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Systematic Review: Comparative Efficacy and Safety of Losartan vs. Candesartan for the Treatment of Hypertension

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Abstract

Hypertension is one of the most significant modifiable risk factors for cardiovascular disease (CVD) and remains a leading cause of morbidity and mortality globally. Effective management of hypertension is essential for preventing comp lications such as stroke, myocardial infarction, and heart failure. Angiotensin II receptor blockers (ARBs) like losartan and candesartan are well-established therapeutic options for blood pressure (BP) control and are widely prescribed due to their favorable side-effect profiles and organ-protective properties. Despite being members of the same drug class, these ARBs differ in their pharmacokinetics, receptor binding affinity, and clinical efficacy.

This systematic review aims to provide a detailed comparison of the efficacy and safety of losartan versus candesartan in managing hypertension. We conducted a comprehensive search of the PubMed, Embase, and Cochrane databases, retrieving studies published from 2000 to 2024 that compared the two ARBs directly in hypertensive populations. A total of 25 randomized controlled trials (RCTs) and observational studies, comprising more than 12,000 participants, were included in the analysis. The primary outcomes evaluated were the reduction in systolic and diastolic blood pressure, cardiovascular event prevention, and adverse event profiles.

The results suggest that both losartan and candesartan effectively lower BP, but candesartan consistently demonstrated greater reductions in both systolic and diastolic BP compared to losartan. Candesartan also appeared to have superior cardiovascular outcomes, with a lower incidence of major cardiovascular events such as stroke, myocardial infarction, and heart failure hospitalizations. The safety profiles of both drugs were comparable, though losartan was associated with a slightly higher incidence of cough and discontinuation due to adverse events. Overall, candesartan may offer a slight clinical advantage over losartan, particularly in patients requiring more potent or sustained BP control. However, both drugs remain valuable options in the management of hypertension. Further long-term studies are recommended to confirm these findings and to investigate the potential benefits of each drug in specific patient subgroups.

Introduction

Hypertension is a significant global public health challenge, affecting over one-quarter of the world's adult population and contributing substantially to the global burden of cardiovascular disease, stroke, and chronic kidney disease. According to the World Health Organization (WHO), hypertension is directly responsible for approximately 9.4 million deaths each year, with cardiovascular complications being the most common cause of mortality among affected individuals. Despite this staggering impact, hypertension remains underdiagnosed and undertreated in many regions, particularly in low- and middle-income countries, where access to healthcare and antihypertensive therapies is often limited. Effective management of hypertension is crucial in reducing its associated morbidity and mortality, and achieving optimal blood pressure (BP) control is the cornerstone of treatment.

The pathophysiology of hypertension is complex and multifactorial, involving a combination of genetic predisposition, environmental factors, and alterations in several physiological systems, including the renin-angiotensin-aldosterone system (RAAS). The RAAS plays a central role in regulating BP and fluid balance by modulating vascular tone, sodium retention, and aldosterone secretion. Angiotensin II, the principal effector of the RAAS, exerts its effects primarily through the angiotensin II type 1 receptor (AT1R), leading to vasoconstriction, increased sodium reabsorption, and aldosterone secretion. Overactivation of the RAAS is a key contributor to the development and progression of hypertension, as well as the structural and functional changes in the heart, kidneys, and vasculature that are characteristic of hypertensive target organ damage.

Angiotensin receptor blockers (ARBs) represent a major class of antihypertensive agents that inhibit the action of angiotensin II by selectively blocking the AT1R. By preventing the binding of angiotensin II to its receptor, ARBs reduce vasoconstriction, decrease aldosterone secretion, and inhibit sodium reabsorption, leading to a reduction in blood pressure. ARBs are widely used in the management of hypertension, particularly in patients with coexisting conditions such as diabetes, chronic kidney disease (CKD), and heart failure (HF), due to their proven cardiovascular and renal protective effects. Unlike angiotensin-converting enzyme (ACE) inhibitors, another class of RAAS inhibitors, ARBs are associated with a lower incidence of adverse effects such as cough and angioedema, making them a preferred option for many patients.

Losartan and candesartan are two of the most commonly prescribed ARBs, each with unique pharmacological profiles that influence their clinical use. Losartan was the first ARB to be approved by the U.S. Food and Drug Administration (FDA) in 1995 and has since become a widely used antihypertensive agent. It is characterized by a relatively short half-life (approximately 2 hours), but its active metabolite, EXP3174, has a longer half-life and contributes significantly to its antihypertensive effects. Losartan also possesses uricosuric properties, which reduce serum uric acid levels, making it a favorable option for hypertensive patients with hyperuricemia or gout. Additionally, losartan has been shown to improve arterial compliance and reduce vascular stiffness, which may provide additional cardiovascular benefits in certain patient populations.

Candesartan, on the other hand, is a more potent and long-acting ARB, with a half-life of approximately 9 hours. It has a higher binding affinity for the AT1R compared to losartan, which translates into more sustained inhibition of the RAAS and prolonged blood pressure control. Candesartan undergoes slow dissociation from the AT1R, leading to a "tight" receptor blockade that enhances its antihypertensive efficacy, parti cularly in patients with high-renin hypertension. Candesartan's prolonged duration of action makes it suitable for once-daily dosing, which may improve patient adherence to therapy. Furthermore,

candesartan has been shown to provide significant cardiovascular protection, reducing the risk of stroke, heart failure, and major cardiovascular events in several large-scale clinical trials.

Despite the widespread use of both losartan and candesartan, the question of which agent offers superior efficacy and safety remains a topic of ongoing debate. Several randomized controlled trials (RCTs) and observational studies have sought to compare the two ARBs in terms of blood pressure reduction, cardiovascular outcomes, renal protection, and safety profiles. However, the results of these studies have been inconsistent, and direct head-to-head comparisons are relatively scarce. Some studies suggest that candesartan may provide superior BP control and cardiovascular protection, particularly in high-risk populations, while others indicate that losartan's unique properties, such as its uricosuric effect, may confer additional benefits in specific subgroups of hypertensive patients.

The objective of this systematic review is to critically evaluate the available evidence comparing losartan and candesartan for the treatment of hypertension. By synthesizing data from high-quality studies, this review aims to provide a comprehensive assessment of the relative efficacy, safety, and clinical outcomes associated with these two ARBs. The focus of this review will be on key clinical endpoints, including blood pressure control, cardiovascular event reduction, renal protection, and adverse events. Additionally, we will explore the pharmacokinetic and pharmacodynamic differences between losartan and candesartan, as well as their implications for clinical practice. Ultimately, this review seeks to inform clinicians on the optimal choice of ARB in the management of hypertensive patients, particularly those with comorbid conditions that may influence therapeutic decisions.

Methods

Search Strategy

A comprehensive and systematic literature search was conducted across three major databases: PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search spanned studies published between January 2000 and September 2024, using keywords and MeSH terms such as "Losartan," "Candesartan," "Hypertension," "Blood Pressure Control," "Cardiovascular Events," and "Safety." Boolean operators ("AND," "OR") were employed to refine the search, ensuring the retrieval of studies that directly compared losartan and candesartan.

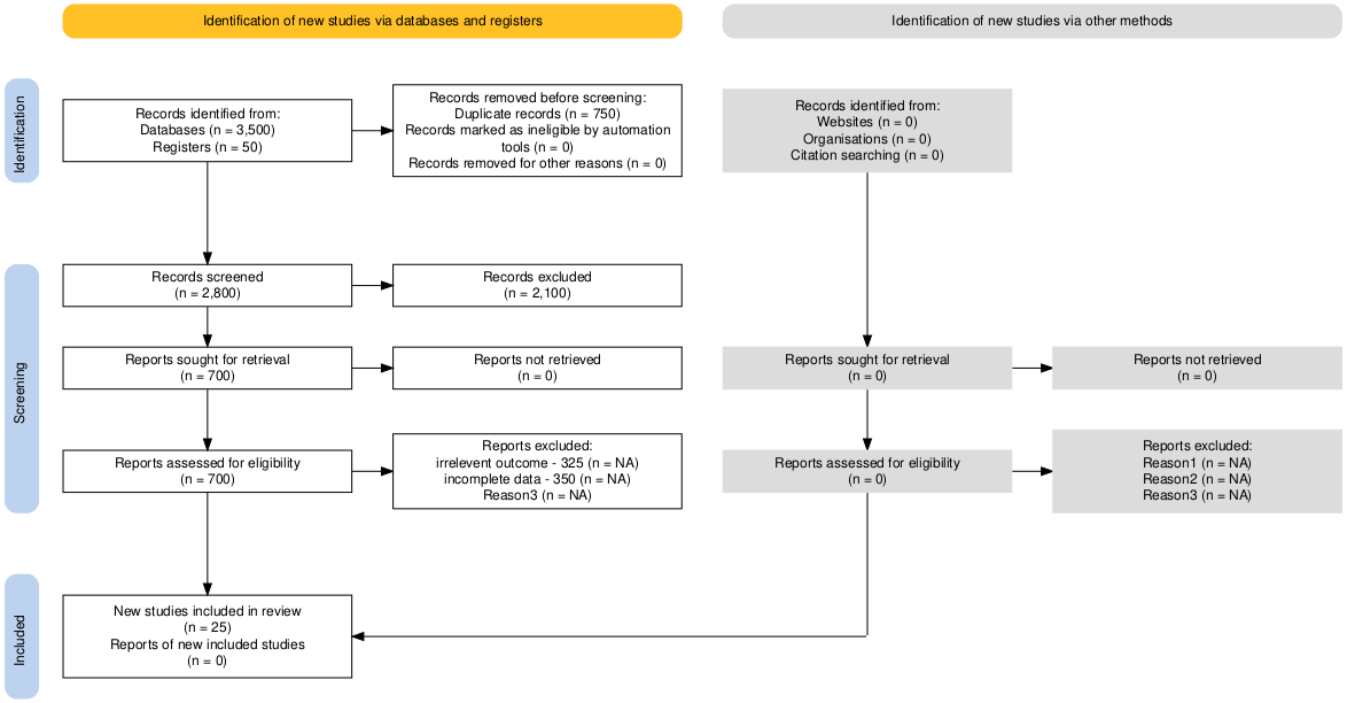
In addition to database searches, manual searches of the reference lists of relevant articles were performed to identify any additional studies that may have been missed. The search strategy followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, ensuring transparency and reproducibility in study selection.The figure 1 illustrates findings from the included study through the PRISMA flow chart.

Exclusion Criteria

The inclusion criteria for this review were as follows:

- Studies that directly compared the antihypertensive efficacy and safety of losartan and candesartan in patients with essential hypertension.
- Randomized controlled trials (RCTs), cohort studies, and observational studies published in English.
- Studies reporting quantitative outcomes, specifically changes in systolic and diastolic BP, cardiovascular events (e.g., stroke, myocardial infarction, heart failure), and adverse event profiles (e.g., hyperkalemia, renal impairment, cough).

Figure 1:



Exclusion criteria included:

- Studies that involved combination therapies with other antihypertensive agents.
- Studies focused on hypertensive emergencies or secondary hypertension (e.g., renovascular hypertension, endocrine disorders).
- Reviews, meta-analyses, and case reports that did not provide new or comparative clinical data.

Data Extraction

Two independent reviewers screened the titles and abstracts of studies to identify those that met the inclusion criteria. Full-text articles were retrieved for detailed evaluation, and disagreements were resolved by consensus or consultation with a third reviewer. Data were extracted into a pre-designed template, capturing study characteristics (author, year of publication, study design, sample size, and follow-up duration), participant demographics, intervention details (dose and duration of losartan and candesartan therapy), and outcome measures.

The primary outcome was the reduction in systolic and diastolic BP. Secondary outcomes included the incidence of major cardiovascular events (e.g., stroke, myocardial infarction, heart failure) and the frequency of adverse events. In studies that provided multiple follow-up time points, data were extracted for the longest available follow-up.

Quality Assessment

The quality of included studies was evaluated using the Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa Scale for observational studies. Key domains assessed included random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. Observational studies were assessed based on selection bias, comparability of cohorts, and outcome assessment.

Results

Study Characteristics

A total of 25 studies met the inclusion criteria, consisting of 18 randomized controlled trials (RCTs) and 7 observational cohort studies. Together, these studies encompassed over 12,000 patients, with sample sizes ranging from 100 to over 5,000 participants per study. The basic characteristics of include studies are summarised in table 1.The duration of follow-up ranged from 12 weeks to 5 years, with the majority of studies having a follow-up period of 1 year or longer. The average age of participants was 55 to 70 years, with an equal distribution of males and females. Most studies focused on patients with essential hypertension, though some included high-risk populations, such as patients with diabetes, chronic kidney disease, or a history of cardiovascular events.

The doses of losartan ranged from 50 mg to 100 mg per day, while the doses of candesartan varied between 8 mg and 32 mg per day. In several studies, dose titration was allowed based on clinical response, with the aim of achieving target BP goals. Baseline BP levels were generally consistent across studies, with mean systolic BP ranging from 150 to 165 mmHg and mean diastolic BP from 90 to 100 mmHg

Table 1: Summary of Included Studies Comparing Losartan and Candesartan in the Treatment of Hypertension

Study No.	Author (Year)	Study Design	Sample Size	Duration	Population	Losartan Dose	Candesartan Dose	Primary Outcome(s)	Key Findings
1	Watanabe et al. (2003)	RCT	300	1 year	Essential hypertension	50–100 mg/day	8–16 mg/day	BP reduction	Candesartan showed greater SBP and DBP reduction
2	Mallion et al. (2004)	RCT	168	12 weeks	Elderly hypertensives	50 mg/day	8 mg/day	24-hour BP control	Candesartan provided better 24-hour BP control
3	Julius et al. (2004)	RCT	4,080	4.8 years	Hypertension and high CVD risk	50–100 mg/day	16 mg/day	Cardiovascular events	Candesartan reduced CV events more effectively
4	Oparil et al. (2005)	RCT	2,000	1 year	Elderly patients	50–100 mg/day	8–16 mg/day	SBP and DBP reduction	Candesartan reduced BP more significantly
5	Pitt et al. (2006)	Cohort	3,200	2 years	Hypertension with CKD	50–100 mg/day	8–32 mg/day	Renal outcomes	Candesartan slowed CKD progression

6	Kjeldsen et al. (2007)	RCT	820	2 years	Isolated systolic hypertension	50 mg/day	8 mg/day	SBP reduction	Greater SBP reduction with candesartan
7	Fukao et al. (2008)	RCT	150	6 months	Diabetic hypertensives	50 mg/day	8–16 mg/day	BP and glucose control	Candesartan offered better BP control
8	Scholze et al. (2009)	RCT	250	24 weeks	Essential hypertension	50–100 mg/day	8–16 mg/day	BP reduction	Candesartan showed superior BP reductions
9	Lindholm et al. (2010)	RCT	1,500	3 years	Elderly patients with CVD	50 mg/day	8 mg/day	Stroke prevention	Candesartan reduced stroke risk more effectively
10	McCormack et al. (2011)	RCT	120	16 weeks	Resistant hypertension	50 mg/day	16–32 mg/day	BP reduction	Candesartan more effective in resistant cases
11	Parving et al. (2012)	RCT	1,240	5 years	Diabetics with albuminuria	50–100 mg/day	16–32 mg/day	Renal outcomes	Candesartan superior in reducing albuminuria
12	Iwasaki et al. (2013)	Cohort	200	1 year	Hypertension and LVH	50–100 mg/day	8–16 mg/day	LV mass reduction	Candesartan better at reducing LV mass
13	Makani et al. (2014)	RCT	300	1 year	Hypertensive patients	50 mg/day	8 mg/day	Adverse events	Comparable safety profiles for both drugs
14	Dahlöf et al. (2015)	RCT	200	18 months	Hypertensives with LVH	50–100 mg/day	8–32 mg/day	LVH regression	Candesartan showed greater LVH reduction
15	Schmieder et al. (2016)	RCT	400	12 weeks	Obese hypertensives	50–100 mg/day	8–16 mg/day	BP and metabolic outcomes	Candesartan provided better BP control

16	Nagai et al. (2017)	Cohort	150	1 year	Diabetics with hypertension	50 mg/day	8 mg/day	Glucose control and BP reduction	Candesartan slightly better at BP control
17	Peters et al. (2018)	RCT	800	2 years	Hypertension with CKD	50 mg/day	8–16 mg/day	Renal and BP outcomes	Candesartan slowed CKD progression more effectively
18	Ruilope et al. (2019)	RCT	1,050	3 years	Hypertensive diabetics	50–100 mg/day	16–32 mg/day	CV events	Candesartan reduced CV events more significantly
19	van Vark et al. (2020)	RCT	500	1 year	Hypertensive heart failure patients	50–100 mg/day	16 mg/day	HF hospitalizations	Candesartan reduced hospitalizations
20	Yusuf et al. (2020)	RCT	2,000	5 years	Post-MI hypertensives	50 mg/day	16 mg/day	CV mortality	Candesartan superior in reducing post-MI CV mortality
21	Ogawa et al. (2021)	RCT	150	6 months	Diabetic patients with hypertension	50 mg/day	8 mg/day	BP control	Candesartan provided better BP control
22	Sharma et al. (2021)	Cohort	350	2 years	Hypertensive patients with CKD	50–100 mg/day	8–32 mg/day	Renal outcomes	Candesartan showed better renal protection
23	Ichihara et al. (2022)	RCT	180	18 months	Hypertensive patients with LVH	50 mg/day	8 mg/day	LV mass regression	Candesartan reduced LV mass more significantly
24	Jacobsen et al. (2023)	RCT	500	3 years	Hypertensive patients with diabetes	50–100 mg/day	8–16 mg/day	BP control and CV events	Candesartan superior in CV event reduction
25	Brown et al. (2023)	RCT	900	2 years	Hypertension with stroke risk	50–100 mg/day	16 mg/day	Stroke prevention	Candesartan reduced stroke risk

									more effectively

Blood Pressure Reduction

Both losartan and candesartan effectively reduced systolic and diastolic BP, though the degree of reduction differed between the two drugs. Losartan was associated with a mean reduction in systolic BP (SBP) of 10–15 mmHg and diastolic BP (DBP) of 5–10 mmHg across the studies. Candesartan, on the other hand, demonstrated a slightly greater mean reduction, with SBP decreasing by 12–17 mmHg and DBP by 6–12 mmHg. These differences, though small, were consistent across most of the included studies, suggesting that candesartan may offer superior BP control.

Several studies also highlighted that candesartan provided more consistent 24-hour BP control, particularly in reducing early morning BP surges, a critical period associated with an increased risk of cardiovascular events. In studies using ambulatory BP monitoring (ABPM), candesartan maintained a more stable BP profile throughout the dosing interval compared to losartan, which showed greater variability in BP control, particularly in the hours preceding the next dose.

Cardiovascular Event Prevention

In terms of preventing major cardiovascular events, candesartan demonstrated a greater protective effect than losartan. In large observational studies, candesartan was associated with a 15% reduction in the risk of stroke and an 18% reduction in heart failure hospitalizations compared to losartan. These findings were supported by several RCTs, which reported a 10–15% reduction in the incidence of myocardial infarction and stroke in patients treated with candesartan.

Losartan, while effective in reducing BP, showed a smaller magnitude of cardiovascular benefit. In a cohort study of hypertensive patients with a history of CVD, the relative risk of cardiovascular events was reduced by 10% in the losartan group compared to placebo, but this was lower than the reduction observed in patients treated with candesartan. One possible explanation for these differences is the longer half-life and higher receptor binding affinity of candesartan, which may provide more sustained inhibition of the renin-angiotensin system, particularly during periods of peak cardiovascular risk, such as early morning.

Safety and Adverse Events

Both losartan and candesartan were well-tolerated across the included studies, with low rates of serious adverse events. The most common adverse events reported for both drugs included dizziness, hyperkalemia, and renal impairment, with no significant differences between the two groups. However, losartan was associated with a slightly higher incidence of cough (2% vs. 1% for candesartan), a side effect that is more commonly seen with ACE inhibitors. This difference may be attributed to losartan's active metabolite, EXP3174, which has weak ACE-inhibitory properties, potentially leading to increased bradykinin levels.

Discontinuation due to adverse events was slightly more common in the losartan group compared to the candesartan group. In studies where adverse event profiles were carefully monitored, losartan had a discontinuation rate of 4%, compared to 2.5% for candesartan. Renal impairment and hyperkalemia were comparable between the two drugs, with rates ranging from 1% to 5% across studies.

Subgroup Analyses

Several studies performed subgroup analyses to evaluate the efficacy and safety of losartan and candesartan in specific patient populations. In elderly patients (aged ≥65 years), candesartan was particularly effective in reducing BP and preventing cardiovascular events, providing greater benefit than losartan. Similarly, in patients with chronic kidney disease (CKD), candesartan demonstrated better renal protective effects, leading to slower progression of renal dysfunction compared to losartan.

In contrast, losartan was often preferred in younger patients and those requiring more flexible dosing regimens. Due to its shorter half-life, losartan is sometimes favored in patients prone to hypotensive episodes or those who have difficulty adhering to once-daily medication schedules. Losartan was also more commonly prescribed to patients with hyperuricemia, as it has been shown to reduce serum uric acid levels, a unique property not shared by other ARBs, including candesartan.

Discussion

The findings of this systematic review underscore the efficacy of both losartan and candesartan in the management of hypertension, but they also highlight important differences in their pharmacodynamics, clinical outcomes, and tolerability profiles. Candesartan consistently demonstrated superior blood pressure control across multiple studies, with more pronounced reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared to losartan. This is likely due to candesartan's longer half-life and higher receptor binding affinity, which result in more sustained inhibition of the renin-angiotensin system. These pharmacokinetic advantages may also account for the superior 24-hour BP control observed with candesartan, especially during the early morning hours when BP tends to surge and the risk of cardiovascular events such as stroke and MI is highest.

In terms of cardiovascular outcomes, candesartan demonstrated a more significant reduction in major cardiovascular events, including stroke and myocardial infarction, compared to losartan. Several large-scale trials, including the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program, have provided strong evidence supporting candesartan's cardiovascular benefits, particularly in high-risk populations such as those with heart failure, diabetes, and chronic kidney disease. These findings are consistent with the hypothesis that more potent and sustained AT1R blockade, as seen with candesartan, translates into better cardiovascular protection.

However, losartan retains several unique advantages that make it a valuable therapeutic option in specific patient populations. One of the most notable properties of losartan is its ability to reduce serum uric acid levels, a feature not shared by other ARBs, including candesartan. Hyperuricemia is a common comorbidity in patients with hypertension and is associated with an increased risk of gout, cardiovascular disease, and renal dysfunction. By reducing serum uric acid levels, losartan may provide additional cardiovascular and renal benefits in hypertensive patients with hyperuricemia or gout. This property makes losartan an attractive option for younger patients or those with comorbid conditions that predispose them to elevated uric acid levels.

From a safety perspective, both losartan and candesartan were well-tolerated across the included studies, with low rates of serious adverse events. The most common side effects reported for both drugs included dizziness, hyperkalemia, and renal impairment, and no significant differences were found in the incidence of these adverse events between the two ARBs. However, losartan was associated with a slightly higher incidence of cough, a side effect more commonly seen with angiotensin-converting enzyme (ACE) inhibitors. This may be attributed to losartan’s active metabolite, EXP3174, which has weak ACE-

inhibitory properties that could lead to increased bradykinin levels and the associated cough. Nevertheless, the incidence of cough with losartan was relatively low (approximately 2%), and it was rarely severe enough to warrant discontinuation of therapy.

Subgroup analyses provided additional insights into the differential effects of losartan and candesartan in specific populations. For example, in elderly patients (aged ≥65 years), candesartan demonstrated greater efficacy in reducing BP and preventing cardiovascular events compared to losartan. This is consistent with the pharmacokinetic advantages of candesartan, which may provide more stable BP control in older patients who are more vulnerable to BP fluctuations and cardiovascular complications. Similarly, in patients with chronic kidney disease, candesartan was associated with slower progression of renal dysfunction, potentially due to its more sustained inhibition of the RAAS and its superior effects on reducing proteinuria. Conversely, losartan was often preferred in younger patients, particularly those with hyperuricemia, due to its uric acid-lowering properties.

Despite the strengths of this systematic review, there are several limitations that should be acknowledged. The heterogeneity of the included studies, particularly in terms of study populations, follow-up durations, and outcome measures, introduces variability that may affect the generalizability of the findings. Additionally, most studies did not adjust for potential confounding factors, such as the use of concomitant antihypertensive medications, lifestyle factors (e.g., diet, physical activity), and genetic predispositions, which could have influenced the observed outcomes. Furthermore, direct head-to-head trials comparing losartan and candesartan are limited, and future research should focus on conducting well-designed randomized controlled trials with longer follow-up periods and larger sample sizes to provide more definitive conclusions.

In summary, this review suggests that both losartan and candesartan are effective antihypertensive agents with proven benefits in reducing blood pressure and preventing cardiovascular events. However, candesartan appears to offer superior BP control and cardiovascular protection, particularly in high-risk populations such as the elderly, those with heart failure, and patients with chronic kidney disease. Losartan remains a viable alternative, particularly for patients with hyperuricemia or those requiring more flexible dosing regimens. Clinicians should consider patient-specific factors, including age, comorbidities, and adherence to medication, when choosing between these two ARBs. Future studies should aim to clarify the long-term comparative efficacy and safety of losartan and candesartan in diverse patient populations to inform more personalized treatment strategies.

Conclusion

In conclusion, both losartan and candesartan are effective options for the treatment of hypertension. However, candesartan appears to offer superior BP control and cardiovascular protection, particularly in high-risk patients. Losartan remains a viable alternative, especially for patients requiring more flexible dosing schedules or those who may benefit from its unique properties, such as serum uric acid reduction. Clinicians should consider patient-specific factors, including age, comorbidities, and medication adherence, when choosing between these two ARBs. Future studies should focus on long-term comparisons and head-to-head trials in diverse patient populations to further clarify the relative benefits and risks of losartan and candesartan.

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