Review article

Swotting effective hypertension therapy: Ramipril versus telmisartan

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ABSTRACT

One of the most important, globally controllable risk factors for cardiovascular diseases and early mortality is hypertension. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, both of which inhibit the renin-angiotensin system, are becoming more common as initial treatments for the management of hypertension patients with which ramipril and telmisartan being the most frequently used. Telmisartan has the highest affinity for the AT1 receptor of all the ARBs.Ramipril and telmisartan both are found to provide a variety of therapeutic advantages. In this study, a detailed comparative analysis has been done between ramipril and telmisartan regarding their efficacy, safety, monotherapy as well as combination therapy outcome and measures to be taken while considering both drugs. This study focused on which one is more successful in treating hypertension individuals, while also having a superior safety profile and combining the two medications which one is linked to more side effects, additional benefits, or other important information to eliminate the hazards connected to blood pressure increase while minimizing negative effects on quality of life.

INTRODUCTION

The Cardiovascular Disease, Living, and Aging (CARLA) study found that hypertension affects 74.4 percent of the adult population [1]. For almost all forms of cardiovascular disease, including coronary artery disease, left ventricular hypertrophy, and valvular heart disease, as well as cardiac arrhythmias like atrial fibrillation, cerebral stroke, and renal failure, hypertension is the primary risk factor or one of the primary risk factors. Due to the ongoing relationship between blood pressure and cardiovascular and renal issues, the distinction between high normal blood pressure and hypertension is dependent on arbitrary cut-off values for blood pressure [2]. The prevalence of hypertension is rapidly increasing in emerging regions, where insufficient hypertension therapy and control contribute to the rising cardiovascular disease epidemic. In the modern world, high blood pressure is to blame for 50% of all ischemic heart disease cases and 2/3 of all stroke cases. Because of this, high blood pressure continues to be one of the major global public health issues and the top cause of mortality globally [3]. Anti-hypertensive drugs frequently improve heart function and decrease blood volume, and vascular stiffness [4]. Diuretics, calcium-channel blockers (CCB), angiotensin receptor antagonists (ACE-I), angiotensin-converting enzyme inhibitors (ACE-I), and angiotensin

receptor blockers (ARBs) are some of the therapeutic medication classes that are most frequently used to treat hypertension [5]. The American Diabetes Association recommends ACEIs for the treatment of HTN in patients with T2DM to protect kidney function in their guidelines for the management of cardiovascular disease in diabetic patients. In addition to lowering blood pressure in these patients, antihypertensive medications may also have additional effects on the renin-angiotensin-aldosterone system (RAAS), insulin resistance (IR), and anti-inflammation [6].

In addition, the American Society of Hypertension advises patients who have a BP reduction treatment goal of >20/10 mmHg to begin combination therapy as soon as possible. The use of a single pill that contains both an ACE inhibitor and an ARB is encouraged by the 2020 International Society of Hypertension recommendations [7]. Despite the availability of powerful, contemporary anti-hypertensive medicines, the majority of patients still have inadequate blood pressure management. Most hypertensive patients need a combination of anti-hypertensive medications to achieve therapeutic goals; recent recommendations suggest beginning treatment with two medications in patients with a systolic blood pressure >20 mm Hg and/or a diastolic blood pressure >10 mm Hg above the goals, as well

as those with a high cardiovascular risk. In addition, about 25% of patients need three anti-hypertensive medications to achieve therapeutic goals [8]. The renin-angiotensin-aldosterone system (RAAS), which is categorized as an endocrine system, is responsible for maintaining blood pressure, electrolyte, and fluid balance. Renin, angiotensinogen (AGT), angiotensin-converting enzyme (ACE), angiotensin II type 1 receptor (AT1R), and AT2R made up the RAAS genes [9].

ACE inhibitors prevent the production of angiotensin II by restricting the conversion of angiotensin I to angiotensin II. Bradykinin has important anti-proliferative and vasodilator properties, so they also prevent its breakdown. ARBs, on the other hand, block the AT 1 receptor competitively and selectively, preventing the activation of angiotensin II without altering the breakdown of bradykinin. Because of this, ARBs operate differently from ACE inhibitors [10]. In patients with atherosclerosis who have no known signs of LVSD or heart failure, ACE inhibitors lower major vascular events. As a result, ACE inhibitor use should be evaluated in all atherosclerosis patient populations [11].

Ramipril Monotherapy

ACE inhibitors are used to treat several illnesses, including myocardial infarction (MI), stable chronic heart failure, essential hypertension, and diabetic nephropathy. For ACE inhibitors, the dose-response curves are often flat. Even though the majority of ACE inhibitors are taken once daily, only the ACE inhibitors fosinopril, ramipril, and trandolapril have trough-to-peak impact ratios of greater than 50% [12]. Because ACE medications can stop angiotensin I from turning into angiotensin II, the AT1 and AT2 receptors are less active. Angiotensin II type 1 receptor play a major role in the adverse consequences of angiotensin II, including vasoconstriction and other blood pressure-raising activities, vascular hypertrophy, endothelial dysfunction, atherosclerosis, inflammation, and apoptosis. However, angiotensin II type 2 receptors mostly mediate opposing and beneficial activities, promoting differentiation, regeneration, and anti-proliferation [13].

Due to their lack of direct interactions with other RAS members and the fact that the majority of their clinical effects are brought on by the reduction in angiotensin II production, ACE inhibitors are very selective medications. The pharmacological effects of ACE inhibitors are also influenced by the stimulation of prostaglandin production caused by an increase in bradykinin levels. It lowers systemic vascular resistance and mean, diastolic, and systolic blood pressure in a variety of hypertensive conditions [14]. Both ultimately combine to block angiotensin II's effects on the body, producing beneficial outcomes such as vasodilation, a decrease in sympathetic outflow, a decrease in the production of aldosterone, and the preservation of kidney function. Both ACE inhibitors and

ARBs can cause RAAS-related side effects including hyperkalemia, hypotension, and acute renal injury. But it is thought that the usage of ACE inhibitors is related to the adverse effects of dry cough and angioedema, which are frequently noticed in clinical trials because of increased bradykinin levels [15]. It has been demonstrated that ACE inhibition reduces vascular disease indicators, such as arterial stiffness, in patients with peripheral artery disease [16]. 216 people with mild to moderate essential hypertension were given ramipril capsules (1.25, 2.5, 5, or 10 mg) or placebo capsules once daily for 12 weeks, according to Schnaper HW *et.al*, at the end of the trial, the ramipril 2.5, 5 and 10 mg treatment groups had significantly lower supine and standing diastolic and systolic blood pressures than the placebo group. At higher doses, the anti-hypertensive impact was stronger. The ramipril dosage that was still effective was 2.5 mg once daily [17]. Ramipril was also found to be a successful treatment in a 48-week study by Verho M *et.al* for those with therapy-resistant hypertension, allowing concurrent drug doses to be reduced. From week 8 through the trial's end, 82 percent of patients' ramipril dosages remained the same. Following the trial, 45% of patients received ramipril in doses of 5 mg, 33% received 10 mg, and 22% received 20 mg daily. Ramipril was added, and the dosages of concurrent therapies—particularly beta-blockers and vasodilators—were decreased. The safety was good, and there were no negative side effects [18]. Dark-skinned people are more likely to experience coughs and fatalities connected to ACE inhibitors. There is now little to no scientific rationale to use ACE inhibitors for the treatment of hypertension and other ostensibly compelling reasons given that efficacy is equal but adverse effects are less common with ARBs [19].

Telmisartan Monotherapy

Telmisartan is a well-known anti-hypertensive drug that is now utilized in therapeutic settings. Telmisartan's angiotensin receptor blocking and partial PPAR agonistic activities have been proven to provide several therapeutic benefits, including cardiovascular and anti-diabetic effects. Telmisartan is additionally said to have PPAR and PPAR agonist activity. Patients with T2DM, hypertension and other cardiovascular diseases would benefit greatly from the dual-purpose alternative drug telmisartan [20]. Telmisartan has the highest affinity for the AT1 receptor of all the ARBs [21]. The drug telmisartan is not a peptide. It is an extremely effective antagonist of the AT1 angiotensin II receptor. Telmisartan is a long-lasting AT1 receptor antagonist that is therapeutically used to treat essential hypertension. It works as a specific AT1 receptor blocker to stop angiotensin II from activating the receptors. Telmisartan offers a selective action without the severe side effects that typically result from medicines' non-specific interactions with non-target receptors. Telmisartan does not interact with other receptors involved in cardiovascular control [22]. This action is due to a combination of

factors including high lipophilicity, which allows for rapid membrane penetration to the receptor site, precise and unbreakable receptor binding, the longest plasma half-life of roughly 24 hours, and a large volume of distribution [23]. Telmisartan lowers blood pressure by specifically inhibiting angiotensin II from interacting with the AT 1 receptor found in the adrenal gland and vascular smooth muscle. Angiotensin II production is unaffected, but aldosterone secretion and angiotensin II-induced vasoconstriction are inhibited. Telmisartan has a 3000-fold greater affinity for the AT1 receptor than the AT2 receptor [24]. Even though the cytochrome P450 system does not metabolize it, telmisartan rarely interacts with other medications. The elderly can gain from this since they frequently take many drugs, which increases the danger of drug interactions. A terminal half-life of 24 hours, longer than any other ARB currently on the market, is observed in those with mild to moderate hypertension [25].

The average daily SBP and DBP were found to have significantly decreased. It was also discovered that the main group's serum adiponectin concentration had increased while the control group had decreased and that the main group's level of highly sensitive C-reactive protein had decreased when compared to the control group. When treating individuals with obesity and refractive arterial hypertension with a multi-component therapy, telmisartan might be thought of as the medicine of preference [26]. When used alone or in combination, telmisartan demonstrated more significant blood pressure management and offered all-day protection from high blood pressure, particularly during the early stages of arousal. Additionally, the inclusion of cardiovascular protection, well-tolerance, and fewer side effects, especially when combined, aids in lowering cardiovascular problems. In addition, telmisartan distributes and absorbs more quickly to the peak plasma level than other ARBs including losartan, candesartan, and valsartan [27]. In comparison to valsartan, losartan, or amlodipine, Alghamdi S.A. *et.al*, reported having a considerably reduced mean ambulatory blood pressure in the latter 4-6 hours of the dosing period. Additionally, telmisartan provides superior 48-hour protection against uncontrolled blood pressure that results in a missed dose than valsartan, which reassures patients who occasionally forget to take their medication [28].

An alternate dosage form for telmisartan tablets, telmisartan fast-dissolving tablets, was explored by Kumar *et.al*. The rate of drug release from the dosage form increased, causing an increase in the dissolution rate. Additionally, telmisartan's bioavailability has increased. The preparation process is easy, affordable, and scalable [29]. Ingino C *et.al*, evaluated the trial of efficacy and safety of telmisartan in the treatment of patients with mild to moderate essential hypertension, either alone or in combination with other drugs. Over 12 weeks, patients received

telmisartan 40–80 mg once daily. When administered as monotherapy or as an add-on therapy, telmisartan was shown to be efficient and well-tolerated; the most frequent side effects were headache and dizziness as drug-related adverse events [30]. According to Parra Carrillo JZ *et.al*, Telmisartan (80 mg) effectively controlled blood pressure over 24 hours in persons with mild to moderate hypertension who had previously failed to respond to anti-hypertensive medication [31]. Additionally, Plavnik FL *et.al* confirmed that once-daily telmisartan lowers blood pressure steadily and progressively over 24 hours in compliance with ABPM [32]. According to Littlejohn T *et.al*, telmisartan 80 mg once daily outperformed valsartan 80 mg once daily when it came to lowering diastolic blood pressure in the final six hours of the 24-hour dosage period. These outcomes may be explained by the longer plasma half-life or higher potency of telmisartan in comparison to valsartan, given that a larger dose of valsartan causes effects comparable to those of 80 mg of telmisartan [33].

Telmisartan was prescribed to individuals who had previously taken losartan, Uchida H *et.al* found that doing so significantly decreased optimal blood pressure at two months. They found that telmisartan 40 mg/day decreased MHBP and arterial wall stiffness in patients with mild to moderate hypertension, which may minimize the risk of cerebral cardiovascular mortality [34]. Even in a primary care setting, Satoh *et.al* suggested telmisartan for kidney protection [35]. One of two different groups getting anti-hypertensive therapy—was randomly assigned to patients with hypertension who needed immediate care (B.P.). Anti-hypertensive drug effectiveness in these patients was assessed at rest by Park SK *et.al*. After two hours, the decreases in SBP or DBP between the two groups did not statistically differ from one another. They discovered that patients with hypertension who were receiving anti-hypertensive medication when they were at rest had little change in their blood pressure [36]. According to a study by Liu CH *et.al*, telmisartan therapy in hypertensive T2DM patients may reduce the incidence of dementia and other IS events in an East Asian population [37].

Ramipril versus Telmisartan

Both the European Society of Cardiology and the European Society of Hypertension recommend the use of ACE inhibitors and ARBs as first-line antihypertensive drugs at the beginning of antihypertensive therapy [38-39]. According to Unger T *et.al*, ARBs should still be used as first-line antihypertensives in line with the 2020 International Society of Hypertension guidelines. It may also be appropriate to prescribe ARBs for hypertension more frequently than ACE inhibitors in light of the COVID-19 pandemic [40]. However, using combination therapy instead of high doses of monotherapy has more antihypertensive potency due to the addition of multiple mechanisms of action that block different pathways of elevated blood

pressure, as well as improved protection for the target organs and a lower risk of adverse effects [41]. The findings of this study indicate that telmisartan and ramipril combination therapy is a successful method for treating hypertension and the side effects of hypertensive illnesses [42].

Arora S *et.al* claim that ARBs were created due to their better efficacy and fewer negative effects than angiotensin-converting enzyme inhibitors [43]. According to some recommendations, persons with micro-albuminuria should take ACEI and ARBs since they reduce all-cause mortality, cardiovascular events, and CKD progression [44]. In obese hypertensive Emirati patients with type 2 DM, the use of antihypertensive medicines, particularly ACE inhibitors, and ARBs, appears to be a risk factor for the development of low DBP and diastolic hypotension [45-46].

Adults with mild to severe hypertension received either telmisartan 40 mg/80 mg or ramipril 2.5 mg/5 mg/10 mg once daily in the morning for 14 weeks. Even though the medication had few side effects, ramipril users coughed more frequently than telmisartan users. Over 24 hours, telmisartan 80 mg reduced blood pressure better than ramipril 10 mg, and both drugs were well-tolerated [47]. ARBs rather than ACE inhibitors may be prescribed for individuals who have a higher risk of acquiring ACE inhibitor-induced angioedema, such as those who have had past episodes of the condition, a history of ACE inhibitor-induced cough, or who are also taking dipeptidyl peptidase-4 inhibitors. By enabling a functional ACE enzyme, the administration of an ARB would lower the risk of angioedema in COVID-19 patients. Early identification, tracheal intubation in cases of airway compromise, and complete avoidance of re-challenge are crucial, and their usage should be avoided in high-risk people [48-50].

According to a study by Ansari *et.al*, telmisartan and ramipril influenced the controlling blood pressure. Telmisartan has a statistically significant impact on halting the progression of stage 1 hypertension patients with prediabetes to diabetes mellitus when compared to ramipril. Telmisartan, compared to ramipril, more effectively reduced the progression of fasting blood sugar and glycosylated hemoglobin in stage 1 hypertension patients with prediabetes [51]. In all four dipping groups, telmisartan outperformed ramipril in terms of SBP reduction and smoothness index, according to Gosse P *et.al*, Additionally, those receiving telmisartan rather than ramipril experienced substantially more frequent drops. In more persons than ramipril, telmisartan has been seen to stabilize the circadian blood pressure pattern to a dipper profile. Additionally, it has been observed to lessen high-risk individuals' early-morning SBP spike, suggesting a possible advantage [52]. Yusuf S *et.al,* performed randomized testing on 8576 participants, giving them daily doses of

10 mg of ramipril, 80 mg of telmisartan, or 8502 daily dosages of both medications (combination therapy). In comparison to the ramipril group, the mean blood pressure was lower in the telmisartan and combination therapy groups. In comparison to the ramipril group, the telmisartan group displayed higher rates of hypotensive symptoms, lower rates of cough and angioedema, and a similar rate of syncope. In patients with vascular disease or high-risk diabetes, telmisartan was equivalent to ramipril and was linked to decreased angioedema. Combining the two medications were linked to higher side effects but no additional benefits [53]. In high-risk patients, ACEI ramipril and ARB telmisartan are equally effective at preventing CV events, but when taken simultaneously, the two drugs had higher side effects than when taken separately, according to Mann *et.al*, when dual blocking may be necessary and angiotensin escape mechanisms are expressed in severe HF, the study does not entirely refute the use of the ACEI + ARB combination [54]. Over 12 weeks, Formosa V *et.al* evaluated the effects of telmisartan and ramipril on 60 hypertension individuals over the age of 65. In the final 4-6 hours between the first and second doses of the medication, when cardiovascular and cerebrovascular events are more frequent, telmisartan use leads to a greater drop in blood pressure (between 6.00 and 10.00 a.m.). In the final 4-6 hours after medication delivery, telmisartan provided better blood pressure control than ramipril [55]. Ramipril decreased the estimated glomerular filtration rate when compared to telmisartan or combination treatment, according to Mann JF *et. al,* With telmisartan or combination therapy, urinary albumin excretion increased more gradually than with ramipril.

Telmisartan and Ramipril have equal effects on significant renal outcomes in patients with high vascular risk. Combination therapy generally has a major impact on renal outcomes, but monotherapy lowers proteinuria more than it does [56]. In Pediatr Nephrol, Stotter*et. al* highlighted the clear advantages of using ACE and ARBs to treat hypertension, proteinuria, and the progression of CKD in both adults and children who have both diabetic and non-diabetic kidney problems. This emphasizes the significant part local RAAS activation plays in the pathophysiology of CKD, including inflammation, the generation of reactive oxygen species, cellular proliferation, and fibrosis [57]. The Renoprotective effects of these medications are independent of their capacity to lower blood pressure and proteinuria. According to a comprehensive study by Ruijun Chen et al., ARBs do not significantly outperform ACE inhibitors in terms of long-term cardiovascular outcomes. Additionally, they have a higher safety record.

The evidence that is now available demonstrates that ARBs are more successful in treating hypertension individuals than ACEi while also having a superior safety profile. both as monotherapies and

in conjunction with other pharmacological classes, ACEi, and ARBs are equally recommended as first-line treatments under current US and European guidelines. For nine weeks, 96 patients with type 2 diabetes, hypertension, a glomerular filtration rate greater than 80 ml/min, and normal- or microalbuminuria received telmisartan or ramipril at doses of 40/80 mg or 5/10 mg once daily. This medication may have aided in the maintenance of cardiovascular and renal function. It was found that in patients with type 2 diabetes, telmisartan, and ramipril both markedly increased the lack of activity of the renal endothelium [58]. Both ACEIs and ARBs exhibit equal antihypertensive activity, according to Omboni S *et.al*, but ARBs have a lower incidence of side effects and promote better adherence to therapy. For certain patient populations, such as the elderly, diabetics, and those with metabolic syndrome, the recent expansion of clinical practice for ARBs presents considerable therapeutic potential, either alone or in combination. The higher BP stability that was attained in these individuals with ARBs throughout a full 24-hour period may have a significant impact on the prevention of stroke and cardiovascular events [59]. ARBs were found to have slightly reduced rates of negative clinical cardiovascular outcomes in older MI patients compared to ACEIs, despite prior worries about them. There may be a sex difference in effectiveness that accounts for the observed disparity in clinical results.

Bhardwaj RK *et.al* found that ramipril and telmisartan work equally well together to reduce blood pressure and improve quality of life in diabetic hypertensive individuals. However, telmisartan is better tolerated than ramipril and RT therapy and has fewer side effects (no dry cough). As a result, diabetic patients should choose ramipril or telmisartan to treat their hypertension. According to a study by Valeria *et.al*, ARBs may be better tolerated by patients than ACE inhibitors by themselves. Although the results of this experiment and similar trials are still preliminary, the data demonstrate that patients with albuminuria, diabetes, or other cardiovascular risk factors who receive ACE inhibitors or ARBs as dual or monotherapy do not experience any changes in mortality or renal outcomes [60].

CONCLUSION

Discussing the availability of various drugs for the treatment of hypertension which has been creating alarming scenarios across the globe, ACE inhibitors and ARBs are considered first-line agents for antihypertensive therapy. Utilizing ACE and ARBs to treat hypertension, proteinuria, and chronic kidney disease has benefits (CKD). Inflammation, the production of reactive oxygen species, cellular proliferation, and fibrosis are only a few of the pathophysiology of CKD that is significantly influenced by local RAAS activation. The protective effects of these medications on Reno occur independently of their ability to lower blood pressure and

proteinuria.

Telmisartan has been observed to stabilize the circadian blood pressure pattern to a dipper profile in a higher proportion of people than ramipril. It has also been seen to reduce the early-morning SBP surge in high-risk people, suggesting a potential benefit. The mean blood pressure was lower in the telmisartan and combination therapy groups compared to the ramipril group. The telmisartan group had higher rates of hypotensive symptoms and lower rates of cough and angioedema as compared to the ramipril group.

When compared to ramipril, telmisartan significantly reduced the likelihood that stage 1 hypertension individuals with prediabetes will develop diabetes mellitus. In stage 1 hypertension individuals with prediabetes, telmisartan better controlled the progression of fasting blood sugar and glycosylated hemoglobin than ramipril. With telmisartan or combination therapy, urinary albumin excretion increased more gradually than with ramipril. Telmisartan has been demonstrated to have a similar impact to Ramipril on significant renal outcomes in patients with high vascular risk. Similarly, compared to telmisartan or combination therapy, ramipril lowered the estimated glomerular filtration rate. While combination therapy reduces proteinuria more than monotherapy does, it generally has a significant impact on renal outcomes.

Hence, recommendation and utilization of the above-analyzed antihypertensive drugs should be done based on the health status and conditions of the patients, moreover, focusing on the risk and benefit ratio.

Future study:

As a result of our findings, there are various knowledge gaps regarding public involvement in research that merit additional investigation, including combination therapy with ramipril and telmisartan and the impact of blood pressure on both adults and elderly patients. The reduction of risk may be investigated through more studies of both positive and negative impacts, economic impact, and side effects. Long-term prospective trials and observational research are required to confirm these findings.

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