2.5 mg combined with aspirin 100 mg vs. Rivaroxaban 5 mg alone in patients with CAD, patients with PAD and in total CAD and PAD patients without separation.

Materials and methods

This is an economic evaluation to study the cost-effectiveness and cost-utility of rivaroxaban with or without aspirin than aspirin alone in patients with PAD or CAD using the Markov model.

Study population

The target population was 10,000 hypothetical patients with two diseases, CAD and PAD, without drug contraindications, concomitant diseases, or simultaneous treatments. The average age of patients is 54 years based on the average age of this disease in Iran [18]. Furthermore, based on COMPASS clinical trial studies, it was assumed that these patients had no higher bleeding risk, a recent history of stroke or hemorrhagic stroke, severe HF, advanced chronic kidney disease (estimated GFR less than 15 ml/min). Besides, they were assumed not to receive dual antiplatelet, anticoagulant, or other antithrombotic therapy with no cardiovascular conditions related to a poor prognosis [19–21].

Perspective

The analysis of this study was done from the perspective of insurance, so only direct medical costs are included.

Comparators

Three possible options are rivaroxaban only 5 mg twice a day, combined rivaroxaban 2.5 mg twice daily with

aspirin 100 mg once a day, and an aspirin regimen only with a dose of 100 mg once a day, were considered.

Time horizon

Early determination of clinical outcomes, and economic costs of CAD and PAD diseases is difficult. Therefore, the time horizon of the analysis with a cycle length of 3 months for 20 years (up to the life expectancy at birth in Iran) [22] was used.

Discount rate

Since the time horizon of study was a lifetime, discounting was necessary, and costs and utility values were discounted at a discount rate of 5.8% and 3%, respectively [23].

Choice of outcomes measures

Since CAD and PAD diseases affect the quality of life and longevity of patients, health consequences were evaluated based on effectiveness LYG (Life Years Gained), cost, incremental cost-effectiveness ratio (ICER), QALY, and incremental cost-utility ratio (ICUR).

Model structure

A Markov model with three-month cycles was designed based on COMPASS clinical trial studies. Each cycle in Markov model had two conditions, such as acute events and states. The states include six scenarios: post-myocardial infarction (MI), stable cardiovascular diseases (CVDs) without clinical events, post-ischemic stroke (IS), post-heart failure (HF), post-hemorrhagic stroke (HS), and death. Thus, the acute events considered based on the most usual complications presented in the clinical trials in the model include recurrent CVDs (HS, MI, IS, acute limb ischemia [ALI], and cardiovascular death), non-recurrent CVDs, venous thromboembolism (VTE), HF, minor bleeding, major bleeding, and death. Markov model diagram is shown in Fig. 1.

Therefore, this model has assumptions: 1- All patients in the first cycle had stable CVD, and no clinical events happened in the first cycle. 2- For the patients who experienced events of VTE, ALI, major bleeding, or minor bleeding, treatment was discontinued for them for one month. 3- The patients who suffered MI stopped the diet, and dual antiplatelet drugs were prescribed. 4- The treatment effect was considered the same in all cycles. 5- The treatment conditions considered in the model were supposed to be independent and could not co-occur.

ICUR results were used to determine the cost-utility of interventions with threshold amount in Iran, which was equal to 1 time of 15222 PPP dollars [24]. All were done in Excel 2016 and Treeage 2020 software.

Resources and costs

Price date, currency, and conversion

Since this study was performed from the insurance perspective, only the direct medical costs were included. Three cardiology specialists extracted the number and type of medical services utilized by patients in two disease groups, CAD and PAD. To calculate the costs of medical services, we used the tariffs set by the Ministry of Health in Iran in 2022. Moreover, to get the prices of drugs from the official website of the Food and Drug Organization, with the link address irc.fda.gov.ir. The details of cost based on treatment events and states are given in Table 1. PPP dollars were utilized for converting the rate of Rial to Dollar, where each dollar equals 30697 PPP dollars [25].

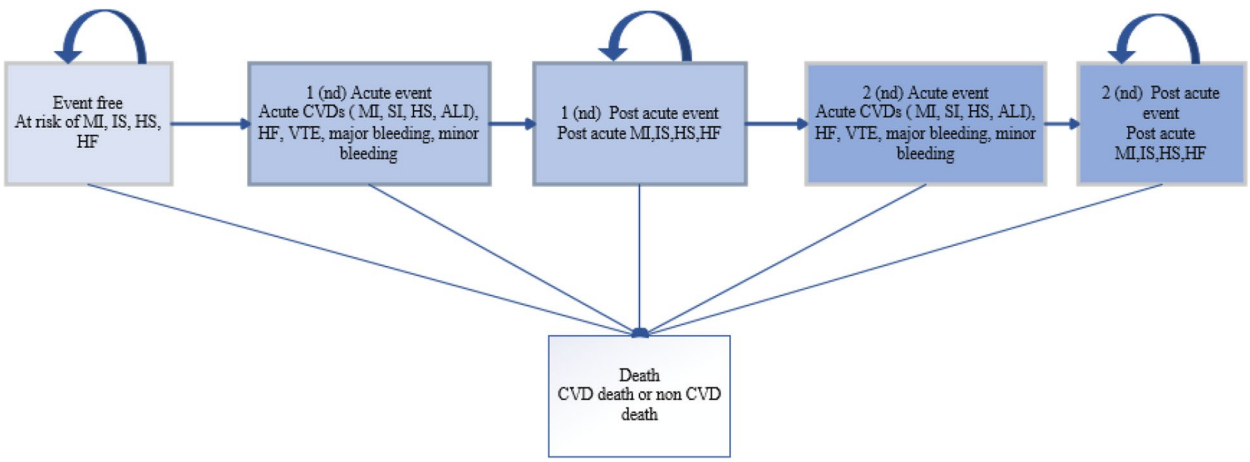

Fig. 1 Markov model diagram. CVD: Cardiovascular Disease, ALI: acute limb ischemia, HS: hemorrhagic stroke, HF: heart failure, IS: ischemic stroke, VTE: venous thromboembolism

Table 1 Model cost and utility inputs

Variable	Base case	Standard deviation	distribution	ref
Three months cost				
Rivaroxaban (2.5 mg twice per day)	158	31.6	gamma	[26]
Rivaroxaban (5 mg twice per day)	316	63.2	gamma	[26]
Aspirin (100 mg once per day)	8.2	1.64	gamma	[26]
Stable cardiovascular diseases	262	52.4	gamma	[27]
Myocardial infarction				
Event cost	5406	1081	gamma	[27]
State cost	292	58.4	gamma	[27]
Ischemic stroke				
Event cost	2851	570.2	gamma	[27]
State cost	583	116.6	gamma	[27]
Hemorrhagic stroke				
Event cost	2912	582.4	gamma	[27]
State cost	577	115.4	gamma	[27]
Acute limb ischemia	4883	976.6	gamma	[27]
Venous thromboembolism	2306	461.2	gamma	[27]
Heart failure				
Event cost	3045	609	gamma	[27]
State cost	1961	392.2	gamma	[27]
Major bleeding	2745	549	gamma	[27]
Minor bleeding	497	99.4	gamma	[27]
Utility score				
Stable cardiovascular disease	0.738	0.073	beta	[28]
Myocardial infarction	0.704	0.07	beta	[28]
Ischemic stroke	0.65	0.065	beta	[28]
Hemorrhagic stroke	0.65	0.065	beta	[28]
Heart failure	0.636	0.063	beta	[28]
Utility decrements for health events				
Acute limb ischemia	−0.157	0.016	beta	[29]
Venous thromboembolism	−0.111	0.01	beta	[29]
Decrement for major bleeding	−0.181	0.02	beta	[28]
Decrement for minor bleeding	−0.058	0.006	beta	[28]
Decrement for age	−0.0016	0.0007	beta	[28]

Utilities

To extract the patients' quality of life, the results of similar studies were used due to the lack of related paper in Iran. The utility values are considered the same in both treatment regimens. Clinical events that were not chronic, such as bleeding conditions, were considered to have disutility values. The utility values were adjusted based on the duration of model cycles. The utility values are provided in Table 1.

Transition probabilities

Transmission probabilities (probabilities of experiencing events) for the rivaroxaban plus aspirin arm, and the aspirin alone arm in CAD and PAD patients and total CAD and PAD patients were estimated from COMPASS clinical trials [19–21]. Detailed data on how to derive transition probabilities are provided in Table 2.

Transmission probabilities based on COMPASS trial data for various clinical events were reported for 23 months. These probabilities should be converted to three-month probabilities based on model cycles, so this adjustment was made according to the study of Briggs et al. [30]. The transmission probabilities for "death from no cardiovascular causes" were calculated by subtracting the probability of cardiovascular mortality from the probability of death from all causes in

Table 2 Clinical data input

Parameter	PAD	CAD	CAD and PAD	distribution	Ref
Risk of acute main events in ASA arm, 3 month probability					
MI	0.0027	0.003	0.0024	beta	[19–21]
IS	0.0015	0.0012	0.0016	beta	[19–21]
HS	0.00049	0.0003	0.00029	beta	[19–21]
ALI	0.0042	0.0037	0.0016	beta	[19–21]
VTE	0.00078	0.0012	0.0016	beta	[19–21]
Major bleeding	0.0008	0.0012	0.0016	beta	[19–21]
Minor bleeding	0.0031	0.0037	0.0049	beta	[19–21]
CVD death	0.0035	0.0024	0.0024	beta	[19–21]
Risk of acute main events in ASA + RIV arm, 3 month probability					
MI	0.0024	0.0025	0.0016	beta	[19–21]
IS	0.0013	0.0008	0.0009	beta	[19–21]
HS	0.00056	0.00036	0.00029	beta	[19–21]
ALI	0.0018	0.0018	0.0008	beta	[19–21]
VTE	0.00051	0.0008	0.0008	beta	[19–21]
Major bleeding	0.0011	0.0018	0.0024	beta	[19–21]
Minor bleeding	0.0035	0.0049	0.0066	beta	[19–21]
CVD death	0.0036	0.0018	0.0019	beta	[19–21]
Risk of acute main events in RIV arm, 3 month probability					
MI	NA	0.0028	0.002	beta	[19–21]
IS	NA	0.001	0.0013	beta	[19–21]
HS	NA	0.00037	0.00032	beta	[19–21]
ALI	NA	0.003	0.0012	beta	[19–21]
VTE	NA	0.0008	0.0009	beta	[19–21]
Major bleeding	NA	0.0018	0.0024	beta	[19–21]
Minor bleeding	NA	0.0049	0.0066	beta	[19–21]
CVD death	NA	0.0024	0.0022	beta	[19–21]

ASA aspirin, *RIV* rivaroxaban, *CVD* Cardiovascular Disease, *ALI* acute limb ischemia, *HS* hemorrhagic stroke, *HF* heart failure, *IS* ischemic stroke, *VTE* venous thromboembolism

Iran. The transmission probabilities for deaths from no cardiovascular causes were dynamically calculated with increasing age in patients.

Sensitivity analysis

Several sensitivities were analyzed to test the model assumptions, the uncertainty of the estimated values, and how different values of the variables affect the model outcome. One-way sensitivity analysis was carried out on all the usefulness, effectiveness, and cost variables of both treatment regimens within the acceptable ranges provided in above tables. From previous literature, the value ranges using 95% confidence intervals (CI) when available or calculating 20% ranges for cost data, and 10% was obtained for effectiveness and probabilities variables. Besides, a probabilistic sensitivity analysis (PSA) was conducted to assess the joint uncertainty in the model parameters on the cost-effectiveness results; 10000 ICER was calculated via Monte Carlo simulations and in PSA. All input variables were simultaneously changed with the determined distributions. In Monte Carlo simulation, beta distribution was utilized for utility values and probabilities, and gamma distribution was applied for costs. PSA results are shown in the cost-effectiveness acceptability curve and the scatterplot plane.

Budget impact analysis

A budget impact analysis (BIA) was performed to assess the total annual financial burden of rivaroxaban use in CAD and PAD patients according to the costs resulting from the Markov model. Therefore, in the budget impact model, the overall treatment costs of patients (drug, diagnostic, visit, hospitalization, laboratory, etc.) in the group treated with aspirin alone, the combination of aspirin and rivaroxaban, and rivaroxaban alone were included. The impact of the budget from the perspective of the insurance organization was based on cost calculations from the cost-effectiveness model with a 5-year time horizon [31, 32]. We extracted costs (costs related to event and treatment) from the model for each patient during one year for rivaroxaban alone, rivaroxaban with aspirin, and aspirin alone. The extracted costs per patient were multiplied by the total annual number of patients with PAD and CAD in Iran. Epidemiological information was used to calculate the number of people with PAD and CAD diseases in Iran. The prevalence rate of CAD in the age group of 45–75 years is 1% and in people over 75 years old is 4% [33]. Also, the prevalence rate of PAD disease in the age group 40–70 years old is 4.2% and in people over 70 years old is 10% [34]. The overall budget impact was calculated by assuming a 5%, 10%, 15%, 20% and 25% uptake of rivaroxaban from reference aspirin in years 1, 2, 3, 4 and 5, respectively.

Result

Base case analysis

In CAD patients, for the rivaroxaban regimen alone, QALY value obtained was 15.06, and LYG value was 18.16, higher than the amount of QALY and LYG obtained in the other two treatments.

The costs of the rivaroxaban group and the mixture of rivaroxaban with aspirin had higher treatment costs, offset partially by reducing other medical care costs in terms of complications. Therefore, direct medical cost in PAD and CAD patients, and the total of CAD and PAD patients for the combination regimen of rivaroxaban with

aspirin than aspirin alone was equal to 1937, 2845, and 2255 dollars, respectively.

The ratio of ICER and ICUR from comparing the combined regimen (rivaroxaban with aspirin) with rivaroxaban and aspirin alone was lower significantly in PAD and CAD patients with an amount of 3348 and 4594 than in other two disease groups. ICER and ICUR indices for the two regimens of rivaroxaban alone, in comparison to aspirin alone, were below the threshold of $15,222 for total PAD and CAD patients. In CAD patients, the combination of rivaroxaban and aspirin was neither more cost-effective nor more cost-utility. In contrast, in CAD patients, for the regimen of rivaroxaban alone, ICER was close to the threshold, and ICUR was below the threshold. PAD patients with the combined regimen of rivaroxaban and aspirin have benefited from the cost-utility necessary and cost -effectiveness compared to aspirin. Table 3 displays the outcomes of cost-effectiveness and cost-effectiveness analysis.

Sensitivity analysis

One-way sensitivity analyses

One-way sensitivity results were shown in Fig. 2. In patients with PAD or CAD, rivaroxaban price, the favorability state in a stable CVD state, and the probability of significant bleeding in the aspirin regimen were the most sensitive. However, the ICUR results for the rivaroxaban regimen combined with aspirin in PAD patients remain unchanged, and the ICUR remains below the threshold. Nevertheless, the model is highly susceptible to changes in the rivaroxaban arm in CAD disease due to the fact that the ICUR is nearly the threshold. In total, ICUR in CAD and PAD patients were most sensitive to the rivaroxaban price, the probability of death in an aspirin regimen, and the utility amount in a stable CVD state. However, these changes did not change the ICUR results from the combined regimen of rivaroxaban with aspirin. However, they led to changes in ICUR in the rivaroxaban regimen only above threshold limit.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was utilized to determine the model's uncertainties. The results showed that in CAD patients, the combination regimen of rivaroxaban with aspirin is only cost-effective in 28% of cases, and the rivaroxaban regimen is more cost-effective in 50% of cases than aspirin alone. The combined regimen of rivaroxaban with aspirin was compared to aspirin in 80% of CAD and PAD patients, and the rivaroxaban regimen was below the threshold in only 55% of cases. Therefore, in 59% of cases, the cost-effectiveness results were in favor of the combination regimen of aspirin and rivaroxaban in PAD patients (Fig. 3).

Acceptability curve

In combination with aspirin, rivaroxaban is a preferred treatment strategy (cost-effectiveness) based on the willingness to pay threshold in two nodes of PAD patients and the total of CAD and PAD patients according to the result of acceptability curve Fig. 4. In CAD patients, the rivaroxaban regimen is close to the willingness to pay threshold and has a slightly lower preference than the aspirin regimen alone.

Budget impact analysis

According to the results of BIA, after covering the combination regimen of rivaroxaban plus aspirin by insurance system, it causes an increasing trend in *costs* in the years 2023 to 2027 included 0.06%, 0.12%, 0.19%, 25%, and 31% respectively. In other words, adding rivaroxaban combination with aspirin regimen to the treatment portfolio of patients with CAD and PAD will increase the health system's costs by $28,253,135 in 5 years. Also, if we consider the scenario where patients with rivaroxaban are treated

Table 3 The cost utility and cost-effectiveness analysis results

Items	PAD		CAD			CAD & PAD		
	RIV + ASA	ASA	RIV + ASA	ASA	RIV	RIV + ASA	ASA	RIV
Treatment cost	6132	4196	8745	5900	11,000	6790	4535	**8801**
Treatment effect (QALY)	12.67	12.5	14.82	14.72	15.06	11.52	11.03	**11.35**
Treatment effect (LYG)	15.26	15.07	17.86	17.75	18.16	15.79	15.12	**15.55**
Incr cost	1937	NA	2845	NA	5509	2255	NA	**4266**
Incr effect (QALY)	0.16	NA	0.09	NA	0.034	0.49	NA	**0.31**
Incr effect (LYG)	0.2	NA	0.12	NA	0.29	0.67	NA	**0.43**
ICUR	11929	NA	30539	NA	15141	4594	NA	**13601**
ICER	9896	NA	24728	NA	12473	3348	NA	**9901**

ASA aspirin, *RIV* rivaroxaban, *Incr* Incremental, *QALY* Quality-adjusted life year, *LYG* Life Years Gain, *ICER* Incremental Cost-Effectiveness Ratio, *ICUR* Incremental Cost-Utility Ratio

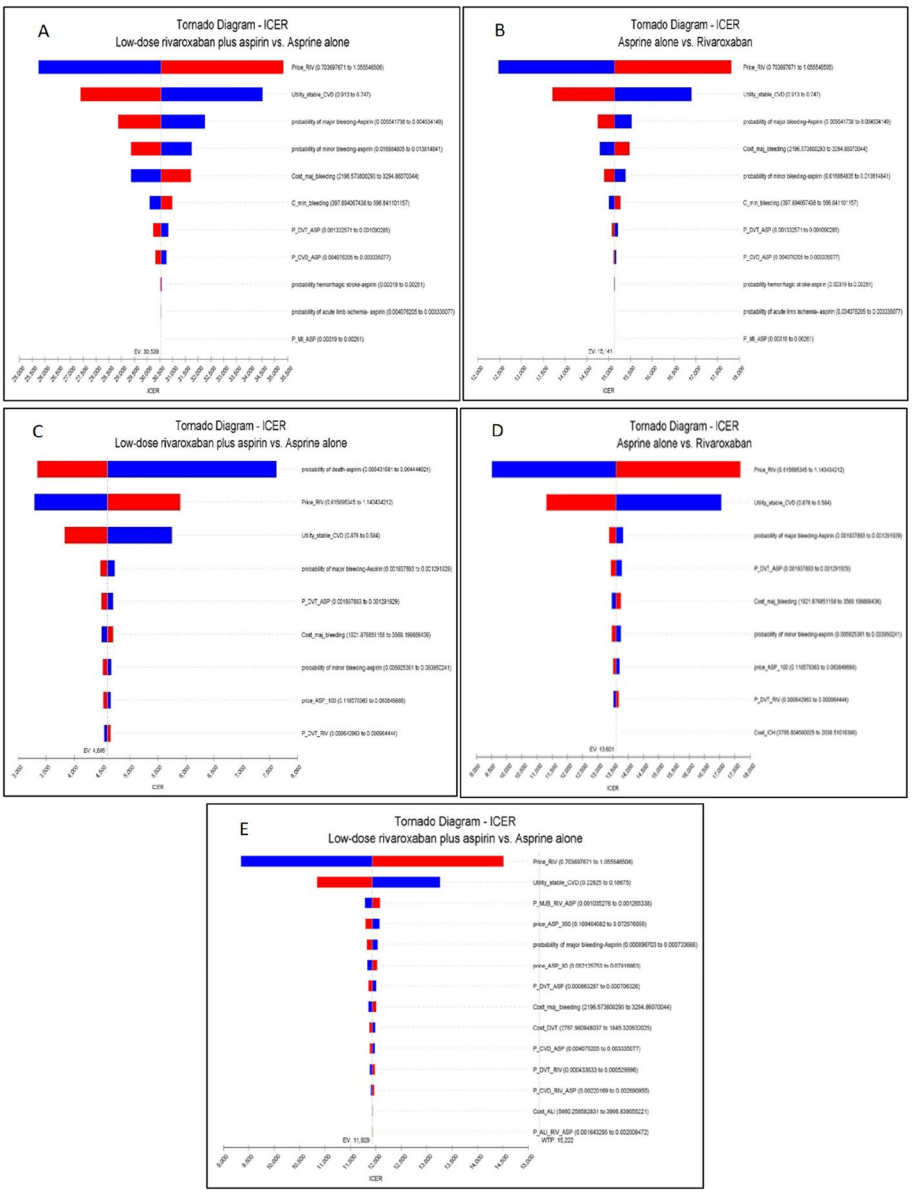

Fig. 2 Tornado chart of the one-way deterministic analyses. The included populations are A&B: CAD; C&D: CAD & PAD; E: PAD. The red bar on the right side of the threshold shows the increasing changes in the variables related to rivaroxaban or rivaroxaban + aspirin treatment and the blue bar indicate the decreasing changes related to the aspirin treatment variables. P:probability, mjb: major, RIV: rivaroxaban, ASP: aspirin, CVD: Cardiovascular Disease, ALI: acute limb ischemia, HS: hemorrhagic stroke, HF: heart failure, IS: ischemic stroke, VTE: venous thromboembolism

alone, this increase in budget for the insurance organization will be $292,593,909 at the end of 5 years. Table 4 shows the budgetary impact of rivaroxaban drug coverage on insurance organizations from 2023 to 2027.

Discussion

In this work, we conducted the cost utility and cost-effectiveness of Rivaroxaban plus aspirin in comparison to Rivaroxaban and aspirin alone in patients with CAD and PAD in Iran. Based on our knowledge, the cost-effectiveness of Rivaroxaban compared with aspirin was not determined in Iran. Therefore, we analyzed the cost-effectiveness in three group of patients, including patients with PAD, CAD, and patients with PAD and CAD with three different regimens.

Rivaroxaban plus aspirin was more effective than others in the base case analysis, with average QALYs and LYG of 15.79 and 11.52 in PAD and CAD patients, respectively. Similarly, this result was confirmed in PAD patients with average QALYs of 12.67. Based on a recent

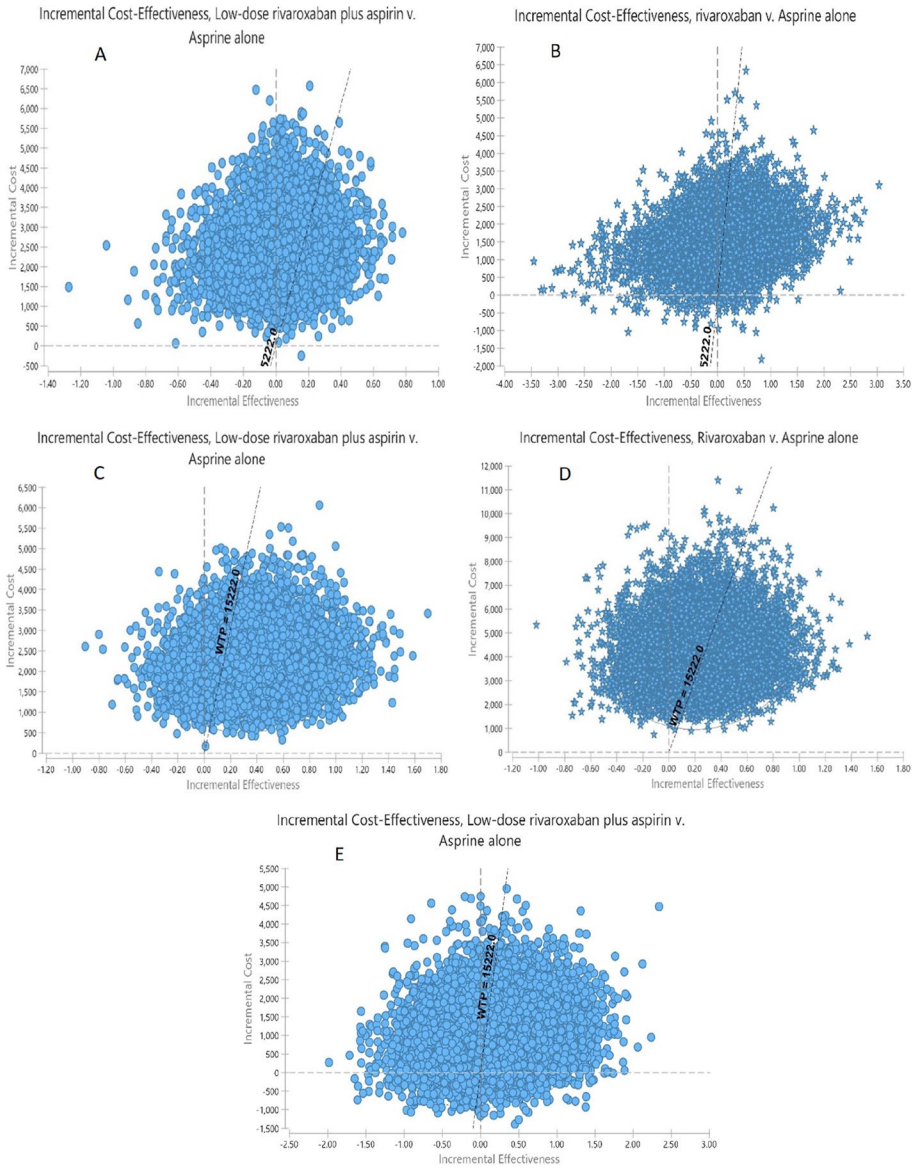

Fig. 3 Scatter plot of PSA. Populations included are A&B: CAD; C&D: CAD & PAD; E: PAD. In the scatter plot diagram, all points in the northeast and below the threshold, southeast and southwest and above the threshold are cost-effective points

systematic review of Randomized Controlled Trials, adding Rivaroxaban to the aspirin regimen than aspirin alone led to reduced cardiovascular disease in patients with CAD and PAD. Although they recommended low doses of aspirin to fall thromboxane-dependent platelet activation [35]. It is strongly confirmed that Rivaroxaban plus aspirin would be a significant advance in managing patients with PAD and CAD [36]. In our analysis, rivaroxaban combined with aspirin in patients with CAD was not cost-effective, and treatment with rivaroxaban alone had higher QALYs (15.06) and LYG (18.16) than other regimens. The sensitivity analysis confirmed the finding. It might relate to higher probabilities of major bleeding and mortality in CAD patients.

Our analysis found in CAD and PAD patients, adding Rivaroxaban to an aspirin regimen was associated with higher medical expenses than aspirin alone. The cost difference is mainly because of the difference in the Rivaroxaban price compared with aspirin in Iran. In contrast, the financial burden will be reduced due to the low probability of thromboembolic events in CAD and PAD patients following the use of Rivaroxaban. It is noteworthy that rivaroxaban versus aspirin alone can save over $537,174 per year in the USA since treatment with

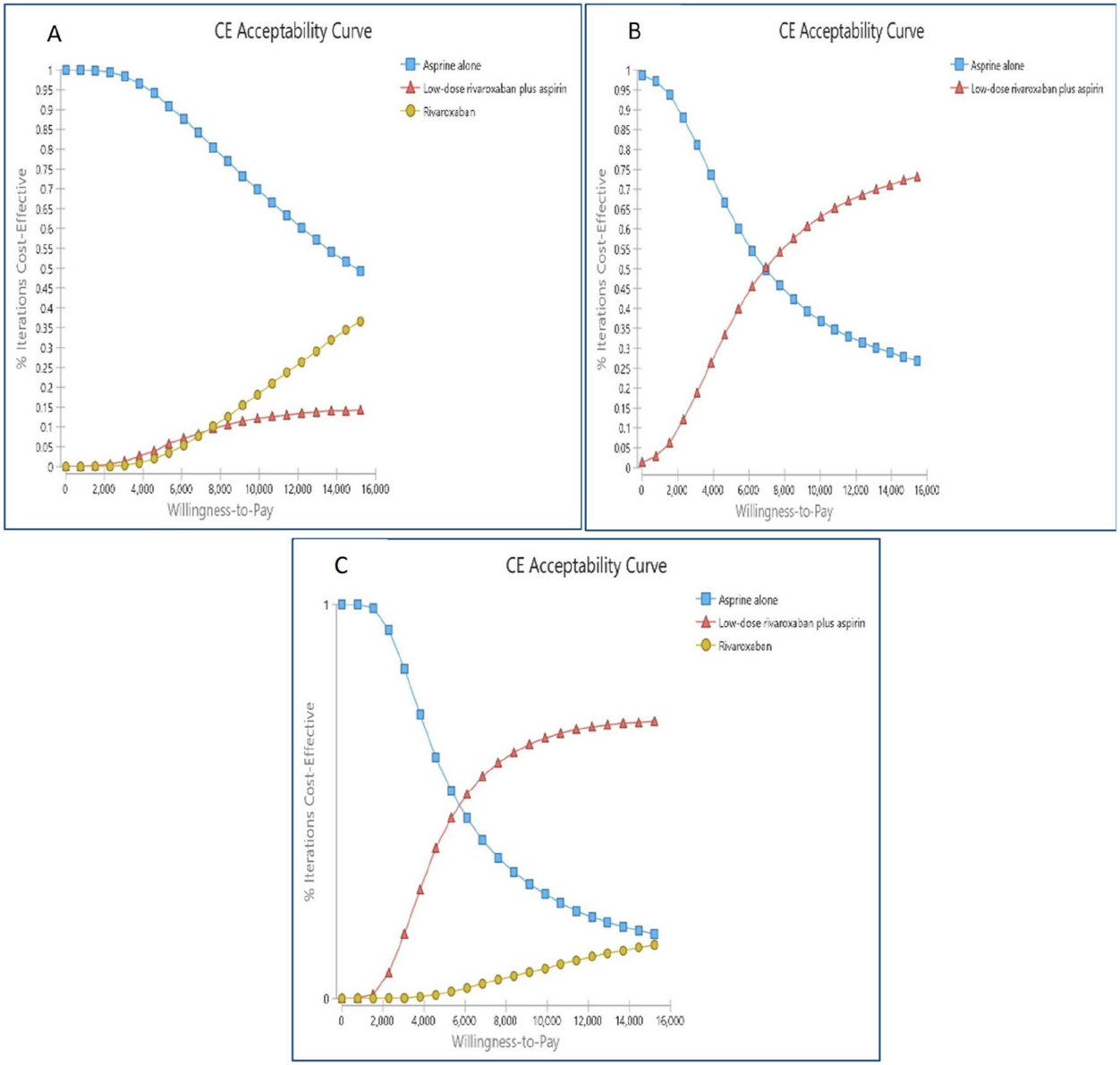

Fig. 4 Monte Carlo Simulation cost effectiveness Acceptability curve at WTP. Populations included are A: CAD; B: PAD; C: CAD & PAD

Table 4 The results of the budget effect analysis

Year	2023	2024	2025	2026	2027
Iran population	86369815	87406253	88455128	89516589	90928011
number of patients of CAD	265452	268606	271761	274916	278071
number of patients of PAD	1373438	1389760	1406083	1422405	1438727
RIV or RIV + ASA market share	0.05	0.1	0.15	0.2	0.25
Scenario 1(without rivaroxaban)	28845445	29192370	29539294	29886218	30233143
Scenario 2 (with rivaroxaban + aspirin)	30665093	32875432	35212593	37427419	39769067
Scenario 3(with rivaroxaban alone)	33481567	38576126	43993804	49099797	54528909
financial impact in scenario 1&2	1819648 (.06%)	3683062 (12%)	5673299 (19%)	7541201 (25%)	9535925 (31%)
financial impact in scenario 1&3	4636121 (16%)	9383757 (32%)	14454510 (50%)	19213578 (64%)	24295766 (80%)

rivaroxaban was related to the lowering risk of complications, major adverse CV events (MACE), myocardial infarction, and major adverse limb events (MALE), and acute limb ischemia, and amputation resulting from vascular events [16]; in patients with PAD and CAD.

One of the significant results of our study is that rivaroxaban combined with aspirin than aspirin and rivaroxaban alone is related to an increase in QALYs and costs in CAD or PAD patients. In other words, the ICER for rivaroxaban in conjunction with aspirin was 4594 per QALY gained in CAD and PAD patients, which was lower than the threshold of $15222 per QALY. Similarly, this finding is verified in individuals with PAD. Although, in CAD patients, rivaroxaban combined with aspirin alone, with $30539 per QALY gained, was not cost-effective. Then, we found that the proposed regimen is more cost-effective than aspirin and Rivaroxaban alone in all patients with CAD and PAD in Iran. This result was compatible with other economic analyses in different countries like Australia [17, 37], the USA [16], Italy [29], and the Netherlands [38]. For example, in Australia, rivaroxaban plus aspirin was considered more cost-effective than aspirin alone in preventing major adverse limb events in patients with PAD or CAD. They reported an ICER of AU$26,769 per QALY. Another study in Australia perspective reported an ICER per QALY gain of $17,764 that was introduced as a cost-effective treatment. A Dutch study indicated rivaroxaban combined with aspirin is a cost-effective treatment strategy in stable PAD or CAD patients.

Based on the sensitivity analysis, the model was sensible to the cost of rivaroxaban and the utility of CVD state parameters. The ICER of rivaroxaban plus aspirin was cost-effective in PAD patients and patients with PAD and CAD, despite the fact that the parameters were varied. The PSA also showed that the rivaroxaban + aspirin was cost-effective in 80% and 59% of simulations in PAD patients and patients with PAD and CAD who were below the threshold. In this regard, our finding is in line with Lamy et al. [39], Ademi et al. [37] and Jia et al. [40].

Since the lack of a cost-efficiency threshold in Iran, we considered a threshold of 15222 dollars per QALY gained based on WHO recommendation for developing countries. In general, proposed regimen will generate more benefits for the patients with PAD and CAD. In this area, a question arises about how much the Iranian health insurance organization will allocate based on three scenarios. For this reason, we conducted a BIA. Based on the results, the proposed regimen, rivaroxaban plus aspirin, will increase the insurance system costs by 87% in 2027. However, the value for the mentioned regimen than rivaroxaban alone has a lower financial burden and a higher clinical impact.

The present study faced several limitations. First, our study analysis was based on the COMPASS population. This may differ from a real-world population as a test population. Nevertheless, real-world populations are at higher risk generally for health events, and rivaroxaban plus aspirin may be even more cost-effective. Nevertheless, all input parameters were examined in different sensitivity analyses and did not change the results of the pharmacological conclusions. Second, Iran reached no general consensus on the WTP threshold, and the cost-effectiveness results may change at different thresholds [41]. Third, current analysis was conducted based on the insurance system, and only direct medical costs were included. But, considering the effect of these treatments on reducing the complications of cardiovascular events, the pharmacological benefits need to be comprehensively evaluated, by considering parameters from a social perspective, like social services, reducing productivity, and the quality of life required. Fourth, according to the model structure, there is a probability of cardiovascular events in the form of primary and secondary recurrence, but because the studies did not report the state of primary and secondary recurrence separately, we equate the probability of secondary recurrence with the probability of primary recurrence.

Conclusions

Based on clinical data from the COMPASS trial within the 23 month observation period and a readiness to pay 15222 dollars per QALY gained, our results indicate Rivaroxaban (2.5 mg two times daily) plus aspirin (100 mg once daily) is cost-effective to treat patients with CAD and PAD in Iran. Based on PSA results, the cost-effectiveness of the proposed regimen was confirmed at 80% in patients with PAD and CAD but only 59% in patients with PAD. However, the proposed regimen had a considerable impact on the insurance companies. We recommend this treatment regimen in clinical care and future research since positive clinical impact on patients with CAD and PAD.

Authors' contributions

ZA, ZN, and MM designed the study. ZG, MB, KK gathered the required data. ZG, MM, ZN and AG analysed and interpreted the results. ZG, ZN and KK prepared the first report draft. The ultimate version and responsibility for its content were approved by all authors.

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Data availability

The datasets used during the current study are available fromthe corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval for this work was achieved from Ethics Committee of the Shiraz University of Medical Sciences (ethic number: IR.SUMS.REC.1401.314). In this study, we did not use patient samples, so participant consent was not required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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