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SYSTEMATIC REVIEW



# Economic evaluation of ivabradine in treatment of patients with heart failure: a systematic review

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**ABSTRACT**

**Background:** Chronic heart failure (CHF) is a clinical status and a progressive health disorder extremely related to increased morbidity and mortality worldwide. Accordingly, this study aimed to assess systematic review of literature on cost-effectiveness done in patients with heart failure receiving Ivabradine plus standard treatment compared with standard treatment alone.

**Areas covered:** This study is a systematic review in which all published articles related to the study topic were assessed in time range of 2014–2020. In order to find articles, internet search in foreign databases of PubMed, Embase, ISI/Web of Science (WoS), SCOPUS, Global Health databases, through keywords related to the objective was performed. Six articles out of 1524 article related to final topic were assessed. In addition, quality of studies was evaluated using CHEERS checklist. In six countries investigated (Iran, Thailand, Australia, United States of America, United Kingdom, and Greece), willingness-to-pay (WTP) thresholds higher cost per QALY, and highest ICER for Ivabradine was in USA (55,600 $/QALY) and the lowest was in Thailand (10,616$/QALY). Most items of CHEERS were estimated in the studies and studies had good quality.

**Expert opinion:** Regarding our investigation, ivabradine combined with standard care was more cost-effective than standard care alone in most of the evaluated studies, although the cost of this intervention was higher than its effectiveness. However, the threshold chosen by each country can have a significant impact on these results. And to have a more accurate result, it is required to pay more attention to the income level in different countries.

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**KEYWORDS**
Cost-effectiveness analysis; ivabradine; heart failure; heart rate; economic evaluation

## 1. Introduction

Chronic heart failure (CHF) is a clinical status and a progressive health disorder extremely related to increased morbidity and mortality worldwide [1,2]. It is ranked and differed as the second to third death reason and accounted for higher than 20 million affected patients [3,4]. It expected to increase by 25,000–30,000 new cases each year [5,6]. Furthermore, it is estimated that there are one to two HF cases in every 100 individuals, and at least one patient in every 10 elderlies over 70 years old [7].

Recently, it has been reported that the pooled survival rates of CHF at 1 month to 5 years reduced from 95.7% (95% confidence interval 94.3–96.9) to 56.7% (54.0–59.4) and therefore it is known as a poor prognosis disorder in which more patients die within a year from the diagnosis date and despite considerable progressions in patient's survival rate, death numbers since CHF remains a serious obstacle [8].

Considering patients' disabilities and challenges which lead to more hospitalization rate, there is more concern about significant economic burden on the health-care shoulders that introduces HF as a costly disorder in different countries. In this issue, the main one is the cost of drug components that imposes a great cost on patients and governments [9,10].

Epidemiological and clinical investigations demonstrated that the important risk factor for mortality and morbidity in CHF patients is higher heart rate (HR) in sinus rhythm and lower HR is associated with better clinical status of patients [11–13], so that heart rate deduction strategy results in outcomes improvement in patients with CHF that the traditional and present drugs are attributed. The ongoing traditional treatment includes β-blockade, angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptors blockers (ARBs), aldosterone antagonists, and diuretics [14–16]. Nevertheless, β-blockers are not always successful and in some patients resting heart rate cannot be reduced because of target dosage tolerance which increase demands for new therapeutic drugs [13–17].

Given this, in recent decade, Ivabradine (Corlanor®; Amgen Inc., Thousand Oaks, CA) has been introduced and evaluated as a new therapeutic option additional or adjuvant to the standard treatment protocol for patients with reduced ejection fraction, sinus rhythm, and heart rate ≥70 bpm. It is the first-in-class selective sinoatrial node $I_f$ channel blocker that slows HR by the cardiac pacemaker $I_f$ inhibition and so the HR

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regulation [11,18]. Ivabradine, as an $I_f$ channel blocker, reduces heart rate by inhibiting the pacemaker flow of sinus node cells without affecting on lowering blood pressure, or modifying heart contraction, or adverse modulating on the sympathetic system [6].

For the first time, Ivabradine has been examined in the Systolic Heart failure treatment with the $I_f$ inhibitor ivabradine Trial (SHIFT). SHIFT worked as a large randomized controlled trial of ivabradine plus standard treatment in 6558 adult patients with New York Heart Association class II to IV with symptomatic HF with a prior hospitalization for HF within 12 months and a baseline resting heart rate ≥70 bpm (in different publications ranging from 70 to 77). The results of SHIFT indicated that the primary end point composite significantly reduced with ivabradine therapy plus standard treatment (CV death or hospitalization for worsening HF; hazard ratio: 0.82, 95% CI: 0.75, 0.90, $P < 0.0001$) [13,18]. In the SHIFT study, researchers added 5.7 mg of ivabradine twice daily to standard treatment for patients with left ventricular ejection fraction less than 35% and showed a significant reduction in cardiovascular mortality and hospitalization. In SHIFT trial, baseline heart rate was considered as a modifier in the treatment effect of ivabradine; results showed a significant effectiveness in patients with an HR ≥77 bpm compared with ≤77 bpm (hazard ratios of 0.75 and 0.93, respectively; p for interaction = 0.029) and in a pre-specified high HR subgroup (baseline HR ≥77 bpm; n = 3357), treatment with ivabradine reduced the rates of death from HF (0.022/year, as compared with 0.036/year in the placebo group; hazard ratio, 0.61; $p = 0.0017$), death from cardio-vascular causes (0.085/year vs 0.105/year; hazard ratio, 0.81; $p = 0.0137$), death from any cause (0.095/year vs 0.117/year; hazard ratio, 0.81; $p = 0.0074$), and worsening HF as a reason for hospitalization (0.110/year vs 0.161/year; hazard ratio, 0.69; $p < 0.0001$). SHIFT results overall showed that ivabradine added to conventional therapy reduced hospitalization by 26% due to worsening heart failure. Besides, SHIFT demonstrated that a combination of ivabradine and routine care was linked to particularly less critical adverse events. There was also a reduction in overall cardio-vascular mortality (0.91; 95% CI 0.80 to 1.03, $p = 0.128$) [5,6,13,16].

Ivabradine is a new treatment that has now been added to standard treatment for patients with a heart rate of 75 beats per minute and class II to IV in systolic heart failure. Ivabradine as a reducing agent takes a specific action on the sinus node and inhibits the heartbeat of peacemakers.

Although this finding may help in patient's lifespan, the economic effectiveness of adding ivabradine to traditional treatment remains unclear and under investigation. In addition, because of budget limitations, it is highly recommended that resources be allocated in a proper way for the best results. Therefore, a large number of cost analysis studies were conducted to investigate cost effectiveness of adding Ivabradine to standard treatment.

Cost-effectiveness analysis (CEA) is a main procedure in health care decision-making worldwide considering the limited health-care resources and also in order to support and inform health-care decision and policymakers, evidence-based cost-effectiveness studies demanded [19–21].

Hence, to summarize the findings of the existed investigations in this matter, to reach a consensus and, fill this gap in knowledge, the present study aimed at systematically reviewing the cost-effectiveness of Ivabradine plus standard treatment compared with standard treatment alone.

## 2. Method

### 2.1. Identification of studies

This study is a systematic review, in which all published articles relevant to cost-effectiveness of Ivabradine compared with standard treatment alone in patients with heart failure in English language in time range of 2014–2020 were evaluated. Search strategy in this systematic review includes a combination of keywords and medical subject headings (MeSH).

In order to find articles, internet search was performed in foreign databases consisting PubMed/MEDLINE, Embase Scopus, ISI/Web of Science, Database of Abstracts of Reviews of Effects (DARE), the Cochrane Library, Health Technology Assessment (HTA) Database, the Tufts Medical Center 'Cost-Effectiveness Analysis Registry,' 'National Institute for Health and Care Excellence' (NICE), the Institute for Clinical and Economic Review (ICER), and National Health Service Economic Evaluation Database (NHS EED). Keywords of 'Heart Failure,' 'Ivabradine,' 'standard treatment,' 'cost-utility analysis,' 'Cost- benefit Analysis,' And 'cost-effectiveness analysis' were used to find relevant articles.

### 2.2. Main outcomes

One of the key outcomes considered in this systematic review was Life years gained (LYG), Quality-adjusted life year (QALY), and the incremental cost-effectiveness ratio (ICER) related to using Ivabradine plus standard treatment compared with standard treatment alone.

### 2.3. Inclusion and exclusion criteria

#### 2.3.1. Inclusion criteria

Inclusion criteria in this study include: patients with symptomatic HF with reduced ejection fraction, sinus rhythm, and a baseline resting heart rate ranging from 70 to 77 bpm; patients with preserved left ventricular ejection fraction (LVEF) <35%, articles comparing Ivabradine and standard treatment; articles published among years 2014–2020; articles published in English; articles which include economic evaluation (cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis), and articles with accessible full text.

#### 2.3.2. Exclusion criteria

Exclusion criteria were as follows: articles including evaluation of partial economy (cost-of-illness (CoI), cost-analysis, cost-minimization analysis); articles not reporting outcomes of LYG, QAL, and ICER; articles published in congresses and

conferences; reviews article, protocols, conference abstracts, commentaries, letters to the editors, editorials.

### 2.4. Data extraction

All the articles after extraction from the databases using relevant keywords were assessed by two authors. Then, two authors extracted the data using data extraction form. Data include author, year, population, age, country, intervention and comparison, health outcome, vision, time horizon, sensitivity analysis, discount rate, cost type, modeling type, threshold, QALY value, LYG value, expense in intervention an comparison groups, and ICER. Any parallax among two authors was referred to a third person, and it was discussed. After qualitative evaluation of studies, data of each study were entered in information for data gathering tool.

### 2.5. Quality assessment of the studies

Quality evaluation of studies was done by two authors and using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist and any parallax among two authors was referred to third author. This checklist includes 24 questions in which sign of 'Y' represents that item of checklist in the study was thoroughly adapted and received score of 1, sign of 'P' with score of 0.5 shows items which were approximately adapted, and items which were not met from the checklist were identified with the sign of 'N' with a score of zero. Studies are classified as high quality (>85%), very good quality (<70–85%), good (<55–70%), and low quality (<55%) [22].

## 3. Results

### 3.1. Literature search results

In this study, Figure 1 provides an overview of the search steps based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [23,24]. In the primary search, in total, 1564 studies relevant to the study topic were found. Then, 985 cases were omitted since they were duplicated. Out of 579 articles remaining, 532 ones were not related to keywords and title and abstract and totally 47 articles were identified as relevant. After assessment of full-text of remaining articles, 41 other articles were omitted due to not meeting

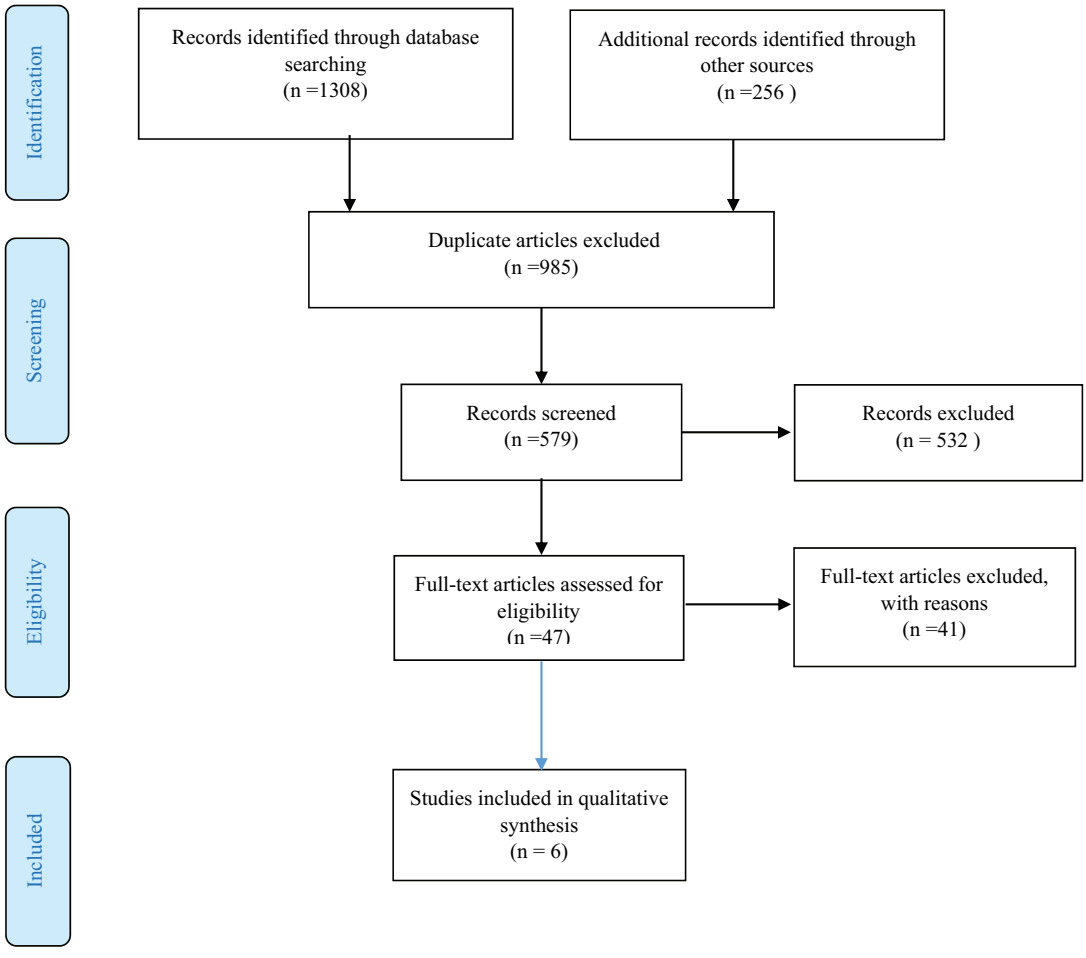


Figure 1. Process of the systematic literature search, according to the preferred reporting items for systematic review.

Table 1. Characteristics of included studies in the review.

| Study, Year | Country | Age | Patient population | Perspective | Time horizon | Health outcomes | Intervention/ Comparator | Sensitivity analysis | Discount rate | Types of costs |
|---|---|---|---|---|---|---|---|---|---|---|
| Taheri 2018,[25] | Iran | ≥60 years | HR ≥ 75 | Health-care payers | 10 years | QALY | Ivabradine+ (SoC)/ SoC | One-way sensitivity analyses & PSA | Cost: 7.2% Eff: 5% | Drug cquisition, hospitalization, medical care, HF management, adverse events |
| Krittayaphong 2019,[6] | Thailand | ≥60 years | HR≥77 | Health-care system | Lifetime | QALY/ LYG | Ivabradine+ (SoC)/ SoC | One-way sensitivity analyses & PSA | Cost: 3% Eff: 3% | Drug acquisition, medications and hospitalization |
| Adena 2018,[5] | Australia | - | HR≥77,70 | Health-care system | 10 years | QALY/ LYG | Ivabradine+ (SoC)/ SoC | One-way sensitivity analyses | Cost & Eff: 5% | Drug acquisition, medications, hospitalization |
| Kansal 2016,[18] | US | - | HR ≥70 | Third-party payer | 10 years | QALY | Ivabradine+ (SoC)/ SoC | One-way sensitivity analyses & PSA | - | Drug acquisition costs, specialist visit unit cost Hospitalization, adverse events |
| Griffiths 2014, [13] | UK | < or ≥75 years old | HR ≥75, 70 bpm, | Health-care payers | Lifetime | QALY/ LYG | Ivabradine+ (SoC)/ SoC | One-way sensitivity analyses & PSA | Costs & Eff: 3.5% | Drug acquisition costs, Hospitalization |
| Kourlaba 2014,[16] | Greece | - | HR ≥75 | Third-party payer | Lifetime | QALY/ LYG | Ivabradine+ (SoC)/ SoC | One-way & PSA | Costs & Eff: 3.5% | Drug acquisition, hospitalization, HF management, |

SOC: (b-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, and diuretics); HR: heart rate QALY, quality-adjusted life-year; LY: life year; PSA: probability sensitivity analysis

Table 2. CHEERS checklist.

| Item | Item No | Taheri et al. | Krittayaphong et al. | Adena et al. | Kansal et al. | Griffiths et al. | Kourlaba et al. |
|---|---|---|---|---|---|---|---|
| Title | 1 | Y | Y | Y | Y | Y | Y |
| Abstract | 2 | Y | Y | Y | Y | Y | Y |
| Background and objective | 3 | Y | Y | Y | Y | Y | Y |
| Target population and subgroup | 4 | Y | Y | Y | Y | Y | Y |
| Setting and location | 5 | Y | Y | Y | Y | Y | Y |
| Study perspective | 6 | Y | Y | Y | Y | Y | Y |
| Comparators | 7 | Y | Y | Y | Y | Y | Y |
| Time horizon | 8 | Y | Y | Y | Y | Y | Y |
| Discount rate | 9 | Y | Y | Y | N | Y | Y |
| Choice of health outcomes | 10 | Y | Y | Y | Y | Y | Y |
| Measurement of effectiveness(single study-based estimates) | 11a | Y | Y | Y | Y | Y | Y |
| Measurement of effectiveness(synthesis-based estimates) | 11b | NA | NA | NA | NA | NA | NA |
| Measurement and valuation of preference based outcomes | 12 | Y | Y | Y | Y | Y | Y |
| Estimate resources and cost(single study-based economic evaluation) | 13a | NA | NA | NA | NA | NA | NA |
| Estimate resources and cost (model-based economic evaluation) | 13b | Y | Y | Y | Y | Y | Y |
| Currency, price date, and conversion | 14 | Y | Y | Y | N | Y | Y |
| Choice of model | 15 | Y | Y | Y | Y | Y | Y |
| Assumptions | 16 | Y | Y | P | Y | P | P |
| Analytic method | 17 | Y | Y | Y | Y | Y | Y |
| Study parameters | 18 | Y | Y | Y | Y | Y | Y |
| Incremental costs and outcomes | 19 | Y | Y | Y | Y | Y | Y |
| Characterizing uncertainty(single study-based economic evaluation) | 20a | Y | Y | Y | Y | Y | Y |
| Characterizing uncertainty(model-based economic evaluation) | 20b | NA | NA | NA | NA | NA | NA |
| Characterizing heterogeneity | 21 | Y | N | N | N | N | P |
| Study funding .limitation, generalizability, and current knowledge | 22 | Y | Y | N | Y | P | N |
| Source funding | 23 | Y | N | Y | Y | Y | Y |
| Conflict of interest | 24 | Y | Y | N | N | Y | Y |
| Total percentage | | 24 | 22 | 20.5 | 20 | 22 | 22 |

inclusion criteria. In total, six studies were identified and underwent final evaluation.

### 3.2. General characteristics of the studies

Main properties of the studies are presented in Table 1. Six studies underwent final evaluation in this systematic review based on inclusion and exclusion criteria, which were published among years 2014–2019 [5,6,13,16,18,25]. The entered studies include economic evaluation in many developed or developing countries. Most studies were performed in developed and high-income studies and studies were done in America, England, Canada, USA, Greece, Australia, Thailand, and Iran [5,6,13,16,18,25].

The population under consideration slightly differed across the studies. Thailand study included the treatment of patients with heart rate≥77 bpm [6]; Iranian and Greek studies included the treatment of patients with heart rate ≥75 bpm [16,25], Australia study with heart rate ≥70 and heart rate ≥77 bpm [5], UK study with heart rate ≥70 and heart rate ≥75 bpm [13], and US study included the treatment of patients with heart rate ≥70 bpm [18].

Time horizon were mostly lifetime studies [6,13,16] and three studies considered 10 years as time horizon [5,18,25]. Except for one study [18], the remaining studies identified discount rate of costs and effects. Discount rate of costs in studies was among 3–7.2% and for decreasing effects was among 3–5%. Amongst the studies entered, two studies were from the viewpoint of health-care system [5,6], two studies were form the viewpoint of health-care payers [13,16,25], and two studies was from the viewpoint of third-party payer [16,18]. All studies used Markov model to assess cost-effectiveness and type of economic evaluation in all studies was cost-effective. In all studies, only direct medical cost was computed which consists of costs of drug acquisition, medications and hospitalization, etc.; additionally, in these two studies, costs of adverse event were also computed (Table 1).

Based on the quality of CHEERS instrument, all of the six studies were classified as good quality. The scores of the included studies ranged from 20 to 24, with an average score of 21.7. The study by Taheri et al. [25] from Iran was of the highest quality with a score of 24 (Table 2).

Y: fully reported (1 score), P: partially reported (0.5 score), N: no reported (0 score), NA: not applicable, [a] single-study-based estimates, [b] synthesis-based estimates.

In all studies, the intervention was ivabradine plus standard of care (SoC) in treatment of heart failure compared to SoC alone. Exceptionally, one study used QALY as outcome health [18] and the remaining used QALY, LYG [5,6,13,16,25]. Mean QALY was 0.31 in various studies and the median was 0.28, where the highest QALY was related to Thailand, and in patients with heart rate ≥77 and the lowest was related to Australia (QALY 0.10).

In addition, mean LY in various studies was 0.31 and the median was 0.25 where the highest LY was related to Thailand with 0.80 LY and the lowest was related to Australia with 0.11 LY. In all studies, sensitivity analysis of one way and probabilistic sensitivity analysis was applied to determine the effect of

Table 3. Summary results of included economic evaluation studies.

| Study, Year | Price/ Year | Study model | Threshold | Health outcomes | Cost(Ivabradine+SOC/ SOC alone) | ICER |
|---|---|---|---|---|---|---|
| Taheri 2018,[25] | $2017 | Markov&Decision Tree | $6,550 -$19,650 | 0.41 QALY | $5212/3005 | $5437QALY |
| Krittayaphong2019, [6] | $2018 | Analytical decision model | $4866.18 | (0.8 LY, 0.61 QALY) | ($2117.61/523.33) | ($1997.88 LY, 2625.20QALY) |
| Adena 2018,[5] | $(2017) 2017 | Markov model | $26508 | Senario1:HR ≥70(0.10LY, 0.09QALY) Senario2:HR ≥77(0.115LY, 0.108QALY) | Senario1:HR≥70 (A$10619/ 8700) Senario2:HR≥77(A$10916/ 9302) | Senario1: HR ≥70(A$19105 LY,19764 ALY) Senario2: HR ≥77 (A $14087LY,14905QAY) |
| Kansal 2016,[18] | $(2015) 2015 | Markov mode | $30000-50,000 | (0.16 LY, 0.20 QALY) | ($227125/222212) | $24,920 QALY |
| Griffiths 2014,[13] | £(2011) | Markov model | £20000-30000 | Senario1: HR ≥75(0.25 LY, 0.28 QALY) Senario2: HR ≥70 (0.14 LY, 0.18 QALY) | Senario1: HR ≥75 (£11 822/ 9446) Senario2: HR ≥70 (£11796/ 9312) | Senario1: HR≥75(£9363LY, 8498QALY) Senario2: HR ≥70(£17 875LY, 13764QALY) |
| Kourlaba 2014,[16] | €(2013) | Markov&Decision Tree | €36000 | (0.25 LY, 0.28 QALY) | (€8665/5873) | (€11002LY,9986QALY) |

SOC: (b-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, and diuretics); HR: heart rate; QALY: quality adjusted life-year; LYG: Life Years gained

indefinite parameters. The results of the studies show that Ivabradine decreases mortality rate and increases survival (Table 3).

Data of whole cost based on US dollars (2020) show that Ivabradine has the highest cost in USA, England, and Greece (248,587.10, USD 19,748.54$, and 15,009.84$, respectively) and lowest cost in Iran and Thailand (5415.46$ and 2161.83$, respectively). Results show that in all selected countries (Iran, Thailand, Australia, USA, England, and Greece), threshold of willingness to pay (WTP) is greater than the cost per each QALY, indicating that at the current thresholds used by healthcare systems, Ivabradine was more cost-effective in patients with heart failure (Table 3).

## 4. Discussion

Economic evaluation including cost-effectiveness with determination, calculating and comparing costs and benefits of health and treatment interventions help health system policymakers to apply health and treatment interventions at high benefit or higher effectiveness [26]. Based on our knowledge, this study is the first systematic review which has been done with the aim of investigating cost-effectiveness of ivabradine plus SoC in comparison with current SoC alone in patients with HF.

In all studies, cost-effectiveness in various countries has been reported by considering national threshold of that country. Therefore, to compare cost-effectiveness among studies, ICERs are changed into US dollar (based on the gross domestic product purchasing power parity in 2020) where its range is among 2727.68 USD per QALY to 27,274.81 USD per QALY. The average value was 15,833.08 USD per QALY and the median one was 18,088.01 USD per QALY (Table 3).

We aimed to investigate and compare the threshold and cost-effectiveness in various countries, investigate uncertainty analysis, and compare cost among two therapeutic interventions.

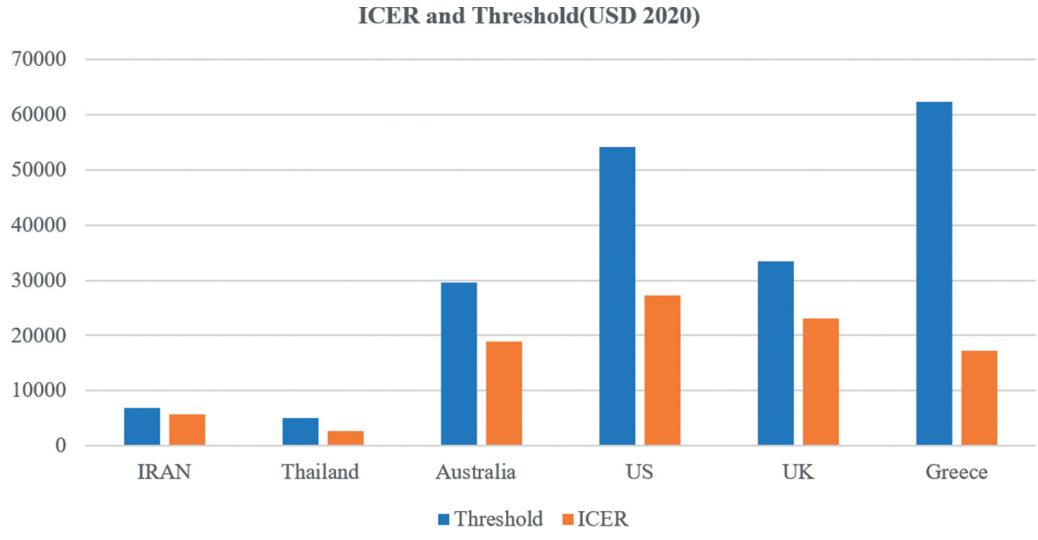


Figure 2. Cost per QALY and WTP threshold in selected countries.

### 4.1. Comparing threshold and ICER for selected countries

All six final studies include cost reported for each QALY and threshold limit of the current study. Despite differences in models of analysis of decision and Markov, vision, time horizon, and decrease rate among various countries which lead to estimate different ICERs, none of individual ICERS was higher than threshold of WTP of that country. Figure 2 shows that the highest ICER for Ivabradine was in USA (55,600$/QALY) and lowest one was in Thailand (10,616 $/QALY). One of the reasons for high cost of QALY in USA is higher cost of this therapeutic method (4913$) compared to other countries. Of course, despite high costs in USA for this medication, this country has highest willingness threshold for paying after Greece (50,000 to 100,000$ per each QALY), while the threshold in a country such as Thailand is 5076.92$/QALY.

Figure 2 shows that in each six countries (Iran, Thailand, Australia, USA, England, and Greece), willingness to pay threshold is higher than cost per each QALY, indicating that at the current threshold used by health systems of selected countries such as NICE in England (30,000 Pounds per each QALY obtained), and in Greece (36,000€/QALY), Ivabradine was cost-effective; the only country in which its ICER and threshold are close to each other was Iran (6550$/QALY for ICER and 5437$/QALY for threshold) which is lower compared to other countries and also has a lower threshold. In addition, Greece has the highest difference in threshold and cost of each QALY (9986€ for ICER and 36,000€/QALY for threshold limit), which represents high probability of cost-effectiveness of this medication in this country.

### 4.2. Uncertainty analysis

Sensitivity analysis in six studies was done to determine effect of input parameters on stability of ICER value in the model. All studies used univariate analyses and probabilistic sensitivity analyses in uncertainty analysis. In the study by Krittayaphong et al., results of one-way sensitivity analysis show variables influencing cost-effectiveness of risk of non-hospitalization cardiovascular death are costs of hospitalization and ivabradine, utility of stable HF states, and discount rate.

So, by daily decrease of ivabradine to 56 THB, ICER lesser than threshold will be accepted in Thailand, and by calculating this cost, cost-effectiveness of Ivabradine will be 60%. In this study, by daily decrease in cost of Ivabradine to 56 THB, its cost-effectiveness reaches to lesser than threshold limit of willingness to payment in Thailand (160,000 THB/QALY), and also in this threshold limit, cost-effectiveness of Ivabradine is increased to 60%. In all studies, although cost of Ivabradine was higher, it leads to higher life quality.

In the study by Griffiths et al. at a threshold of £20,000 per QALY, Ivabradine plus standard care is probably 95% more cost-effective than the standard care alone in patients with a heart rate ≥75 bpm and 70% in patients with ≥70 bpm. In the study by Taheri et al., the most effective factors were ivabradine mortality HR, ivabradine price, and ivabradine improvement coefficient. According to results of this study, Ivabradine at threshold limit of 6550$ per QALY is probably 60% cost-effective.

### 4.3. Comparing total costs for ivabradine plus Standard of Care (SoC) in comparison with current SoC alone

Studies were performed in developing and developed countries, and despite innate differences in health-care systems, costs of two interventions and threshold limit of willingness to pay in study countries, Ivabradine plus standard care is more expensive than the standard care alone.

Total data of cost based on 2020 dollar show that Ivabradine has the highest cost in USA, England, and Greece (248,587.10$, 19,748.54$, 15,009.84$, respectively) and lowest cost was in Iran and Thailand (2,161.83$ and 5,415.46, respectively).

Systematic results of studies show that despite higher costs, Ivabradine leads high QALY and LYQs and lesser mortality compared to standard care and has sufficient benefit for compensation of excess costs caused by treatment. In all studies which present indices of QALY and LYQs, Ivabradine was more effective, indicating that Ivabradine decreases hospitalization in hospital, increases life expectancy, decreases mortality rate, and improves life quality in patients with heart failure.

## 5. Limitations

Most studies investigate cost-effectiveness of Ivabradine from the viewpoint of the payer, where it will not show direct and indirect costs of patient and healthcare properly, and therefore using more complete analysis (viewpoint of society) might show real costs properly.

This systematic review did not consider studies that did not report QALYs and LY as a utility measure, models published only as conference abstracts, or cost-consequence models that did not report an ICER. Results of the studies should be cautiously generalized, since most studies obtain clinical effectiveness data of Ivabradine from a randomized controlled test, which is done in a controlled status and in definite criteria, which could be lesser generalized for each country based on the population and specific condition of the patients.

## 6. Conclusions

Results obtained from the systematic review show that in heart failure with reduced ejection fraction (HFrEF) patients with left ventricular ejection fraction (LVEF) <35%, Ivabradine plus standard treatment compared with standard treatment alone increases life expectancy and improves life quality and is also a more cost-effectiveness therapeutic method. In addition, in six selected countries, willingness-to-pay threshold is greater than the cost per QALY.

## 7. Expert opinion

Regarding our investigation, Ivabradine combined with standard care was more cost-effective than standard care alone in most of the evaluated studies, although the cost of this intervention was

higher than its effectiveness. Various factors seem to play a key role in determining this trend. As in some examples, social perspectives, as well as other costs, can affect the cost-effectiveness of using this intervention. However, the threshold chosen by each country can have a significant impact on these results. And to have a more accurate result, it is required to pay more attention to the income level in different countries. It is certainly easier to allocate more financial resources for the intervention, with greater effectiveness, in high- and middle-income countries than for low-income countries. Although ivabradine is currently used in different countries, for the reasons mentioned above, conducting an economic evaluation and estimating the different types of costs and effectiveness of this intervention along with routine care, to achieve a comprehensive result in the countries that intend whether to include ivabradine in their healthcare system, is strongly recommended.

## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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## References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Azad N, Lemay G. Management of chronic heart failure in the older population. J Geriatric Cardiol. 2014;11(4):329–337.
2. Ramani GV, Uber PA, Mehra MR. Chronic heart failure: contemporary diagnosis and management. Mayo Clin Proc. 2010;85 (2):180–195.
3. Savarese G, Lund LH. Global public health burden of heart failure. Card Fail Rev. 2017;3(1):7–11.
4. Askoxylakis V, Thieke C, Pleger ST, et al., Long-term survival of cancer patients compared to heart failure and stroke: a systematic review. BMC Cancer. 2010;22(10): 105.
•• **This paper presents the economic evaluation of ivabradine in treatment of patients with heart failure in Australia.**
5. Adena MA, Hamann G, Sindone AP. Cost-effectiveness of ivabradine in the treatment of chronic heart failure. Heart Lung Circ. 2019;28(3): 414–422.
•• **This paper presents the economic evaluation of ivabradine in treatment of patients with heart failure in Thailand**
6. Krittayaphong R, Yadee J, Permsuwan U. Cost-effectiveness analysis of the adjunctive therapy of ivabradine for the treatment of heart failure with reduced ejection fraction. CDATA. 2019;11:767–777.
7. Van Riet EE, Hoes AW, Wagenaar KP, et al. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail. 2016;18(3):242–252.
8. Jones NR, Roalfe AK, Adoki I, et al. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. Eur J Heart Fail. 2019;21(11):1306–1325.
9. Braunschweig F, Cowie MR, Auricchio A. What are the costs of heart failure? Europace. 2011;2(ii):13–17.
10. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia. Updated. 2011 October.
11. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376(9744):875–885.
12. Kjekshus J, Gullestad L. Heart rate as a therapeutic target in heart failure. Eur Heart J. 1999;1: H64–9.
•• **This paper presents the economic evaluation of ivabradine in treatment of patients with heart failure in U.K.**
13. Griffiths A, Paracha N, Davies A, et al. Sculpher M. The cost effectiveness of ivabradine in the treatment of chronic heart failure from the U.K. National health service perspective. Heart. 2014;100 (13):1031–1036.
14. Black J. Drugs from emasculated hormones: the principle of syntopic antagonism. Science. 1989;245(4917):486–493.
15. McMurray JJ, Adamopoulos S, Anker SD, et al., Guidelines ESCCfP: ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33 (14): 1787–1847.
•• **This paper presents the economic evaluation of ivabradine in treatment of patients with heart failure in Greece.**
16. Kourlaba G, Parissis J, Karavidas A, et al. Economic evaluation of ivabradine in the treatment of chronic heart failure in Greece. BMC Health Serv Res. 2014;14(1):631.
17. Krum H. Driscoll A Management of heart failure. Med J Aust. 2013;199(5): 334–339.
•• **This paper presents the economic evaluation of ivabradine in treatment of patients with heart failure in US.**
18. Kansal AR, Cowie MR, Kielhorn A, et al. Cost-effectiveness of ivabradine for heart failure in the United States. J Am Heart Assoc. 2016;6(5):e003221.
19. Butt T, Liu GG, Kim DD, et al. Taking stock of cost-effectiveness analysis of healthcare in China. BMJ Glob Health. 2019;4(3): e001418.
20. Edlin R, McCabe C, Hulme C, et al. Cost effectiveness modelling for health technology assessment. Springer; 2015.
21. Yaghoubi M, Aghayan HR, Arjmand B, et al. Cost-effectiveness of homograft heart valve replacement surgery: an introductory study. Cell Tissue Bank. 2011;12(2):153–158.
22. Nargesi S, Rezapour A, Souresrafil A, et al. Cost-effectiveness analysis of pulse oximetry screening in the full-term neonates for diagnosis of congenital heart disease: a systematic review. Iran J Pediatr. 2020;30(5):e105393.
23. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
24. Nargesi S, Abutorabi A, Alipour V, et al. Cost-effectiveness of endovascular versus open repair of abdominal aortic aneurysm: a systematic review. Cardiovasc Drugs Ther. 2021.
25. Taheri S, Heidari E, Aivazi MA, et al. Cost-effectiveness analysis of Ivabradine in treatment of patients with heart failure in Iran. Int J Technol Assess Health Care. 2018;18:1–8.
26. Verguet S, Feldhaus I, Kwete XJ, et al. Health system modelling research: towards a whole-health-system perspective for identifying good value for money investments in health system strengthening. BMJ Glob Health. 2019;4(2):e001311.