



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

Said Salim Said^{1,*}, Burhani Simai¹, Sabra Salim Rashid¹, Ahmad Makame Mwadini¹, Ussi Hamza Ussi²

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

² School of Health & Medical Sciences, The State University of Zanzibar, Zanzibar P.O. Box 146, Tanzania

Article History

Received: April 04, 2026

Accepted: August 30, 2026

Abstract

Chronic kidney disease characterized by progressive deterioration in kidney function, driven by multiple pathophysiological mechanisms. This disease still has a considerable effect on the health care system, particularly regarding its association with cardiovascular disease. Progressive deterioration in kidney function is driven by complex mechanisms in the renin-angiotensin system and the inflammatory response, leading to permanent nephron damage. Angiotensin-converting enzyme inhibitors play an integral role in managing chronic kidney disease. This is because, in addition to managing blood pressure, they produce renoprotective effects at the molecular level. In addition to providing a comprehensive overview, this review includes an in-depth discussion of the mechanistic basis for the therapeutic effects of ACE inhibitors, especially regarding their effects on the renin-angiotensin-aldosterone system, reductions in intraglomerular pressure and proteinuria, and anti-inflammatory effects. The long-term effects of ACE inhibitors are also discussed, particularly regarding the results from clinical studies on delayed progression to end-stage renal failure, survival, and cardiovascular complications. Emphasis is placed on the pharmacodynamic effects of therapy initiation, particularly its effect on glomerular filtration rate. The side effect profile of the long-term use of ACE inhibitors is also discussed, particularly regarding hyperkalemia, acute kidney injury, and bradykinin-mediated adverse effects. Other potential therapies, especially SGLT2 inhibitors, are also discussed. This comprehensive review of 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

1. Introduction

Chronic Kidney Disease (CKD) has become a global health issue and 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 symptoms, 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 m² 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 pa-

* Corresponding Author:

Said Salim Said, Zanzibar Food and Drug Agency, Trials And Vigilance Division, P.O. BOX 3595 Zanzibar, Tanzania; saidalriyamy67@gmail.com



© 2026 Copyright by the Authors.

Licensed as an open access article using a [CC BY 4.0 license](https://creativecommons.org/licenses/by/4.0/).

tient may require dialysis and/or transplantation, 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 [6]. At the same time, metabolic diseases like diabetes mellitus have also been recognized to contribute significantly to the development of CKD through the action of hyperglycemia, resulting in the formation of advanced glycation end products, oxidative stress, and mesangial cell expansion [7]. This leads to glomerular hyperfiltration in the early stages of the disease process, followed by nephron loss and hypertrophy of the remaining nephrons. As the disease process advances, hypertrophy becomes maladaptive and accelerates the progression of CKD, resulting in tubulointerstitial fibrosis, which is the hallmark of permanent kidney damage [8]. Another critical aspect of the progression of CKD is the activation of the renin-angiotensin-aldosterone system (RAAS), a critical endocrine system that plays a vital role in the regulation of blood pressure, fluid and electrolyte balance, and circulatory stability [9].

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, activation of the renin-angiotensin-aldosterone system plays a crucial role in regulating circulatory stability [10]. In CKD, activation of the renin-angiotensin-aldosterone system is detrimental to the kidneys. 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].

Beyond its hemodynamic effects, angiotensin II plays a crucial role in mediating renal damage through various mechanisms. It promotes the synthesis of reactive oxygen species, leading to endothelial dysfunction and oxidative stress. In addition, angiotensin II promotes the synthesis of pro-inflammatory cytokines and chemokines, thereby leading to inflammation in the renal parenchyma [11]. It

also promotes the synthesis of fibrogenic factors, leading to renal fibrosis. All these mechanisms contribute to renal damage. In this context, the role of angiotensin-converting enzyme inhibitors in the management of chronic kidney disease has been established. Inhibiting the action of angiotensin II through angiotensin-converting enzyme inhibition effectively counters the role of the renin-angiotensin system in the mediation of renal damage through both hemodynamic and molecular mechanisms. Inhibition of angiotensin II dilates the efferent arteriole, thereby reducing intraglomerular pressure. In addition, it counters angiotensin II's role in the synthesis of various inflammatory cytokines and fibrogenic factors [13]. It also counters oxidative stress and endothelial dysfunction. In addition, ACE inhibitors have another advantage in the management of renal damage. ACE inhibition increases bradykinin levels, promoting the production of nitric oxide and prostaglandins [12]. In recent decades, there has been a remarkable increase in the application of these drugs, not only for the treatment of hypertension, as originally intended, but also for the treatment of CKD as disease-modifying agents for long-term kidney protection [14].

The effectiveness of ACE inhibitors in treating 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 [15]. 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 [13]. In addition, the effectiveness of ACE inhibitors has been demonstrated, 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 progression of chronic kidney disease (CKD) results from 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 effectiveness of ACE inhibitors is particularly relevant given the high cardiovascular complication rate among CKD patients [19,20]. However, the use of ACE inhibitors requires observation, partic-

ularly 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 [21].

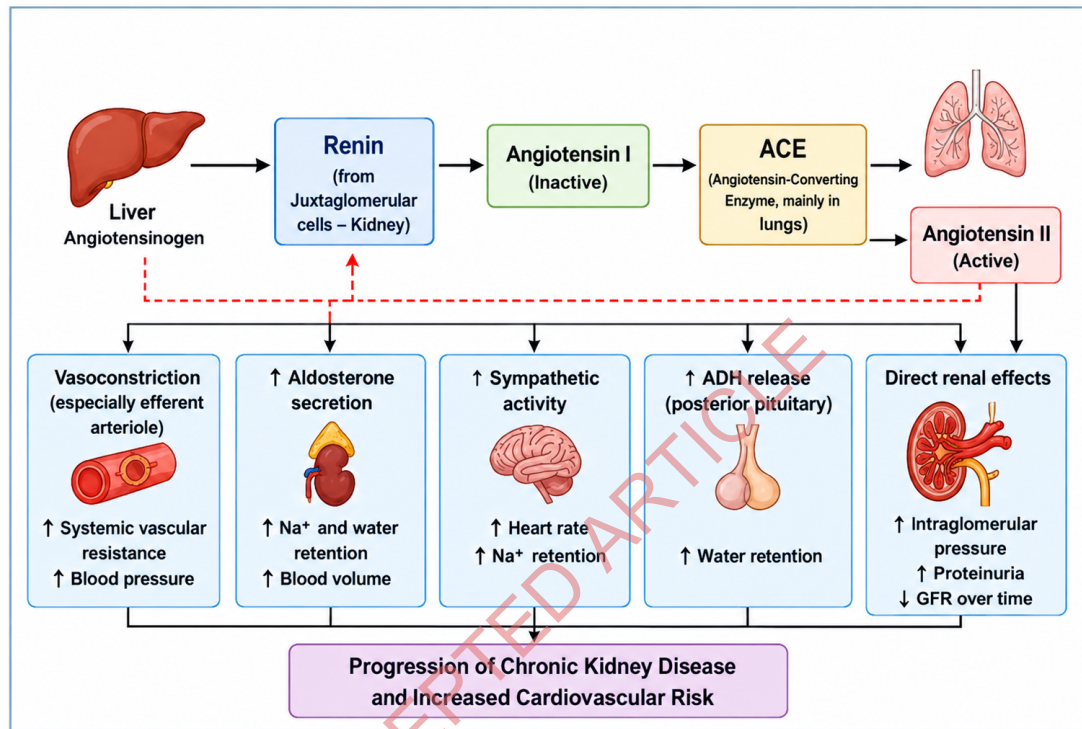


Figure 1: Role of renin–angiotensin–aldosterone system activation in chronic kidney disease progression.

2. 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 to identify relevant articles from

the existing scientific literature. In addition, the reference lists of selected articles were also used to identify additional articles relevant 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 from the last twenty years, with greater emphasis 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. Data extraction was conducted by reading and evaluating the selected literature. Relevant information, such as the study design, the patients involved, the intervention, and the results, was extracted. Particular emphasis was placed on the adverse effects and safety profile of ACE inhibitors. The quality of the literature was evaluated to assess the reliability of the results. The extracted data were 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 placed on areas of agreement and disagreement. This methodology provides a robust framework for the evaluation of the current knowledge base of ACE in-

hibitors in the treatment of long-term kidney impairment. The conclusions drawn are based on reliable scientific evidence

3. 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 [22] leads to selective dilation of the efferent arteriole, reducing intraglomerular pressure and alleviating hyperfiltration-induced stress on the glomeruli.

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

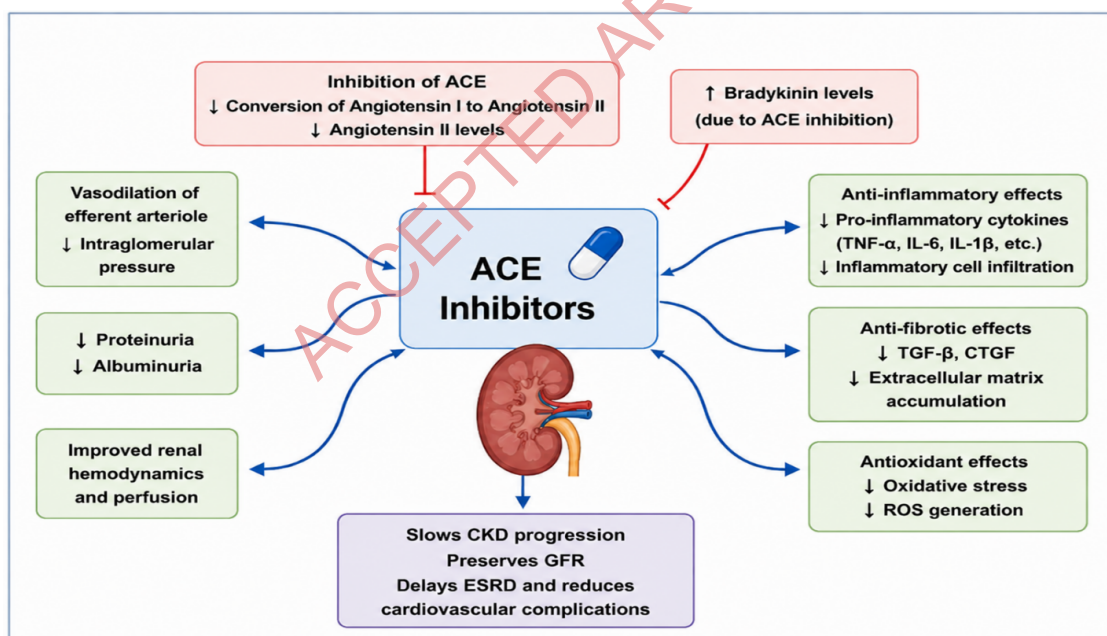


Figure 2: Molecular and hemodynamic mechanisms of ACE inhibitors in renal protection.

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 [23]. By normalizing glomerular pressure, ACE inhibitors help maintain the structural and functional integrity of the filtration barrier, protecting nephrons from mechanical damage [24]. Beyond hemodynamic mod-

ulation, 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 [25]. 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 [26]. This decreases inflammatory cell infiltration and reduces 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 [27]. 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 [28]. 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 [29].

4. 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 substantial body of evidence regarding the therapeutic benefits in the treatment of kidney diseases [30]. 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 disease. Long-term treatment with ACE inhibitors has shown the potential for slowing the progression of kidney disease by reducing 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 [31].

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

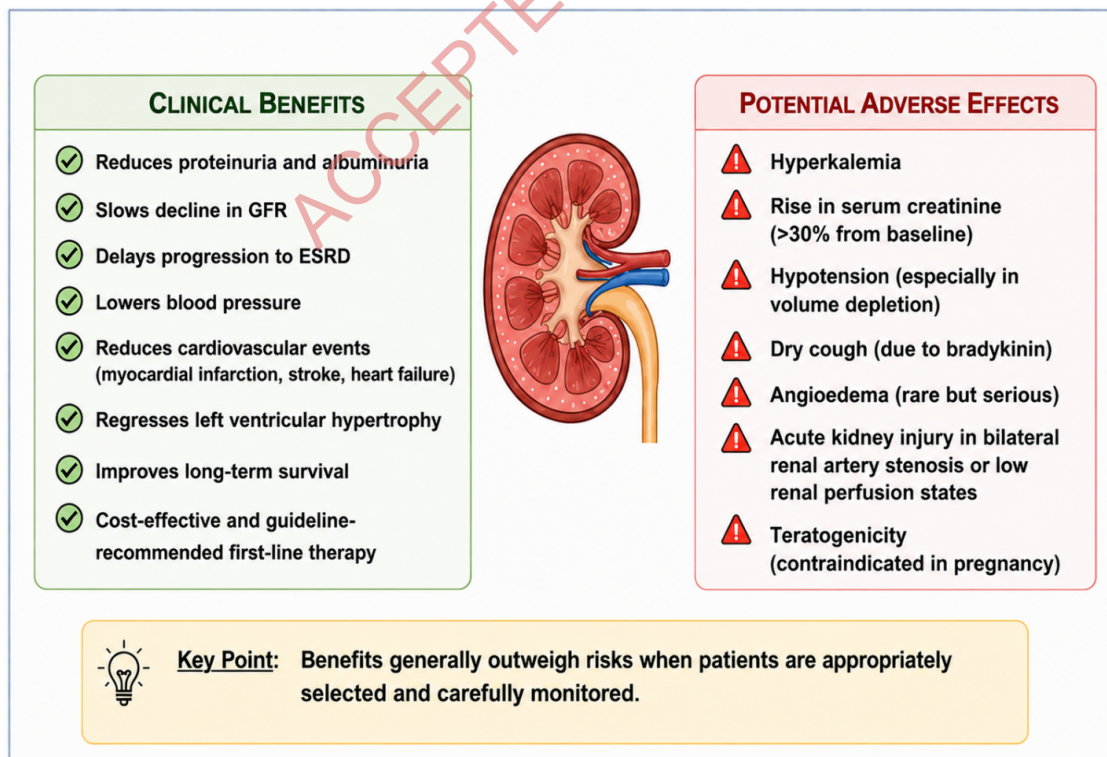


Figure 3: Clinical effects and adverse effects of ACE inhibitors.

The therapeutic benefits of ACE inhibitors in kidney disease management include cardiovascular protection, which is important because cardiovascular complications are common in patients with kidney disease [32]. This group of agents has shown potential to reduce systemic blood pressure and intraglomerular pressures, attenuate left ventricular hypertrophy, improve arterial compliance, and reduce the risk of cardiovascular complications, including myocardial infarction and stroke [33]. In addition, ACE inhibitors have shown potential to improve endothelial function and reduce inflammation in the cardiovascular system, thus providing cardiovascular protection in the management of kidney disease [34]. Although these effects are highly beneficial, starting this therapy can cause a modest increase in serum creatinine levels. This does not necessarily indicate nephrotoxicity; rather, it may result from decreased intraglomerular pressure [35]. It is recommended that creatinine levels be monitored in the early stages of ACE inhibitor treatment to achieve the best possible therapeutic outcomes. The beneficial effects of long-term use of these inhibitors are more significant when therapy is initiated early in patients with proteinuria, diabetes mellitus, or hypertension [36]. In addition, the synergistic potential of these inhibitors in the management of CKD is evident in their use in conjunction with other therapeutic agents such as mineralocorticoid receptor antagonists or sodium-glucose cotransporter-2 inhibitors [37]. This synergistic potential is further reflected in the enhancement of the nephroprotective effects of the inhibitors when combined with other agents. These findings point to the pivotal role of these inhibitors in managing chronic kidney disease [38].

5. 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 because 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 [39]. Acute kidney injury is another limitation of these medications. This is particularly relevant in patients with compromised renal perfusion. These patients may have conditions such as bilateral renal artery stenosis,

severe dehydration, congestive heart failure, or hypotension [40]. These patients are heavily dependent on angiotensin II-mediated efferent arteriole vasoconstriction to maintain glomerular filtration. This can sometimes precipitate a sudden decline in glomerular filtration rate as a result of ACE inhibition. This decline can be reversible but may compromise renal function if not recognized [41]. Thus, these medications need to be used cautiously in patients with compromised renal perfusion. In addition, bradykinin, which contributes to certain adverse effects of ACE inhibitor therapy, is also implicated in the common side effect of persistent dry cough.

Although less common, angioedema is a life-threatening side effect of ACE inhibitor therapy that is also ascribed to bradykinin [42]. The side effects, which occur as a consequence of bradykinin, often necessitate the discontinuation of therapy with ACE inhibitors, thereby requiring alternative therapy with other agents, such as ARBs, which offer renoprotective advantages without bradykinin-mediated side effects [43]. The other adverse effects 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 benefits of ACE inhibitor therapy outweigh its risks [44]. The benefits of ACE inhibitor therapy can be maximized if its risks are recognized and addressed to improve patient outcomes with chronic kidney disease [45].

6. 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. An important addition to current therapy is sodium-glucose cotransporter-2 inhibitor therapy. The new therapy has proven effective in slowing the progression of chronic kidney disease. The therapy exerts its renoprotective effects by modulating tubuloglomerular feedback and intraglomerular pressure, inhibiting glomerular hyperfiltration, and reducing inflammatory responses in the renal parenchyma [46]. The therapy demonstrates synergistic 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 [47]. Moreover, therapy for chronic kidney disease has increasingly moved toward precision medicine. This has been possible because

of the discovery and application of various biomarkers in the therapy of chronic kidney disease [48].

These biomarkers include fibrosis, inflammatory, and oxidative stress biomarkers. The application of biomarkers has enabled clinicians to identify patients at high risk of rapid progression of chronic kidney disease [49]. This has also enabled the clinician to optimize patients' therapy by adjusting the dosage and type of therapy administered. Moreover, researchers are developing new therapeutic agents that specifically target fibrosis and inflammation. These include antifibrotic agents, TGF-beta signaling pathway modulators, and anti-inflammatory biologics. These agents may be used synergistically with ACE inhibitors to treat CKD by targeting major CKD pathophysiological mechanisms not addressed by the RAAS. These agents have shown promising results in preclinical and clinical studies by enhancing renal protection, reducing kidney damage, and providing long-term benefits to CKD patients through synergy with existing treatments [50]. Emerging trends in the treatment of CKD include lifestyle and dietary changes that

complement existing treatments. These include sodium restriction, protein restriction, and weight loss [51]. 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 CKD treatment emphasize the importance of a holistic approach to managing CKD [52]. These emerging approaches also underscore the continued importance of ACE inhibitors in CKD treatment.

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.

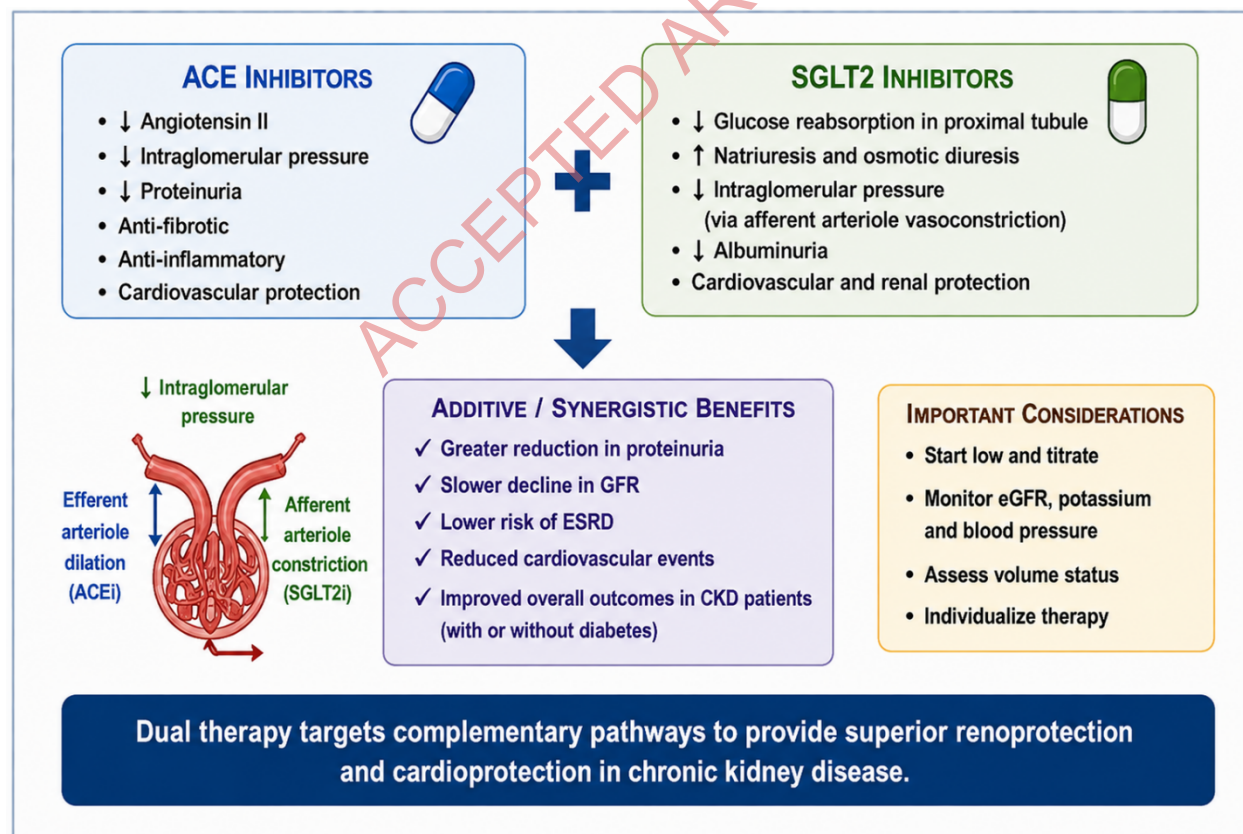


Figure 4: Complementary therapeutic approach of ACE inhibitors and SGLT2 inhibitors in the management of chronic kidney disease.

7. Conclusions

Angiotensin-converting enzyme inhibitors remain central to managing chronic kidney disease because their multiple mechanisms of action address the hemodynamic and molecular mechanisms of the disease. Reducing intraglomerular pressure, preserving the integrity of the glomerular filtration apparatus, and reducing proteinuria preserve nephron function, helping prevent progression from chronic kidney disease to end-stage renal disease. At the molecular level, the inhibitors attenuate key proinflammatory and profibrotic pathways involving TGF- β and oxidative stress, thus preventing renal fibrosis. These effects not only preserve kidney structure and function but also offer significant cardiovascular benefits by preventing left ventricular hypertrophy, myocardial infarction, and stroke, which are commonly associated with chronic kidney disease. Although these inhibitors are highly effective in managing chronic kidney impairment, they can cause adverse effects such as hyperkalemia, acute kidney injury in patients with compromised renal perfusion, persistent cough, and, rarely, angioedema. Integrating these agents with newer therapies such as SGLT2 inhibitors, along with precision medicine approaches based on individual patient characteristics, offers great promise in managing chronic kidney disease.

In conclusion, the role of these inhibitors in managing chronic kidney disease cannot be overstated. The inhibitors remain central to managing chronic kidney impairment because their multiple mechanisms of action address both the hemodynamic and molecular pathways of chronic kidney disease. These inhibitors not only preserve kidney structure and function but also offer significant cardiovascular benefits by reducing the risk 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. 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: S.S.S.; Methodology: S.S.R., A.M.M.; Investigation: A.M.M., U.H.U.; Supervision: B.S.; Writing—Original Draft: S.S.S.; Writing—Review & Editing: S.S.S., B.S., S.S.R., A.M.M., U.H.U. 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 no conflicts of interest.

Funding

The study did not receive any external funding and was conducted using only institutional resources.

Acknowledgments

The authors sincerely appreciate 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 Microsoft PowerPoint for scientific illustration.

AI Declaration

The authors confirm that no AI tools were used to generate any content of this manuscript. The authors take full responsibility for the accuracy, originality, integrity, and scientific content of the manuscript.

References

- [1] Ortiz, A.; Lees, J.S.; Torra, R.; Stel, V.S.; Kramer, A.; Mark, P.B. The Updated Global Burden of Chronic Kidney Disease: One Death Every 20 Seconds. *Nephrol. Dial. Transplant.* **2026**, gfg040. [[CrossRef](#)] [[PubMed](#)]
- [2] Yi, T.; O'Hara, D.V.; Levin, A. Global Kidney Health: Are We Failing the Silent Pandemic? *J. Intern. Med.* **2026**, 300(1), 26–38. [[CrossRef](#)] [[PubMed](#)]
- [3] Vaidya, S.R.; Aeddula, N.R. Chronic Kidney Disease. In *StatPearls*; StatPearls Publishing: Treas-

- sure Island, FL, USA, 2026. Available online: <http://www.ncbi.nlm.nih.gov/books/NBK535404/> (accessed on 27 July 2026).
- [4] Rout, P.; Aslam, A. End-Stage Renal Disease. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2026. Available online: <http://www.ncbi.nlm.nih.gov/books/NBK499861/> (accessed on 27 July 2026).
 - [5] Arreola Guerra, J.M.; Martinez-Martinez, J.-I. Multifactorial Chronic Kidney Disease. *Nephrol. Dial. Transplant.* **2026**, *41*(2), 233–242. [[CrossRef](#)] [[PubMed](#)]
 - [6] Griffin, K.A.; Pothugunta, K.; Polichnowski, A.J.; Bidani, A.K. The Role of Systemic Blood Pressure in the Progression of Chronic Kidney Disease. *Curr. Cardiovasc. Risk Rep.* **2015**, *9*(5), 23. [[CrossRef](#)]
 - [7] Oe, Y. Editorial for the Special Issue: Pathophysiology of Chronic Kidney Disease and Its Complications. *Biomedicines* **2024**, *12*(2), 416. [[CrossRef](#)] [[PubMed](#)]
 - [8] Kanbay, M.; Copur, S.; Bakir, C.N.; Covic, A.; Ortiz, A.; Tuttle, K.R. Glomerular Hyperfiltration as a Therapeutic Target for CKD. *Nephrol. Dial. Transplant.* **2024**, *39*(8), 1228–1238. [[CrossRef](#)] [[PubMed](#)]
 - [9] Diwyanjalee, G.R.; Wimalawansa, S.J. The Silent Epidemic of CKDu: Advances, Challenges, and Strategies for Sustainable Eradication—A Narrative Review. *Clin. Exp. Nephrol.* **2025**, *29*(10), 1313–1330. [[CrossRef](#)] [[PubMed](#)]
 - [10] CV Physiology | Renin-Angiotensin-Aldosterone System. Available online: <https://cvphysiology.com/blood-pressure/bp015> (accessed on 26 August 2026).
 - [11] Wang, Y.; Chen, J.; Wang, W.; Yi, X.; Xing, S.; Lei, X.; Chen, H.; Xie, X. The Core Mechanism of Hypertension-Linked Renal Fibrosis: “RAAS-ROS-Inflammation-Fibrosis” Axis. *iScience* **2026**, *29*, 115353. [[CrossRef](#)] [[PubMed](#)]
 - [12] Renal Fibrosis: Research Progress on Mechanisms and Therapeutic Strategies. Available online: <https://www.krcp-ksn.org/journal/view.php?doi=10.23876/j.krcp.24.158> (accessed on 27 July 2026).
 - [13] Avula, A.; Johal, L.K.; Ali, F.; Amir, S.; Yadav, S.; Murtuza, M.; Zia, U.; Janjua, F.F.; Raza, A.; Lal, K.; 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* **2025**, *17*, e93707. [[CrossRef](#)] [[PubMed](#)]
 - [14] Suprapti, B.; Thaha, M.; Nilamsari, W.P.; Muhyidin, I.; Tanaem, V.S.; Beting, E.G. (PDF) The Use of Antihypertensive Drugs in Pre-Dialysis Chronic Kidney Disease Patients. *Indones. J. Pharm. Educ.* **2026**, *6*(2), 266–278. [[CrossRef](#)]
 - [15] Reisch, J.F.M.; Ritz, E. Use of Angiotensin-Converting Enzyme Inhibitors for the Preservation of Kidney Function. *Nephron* **1990**, *55*, 38–42. [[CrossRef](#)] [[PubMed](#)]
 - [16] ACE & ARBs-Uses, Types, Effectiveness, Side Effects | National Kidney Foundation. Available online: <https://www.kidney.org/kidney-topics/ace-inhibitors-and-arbs> (accessed on 27 July 2026).
 - [17] Momoniat, T.; Ilyas, D.; Bhandari, S. ACE Inhibitors and ARBs: Managing Potassium and Renal Function. *Cleve. Clin. J. Med.* **2019**, *86*(9), 601–607. [[CrossRef](#)] [[PubMed](#)]
 - [18] Staff, M.C. Angiotensin-Converting Enzyme (ACE) Inhibitors. Mayo Clinic. Available online: <https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/in-depth/ace-inhibitors/art-20047480> (accessed on 27 July 2026).
 - [19] Rovin, B.H.; Jayne, D.R.W.; Sanders, J.-S.F.; Tesar, V.; Floege, J. Kidney Disease: Improving Global Outcomes (KDIGO) Responds to the Retraction of the ADVOCATE Trial of Avacopan for the Treatment of ANCA-Associated Vasculitis. *Kidney Int.* **2026**. [[CrossRef](#)] [[PubMed](#)]
 - [20] Singh, B.; Cusick, A.S.; Goyal, A.; Patel, P. ACE Inhibitors. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2026. Available online: <http://www.ncbi.nlm.nih.gov/books/NBK430896/> (accessed on 27 July 2026).
 - [21] Brown, N.J.; Vaughan, D.E. Angiotensin-Converting Enzyme Inhibitors. *Circulation* **1998**, *97*(14), 1411–1420. [[CrossRef](#)] [[PubMed](#)]
 - [22] Diabetic Nephropathy (Kidney Disease)-Symptoms and Causes-Mayo Clinic. Available online: <https://www.mayoclinic.org/diseases-conditions/diabetic-nephropathy/symptoms-causes/syc-20354556> (accessed on 27 July 2026).
 - [23] Prajapati, M.; Dhoke, S.M. The Role of ACE Inhibitors in Slowing Diabetic Nephropathy Progression: A Comprehensive Review. *Int. J. Pharm. Sci.* **2025**, *3*, 1524–1533. [[CrossRef](#)]
 - [24] RPh, D.B. ACE Inhibitors’ Mechanism of Action: Here’s What They Do. GoodRx. Available online: <https://www.goodrx.com/classes/ace-inhibitors/what-do-ace-inhibitors-do> (accessed on 27 July 2026).
 - [25] Zhou, N.; Zhong, S.-Y.; Gao, P.; He, F.-F.; Zhang, C. Hypertension-Induced Renal Injury: From Pathophysiology to Therapeutic Perspectives. *Biomedicines* **2026**, *14*, 595. [[CrossRef](#)] [[PubMed](#)]
 - [26] Ravarotto, V.; Bertoldi, G.; Innico, G.; Gobbi, L.; Calò, L.A. The Pivotal Role of Oxidative Stress in the Pathophysiology of Cardiovascular-Renal Remodeling in Kidney Disease. *Antioxidants* **2021**, *10*(7), 1041. [[CrossRef](#)] [[PubMed](#)]
 - [27] Mikrut, K.; Kupsz, J.; Koźlik, J.; Krauss, H.; Pruszyńska-Oszmałek, E.; Gibas-Dorna, M. Angiotensin-Converting Enzyme Inhibitors Reduce Oxidative Stress Intensity in Hyperglycemic Conditions in Rats Independently from Bradykinin Receptor Inhibitors. *Croat. Med. J.* **2016**, *57*, 371–380. [[CrossRef](#)] [[PubMed](#)]

- [28] Măgureanu, D.C.; Pop, R.M.; Bocsan, I.C.; Neag, M.A.; Cozma, A.; Levai, A.M.; Chedea, V.S.; Buzoianu, A.D. From Plants to Protection: Cardiorenal Benefits in Non-Diabetic Chronic Kidney Disease and Heart Failure. *Molecules* **2025**, *30*, 3982. [CrossRef] [PubMed]
- [29] Popa, C.A. ACEing the Management of Advanced CKD. *NephJC*. Available online: <http://www.nephjc.com/news/aceing-ckd> (accessed on 27 July 2026).
- [30] Polychronopoulou, E.; Wuerzner, G.; Burnier, M. How Do I Manage Hypertension in Patients with Advanced Chronic Kidney Disease Not on Dialysis? Perspectives from Clinical Practice. *Vasc. Health Risk Manag.* **2021**, *17*, 1–11. [CrossRef] [PubMed]
- [31] Sarafidis, P.; Papadopoulos, C.E.; Kamperidis, V.; Giannakoulas, G.; Doulas, M. Cardiovascular Protection With Sodium-Glucose Cotransporter-2 Inhibitors and Mineralocorticoid Receptor Antagonists in Chronic Kidney Disease: A Milestone Achieved. *Hypertension* **2021**, *77*(5), 1442–1455. [CrossRef]
- [32] Sayin, B.Y.; Oto, A. Left Ventricular Hypertrophy: Etiology-Based Therapeutic Options. *Cardiol. Ther.* **2022**, *11*(2), 203–230. [CrossRef] [PubMed]
- [33] Njoh, R.F.; Njei, B.; Nguyen, A.T. 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* **2012**, *60* (Suppl. 1), A124. [CrossRef]
- [34] Hejnova, L.; Drastichova, Z.; Boroš, A.; Hrdlicka, J.; Behuliak, M.; Neckar, J.; Zicha, J.; Novotny, J. Modulation of Left Ventricular Hypertrophy in Spontaneously Hypertensive Rats by Acetylcholinesterase and ACE Inhibitors: Physiological, Biochemical, and Proteomic Studies. *Front. Cardiovasc. Med.* **2024**, *11*, 1390547. [CrossRef] [PubMed]
- [35] Vivian, E.; Mannebach, C. Therapeutic Approaches to Slowing the Progression of Diabetic Nephropathy—Is Less Best? *Drugs Context* **2013**, *2013*, 212249. [CrossRef] [PubMed]
- [36] Morales, J.; Handelsman, Y. Cardiovascular Outcomes in Patients With Diabetes and Kidney Disease. *J. Am. Coll. Cardiol.* **2023**, *82*(2), 161–170. [CrossRef] [PubMed]
- [37] Dobre, D.; Lambers Heerspink, H.J.; de Zeeuw, D. Reducing Cardiovascular Risk: Protecting the Kidney. *Eur. Heart J. Suppl.* **2009**, *11* (Suppl. F), F39–F46. [CrossRef]
- [38] Adameczak, M.; Kurnatowska, I.; Naumnik, B.; Stompór, T.; Tylicki, L.; Krajewska, M. 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.* **2024**, *25*(23), 12941. [CrossRef] [PubMed]
- [39] McDaniel, B.L.; Bentley, M.L. The Role of Medications and Their Management in Acute Kidney Injury. *Integr. Pharm. Res. Pract.* **2015**, *4*, 21–29. [CrossRef] [PubMed]
- [40] Renovascular Hypertension: Practice Essentials, Background, Pathophysiology. Available online: <https://emedicine.medscape.com/article/245140-overview> (accessed on 28 July 2026).
- [41] CV Pharmacology | Angiotensin Converting Enzyme (ACE) Inhibitors. Available online: <https://cvpharmacology.com/vasodilator/ace> (accessed on 28 July 2026).
- [42] ACE-Inhibitors: Be Aware of the Distinction Between Bradykinin- and Histamine-Mediated Angioedema, as Treatment Strategies Differ Significantly. GOV.UK. Available online: <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> (accessed on 28 July 2026).
- [43] Ace Inhibitors: Uses, Side Effects, and Safety-Acibadem Hospitals Group. Available online: <https://acibademinternational.com/health-library/ace-inhibitors-what-patients-need-to-know/> (accessed on 28 July 2026).
- [44] Zhang, Y.; He, D.; Zhang, W.; Xing, Y.; Guo, Y.; Wang, F.; Jia, J.; Yan, T.; Liu, Y.; Lin, S. 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* **2020**, *80*(8), 797–811. [CrossRef] [PubMed]
- [45] Chen, X.; Hoher, C.-F.; Shen, L.; Krämer, B.K.; Hoher, B. Reno- and Cardioprotective Molecular Mechanisms of SGLT2 Inhibitors Beyond Glycemic Control: From Bedside to Bench. *Am. J. Physiol.-Cell Physiol.* **2023**, *325*(3), C661–C681. [CrossRef] [PubMed]
- [46] Combination Therapy for Kidney Failure in Diabetes. Available online: <https://reference.medscape.com/viewarticle/ckd-t2d-combination-therapy-kidney-protection-2026a10006me> (accessed on 28 July 2026).
- [47] Gupta, A.; Sontakke, T.; Acharya, S.; Kumar, S. A Comprehensive Review of Biomarkers for Chronic Kidney Disease in Older Individuals: Current Perspectives and Future Directions. *Cureus* **2024**, *16*(10), e70262. [CrossRef] [PubMed]
- [48] Chen, Y.; Liu, X.; Shengbu, M.; Shi, Q.; Jiaqiu, S.; Lai, X. Biomarkers: New Advances in Diabetic Nephropathy. *Nat. Prod. Commun.* **2025**, *20*(6), 1934578X251321758. [CrossRef]
- [49] Delrue, C.; Eisenga, M.F.; Delanghe, J.R.; Speck-aert, M.M. Personalized Antifibrotic Therapy in CKD Progression. *J. Pers. Med.* **2024**, *14*(11), 1141. [CrossRef] [PubMed]
- [50] Uchiyama-Tanaka, Y. Chronic Kidney Disease and Diet. *Ren. Replace. Ther.* **2025**, *11*(1), 71. [CrossRef]
- [51] NKF KDOQI Guidelines. Available online: https://kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_bp/guide_11.htm (accessed on 28 July 2026).

[52] Biglari, S.; Mischak, H.; Beige, J.; Latosinska, A.; Siwy, J.; Banasik, M. The Future of Chronic Kidney Disease Treatment: Combination Therapy (Polyp-

ill) or Biomarker-Guided Personalized Intervention? *Biomolecules* **2025**, *15*, 809. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher's Note: The views expressed in this article are those of the author(s) and do not necessarily reflect the views of the publisher or editors. The publisher and editors assume no responsibility for any injury or damage resulting from the use of information contained herein.

ACCEPTED ARTICLE