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https://doi.org/10.31925/farmacia.2026.3.21 **ORIGINAL ARTICLE**

COST-EFFECTIVENESS ANALYSIS OF ESAXERENONE IN RESISTANT HYPERTENSION MANAGEMENT: A PARTITIONED SURVIVAL HEALTH ECONOMIC MODEL

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Abstract

This is the cost-effectiveness study of esaxerenone in patients with resistant hypertension (RH). The partitioned-survival model compared esaxerenone, spironolactone, eplerenone, finerenone, and baxdrostat. Health states were uncomplicated RH, RH with non-fatal complications, and death. Inputs were sourced from the literature. Intervention costs were referenced from the Republic Fund of Health Insurance of Serbia (RSD). Quality-Adjusted Life Years (QALY) were calculated using the EQ-5D. Treatment benefits are reflected through better blood pressure control. Analysis was from a third-party payer perspective with 3-month cycles, a 10-year modeling period, and an annual 5% discount. The outcomes were the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB). The willingness-to-pay was 4,393,536 RSD/QALY. Sensitivity analyses assessed robustness. The results showed that esaxerenone was dominant in the base-case scenario. Spironolactone, eplerenone, and finerenone were more effective than baxdrostat. Spironolactone and finerenone dominated eplerenone. Spironolactone yielded cost savings *versus* finerenone but also had lower effectiveness (-85,810 RSD cost increment, -0.0066 QALY increment, and 56,890 RSD NMB at 10-year endpoint). Sensitivity analyses demonstrated stable findings, except for spironolactone *versus* finerenone and esaxerenone comparisons (which significantly relied on extrapolated effectiveness).

Rezumat

Scopul acestui studiu a fost efectuarea unei analize cost-eficiență privind utilizarea esaxerenonei la pacienții cu hipertensiune arterială rezistentă (HTAR). A fost utilizat modelul *partitioned-survival model* pentru compararea esaxerenonei cu spironolactona, eplerenona, finerenona și baxdrostat. Patologiile incluse în model au fost: HTAR necomplicată, HTAR asociată cu complicații nonfatale și HTAR asociată cu deces. Costurile intervențiilor au fost estimate pe baza tarifelor Fondului Republican de Asigurări de Sănătate din Serbia (RSD). *Quality-Adjusted Life Years* (QALY) s-a calculat utilizând instrumentul EQ-5D. Analiza a fost realizată din perspectiva unui terț plătitor, utilizând cicluri de 3 luni, un orizont temporal de modelare de 10 ani și o rată anuală de actualizare de 5%. Rezultatele evaluate au inclus raportul de cost-eficiență incremental (ICER) și beneficiul monetar net (NMB). Pragul de disponibilitate de plată a fost stabilit la 4.393.536 RSD/QALY. Rezultatele au arătat că esaxerenona a fost strategia dominantă în scenariul de bază. Spironolactona, eplerenona și finerenona s-au dovedit mai eficiente decât baxdrostatul. De asemenea, spironolactona și finerenona au fost mai dominante decât eplerenonă. Comparativ cu finerenona, spironolactona a generat economii de cost, însă a fost asociată cu o eficacitate ușor inferioară (increment de cost de -85.810 RSD, increment de -0,0066 QALY și un beneficiu monetar net de 56.890 RSD la orizontul de 10 ani).

Keywords: hypertension resistant to treatment, cost-utility analysis, esaxerenone (CS-3150), mineralocorticoid receptor antagonists, and aldosterone synthase inhibitor

Introduction

Resistant hypertension (RH) is a complex form of hypertension characterized by an inappropriate response to medication treatment. This leads to a worsening prognosis due to the damage of vital organ systems, a close association with the occurrence of other cardiovascular diseases, and premature death. According to the latest research in the Serbian population, a cross-sectional study reported a standardized prevalence of hypertension among adults and adolescents of 34.5%, with slightly more than half of them receiving any kind of medication treatment. However, only 35.2% of treated patients had normal blood pressure levels, suggesting that two-thirds of patients did not have an adequate treatment response (1). These results indicate a concerning frequency of RH in the Serbian population.

According to the International Society of Hypertension (ISH) guidelines, RH is diagnosed when a patient has high blood pressure despite treatment with maximum-tolerated doses of three antihypertensives from different pharmacological groups (including a diuretic). At first, patients should consider lifestyle modifications, optimize standard hypertension

management, and identify potential underlying causes (interactions, adherence, external factors, *etc*.) before initiating RH treatment. If the blood pressure remains uncontrolled, a health professional should add a fourth antihypertensive. The first-choice medications are mineralocorticoid receptor antagonists (spironolactone and eplerenone), if the kidney function is preserved and there is no hyperkalemia (2).

Spironolactone is a preferred choice because there is more published evidence of its efficacy. Multiple clinical trials and meta-analyses have shown that adding spironolactone significantly reduces blood pressure in patients with RH. In addition, direct and indirect comparisons have reported spironolactone's persistent efficacy and superiority over other treatments. Still, there is a lack of published analyses comparing the effects of spironolactone and eplerenone in the RH population. One of the potential reasons is a lack of studies that assessed eplerenone efficacy in larger populations with RH diagnosis. The use of eplerenone is primarily based on the small-sample clinical trials, including patients with resistant or uncontrolled hypertension, and the real-world clinical experience (3).

Esaxerenone is an innovative, non-steroidal, selective antagonist of mineralocorticoid receptors, approved in Japan in 2018 for the treatment of essential hypertension. Randomized clinical trials reported high efficacy in lowering blood pressure among patients with primary or complicated hypertension. The efficacy and safety of esaxerenone were demonstrated when used as monotherapy, in combination with other antihypertensives, and in subpopulations with heart failure, diabetes mellitus, albuminuria, or primary aldosteronism. Also, esaxerenone in 5 mg doses showed superior efficacy when compared to 50 mg eplerenone in hypertensive patients (4). Although clinical trial evidence in RH is lacking, retrospective real-world studies imply that it is being prescribed in clinical practice for this diagnosis. Esaxerenone showed a significant reduction in blood pressure and a favorable safety profile in these studies as the fourth antihypertensive (5, 6). Other medications similar to esaxerenone are also being investigated in clinical trials for the treatment of RH. One of them is finerenone, a mineralocorticoid receptor antagonist with promising antihypertensive effects in patients with RH and chronic kidney disease (7, 8). Baxdrostat is an investigational aldosterone synthase inhibitor that demonstrated great efficacy and safety among patients with RH in a recent Phase 2 trial (9).

High disease burden and serious consequences of RH require the prompt introduction of effective and affordable pharmacological treatment that would quickly reduce blood pressure levels to the target values. However, the most recently published health economic studies on RH have focused on invasive procedures, such as endovascular ultrasound renal denervation, rather than medications (10-12). Although endovascular ultrasound renal denervation is cost-effective compared to the standard of care, the cost-effectiveness of medications for RH management remains unknown, particularly for new drugs in clinical research or practice. The unclear positioning of innovative treatments and the lack of health economic comparisons among approved first-choice medications may pose challenges for healthcare decision-making.

The main objective of this study is to compare the cost-effectiveness of esaxerenone to other approved and investigational pharmacological treatments used as a fourth medication for RH (spironolactone, eplerenone, finerenone, and baxdrostat). The secondary aim of this study is to fill the literature gap by assessing the cost-effectiveness of other medications included in the model.

Materials and Methods

This health economic analysis is in line with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines, published by the Professional Society for Health Economics and Outcomes Research (ISPOR) in 2022 (13). There are no relevant ethical statements or conflicts of interest to disclose, as this is a theoretical research study based solely on the mathematical principles of health economic modeling and publicly available literature. The analysis plan was uploaded by the authors to the Open Science Framework (OSF) prior to study initiation. The OSF is an open-source platform to publish research outputs, from documenting study design and planning methods to final publication and dissemination. Briefly, the authors used the platform to publish the study objective, hypothesis, and initial design before model development. The model design is consistent with the methods described in this section of the manuscript. Authors also claimed that the model design was unique at the time, that no similar studies had been detected in a thorough scientific literature search, and discussed the expected results based on the available clinical evidence (14).

The study is based on the principles of partitioned survival models, with cost-effectiveness analysis incorporated. The model scheme is presented in Figure 1. The model had three health states – RH without complications (uncomplicated RH), RH with non-fatal complications, and death. Relevant RH complications were identified based on the comprehensive Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study (15). To ensure a reliable and fair comparison, disease stages had to be assigned to each complication so that the gathered literature evidence would be

sourced from populations with similar characteristics. Hence, the non-fatal complications included in the model were acute myocardial infarction (with or without ST elevation), stroke (ischemic or hemorrhagic), chronic heart failure (with ejection fraction <40% and/or urgent hospitalization), chronic kidney disease (glomerular filtration <15 ml/min/1.73m2 and/or dialysis-dependent patients), and peripheral artery disease (requiring amputation).

The model was designed from the perspective of a third-party payer, using three-month cycles and a 10-year modeling period.

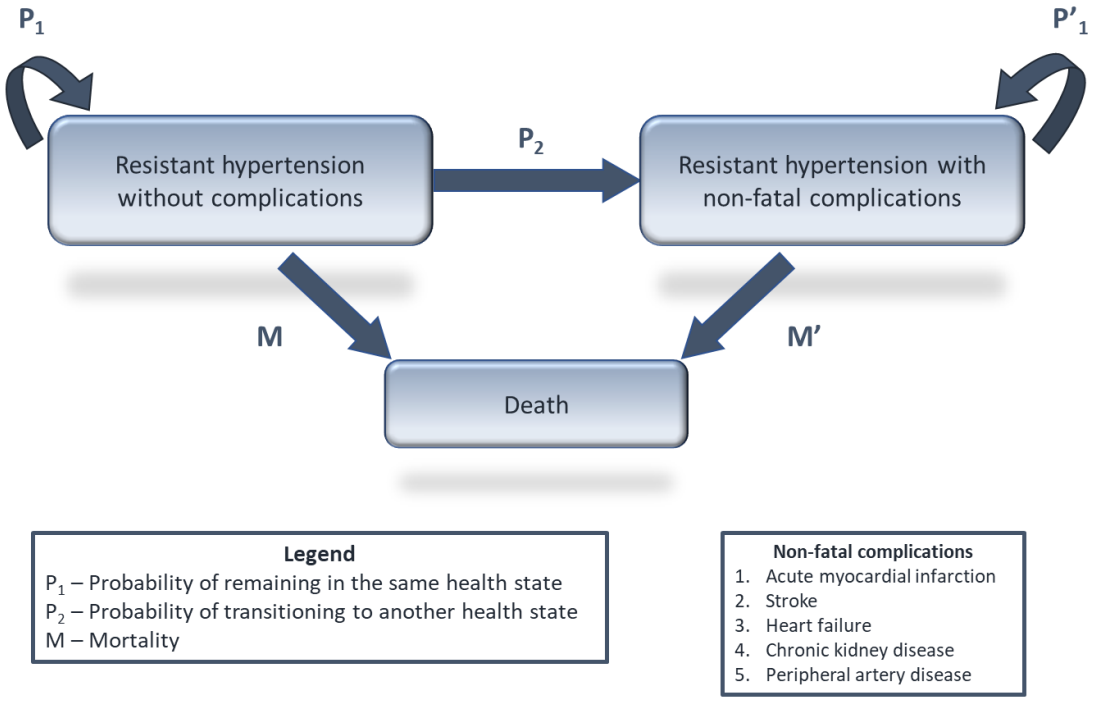

Figure 1.
Model scheme

Model population

The target population included patients with diagnosed RH. The main intervention was innovative antihypertensive medication esaxerenone. At the same time, the comparators of interest were approved mineralocorticoid receptor antagonists for RH (spironolactone and eplerenone) and other novel treatments for RH (finerenone and baxdrostat). The cohort of 1,000 patients entered the model, assuming they all received and adhered to the same standard triple antihypertensive treatment, but still had uncontrolled blood pressure. Then, a fourth antihypertensive was introduced – esaxerenone (2.5 – 5 mg, oral route), spironolactone (25 – 50 mg, oral route), eplerenone (25 – 50 mg, oral route), finerenone (10 – 20 mg, oral route), or baxdrostat (0.5 – 2 mg, oral route). The entire population starts the model in the uncomplicated RH state. Based on the fourth medication's efficacy in controlling blood pressure in RH, patients start developing non-fatal complications or experience premature death, which is simulated by transitioning to other health states in the model.

Model parametrization

The transitioning probabilities depended on the frequency of complications in this population and the efficacy of model comparators in controlling the blood pressure.

The probability of non-fatal complications or death occurring in the RH population with controlled and uncontrolled blood pressure at specific time points was sourced from the literature. The partitioned survival curve was plotted for each outcome separately by the best-fit method. The equation was then used to extrapolate the risk of complications or death occurring at model-relevant time points by calculating the area under the curve (AUC) for each model cycle. The same steps were performed for controlled and uncontrolled RH.

The efficacy of the medications in the model was sourced from published clinical trials reporting the rate of RH patients with controlled blood pressure after the specified treatment duration. More effective treatment had a higher rate of normotensive patients who were at a lower risk of developing complications or experiencing a fatal outcome than those with uncontrolled blood pressure.

All health states in the model had assigned healthcare costs and quality-of-life values. The microcosting method was applied to estimate the economic burden of RH in this population. For patients without complications, the total economic burden

was equivalent to the costs of antihypertensive treatment (model medication and standard triple therapy) and regular check-up visits. For each non-fatal complication, the most relevant international treatment guidelines at the time of the study were analyzed to identify the healthcare resources used in clinical practice for its management (diagnostic and treatment procedures, medications, and healthcare visits). Utilization measures for each resource were identified from the published literature. Unit prices for all the resources were referenced from the Republic Fund of Health Insurance of Serbia (in national currency – RSD). Utilization rates and unit costs for each healthcare resource were used to estimate the total cost of the respective complication (Table I).

Table I

Healthcare cost model input values

Input	Value
Health state costs	
AMI, cost for model cycle 1	104,594 RSD
AMI, cost for model cycles 2-4	17,903 RSD
AMI, cost for model cycles 5-40	5,106 RSD
Stroke, cost for model cycle 1	103,595 RSD
Stroke, cost for model cycles 2-40	2,439 RSD
Heart failure, cost for model cycle 1	254,364 RSD
Heart failure, cost for model cycles 2-40	10,594 RSD
CKD, cost for model cycle 1	147,568 RSD
CKD, cost for model cycles 2-40	117,630 RSD
PAD, cost for model cycle 1	175,097 RSD
PAD, cost for model cycles 2-40	17,231 RSD
RH without complications, cost for model cycles 1-40	312 RSD
Medication costs	
Spironolactone	1,088 RSD
Eplerenone	3,785 RSD
Esaxerenone	1,088 RSD
Finerenone	20,225 RSD
Baxdrostat	1,088 RSD

*Abbreviations: AMI – acute myocardial infarction, CKD – chronic kidney disease, PAD – peripheral artery disease, RH – resistant hypertension

Quality-of-life scores were also extracted from the published literature (Table II). The EuroQol 5-Dimension (EQ-5D) was the most referenced tool in this research area. EQ-5D index and visual analog scale (VAS) scores were used to estimate quality-adjusted life years (QALY) as a measure of treatment effectiveness in the model. The base-case analysis used EQ-5D index values, while the alternative scenario focused on the EQ-5D VAS. If EQ-5D VAS values were not captured in the literature, EQ-5D index values were used instead. Both EQ-5D 3-level (EQ-5D-3L) and EQ-5D 5-level (EQ-5D-5L) versions were considered relevant for the model. EQ-5D value sets were not specified during the literature search. The crosswalk between EQ-5D-3L and EQ-5D-5L, and the harmonization of EQ-5D value sets, were not feasible, as the inputs were sourced from published studies (aggregated results) and patient-level data were unavailable.

Table II

Health utility model input values (EQ-5D)

Health state	Tool	Model cycle	Value	Country	Study
Base-case scenario					
AMI	EQ-5D-3L index	Cycles 1-4	0.7200	England	(16)
		Cycles 5-40	0.7800		
Stroke	EQ-5D-5L index	Cycles 1-4	0.6000	UK and Spain	(17, 18)
		Cycles 5-8	0.5112		
		Cycles 9-12	0.4756		
		Cycles 13-40	0.4600		
Heart failure	EQ-5D-5L index	Cycle 1	0.6500	Malaysia and Thailand	(19, 20)
		Cycles 2-40	0.6770		
CKD	EQ-5D index (not specified)	Cycles 1-40	0.7740	Global (meta-analysis)	(21)
PAD	EQ-5D-3L index	Cycles 1-4	0.1578	Sweden	(22)
		Cycles 5-40	0.4256		
RH without complication	EQ-5D-5L index	Cycles 1-4	0.8210	The Netherlands	(23)
		Cycles 5-40	0.8847		

Health state	Tool	Model cycle	Value	Country	Study
Alternative scenario					
AMI	EQ-5D-3L VAS	Cycles 1-4	0.6330	England	(16)
		Cycles 5-40	0.7390		
Stroke	EQ-5D-5L index	Cycles 1-4	0.6000	UK and Spain	(17, 18)
	EQ-5D-3L VAS	Cycles 5-8	0.5600		
		Cycles 9-12	0.5200		
		Cycles 13-40	0.5500		
Heart failure	EQ-5D-5L index	Cycle 1	0.6500	Malaysia and Thailand	(19, 20)
	EQ-5D-5L VAS	Cycles 2-40	0.6540		
CKD	EQ-5D-3L VAS	Cycles 1-40	0.6010	Nordics	(24)
PAD	EQ-5D-3L index	Cycles 1-4	0.1578	Sweden	(22)
		Cycles 5-40	0.4256		
RH without complication	EQ-5D-5L VAS	Cycles 1-4	0.7010	The Netherlands	(23)
		Cycles 5-40	0.7010		

*Abbreviations: AMI – acute myocardial infarction, EQ-5D-3L – EuroQol 5-Dimension 3-Level, EQ-5D-5L – EuroQol 5-Dimension 5-Level, UK – United Kingdom, CKD – chronic kidney disease, PAD – peripheral artery disease, RH – resistant hypertension, VAS – visual analog scale

The death health state had assigned 0 RSD costs and 0 QALY. An annual discount rate of 5% was applied to cost and effect inputs. As the national guidelines do not specify a discount value, the rate was defined by the recommendations for Croatia as a country with a similar healthcare system and geo-national characteristics of the general population (25).

Thorough literature reviews were conducted to identify the most recent and reliable studies reporting results relevant to the model. If multiple sources reported relevant results, the input value was the weighted mean of those results. The calculations were then applied as explained in the previous paragraphs.

Assumptions

The efficacy of esaxerenone in patients with RH was not investigated in clinical trials at the time of the study. Hence, the rate of patients with controlled blood pressure was estimated based on the available evidence. This rate was published in the phase 3 esaxerenone *versus* (*vs.*) eplerenone trial, including patients with uncontrolled hypertension (26). The proportion of rates from this clinical trial was applied to the model input reflecting eplerenone efficacy to estimate the rate of normotensive patients on esaxerenone.

Two publications reported the efficacy of finerenone among patients with RH at the time of this study. Although both included patients with certain complications (chronic kidney disease and/or diabetes mellitus), the reported changes in blood pressure levels after the treatment were similar (7, 8). Therefore, it was assumed that the same efficacy would apply to the population in the model.

Esaxerenone and baxdrostat are not yet approved in Serbia. Hence, prescription costs for these medications were assumed to equal those of the cheapest model comparator. The impact of this assumption on model findings was diminished in the scenario analysis.

Study outcomes

The primary outcome of this analysis is the incremental cost-effectiveness ratio (ICER), calculated as the difference in healthcare costs and effectiveness between two model comparators. ICER (RSD/QALY) was reported at 1-, 2-, 5-, and 10-year endpoints for each comparison. ICER indicates which comparator is cost-effective in the management of RH by comparing the result to the willingness-to-pay (WTP) threshold. According to the most recent recommendations at the time of the study, the WTP threshold for Serbia should be 3 times higher than the national gross domestic product (GDP) *per* capita (27). GDP *per* capita was 1,464,512 RSD in 2024 (28). Hence, the WTP threshold value for this analysis was 4,393,536 RSD/QALY (approximately €37,500 *per* QALY).

The secondary outcome in this analysis is net monetary benefit (NMB). It is an alternative to ICER that avoids ratio-related statistical issues (*e.g.*, when the QALY increment is 0). NMB converts health outcomes into monetary units using the WTP threshold. The NMB of an intervention relative to the comparator is calculated by multiplying the QALY increment by the WTP threshold and subtracting the cost increment. If the result is higher than 0, the intervention is cost-effective and vice versa. If NMB equals 0, the intervention's cost equals the value of its benefits against the specified comparator, given a specific WTP threshold.

If the intervention has a lower cost but is also less effective than the comparator (negative cost increment and negative QALY increment), the ICER value is positive and located in the South-West (SW) quadrant. Even though such interventions are not ideal, they remain an additional treatment option that may be more affordable for patients and could improve overall health outcomes by reallocating resources to other therapies. A recent ISPOR publication guides interpreting the results of economic

models with ICER in the SW quadrant by analyzing National Institute for Health and Care Excellence (NICE) health technology assessment reports (29). Although the report states that ICER remains a crucial factor for decision-makers, the results in the SW quadrant could be very sensitive to small differences in QALY. Hence, NMB may be used to facilitate the interpretation of results in such cases.

Statistical analysis

The research was based on publicly available literature and health-economic modeling principles with a partitioned-survival design and applied cost-effectiveness analysis rather than a hypothesis-testing framework. Therefore, a conventional hypothesis testing using statistical tests and reporting statistical significance was not performed. Instead, uncertainty and generalizability were assessed using sensitivity and scenario analyses. Probabilistic sensitivity analysis (PSA), deterministic univariate one-way sensitivity analysis (OWSA), and scenario analyses were conducted to assess model robustness, the reliability of the findings, and the validity of the study conclusions.

For PSA, all input values were assigned corresponding distributions based on the data type. Input values varied, and results were calculated for the specified number of iterations to explore model convergence. In this study, the number of iterations was 5,000 and the results were presented as the standard measures of central tendency (mean, standard deviation [SD], median, interquartile range [IQR], and 95% confidence intervals [CI]), scatter plots of cost and QALY increments for each simulation, and the cost-effectiveness acceptability curves showing the probability of interventions being cost-effective to the comparators.

OWSA demonstrated the impact of a single parameter on the results by varying all the input values by a prespecified rate, depicting the one with the greatest effect on study findings. The variability rate used in this study was ±20%, which is one of the most common values used in health economic research. OWSA also assessed the model's consistency by examining whether variability in certain inputs would lead to a significant change in the study's conclusions. OWSA results were plotted on the tornado charts for both base-case and alternative scenarios.

Multiple scenario analyses were performed to assess the robustness of the findings by adjusting key model assumptions. Pricing scenario analysis was conducted to diminish the impact of differences in medication costs on the study findings. Some medications in the model are not yet approved in Serbia, while the prescription costs of approved medications also differ. Therefore, the ICER was calculated under the assumption that the prescription costs *per* model cycle for the compared medications were equal. Effectiveness scenario analysis was performed to assess the consistency of findings after adjusting the esaxerenone blood pressure control rate, as this input was approximated using the most relevant available literature (phase 3 uncontrolled hypertension trial, esaxerenone *vs*. eplerenone) (26). In line with the conservative null-difference assumption, the blood pressure control rate for esaxerenone was set to match the eplerenone rate. Also, the esaxerenone blood pressure control rate was varied by ±50% to reflect the real-world uncertainty of this extrapolated parameter when modeled with a wider distribution.

Model development, cost-effectiveness calculations, and sensitivity and scenario analyses were performed in Microsoft Excel® software (version Microsoft 365). Figures were designed in Microsoft Excel® and formatted in Microsoft PowerPoint® software (version Microsoft 365).

Results and Discussion

Main results

The total cost for esaxerenone at Year 1 was 2,386,271 RSD, with 0.7836 QALY in the base-case scenario (using the EQ-5D index) and 0.6694 QALY in the alternative scenario (using the EQ-5D VAS). At Year 10, the costs of patients on esaxerenone increased to 69,952,137 RSD with 5,8875 QALY and 4.7819 QALY in the base-case and alternative scenarios, respectively. Esaxerenone was a dominant intervention in base-case and alternative scenarios compared to other medications included in the model at 1-year, 2-year, 5-year, and 10-year endpoints. All ICER values were negative due to the negative cost increments and the positive QALY increments in both the base-case and alternative scenarios. NMB values were higher than 0, indicating that esaxerenone was a cost-effective treatment compared to other medications in the model. The results of esaxerenone comparisons are listed in Table III.

The main results of comparisons between other medications showed that spironolactone was the dominant intervention over eplerenone and baxdrostat at all endpoints in base-case and alternative scenarios. ICER values were negative due to the negative cost increments but positive QALY increments, and NMB values were positive. On the other hand, the results of spironolactone *vs*. finerenone differed.

Spironolactone had lower costs and lower effectiveness across all study endpoints (*i.e.*, -49,351 RSD cost increment and -0.001 QALY increment at Year 1 in the base-case scenario). This led to a positive ICER value in the SW quadrant of the cost-effectiveness plane (Figure 2), indicating that spironolactone is a chea*per* but less effective treatment than finerenone. Although ICER values were higher than the pre-defined WTP threshold (4,393,536 RSD/QALY), differences in QALY between spironolactone and finerenone were minimal, while NMB

values were positive across all study endpoints in base-case and alternative scenarios.

Table III

Cost increments, QALY increments, and ICER values for esaxerenone comparisons in the model

Endpoint	Cost increment (RSD)	QALY increment, base-case	ICER (RSD *per* QALY), base-case	NMB (RSD), base-case	QALY increment, alternative	ICER (RSD *per* QALY), alternative	NMB (RSD), alternative
Esaxerenone *vs.* Spironolactone							
Year 1	-82,983	0.0007	Dominant	85,843	0.0005	Dominant	85,295
Year 2	-231,521	0.0026	Dominant	243,081	0.0019	Dominant	240,017
Year 5	-1,093,013	0.0142	Dominant	1,155,331	0.0101	Dominant	1,137,187
Year 10	-3,199,407	0.0416	Dominant	3,382,125	0.0291	Dominant	3,327,199
Esaxerenone *vs.* Eplerenone							
Year 1	-178,588	0.0012	Dominant	183,720	0.0009	Dominant	182,735
Year 2	-442,271	0.0046	Dominant	462,264	0.0033	Dominant	456,982
Year 5	-1,940,924	0.0243	Dominant	2,047,617	0.0172	Dominant	2,016,576
Year 10	-5,576,122	0.0711	Dominant	5,888,469	0.0497	Dominant	5,794,602
Esaxerenone *vs.* Finerenone							
Year 1	-132,334	0.0005	Dominant	134,632	0.0004	Dominant	134,192
Year 2	-328,175	0.0022	Dominant	337,801	0.0016	Dominant	335,242
Year 5	-1,246,433	0.0119	Dominant	1,298,815	0.0084	Dominant	1,283,553
Year 10	-3,285,216	0.0350	Dominant	3,439,015	0.0245	Dominant	3,392,770
Esaxerenone *vs.* Baxdrostat							
Year 1	-192,302	0.0017	Dominant	199,911	0.0014	Dominant	198,454
Year 2	-606,603	0.0073	Dominant	638,479	0.0053	Dominant	630,003
Year 5	-3,009,472	0.0395	Dominant	3,182,923	0.0280	Dominant	3,132,386
Year 10	-8,884,614	0.1159	Dominant	9,393,885	0.0811	Dominant	9,240,756

Abbreviations: QALY – quality-adjusted life years, ICER – incremental cost-effectiveness ratio, NMB – net monetary benefit

Because the QALY difference was extremely small, NMB was a more objective decision metric in this case. This suggests that although finerenone treatment yielded slightly more QALYs, the cost savings with spironolactone exceeded the marginal QALY loss at the predefined WTP threshold. Regarding other comparisons, ICER and NMB results showed that both eplerenone and finerenone dominated baxdrostat, with finerenone being the dominant intervention over eplerenone.

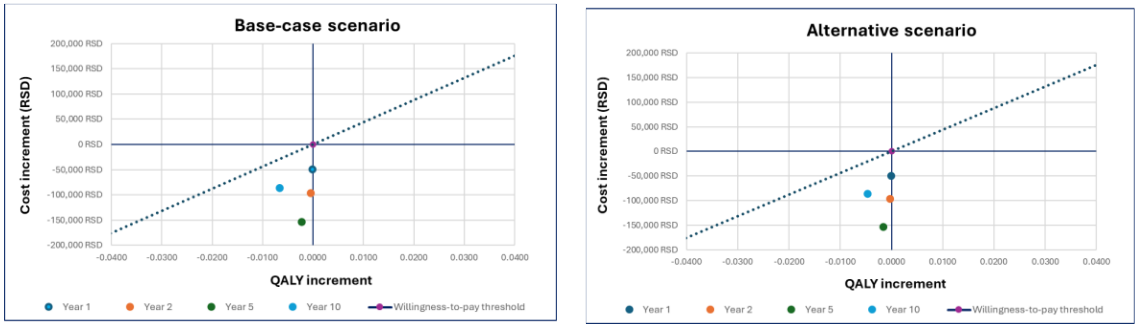

Figure 2.

The cost-effectiveness plane of spironolactone *vs.* finerenone comparison in base-case and alternative scenarios

OWSA

OWSA depicted the long-term uncomplicated RH utility (for model cycles 5-40) and chronic kidney disease management cost (for model cycles 5-40) as the most influential input values on the study findings regarding esaxerenone comparisons. However, varying any of the values by ±20% did not change the conclusions for any of these comparisons. Esaxerenone was still the dominant intervention compared to other model medications in both the base-case and alternative scenarios. Esaxerenone treatment was associated with lower costs (negative incremental cost) and higher QALYs (positive incremental effect), leading to negative 10-year ICERs. Regarding the comparisons between other medications in OWSA, long-term uncomplicated RH utility (for model cycles 5-40) and chronic kidney disease management cost (for model cycles 5-40) also had the greatest impact on 10-year ICER values. However, the study's conclusions remained consistent across all input values within the predefined range. The only exception was the comparison between

spironolactone and finerenone. The finerenone price *per* model cycle was the input with the highest and most significant impact on the findings. Lowering this value by 20% showed that finerenone would be the dominant intervention compared to spironolactone in both scenarios (negative ICER due to the positive cost and negative QALY increments). On the other hand, increasing the finerenone price *per* model cycle by 20% would result in a significant increase of 10-year ICER, from 13,036,380 RSD/QALY to 32,369,858 RSD/QALY in the base-case scenario and from 18,628,645 RSD/QALY to 46,255,677 RSD/QALY in the alternative scenario. Another factor that significantly impacted the findings was the cost of chronic kidney disease management from the 5th to the 40th model cycle. Increasing this input by 20% led to a decrease in ICER to 73,148 RSD/QALY in the base-case scenario and 104,526 RSD/QALY in the alternative scenario. This change would position spironolactone as the cost-effective intervention compared to finerenone, as the results were lower than the WTP threshold. Tornado charts comparing spironolactone and finerenone are presented in Figure 3.

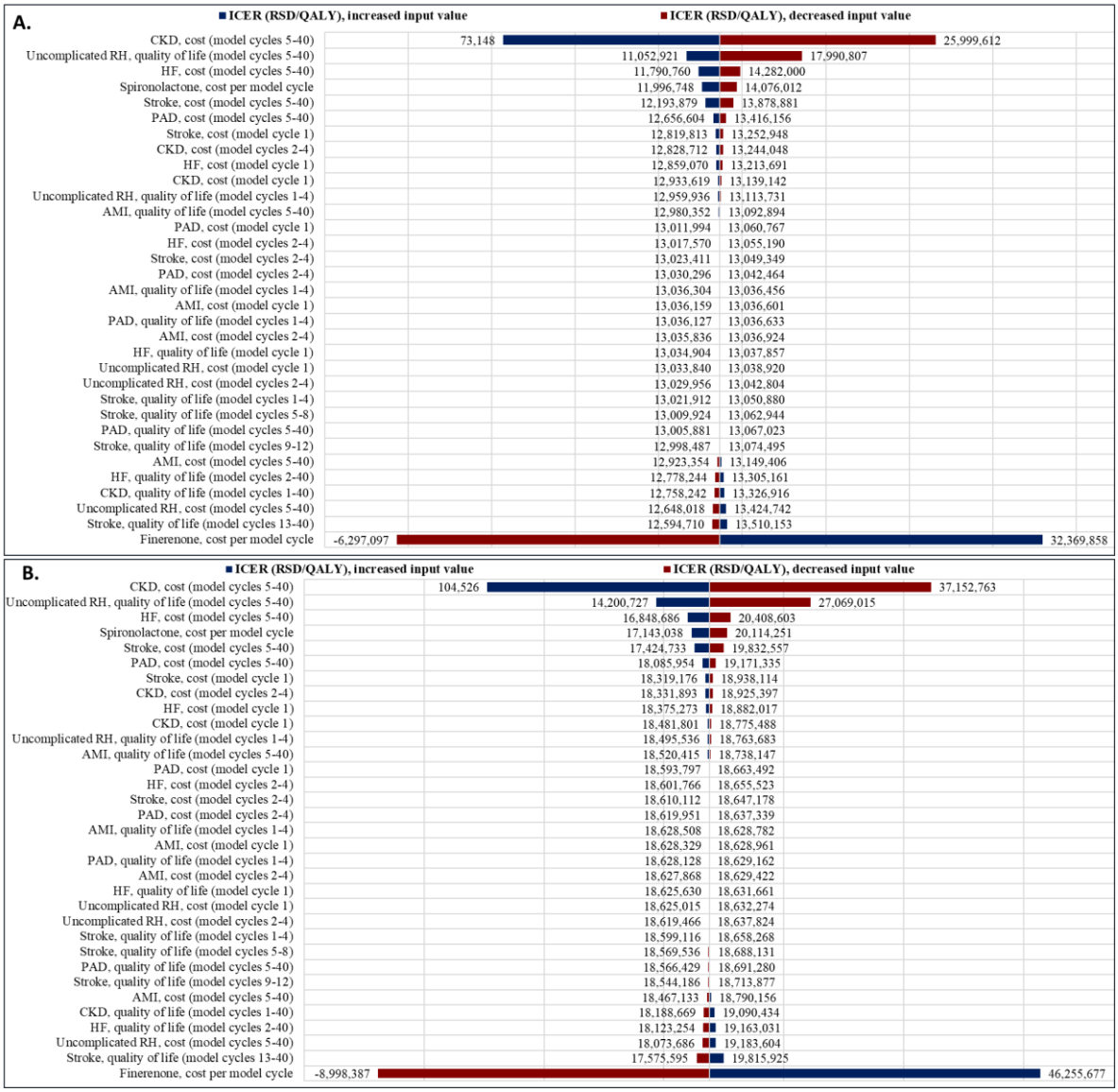

Figure 3.

Tornado charts for spironolactone *vs*. finerenone, base-case (A) and alternative scenarios (B)
Abbreviations: ICER – incremental cost-effectiveness ratio, QALY – quality-adjusted life years, CKD – chronic kidney disease, RH – resistant hypertension, HF – heart failure, PAD – peripheral artery disease, AMI – acute myocardial infarction

PSA

PSA demonstrated the model's robustness with consistent findings for esaxerenone comparisons. Esaxerenone was a dominant intervention compared to other model medications, with negative average and median 10-year ICERs driven by negative

QALYs and positive cost increments. All esaxerenone cost-effectiveness acceptability curves had gentle (wide) slopes, indicating consistent model conclusions across WTP thresholds. Also, esaxerenone acceptability rates were generally high. The highest acceptability rates were observed when comparing esaxerenone to finerenone (99.58%) and the lowest when comparing esaxerenone to eplerenone (84.64%), using the model's WTP threshold value. Cost-effectiveness acceptability rates for all model comparisons are reported in Table IV.

Table IV

PSA cost-effectiveness acceptability rates using the model's WTP threshold, base-case, and alternative scenarios

Comparison	Acceptability rate, base-case scenario	Acceptability rate, alternative scenario
Esaxerenone *vs.* spironolactone	90.52%	90.22%
Esaxerenone *vs.* eplerenone	84.96%	84.64%
Esaxerenone *vs.* finerenone	99.58%	99.56%
Esaxerenone *vs.* baxdrostat	97.42%	97.22%
Spironolactone *vs.* eplerenone	78.64%	78.40%
Spironolactone *vs.* finerenone	0.88%	0.68%
Spironolactone *vs.* baxdrostat	99.04%	99.04%
Eplerenone *vs.* finerenone	1.10%	0.72%
Eplerenone *vs.* baxdrostat	92.12%	91.94%
Finerenone *vs.* baxdrostat	93.66%	93.28%

The spironolactone *vs*. finerenone comparison yielded mean 10-year ICER values of 133,325,959 RSD/QALY (95% CI: -231,483,684 to 665,265,489) and 192,756,369 RSD/QALY (95% CI: -316,121,415 to 1,003,986,984) for base-case and alternative scenarios, respectively. Although the wide 95% CIs indicate that the ICERs were highly variable in PSA, the low acceptability rates (0.88% in the base-case scenario and 0.68% in the alternative scenario) suggest the results were rarely in favor of spironolactone.

Scenario analyses

Pricing scenario analysis revealed that the prescription costs of the compared medications had a minimal impact on model findings in most cases. Esaxerenone remained a dominant intervention compared to other medications, with the negative ICER (due to lower costs and higher QALY) and positive NMB values. Also, spironolactone was dominant over eplerenone and baxdrostat, eplerenone was dominated by finerenone, and eplerenone and finerenone were dominant over baxdrostat. Spironolactone *vs*. finerenone was the only exception that yielded different results in the scenario analysis. Unlike in the main analysis, spironolactone was dominated by finerenone if their prescription costs *per* model cycle were equal. Finerenone demonstrated lower cost and higher QALY at all model endpoints, with negative NMB values (Table V).

Table V

Pricing scenario analysis results for spironolactone *vs*. finerenone comparison

Endpoint	Cost increment (RSD)	QALY increment, base-case	ICER, base-case	NMB (RSD), base-case	QALY increment, alternative	ICER, alternative	NMB (RSD), alternative
Spironolactone *vs.* Finerenone							
Year 1	24,908	-0.0001	Dominated	-25,470	-0.0001	Dominated	-25,362
Year 2	48,328	-0.0004	Dominated	-50,261	-0.0003	Dominated	-49,757
Year 5	184,158	-0.0023	Dominated	-194,094	-0.0016	Dominated	-191,212
Year 10	516,269	-0.0066	Dominated	-545,189	-0.0046	Dominated	-536,507

Abbreviations: QALY – quality-adjusted life years, ICER – incremental cost-effectiveness ratio, NMB – net monetary benefit

Effectiveness scenario analyses examined results under conditions in which esaxerenone effectiveness varied. The first scenario assumed equal blood pressure control rates of esaxerenone and eplerenone. ICER values suggested that esaxerenone remained dominant over baxdrostat (lower costs, greater QALY) and eplerenone (same effectiveness, lower costs) at all endpoints. However, spironolactone was the dominant intervention over esaxerenone across all endpoints in this scenario. Finerenone was dominant to esaxerenone at Year 2, Year 5, and Year 10. At Year 1, esaxerenone yielded lower costs (-14,656 RSD cost increment) and less QALY than finerenone (-0.0005 QALY increment), placing a positive ICER value in the SW quadrant. Since the NMB was positive (12,297 RSD), cost savings with esaxerenone were dominating over the small QALY gain by finerenone treatment. In the second scenario, esaxerenone blood pressure control rate was varied by ±50%. When the rate was increased, esaxerenone was the dominant intervention across all endpoints and comparators. On the other hand, reducing the esaxerenone rate for 50% led to opposite results. All

comparators at all endpoints had lower costs and higher QALY than esaxerenone.

Discussion of model findings

The findings of this study demonstrated the superiority of esaxerenone to other similar add-on antihypertensives for RH from the cost-effectiveness perspective. At all model endpoints in the base-case scenario, esaxerenone was the dominant intervention compared to spironolactone, eplerenone, finerenone, and baxdrostat. PSA (5,000 iterations) and OWSA (±20% input value variability) demonstrated that the model was robust and the findings were consistent. The highest impact on ICER had long-term uncomplicated RH utility score (value for model cycles 5-40) and cost of chronic kidney disease treatment (value for model cycles 5-40), but varying these inputs did not affect model conclusions. However, scenario analyses showed inconsistent model findings. Similar conclusions to the base-case analysis were drawn from alternative (using EQ-5D VAS instead of EQ-5D index utility values) and pricing scenario analyses (equal prescription costs for the esaxerenone and comparator drugs). Esaxerenone treatment was associated with lower healthcare costs and higher QALY than other medications at all endpoints. Yet, varying the input value reflecting blood pressure control rate with esaxerenone yielded different results. This input was extrapolated from the esaxerenone *vs*. eplerenone trial due to a lack of published evidence at the time of the model development. Assuming the same blood pressure control rate of esaxerenone and eplerenone, spironolactone and finerenone were then dominant to esaxerenone, except at Year 1 for finerenone. In addition, varying the esaxerenone blood pressure control rate by ±50% led to significant changes in the model findings. The effectiveness scenario analysis results imply that the extrapolated blood pressure control rate after esaxerenone use in patients with RH is a major driver of the model findings. This should be taken into consideration when interpreting the model results.

Based on the currently available data, all comparators dominated baxdrostat, while spironolactone and finerenone were dominant over eplerenone. The stability of these findings was also demonstrated in OWSA, PSA, and scenario analyses. The comparison of spironolactone *vs*. finerenone showed inconsistent findings between base-case and sensitivity analyses. The positive NMB values suggested that the cost savings from spironolactone treatment exceeded the small QALY benefits of finerenone treatment across all endpoints in the base-case analysis. The results were significantly impacted by the substantial difference in prescription costs *per* model cycle for spironolactone and finerenone (1,088 RSD *vs*. 20,225 RSD, respectively). Varying these input values in OWSA, PSA, and scenario analyses significantly affected the study's findings. Another input with a significant impact on the ICER of the spironolactone *vs*. finerenone comparison was the long-term cost of chronic kidney disease management (input for model cycles 5 to 40).

Review of published literature in this research area

A thorough literature search conducted at the time of the study did not yield any published cost-effectiveness analyses that included mineralocorticoid receptor antagonists or baxdrostat for the management of RH. Hence, this is the first such health economic model with cost-effectiveness analysis to the authors' knowledge. Other published studies with a similar design have focused on interventional therapies, such as renal denervation, baroreceptor activation, and central venous anastomosis, which were compared to a standard of care or optimal therapy. Sorato *et al*. (2020) (30) performed a systematic review to gather and summarize published pharmacoeconomic studies of interventional therapies for RH. Twelve country-specific studies were included from around the world, with eleven of them evaluating the cost-effectiveness of renal denervation therapy. The ICER for renal denervation was lowest in the Netherlands ($1,709.84 *per* QALY) and highest in Australia ($66,380.3 *per* QALY). This intervention was cost-effective in the US, UK, Australia, Canada, the Netherlands, Germany, Russia, and Korea, but was considered not cost-effective only in Mexico. The Rheos system (baroreceptor stimulation implant) was also considered cost-effective in a single US analysis ($64,400 *per* QALY). The results mainly depended on the effect on blood pressure control, the rate of non-responders, and the procedure costs (30). More recent models also focused on endovascular ultrasound renal denervation, primarily comparing it with the standard of care using data from the RADIANCE-HTN TRIO trial. The intervention was considered cost-effective in both European and US studies (10-12). Future health economic models should focus on providing more precise evidence by comparing interventional procedures for RH (mainly renal denervation) with specific pharmacological treatments for RH.

The cost-effectiveness of mineralocorticoid receptor antagonists was explored in indications other than RH. Multiple models reported the cost-effectiveness of finerenone in patients with chronic kidney disease and diabetes mellitus. Adding finerenone to the standard of care was a cost-effective treatment compared to providing only standard of care to patients in the UK (£8,808 *per* QALY), Japan (¥1,959,516 *per* QALY), and China (dominant) (31-33). The cost-effectiveness of mineralocorticoid receptor antagonists was also investigated in the management of heart failure (34-37). Mineralocorticoid receptor antagonists demonstrated lower costs ($63,135.52 *vs*. $80,365.31, respectively) and higher QALY (2.53 *vs*. 2.49, respectively) than sodium-glucose

transporter-2 inhibitors over 5 years of treatment (36). Another Brazilian study reported that the utilization of spironolactone or eplerenone was cost-effective in heart failure with reduced ejection fraction compared to not using any mineralocorticoid receptor antagonist (Int$7,955 *per* QALY and Int$6,460 *per* QALY, respectively). Finerenone was not a cost-effective intervention in this setting (Int$109,840 *per* QALY), whereas eplerenone was cost-effective compared to spironolactone in patients with heart failure with reduced ejection fraction (Int$6,178) (37).

Strengths and limitations

Although multiple published economic evaluations of mineralocorticoid receptor antagonists exist, none have examined cost-effectiveness among patients with RH. The unique model design and the reliability of the findings make this study a valuable addition to the published literature. Still, several study limitations should be considered when interpreting the findings. The primary limitation concerns the basic constraints of health economic modeling. Since the models are primarily based on publicly available data, assumptions about certain model inputs are usually necessary to perform these analyses. However, all approximations are in line with the conservative modeling approach and are rationalized using available evidence to mimic real-world clinical practice. Second, the literature data used to populate the model were not region-specific. The costs of healthcare resources were sourced from the Republic Fund of Health Insurance of Serbia, while the utilization measures and other inputs were not specific to the Serbian population. Country restrictions had to be removed since the model required a lot of specific data that were not available in the literature at the time of the study. However, the model is easily adaptable to other countries or regions if needed. Third, the QALY calculations were based only on the EQ-5D index and VAS scores. Using other quality-of-life questionnaires may affect study outcomes. The EQ-5D was used in this study because insufficient data were available for other questionnaires to incorporate into the model. Also, the crosswalk between EQ-5D-3L and EQ-5D-5L versions, as well as the recalculation of values from different sources and value sets to a single national tariff, was not feasible due to a lack of patient-level data. Fourth, baxdrostat is still under investigation in clinical trials. The model results are based solely on the available evidence at the time of the study (Phase 2 clinical trial) and should be updated after the publication of the results from ongoing clinical trials.

Conclusions

This study suggests that esaxerenone may be a cost-effective add-on medication for RH management compared to spironolactone, eplerenone, finerenone, and baxdrostat. However, the results were significantly driven by the extrapolated input, reflecting the effectiveness of esaxerenone in real-world clinical practice. Regarding other comparisons, baxdrostat was the least cost-effective treatment based on the currently available evidence from clinical trials. Spironolactone and finerenone were cost-effective compared to eplerenone. In contrast, the superiority of spironolactone over finerenone was significantly affected by prescription costs and the cost of chronic kidney disease management. The results of this study should encourage researchers to investigate the real-world clinical benefits of new antihypertensive medications in the RH population. Model findings should be updated upon completion of ongoing clinical trials or publication of novel and relevant evidence regarding the included or innovative medications. This will help inform the positioning of innovative and approved medications for RH in real-world clinical practice. Future health economic studies should also incorporate other investigational treatments and interventional procedures for RH.

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Availability of data and materials

The main data generated in the present study are included in the figures and/or tables of this article. The additional data generated in the present study may be requested from the corresponding author.

Ethics approval and consent to participate

Not applicable.

AI use disclosure

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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