Center for Innovative Drug Development and Therapeutic Trials for Africa

CARDIOVASCULAR EFFICACY AND SAFETY OF CALCIUM CHANNEL BLOCKERS, ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS IN PATIENTS WITH PRIMARY HYPERTENSION:

A SYSTEMATIC REVIEW AND NETWORK METAANALYSIS

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A thesis submitted to Addis Ababa University, College of Health Science, CDT-Africa in partial fulfillment of the requirements for the Master of Science Degree in Clinical Trials

By

Dr ANATIA KIFLE (MD, MSc in Clinical Trials Candidate)

MSc in Clinical Trials

Advisors: Professor Eyasu Makonnen

Professor Anteneh Belete

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Addis Ababa, Ethiopia

Approval by examining board **Signature**

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Advisors

Principal advisor

- **Professor. Eyasu Makonnen**

  Signature: ……..

  Date: ……

Co-advisor

- **Professor. Anteneh Belete**

  Signature: ……

  Date: ……

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List of Acronyms/ Abbreviations

ACE	Angiotensin Converting Enzyme
ACEi	Angiotensin Converting Enzyme inhibitor
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ARBs	Angiotensin Receptor Blockers
BP	Blood Pressure
Ca	Calcium
CCBs	Calcium Channel Blockers
CDT-Africa	Center for Innovative Drug Development and Therapeutic Trials for Africa
CENTRAL	Cochrane Central Register of Controlled Trials
CHD	Coronary Heart Disease
CMA	Comprehensive Meta-analysis
CI	Confidence Interval
CT	Clinical Trial
CVS	Cardiovascular System
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
HOPE	Heart Outcomes Prevention Evaluation
HTN	Hypertension
ID	Identification
ISH	International Society of Hypertension
ITT	Intention To Treat
MD	Mean Difference
MeSH	Medical Subject Headings
NMA	Network Meta-Analysis
PICO	Population, Intervention, Control and Outcome
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA-	Preferred Reporting Items for Systematic Review and Meta-

NMA	Analysis- Network Meta-Analysis
RAAS	Renin Angiotensin Aldosterone System
RCT	Randomized Controlled Trial
REACH	Reduction of Atherothrombosis for Continued Health
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SEA	South East Asia
SMD	Standardized Mean Difference
VALUE	Valsartan Antihypertensive Long-Term Use Evaluation
WHO	World Health Organization

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Abstract

Background: Cardiovascular disease (CVD), such as myocardial infarction (MI), stroke, and heart failure, are major global health concerns, with hypertension being a key risk factor. This study evaluates the efficacy and safety of three common antihypertensive drug classes—calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEi's), and angiotensin receptor blockers (ARBs)—in preventing major cardiovascular events. These findings provide valuable information for clinicians in selecting appropriate treatment strategies for hypertensive patients who are at risk of cardiovascular complications, helping improve patient outcomes and reduce the global burden of CVD

Methods: This systematic review and network meta-analysis was conducted following the PRISMA and PRISMA-NMA 2020 guidelines and registered on the PROSPERO database. Eligible studies included randomized controlled trials (RCTs) published between 2000 and 2024, with a minimum follow-up of three months, focusing on adults (≥18 years) with hypertension (BP 140/90–179/109 mmHg). Trials evaluating safety and efficacy of calcium channel blockers, angiotensin receptor blockers (ARBs), or angiotensin-converting enzyme inhibitors (ACEi's) for cardiovascular outcomes (e.g., myocardial infarction, stroke, heart failure) were included. Studies with incomplete data or secondary hypertension were excluded. Data were sourced from PubMed, Embase, and Scopus using a detailed search strategy based on PICO criteria. Two independent reviewers screened the studies, and data were extracted using a structured format. The risk of bias was assessed using the Cochrane tool. Network meta-analysis was performed with a random-effects model using R-Studio. Efficacy was measured by blood pressure reduction and cardiovascular events, while safety was assessed by adverse events (e.g., edema, syncope) observed.

Results: This study evaluated the efficacy and safety of calcium channel blockers (Amlodipine), angiotensin-converting enzyme inhibitors (Enalapril, Ramipril, Lisinopril), and angiotensin receptor blockers (Losartan, Candesartan, Irbesartan, Valsartan) in hypertensive patients. Candesartan was 2.4 times more effective than Amlodipine in reducing systolic blood pressure and showed a 20% greater reduction in diastolic blood pressure. Amlodipine showed a 47% lower risk of myocardial infarction (MI) compared to Enalapril and a 62% lower risk compared to Irbesartan. However, there was no significant difference in death due to stroke and cardiovascular disorders across the drug classes.

Amlodipine was associated with the lowest syncope incidence but the highest rates of edema. ARBs, particularly Valsartan, had the lowest edema incidence, while Enalapril had the smallest number of adverse events. Hospitalization rates for MI were lowest with Valsartan and Irbesartan.

Conclusion: This study highlights the comparative cardiovascular efficacy and safety of calcium channel blockers (Amlodipine), angiotensin-converting enzyme inhibitors (Enalapril, Ramipril, Lisinopril), and angiotensin receptor blockers (Losartan, Candesartan, Irbesartan) in hypertensive adult patients. While ARBs were most effective in reducing blood pressure, no significant differences were found between drug classes for major cardiovascular events, like stroke, cardiovascular death, and hospitalization for heart failure. Amlodipine demonstrated the lowest incidence of myocardial infarction, while ARBs were most beneficial in reducing heart failure risk. Regarding safety, Amlodipine was associated with the lowest syncope incidence but the highest rates of edema, while Enalapril showed the smallest number of total adverse events. These findings suggest that treatment selection should be individualized based on both efficacy and safety profiles, considering patient-specific factors.

CHAPTER ONE: INTRODUCTION

1.1 Background

Cardiovascular Disease(CVD) poses a significant public health challenge, accounting for 32% of the global disease burden (1). CVD encompasses coronary heart disease, primarily myocardial infarction, stroke, heart failure, and other conditions that affect the heart and blood vessels (2). Myocardial infarction (MI), stroke, and heart failure are some of the most common and widespread cardiovascular diseases (3). They all account for a significant share of cardiovascular events, impacting millions of people globally (3). Myocardial infarction and stroke are major causes of death, with MI being the most immediate fatal event. These conditions contribute significantly to cardiovascular-related deaths, highlighting their importance in efforts to improve cardiovascular health (4).

Heart failure, especially in its advanced stages, also plays a significant role in mortality. While it may not be as fatal as MI or stroke, its long-term effects and high death rate due to complications make it a major concern (5). Heart failure is a significant cause of both illness and death. It is estimated that 64 million people worldwide are living with heart failure (6).

Cardiovascular disease, as the leading cause of death worldwide, is a critical matter of life or death. Generally, CVD impacts individuals later in life, with its incidence increasing significantly after the 30-44 age range (7). Globally, it is estimated that approximately 17.9 million people die from CVD each year, with MI accounting for around 7 million of these deaths and stroke around 6 million. The number of deaths attributed to cardiovascular disease is projected to increase by more than 33% over the next two to three decades (8).

The major risk factor for cardiovascular disease is increase in Blood Pressure(BP) (9). Multiple studies have found that a history of hypertension is linked to a higher incidence of negative outcomes including myocardial infarction, stroke, heart failure, and cardiovascular death (10). Observational studies have demonstrated a strong and direct link between blood pressure levels and the relative risks of stroke and heart disease (10). Hypertension is the primary cause of cardiovascular disease (CVD) and premature death globally, particularly in low- and middle-income countries. Worldwide, the prevalence of hypertension can reach up to 79% in individuals aged 65 to 74 and 77% in those aged 75 to 79 (9).

According to the International Society of Hypertension (ISH), hypertension is classified as Grade 1(BP=140-159/90-99 mmHg), Grade 2(BP=160-179/100-109 mmHg) and Grade 3(BP 180/110mmHg or higher) (11). Grade 2 and Grade 3 Blood pressures are considered as severe hypertension. The

importance of BP, especially Systolic Blood Pressure (SBP), as an independent risk factor for coronary events, stroke and heart failure (HF) is well documented (12).

Based on the cause, hypertension can be classified as primary hypertension and secondary hypertension (11,13). Primary hypertension is high blood pressure with no identifiable cause. It develops gradually over many years and is the most common type of hypertension. It is typically influenced by genetic factors, lifestyle choices (such as diet, physical activity, and stress), and other environmental factors (13). Secondary hypertension is high blood pressure that is caused by an underlying condition or another health problem. It often develops suddenly and is more severe than primary hypertension. Common causes include kidney disease, hormonal disorders (like hyperthyroidism or adrenal gland tumors), pheochromocytoma, certain medications (e.g., birth control pills or steroids), and sleep apnea. Treating the underlying condition can often help control secondary hypertension (11,13).

A six-year follow-up study found that hypertensive patients with a blood pressure of 140/90 or higher had a 2.6 times greater risk of cardiovascular disease compared to those with a blood pressure below 130/85. As a result, preventing and managing high blood pressure is considered a key priority for public health promotion. Hypertension treatment typically begins with monotherapy in the initial stage, progressing to dual combination therapy in the second stage or higher (14).

A recent large-scale review revealed that for every 20mmHg decrease in usual systolic blood pressure, the risk of stroke was reduced by 33% in individuals aged 80-89 and by 62% in those aged 50-59 (15).

The benefits of regimens to lower blood pressure based on different drug classes are largely comparable across age groups (16).

The timely use of guideline-recommended treatments, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers, has led to a decrease in cardiovascular events (13).

Description of Guideline Recommended First Line Antihypertensive Treatments

Pharmacological treatments are vital in managing cardiovascular disease (CVD) and preventing complications (11). Since CVD accounts for a large share of global morbidity and mortality, effective treatment is critical to improving patient outcomes (16). The availability of various drug classes, each with unique mechanisms, allows for personalized treatment approaches. For instance, angiotensin-converting enzyme inhibitors (ACEi's), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) are proven to effectively lower blood pressure. Therefore, timely initiation of

guideline-recommended therapies is crucial for managing hypertension, a key contributor to CVD, and ultimately reducing the global burden of cardiovascular diseases (3,17).

The World Health Organization (WHO) recommends starting pharmacological antihypertensive treatment for individuals with a confirmed diagnosis of hypertension and a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg (11). For adults with hypertension who need medication, WHO advises the use of drugs such as angiotensin-converting enzyme inhibitors (ACEis), angiotensin-receptor blockers (ARBs), or calcium channel blockers (CCBs) as first line Antihypertensives (18).

Calcium antagonists, or calcium channel blockers (CCBs), are some of the most commonly used medications in cardiovascular care. They work by blocking calcium from entering vascular smooth muscle cells through voltage-operated calcium channels (and, to a lesser extent, receptor-operated channels) in the cell membrane, which enhances vasodilation and helps lower blood pressure (17). Calcium channel blockers (CCBs) are used to treat conditions such as angina, tachyarrhythmias, and hypertension, among others. Some examples of drugs in this class include amlodipine, felodipine, lacidipine, nifedipine, and verapamil, with amlodipine being the most commonly prescribed for hypertension treatment (17,19). Amlodipine, a charged long acting dihydropyridine type of CCB, is commonly used to treat chest pain due to myocardial infarction and hypertension (20).

Angiotensin-converting enzyme inhibitors (ACEi's) play an expanding role in managing cardiovascular risk, including hypertension (3). ACEi's are generally well tolerated, with the exception of cough and some non-specific upper respiratory tract symptom (21). Examples of this family includes; Captopril, Enalapril, Fosinopril, Lisinopril and Ramipril (3,22). These medications work by competitively inhibiting the action of angiotensin-converting enzyme (ACE), preventing the conversion of the inactive decapeptide angiotensin I into the active octapeptide angiotensin II. Angiotensin II causes strong blood vessel constriction, promotes the release of aldosterone, enhances sympathetic activity, and may contribute to further harmful effects on the cardiovascular system (22).

Angiotensin Receptor Blockers (ARBs) have similar hemodynamic effects to ACE inhibitors (ACEi's) but are generally better tolerated (23). Examples of drugs in this class include candesartan, irbesartan, losartan, telmisartan, and valsartan. The primary mechanism of ARBs is the reduction in blood pressure due to vasodilation following the blockade of angiotensin receptors (3,23).

1.2 Statement of the problem

Preventing cardiovascular heart disease is viewed as a key aspect of managing patients with hypertension (24). The management of cardiovascular disease (CVD) remains a complex challenge, largely due to the lack of consensus and comparative evidence on the efficacy and safety of different antihypertensive drugs (1). Currently, the treatment of patients with hypertension and cardiovascular disease mainly aims at lowering blood pressure, as there are no specific medications for hypertension and CVD (11).

All major classes of antihypertensive drugs have been shown to reduce the risk of stroke and major cardiovascular events compared to placebo. However, when some antihypertensive drugs are directly compared to each other, these drug classes did not demonstrate any significant difference in reducing the risk of major cardiovascular events (15).

A meta-analysis conducted to evaluate the cardiovascular efficacy of specific antihypertensive medications found that there was little to no difference in cardiovascular risk reduction among them (1). Furthermore, another network meta-analysis found that antihypertensive medications in general reduced the risk of major cardiovascular events compared to placebo (25).

ACE inhibitors (ACEi) are recognized for their cardioprotective effects, and their safety profile is similar to that of angiotensin II receptor blockers (ARBs). However, the reason behind the increased risk of myocardial infarction associated with ARBs remains unclear (22). Another clinical trial assessed that calcium channel blockers increase the risk of myocardial infarction and heart failure (26).

Despite these findings, there are no data from individual trials to rank the various classes of antihypertensive drugs based on their preventive effects. Given that millions of people are on medication for hypertension, the selection of the appropriate drug remains a crucial issue (26). The connection between hypertension and major cardiovascular disease (CVD) outcomes has always been a key concern for clinicians (27). However, the different head-to-head trials for antihypertensives have produced varying conclusions, and it is important to highlight that there is insufficient evidence on clinically relevant outcomes across various treatment regimens to make definitive conclusions about the most effective antihypertensive treatment (28).

1.3 Significance of the study

This study offers a thorough synthesis of existing evidence on the efficacy and safety of three commonly prescribed antihypertensive drug classes—CCBs, ACEi's, and ARBs. By analyzing data from multiple studies, it aims to provide a deeper understanding of how these medications compare in preventing cardiovascular complications. Despite their widespread use, there is ongoing uncertainty about which class is most effective in preventing major cardiovascular events in diverse patient populations. The lack of direct head-to-head clinical trials has left clinicians with limited guidance in selecting the best treatment for their patients. This network meta-analysis will help bridge that gap by offering robust, evidence-based insights.

For clinicians, this research has the potential to optimize treatment strategies by providing a clearer comparison of the efficacy and safety of these drug classes. It will assist clinicians in making more informed decisions and the ability to rank and compare the three drug classes based on various clinical outcomes will give clinicians greater confidence in their treatment choices, ultimately enhancing patient care.

For policymakers and guideline developers, the findings from this study could play a crucial role in shaping clinical guidelines and healthcare policies. By identifying the most effective antihypertensive drug class this research could inform policy decisions aimed at optimal resource allocation, improved patient care, and better health outcomes across the population.

This study could also help decrease hospitalizations, reduce adverse outcomes, and improve the quality of life for patients. The potential to reduce the global burden of cardiovascular disease through better treatment strategies and improved patient outcomes makes this study a vital step in advancing both clinical practice and healthcare policies worldwide.

The need for a systematic review and network meta-analysis to consolidate existing evidence is more pressing than ever. Given the considerable gaps in available data and the lack of conclusive head-to-head trials, a thorough network meta-analysis would offer valuable insights into the comparative efficacy and safety of widely used antihypertensive medications specifically CCBs, ACEi's and ARBs. By combining data from multiple studies, this analysis would address key knowledge gaps, support clinicians in making better-informed treatment choices, and strengthen the evidence foundation for creating clinical guidelines that improve patient outcomes worldwide.

CHAPTER TWO: LITERATURE REVIEW

Cardiovascular Efficacy and Safety of CCBs

Large-scale prospective outcome studies have shown that calcium channel blockers provide cardiovascular protection, with benefits at least comparable to those of other antihypertensive medications (19). CCBs are known for their constant regulation of blood pressure compared to angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEis) (3,29). Research indicates that amlodipine, the most frequently prescribed CCB, results in a 10% reduction in total cardiovascular events and a 5% reduction in total mortality compared to non-CCB antihypertensive treatments. Additionally, amlodipine has a protective effect against myocardial infarction (MI) and stroke (19).

However, some studies suggest that there may be a higher incidence of myocardial infarction in patients taking CCBs compared to other drug classes (19,29). Despite this, a meta-analysis has confirmed that CCBs offer protection against both stroke and myocardial infarction (30). The VALUE trial showed that an amlodipine-based regimen had a more pronounced blood pressure-lowering effect than a valsartan-based regimen, especially during the first 6 months. However, the primary composite endpoint was similar between the two regimens, and myocardial infarction occurred less frequently in the amlodipine group (31). Furthermore, CCBs may be more effective in preventing stroke compared to other drug classes (19). The difference in clinical effects could be due to varying impacts on neurohumoral systems, metabolic effects, or differences in blood pressure profiles among patients (32).

Interestingly, a study conducted in Korea found that CCB therapy was associated with a decreased mortality risk in patients with heart failure (33). Despite the benefits, CCBs are known for their side effects, particularly peripheral edema. The occurrence of peripheral edema tends to rise with increasing doses of CCBs, though it does not always follow a strict, dose-proportional pattern (34). On the other hand, CCBs are also known to have a protective effect against syncope (14,35). Some studies report a protective effect of CCBs on orthostatic hypotension, while others indicate an increased risk associated with their use (36).

Overall, significant benefits in preventing major cardiovascular morbidity and mortality in high-risk populations have been observed with calcium antagonists (29).

Cardiovascular Efficacy and Safety of ACEi

The first evidence of the efficacy of ACE inhibitors in preventing cardiovascular events came from the HOPE trial, which showed that the ACE inhibitor ramipril significantly reduced the incidence of cardiovascular events in a diverse group of high-risk patients (22). ACE inhibitors have since played an increasingly important role in managing cardiovascular risk, including hypertension. Large-scale prospective outcome trials have shown that ACE inhibitors provide cardiovascular protection similar to other antihypertensive medications. Moreover, they have been reported to offer cardiovascular and renal protective effects beyond what would be expected from blood pressure reduction alone, particularly in high-risk patient groups (21).

In a study involving over 30,000 high-risk patients with hypertension, no significant difference was found in the incidence of cardiovascular disease between the calcium antagonist amlodipine and the ACE inhibitor lisinopril. The study concluded that calcium channel blockers (CCBs) are effective in managing hypertension and preventing related complications (17).

Another study indicated that a 5-year treatment with enalapril was linked to a reduced incidence of myocardial infarction. Additionally, this study recommended ACE inhibitors over calcium channel blockers (CCBs) for the prevention of cardiovascular complications, particularly myocardial infarction (7).

The benefits of ACE inhibitors in patients with systolic heart failure are well-documented, but their effects in diastolic heart failure are less understood. However, ACE inhibitors may still play a crucial role in diastolic heart failure by helping to reduce cardiac remodeling, myocardial mass, fibrosis, and stiffness (37).

Cardiovascular Efficacy and Safety of ARBs

In a case of conflicting data, the REACH (Reduction of Atherothrombosis for Continued Health) registry study found that patients on ARBs had a 10% reduction in cardiovascular events, while another study suggested that ARBs actually increased the risk of myocardial infarction. Both ARBs and ACE inhibitors are recommended as first-line treatments, with ACE inhibitors being much more commonly prescribed for hypertension, particularly lisinopril, which is the most widely used antihypertensive drug. Systematic reviews and meta-analyses have shown that ARBs offer similar efficacy to ACE inhibitors, with the added benefit of improved tolerability and fewer side effects. Cohort studies

indicate no statistically significant difference in the effectiveness of ACE inhibitors versus ARBs, but ARBs tend to have a better safety profile (38).

Large-scale prospective outcome trials have shown that ARBs provide cardiovascular protection comparable to ACE inhibitors and other antihypertensive medications. Additionally, ARBs may offer extra benefits for patients with type 2 diabetes and heart failure (23).

Another study reassured that ARBs are safe drugs and do not increase risk of death, MI and stroke (39).

CHAPTER THREE: OBJECTIVES

Systematic Review Question

What are the comparative effects on cardiovascular efficacy and safety of calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in adult patients with primary hypertension?

Primary Objective

To compare the cardiovascular efficacy and safety of calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in adult patients with primary hypertension.

Secondary Objectives

1. To compare the risk of hospitalization for heart failure in adult patients with primary hypertension treated with calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers.
2. To compare the risk of hospitalization for myocardial infarction in adult patients with primary hypertension treated with calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers.

Hypothesis

Null Hypothesis (Ho):

There is no significant difference in the cardiovascular efficacy and safety between calcium channel blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers in adults with primary hypertension.

Alternative Hypothesis (H1):

There is a significant difference in the cardiovascular efficacy and safety between calcium channel blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers in adults with primary hypertension.

CHAPTER FOUR: METHODS

4.1 Protocol and Registration

The methods of this systematic review and network metaanalysis is written in accordance with the Preferred Reporting Items for Systematic Review and Network Meta-analysis (PRISMA-NMA 2020) guideline (40). This protocol has been registered at the International Prospective Register of Systematic Reviews (PROSPERO) database (41).

4.2 Eligibility Criteria

Inclusion Criteria

The eligible studies for this review include randomized controlled clinical trials with a parallel group study design, and there are no geographical restrictions on their origin. These trials must have been published between the years 2000 and 2024 and written in English. Only trials with a follow-up period of three months or more are considered. Additionally, the trials should include both male and female patients (non-pregnant and non-lactating) aged 18 years or older, and the patients should be diagnosed with primary hypertension, with blood pressure ranging from 140/90 mmHg to 179/109 mmHg. The trials must involve patients treated with either calcium channel blockers, angiotensin receptor blockers, or angiotensin-converting enzyme inhibitors. Lastly, the trials should focus on outcomes related to the reduction of blood pressure and/or cardiovascular events, including heart failure, stroke, myocardial infarction, cardiac death and safety profiles such as syncope, edema and over all adverse events.

Exclusion criteria

Studies will be excluded if they don't provide complete information on the efficacy and safety parameters of calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Additionally, studies involving patients diagnosed with secondary hypertension or severe hypertension will also be excluded from the review.

Study design and settings

The study design is randomized controlled trials (RCTs) with a parallel group design. There are no geographical restrictions on the origin of the studies, meaning the trials could be conducted in any geographical location. And should focus on adults with primary hypertension, comparing the efficacy and safety of different antihypertensive drugs

4.3 Information Sources

An electronic systematic search method from online databases like PubMed, Embase, as well as Scopus and those that were published between 2000 and 2024 were included. The search was conducted corresponding to the direction presented in the Cochrane Handbook for Systematic Reviews of Interventions (42).

The search was done considering publications of randomized clinical trials which were done in the past 24 years. Medical Subject Headings (MeSH) and keyword terms was used with a Boolean operator like "OR", "AND", and" NOT". The search strategy was constructed Using PICO.

4.4 Search methods for identification of studies

Electronic searches

The searching process was demonstrated as follow by taking PubMed data base as an example and the step was applied on the rest. MeSH Cardiovascular OR Circulatory OR Vascular OR Heart AND Hypertension OR Increased Blood Pressure OR Raised Blood Pressure AND Safety OR Protection OR Wellbeing OR Assurance AND CCBs OR Calcium Channel Blockers OR Calcium antagonist OR Calcium entry blocker OR Calcium ion channel antagonist OR calcium channel antagonist AND ARBs OR Angiotensin receptor antagonist OR Angiotensin receptor blockers AND ACEi OR Angiotensin converting enzyme blockers OR Angiotensin converting enzyme antagonists OR Enalapril OR Captopril OR Cilazapril OR Fosinopril OR Lisinopril OR Moexipril OR Prindopril OR Quinapril, OR Ramipril OR Trandolapril OR Zofenopril AND Candesartan OR Eprosatran OR Irbesartan OR Olmesartan OR Losartan OR Telmisartan OR Valsatran AND Nifedipine OR Felodipine OR Amlodipine AND Myocardial Infarction OR Chest Pain OR MI AND Heart Failure OR Decreased Cardiac Output AND Stroke OR Cerebrovascular Accident OR Cerebral Infarction OR Cerebral Hemorrhage AND Cardiovascular Death OR Cardiac Death AND Syncope OR Loss of consciousness AND Edema OR Fluid collection on the legs.

The reference sections of the selected studies and other relevant reviews were also checked for the possibility of any additional papers.

The searching strategy for Pubmed, Scopus and Embase are found on the Annex Section (ANNEXES).

4.5 Selection of studies

Two independent reviewers were involved in selecting the studies. To import the research articles from the electronic databases and remove duplicates, we used ZOTERO software version 7.0.11 The

searched literatures and full-text copies of all potentially related trials were independently reviewed by two authors. Also, multiple publications from the same dataset were checked and studies included in this review based on the inclusion criteria. Disagreements were resolved through discussion**.**

4.6 Data Collection

The Cochrane Handbook for Systematic Reviews of Interventions (42)was followed. Furthermore, the software package provided by Cochrane (RevMan 5.4) for risk of bias assessment and additionally, for analysis, R- studio Version 4.3.1 was used.

The title and abstract were produced from the electronic search, and was independently screened by two reviewers based on RCTs that assessed cardiovascular efficacy and safety of patients with primary hypertension. The information collected were trial characteristics including methods, participants, interventions, and outcomes. Also, relevant information such as title, study design, study setting, inclusion and exclusion criteria, follow-up period, sample size, and adverse events were extracted from each article using the well-prepared extraction format in the form of a table adapted from Cochrane and modified to make suitable for this study (42).

Furthermore, the number of participants randomized, and the number analyzed outcomes of each treatment group were also collected. Any discrepancies between the reviewers were settled by consensus. One author independently extracted data and information collected was cross-checked by another investigator. Missing data were requested from the authors whenever necessary.

Furthermore, the number of subjects with an event and the total number of subjects in each treatment arm were recorded for dichotomous outcomes and the arithmetic means and standard deviations (SD) for each treatment arm were extracted for continuous outcomes.

4.7 Data Items

PICO for searching strategy

Population – Patients with primary hypertension.

Intervention- ARBs and ACEi

- ARBS were represented by Valsartan, Losartan, Telmisartan, Irbesartan and Candesartan
- ACEis were represented by Enalapril, Lisinopril and Ramipril

Comparator- Calcium channel blockers (represented by Amlodipine)

Outcome- Cardiovascular Efficacy and Safety

- Cardiovascular efficacy was assessed by reduction of Blood Pressure, incidence of myocardial infarction, incidence of Heart failure, incidence of stroke, incidence of cardiovascular death, hospitalization rate for heart failure and hospitalization rate for myocardial infarction (28).
- Cardiovascular safety was assessed by incidence of adverse events such as syncope, edema, and any other adverse events (43).

Primary outcome measures

1. **Cardiovascular efficacy was measured by (8).**
   - **BP reduction:** BP at the start of the trial and BP at the end of the follow up was checked and the mean difference of both systolic and diastolic BP was extracted
   - **Cardiovascular events:** Incidence for Myocardial infarction, Heart failure and Stroke was extracted
   - **Cardiovascular death:** Cardiovascular death includes death resulting from MI, death due to heart failure, death due to stroke.
2. **Cardiovascular safety was measured by(39).**

Adverse Events

- **Hypotension/scope**: Defined as a blood pressure level </= 90/60
- **Dizziness**
- **Edema:** swelling on the legs, ankles or feet.
- **Serious adverse events** (death, life-threatening, causing admission to hospital, or discontinuation of treatment).

Secondary outcome measure

1. **Hospitalization rates for Heart Failure:** Patients who were not hospitalized before but got hospitalized for the diagnosis of Heart failure after starting any of the antihypertensive drugs.
2. **Hospitalization rate for Myocardial infarction:** Patients who were not hospitalized before but got hospitalized for the diagnosis of Myocardial infarction after starting any of the antihypertensive drugs.

4.8 Network meta-analysis

The network meta-analysis was done using R- studio Version 4.3.1. Also, the network meta- analysis was performed using the frequentist network meta-analysis with random effects model for each treatment comparison, using the Netmeta package.

4.8.1 Geometry of network

Nodes were used to represent different treatments and edges to represent the head-to-head comparisons between network nodes. The nodes' size and edge thickness represented sample sizes of intervention and numbers of included trials, respectively. The network nodes were categorized as follows: 1. Enalapril, 2. Lisinopril, 3. Ramipril, 4. Candesartan, 5. Irbesartan, 6. Losartan, 7. Telmisartan, 8. Valsartan, 9. Nifedipine, and 10. Amlodipine.

4.9 Assessment of risk of bias in the included studies

The risk of bias for each trial was evaluated by two review authors independently using the Cochrane Collaboration's tool for assessing the 'Risk of bias' (42). To decrease the risk of bias amongst six domains: sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other sources of bias, this guidance was used. The ratings were done (i.e., high risk, unclear risk, and low risk) for the risk of bias, and interpretations of the presented data were guided by this information. For unclear judgment, the trial authors were contacted for clarification and differences of opinion were addressed through discussion.

Table 1: Risk of Bias Assessment (42).

Bias	Low risk	Unclear risk	High risk
Allocation Sequence Generation	Random methods like computer number generation or independent methods (e.g., drawing lots, tossing a coin) performed by someone not involved in the study.	Method of sequence generation not specified	Sequence generation method was not random
Allocation Concealment	Allocation could not be foreseen in advance; controlled by a central, independent unit (e.g., opaque sealed envelopes).	Method of allocation concealment not described, allocation may have been foreseen.	Investigators likely knew the allocation sequence.
Blinding of Participants and Personnel	Blinding ensured or unlikely to be broken; or no blinding, but outcome unlikely influenced by the absence of blinding.	Insufficient information to judge, or no blinding addressed.	Unblinding or incomplete blinding; outcome likely influenced by lack of blinding
Blinded Outcome Assessment	Blinding of outcome assessment ensured or unlikely to be broken; or no blinding, but outcome unlikely influenced by lack of blinding	Insufficient information to judge, or no blinding addressed	Unblinding of outcome assessment; outcome measurement likely influenced by lack of blinding

Incomplete Outcome Data	Missing data unlikely to affect results; study used methods (e.g., multiple imputations) to handle missing data	Insufficient information to assess the impact of missing data how they were handled	Missing data likely biased results
Selective outcome Reporting	At least one of the primary outcomes is reported.	Not all predefined outcomes reported, or unclear if all outcomes were recorded	None of the predefined outcomes reported
Other Bias	No other factors or bias domains affecting the study.	Potential for other bias factors, but unclear if they influence the results	Factors present that may bias the study
Overall Bias Assessment	Domains classified as low risk of bias	One or more domains classified as unclear risk	One or more domains classified as high o unclear risk.

4.10 Summary Measures

Risk ratios (RRs) were deemed the appropriate measure for dichotomous outcomes such as myocardial infarction, stroke, heart failure, cardiovascular death, as well as for the adverse events like edema, syncope as they provide a direct measure of the relative risk of the outcome event occurring in treatment groups compared to a control group.

For continuous outcomes such as systolic blood pressure, diastolic blood pressure, mean differences (MDs) provided a straightforward measure of the average difference in outcome values between treatment groups Risk ratios and mean differences were escorted by 95% CIs.

Unit of analysis issues

Participants of the studies were included according to the treatment group to which they were randomly assigned in the included randomized clinical trials. This ensured that the treatment groups were comparable at baseline and minimized the risk of selection bias. The unit of analysis was the individual study, meaning that data from each study was included.

Dealing with missing data

The trial authors were approached for more information if the data from the trial reports is inadequate, ambiguous, or missing. The imputation approach was applied for the authors who did not respond. The data were removed from the meta-analysis with a detailed explanation provided if the missing data made the result questionable.

4.11 Assessment of heterogeneity

To determine the degree of heterogeneity among the trials, the forest plots was examined to identify any overlapping confidence intervals (CIs). The Cochrane Q and I2 statistic were also utilized to quantify the heterogeneity among the trials in each analysis (40,42). The results were interpreted in accordance with Cochrane Handbook for Systematic Reviews of Interventions Version 6.0, Chapter 10: carrying out meta-analyses and data analysis (42).

4.12 Data synthesis

The network meta-analyses was done coherent with the Cochrane recommendations(42)**.** To help reading, individual codes were given to included trials together with the first author, year of publication, and three first letter of the country where the trial was conducted. Since the studies were conducted by different researchers and managed independently, the random effect model was used. Because, it could be unlikely that all the studies had functional equivalence and had a common effect estimate.

Publication Bias

Given the small number of included studies, a funnel plot analysis to assess publication bias would have lacked sufficient statistical power to detect meaningful asymmetry. Therefore, a funnel plot was not generated

Sensitivity Analysis

A series of sensitivity analyses were conducted to explore the potency of the methodology used in the primary analysis and to reinstate the reliability of the randomization process the following steps were used: adding and excluding trials which were classified as high risk for bias back into the analysis in a stepwise fashion, and to explore the effect of large-study effects on the results of our meta-analysis, fixed-effect and random-effects estimates of the intervention effect were compared.

4.13 Quality of evidence

4.13.1 Confidence in Network Meta-Analysis (CINEMA)

The confidence in the network meta-analysis (NMA) evidence was assessed using the Confidence in Network Meta-Analysis (CINEMA) tool, which evaluates the quality of evidence based on several key factors (44). These factors reflect limitations within the design and conduct of the studies included in the network, providing insight into the reliability of the findings.

The following factors were taken into account when assessing the quality of evidence:

1. **Risk of Bias**: The extent to which study design and implementation may lead to systematic errors, influencing the results and their interpretation.
2. **Indirectness**: Refers to how applicable the evidence is to the population, intervention, comparison, and outcomes that are of interest. A lack of direct evidence may require downgrading of confidence.
3. **Inconsistency:** If there is significant variability or heterogeneity in the results across studies that cannot be explained, the confidence in the estimates may be reduced.
4. **Imprecision:** The precision of the results is assessed by considering the width of confidence intervals. Wider intervals indicate greater uncertainty about the true effect, leading to a lower level of confidence.
5. **Publication Bias**: Since publication bias was not assessed, all studies were categorized as low risk

Each of the above domains were graded as Low Concern, Some Concern or High Concern for the four domains (namely, Risk of bias, indirectness, inconsistency and imprecision). Publication bias was assessed as low risk and the quality was graded as High, Moderate or Low confidence

CHAPTER FIVE: RESULTS

5.1 Description of the Search Findings

We conducted the search from July 2024 to December 2024 and identified a total of 1867 studies of which 1439 of them were duplicates. After screening titles and abstracts, we collected the full text copies of 428 studies of which, 403 trials were excluded for reasons mentioned in Figure 1, We included 25 studies (one 3 arm trial and 24 two arm trials) for both qualitative and quantitative synthesis.

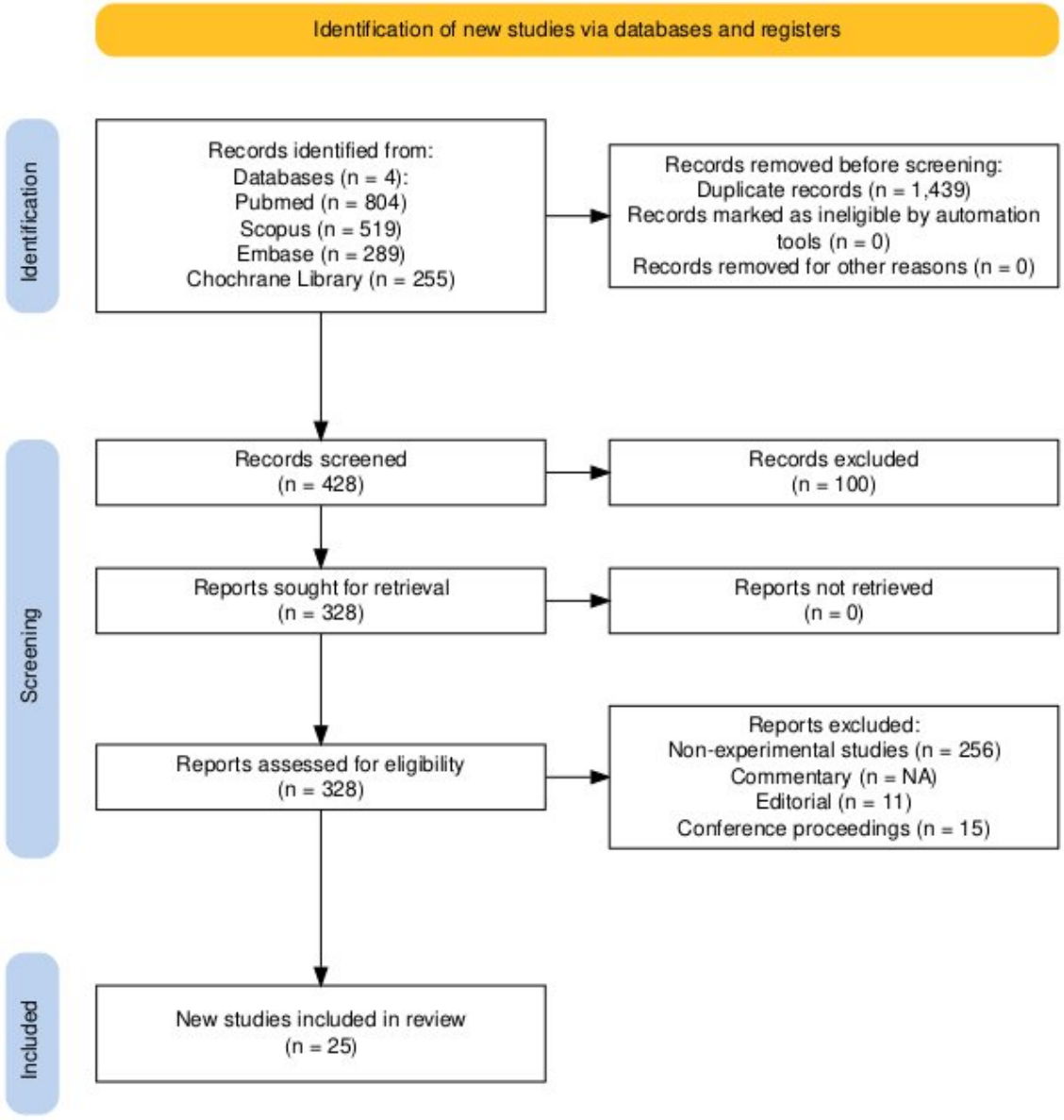

Figure 1: PRISMA Study Flow Diagram

5.2 Included studies

We included 25 trials which enrolled 75,988 subjects with hypertension in this review. The trials were conducted all over the world with most of them being in Japan. Most of the trial sites in the 9 studies included patients above 18 years of age. Totally 38,038 patients were randomized to intervention group and 37,950 were enrolled in to the control group in the studies. Fourteen trials had included patients with non-cardiovascular comorbidity

5.3 Risk of Bias in the included studies

In the risk of bias assessment, each study was evaluated using the Cochrane Collaboration's instrument based on six important domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Of the 25 included studies, fifteen were blinded studies, while ten were open-label. Figure 2 shows the risk of bias assessment graph, and the review authors' judgments about each risk of bias item are presented as percentages across all included studies in Figure 3.

5.3.1 Random sequence generation (Selection bias)

Out of 25 studies, 18 (72%) adequately described the random sequence generation technique, while the remaining 7 studies were deemed unclear regarding this aspect. Additionally, 17 studies were assessed to have a low risk of selection bias, whereas one study was judged to have a high risk of selection bias. The details of which studies had high and unclear risk can be found in Figure 2.

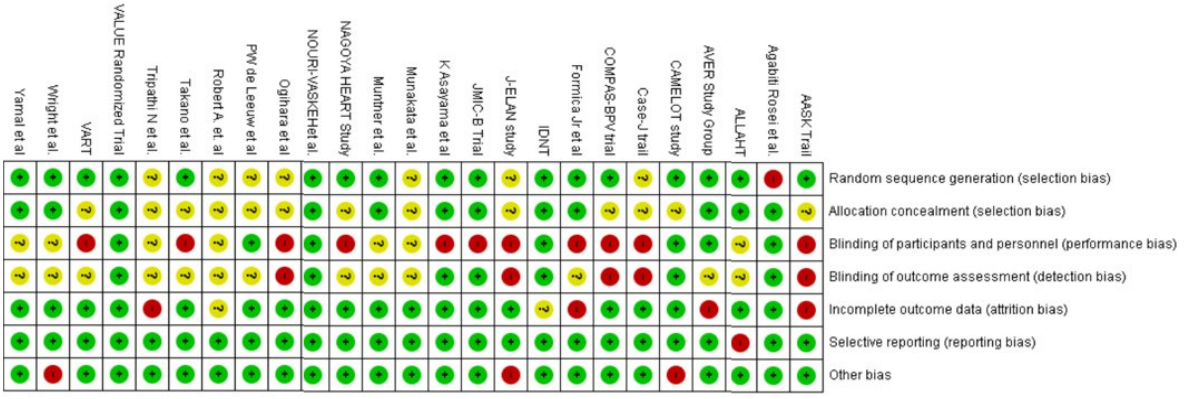

Figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

5.3.2 Allocation concealment (Selection bias)

In the review of the included studies, twelve were assessed to have a low risk of bias regarding allocation concealment. Conversely, thirteen studies were deemed unclear concerning selection bias due to inadequate descriptions of their allocation concealment methods. Importantly, none of the studies were classified as having a high risk of bias in terms of allocation concealment. The details of which studies had high and unclear risk can be found in Figure 2.

5.3.3 Blinding of Participants and Personnel (Performance bias)

In the assessment of performance bias across the included studies, seven studies were found to have adequately blinded both study participants and personnel, resulting in a classification of low risk for performance bias. Conversely, eleven studies did not implement adequate blinding measures, leading to a high risk for performance bias. Additionally, seven studies were categorized as having unclear risk for performance bias due to insufficient descriptions of their blinding procedures. The details of which studies had high and unclear risk can be found in Figure 2.

5.3.4 Blinding of outcome assessor (Detection bias)

In the evaluation of detection bias across the included studies, seven studies successfully blinded the outcome assessors, resulting in a classification of low risk for detection bias. In contrast, five studies were deemed to have a high risk for detection bias due to inadequate blinding of the outcome assessors. Furthermore, thirteen studies were classified as having an unclear risk for detection bias, as they did not provide sufficient information regarding the blinding procedures for outcome assessors. The details of which studies had high and unclear risk can be found in Figure 2.

5.3.5 Incomplete data outcome (Attrition bias)

In the assessment of attrition bias across the included studies, nineteen studies were classified as having a low risk of attrition bias. This classification was based on the absence of missing data, balanced handling of missing data, or the rationale that any missing outcome data were unlikely to be related to the true outcomes. Conversely, four studies were identified as having a high risk of attrition bias due to the exclusion of a significant proportion of participants from the final analysis. Additionally, two

studies were categorized as having an unclear risk for attrition bias because they did not provide adequate information regarding the proportion of participants excluded from their analyses. The details of which studies had high and unclear risk can be found in Figure 2.

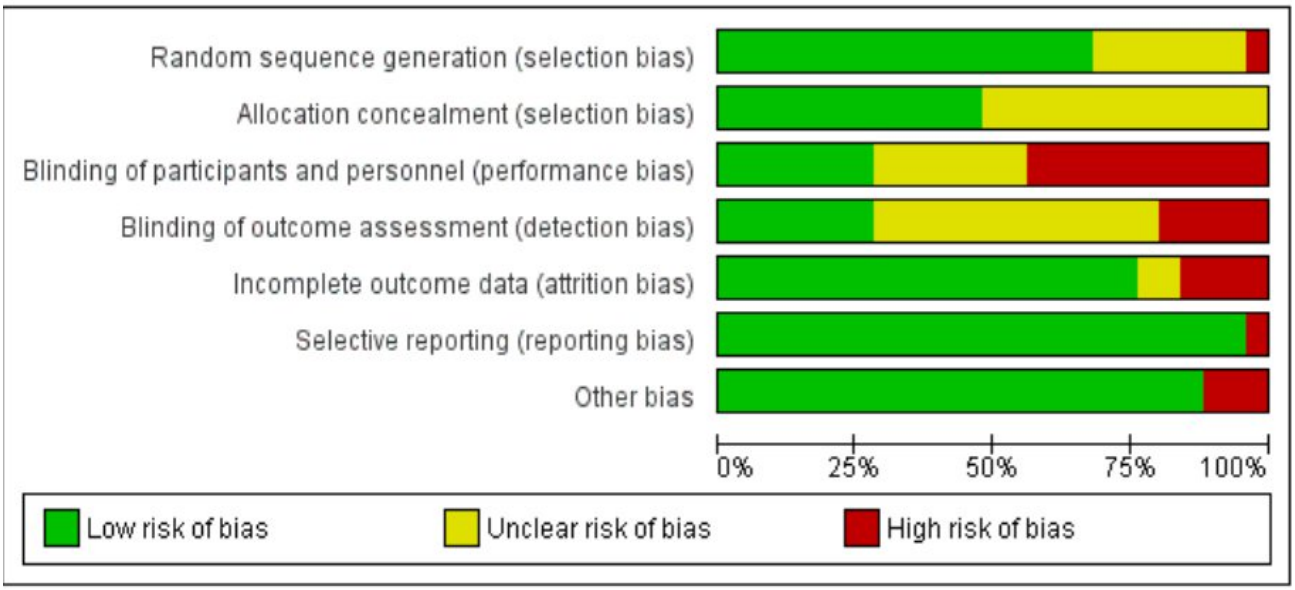

Figure 3: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

5.3.6 Selective reporting (Reporting bias)

One of the included studies was judged to be high risk for reporting bias for not clear indicating the final outcome of one of the treatment arms. The remaining twenty-four studies were judged to be low risk for reporting bias for they were not having selective reporting. The details of which studies had high and unclear risk can be found in Figure 2.

5.3.7 Other source of bias

Three studies were identified as having a high risk of other sources of bias, primarily due to the involvement of funding pharmaceutical companies in various aspects of the research process, including study design, performance, analysis, and data interpretation. Additionally, one study was flagged for including fewer participants than initially specified prior to the trial's commencement, which could impact the validity and generalizability of its findings. In contrast, while several stakeholders and pharmaceutical agencies provided funding and support for the other seventeen studies included in the

review, but none of these funding bodies were involved in the design, analysis, or interpretation of the data. The details of which studies had high and unclear risk can be found in Figure 2.

5.4 Cardiovascular Efficacy

Systolic BP

In the present analysis, a total of 17 distinct studies were incorporated, encompassing 16 pairwise comparisons across 8 treatment groups. The accompanying network diagram (Figure 4)illustrates that the predominant focus of these studies was the comparative evaluation of Amlodipine against Losartan.

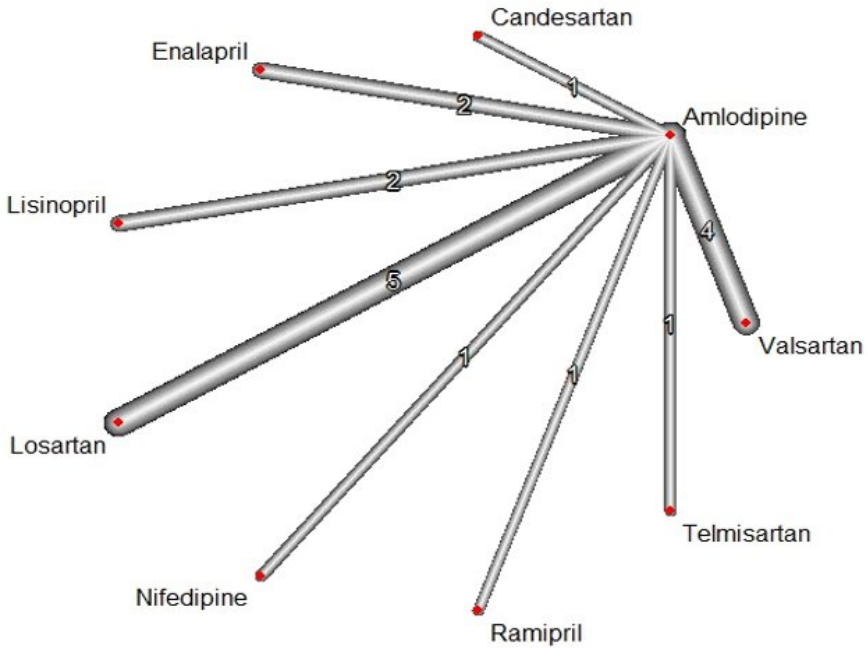

Figure 4: Net graph of Intervention and Comparator Antihypertensives in reducing Systolic Blood Pressure

Furthermore, the forest plot (Figure 5) reveals that no statistically significant difference was observed between the treatments in their efficacy in reducing Systolic Blood Pressure. Additionally, a comprehensive assessment of heterogeneity across the studies yielded significant results, as evidenced by the substantial heterogeneity ($p < 0.0001$, $tau^2 = 4.24$, $tau = 2.06$, $I^2 = 93.5\%$).

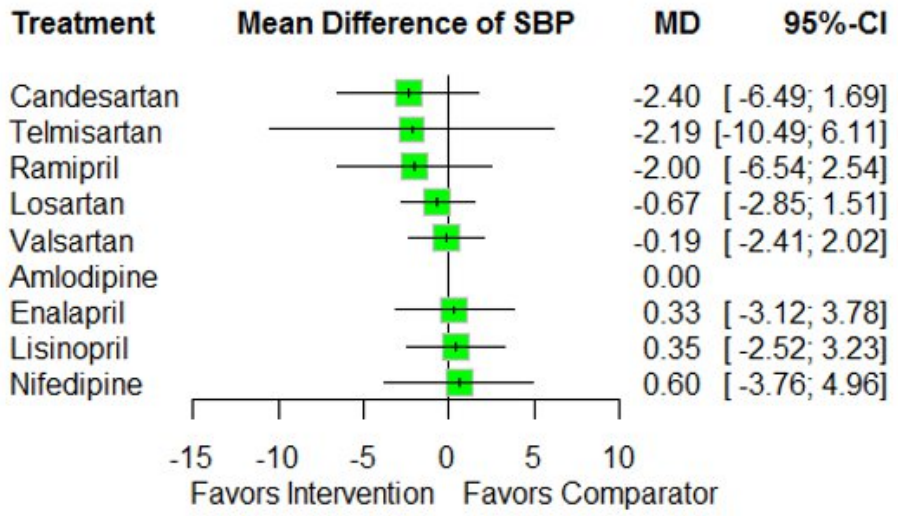

Figure 5: Forest plot of Intervention and Comparator Antihypertensives in reducing Systolic BP

Leave one out for Systolic BP

A leave-one-out analysis was performed to mitigate heterogeneity, incorporating 13 studies, 13 pairwise comparisons, and 7 treatment groups. The resulting network diagram in Figure 6 demonstrates that the majority of the studies focused on comparing Amlodipine with Losartan.

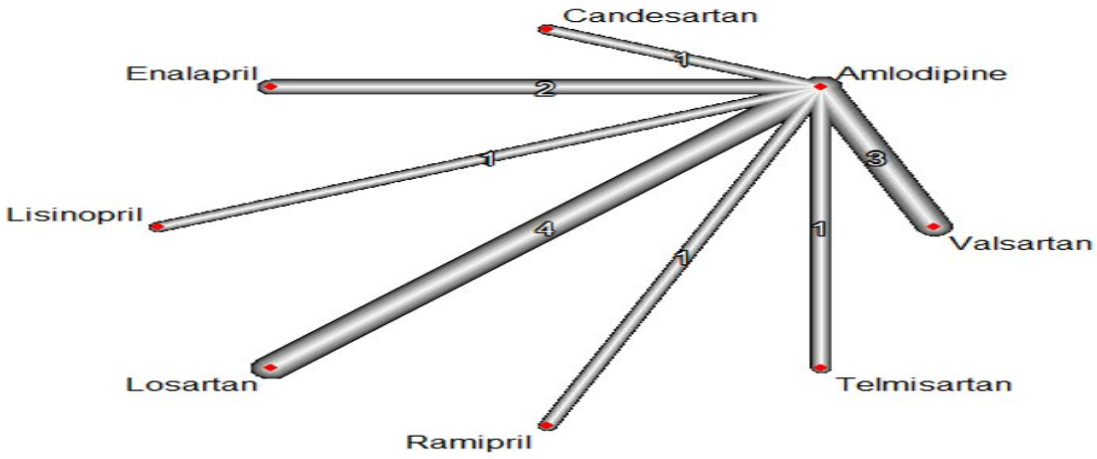

Figure 6 : Net graph of Intervention and Comparator Antihypertensives in reducing Systolic Blood Pressure after Leave one out Analysis

Additionally, the forest plot (Figure 7) reveals that Candesartan was found to reduce systolic blood pressure 2.4 times more effectively than Amlodipine. The overall heterogeneity of the analysis was assessed, yielding a significant result ($p = 0.025$), with heterogeneity statistics indicating $tau^2 = 0.9215$, $tau = 0.9552$, and $I^2 = 58.4\%$, with a 95% confidence interval ranging from 3.9% to 82%.

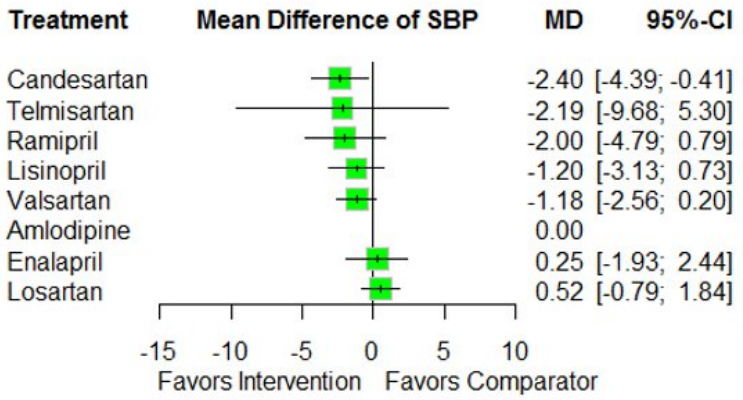

Figure 7: Forest Plot of Intervention and Comparator Antihypertensives in reducing Systolic Blood Pressure after Leave one out analysis

Candesartan, an angiotensin II receptor blocker (ARB), emerged as the top-ranked treatment in terms of its efficacy in reducing systolic blood pressure. This is clearly illustrated in the rankogram graph presented below in Figure 8, which visually represents the comparative performance of various treatments included in the analysis. The graph indicates that Candesartan consistently outperformed other interventions in its ability to lower systolic blood pressure, positioning it at the forefront of the treatment options assessed in this study

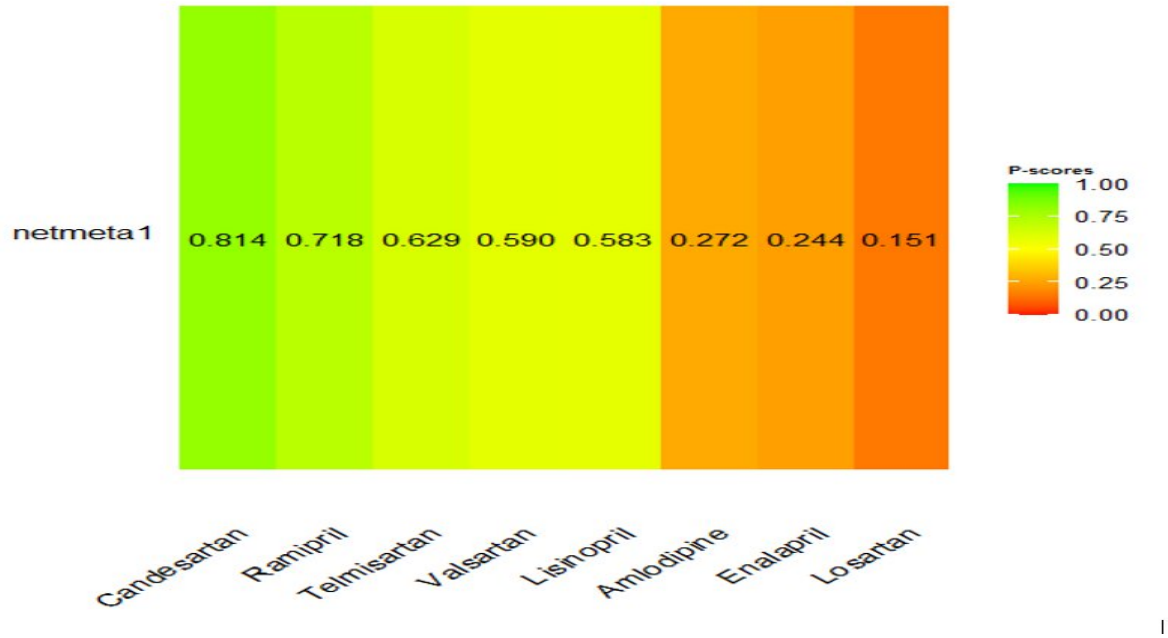

Figure 8: Net rank of Intervention and Comparator Antihypertensives in reducing Systolic Blood Pressure

Diastolic BP

In the current analysis, a total of 18 studies were incorporated, encompassing 18 pairwise comparisons and involving 10 distinct treatment groups. The network diagram (Figure 9) provides a visual representation of the relationships between these treatments, revealing that the majority of the studies focused on comparing Amlodipine with Valsartan.

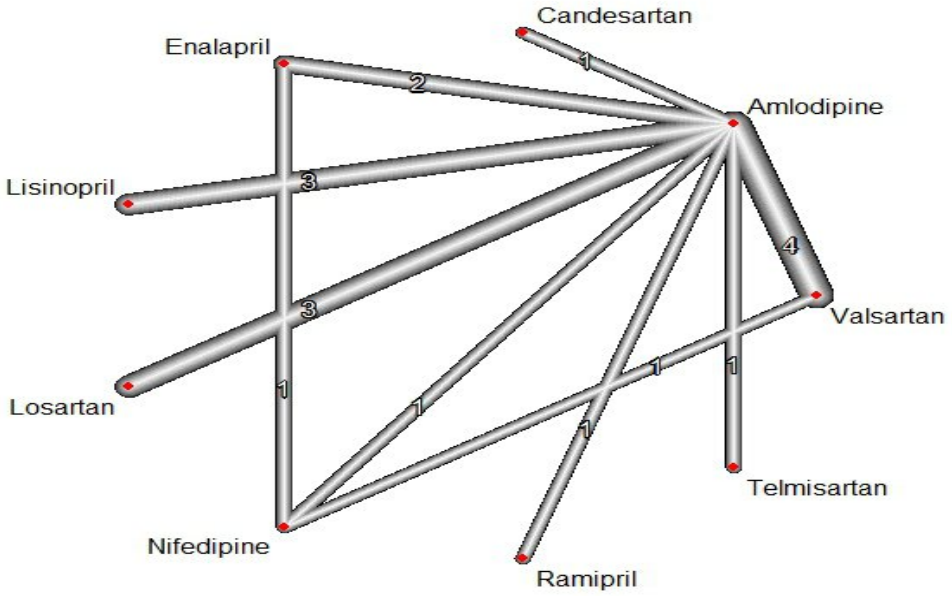

Figure 9: Net graph of Intervention and Comparator Antihypertensives in reducing Diastolic Blood Pressure

The forest plot Figure 10 illustrates the findings related to Diastolic Blood Pressure (BP), indicating that there was no statistically significant difference between the treatments in their ability to reduce Diastolic BP. This suggests that, within the scope of the included studies, the various treatments evaluated were similarly effective in managing Diastolic BP.

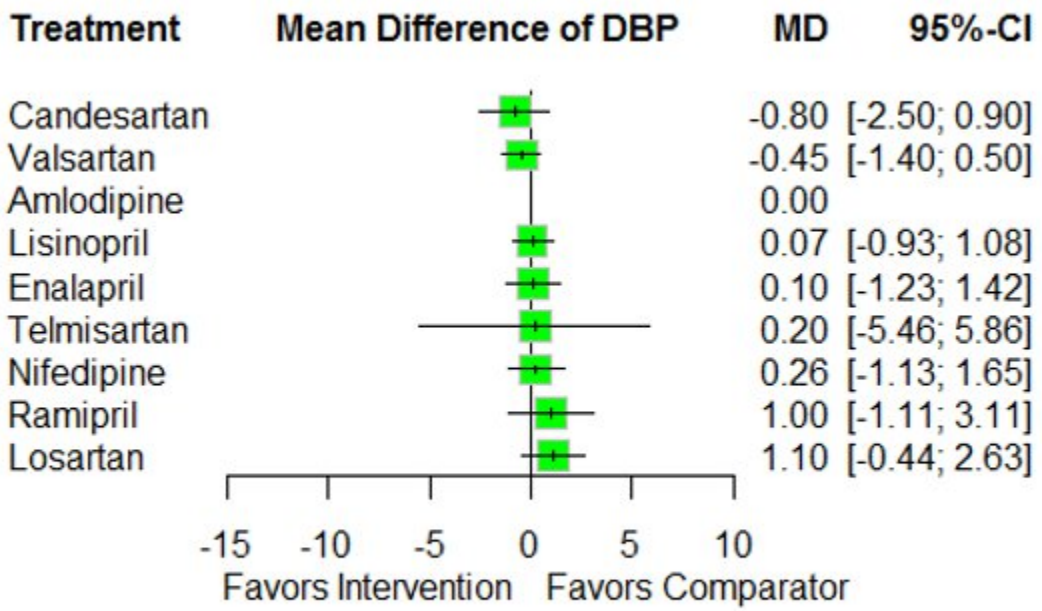

Figure 10: Forest Plot of Intervention and Comparator Antihypertensives in reducing Diastolic Blood Pressure

Furthermore, an assessment of the overall heterogeneity was conducted, with the results showing significant variability in the treatment effects ($p < 0.0001$). The heterogeneity statistics indicated $tau^2 = 0.7186$, $tau = 0.8477$, and $I^2 = 84.6\%$ demonstrating a high level of inconsistency across the studies.

Leave one out analysis for Diastolic BP

In this analysis, a total of 10 studies were included, comprising 10 pairwise comparisons across 9 distinct treatment groups. The network diagram (Figure 11) illustrates the structure of these comparisons, revealing that the majority of the studies focused on comparing Amlodipine with Valsartan and Enalapril.

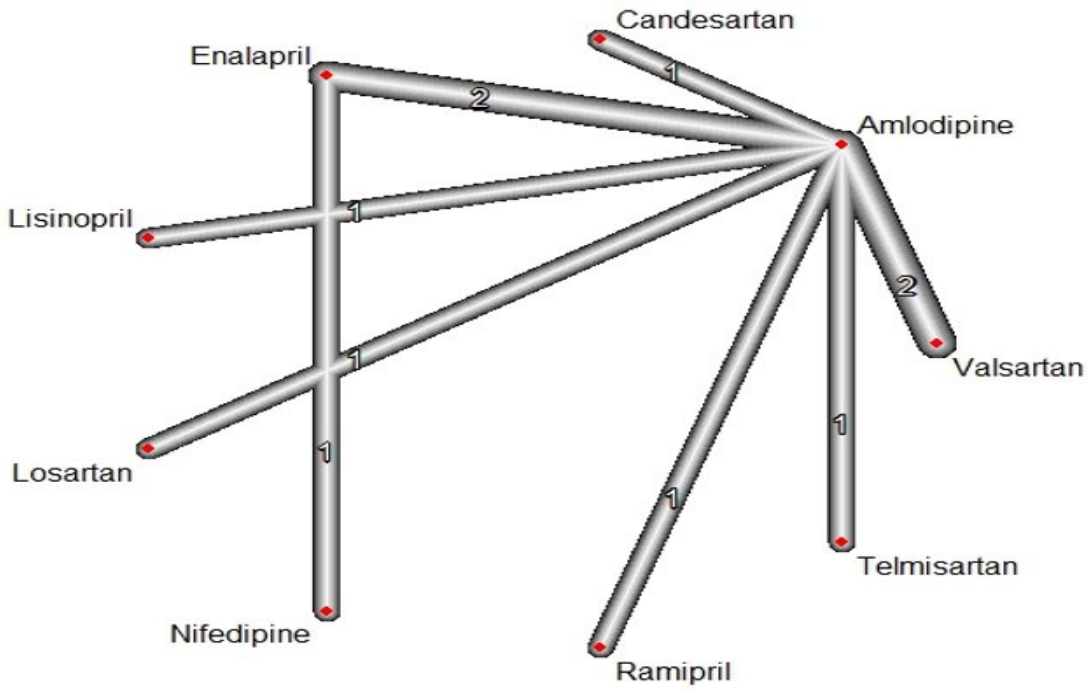

Figure 11: Net graph of Intervention and Comparator Antihypertensives in reducing Diastolic Blood Pressure after Leave one out Analysis

Figure 12 further highlights that Candesartan was associated with a 20% reduction in diastolic blood pressure compared to Amlodipine. Specifically, the relative risk (RR) for this comparison was 0.80, with a 95% confidence interval ranging from -1.30 to -0.30 Additionally, an evaluation of the overall heterogeneity within the analysis revealed no significant inconsistency across the studies. The heterogeneity statistics indicated $tau^2 = 0$, $tau = 0$, and $I^2 = 0\%$.

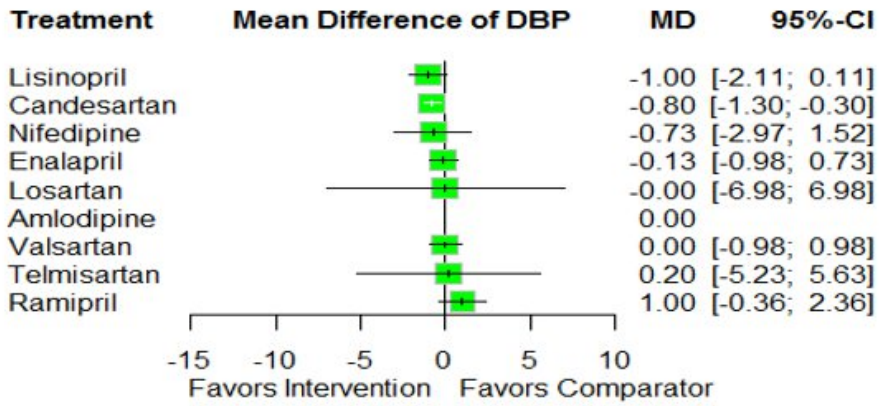

Figure 12: Forest plot of Intervention and Comparator Antihypertensives in reducing Diastolic Blood Pressure after Leave one out Analysis

Candesartan, an angiotensin II receptor blocker (ARB), emerged as the top-ranked treatment in terms of its efficacy in reducing Diastolic blood pressure. This is clearly illustrated in the rankogram graph presented below in Figure 13, which visually represents the comparative performance of various treatments included in the analysis. The graph indicates that Candesartan consistently outperformed other interventions in its ability to lower diastolic blood pressure, positioning it at the forefront of the treatment options assessed in this study.

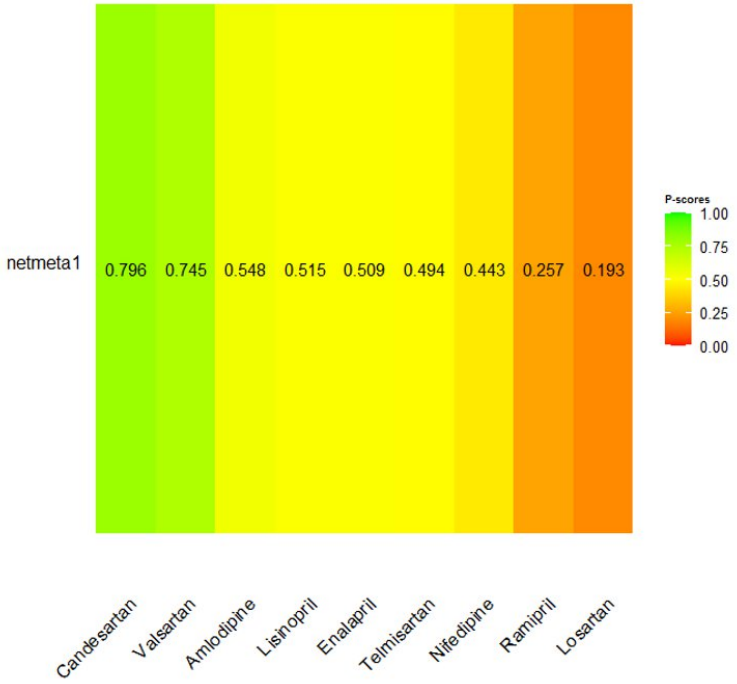

Figure 13: Net rank of Intervention and Comparator Antihypertensives in reducing Diastolic Blood Pressure

Cardiovascular Death

In this analysis, a total of 12 studies were included, involving 12 pairwise comparisons across 7 distinct treatment groups. The network diagram (Figure 14) provides a visual representation of these comparisons, highlighting that the majority of the studies focused on comparing Amlodipine with Lisinopril, two commonly prescribed antihypertensive medications. This network diagram illustrates the interrelationships between the treatments, making it clear that Amlodipine and Lisinopril were central to the majority of the analyses conducted.

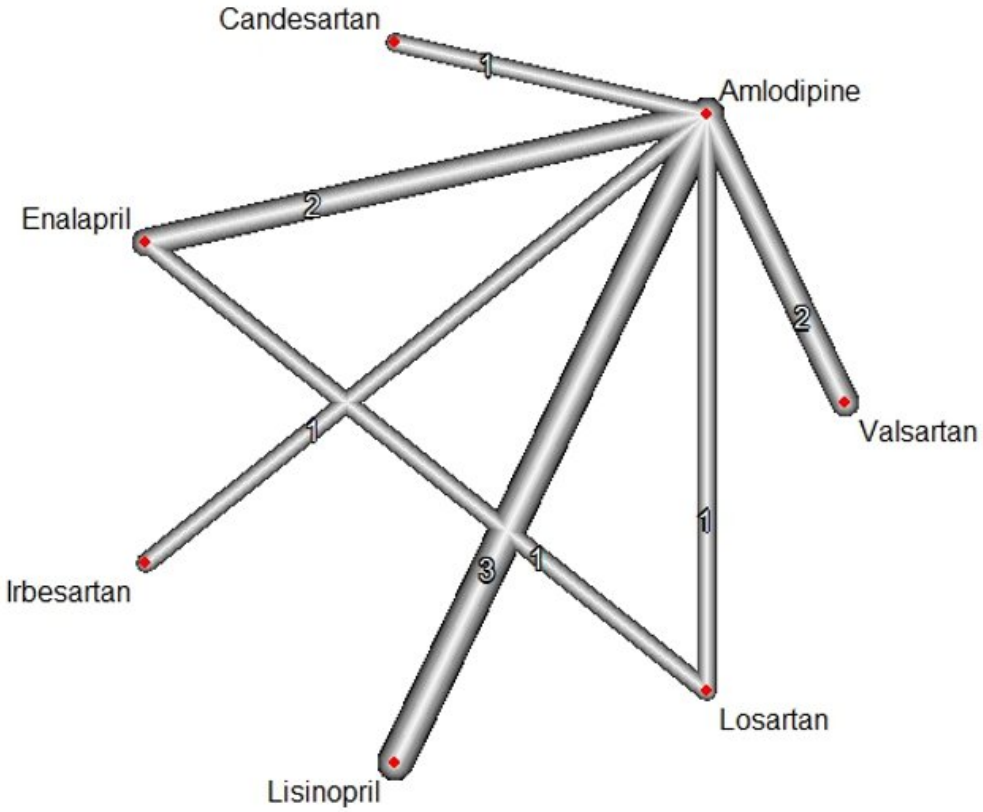

Figure 14: Net graph of Intervention and Comparator Antihypertensives in reducing incidence Cardiovascular death

The forest plot (Figure 15) presents the findings related to cardiovascular death, showing that there was no significant difference between the treatments in their ability to reduce the incidence of cardiovascular mortality. This suggests that, in the context of the included studies, the various

treatments were similarly effective (or ineffective) in preventing cardiovascular death, with no substantial evidence supporting one treatment as superior over another in this regard.

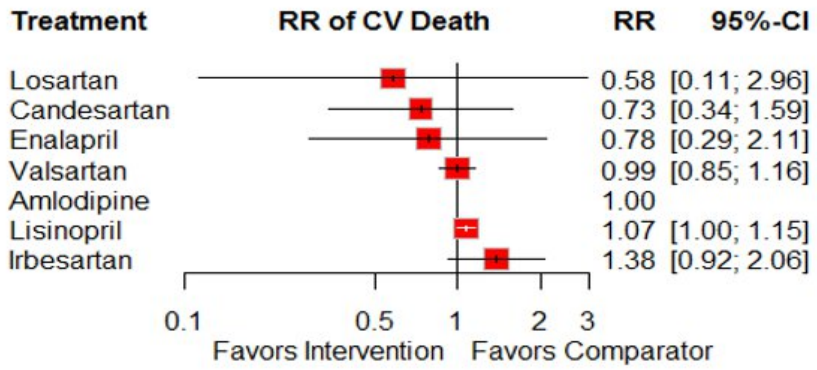

Figure 15: Forest plot of Intervention and Comparator Antihypertensives in reducing incidence of cardiovascular death

Furthermore, the overall heterogeneity of the analysis was assessed to determine the consistency of treatment effects across the studies. The heterogeneity statistics indicated $tau^2 = 0$, $tau = 0$, and $I^2 = 0\%$.

Myocardial Infarction

In this analysis, a total of 10 studies were included, which involved 10 pairwise comparisons across 6 distinct treatment groups. The network diagram (Figure 16) visually represents these pairwise comparisons, indicating that the majority of the studies focused on comparing Amlodipine with several other drugs, specifically Candesartan, Enalapril, Lisinopril, and Valsartan. This network diagram serves to clarify the relationships between the various treatment options and illustrates the scope of the comparisons made across the studies.

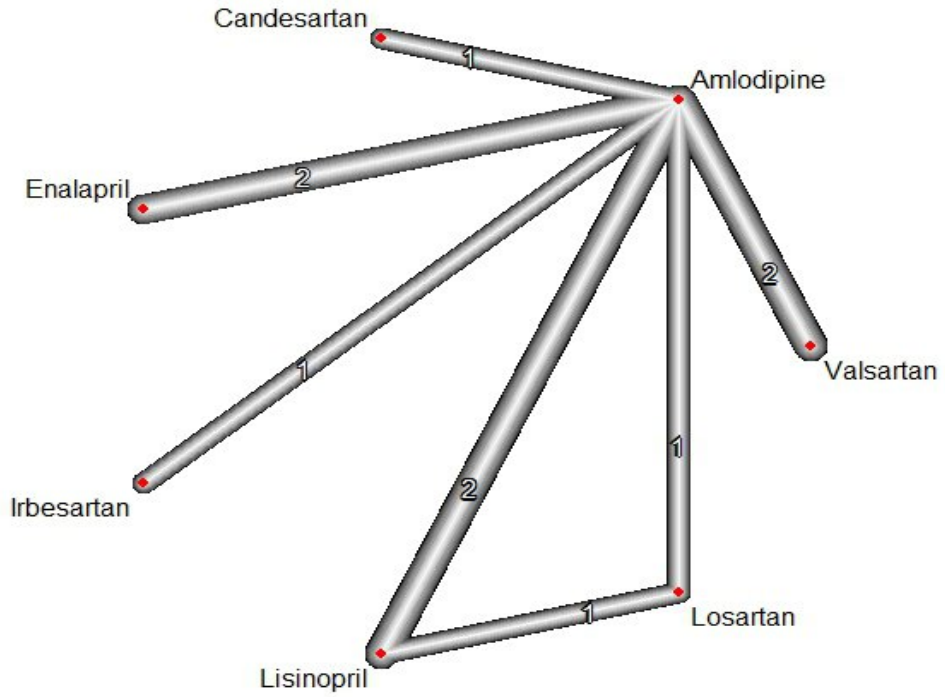

Figure 16: Net graph of Intervention and Comparator Antihypertensives in reducing incidence of Myocardial Infarction

The forest plot above further highlights that Enalapril increase risk of myocardial infarction compared to Amlodipine by 47%. Specifically, the relative risk (RR) for this comparison was 1.47, with a 95% confidence interval ranging from 1.09 to 1.99. In addition, Irbesartan was associated with a 62% increase in risk of myocardial infarction compared to Amlodipine. Specifically, the relative risk (RR) for this comparison was 1.62, with a 95% confidence interval ranging from 1.0 to 2.53.

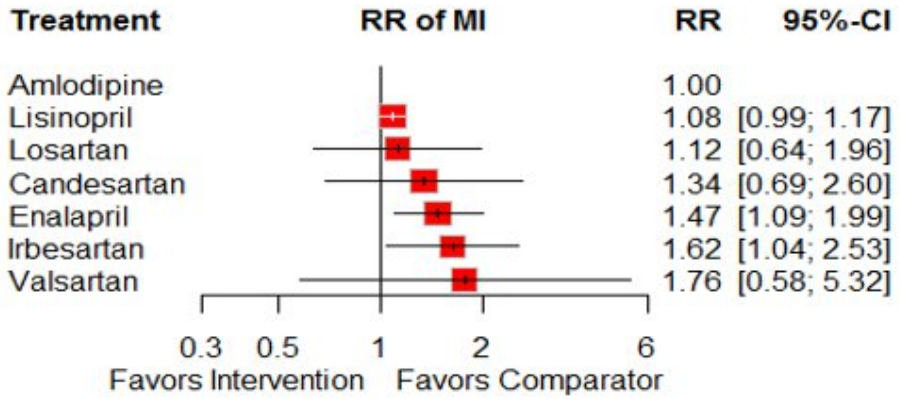

Figure 17: Forest plot of Intervention and Comparator Antihypertensives in reducing Myocardial Infarction

Furthermore, an assessment of the overall heterogeneity was conducted to evaluate the consistency of treatment effects across the studies. The heterogeneity statistics indicated that the overall heterogeneity was not significant, with a p-value of 0.12. The tau^2 was calculated to be 0.06, and tau was 0.26, suggesting relatively low variability in the treatment effects. The I^2 value was 43.9%, which indicates moderate heterogeneity, but it did not reach a level that would be considered highly significant.

The rankogram generated for this analysis revealed that Amlodipine was associated with the lowest incidence of Myocardial Infarction among the treatment options evaluated. The rankogram, which visually represents the comparative effectiveness of each drug in reducing MI risk, positioned Amlodipine as the most favorable treatment in terms of minimizing the occurrence of MI.

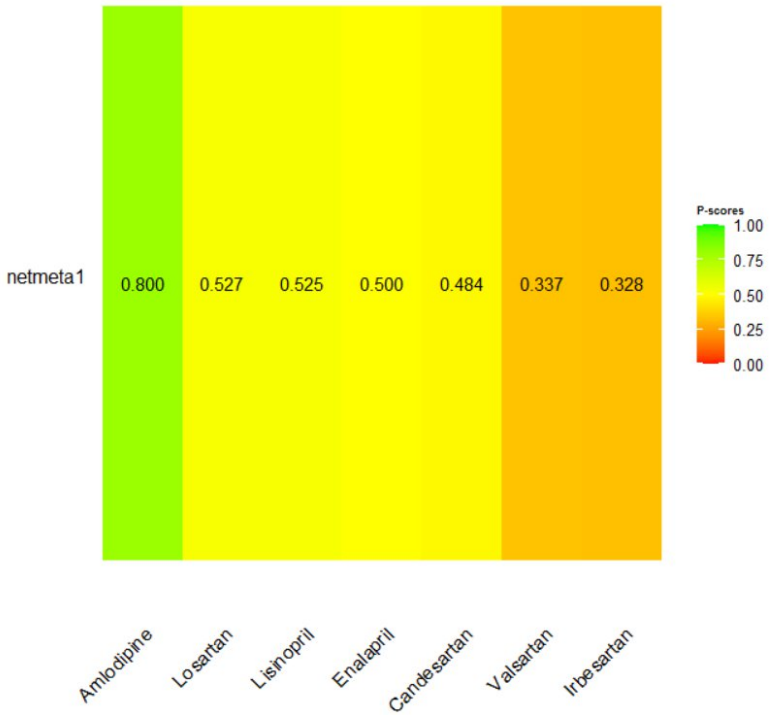

Figure 18: Net rank of Intervention and Comparator Antihypertensives in Incidence of MI

Stroke

In this analysis, a total of 11 studies were included, encompassing 11 pairwise comparisons across 8 distinct treatment groups. These studies were selected to evaluate the comparative effectiveness of various antihypertensive treatments. The network diagram (Figure 19) visually represents the relationships between the different treatments, showing that the majority of the studies focused on comparing Amlodipine with Valsartan.

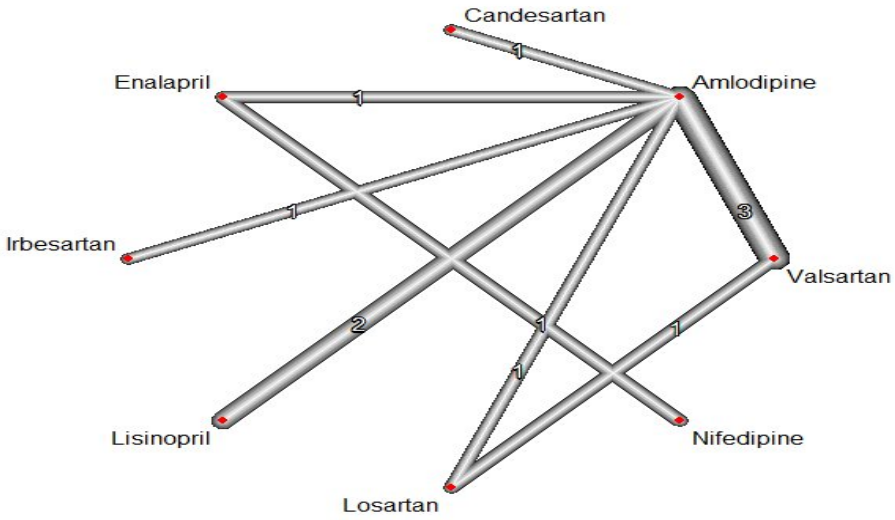

Figure 19: Net graph of Intervention and Comparator Antihypertensives in reducing incidence of Stroke

The forest plot (Figure 20) presents the findings related to the reduction of stroke incidence. The results of this analysis indicated that there was no significant difference between the treatments in their ability to reduce the occurrence of stroke. This suggests that, within the scope of the included studies, none of the treatments, including Amlodipine and Valsartan, demonstrated superior efficacy in preventing stroke compared to the others

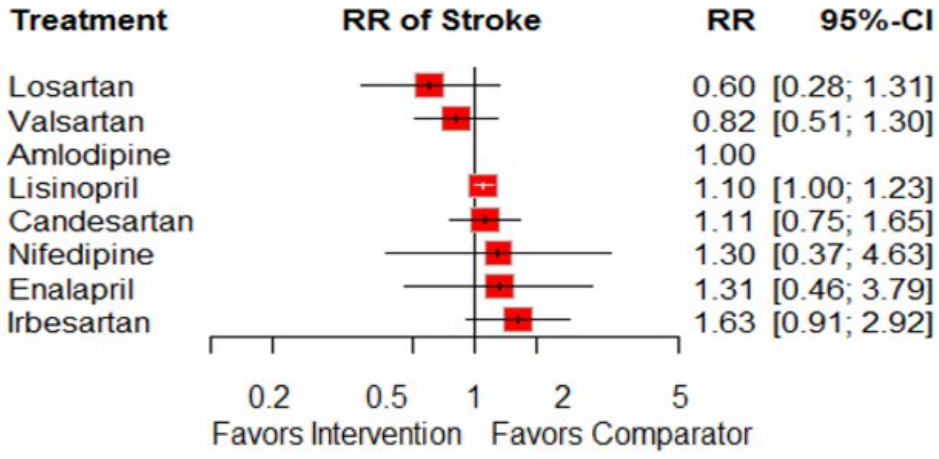

Figure 20: forest plot of Intervention and Comparator Antihypertensives in reducing incidence of stroke

Additionally, an assessment of the overall heterogeneity of the data was performed to examine the consistency of the treatment effects across the studies. The heterogeneity statistics revealed that the overall heterogeneity was not statistically significant, with $tau^2 = 0.032$, tau = 0.0561, and $I^2 = 27.1\%$. with a p value of 0.02

Heart Failure

In this analysis, a total of seven studies were included, comprising seven pairwise comparisons across six distinct treatment groups. The treatment groups evaluated in the studies were Amlodipine, Lisinopril, Valsartan, Irbesartan, and other commonly used antihypertensive drugs. The network diagram (Figure 21) provides a visual representation of the treatment comparisons, highlighting that the majority of the studies focused on comparing Amlodipine with Lisinopril and Valsartan. This network diagram illustrates the interrelationships between the treatments, showing how Amlodipine is central to most of the comparisons.

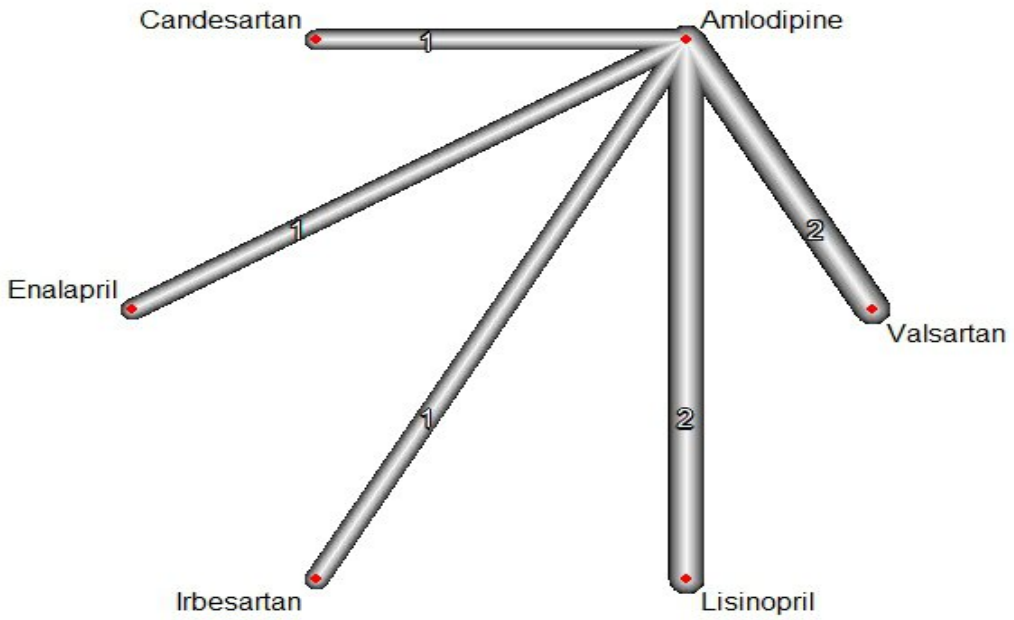

Figure 21: Net graph of Intervention and Comparator Antihypertensives in reducing incidence of Heart Failure

The forest plot (Figure 22) presents the findings related to the risk of developing heart failure. The analysis revealed that the risk of heart failure was 45% lower in patients treated with Irbesartan compared to those treated with Amlodipine. Specifically, the relative risk (RR) for this comparison was 0.55, with a 95% confidence interval (CI) ranging from 0.41 to 0.74.

Additionally, the analysis found that the risk of heart failure was 79% lower in patients taking Valsartan compared to those taking Amlodipine. The relative risk for this comparison was 0.21, with a 95% confidence interval ranging from 0.07 to 0.67.

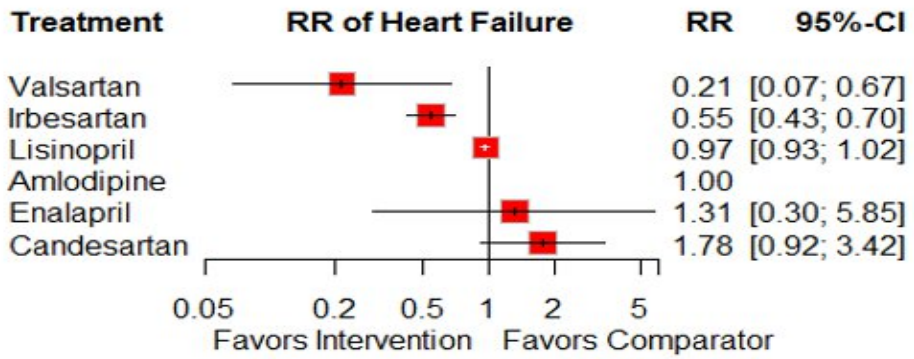

Figure 22: Forest Plot of Intervention and Comparator Antihypertensives in reducing incidence of Heart Failure

An assessment of the overall heterogeneity of the data was also conducted to evaluate the consistency of the treatment effects across the studies. The heterogeneity statistics showed that the overall heterogeneity was not significant, with a p-value of 0.054, suggesting moderate variation in the study results. The tau^2 value was 0.0065, and tau was 0.0809, which further indicates minimal inconsistency in the treatment effects. The I^2 value was 65.6%, suggesting moderate heterogeneity, but not enough to significantly impact the interpretation of the analysis. These suggest that while some variability exists across the included studies, the overall results are consistent and reliable.

According to the rankogram generated for this analysis, Valsartan was identified as the drug associated with the lowest incidence of heart failure. The rankogram, which visually represents the comparative effectiveness of the treatments, positions Valsartan as the most favorable option in terms of minimizing the occurrence of heart failure among the treatment options evaluated. This finding suggests that, relative to other antihypertensive drugs included in the analysis, Valsartan may offer a superior benefit in reducing the risk of heart failure.

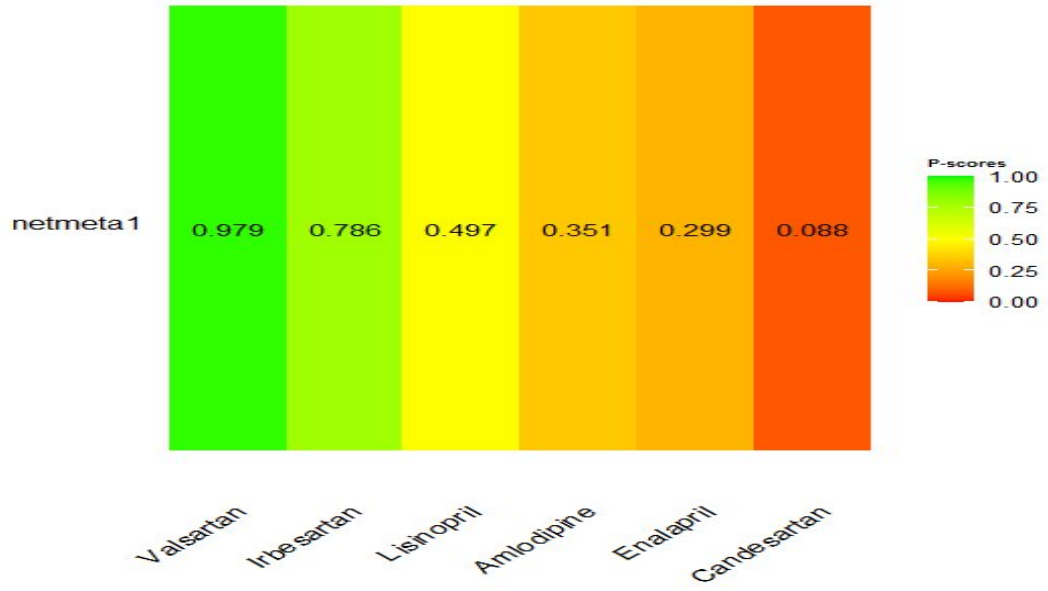

Figure 23: Net rank of Intervention and Comparator Antihypertensives in reducing Heart Failure

Outlier assessment for Heart Failure

In this updated analysis, the same two studies with large sample sizes were removed from the original dataset. After this exclusion, a total of five studies were included, involving five pairwise comparisons across five distinct treatment groups. The treatment options evaluated were Amlodipine, Valsartan, Irbesartan, and other commonly used antihypertensive drugs. The network diagram in Figure 24 illustrates the revised structure of the comparisons, showing that most of the studies focused on comparing Amlodipine with Valsartan, with additional comparisons involving Irbesartan. This diagram

visually represents the relationships between the different treatment groups, highlighting the central role of Amlodipine in the analysis.

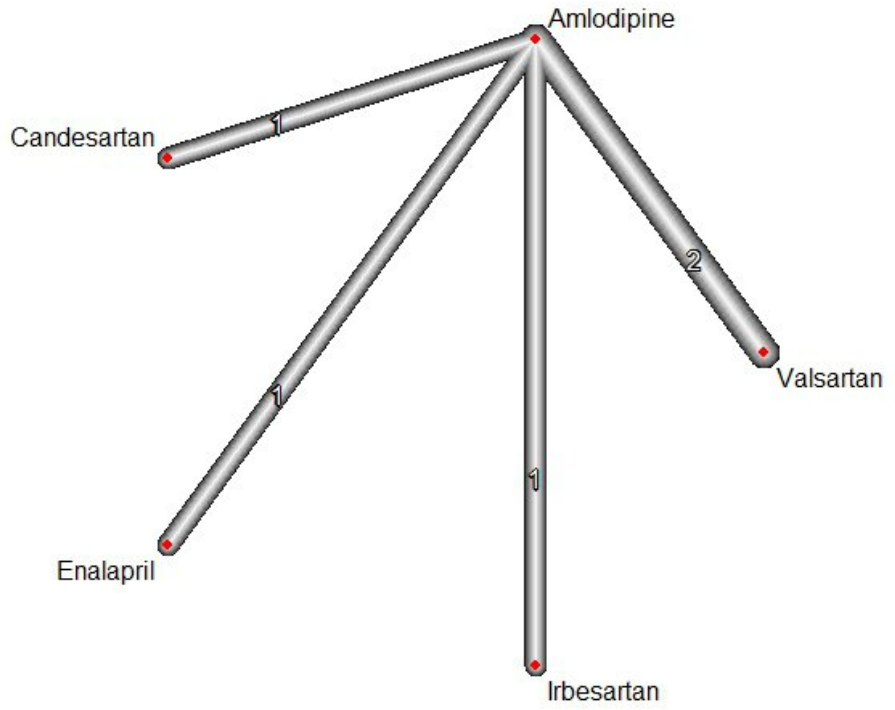

Figure 24:Net graph of Intervention and Comparator Antihypertensives in reducing incidence of Heart Failure after leave one out analysis

The forest plot in Figure 25 presents the findings related to the risk of patients developing heart failure. The analysis revealed that the risk of heart failure was 79% lower in patients taking Valsartan compared to those taking Amlodipine, with a relative risk (RR) of 0.21 (95% CI: 0.07 to 0.67).

Additionally, the analysis showed that the risk of heart failure was 45% lower in patients taking Irbesartan compared to those treated with Amlodipine. The relative risk for this comparison was 0.55 (95% CI: 0.43 to 0.70).

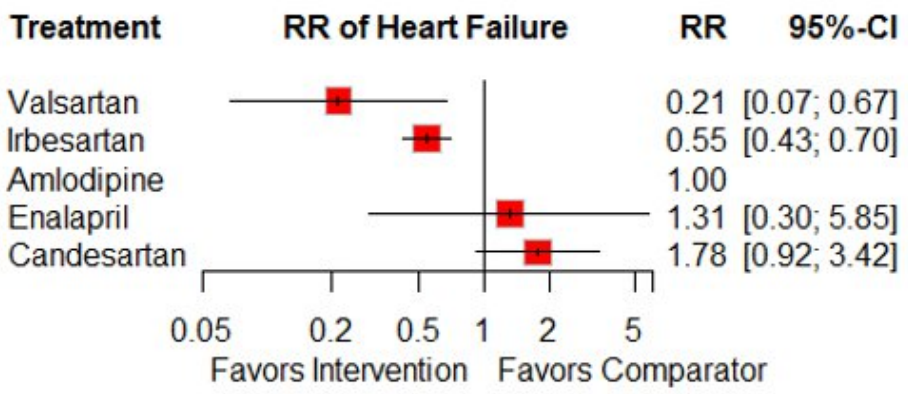

Figure 25:Forest Plot of Intervention and Comparator Antihypertensives in reducing incidence of Heart Failure after leave one out analysis

An assessment of the overall heterogeneity was also conducted to evaluate the consistency of treatment effects across the studies. The heterogeneity statistics indicated that the overall heterogeneity was not significant, with a p-value of 0.7857. The tau² value was 0, indicating no variance in the treatment effects, and tau was 0, reflecting no inconsistency across the studies. The I^2 value was 0%, suggesting no variability between the results of the included studies. These findings indicate that the treatment effects across the studies were consistent and reliable, reinforcing the robustness of the conclusions drawn from this analysis.

The rankogram generated for this analysis revealed that Valsartan was associated with the lowest incidence of heart failure among the treatment options evaluated. The rankogram, which visually represents the comparative effectiveness of each drug in reducing heart failure risk, positioned Valsartan as the most favorable treatment in terms of minimizing the occurrence of heart failure. This finding suggests that, relative to other antihypertensive agents included in the analysis, Valsartan may offer a superior benefit in reducing the risk of heart failure.

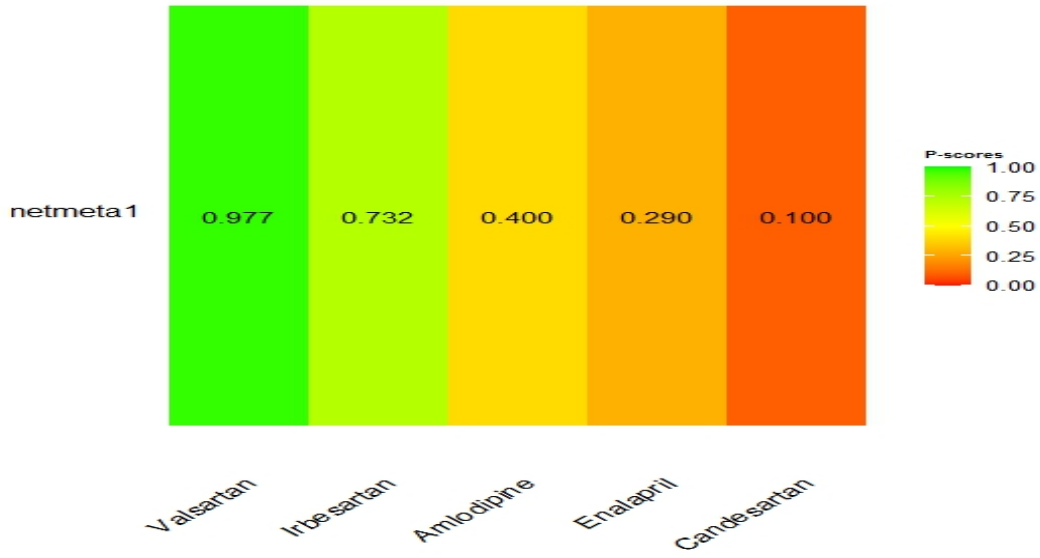

Figure 26: Net rank of Intervention and Comparator Antihypertensives in reducing incidence of Heart Failure

5.5 Cardiovascular Safety

Syncope

In this analysis, 2 studies, and 2 pairwise comparisons and 3 treatment groups were included. The network diagram shows that Amlodipine was compared with Ramipril and Valsartan (Figure 27).

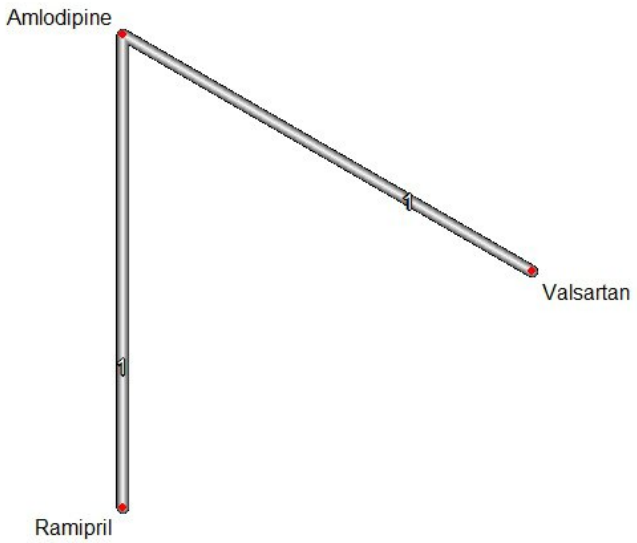

Figure 27: Net graph of Intervention and Comparator Antihypertensives in reducing incidence of syncope

The forest plot show that the risk of developing syncope was 3 times higher with RR 2.99 (95% CI 1.18; 7.59, P = 0.07) in patients who were treated with Ramipril than Amlodipine. The risk of developing syncope in patients treated with Valsartan was 71% higher than patients taking Amlodipine, RR 1.71(95% CI 1.29;2.27).

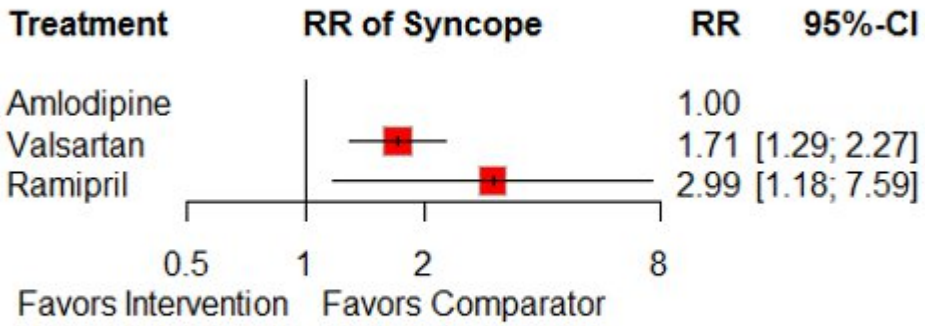

Figure 28: Forest plot of Intervention and Comparator Antihypertensives in reducing incidence of Syncope

The rankogram generated for this analysis revealed that amlodipine was associated with the lowest incidence of syncope among the treatment options evaluated. The rankogram, which visually represents the comparative occurrence of syncope across each drug, positioned amlodipine as the most favorable treatment in terms of minimizing syncope events. This finding suggests that, relative to other antihypertensive agents included in the analysis, amlodipine may offer a superior benefit in reducing the risk of syncope.

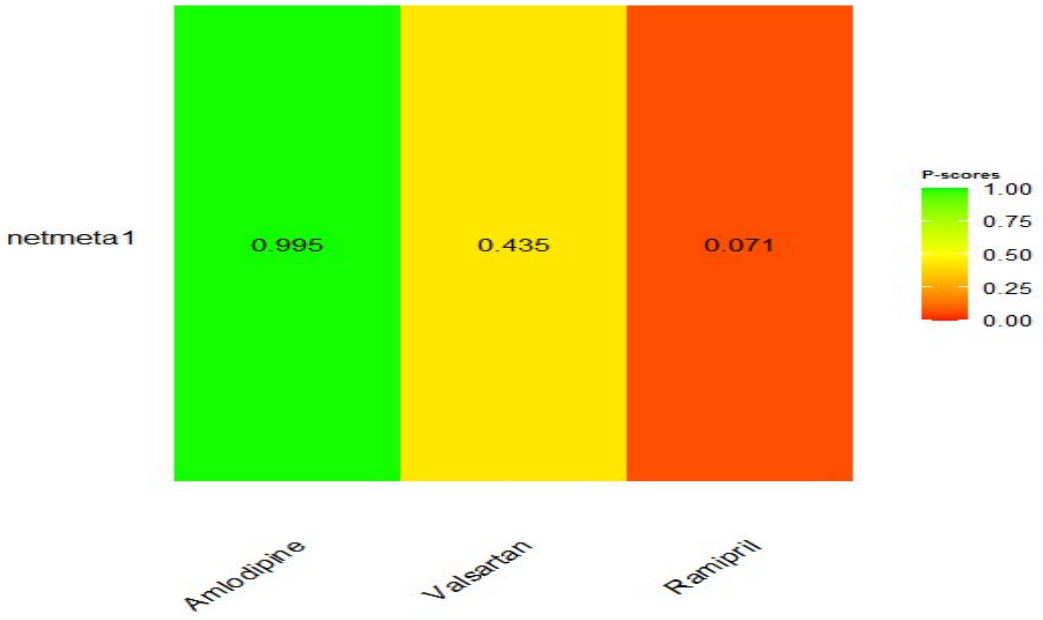

Figure 29: Net rank of Intervention and Comparator Antihypertensives in reducing the incidence of Syncope

Edema

In this analysis, 4 studies, and 4 pairwise comparisons and 5 treatment groups were included. The network diagram shows that Amlodipine was compared with Ramipril, Valsartan, Losartan and Enalapril (Figure 30).

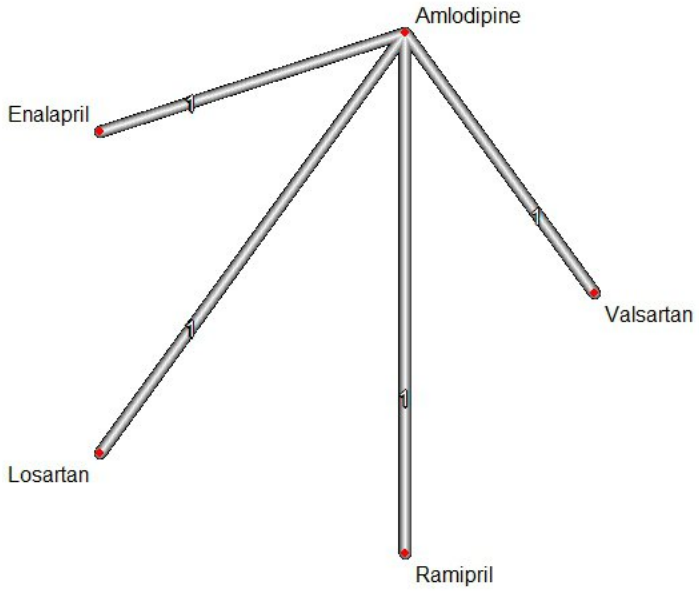

Figure 30: Net graph of Intervention and Comparator Antihypertensives in reducing incidence of Edema

The forest plot show that the risk of developing Edema was 85% lower with RR 0.15 (95% CI 0.07; 0.31) in Enalapril than patients who were treated with Amlodipine. The risk of developing Edema in patients treated with Valsartan was 55% lower than patients taking Amlodipine, RR 0.45(95% CI 0.42;2.0.48, P= 0.73). Additionally, Ramipril had a decreased incidence of edema by 23% compared to Amlodipine with a RR of 0.77(95%CI 0.66 0.89).

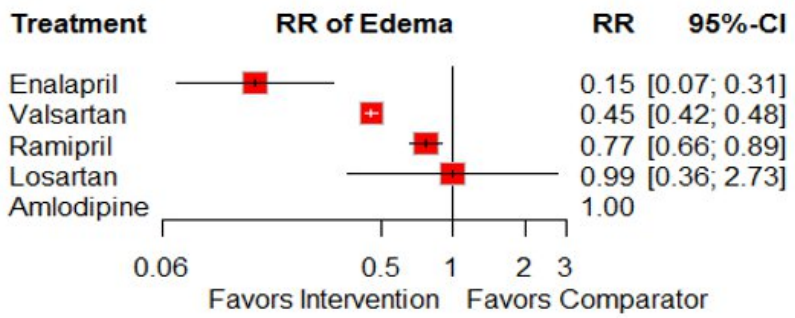

Figure 31: Forest Plot of Intervention and Comparator Antihypertensives in reducing incidence of Edema

The rankogram generated for this analysis revealed that enalapril was associated with the lowest incidence of edema among the treatment options evaluated. The rankogram, which visually represents the comparative occurrence of edema across each drug, positioned enalapril as the most favorable treatment in terms of minimizing edema events. This finding suggests that, relative to other antihypertensive agents included in the analysis, enalapril may offer a superior benefit in reducing the risk of edema.

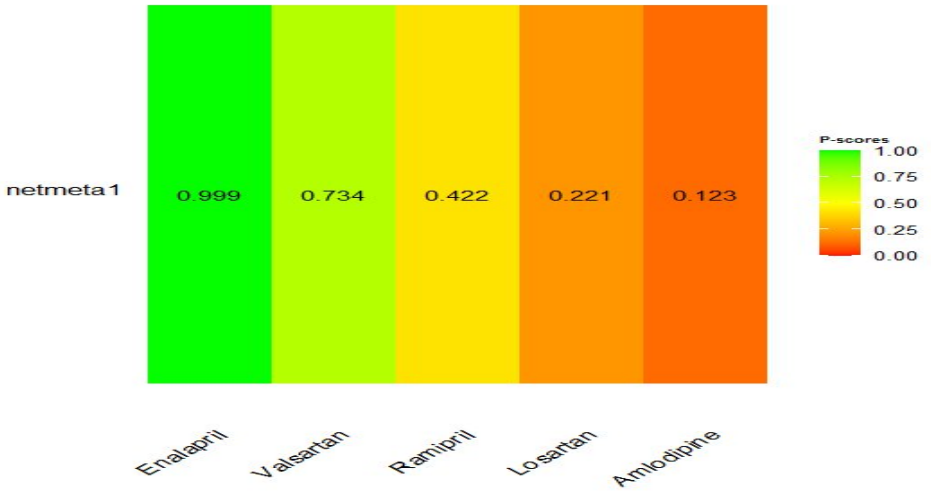

Figure 32: Net rank of Intervention and Comparator Antihypertensives in reducing incidence of Edema

Hospitalization rate for Heart Failure

In this analysis, two studies were included, comprising two pairwise comparisons across three distinct treatment groups. The treatment groups evaluated were Amlodipine, Lisinopril, and Enalapril. The network diagram (Figure 33) provides a visual representation of the relationships between these treatments, demonstrating that Amlodipine was compared with both Lisinopril and Enalapril. This diagram illustrates the comparative structure of the analysis, highlighting the interconnections between the treatments.

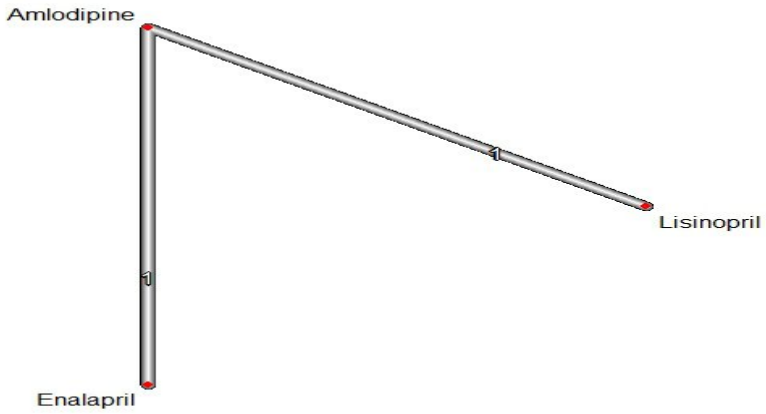

Figure 33: Net graph of Intervention and Comparator Antihypertensives in reducing the incidence of Hospitalization for Heart Failure

The forest plot (Figure 34) presents the findings related to the hospitalization rate for heart failure. The analysis revealed that there was no significant difference between the treatments in reducing the hospitalization rate for heart failure. This suggests that, within the scope of the included studies, Amlodipine, Lisinopril, and Enalapril demonstrated similar effectiveness in preventing hospitalizations due to heart failure. The lack of a significant difference implies that the treatment choice, at least within this analysis, did not substantially impact the rate of heart failure-related hospitalizations.

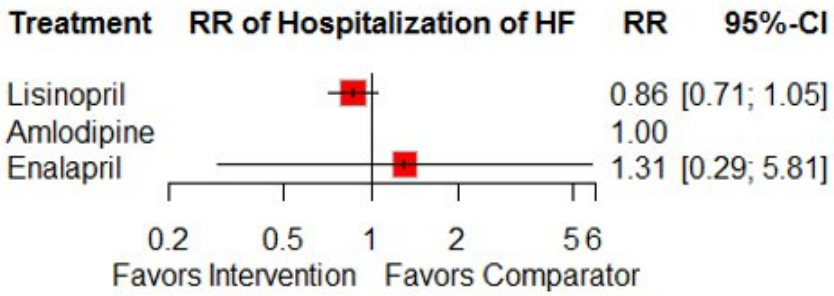

Figure 34: Forest plot of Intervention and Comparator Antihypertensives in reducing incidence of Hospitalization for Heart Failure

Hospitalization for Myocardial Infarction

In this analysis, 3 studies, and 3 pairwise comparisons and 4 treatment groups were included. The network diagram shows that Amlodipine was compared with Lisinopril, Valsartan and Enalapril (Figure 35).

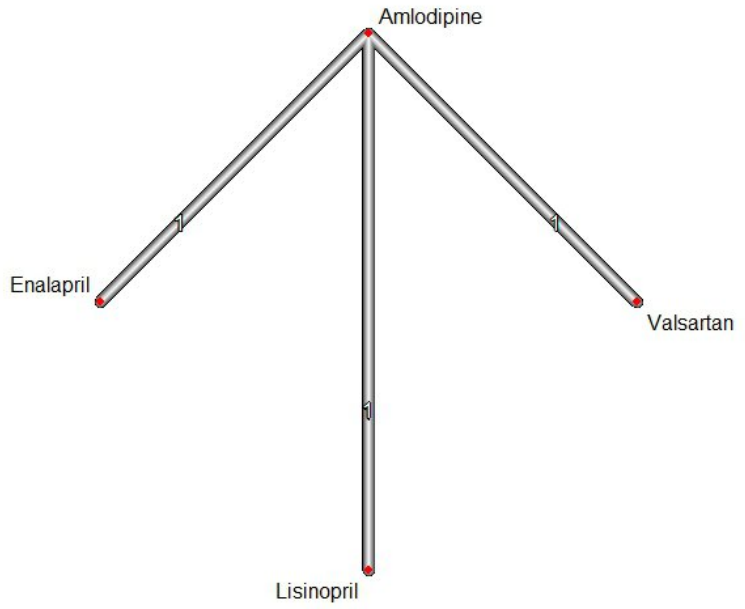

Figure 35: Net graph of Intervention and Comparator Antihypertensives in reducing incidence of hospitalization for Myocardial Infarction

The forest plot show that Enalapril increase incidence of hospitalization for myocardial infarction by 65% compared with Amlodipine with a relative risk of 1.65 and CI (1.9-2.30).

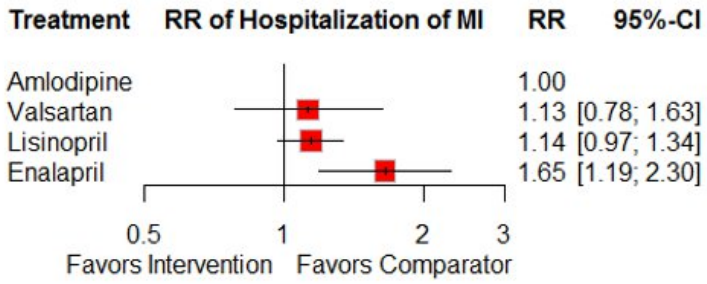

Figure 36: Forest Plot for Intervention and Comparator Antihypertensives in reducing incidence of Hospitalization for Myocardial Infarction

The rankogram generated for this analysis revealed that amlodipine was associated with the lowest incidence of hospitalization for myocardial infarction among the treatment options evaluated. The

rankogram, which visually represents the comparative occurrence of hospitalization for myocardial infarction across each drug, positioned amlodipine as the most favorable treatment in terms of minimizing hospitalization events. This finding suggests that, relative to other antihypertensive agents included in the analysis, amlodipine may offer a superior benefit in reducing the risk of hospitalization for myocardial infarction.

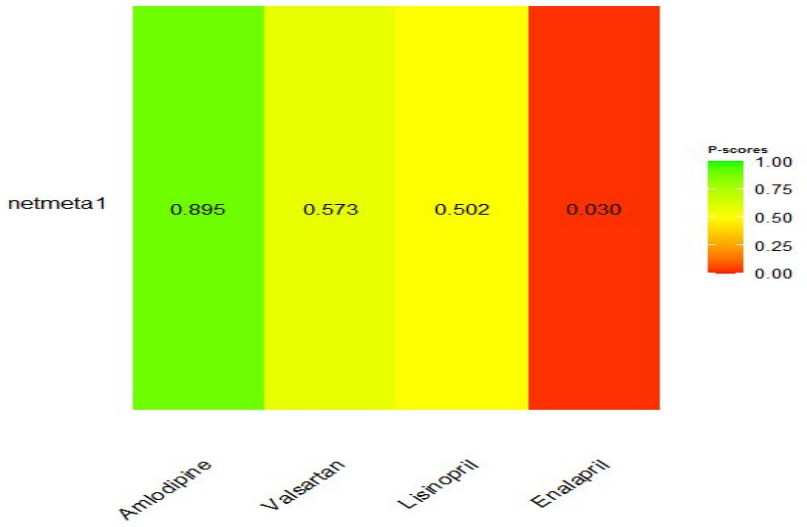

Figure 37: Net rank of Intervention and Comparator Antihypertensives in reducing incidence of Hospitalization for Myocardial Infarction

Adverse Events

In this analysis, six studies were included, comprising six pairwise comparisons across five distinct treatment groups. The primary treatments evaluated were Amlodipine, Enalapril, Losartan, and Valsartan, among others. The network diagram (Figure 38) illustrates the relationships between these treatment options, with a clear focus on comparisons involving Amlodipine, which was frequently compared with Enalapril and Losartan. This diagram provides a visual representation of the treatment landscape, indicating how the studies were interconnected in terms of the treatments being compared

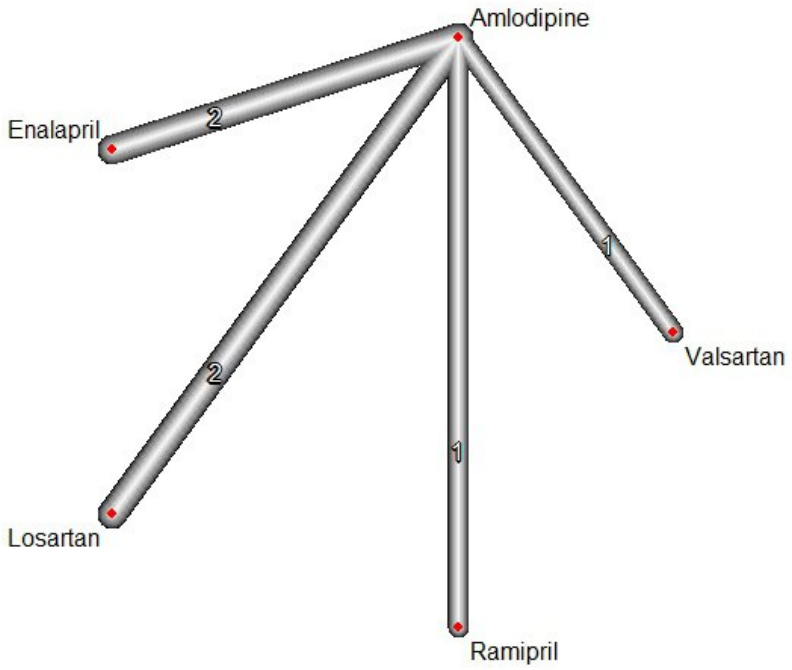

Figure 38: Net graph of Intervention and Comparator Antihypertensives in reducing incidence of adverse events

The forest plot (Figure 39) presents the findings related to the risk of developing adverse events. The analysis revealed that patients treated with Enalapril experienced a 48% lower risk of adverse events compared to those treated with Amlodipine, with a relative risk (RR) of 0.52 (95% CI: 0.44 to 0.61), which indicates a statistically significant increase in risk for Amlodipine relative to Enalapril. The p-value of 1.00, however, suggests that while the relative risk was notable, the overall comparison was not significant at conventional levels, potentially reflecting the broad confidence interval or a lack of statistical power.

Additionally, the analysis indicated that the risk of adverse events was 31% lower in patients taking Valsartan compared to those taking Amlodipine, with a relative risk of 0.69 (95% CI: 0.66 to 0.71).

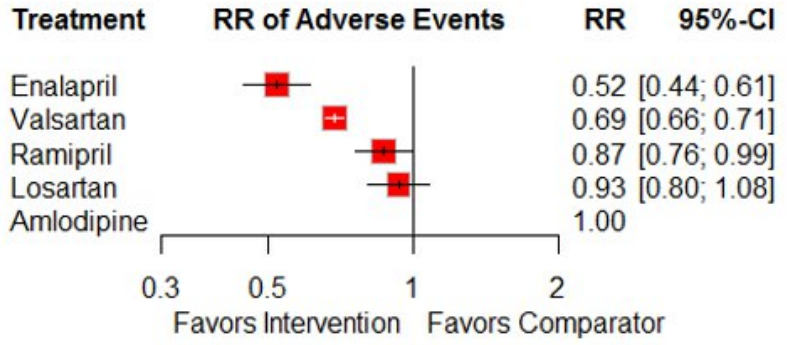

Figure 39: Forest Plot of Intervention and Comparator Antihypertensives in reducing the incidence of adverse events

Furthermore, an assessment of the overall heterogeneity across the studies was performed to examine the consistency of the treatment effects. The heterogeneity statistics indicated that the overall heterogeneity was not statistically significant, with a p-value of 0.851. The tau^2 value was 0, indicating no variance in the treatment effects, and tau was 0, reflecting no inconsistency. The I^2 value was 0%, suggesting that the variability between study results was negligible. These findings indicate a high level of consistency across the studies included in this analysis, supporting the reliability of the results derived from the pooled data. The absence of significant heterogeneity strengthens the conclusions drawn from the analysis, implying that the treatment effects across the included studies were generally uniform.

The rankogram generated for this analysis revealed that enalapril was associated with the lowest incidence of adverse events among the treatment options evaluated. The rankogram, which visually represents the comparative occurrence of adverse events across each drug, positioned enalapril as the most favorable treatment in terms of minimizing adverse events. This finding suggests that, relative to other antihypertensive agents included in the analysis, enalapril may offer a superior benefit in reducing the risk of adverse events.

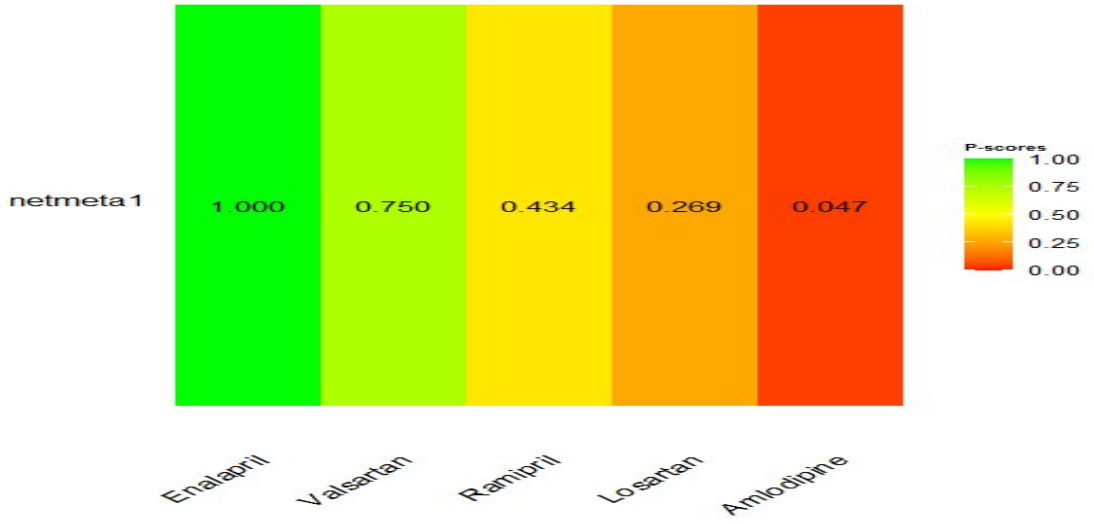

Figure 40: Net rank of Intervention and Comparator Antihypertensives in reducing incidence of adverse events

5.6 Exploration for Inconsistency

In the context of evaluating inconsistency within the network of studies, five pairwise comparisons for the outcome of systolic blood pressure were identified that contributed both direct and indirect evidence. These comparisons included data derived from both direct head-to-head studies and indirect evidence based on common comparators. Upon thorough analysis, the direct and indirect estimates of treatment effects within each of these pairwise comparisons were consistent with one another, indicating that the results from different sources of evidence (direct and indirect) did not diverge significantly.

Three pairwise comparisons were identified for the outcome of Cardiovascular death each contributing both direct and indirect evidence to the overall evaluation. These comparisons involved data from direct head-to-head trials, as well as from indirect evidence derived through common comparators. A thorough examination was conducted to determine whether any discrepancies existed between the direct and indirect estimates for these comparisons. Upon review, no evidence of inconsistency was found for any of these three pairwise comparisons. This suggests that the estimates of treatment effects from the direct and indirect sources were in agreement, and no significant divergence was observed that would suggest the presence of inconsistency in the evidence.

In the analysis of inconsistency, three pairwise comparisons were identified for the outcome of myocardial infarction, which contributed both direct and indirect evidence. These comparisons

involved data from direct head-to-head clinical trials, as well as indirect evidence derived from studies involving common treatment comparators. To assess inconsistency, the direct and indirect estimates for each of these three pairwise comparisons were carefully examined, no evidence of inconsistency was found for any of the three pairwise comparisons. This means that the direct and indirect estimates of treatment effects were in agreement, with no significant discrepancies between them.

In the evaluation of inconsistency within the network analysis, three pairwise comparisons were identified for outcome of reduction of stroke as contributing both direct and indirect evidence. These comparisons involved data from direct head-to-head trials, where treatments were directly compared, as well as from indirect evidence, which was derived by comparing treatments through common comparators. upon careful review of the data for these three pairwise comparisons, no evidence of inconsistency was found. This means that the estimates derived from the direct comparisons between treatments were in agreement with those inferred from the indirect evidence.

5.7 Sensitivity analysis

To explore the robustness of the methodology applied in the main analysis, a series of sensitivity analyses were done. This analysis aimed to restore the reliability of the randomization process. We have done the analysis by adding removed groups back into the analysis in a stepwise fashion and by removing studies classified as high risk of bias. Furthermore, to assess the influence of small-study effects on the results of our network meta-analysis, we have compared random-effects and fixed-effect estimates of the intervention effect. However, we haven't seen any change in the result of the primary outcome.

5.8 Confidence in Network Meta Analysis (CINEMA)

The results of CINEMA suggest that for most outcomes (diastolic BP reduction, cardiovascular death, heart failure, myocardial infarction, and stroke), the evidence is of high confidence, meaning the findings are likely to be reliable. However, systolic BP reduction has a mix of moderate and high confidence, and the low-confidence study should be considered when interpreting the results. Despite this, the overall conclusions are likely to be consistent and trustworthy for most outcomes. The details can be found on the following tables below.

Systolic BP Reduction

Table 2: CINEMA of Intervention and Comparator Antihypertensives in reducing Systolic BP

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Amlodipine: Candesartan	1	No concerns	Low risk	Some concerns	Some concerns	No concerns	No concerns	High
Amlodipine: Enalapril	2	No concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Moderate
Amlodipine: Lisinopril	2	No concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Moderate
Amlodipine: Losartan	5	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High
Amlodipine: Nifedipine	1	No concerns	Low risk	Some concerns	Some concerns	Some concerns	No concerns	Moderate
Amlodipine: Ramipril	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	High
Amlodipine: Telmisartan	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
Amlodipine: Valsartan	4	No concerns	Low risk	No Concerns	No concerns	Major concerns	No concerns	Moderate

Diastolic BP Reduction

Table 3: CINEMA of Intervention and Comparator Antihypertensives in reducing Diastolic BP

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Amlodipine: Candesartan	1	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High
Amlodipine: Enalapril	2	No concerns	Low risk	Some concerns	No concerns	No concerns	No concerns	High
Amlodipine: Lisinopril	3	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Amlodipine: Losartan	3	No concerns	Low risk	Some concerns	No concerns	Some concerns	No concerns	High
Amlodipine: Nifedipine	1	No concerns	Low risk	Some concerns	No concerns	No concerns	No concerns	High
Amlodipine: Ramipril	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Amlodipine: Telmisartan	1	Major concerns	Low risk	Some concerns	Some concerns	No concerns	No concerns	Low
Amlodipine: Valsartan	4	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Enalapril: Nifedipine	1	No concerns	Low risk	Some concerns	No concerns	No concerns	No concerns	High
Nifedipine: Valsartan	1	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High

Cardiovascular Death

Table 4: CINEMA of Intervention and Comparator Antihypertensives in Reducing Incidence of Cardiovascular Death

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Amlodipine: Candesartan	1	No concerns	Low risk	--	Some concerns	Some concerns	No concerns	High
Amlodipine: Enalapril	2	No concerns	Low risk	--	Some concerns	No concerns	No concerns	High
Amlodipine: Irbesartan	1	No concerns	Low risk	--	No concerns	No concerns	No concerns	High
Amlodipine: Lisinopril	3	No concerns	Low risk	--	No concerns	No concerns	No concerns	High
Amlodipine: Losartan	1	No concerns	Low risk	--	Some concerns	No concerns	No concerns	High
Amlodipine: Valsartan	2	No concerns	Low risk	--	No concerns	No concerns	No concerns	High
Enalapril: Losartan	1	No concerns	Low risk	--	Some concerns	No concerns	No concerns	High

Heart Failure

Table 5: CINEMA of Intervention and Comparator Antihypertensives in reducing incidence of Heart Failure

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Amlodipine: Candesartan	1	No concerns	Low risk	Some concerns	Some concerns	Some concerns	Some concerns	High
Amlodipine: Enalapril	1	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Amlodipine: Irbesartan	1	No concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	High
Amlodipine: Valsartan	2	No concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	High

Myocardial Infarction

Table 6: CINEMA of Intervention and Comparator Antihypertensives in reducing incidence of Myocardial Infarction

Comparison	Number of studies	Within-Study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Amlodipine: Candesartan	1	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	High
Amlodipine: Enalapril	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Amlodipine: Irbesartan	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Amlodipine: Lisinopril	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Amlodipine: Losartan	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Amlodipine: Valsartan	2	No concerns	Low risk	Some concerns	No concerns	No concerns	No concerns	High
Lisinopril: Losartan	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High

Stroke

Table 7: CINEMA of Intervention and Comparator Antihypertensives in reducing incidence of Stroke

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Amlodipine: Candesartan	1	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High
Amlodipine: Enalapril	1	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Amlodipine: Irbesartan	1	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Amlodipine: Lisinopril	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
Amlodipine: Losartan	1	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High
Amlodipine: Valsartan	3	No concerns	Low risk	Some concerns	No concerns	No concerns	No concerns	High
Enalapril: Nifedipine	1	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High
Losartan: Valsartan	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	High

Adverse Event

Table 8: CINEMA of Intervention and Comparator Antihypertensives in reducing incidence of Adverse Event

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Amlodipine: Enalapril	2	No concerns	Low risk	Some concerns	No concerns	No concerns	Some concerns	High
Amlodipine: Losartan	2	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	High
Amlodipine: Ramipril	1	No concerns	Low risk	Some concerns	No concerns	No concerns	No concerns	High
Amlodipine: Valsartan	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High

CHAPTER SIX: DISCUSSION

6.1 Summary of Findings

This study was designed to explore the cardiovascular efficacy and safety of calcium channel blockers (Amlodipine), angiotensin converting enzyme inhibitors (Enalapril, Ramipril, Lisinopril) and angiotensin receptor blockers (Valsartan, Candesartan, Irbesartan and Losartan) in adult patents with primary hypertension.

Regarding cardiovascular efficacy, systolic blood pressure reduction was assessed and Candesartan was found to reduce systolic blood pressure 2.4 times more effectively than Amlodipine. Regarding diastolic blood pressure Candesartan was associated with a 20% reduction compared to Amlodipine.

Amlodipine was associated with a 47% reduction in risk of myocardial infarction compared to Enalapril, and a 62% reduction in risk of myocardial infarction compared to Irbesartan.

The risk of heart failure was 79% lower in patients taking ARBs specifically, Valsartan and 45% lower in patients raking the ARB drug Irbesartan.

Cardiovascular safety was assessed and syncope incidence was the lowest in Calcium channel blocker, Amlodipine.

Edema was the lowest in angiotensin converting enzyme inhibitor, Enalapril and lower in angiotensin receptor blockers, Valsartan but was highest in Amlodipine.

Hospitalization rate for myocardial infarction was lowest in Valsartan and Irbesartan, both which are ARB classes.

Total adverse events were the lowest with enalapril and highest with amlodipine.

There was no significant difference between the three drug classes in the outcomes of cardiovascular death, stroke and hospitalization rate for heart failure.

6.2 Cardiovascular Efficacy

In our study, angiotensin receptor blocker specifically, candesartan was found to reduce both systolic and diastolic blood pressure more effectively than angiotensin converting enzyme inhibitors and the calcium channel blocker, amlodipine. This finding is inconsistent with several large-scale studies and meta-analyses that have shown that most antihypertensive drugs, including CCBs, ACEi's, and ARBs, have comparable efficacy in lowering blood pressure, meaning there was no significant difference between those drugs in reducing blood pressure (9,15,32). In contrast, some studies

suggested that CCBs, particularly long-acting agents like Amlodipine, may offer superior Diastolic Blood Pressure (DBP) control compared to other drug classes (26,32). This difference in Diastolic Blood Pressure (DBP) reduction could be of clinical importance, especially in populations where elevated diastolic pressure is a major concern for cardiovascular risk.
These findings suggest that the choice between these drug classes may not be driven solely by their effects on blood pressure but rather by their broader cardiovascular outcomes and safety profiles.

In terms of major cardiovascular events, this study found that the incidence of myocardial infarction (MI) was the lowest in patients treated with CCBs, Amlodipine. Previous literatures have disagreements as some suggested that ACEi's and ARBs may have a protective effect against MI due to their impact on the renin-angiotensin-aldosterone system (RAAS), while other literatures emphasizes that CCBs have protective effect against MI (3,7,25).Notably, while the result in this study were significant, they were not universally observed in all clinical trials, highlighting the need for caution when interpreting these results in isolation.
The result of the current study also showed that stroke incidence was the same in patients treated with ARBs, ACEi's and CCBs .These findings are not in consistent with some studies that established the role of calcium channel blockers in reducing the risk of stroke, especially in patients with hypertension and heart failure (7,15,32).

Regarding heart failure (HF), this study found that the incidence of heart failure was the lowest in patients treated with ARBs specifically, Irbesartan and Valsartan compared to those treated with Amlodipine. This is consistent with most of the literatures, where ARBs have been shown to improve outcomes in patients with hypertension and heart failure (5). The differences in HF outcomes among ARBs may be attributed to variations in their specific pharmacological profiles, with Valsartan and Irbesartan showing more pronounced benefits in reducing morbidity and mortality in heart failure patients.
Hospitalization rate for myocardial infarction was the highest in patients treated with ACEi's and it goes in line with previous literatures which suggested hospitalization rate for myocardial infarction was lower for CCBs but higher in ACEi's (3).

This study found that there was no significant difference in reducing hospitalization rate for heart failure as compared to metaanalysis which was done before which suggested Hospitalization rate for heart failure was higher with CCBs but lower in ARBs and ACEi's (21).

The other outcomes that this study found to have no difference between the three drug classes is cardiovascular death. This result goes in line with a literature which also suggested there was no drug class that was found to be superior regarding to reducing cardiovascular death (1).

As noted in earlier meta-analyses, ACEi's, ARBs, and CCBs all effectively reduce the risk of major cardiovascular events when compared to placebo (39). However, our findings suggest that for patients who benefit with reduction of Blood Pressure and at risk of developing heart failure, ARBS specifically, Candesartan should be the drug of choice. For patients who are at risk of developing myocardial infarction CCBs should be chosen.

6.3 Cardiovascular Safety

Safety issue was an important aspect of this analysis, and the results revealed several key differences in adverse event profiles across the drug classes. Syncope incidence was lowest in patients treated with CCBs, a finding that reflects the established safety of CCBs, especially long-acting formulation, amlodipine in terms of maintaining vascular tone and reducing the risk of sudden blood pressure drops (35,45). Conversely, Amlodipine was associated with the highest rates of edema, a known side effect of CCBs, which may be a limiting factor in their use, particularly in elderly patients.

The incidence of edema was significantly lower in patients treated with ACEi's and ARBs, particularly Valsartan. This two observations align with prior studies demonstrating that ARBs tend to have a more favorable safety profile compared to CCBs, particularly in terms of fluid retention and peripheral edema (3,29). Regarding total adverse events, ACEi's, in this study, enalapril had the lowest incidence. These findings are in line with previous research suggesting that the safety profile of ACEi's are favorable depending on patient characteristics and concurrent therapies (7,22,45). CCBs may offer a more favorable safety profile in terms of adverse events such as syncope. These differences highlight the importance of individualizing treatment plans based on the patient's clinical presentation, comorbidities, and the specific safety concerns associated with each drug classes.

6.4 Study Limitation

This network meta-analysis is limited by the relatively small number of studies and comparisons for certain outcomes further reducing statistical power. Additionally, the majority of studies had short follow-up periods, limiting long-term outcome assessments. These factors highlight the need for further research with larger, more consistent datasets.

Publication bias and subgroup analysis were not conducted due to the small number of studies available for each outcome, which limits the statistical power needed for reliable analysis.

CHAPTER SEVEN: CONCLUSION

This study evaluated the cardiovascular efficacy and safety of calcium channel blockers (Amlodipine), angiotensin converting enzyme inhibitors (Enalapril, Ramipril, Lisinopril), and angiotensin receptor blockers (Losartan, Candesartan, Irbesartan) in primary hypertensive adult patients. The findings suggest that systolic blood pressure and diastolic blood pressure reduction is highest in ARBs. The risk of major cardiovascular events such as stroke, cardiovascular death and hospitalization risk for heart failure showed no significant differences between the drug classes, but the incidence of myocardial infarction was the lowest with calcium channel blocker: amlodipine and the risk for heart failure was the lowest in ARBs. The safety profiles varied, with Amlodipine showing the lowest incidence of syncope and the highest incidence of edema, while Enalapril had the lowest total adverse events.

CHAPTER EIGHT: RECOMMENDATION

8.1 Recommendation for Clinicians

Clinicians should consider individual patient profiles when prescribing antihypertensive medications, taking into account not only the blood pressure-lowering efficacy but also the broader cardiovascular outcomes and safety profiles of each drug class. For instance, ARBs like Candesartan may offer superior blood pressure control, while CCBs like Amlodipine could be preferred for their favorable safety profile of syncope. It is essential to monitor patients for side effects, particularly edema in those on CCBs, and tailor treatment to minimize adverse events. Clinicians should also consider ARBs or ACEIs in patients with hypertension and heart failure, as they have been shown to improve cardiovascular outcomes in this population.

8.2 Recommendation for Researchers

Further research is needed to explore the inconsistencies between the studies in the efficacy of different drug classes on blood pressure and major cardiovascular events, particularly myocardial infarction (MI) and stroke. Large-scale, long-term studies are essential to validate the findings and address the gaps in understanding the comparative efficacy and safety of CCBs, ARBs, and ACEIs. Additionally, more investigation is required into the differential impact of ARBs like Valsartan and Irbesartan on heart failure outcomes and their hospitalizations rates compared to other antihypertensive drugs.

8.3 Recommendation for Policymakers

Policymakers should support the continued funding of research that examines the cardiovascular efficacy and safety profiles of antihypertensive medications in diverse populations. Given the differences in efficacy and side effects, including the significant higher rates of hospitalization for MI with ACEis, policies could encourage personalized treatment approaches based on patient risk factors and comorbidities. Guidelines should be updated to reflect the latest evidence, ensuring that healthcare providers have the most current data to inform their treatment decisions. Additionally, access to a variety of antihypertensive drugs, including ARBs, ACEi’s, and CCBs, should be ensured to allow for individualized patient care.

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ANNEXES

Appendix A: Detailed search strategy

Search set	**PUBMED**	**SCOPUS**	**EMBASE**
1.	Cardiovascular	Cardiovascular	Cardiovascular
2.	Calcium channel blocker	Calcium channel blocker	Calcium channel blocker
3.	Angiotensin receptor blocker	Angiotensin receptor blocker	Angiotensin receptor blocker
4.	Angiotensin converting enzyme inhibitor	Angiotensin converting enzyme inhibitor	Angiotesin converting enzyme inhibitor
5.	Amlodipine	Amlodipine	Amlodipine
6.	Lisinopril	Lisinopril	Lisinopril
7.	Losartan	Losartan	Losartan
8.	Enalapril	Enalapril	Enalapril
9.	Nifedipine	Nifedipine	Nifedipine
10.	safety	safety	safety
11.	Tolerability	Tolerability	Tolerability
12.	Usability	Usability	Usability

Appendix B: Characterization of the studies

Characterization of the Studies								
No.	Author, Year	Country	Sample Size (In each group)	Intervention information	Design	Inclusion Criteria	Exclusion Criteria	Outcomes
1	VALUE, 2022	Countries in Asia, Africa, Europe, North and South America	7649 in intervention group, 7596 in control group	Valsartan, 80, 160mg	RCT	age > 50, those with hypertension, high risk for cardiac events and those with cardiac disease, Men or women of Any racial background	Renal artery stenosis, pregnancy, Percutaneous transluminal patients, Severe renal failure, Acute MI	Time to first cardiac event, MI, Heart failure, Stroke, new onset of diabetes
2	AASK, 2022	USA	436 in intervention group, 217 in control group	Ramipril, 2.5-10mg or Metoprolol, 50-200mg	RCT	Age 18-70, those with hypertension, those with GFR 20-65 ml/min /1.73m2, African american men and women	Diastolic: Bp<95mmhg, Known history of DM, Secondary hypertension, Serious systemic disease	BP reduction, rate of change in GFR, ESRD or death
3	NOURI-VASKEH et al., 2020"	Iran and USA	41 in intervention group and 41 in control group	Losartan, 25mg	RCT	Age>18, those with Primary hypertension, and hospitalized for Covid 19	Pregnant and lactating patients, Severe hepatic and renal failure, bilateral renal artery stenosis	30 days mortality, length of hospital stay
4	JMICB, 2003	Japan	822 in Intervention group, 828 in control group	Enalapril 5-10mg	PROBE	Age>75 and those diagnosed with hypertension and coronary artery disease	patients with acute myocardial infarction and unstable angina	Overall incidence of cardiac event, BP Reduction Adverse events
5	Tripathi	India	58 in	Telmisartan	RCT	Age>40,	Severe cardiac	BP Reduction,

	etal, 2016		intervention group, 41 in control group			Diagnosed to be hypertensive	or cerebrovascular disease, Clinically relevant hyperkalemia, Bilateral renal artery stenosis, Single renal artery stenosis and pregnant ladies	Onset of diabetes, Total Cholesterol
6	COMPAS BPV, 2020	Korea	71 in intervention, 73 in control group	Losartan, 50mg	RCT	Age between 20 to 80, patients who did not take antihypertensive drugs, patients with BP >/= 140/90	Pregnant and lactating patients, Secondary hypertension, BP>/= 180/120, hepatic or renal impairment	Bp Variation
7	INDT, 2003	Australia, Newzeland, southeast asia, Europe, Uk, Israel, Latin america, North america	579 in intervention, 567 in control group	Irbesartan	RCT	Age between 30-70, those with T2DM, Overt nephropathy	Pregnant and lactating mothers	Cardiovascular death, CHF, Myocardial Infarction, CVA
8	AVER Study Group, 2008	Russia, Norway, France, UK, Belgium, Spain, Romania, Budapest, Slovakia	260 in intervention, 260 in control group	Enalapril, 5mg	RCT	Age between 18-80, those with hypertension	Nephrotic proteinuria, Secondary hypertension, Major Cardiovascular event with in 3 months, uncontrolled arrythmia, women of child bearing age not using contraception	BP, Adverse event, Renal event
9	Formica Jr	USA	29 in	Losartan	RCT	Patients requiring	Pregnancy, Normotensive, Clinical evidence	BP, Serum potassium,

	et al., 2006		intervention, 27 in control group			renal donor Requiring therapy for hypertension	of volume depletion	Serum creatinine and hemoglobin
10	CASE-J, 2008	Japan	2364 in intervention, 2364 in control group	Candesartan	PROBE	Age 20-84, patients with hypertension, Diabetes, history of MI, stroke or renal dysfunction	Pregnancy, Lactating mothers	BP, Cardiovascular events, Sudden death, Cerebrovascular accidents, Renal events
11	VART, 2007	Japan	399 in intervention, 398 In control group	Valsartan, 80, 160mg	PROBE	Age >30, patients with newly diagnosed hypertension	Secondary hypertension, Severe valvular or structural disease, pregnancy, active cancer, renal or hepatic dysfunction	Cardiac event, cerebrovascular event, all cause mortality, new onset of DM
12	J-Elan, 2010	Japan	29 in intervention, 28 in control group	Losartan, 50mg	PROBE	Age>/= 20, presence of hypertensin, presence of LV hypertrophy	Patients who were treated with ACEi or ARBS in the past 5 months	Stroke, Ischemic heart disease, cardiovascular mortality, all-cause mortality
13	K Asayama et al , 2012	Belgium, Netherlands and Japan	1172 In intervention, 1171 In control group	Lisinopril	PROBE	Age>/=40, with mild to moderate hypertension	Severe hypertension, isolated hypertension and Contraindication for any of the antihypertensives	Cardiovascular death, MI, Stroke
14	K Asayama et al ,	Belgium, Netherlands	1175 in	Valsartan, 80, 160mg	PROBE	Age>/=40, with	Severe hypertension,	Cardiovascular death, MI,

	2012	and Japan	intervention, 1171 in control group			mild to moderate hypertension	isolated hypertension and Contra indication for any of the antihypertensives	Stroke
15	PW de Leeuw et al , 2017	Belgium, Russia, USA, Czech, France And Netherlands	105 in intervention, 106 In control group	Losartan 50mg	RCT	Age > 65, those with hypertension,	Major cardiovascular event with in month, significant liver disease	BP, Adverse events
16	Robert etal, 2003	USA	222 in intervention, 208 In control group	Losartan	RCT	Age 45-80, those with hypertension	Secondary hypertension, Hepatic or renal disease, DM, had history of CVA or MI in the past 6 months, history of gout, pregnancy	BP, adverse event
17	Muntner et al., 2014	USA, Canada and portorico	6335 in intervention, 6554 In control group	Lisinopril	RCT	Age>/= 60, those with hypertension	Those with CHD, stroke	BP variability
18	Munakata et al., 2004	Japan	21 in intervention, 20 in control group	Valsartan, 80mg	RCT	Age 20-70, those with hypertension,	secondary hypertension, renal failure, severe hyper cholesteremia, pregnancy	Brachial pulse wave velocity, BP
19	NAGOYA HEART Study, 2012		575 in intervention, 575 in control group	Valsartan	PROBE	Age 30-75, those with hypertension and DM		MI, Stroke, heart failure

20	CAMELOT, 2004	North America and Europe	675 in intervention, 665 in control group	Enalapril, 20mg	RCT	Age 30-79, requiring coronary angiography	Left main coronary artery obstruction >50%, Ejection fraction<40%, moderate to severe congestive heart failure	Incidence of Cardiovascular event, cardiovascular death, hospitalization for Mi, Stroke or Heart failure
21	Ogihara et al , 2008	Japan	2354 in the intervention group And 2349 in the control group	Candesartan	PROBE	Age 30-75, those with hypertension and DM		sudden death, stroke or transient ischemic attack, cardiac event and renal event
22	Agabiti Rosei et al., 2005	Italy	98 In intervention, 114 in control group	Enalapril 20mg	PROBE	Age >/= 22, those with hypertension,	Grade 3 hypertension, orthostatic hypotension, history of cardiovascular or cerebrovascular events in the past 6 month	BP, Biochemical parameters like E-Selectin
23	Takano et al., 2012	Japan	305 in intervention and 316 in Control group	Valsartan	RCT	Age>/= 30, diagnosed with hypertension	Secondary hypertension, serious valvular disease or congenital heart disease, dilated or hypertrophic cardiomyopathy, Serious renal dysfunction, occurrence of stroke in the past 3 months	All cause death, Sudden death, Cardiovascular event, new onset of diabetes
24	ALLHAT,2002	USA, Canada, Puerto Rico, US	9054 in intervention,	Lisinopril 10 to 40mg	RCT	Age >/= 55, those with hypertension	History of heart failure, EF<35%	MI, all cause mortality, stroke

		Virgin Islands	9048 in control group			and at least one additional risk factor for CHD event		
25	Wright et al., 2005	USA, Canada, Puerto Rico, US Virgin Islands	3210 in intervention, 3213 in control group	Lisinopril	RCT	Age>/= 55, those with hypertension,	History of heart failure, EF<35%	MI, cardiovascular mortality, all cause mortality, stroke

Appendix C: PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	.	
ABSTRACT			
Structured summary	2		
INTRODUCTION			
Rationale	3	.	
Objectives	4		
METHODS			
Protocol and registration	5		
Eligibility criteria	6		
Information sources	7		
Search	8		
Study selection	9		
Data collection process	10		
Data items	11		
Geometry of the network	**S1**		
Risk of bias within individual studies	12		
Summary measures	13		
Planned methods of analysis	14		
Assessment of Inconsistency	**S2**		
Risk of bias across studies	15		
Additional analyses	16		
RESULTS†			
Study selection	17		
Presentation of network structure	**S3**	.	
Summary of network geometry	**S4**		
Study characteristics	18		
Risk of bias within studies	19		
Results of individual studies	20		
Synthesis of results	21		

Exploration for inconsistency	**S5**	
Risk of bias across studies	22	
Results of additional analyses	23	
DISCUSSION		
Summary of evidence	24	
Limitations	25	
Conclusions	26	
FUNDING		
Funding	27	

Appendix D: Data collection form

Study Characteristics	Eligibility criteria *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	Eligibility criteria met? Yes No Unclear	Location in text or source *(pg & ¶/fig/table/other)*
Type of study		☐ ☐ ☐	
		☐ ☐ ☐	
Participants		☐ ☐ ☐	
Types of intervention		☐ ☐ ☐	
Types of comparison		☐ ☐ ☐	
Types of outcome measures		☐ ☐ ☐	
INCLUDE ☐	EXCLUDE ☐		
Reason for exclusion			
Notes:			