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The Function of Angiotensin-Converting Enzyme Inhibitors in Chronic kidney disease: Pathophysiological Mechanisms and Implications for Practice

Said Salim Said [1], Burhani Simai [1,] Sabra Salim Rashid [1], Ahmad Makame Mwadini[1], Ussi Hamza Ussi[2]

[1)] Zanzibar Food and Drug Agency, P.O. BOX 3595 Zanzibar, Tanzania

[2)] School of Health & Medical Sciences, The State University of Zanzibar, Zanzibar, Tanzania

S/n	Name	ORCID Number	Email Address
1.	Said Salim Said	0009-0009-8055-8744	saidalriyamy67@gmail.com
2.	Sabra Salim Rashid	0009-0001-5331-0753	sunda015@gmail.com
3.	Ahmad Makame Mwadini	0009-0001-1373-2329	ahmadmakame9@gmail.com
4.	Burhani Simai	0009-0009-3489-5782	bsimai@yahoo.com
5.	Ussi Hamza Ussi	0009-0007-2089-8160	ussihamza92@gmail.com

Corresponding Author:

Said Salim Said

Zanzibar Food and Drug Agency

Trials And Vigilance Division

P.O. BOX 3595 Zanzibar, Tanzania

Email; saidalriyamy67@gmail.com

Abstract

Chronic kidney disease is defined as a progressive deterioration in the functioning of the kidneys, and its progression is affected by many pathophysiological mechanisms. This disease still has a considerable effect on the health care system, especially concerning its relationship to cardiovascular disease. The progressive deterioration in the functioning of the kidneys is affected by complex mechanisms in the renin-angiotensin system and the inflammatory response, leading to permanent damage to the nephron. It has been found that angiotensin-converting enzyme inhibitors play an integral part in the management of chronic kidney disease. This is because, in addition to managing blood pressure, they produce renoprotective effects at the molecular level. In addition to giving a comprehensive overview, there is an in-depth discussion concerning the mechanistic basis for the therapeutic effects of ACE inhibitors, especially concerning the effect on the renin-angiotensin-aldosterone system, the effect in reducing intraglomerular pressure, proteinuria, and anti-inflammatory effects. The long-term effects of ACE inhibitors are also discussed, especially concerning the results from clinical studies concerning delayed progression to end-stage renal failure, survival, and cardiovascular complications. Emphasis is placed on the pharmacodynamics of the initiation of therapy, especially concerning the effect on the glomerular filtration rate. The side effect profile concerning the long-term effects of ACE inhibitors is also discussed, especially concerning potassium, acute renal failure, and bradykinin. Other potential therapies concerning other agents, especially SGLT2, are also discussed. This comprehensive review concerning the role of ACE inhibitors in the management of chronic kidney disease places great emphasis on the need for personalized medicine.

Keywords: ACE Inhibitors; Chronic Kidney Disease; Renin-Angiotensin-Aldosterone System; Proteinuria; Renal Fibrosis; Glomerular Filtration Rate; Hyperkalemia; Oxidative Stress; Diabetic Nephropathy

Introduction

Chronic Kidney Disease, abbreviated as CKD, has turned out to be a global health issue, and it has significantly contributed to health burdens, especially in low- and middle-income countries[1] It is also called a silent epidemic since, in the early stages of the disease, the patient does not display any specific health issue, and the disease is likely to progress to a point

where considerable and permanent damage to the kidneys has occurred[2] . From a clinical point of view, CKD is defined as a pathological state characterized by a persistent reduction in glomerular filtration rate to less than 60 mL/min/1.73 m^2 and/or abnormal kidney damage, such as abnormal levels of albumin in the urine, abnormal levels of electrolytes, and histopathological abnormalities, for a period of at least three months[3] . The progressive nature of CKD leads to end-stage renal disease, for which the patient is forced to undergo dialysis and/or receive a transplant, which is associated with considerable economic and social burdens [4]. The pathophysiology of CKD is multifactorial and complex, and it involves the intricate interaction of several mechanisms, which are hemodynamic, metabolic, and inflammatory in nature[5]. Among the primary factors that contribute to the pathophysiology of CKD, systemic hypertension plays a critical role in the pathophysiology of CKD [6]. At the same time, metabolic diseases like diabetes mellitus have also been recognized to cause a significant contribution to the development of CKD through the action of hyperglycemia, resulting in the formation of advanced glycosylation end-products, oxidative stress, and mesangial cell expansion [7]. This leads to glomerular hyperfiltration in the early stages of the disease process, followed by the loss of nephrons and hypertrophy of the remaining nephrons. With the progression of the disease process, hypertrophy becomes maladaptive and accelerates the progression of CKD, resulting in tubulointerstitial fibrosis, which is the hallmark of permanent kidney damage[8]. Another very important aspect of the progression of CKD is the activation of the renin-angiotensin-aldosterone system (RAAS), which is a critical endocrine system and plays a vital role in the regulation of blood pressure, fluid and electrolyte balance, and circulatory stability[9].

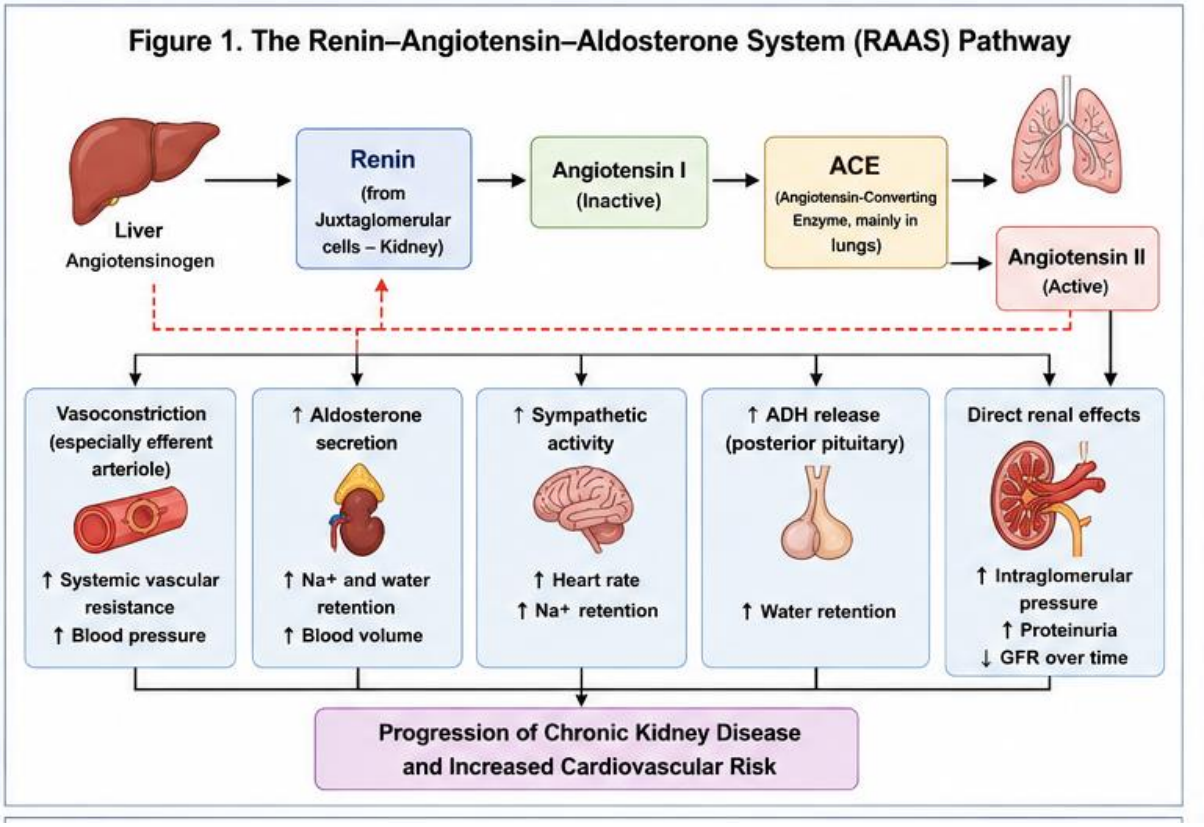

Figure 1: Role of renin–angiotensin–aldosterone system activation in chronic kidney disease progression.

Figure 1 illustrates the contribution of RAAS activation to CKD progression. Increased renin release promotes angiotensin II formation, which induces efferent arteriole constriction, glomerular hypertension, oxidative stress, inflammation, and renal fibrosis, ultimately leading to progressive nephron loss.

In physiological states, the activation of the renin-angiotensin-aldosterone system plays a very crucial role in the regulation of circulatory stability[10]. In the case of CKD, the activation of the renin-angiotensin-aldosterone system is detrimental to the renal system. The activation of the renin–angiotensin–aldosterone system begins with the release of renin from the juxtaglomerular apparatus, which cleaves angiotensinogen to form angiotensin I [11]. Angiotensin I is subsequently converted to angiotensin II through the action of angiotensin-converting enzyme (ACE), primarily in the pulmonary circulation. Angiotensin II is the principal effector peptide of the renin–angiotensin–aldosterone system and causes vasoconstriction, particularly of the efferent arteriole of the glomerulus [12]. Besides the hemodynamic effects, angiotensin II plays a crucial role in the mediation of renal damage through various mechanisms. It plays a crucial role in the synthesis of reactive oxygen species, leading to endothelial dysfunction and oxidative stress. In addition, angiotensin II is known to be involved in the synthesis of pro-inflammatory cytokines and chemokines, thereby leading

to inflammation in the renal parenchyma[11]. It is also known to be involved in the synthesis of fibrogenic factors, leading to fibrosis in the kidney. All these mechanisms contribute to renal damage. In this context, the role of angiotensin-converting enzyme inhibitors in the management of chronic kidney damage has been established. Inhibition of the action of angiotensin II through the inhibition of angiotensin-converting enzyme effectively counters the role of the renin-angiotensin system in the mediation of renal damage through both the hemodynamic and molecular mechanisms. Inhibition of angiotensin II leads to the dilation of the efferent arteriole, thereby reducing the pressure in the glomeruli. In addition, it counters the role of angiotensin II in the synthesis of various inflammatory cytokines and fibrogenic factors[15]. It also counters oxidative stress and endothelial dysfunction. In addition, ACE inhibitors have another advantage in the management of renal damage. The synthesis of bradykinin leads to the synthesis of nitric oxide and prostaglandins[12]. In the last decades, there has been a remarkable increase in the application of these drugs, not only in the treatment of hypertension, as initially done, but also in the current application in the treatment of CKD as disease-modifying Long-term kidney impairment drugs[13]. The effectiveness of ACE inhibitors in the treatment of proteinuria, slowing the progression of GFR decline, and delaying the onset of ESRD has been proven, especially in high-risk patients with diabetic nephropathy, hypertensive nephrosclerosis, and chronic glomerulopathies. Over recent decades, ACE inhibitors have evolved from antihypertensive agents to cornerstone therapies for chronic kidney disease because of their proven renoprotective and cardiovascular benefits[14]. Clinical evidence demonstrates that ACE inhibitors reduce proteinuria, slow the decline in glomerular filtration rate, delay progression to end-stage renal disease, and improve long-term renal outcomes[15]. In addition, the effectiveness of the application of ACE inhibitors has been proven, especially in light of the high cardiovascular complication rate in CKD patients[16]. The administration of ACE inhibitors, however, necessitates careful observation due to the potential for adverse effects, particularly concerning the risk of hyperkalemia and renal impairment. Consequently, the advancement of chronic kidney disease (CKD) represents a multifaceted interaction involving hemodynamic strain, metabolic anomalies, and inflammatory/fibrotic processes, with the renin-angiotensin-aldosterone system (RAAS) playing a crucial role [17]. Furthermore, ACE inhibitors, through their intricate mechanisms, provide a valuable means of mitigating the progression of CKD and safeguarding renal function, especially considering their widespread use across diverse patient populations[18]. This is particularly significant given their essential function in contemporary nephroprotective strategies, underscoring the necessity for continued investigation to refine their clinical

application. Moreover, the efficiency of the application of ACE inhibitors has been proven, particularly in consideration of the high cardiovascular complication rate among CKD patients[19]. However, the application of ACE inhibitors requires observation, particularly in consideration of their possible adverse effects, such as those concerning hyperkalemia and renal impairment. CKD progression results from complex interactions among hemodynamic, metabolic, inflammatory, and fibrotic pathways, with RAAS activation serving as a central pathogenic mechanism[20].

Methodology

This manuscript is a narrative review supported by a structured literature search. A structured search of PubMed, Scopus, Web of Science, and Google Scholar was conducted to identify relevant literature on the role of angiotensin-converting enzyme (ACE) inhibitors in chronic kidney disease (CKD). Search terms included "ACE inhibitors", "chronic kidney disease", "renal fibrosis", "proteinuria", "renin-angiotensin-aldosterone system", "glomerular hemodynamics", and related keywords. Eligible publications were screened based on predefined inclusion and exclusion criteria, and findings were synthesized narratively according to major thematic areas. The search terms, including ACE inhibitors, chronic kidney disease, kidney impairment, renin angiotensin aldosterone system, proteinuria, renal fibrosis, and glomerular hemodynamics, were used alone as well as in combination for searching a variety of articles from the existing scientific literature. In addition, the bibliography of a few selected articles was also used for searching additional articles that contributed to the topic. The articles selected for the present review were based on predefined inclusion and exclusion criteria. Priority was given to peer-reviewed publications published during the last twenty years, with greater emphasis placed on recent high-quality studies. However, several landmark studies and internationally recognized clinical guidelines published before this period were also included because of their continued scientific relevance and foundational contributions to understanding the mechanisms and clinical application of angiotensin-converting enzyme (ACE) inhibitors in chronic kidney disease (CKD). Only articles published in the English language were included in this review. The articles selected for the present review included randomized controlled trials, systematic reviews, meta-analyses, cohort studies, observational studies, and relevant experimental studies that evaluated the role of angiotensin-converting enzyme (ACE) inhibitors in the prevention and management of chronic kidney disease (CKD). Studies focusing exclusively on acute kidney injury (AKI), non-renal diseases, conference

abstracts, editorials, letters to the editor, and non-English publications were excluded from the review. . The process of data extraction was undertaken through a process of reading and evaluation of the chosen literature. Relevant information, such as the nature of the study, the nature of the patients involved, the nature of the intervention, and the results obtained, was extracted. Particular emphasis was laid on the adverse effects and safety profile of the drug. The quality of the literature was evaluated for the reliability of the results obtained. The extracted data was then analyzed using a qualitative synthesis approach. This approach enabled the integration of results obtained from various types of literature into a coherent narrative. The results obtained were then synthesized into various thematic areas. Particular emphasis was laid on the areas of agreement and those of disagreement. This methodology provides a robust framework for the evaluation of the current knowledge base of ACE inhibitors in the treatment of long term kidney impairment. It is evident that conclusions drawn are based on reliable scientific evidence

Mechanistic Insights of ACE Inhibitors in Kidney Protection

The renoprotective actions of ACE inhibitors are mediated through an integrated combination of hemodynamic regulation and direct cellular effects that together slow the progression of renal injury. At the hemodynamic level, inhibition of angiotensin II production [21] leads to selective dilation of the efferent arteriole, which reduces intraglomerular pressure and alleviates hyperfiltration-induced stress on the glomeruli.

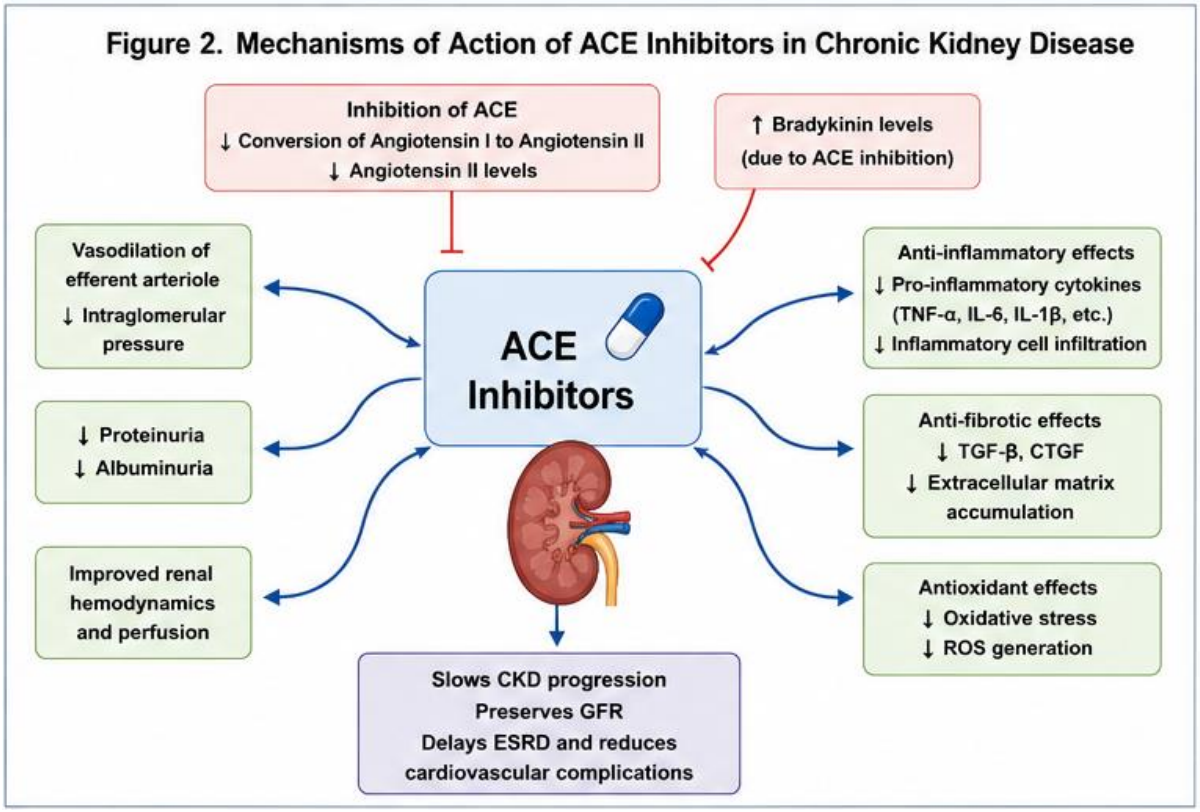

Figure 2:Molecular and hemodynamic mechanisms of ACE inhibitors in renal protection.

Figure 2 summarizes the renoprotective mechanisms of ACE inhibitors, including reduction of angiotensin II formation, efferent arteriole dilation, decreased intraglomerular pressure, reduction of proteinuria, inhibition of inflammatory pathways, suppression of TGF-β-mediated fibrosis, and reduction of oxidative stress.

This effect is particularly important in the early stages of chronic kidney disease, where glomerular hypertension acts as a major driver of progressive nephron injury[22]. By normalizing glomerular pressure, ACE inhibitors help maintain the structural and functional integrity of the filtration barrier, protecting nephrons from mechanical damage[23]. Hemodynamic modulation, ACE inhibitors exert significant molecular effects that contribute to kidney protection. Angiotensin II upregulates transforming growth factor beta expression, which promotes fibroblast activation and excessive deposition of extracellular matrix components[24]. This process contributes to glomerulosclerosis and tubulointerstitial fibrosis, hallmarks of progressive kidney disease. By reducing angiotensin II levels, ACE inhibitors suppress TGF-beta signaling, thereby limiting fibrotic remodeling and preserving renal tissue architecture. In addition, ACE inhibitors inhibit nuclear factor kappa B activity, a key transcription factor responsible for promoting pro-inflammatory cytokine production[25]. This results in decreased infiltration of inflammatory cells and reduced tissue injury, further slowing

disease progression. Oxidative stress represents another critical pathway in CKD pathophysiology. Angiotensin II stimulates reactive oxygen species production through activation of NADPH oxidase, contributing to endothelial dysfunction and direct cellular injury[26]. ACE inhibition mitigates oxidative stress by reducing ROS generation and enhancing endogenous antioxidant defense mechanisms. Additionally, the increase in bradykinin levels associated with ACE inhibition promotes the release of nitric oxide and prostacyclin, which improve endothelial function, enhance renal perfusion, and provide anti-inflammatory benefits[27] Together, these hemodynamic, anti-fibrotic, anti-inflammatory, and antioxidant effects create a multifaceted renoprotective profile for ACE inhibitors. By targeting both vascular and molecular pathways, ACE inhibitors effectively slow the progression of chronic kidney disease (ckd) and preserve renal function over time[28][

Clinical Implications and Therapeutic Benefits

The clinical implications of ACE inhibitors in the management of chronic kidney disease have been clearly defined and supported by a large amount of evidence regarding the therapeutic benefits in the treatment of kidney diseases[29]. These agents have been recommended for the treatment of hypertension and kidney disease because they have shown dual protective effects in the management of kidney diseases. Long-term treatment with ACE inhibitors has shown the potential for slowing the progression of kidney disease by slowing the rate of decline in glomerular filtration rate, delaying the onset of end-stage renal disease, and reducing the need for renal replacement therapy in the form of dialysis and kidney transplantation, thus improving the quality of life in patients with kidney disease[30].

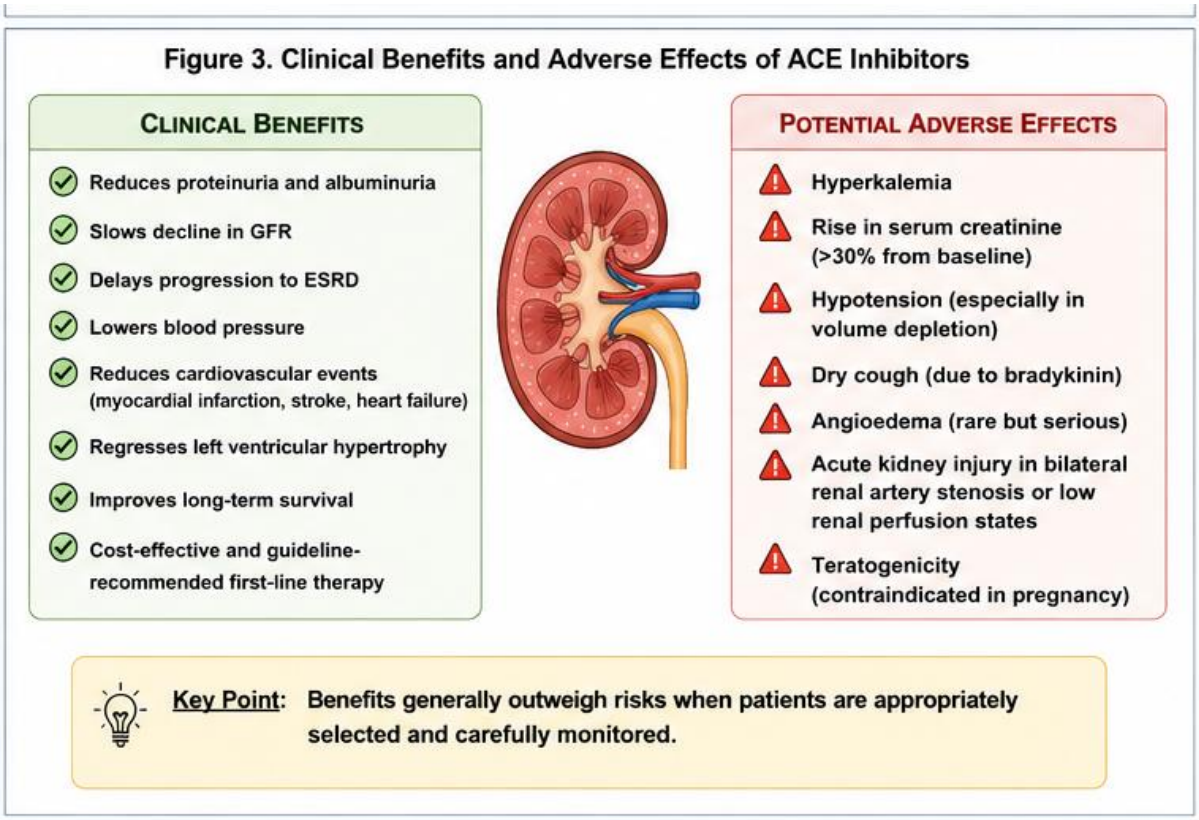

Figure 3: Clinical effects and adverse effects of ACE inhibitors

Figure 3 demonstrates the balance between therapeutic benefits and potential adverse effects of ACE inhibitors. The benefits include reduction of proteinuria, delayed CKD progression, cardiovascular protection, and preservation of renal function, while important safety concerns include hyperkalemia, acute kidney injury, cough, and angioedema.

The therapeutic benefits of ACE inhibitors in the management of kidney disease include cardiovascular protection, which is important because cardiovascular complications are common in patients with kidney disease[31]. This group of agents has shown potential in reducing systemic blood pressure and intraglomerular pressures, thus attenuating left ventricular hypertrophy, improving arterial compliance, and reducing the risk of cardiovascular complications, including myocardial infarction and cerebral stroke[32] . In addition, ACE inhibitors have shown potential in improving endothelial dysfunction and reducing inflammation in the cardiovascular system, thus providing cardiovascular protection in the management of kidney disease[33]. Although these effects are highly beneficial, the initiation of such therapy can be associated with an increase in the levels of creatinine in the blood. This is not a sign of nephrotoxicity; instead, it is the result of decreased intraglomerular pressure[34]. It is recommended that the levels of creatinine be monitored in the early stages

of the treatment with ACE inhibitors in order to obtain the best possible therapeutic outcomes. It is worth noting that the beneficial effects of the long-term use of these inhibitors are more significant when the therapy is initiated in the early stages of the disease in patients with proteinuria, diabetes mellitus, or hypertension[35]. In addition, the synergistic potential of these inhibitors in the management of CKD can be seen in the potential of these inhibitors to be used in conjunction with other therapeutic agents such as angiotensin receptor blockers, mineralocorticoid receptor antagonists, or sodium-glucose cotransporter-2 inhibitors[36]. The synergistic potential of these inhibitors can be seen in the potential of these inhibitors in the management of CKD through the enhancement of the nephroprotective effects of the inhibitors. All these findings point towards the pivotal role of these inhibitors in the management of chronic kidney disease[37].

Adverse Effects and Clinical Limitations

Despite the renoprotective and cardioprotective effects of ACE inhibitors, these medications have a range of adverse effects that need to be monitored and managed on an individual patient basis. One of the most important adverse effects is hyperkalemia, which occurs as a result of decreased aldosterone secretion and impaired renal excretion of potassium. This is particularly dangerous in patients with severe chronic kidney disease or diabetes mellitus or those on medications such as potassium-sparing diuretics, nonsteroidal anti-inflammatory medications, or supplements. This can sometimes require dose adjustment or discontinuation of these medications to correct the imbalance[38].Acute kidney injury is another limitation of these medications. This is particularly relevant in patients where there is compromised renal perfusion. This can include patients with conditions such as bilateral renal artery stenosis, severe dehydration, congestive heart failure, or hypotension[39]. These patients are heavily dependent on angiotensin II-mediated efferent arteriole vasoconstriction to maintain glomerular filtration. This can sometimes precipitate a sudden fall in glomerular filtration rate as a result of ACE inhibition. This can sometimes be reversible but can sometimes compromise renal function if not recognized[40]. Thus, these medications need to be used cautiously in patients with compromised renal perfusion In addition, bradykinin, which is responsible for the side effects of ACE inhibitor therapy, is also implicated in the more common side effect of persistent dry cough. Although less common, angioedema is also a life-threatening side effect of ACE inhibitor therapy, which is also ascribed to bradykinin[41]. The side effects, which occur as a consequence of bradykinin, often necessitate the discontinuation of therapy with

ACE inhibitors, thereby necessitating alternative therapy with other agents, such as ARBs, which offer renoprotective advantages without bradykinin-mediated side effects[42]. The other disadvantages of ACE inhibitor therapy include hypotension, which is more common in volume-depleted patients. In addition, ACE inhibitor therapy is known to interact with other drugs, which can often pose serious risks to renal function. However, despite these disadvantages, it is evident that the advantages of ACE inhibitor therapy outweigh its disadvantages[43]. The advantages of ACE inhibitor therapy can be maximized if its disadvantages are recognized and addressed to improve patient outcomes with chronic kidney disease[44].

Emerging Therapies and Future Perspectives

The approach to the therapy of chronic kidney disease has been constantly evolving, with new therapies being introduced to further enhance the renoprotective effects of ACE inhibitors. The latest in this line of therapy is the use of the sodium-glucose cotransporter-2 inhibitor therapy.The new therapy has been seen to be quite effective in the retardation of the progression of chronic kidney disease. The therapy has been seen to be renoprotective by acting on the mechanisms of tubuloglomerular feedback, intraglomerular pressure, inhibition of glomerular hyperfiltration, and the reduction of inflammatory responses in the renal parenchyma[45]. The therapy has been seen to be synergistic in its renoprotective effects when used in combination with ACE inhibitors in the reduction of proteinuria, the improvement of blood glucose levels in diabetic patients, and the preservation of renal function[46]. Moreover, the trend in the therapy of chronic kidney disease has been seen to be moving towards the application of the concept of precision medicine. This has been possible because of the discovery and application of various biomarkers in the therapy of chronic kidney disease[47]. These biomarkers include fibrosis biomarkers, inflammatory biomarkers, and oxidative stress biomarkers. The application of the biomarkers has enabled the clinician to identify patients who have high levels of risk factors for the rapid progression of chronic kidney disease[48]. This has further enabled the clinician to optimize the approach to the therapy of the patient by adjusting the dosage and the nature of the therapy to be administered. Moreover, new therapeutic agents are being developed to specifically act on fibrosis and inflammation. These include antifibrotic agents, TGF-beta signaling pathway modulators, and anti-inflammatory biologics. These agents have the potential to be used synergistically with ACE inhibitors to treat CKD by acting specifically on the major mechanisms of CKD pathophysiology not addressed by the RAAS system. These

agents have shown promising results in preclinical and clinical studies to enhance renal protection, reduce kidney damage, and provide long-term benefits to CKD patients by acting synergistically with existing treatments[49]. New emerging trends in the treatment of CKD include lifestyle and dietary changes that act synergistically with existing treatments. These include sodium restriction, protein restriction, and weight loss[50]. These have been shown to enhance the effectiveness of ACE inhibitors in treating CKD and minimizing the severity of CKD-related complications. These new trends in the treatment of CKD emphasize the importance of adopting a holistic approach to managing CKD[51]. Although the use of ACE inhibitors is the mainstay in the treatment of CKD, the new trends and developments in the pharmacological agents and the new emerging trends and developments in the treatment of CKD emphasize the potential to improve the management of CKD[52]. Although the new emerging trends and developments in the treatment of CKD emphasize the potential to improve the management of CKD, the new emerging trends and developments in the treatment of CKD emphasize the importance of the use of ACE inhibitors in the treatment of CKD

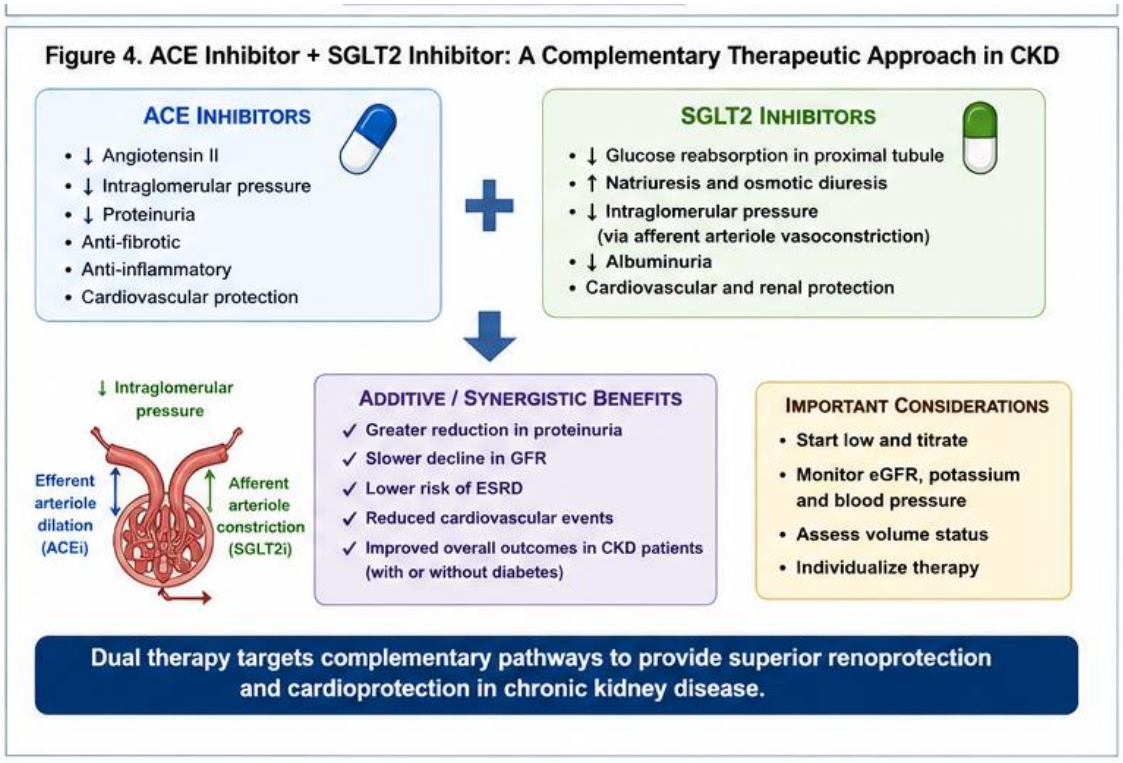

Figure 4:Complementary therapeutic approach of ACE inhibitors and SGLT2 inhibitors in the management of chronic kidney disease.

The figure 4 illustrates the complementary mechanisms of ACE inhibitors and sodium–glucose cotransporter-2 (SGLT2) inhibitors in chronic kidney disease. ACE inhibitors reduce

angiotensin II formation, lower intraglomerular pressure, decrease proteinuria, and suppress inflammation and fibrosis. SGLT2 inhibitors reduce glomerular hyperfiltration, improve metabolic control, promote natriuresis, and provide additional renal and cardiovascular protection. Together, these therapies slow CKD progression, preserve kidney function, and reduce the risk of cardiovascular events.

Conclusion

Angiotensin-converting enzyme inhibitors continue to be at the core of the management of chronic impairment of the kidneys because of their multiple mechanisms of action that address the hemodynamic and molecular mechanisms of chronic kidney disease. The reduction in intraglomerular pressure, the preservation of the integrity of the glomerular filtration apparatus, and the reduction of proteinuria preserve the functional integrity of the nephron, thus preventing the progression of chronic kidney disease towards end-stage renal disease. At the molecular level, the inhibitors block the key proinflammatory/profibrotic effects of TGF-beta and oxidative stress, thus preventing the fibrosis of the kidney. These effects not only preserve the structure and functional integrity of the kidneys but also offer significant cardiovascular benefits in the form of the prevention of left ventricular hypertrophy, myocardial infarction, and stroke, which are commonly associated with chronic kidney disease. Although the inhibitors have been found to be highly effective in the management of chronic impairment of the kidneys, they can be associated with potential adverse effects such as hyperkalemia, acute kidney injury in compromised renal perfusion, persistent cough, and rarely angioedema. The integration of the inhibitors with the newer inhibitors such as SGLT2 inhibitors and the application of precision medicine approaches based on individual patient characteristics offer great promise in the management of chronic impairment of the kidneys.

In conclusion, the role of the inhibitors in the management of chronic impairment of the kidneys cannot be overstated. The inhibitors continue to be at the core of the management of chronic impairment of the kidneys because of their multiple mechanisms of action that address the hemodynamic and molecular mechanisms of chronic kidney disease. The inhibitors not only preserve the structure and functional integrity of the kidneys but also offer significant cardiovascular benefits in the form of the prevention of left ventricular hypertrophy, myocardial infarction, and stroke. ACE inhibitors remain the cornerstone of CKD management because they reduce intraglomerular pressure, limit proteinuria, suppress renal fibrosis, and

provide significant cardiovascular protection that address the hemodynamic and molecular mechanisms of chronic kidney disease. Beyond preserving renal structure and function, ACE inhibitors reduce cardiovascular morbidity and mortality, making them essential in the comprehensive management of patients with CKD.

List of Abbreviations

ACE – Angiotensin-Converting Enzyme

ARB – Angiotensin Receptor Blocker

CKD – Chronic Kidney Disease

ESRD – End-Stage Renal Disease

GFR – Glomerular Filtration Rate

NADPH – Nicotinamide Adenine Dinucleotide Phosphate

RAAS – Renin–Angiotensin–Aldosterone System

ROS – Reactive Oxygen Species

SGLT2 – Sodium–Glucose Cotransporter-2

TGF-β – Transforming Growth Factor Beta

Author Contributions

Conceptualization: Said Salim Said

Methodology: Sabra Salim Rashid, Ahmad Makame Mwadini

Investigation: Ahmad Makame Mwadini, Ussi Hamza Ussi

Supervision: Burhani Simai

Writing – Original Draft: Said Salim Said

Writing – Review & Editing: Said Salim Said, Burhani Simai, Sabra Salim Rashid, Ahmad Makame Mwadini, Ussi Hamza Ussi

All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare there are no conflicts of interest.

Funding

The study didn’t receive any funding.

Acknowledgments

The authors would like to express their sincere appreciation to all individuals who provided valuable support, constructive discussions, and encouragement during the preparation of this manuscript. The authors also thank the editors and anonymous reviewers for their insightful comments and suggestions.

All figures included in this manuscript were originally designed and created by the authors using BioRender and Microsoft PowerPoint for scientific illustration.

AI-declaration:

No AI tools were used for language editing or rephrasing. The authors take full responsibility for all content.

REFERENCES

[1] A. Ortiz, J. S. Lees, R. Torra, V. S. Stel, A. Kramer, and P. B. Mark, “The updated global burden of chronic kidney disease: one death every 20 seconds,” *Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transpl. Assoc. - Eur. Ren. Assoc.*, p. gfag040, Feb. 2026, doi: 10.1093/ndt/gfag040.

[2] T. Yi, D. V. O’Hara, and A. Levin, “Global kidney health: Are we failing the silent pandemic?,” *J. Intern. Med.*, vol. 300, no. 1, pp. 26–38, Jul. 2026, doi: 10.1111/joim.70088.

[3] S. R. Vaidya and N. R. Aeddula, “Chronic Kidney Disease,” in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2026. Accessed: Jul. 27, 2026. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK535404/

[4] P. Rout and A. Aslam, “End-Stage Renal Disease,” in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2026. Accessed: Jul. 27, 2026. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK499861/

[5] J. M. Arreola Guerra and J.-I. Martinez-Martinez, “Multifactorial chronic kidney disease,” *Nephrol. Dial. Transplant.*, vol. 41, no. 2, pp. 233–242, Feb. 2026, doi: 10.1093/ndt/gfaf122.

[6] K. A Griffin, K. Pothugunta, A. J. Polichnowski, and A. K. Bidani, “The Role of Systemic Blood Pressure in the Progression of Chronic Kidney Disease,” *Curr. Cardiovasc. Risk Rep.*, vol. 9, no. 5, p. 23, Mar. 2015, doi: 10.1007/s12170-015-0450-9.

[7] Y. Oe, “Editorial for the Special Issue: Pathophysiology of Chronic Kidney Disease and Its Complications,” *Biomedicines*, vol. 12, no. 2, p. 416, Feb. 2024, doi: 10.3390/biomedicines12020416.

[8] M. Kanbay, S. Copur, C. N. Bakir, A. Covic, A. Ortiz, and K. R. Tuttle, “Glomerular hyperfiltration as a therapeutic target for CKD,” *Nephrol. Dial. Transplant.*, vol. 39, no. 8, pp. 1228–1238, Feb. 2024, doi: 10.1093/ndt/gfae027.

[9] G. R. Diwyanjalee and S. J. Wimalawansa, “The silent epidemic of CKDu: advances, challenges, and strategies for sustainable eradication-a narrative review,” *Clin. Exp. Nephrol.*, vol. 29, no. 10, pp. 1313–1330, Oct. 2025, doi: 10.1007/s10157-025-02751-3.

[10] “CV Physiology | Renin-Angiotensin-Aldosterone System.” Accessed: Aug. 26, 2026. [Online]. Available: https://cvphysiology.com/blood-pressure/bp015

[11] Y. Wang *et al.*, “The core mechanism of hypertension-linked renal fibrosis: ‘RAAS-ROS-inflammation-fibrosis’ axis,” *iScience*, vol. 29, no. 4, p. 115353, Apr. 2026, doi: 10.1016/j.isci.2026.115353.

[12] “Renal fibrosis: research progress on mechanisms and therapeutic strategies.” Accessed: Jul. 27, 2026. [Online]. Available: https://www.krcp-ksn.org/journal/view.php?doi=10.23876/j.krcp.24.158

[13] “(PDF) The Use of Antihypertensive Drugs in Pre-Dialysis Chronic Kidney Disease Patients,” *ResearchGate*, Jul. 2026, doi: 10.37311/ijpe.v6i2.38102.

[14] “Use of Angiotensin-Converting Enzyme Inhibitors for the Preservation of Kidney Function | Request PDF,” *ResearchGate*, Jul. 2026, doi: 10.1159/000186033.

[15] A. Avula *et al.*, “ACE Inhibitors and ARBs in Chronic Kidney Disease: A Systematic Review of Randomized Controlled Trials on Albuminuria Reduction, eGFR Decline, and Safety,” *Cureus*, vol. 17, no. 10, p. e93707, doi: 10.7759/cureus.93707.

[16] “ACE & ARBs - Uses, types, effectiveness, side effects | National Kidney Foundation.” Accessed: Jul. 27, 2026. [Online]. Available: https://www.kidney.org/kidney-topics/ace-inhibitors-and-arbs

[17] T. Momoniat, D. Ilyas, and S. Bhandari, “ACE inhibitors and ARBs: Managing potassium and renal function,” *Cleve. Clin. J. Med.*, vol. 86, no. 9, pp. 601–607, Sep. 2019, doi: 10.3949/ccjm.86a.18024.

[18] M. C. Staff, “Angiotensin-converting enzyme (ACE) inhibitors,” Mayo Clinic. Accessed: Jul. 27, 2026. [Online]. Available: https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/in-depth/ace-inhibitors/art-20047480

[19] Y. Zhang *et al.*, “ACE Inhibitor Benefit to Kidney and Cardiovascular Outcomes for Patients with Non-Dialysis Chronic Kidney Disease Stages 3–5: A Network Meta-Analysis of Randomised Clinical Trials,” *Drugs*, vol. 80, no. 8, pp. 797–811, 2020, doi: 10.1007/s40265-020-01290-3.

[20] B. Singh, A. S. Cusick, A. Goyal, and P. Patel, “ACE Inhibitors,” in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2026. Accessed: Jul. 27, 2026. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK430896/

[21] N. J. Brown and D. E. Vaughan, “Angiotensin-Converting Enzyme Inhibitors,” *Circulation*, vol. 97, no. 14, pp. 1411–1420, Apr. 1998, doi: 10.1161/01.CIR.97.14.1411.

[22] “Diabetic nephropathy (kidney disease) - Symptoms and causes - Mayo Clinic.” Accessed: Jul. 27, 2026. [Online]. Available: https://www.mayoclinic.org/diseases-conditions/diabetic-nephropathy/symptoms-causes/syc-20354556

[23] M. Prajapati and S. M. Dhoke, “The Role of ACE Inhibitors in Slowing Diabetic Nephropathy Progression: A Comprehensive Review,” *Int. J. Pharm. Sci.*, vol. 03, no. 08, pp. 1524–1533, Aug. 2025, doi: 10.5281/zenodo.16872206.

[24] D. B. RPh, “ACE Inhibitors’ Mechanism of Action: Here’s What They Do,” GoodRx. Accessed: Jul. 27, 2026. [Online]. Available: https://www.goodrx.com/classes/ace-inhibitors/what-do-ace-inhibitors-do

[25] “Hypertension-Induced Renal Injury: From Pathophysiology to Therapeutic Perspectives.” Accessed: Jul. 27, 2026. [Online]. Available: https://www.mdpi.com/2227-9059/14/3/595

[26] V. Ravarotto, G. Bertoldi, G. Innico, L. Gobbi, and L. A. Calò, “The Pivotal Role of Oxidative Stress in the Pathophysiology of Cardiovascular-Renal Remodeling in Kidney Disease,” *Antioxidants*, vol. 10, no. 7, p. 1041, Jun. 2021, doi: 10.3390/antiox10071041.

[27] “(PDF) Angiotensin-converting enzyme inhibitors reduce oxidative stress intensity in hyperglicemic conditions in rats independently from bradykinin receptor inhibitors.” Accessed: Jul. 27, 2026. [Online]. Available: https://www.researchgate.net/publication/308024053_Angiotensin-converting_enzyme_inhibitors_reduce_oxidative_stress_intensity_in_hyperglicemic_conditions_in_rats_independently_from_bradykinin_receptor_inhibitors

[28] “From Plants to Protection: Cardiorenal Benefits in Non-Diabetic Chronic Kidney Disease and Heart Failure.” Accessed: Jul. 27, 2026. [Online]. Available: https://www.mdpi.com/1420-3049/30/19/3982

[29] C. A. Popa, “ACEing the management of advanced CKD,” NephJC. Accessed: Jul. 27, 2026. [Online]. Available: http://www.nephjc.com/news/aceing-ckd

[30] E. Polychronopoulou, G. Wuerzner, and M. Burnier, “How Do I Manage Hypertension in Patients with Advanced Chronic Kidney Disease Not on Dialysis? Perspectives from Clinical Practice,” *Vasc. Health Risk Manag.*, vol. 17, pp. 1–11, Jan. 2021, doi: 10.2147/VHRM.S292522.

[31] “Cardiovascular Protection With Sodium-Glucose Cotransporter-2 Inhibitors and Mineralocorticoid Receptor Antagonists in Chronic Kidney Disease | Hypertension.” Accessed: Jul. 28, 2026. [Online]. Available: https://www.ahajournals.org/doi/10.1161/HYPERTENSIONAHA.121.17005

[32] B. Y. Sayin and A. Oto, “Left Ventricular Hypertrophy: Etiology-Based Therapeutic Options,” *Cardiol. Ther.*, vol. 11, no. 2, pp. 203–230, Jun. 2022, doi: 10.1007/s40119-022-00260-y.

[33] R. F. Njoh, B. Njei, and A. T. Nguyen, “Abstract 124: The Effectiveness of Angiotensin Converting Enzyme Inhibitors, Angiotensin II Receptor blocker, or Combination in Reducing Left Ventricular Hypertrophy in Hypertensive Patients: A Systematic Review,” *Hypertension*, vol. 60, no. suppl_1, pp. A124–A124, Sep. 2012, doi: 10.1161/hyp.60.suppl_1.A124.

[34] L. Hejnova *et al.*, “Modulation of left ventricular hypertrophy in spontaneously hypertensive rats by acetylcholinesterase and ACE inhibitors: physiological, biochemical, and proteomic studies,” *Front. Cardiovasc. Med.*, vol. 11, Sep. 2024, doi: 10.3389/fcvm.2024.1390547.

[35] E. Vivian and C. Mannebach, “Therapeutic approaches to slowing the progression of diabetic nephropathy – is less best?,” *Drugs Context*, vol. 2013, p. 212249, Mar. 2013, doi: 10.7573/dic.212249.

[36] J. Morales and Y. Handelsman, “Cardiovascular Outcomes in Patients With Diabetes and Kidney Disease,” *JACC*, vol. 82, no. 2, pp. 161–170, Jul. 2023, doi: 10.1016/j.jacc.2023.04.052.

[37] D. Dobre, H. J. Lambers Heerspink, and D. de Zeeuw, “Reducing cardiovascular risk: protecting the kidney,” *Eur. Heart J. Suppl.*, vol. 11, no. suppl_F, pp. F39–F46, Dec. 2009, doi: 10.1093/eurheartj/sup027.

[38] M. Adamczak, I. Kurnatowska, B. Naumnik, T. Stompór, L. Tylicki, and M. Krajewska, “Pharmacological Nephroprotection in Chronic Kidney Disease Patients with Type 2 Diabetes Mellitus—Clinical Practice Position Statement of the Polish Society of Nephrology,” *Int. J. Mol. Sci.*, vol. 25, no. 23, p. 12941, Jan. 2024, doi: 10.3390/ijms252312941.

[39] B. L. McDaniel and M. L. Bentley, “The role of medications and their management in acute kidney injury,” *Integr. Pharm. Res. Pract.*, vol. 4, pp. 21–29, May 2015, doi: 10.2147/IPRP.S52930.

[40] “Renovascular Hypertension: Practice Essentials, Background, Pathophysiology.” Accessed: Jul. 28, 2026. [Online]. Available: https://emedicine.medscape.com/article/245140-overview

[41] “CV Pharmacology | Angiotensin Converting Enzyme (ACE) Inhibitors.” Accessed: Jul. 28, 2026. [Online]. Available: https://cvpharmacology.com/vasodilator/ace

[42] “ACE-inhibitors: Be aware of the distinction between bradykinin- and histamine-mediated angioedema, as treatment strategies differ significantly,” GOV.UK. Accessed: Jul. 28, 2026. [Online]. Available: https://www.gov.uk/drug-safety-update/ace-inhibitors-be-aware-of-the-distinction-between-bradykinin-and-histamine-mediated-angioedema-as-treatment-strategies-differ-significantly

[43] “Ace Inhibitors: Uses, Side Effects, And Safety - Acibadem Hospitals Group.” Accessed: Jul. 28, 2026. [Online]. Available: https://acibademinternational.com/health-library/ace-inhibitors-what-patients-need-to-know/

[44] Y. Zhang *et al.*, “ACE Inhibitor Benefit to Kidney and Cardiovascular Outcomes for Patients with Non-Dialysis Chronic Kidney Disease Stages 3-5: A Network Meta-Analysis of Randomised Clinical Trials,” *Drugs*, vol. 80, no. 8, pp. 797–811, Jun. 2020, doi: 10.1007/s40265-020-01290-3.

[45] X. Chen, C.-F. Hocher, L. Shen, B. K. Krämer, and B. Hocher, “Reno- and cardioprotective molecular mechanisms of SGLT2 inhibitors beyond glycemic control: from bedside to bench,” *Am. J. Physiol.-Cell Physiol.*, vol. 325, no. 3, pp. C661–C681, Sep. 2023, doi: 10.1152/ajpcell.00177.2023.

[46] “Combination Therapy for Kidney Failure in Diabetes.” Accessed: Jul. 28, 2026. [Online]. Available: https://reference.medscape.com/viewarticle/ckd-t2d-combination-therapy-kidney-protection-2026a10006me

[47] A. Gupta, T. Sontakke, S. Acharya, and S. Kumar, “A Comprehensive Review of Biomarkers for Chronic Kidney Disease in Older Individuals: Current Perspectives and Future Directions,” *Cureus*, vol. 16, no. 9, p. e70262, Sep. 2024, doi: 10.7759/cureus.70262.

[48] Y. Chen, X. Liu, M. Shengbu, Q. Shi, S. Jiaqiu, and X. Lai, “Biomarkers: New Advances in Diabetic Nephropathy,” *Nat. Prod. Commun.*, vol. 20, no. 2, p. 1934578X251321758, Feb. 2025, doi: 10.1177/1934578X251321758.

[49] C. Delrue, M. F. Eisenga, J. R. Delanghe, and M. M. Speeckaert, “Personalized Antifibrotic Therapy in CKD Progression,” *J. Pers. Med.*, vol. 14, no. 12, p. 1141, Dec. 2024, doi: 10.3390/jpm14121141.

[50] Y. Uchiyama-Tanaka, “Chronic kidney disease and diet,” *Ren. Replace. Ther.*, vol. 11, no. 1, p. 71, Sep. 2025, doi: 10.1186/s41100-025-00668-x.

[51] “NKF KDOQI Guidelines.” Accessed: Jul. 28, 2026. [Online]. Available: https://kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_bp/guide_11.htm

[52] “The Future of Chronic Kidney Disease Treatment: Combination Therapy (Polypill) or Biomarker-Guided Personalized Intervention?” Accessed: Jul. 28, 2026. [Online]. Available: https://www.mdpi.com/2218-273X/15/6/809