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| RESEARCH ARTICLE

Novel Diabetic Nephropathy-Based Hypertension Treatment for Type-2 Diabetes Mellitus and CKD Patients: A Mini Review

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| ABSTRACT
Diabetes mellitus is known to result in persistent renal impairment among individuals with the condition and is presently the primary aetiology of terminal-stage renal disease, with more than fifty percent of dialysis patients being affected. The prevalence of diabetes continues to rise, resulting in a decline in individuals' health status and imposing significant financial burdens on healthcare systems. Accurately distinguishing between the various types of diabetes is crucial in order to provide appropriate treatment that mitigates the severity of associated complications and their significant consequences. The co-occurrence of diabetes and renal disease has been found to be linked with a significant fourfold rise in both the frequency and fatality of cardiovascular disease. Pharmacological interventions aimed at reducing blood pressure have been a crucial component in the management of diabetic nephropathy for several decades. The past decade has witnessed a decline in the occurrence of end-stage renal disease, owing to enhanced care measures such as the administration of hypertension medication. It is assumed in clinical practice recommendations that angiotensin-converting enzyme inhibitors and angiotensin-receptor antagonists hold an equivalent status. The efficacy of low doses of ACEI and ARB in reducing proteinuria was found to be superior to that of high doses. The co-administration of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) has been observed to elicit a more pronounced reduction in 24-hour proteinuria and urinary albumin excretion rate (UAER) in comparison to the singular administration of either ACEI or ARB.

| KEYWORDS

ACEI; ARB; Combined Treatment; Diabetic; Chronic Kidney Disease

| ARTICLE INFORMATION

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1. Introduction

The prevalence of diabetes, which currently affects 3-4% of the global population and is projected to rise in the first 30 years of the 21st century, is alarming. Twenty-five to forty percent of diabetes patients develop chronic kidney impairment within twenty-five years after diagnosis (Du et al., 2022), and diabetes is currently the primary cause of end-stage kidney disease, accounting for approximately half of all dialysis patients (Bangalore et al., 2016). Huang et al. (2017) found that diabetes and kidney disease are linked to a fourfold rise in cardiovascular disease and death. For decades, lowering blood pressure with drugs has been essential to treating diabetic kidney disease. Better care, including antihypertensive drugs, is thought to be one reason why the number of people with end-stage renal disease has decreased in the last ten years (Abuissa et al., 2005).

In clinical practice guidelines (Huang et al., 2017), it is assumed that angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) are the same thing. Additionally, concurrent use of these two agents is not advised, partially because concurrent salt restriction or combination therapy with other medications is similarly efficacious and probably safer (Andraws & Brown, 2007). Concerns regarding the dangers of acute kidney injury and hyperkalaemia with combined ACE inhibitor

and ARB medication led to the premature termination of the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study in individuals with diabetes and proteinuria, with no effect on clinical outcomes (Du et al., 2022).

Furthermore, it was suggested in the ongoing Telmisartan alone and in conjunction with Ramipril Global Endpoint Trial (ONTARGET) that the small number of patients with chronic renal disease for whom dual treatment may be selectively successful (Bangalore et al., 2016) could be a reason why the dual treatment did not seem to help (Bangalore et al., 2016). (Du et al., 2022) did not look at ACE inhibitors and ARB therapy in combination to treat high blood pressure in people with diabetes.

2. Findings and Discussion

2.1 Diabetic Nephropathy

Type 2 diabetes is the cause of diabetic nephropathy (DN), a kidney condition. Diabetes is one of the most prevalent underlying causes of end-stage renal disease (ESRD). It has one of the most severe microvascular consequences in diabetic individuals (ESRD) (Abuissa et al., 2005). 1 Continuous albuminuria, elevated blood pressure, and increasing renal impairment are the significant symptoms of DN (Huang et al., 2017). Studies have demonstrated that RAAS blockers can manage blood pressure, decrease proteinuria, limit renal fibrosis, and postpone the rogresssion of DN. Direct renin inhibitors, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin II receptor blockers are the most common RAAS inhibitors (ARB) (Bangalore et al., 2016). ACEI and ARB work at different parts of the RAAS. ACEI blocks the conversion of Ang I to Ang II by blocking the angiotensin-converting enzyme. ARB blocks Ang II from binding to its type 1 receptor (AT1), which lowers the biological activity of Ang II (Du et al., 2022). Previous research has indicated that the administration of ACEI or ARB in isolation may not be adequate for the preservation of renal function in the long run among individuals with advanced diabetic nephropathy. In 2012, the Kidney Disease Outcomes Quality Initiative made a determination that individuals with diabetes who exhibit normal blood pressure and microalbuminuria, as indicated by a urine albumin/creatinine ratio of 30-300 mg/g, are eligible for treatment with ACEI or ARB medications (Elliott & Meyer, 2007; Huang et al., 2017).

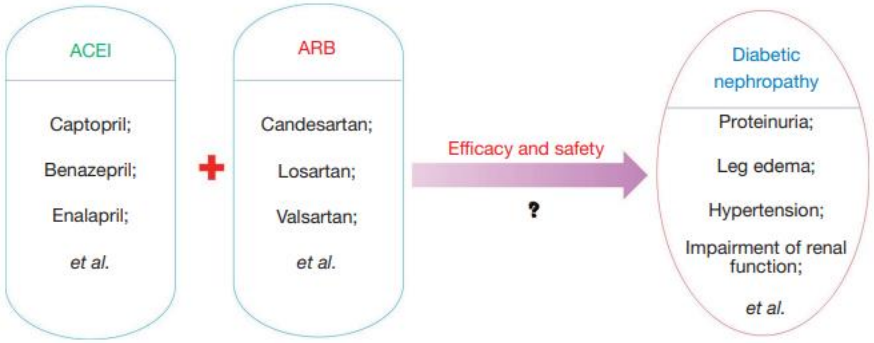

Figure 1. The efficacy and tolerability of ACEIs and ARBs in patients with diabetic nephropathy. Angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs).

ACEI and ARB are commonly used to treat DN. The pathophysiology of dual RAAS blockage is based on various mechanisms that inhibit angiotensin II and aldosterone (Du et al., 2022). Blocking the RAAS can reduce blood flow to the kidneys, slow mesangial cell growth, speed up extracellular matrix production and worsen glomerulosclerosis (Bangalore et al., 2016). Since other enzymes, like chymase, can make angiotensin II without ACE, monotherapy with ACEI or ARB only partially blocks the RAAS. The administration of ACE inhibitors results in an increase in the duration of action of bradykinin, a potent vasodilator with renoprotective effects. Conversely, the use of ARBs does not exhibit this effect on bradykinin's half-life. Consequently, the employment of a combined treatment approach may yield greater efficacy in addressing the renin-angiotensin-aldosterone system (RAAS) compared to monotherapy. The efficacy of a treatment is determined by critical indicators such as UTP, UAER, serum creatinine, GFR, and ESRD. However, it has been documented in the literature that the administration of combination treatment results in the occurrence of hyperkalemia and hypotension (Andraws & Brown, 2007).

The concomitant administration of ACEI and ARB resulted in a more pronounced reduction of proteinuria with low doses compared to high doses. The available data indicates that the employment of combination therapy can lead to a more substantial reduction in proteinuria over an extended period (Abuissa et al., 2005). The combination of ACEI and ARB reduces 24-hour proteinuria and UAER more effectively than either ACEI or ARB alone (Du et al., 2022). Combining low doses of ACEI and ARB is more effective at lowering proteinuria, but it does not help treat ESRD in people with severe DN. Also, combination medication raises the risk of adverse reactions (such as hyperkalaemia and AKI), particularly in patients with severe DN. Hypotension is common in those with mild DN undergoing combination treatment (Bangalore et al., 2016). Our research shows that small doses of ACEI and ARB can be

used to treat people with diabetes and proteinuria. However, people with diabetes with impaired kidney function, especially those with severe renal failure, should be careful when taking ACEI and ARB together.

2.2 *RAAS for Chronic Kidney Disease*

The most efficacious methods for preventing end-stage renal disease were identified as the use of endothelin inhibitors, ACE inhibitors, and ARB medications, either in isolation or in conjunction. Nevertheless, solely an angiotensin receptor blocker (ARB), either alone or in conjunction with an angiotensin-converting enzyme (ACE) inhibitor, exhibited a statistically significant improvement compared to a placebo (Du et al., 2022). Point estimates demonstrated clinically significant effects on potassium and renal function when combined with an ACE inhibitor and an ARB. However, Abuissa et al. (2005) found that the risks of drug-induced acute kidney damage and hyperkalaemia were the same for all medications. (Huang et al., 2017) found that lowering blood pressure did not significantly affect myocardial infarction, stroke, or cardiovascular death. The effects on blood pressure did not change depending on the treatment plan, which supports the idea that pharmacological effects are unrelated to lowering blood pressure (Andraws & Brown, 2007).

Even though ARB monotherapy and the possible benefits of ACE inhibitor treatment were looked into, the usual meta-analytical tools made it hard to tell if these medicines or their combinations had different effects compared to each other (Bangalore et al., 2016). Contemporary global guidelines for the management of blood pressure in cases of chronic renal disease suggest that both ACE inhibitors and ARBs exhibit comparable efficacy in averting renal failure. The finding of a network meta-analysis indicates that the effectiveness of these medications, whether used alone or in combination, has not been established for mortality, end-stage renal disease, or negative treatment outcomes (Du et al., 2022).

If blood pressure goals are unmet after one month of treatment, the JNC recommends adding a diuretic or calcium-channel blocker to an ACE inhibitor or ARB. However, insufficient evidence supports this approach in people with diabetic renal disease (Du et al., 2022). In our study, taking an ACE inhibitor or ARB drug with a calcium-channel blocker made albuminuria disappear without worsening acute kidney damage. However, Abuissa et al. (2005) The limited number of trials conducted did not provide sufficient evidence to ascertain the impact of drug combinations on end-stage kidney disease. The administration of dual therapy involving ACE inhibitors and calcium-channel blockers was found to have a high SUCRA score based on various endpoints, including mortality, surrogate renal outcomes, acute kidney damage, and blood pressure control (Cheng et al., 2012).

In most guidelines for managing people with renal disease, ACE inhibitors and ARBs are recommended interchangeably. The different effects of ACE inhibitors and ARBs on the RAS pathway may help to explain this disparity (Du et al., 2022). The inhibition of bradykinin breakdown through the use of ACE inhibitors (as opposed to ARBs) has been shown to enhance endothelial function. In contrast, Angiotensin Receptor Blockers (ARBs) function by selectively inhibiting the angiotensin II type 1 (AT1) receptor. The absence of opposition to AT2 activity may result in heightened vascular growth, inflammation, and scarring. Prior studies have indicated that angiotensin receptor blockers (ARBs) confer a comparatively reduced advantage in terms of cardiovascular or renal endpoints. Studies have demonstrated that ACE inhibitors exhibit a BP-independent mechanism in reducing the risk of coronary heart disease among individuals with hypertension or cardiovascular disease.

In contrast, ARBs have not shown a similar impact. A meta-analysis of 20 studies (158,998 patients) found that ACE inhibitors lower mortality risk in hypertensive patients, but ARBs do not (Bangalore et al., 2016). In populations with type 2 diabetes, network meta-analysis suggests that ACE inhibitors outperform ARBs regarding renoprotection. In the current analysis, we also discovered that ACE inhibitors were the most likely to reduce the risk of cardiovascular and all-cause death in people with CKD (Cheng et al., 2012).

2.3 RAAS in diabetics

Diabetes mellitus is related to an elevated risk of hypertension, and the combination of diabetes and hypertension is associated with an exponential rise in cardiovascular, cerebrovascular, and renal events (Andraws & Brown, 2007). Past studies have shown that lowering blood pressure in such individuals significantly reduces cardiovascular events, stressing the importance of proactive hypertension care. Nevertheless, whether one class of antihypertensive drugs is preferable to another is debatable (Bangalore et al., 2016). Early trials of RAS blockade in people with diabetes and microalbuminuria showed that it was more "renoprotective" than a placebo, mainly by slowing the progression to clinical proteinuria (Du et al., 2022). Consequently, a prescription of RAS blockers ensued for the treatment of this particular ailment. Subsequently, this directive was expanded to encompass all individuals diagnosed with diabetes. Small-scale comparative studies have evaluated the efficacy of RAS blockers (specifically fosinopril) and calcium channel blockers (specifically amlodipine) in reducing cardiovascular events. One such study, the fosinopril versus amlodipine cardiovascular events randomized trial, involved 380 participants and demonstrated a statistically significant decrease in cardiovascular events. The study's secondary endpoint was the combined outcome of myocardial infarction, stroke, or hospitalization for angina (Abuissa et al., 2005).

The RAS is a hormonal system that controls blood pressure by affecting the tone of the blood vessels and the release of aldosterone. The hemodynamic effects of systemic RAS inhibition may help control blood sugar by stopping angiotensin II from making skeletal muscle or pancreatic islet cells get less blood flow (Pai et al., 2016). This action would result in greater pancreatic insulin secretion and better glucose and insulin transport to the periphery (Andraws & Brown, 2007). Along with improving the way the heart works, RAS inhibition may also improve insulin sensitivity by blocking the direct inhibitory effects of angiotensin II on insulin signalling and glucose transport (Bangalore et al., 2016). The RAS also works at the tissue level in numerous organs, including the pancreas. Angiotensin I and II receptors and prorenin genes are expressed in pancreatic cells (Huang et al., 2017). Advanced glycation end products, hyperlipidaemia, obesity, inflammation, and hypertension are all factors that may promote RAS activation in the pancreas (Du et al., 2022). The activation of the RAS within the pancreas by these or other pathways might cause the onset and development of islet-cell destruction in diabetes (Abuissa et al., 2005). In animal models of DM, RAS inhibition is linked to a decrease in islet fibrosis and an increase in the number of beta cells. This could be because oxidative stress, apoptosis, and profibrotic pathways are slowed down (Elliott & Meyer, 2007).

We discovered that the ACEI-CCB combination treatment of captopril and diltiazem was the most effective strategy for lowering albuminuria, regardless of blood pressure (Huang et al., 2017). However, trandolapril and candesartan ACEI-ARB combination therapy was the most effective intervention for reducing albuminuria in normotensive patients. In contrast, fosinopril and amlodipine ACEI-CCB combination therapy was the most effective intervention for reducing albuminuria in hypertensive patients (Bangalore et al., 2016). The ACEI-ARB combination therapy of trandolapril and candesartan seems to be the best way to reduce albuminuria in normotensive adult diabetic patients with microalbuminuria. In contrast, the ACEI and CCB combination therapy of fosinopril and amlodipine seems to be the best way to reduce albuminuria in hypertensive adult diabetic patients with microalbuminuria (Cheng et al., 2012). ACEI and ARB medications are commonly utilized in therapy. Clinical investigations have proven that these two medications successfully lower urine protein excretion and blood pressure levels (Huang et al., 2017) and have an excellent safety profile (Andraws & Brown, 2007).

The combination of an ACEI and an ARB agent was well tolerated. The use of combination therapy was not observed to be linked with an increased risk of hyperkalaemia-related side effects. Our investigation focuses on the safety of ACEI and ARBs (Cheng et al., 2012). However, it should be highlighted that reports of adverse events were rare or non-existent in most studies. It is unclear if this was due to a lack of incidents or a failure to document them adequately. Systolic and diastolic blood pressure may have an impact (Abuissa et al., 2005). ACEI and ARB treatments can lower systolic and diastolic blood pressure. The BP-lowering impact may have contributed to reducing proteinuria and preserving renal function (Elliott & Meyer, 2007; Pai et al., 2016). These findings demonstrate that it is difficult to determine whether direct or BP-mediated mechanisms are responsible for the antiproteinuric response to RAS inhibition (Andraws & Brown, 2007). Nevertheless, there is no significant difference in MPA decrease between the ACEI and ARB combo treatment and the control group. This finding indicates that systolic and diastolic blood pressure do not affect ACEI and ARB antiproteinuric responses or renal function protection (Huang et al., 2017).

3. Conclusions

In summary, this study sought to examine the impact of ACEIs and ARBs on patients with both DM and CKD. Throughout our investigation, we have successfully reiterated the primary objectives of our study, emphasizing the exploration of combined medication effects. Our findings illuminate significant improvements, indicating that patients utilizing both ACEIs and ARBs concurrently experienced enhanced kidney function, reduced 24-hour urine protein levels, and decreased systolic and diastolic blood pressure when contrasted with those using either medication in isolation. In terms of contributions to the existing literature, our study offers a dual contribution. Primarily, it sheds light on the potential advantages of combining ACEIs and ARBs in the management of individuals with DM and CKD, revealing the multifaceted benefits of this combined therapeutic approach. Additionally, our empirical evidence supports the notion that utilizing both medications in tandem can positively influence crucial renal and cardiovascular parameters, thereby enriching the ongoing discourse on optimal treatment strategies for this specific patient group. It is important, however, to acknowledge the limitations inherent in our study design. The retrospective nature of our data and potential confounding factors may have influenced our observed outcomes. Furthermore, the study's scope was confined to short-term effects, warranting future investigation into the long-term implications of combined ACEI and ARB therapy. In conclusion, our study underscores the potential benefits of simultaneous ACEI and ARB usage for patients with DM and CKD, as evidenced by improvements in kidney function and blood pressure profiles. By addressing the study's objectives, findings, contributions, limitations, and future research directions, we aim to inspire further exploration in this field, ultimately enhancing the care and well-being of individuals navigating the complexities of these medical conditions.

4. Suggestions for Future Researches:

In terms of future research, several promising paths present themselves. Firstly, the implementation of prospective, randomized controlled trials could furnish more robust evidence regarding the advantages and potential risks of utilizing ACEIs and ARBs in tandem for patients with DM and CKD. Secondly, delving into the molecular mechanisms underlying the observed improvements

could provide deeper insights into the biological underpinnings of these effects. Lastly, the examination of diverse dosage regimens and patient-specific variables could facilitate tailored treatment strategies for optimal outcomes.

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