# Observing the uncertainty of the Amlodipine-Candesartan Incremental Cost-Effectiveness ratio using Deterministic Sensitivity Analysis (DSA)

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## Abstract

**Background**: Hypertension treatment is carried out for a long time and can cause quite large costs. This study delves into the economic evaluation of Amlodipine-Candesartan combination therapy, a prominent treatment for hypertension. While the clinical benefits of this regimen are well-documented, its cost-effectiveness remains a critical consideration for healthcare systems. Employing Deterministic Sensitivity Analysis (DSA) is a continuation after ICER is calculated. This study aimed to discern the uncertainty surrounding the Incremental Cost-Effectiveness Ratio (ICER) associated with Amlodipine-Candesartan through comprehensive examination, next to refine economic assessments and offer insights for healthcare policymakers and practitioners.

**Methods**: This retrospective descriptive study at Andalas University Hospital in 2021 analyzed hypertension outpatient data. Of 284 patients, 73 were included. Among them, 28.77% received Amlodipine monotherapy, while 71.23% received Amlodipine-Candesartan combination therapy.

**Results**: The ICER for systolic blood pressure was Rp. 74,738.10 per mmHg decrease, and for diastolic blood pressure, it was Rp. 205,918.24 per mmHg decrease. Both of them are in the northeast quadrant. Next, DSA will be carried out by creating a tornado diagram by providing a change range of 20% (min-max) for the input variables in ICER.

**Conclusion**: The use of amlodipine-candesartan requires a higher cost, but the resulting effect is also better. Our findings contribute to the broader discourse on combination therapies and inform resource allocation strategies for hypertension management. This research attempts to enhance the precision of economic evaluations, ultimately facilitating more informed and efficient healthcare decision-making processes.

**Keywords**: *Amlodipine, Candesartan, Cost-effectiveness, DSA, ICER.*

## Introduction

The primary objective of hypertension therapy is to mitigate the consequences of elevated blood pressure and avert potential complications[1]. Due to the prolonged nature of hypertension treatment, the likelihood of complications is notably high. This has a substantial impact on the financial outcomes borne by patients[2]. Engaging in hypertension therapy necessitates a significant financial commitment. The widespread prevalence, chronicity, and severity of hypertension further amplifies the economic burden on both patients and the healthcare system[3]. Both individuals and the broader population bear a substantial economic burden due to hypertension. In the United States, the estimated annual direct and indirect costs of hypertension are $47.3 billion and $3.9 billion, respectively. Meanwhile, the average expenditure for one adult hypertensive patient undergoing treatment annually is approximately $733[4].

In health economics analysis, a deterministic sensitivity analysis is a technique used to assess how variations or changes in specific input parameters or assumptions affect the results of a health economic model[5]. Unlike probabilistic sensitivity analysis (PSA), which considers uncertainty by using probability distributions for input parameters, deterministic sensitivity analysis involves changing one or more key parameters in a systematic and specific manner. Deterministic sensitivity analysis is useful for providing insights into the robustness of the model's results to changes in specific parameters[6].

By subjecting key model parameters to systematic variations, we seek to provide a comprehensive understanding of the economic implications of adopting this therapeutic regimen[7]. This research contributes to the broader discourse on the pharmacoeconomic evaluation of combination therapies and offers valuable insights for healthcare policymakers and practitioners in optimising resource allocation for hypertension management.

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Through rigorous analysis, this study attempts to observe the precision and reliability of economic assessments, ultimately fostering more informed and efficient healthcare decision-making processes using deterministic sensitivity analysis.

In the realm of healthcare economics and pharmacoeconomics, evaluating the cost-effectiveness of pharmaceutical interventions is of paramount importance. The Amlodipine-Candesartan combination, a widely prescribed dual therapy for hypertension management, has shown promising clinical outcomes[8]. However, the economic considerations surrounding its adoption in healthcare systems warrant closer scrutiny. This study aims to shed light on the uncertainty surrounding the incremental cost-effectiveness ratio (ICER) associated with Amlodipine-Candesartan by applying Deterministic Sensitivity Analysis (DSA)[5,9].

## Materials and Methods

### Research design, target population and location

This study is a retrospective health economics evaluation based on descriptive analysis. We followed the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) checklist provided by the Enhancing the QUAlity and Transparency Of health Research (Equator) network[10–12]. The research was conducted at Andalas University Hospital and focused on hypertensive patients who received medication refills at this institution.

### Materials

The study relies on medical records of hypertensive patients treated at Andalas University Hospital in 2021. These records are subsequently verified by comparing them with billing information in the hospital's management system, known as SIM-RS.

### Interventian and comparator

Specifically, the study compared the effectiveness of amlodipine 5mg and candesartan 8mg (intervention) with amlodipine 5mg alone (comparator). The study employed a purposive sampling method, selecting samples that met the defined inclusion criteria (a minimum duration of drug consumption of 1 month).

### Perspective, time horizon, and index year

The study adopts the hospital perspective (healthcare viewpoint) for cost assessment. It focuses on the expenses borne by the hospital, specifically the fees paid to the hospital. This includes direct medical costs such as hospital administration charges, medication expenses, laboratory tests, and physician consultations. The research analysed the progression of data over a three-month period in 2021, using 2021 as the reference year. No discount for cost and effect for the time horizon less than one year[13–15].

### Incremental Cost-Effectiveness Ratio (ICER)

The gathered information is then recorded in the data collection form. This information encompasses these categories: First is clinical information about the patient, including the specific antihypertensive treatment administered, diagnosed conditions, and the results of the therapy (notably, alterations in both systolic and diastolic blood pressure). Secondly, financial data related to the study encompasses administrative expenses, treatment expenses, support costs, and medication expenses that collectively constitute the overall direct costs.

### Deterministic Sensitivity Analysis (DSA)

One-way deterministic sensitivity analysis is carried out, which is the most frequently used and simplest method. This analysis is carried out by changing the value of one variable while the other variables remain constant. The results of this analysis are often displayed in a diagram. In this diagram, the variables with the greatest influence are located at the top of the diagram, and so on. The tornado diagram is in the form of a graph. The image of this graph is similar to that of a tornado, so it is called a tornado diagram. In this case, we consider a minimum-maximum variation of 20%. These minimum and maximum values were calculated for each parameter that affects ICER[16].

## Result

### Cost-Effect Parameter

In this study, total direct costs were calculated based on the hospital's perspective. This total cost is an accumulation of administration, medication, and visits. Meanwhile, the effect parameters were systolic and diastolic blood pressure.

### Incremental Cost-Effectiveness Ratio

Data on the difference in average direct medical costs and blood pressure reduction between interventions are entered into the ICER formula. To simplify analysis, this study divided blood pressure into two dimensions: a decrease in systolic blood pressure and a decrease in diastolic blood pressure. Therefore, we will get two ICER values: the ICER value for decreasing systolic blood pressure and the ICER value for decreasing diastolic blood pressure. Table 1 shows the calculated incremental cost-effectiveness ratios for systolic and diastolic blood pressure.

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**Table 1.** The ICER value for systolic and diastolic blood pressure

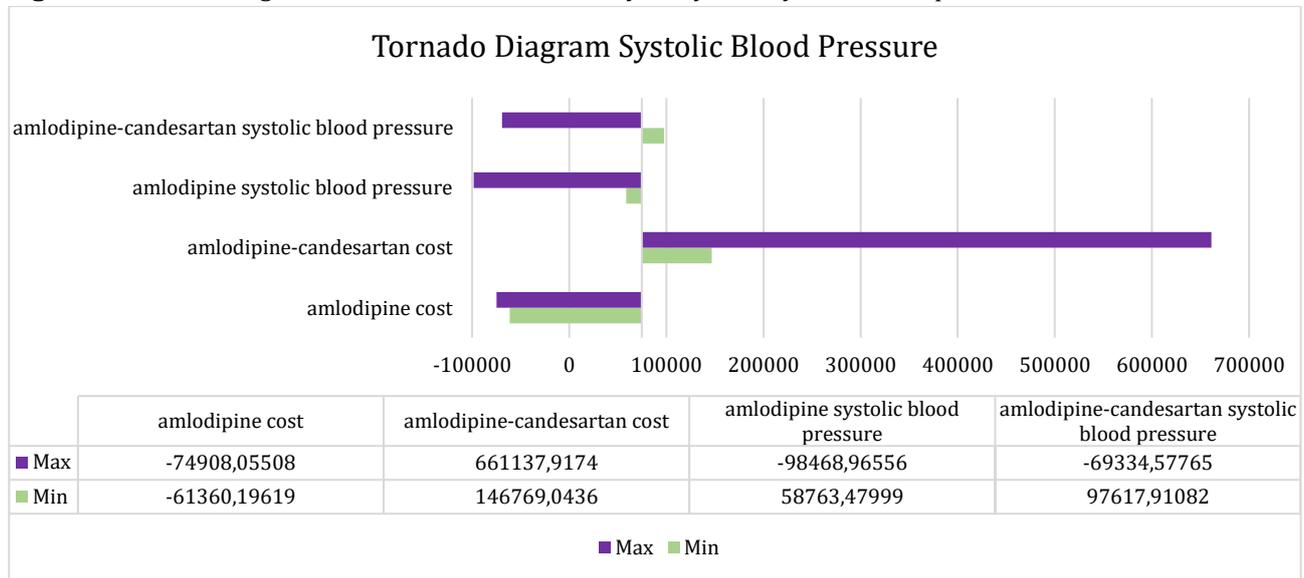| Antihipertensive drugs | Number of patients | Decrease in systolic blood pressure | Decrease in diastolic blood pressure | Direct medical cost (IDR) | ICER systolic | ICER diastolic |
|---|---|---|---|---|---|---|
| Amlodipin | 21 | 13.86 mmHg | 9.24 mmHg | . 735,166.67 | 74,738.10 | 205,918.24 |
| Amlodipin+Candesartan | 52 | 18.71 mmHg | 11 mmHg | 1,097,975.00 | /mmHg | /mmHg |

The incremental cost-effectiveness ratio (ICER) for systolic blood pressure is IDR 74,738.10 per mmHg. This indicates that spending an extra IDR 74,738.10 for the combined administration of amlodipine and candesartan will result in a decrease of 1 mmHg in systolic blood pressure compared to using amlodipine alone. In contrast, the ICER for diastolic blood pressure is IDR 205,918.24 per mmHg. This implies that incurring an additional cost of IDR205,918.24 for the combined use of amlodipine and candesartan will lead to a reduction of 1 mmHg in blood pressure compared to using amlodipine alone.
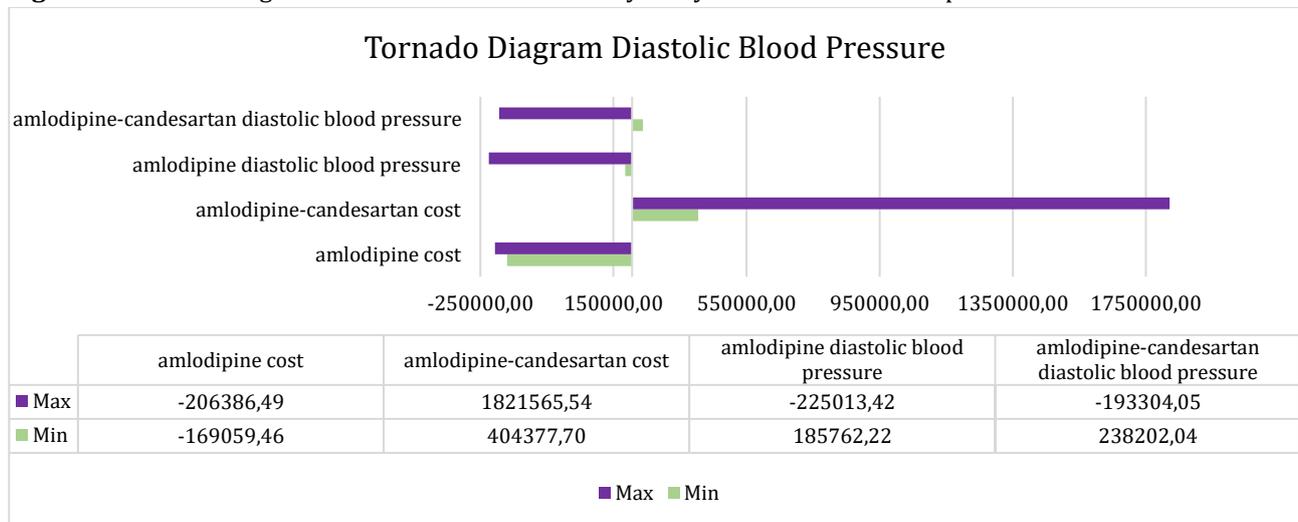
**Deterministic Sensitivity Analysis**

A tornado diagram is an analysis that will produce a bar graph. The purpose of analysis using a tornado diagram is to find out which variables or parameters have the most influence on the output to be evaluated. In this research, we refer to the output as the ICER value. Tornado diagram images can be seen in Figures 1 and 2.

**Figure 1.** Tornado diagram for deterministic sensitivity analysis in systolic blood pressure



Tornado Diagram Systolic Blood Pressure

| | amlodipine cost | amlodipine-candesartan cost | amlodipine systolic blood pressure | amlodipine-candesartan systolic blood pressure |
|---|---|---|---|---|
| Max | -74908,05508 | 661137,9174 | -98468,96556 | -69334,57765 |
| Min | -61360,19619 | 146769,0436 | 58763,47999 | 97617,91082 |

Max    Min

**Figure 2.** Tornado diagram for deterministic sensitivity analysis in diastolic blood pressure



Tornado Diagram Diastolic Blood Pressure

| | amlodipine cost | amlodipine-candesartan cost | amlodipine diastolic blood pressure | amlodipine-candesartan diastolic blood pressure |
|---|---|---|---|---|
| Max | -206386,49 | 1821565,54 | -225013,42 | -193304,05 |
| Min | -169059,46 | 404377,70 | 185762,22 | 238202,04 |

Max    Min

The tornado diagram will test the following variables: the average single cost, the average combined cost, the average single and combined systolic blood pressure drop, and the average single and combined diastolic drop. The tornado diagram reveals which variables significantly influence the

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ICER value. The ICER value on the tornado diagram shows changes if one of the variables is changed to a maximum value and a minimum value.

## Discussion

The two ICER values are located in the same quadrant, namely the northeast quadrant (quadrant 1). Therefore, we can say that the combination of amlodipine and candesartan has better effectiveness in lowering blood pressure than amlodipine alone, but it also requires greater costs. These results are in line with the research results of Abdullah et al. (2021), where the ICER value for systolic and diastolic blood pressure for the combination of amlodipine and valsartan (the same group as candesartan) compared with amlodipine alone falls into quadrant 1[17]. According to research by Park et al. (2017), combination therapy with nifedipine and candesartan is more cost-effective compared with candesartan or nifedipine therapy alone[18]. The ICER value in this study falls into the southeast quadrant (quadrant 2) or dominates. This can happen because in Park's (2017) research, the comorbidities in hypertensive patients were the same[18]. These results suggest that the combination of amlodipine and candesartan will be more widely accepted due to its relatively lower cost and superior effects.

The first tornado diagram shows how changes in systolic blood pressure affect the Incremental Cost-Effectiveness Ratio (ICER) values. The initial ICER value is IDR 74,738.10/mmHg. When we vary the reduction in systolic blood pressure in the single group, setting it to the maximum results in an ICER of IDR -98,468.96/mmHg, while the minimum value yields an ICER of Rp. 58,763.48/mmHg. This indicates that decreasing systolic blood pressure in the single group can lower the ICER, van der Pol et al. report the other use of probabilistic sensitivity analysis effect of using sacubitril/valsartan (2019). In their study, the results showed that sacubitril/valsartan is very unlikely to be cost-saving/dominant[19]. The second tornado diagram examines the impact of changes in diastolic blood pressure on ICER values, following a similar pattern as explained for systolic blood pressure. The details emphasise how variations in each variable affect the ICER values for diastolic blood pressure.

It is clear from both tornado diagrams that the combination group's costs have the greatest influence. The widest horizontal bar demonstrates this. The variable that has the most influence on the average cost-effectiveness ratio value is the cost for the comparator group[20]. In addition, the intervention in this study used three combinations of antihypertensives[20].

This study provides evidence of the efficacy of combination therapy that underscores the potential benefits of combination therapy for hypertensive patients. This study also considers key variables such as systolic and diastolic blood pressure reductions as well as costs, providing valuable insights into the factors influencing Incremental Cost-Effectiveness Ratios (ICERs). This enhances the study's methodological rigor. Still, there are some limitations to this study. The study's lack of detail may limit the generalizability of the findings to broader populations, as different patient groups may respond differently to the combination therapy. While the study demonstrates the effectiveness and cost implications of combined therapy, it does not compare this combination with other potential treatment options. Including such comparisons would offer a more comprehensive evaluation of the therapeutic landscape for hypertensive patients.

## Conclusions

In conclusion, the combination of amlodipine and candesartan proves more effective in reducing blood pressure than amlodipine alone, albeit at higher costs. These findings align with previous studies that also highlight the effectiveness and cost implications of combination therapies in hypertensive patients. Sensitivity analysis indicates that variables such as systolic and diastolic blood pressure reductions and costs play crucial roles in influencing ICER values. Specifically, reductions in blood pressure contribute to lower ICER values, while cost variables can significantly impact the resulting ICER values. Additionally, the combination group's cost variables have a substantial effect on increasing the ICER value.

## Acknowledgment

## Ethical Consideration

This research has received ethical approval from the Faculty of Medicine, Universitas Andalas No. 620/UN/16.2/KEP-FK/2022

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## Author Contribution

| | | |
|---|---|---|
| Study design | : | NF |
| Data acquisition | : | YZS |
| Data analysis | : | YZS, LL |
| Manuscript writing | : | NF, YZS, LL, HN |

## Competing Interests

The author(s) declare no competing interests.

## Abbreviation

| | | |
|---|---|---|
| CHEERS | : | Consolidated Health Economic Evaluation Reporting Standards |
| DSA | : | Deterministic Sensitivity Analysis |
| ICER | : | Incremental Cost-Effectiveness Ratio |
| Rp | : | Rupiah |
| SIM-RS | : | Hospital Information and Management System |

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