Recent advancements in the role of Angiotensin receptor blockers in the management of chronic kidney disease

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Abstract

Chronic kidney disease (CKD) represents a growing global health burden, driven by rising rates of diabetes, hypertension, and aging populations. Angiotensin receptor blockers (ARBs) remain a cornerstone in CKD management owing to their capacity to reduce proteinuria, slow disease progression, and improve cardiovascular outcomes, with a superior tolerability profile compared to angiotensin-converting enzyme inhibitors. This review highlights the pharmacological mechanisms by which ARBs confer renal protection, including antiproteinuric, antifibrotic, and hemodynamic effects, as well as distinctions among individual agents. Recent clinical evidence supports continued use of ARBs even in advanced CKD, with benefits documented across diabetic and non-diabetic populations. Importantly, ARBs form the foundation of modern multidrug regimens, demonstrating synergistic efficacy when combined with sodium–glucose cotransporter-2 inhibitors, non-steroidal mineralocorticoid receptor antagonists, and glucagon-like peptide-1 receptor agonists. Novel dual-acting therapies, such as sparsentan, exemplify the potential of ARB-based innovations in augmenting renoprotection. Despite their established role, challenges such as hyperkalaemia and acute kidney injury risk necessitate vigilant monitoring and, where needed, the use of adjunctive strategies including potassium binders. Future research directions include biomarker-guided precision therapy, potassium binder–enabled ARB optimization, and outcome trials of dual-pathway agents. Collectively, ARBs remain central to CKD management, not only as proven monotherapy but also as the backbone of evolving, personalized, multidrug treatment strategies aimed at reducing kidney failure and cardiovascular morbidity.

Keywords: Angiotensin receptor blockers, chronic kidney disease, proteinuria, hyperkalaemia, multidrug therapy, sparsentan

1. Introduction

1.1. Global burden of CKD

Chronic kidney disease (CKD) imposes a considerable and growing global health burden. According to the Global Burden of Disease Study 2021, over 673 million people worldwide were living with CKD in 2021, resulting in more than 1.5 million deaths and 44.5 million disability-adjusted life years (DALYs). The absolute number of CKD cases nearly doubled since 1990, driven primarily by population aging and the rising prevalence of diabetes and hypertension.[1] This trend underscores the urgency for effective strategies to arrest progression and reduce morbidity and mortality associated with CKD.

1.2. Historical role of RAS inhibition

The renin–angiotensin system (RAS) plays a central role in CKD pathophysiology by promoting vasoconstriction, sodium retention, aldosterone release, glomerular hypertension, and renal fibrosis. Inhibition of RAS via angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) has long been foundational in CKD management. Both classes of agents have consistently demonstrated the ability to reduce progression to kidney failure and lower the incidence of cardiovascular events in CKD populations.[2] Notably, network meta-analyses show that ACEi and ARBs reduce the odds of kidney failure by approximately 39% and 30%, respectively, compared with placebo.[3]

1.3. Rationale for focusing on ARBs

While ACE inhibitors and ARBs both target RAS, ARBs offer distinct advantages—primarily their lower risk of side effects. Unlike ACEi, ARBs do not impair the degradation of bradykinin, resulting in significantly less cough and angioedema—common limitations of ACEi therapy.[4] Moreover, large observational and claims-based studies have confirmed comparable cardiovascular and renal efficacy between ARBs and ACEi, but with improved tolerability and fewer adverse withdrawals.[5] Given these benefits—efficacy, safety, and patient adherence—ARBs are often preferred, particularly in those intolerant to ACE inhibitors.

As newer therapeutics—like sodium-glucose cotransporter-2 inhibitors (SGLT2i), non-steroidal mineralocorticoid receptor antagonists, and dual-mechanism agents—emerge for CKD, ARBs continue to serve as the backbone of combination strategies. Their safety profile and mechanistic complementarity make them indispensable components in comprehensive CKD management, which this review will explore further.

2. Pharmacological basis of ARBs in CKD

2.1. Mechanism of Action

Angiotensin II type 1 receptor blockers (ARBs) exert their primary mechanism of action by selectively antagonizing the AT_1 receptor, thereby thwarting the effects of angiotensin II—

including vasoconstriction, sodium retention, aldosterone secretion, cell proliferation, oxidative stress, and inflammatory signaling. This blockade reduces intraglomerular pressure and mitigates pathways that drive renal injury and fibrosis.[6] Importantly, unlike ACE inhibitors, ARBs do not elevate bradykinin levels, minimizing the risk of side effects such as cough or angioedema (Figure 1).

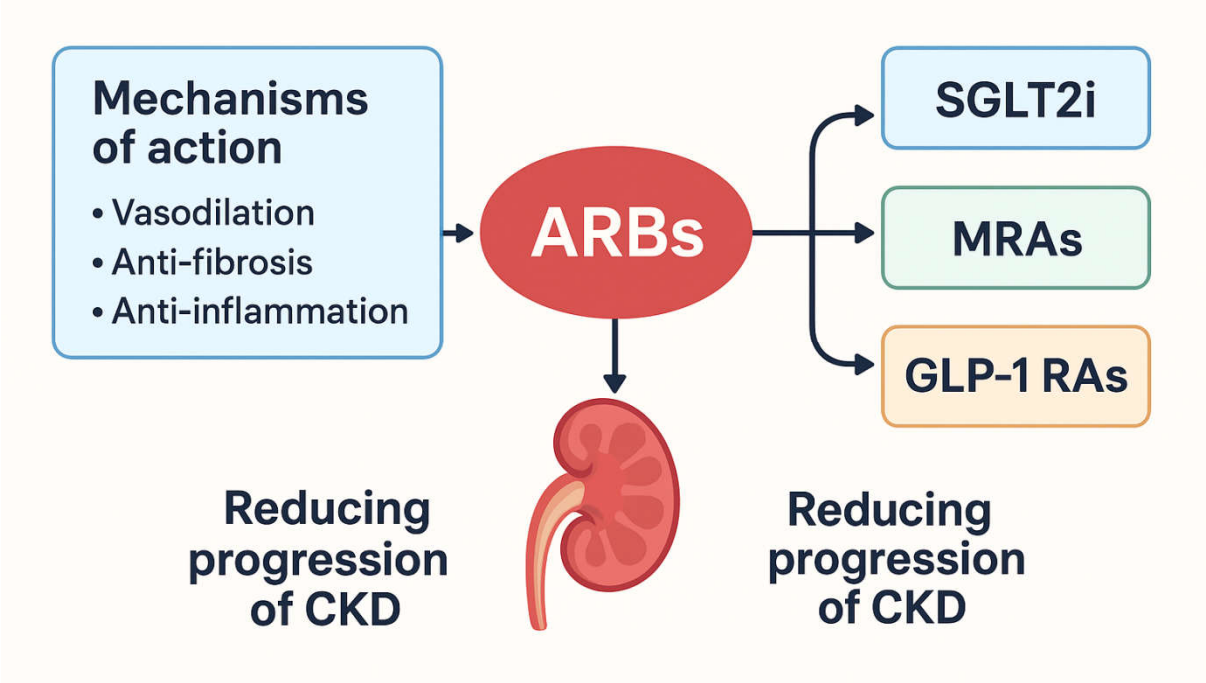

Fig 1. ARBs in CKD management

2.2. Antiproteinuric, Anti-Fibrotic, and Hemodynamic Effects

ARBs are particularly effective at reducing proteinuria—a key surrogate marker and driver of CKD progression. They do this via dual mechanisms: lowering intraglomerular pressure (particularly through dilation of the efferent arteriole) and exerting direct effects on podocytes and mesangial cells to stabilize the glomerular filtration barrier.[7] Additionally, ARBs attenuate fibrotic pathways by inhibiting angiotensin II–induced secretion of profibrotic cytokines like TGF-β and reducing extracellular matrix deposition. They also curb inflammatory cascades and oxidative stress, preserving both tubular and interstitial architecture—actions that extend their benefit beyond simple hemodynamic effects into the realm of genuine disease modification.

2.3. Comparative Pharmacology among ARBs

While ARBs share a common mechanism—AT_1 receptor blockade—they differ notably in pharmacokinetics, receptor affinity, and ancillary pharmacological properties:

- Losartan is metabolized into an active compound known as EXP3174. This metabolite is significantly more potent (approximately 10- to 40-fold) in antagonizing the AT_1 receptor than losartan itself, has a longer half-life (~6–8 hours), and contributes substantially to losartan's therapeutic effects.[8]

- Telmisartan stands out among ARBs for its partial agonist activity at PPAR-γ (peroxisome proliferator-activated receptor gamma). Structural and biophysical studies confirm that telmisartan's unique interaction with PPAR-γ's helix 12 leads to partial activation, potentially offering metabolic benefits such as improved insulin sensitivity and lipid metabolism—traits absent in other ARBs [structural basis of telmisartan's PPAR-γ activity].[9]
- Other ARBs—like valsartan and candesartan—are characterized by high receptor affinity and longer durations of action, supporting sustained blood pressure control and durable RAS inhibition. While the precise clinical relevance of these differences remains to be fully elucidated, they afford clinicians options tailored to individual patient pharmacodynamic needs and comorbidities.

Overall, ARBs offer a multifaceted pharmacological profile, beyond lowering blood pressure, they reduce proteinuria, attenuate inflammation and fibrosis, and—depending on the agent—may confer metabolic advantages. Understanding the nuanced differences among ARBs supports informed, individualized selection in CKD management.

3. Recent clinical evidence

3.1. Efficacy of ARBs across different CKD stages (including advanced disease)

Although concerns about hyperkalaemia and acute kidney function decline often limit the use of RAS inhibition in advanced CKD, recent evidence supports continued therapy where feasible. A randomized controlled trial (STOP-ACEi) compared continuation versus discontinuation of ACEi/ARBs in patients with stage 4–5 CKD and found no benefit to stopping therapy; in fact, there was a trend toward improved kidney outcomes with continuation[10]. A meta-analysis of observational studies also concluded that maintaining RAS blockade in advanced CKD was associated with delayed dialysis initiation and no increase in mortality[11]. These findings highlight that ARBs remain effective even in late-stage disease when used with appropriate monitoring (Table 1).

3.2. Evidence in diabetic vs non-diabetic CKD

The strongest evidence for ARBs originates from diabetic kidney disease. The IDNT trial demonstrated that irbesartan significantly reduced the risk of doubling of serum creatinine, ESRD, or death in patients with type 2 diabetes and nephropathy, independent of blood pressure control. Similarly, the RENAAL study showed that losartan reduced the risk of ESRD and lowered proteinuria in type 2 diabetic nephropathy[12].

For non-diabetic CKD, trials and meta-analyses also support ARB efficacy. In IgA nephropathy, ARBs reduced proteinuria and slowed kidney function decline compared to placebo or non-RAS antihypertensives. The degree of proteinuria reduction with ARBs correlates strongly with long-term renal outcomes across both diabetic and non-diabetic CKD[13].

3.3. Long-term outcome data

Beyond kidney endpoints, ARBs confer cardiovascular protection in CKD patients. The LIFE study demonstrated that losartan was superior to atenolol in reducing cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy, many of whom had CKD. A large network meta-analysis confirmed that ARBs reduce progression to kidney failure and major cardiovascular events in CKD populations, with efficacy similar to ACE inhibitors but better tolerability[4, 14].

Table 1. Key Clinical Trials and evidence on ARBs in Chronic Kidney Disease

Study / Year	Population	Intervention (vs comparator)	Primary Kidney Outcomes	Key Findings
Lewis et al., (2001) [15]	1,715 pts with T2DM, HTN, nephropathy	Irbesartan vs amlodipine/placebo	Doubling of serum creatinine, ESRD, or death	Irbesartan ↓ risk of primary endpoint by 20% vs placebo (p=0.02); effect independent of BP lowering.
RENAAL (2001) [12]	1,513 pts with T2DM + nephropathy	Losartan vs placebo (all on conventional antihypertensives)	Doubling of serum creatinine, ESRD, or death	Losartan ↓ risk of ESRD by 28%; ↓ proteinuria by 35%.
LIFE (2002) [14]	9,193 hypertensive pts (with LVH, some with CKD)	Losartan vs atenolol	CV morbidity and mortality (secondary renal outcomes)	Losartan ↓ risk of stroke by 25% and new-onset diabetes by 25%; renal protective trends noted.
STOP-ACEi (2016) [16]	411 pts with stage 4–5 CKD	Continuation vs discontinuation of ACEi/ARB	Rate of decline in eGFR, dialysis initiation	No benefit from stopping therapy; continuation safe, trend toward fewer ESKD events.
Fu et al., (2021) [17]	10,400 pts with advanced CKD (observational, registry)	Continuers vs discontinuers of RAS inhibitors	Dialysis initiation, mortality	Continuation associated with lower risk of dialysis; no excess mortality.

Xie et al., 2016) [4]	119 RCTs, >64,000 CKD pts	RAS inhibitors (ACEi, ARB, combo) vs placebo/other	Kidney failure, CV outcomes	ARBs ↓ kidney failure risk (RR 0.70); ↓ major CV events; efficacy comparable to ACEi but better tolerated.
PROTECT trials (2023) [18]	Non-diabetic proteinuric CKD (esp. IgA)	ARB vs placebo/other antihypertensives	Proteinuria, eGFR decline	ARBs consistently ↓ proteinuria, slowed GFR decline; benefit proportional to proteinuria reduction.
Heerspink et al. (2020) [19]	4304 participants	Albuminuria reduction as endpoint	CKD progression, ESRD	Albuminuria reduction under ARB therapy strongly predicts long-term renal outcomes.

4. Integration of ARBs in Modern Multidrug Regimens

The modern management of chronic kidney disease (CKD) increasingly relies on combination pharmacotherapy, with angiotensin receptor blockers (ARBs) serving as the foundational therapy on which newer agents are added to achieve complementary mechanisms of renal protection (Figure 2).

4.1. ARBs and SGLT2 inhibitors

Sodium–glucose cotransporter-2 inhibitors (SGLT2i) have reshaped CKD treatment by providing consistent reductions in the risk of CKD progression and major cardiovascular outcomes across trials that largely enrolled patients receiving background RAS blockade. In DAPA-CKD, dapagliflozin reduced the composite risk of sustained decline in eGFR, end-stage kidney disease, or renal/cardiovascular death; most participants were treated with an ACE inhibitor or ARB at baseline, and benefit was seen on top of optimized RAS inhibition. EMPA-KIDNEY likewise demonstrated that empagliflozin reduced the risk of progression of kidney disease or death from cardiovascular causes across a broad CKD population; a large proportion of trial participants were receiving ACEi/ARB background therapy, supporting the clinical strategy of combining ARBs with SGLT2i for additive kidney protection. Mechanistically, ARBs reduce intraglomerular pressure and proteinuria through efferent arteriolar effects and

antifibrotic signaling, while SGLT2i modify tubular handling of sodium, restore tubuloglomerular feedback, reduce intraglomerular hypertension via afferent signaling, and reduce metabolic stress — together producing complementary and often additive nephroprotection[19].

4.2. ARBs with mineralocorticoid receptor antagonists

Non-steroidal, selective mineralocorticoid receptor antagonists such as finerenone have shown incremental cardiorenal benefit when added to a background of optimized RAS blockade in patients with CKD and type 2 diabetes. The FIDELIO-DKD trial found that finerenone lowered the risk of a sustained decline in eGFR, end-stage kidney disease, or renal death compared with placebo in patients already receiving standard of care — which generally included ACE inhibitors or ARBs — while FIGARO-DKD demonstrated cardiovascular benefit across a similar population. Importantly, MR antagonists increase the risk of hyperkalaemia; this risk is modulated by baseline kidney function and concomitant therapies, so clinicians must monitor potassium closely and consider mitigation strategies (dietary measures, potassium binders) when combining MRAs with ARBs. The RAS-blocking background in these trials confirms that finerenone provides additive benefit rather than replacing ARBs[20].

4.3. Combination with GLP-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated cardiovascular and metabolic benefits and are now being evaluated for renal endpoints. The FLOW trial showed that semaglutide reduced the risk of clinically important kidney outcomes in patients with type 2 diabetes and CKD, and most participants were on background RAS blockade, implying additive effects with ARBs. The kidney benefits of GLP-1 RAs appear to be mediated through multiple mechanisms (improvements in glycaemic control, weight loss, blood pressure reduction, anti-inflammatory effects, and reductions in albuminuria), and early evidence suggests that combining GLP-1 RAs with ARBs is safe and potentially synergistic — though definitive data on routine triple therapy (ARBs + SGLT2i + GLP-1 RA) for kidney outcomes are still emerging and require further study[21].

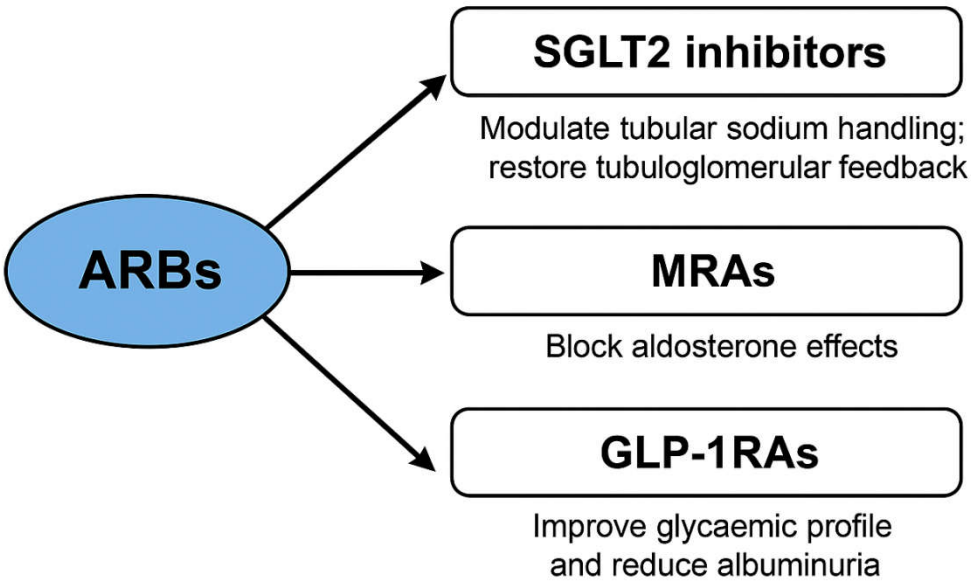

Fig 2. Integration of ARBs in modern multidrug regimens

4.4. Practical considerations and sequencing

In practice, ARBs remain the default starting RAS blocker for patients with hypertension and albuminuria. Recommended sequencing often places ARB initiation and titration to an antiproteinuric dose first, with early laboratory monitoring (creatinine, eGFR, serum potassium within 1–2 weeks). If albuminuria or cardiorenal risk remains elevated despite optimized ARB therapy, adding an SGLT2i is appropriate in most patients (including many without diabetes), followed by consideration of finerenone in eligible patients with type 2 diabetes and persistent albuminuria. GLP-1 RAs may be prioritized in patients with type 2 diabetes and compelling metabolic or cardiovascular indications; their renal benefits add to, rather than replace, ARB therapy. When combining agents, clinicians must monitor for overlapping adverse effects (notably hyperkalaemia with MRAs and eGFR dips after initiation of RAS blockade or SGLT2i) and use mitigation strategies such as potassium binders or dose adjustments if needed (Figure 3)[22].

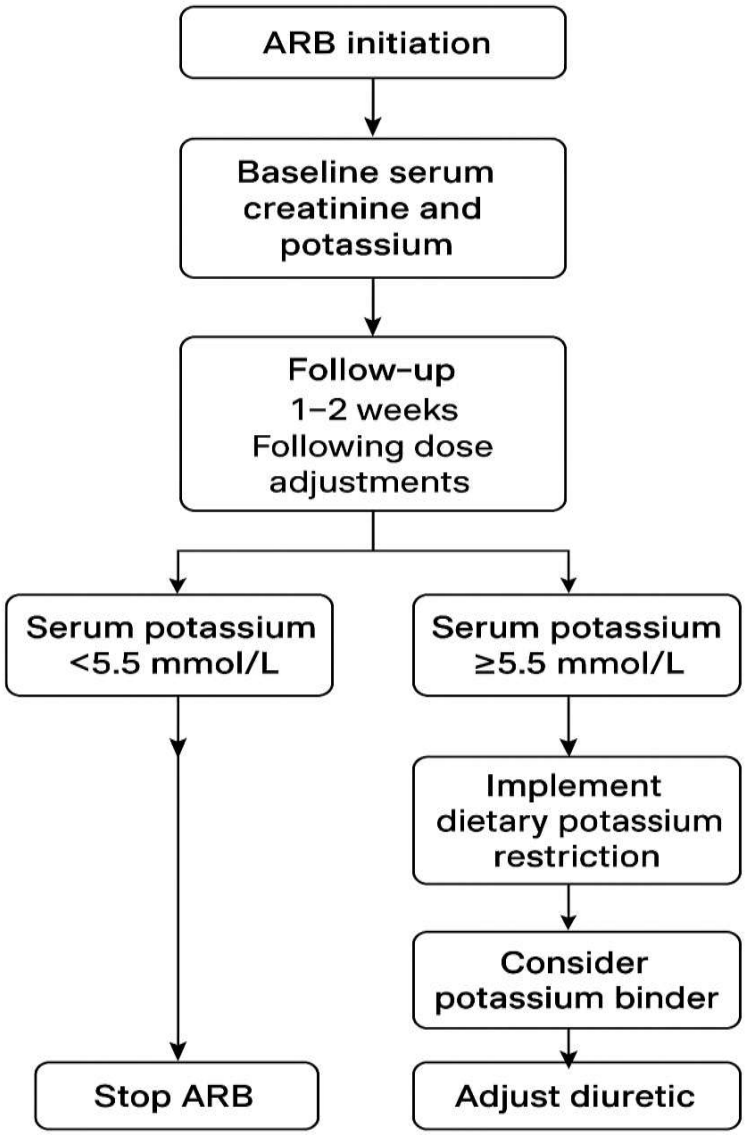

Fig 3. Practical considerations of ARB initiation

5. Novel ARB-Related Therapies

The classical paradigm of single-target angiotensin II type 1 (AT_1) receptor blockade is being extended by drugs that combine ARB pharmacology with additional pathway inhibition to achieve greater antiproteinuric and antifibrotic effects. The most clinically advanced example is sparsentan, a single-molecule dual antagonist of the AT_1 receptor and the endothelin A (ETA) receptor. This dual mechanism aims to harness the complementary biology of the RAS and endothelin systems — angiotensin II promotes efferent arteriolar constriction, proteinuria and profibrotic signaling, while endothelin A activation drives vasoconstriction, inflammation and fibrosis through separate but intersecting pathways. By simultaneously blocking AT_1 and ETA receptors, sparsentan produces more potent and durable reductions in proteinuria than ARB monotherapy in selected glomerular diseases, with attendant signals of kidney-protective benefit in medium-term follow-up[20].

The phase 3 PROTECT trial in IgA nephropathy compared sparsentan with irbesartan and demonstrated significantly greater reduction in proteinuria and favourable trends in hard renal endpoints over two years; treatment-emergent adverse events were generally balanced, though liver-related monitoring and risk management were incorporated in regulatory labeling given signals requiring caution. Sparsentan also showed promising antiproteinuric effects in focal segmental glomerulosclerosis (FSGS) in earlier randomized studies (DUET and subsequent programs), supporting development across proteinuric glomerulopathies where podocyte injury and glomerular hemodynamics contribute to progression[21-23]. Following accelerated regulatory pathways, sparsentan (FILSPARI®) has received approvals/authorizations for IgA nephropathy in major jurisdictions and continues to undergo evaluation for additional indications such as FSGS, with post-marketing safety monitoring focused on hepatic function and reproductive toxicity mitigation via REMS-type programs in some regions[24]. Mechanistic reviews and translational studies attribute sparsentan's enhanced antiproteinuric effect to combined hemodynamic (afferent/efferent balance), direct podocyte protective actions, and antifibrotic/inflammatory modulation afforded by dual receptor blockade[25].

Beyond sparsentan, the success of dual-mechanism ARB-based therapy has catalysed interest in several future directions for ARB-related drug design. These include: (a) multi-target small molecules that combine ARB activity with antagonism of profibrotic or proinflammatory pathways (for example, selective endothelin modulation, TGF-β pathway modulators, or chemokine receptor blockers); (b) biased ligands or allosteric modulators of the AT_1 receptor that favor beneficial signalling (e.g., β-arrestin pathways) while avoiding harmful G-protein mediated effects — a theoretical approach that might separate hemodynamic benefit from adverse remodeling; (c) precision-guided combinations whereby ARB-based dual agents are deployed selectively in biomarker-defined subgroups (for example, those with high endothelin signatures or podocyte gene expression patterns); and (d) conjugated or targeted delivery systems that concentrate ARB activity in the kidney to maximize efficacy and limit systemic adverse effects. While many of these concepts remain preclinical or early translational work, the clinical progress of sparsentan demonstrates that ARB-centric polypharmacology is a feasible and clinically relevant strategy to broaden renoprotective options for proteinuric kidney disease[23].

6. Safety Concerns and Management Strategies

6.1. Hyperkalaemia and acute kidney injury risk

The most significant safety concerns with ARB therapy in CKD are hyperkalaemia and acute kidney injury (AKI). ARBs reduce aldosterone secretion and impair renal potassium excretion, leading to hyperkalaemia risk, especially in advanced CKD, diabetes, or when combined with other potassium-retaining agents[26]. The risk of AKI is related to reductions in glomerular filtration pressure due to efferent arteriolar vasodilation; this is most pronounced in patients with bilateral renal artery stenosis, volume depletion, or concomitant use of NSAIDs and diuretics. Importantly, small and transient increases in serum creatinine after ARB initiation

are often hemodynamic and do not necessitate discontinuation unless the rise exceeds 30% from baseline[27].

6.2. Role of potassium binders (patiromer, sodium zirconium cyclosilicate)

The advent of novel oral potassium binders has enabled safer continuation of ARBs in patients who otherwise would require discontinuation due to hyperkalaemia. Patiromer and sodium zirconium cyclosilicate (SZC) are both effective in lowering serum potassium and preventing recurrent hyperkalaemia in CKD and heart failure patients on RAS inhibitors. The OPAL-HK trial showed that patiromer enabled sustained RAAS blockade by lowering serum potassium in CKD patients with hyperkalaemia[28]. Similarly, the HARMONIZE trial demonstrated that SZC rapidly normalized serum potassium and maintained normokalaemia in patients on RAAS inhibitors. These therapies are now integrated into guidelines as adjuncts to permit ongoing ARB therapy in high-risk patients[29].

6.3. Monitoring protocols and practical clinical considerations

Best practice involves baseline measurement of serum creatinine and potassium prior to ARB initiation, followed by repeat testing within 1–2 weeks and after each dose titration. A serum creatinine rise ≤30% is usually acceptable, while hyperkalaemia thresholds for discontinuation vary; many experts recommend continued therapy with adjunctive measures unless potassium exceeds 6.0 mmol/L or rises rapidly. Adjunctive strategies include dietary potassium restriction, diuretic therapy (loop or thiazide), and use of new potassium binders when indicated. Clinicians should also avoid concomitant nephrotoxic drugs (NSAIDs, dual RAS blockade) and monitor more closely in advanced CKD, elderly patients, or those with comorbidities[30].

7. Future Directions and Research Gaps

7.1. Biomarker-driven precision therapy

One of the most promising directions in CKD therapeutics is the integration of biomarkers to guide ARB use and combination strategies. Traditional “one-size-fits-all” approaches are being replaced by efforts to stratify patients according to molecular signatures of fibrosis, inflammation, or endothelial activation. For example, elevated urinary and plasma biomarkers of tubular injury (NGAL, KIM-1), inflammation (TNFR1/2), and endothelial stress (endothelin-1) may predict progression and response to therapy. In the context of ARBs, such biomarkers could identify patients who will derive the greatest antiproteinuric or antifibrotic benefit and determine who may need early escalation to dual-pathway regimens such as ARB–endothelin blockade. Incorporating biomarker-driven decision-making into clinical trials is a critical next step toward precision nephrology[31].

7.2. Potassium binder–enabled ARB optimization studies

Although ARBs provide well-documented renoprotection, their use is often limited by hyperkalaemia, particularly in advanced CKD. New potassium binders, including patiromer and sodium zirconium cyclosilicate, have demonstrated efficacy in reducing hyperkalaemia and enabling continuation of RAAS blockade in patients with CKD or heart failure[29]. However, long-term outcome studies specifically addressing whether binder-enabled ARB optimization translates into improved kidney and cardiovascular outcomes are lacking. Dedicated randomized trials evaluating strategies of "ARB maximization with potassium binder support" could fill this evidence gap, allowing clinicians to safely maintain higher intensity therapy in high-risk populations.

7.3. Long-term outcome trials of dual-pathway agents

The development of dual-acting agents, such as sparsentan, underscores the potential for multi-target drug design in glomerular diseases. While the PROTECT and DUET trials have demonstrated sustained reductions in proteinuria and promising trends in renal outcomes in IgA nephropathy and FSGS[18,20], confirmatory long-term outcome trials powered for hard endpoints such as kidney failure, dialysis initiation, and mortality remain a priority. Furthermore, trials are needed to clarify safety concerns, including hepatotoxicity and fluid retention, over extended treatment periods. Beyond sparsentan, next-generation ARB-based agents that incorporate biased AT_1 receptor modulation or combined antifibrotic targets (e.g., TGF-β inhibitors) are under preclinical exploration[41]. These strategies represent important research gaps that must be addressed to expand the therapeutic landscape of ARB-related therapies in CKD.

8. Conclusion

Angiotensin receptor blockers remain a cornerstone of chronic kidney disease management. Decades of clinical trial evidence demonstrate their capacity to reduce proteinuria, slow progression to kidney failure, and improve cardiovascular outcomes. Despite the advent of newer agents, ARBs continue to serve as the foundational therapy in CKD with albuminuria, particularly when titrated to maximally tolerated doses with appropriate monitoring. Their favorable tolerability profile and widespread availability ensure ongoing global relevance, including in low- and middle-income settings where therapeutic options may be limited.

Recent advances have not displaced ARBs but instead highlighted their synergistic potential when used in combination regimens. Landmark trials of sodium–glucose cotransporter-2 inhibitors, non-steroidal mineralocorticoid receptor antagonists, and glucagon-like peptide-1 receptor agonists have consistently enrolled patients on background RAS inhibition, underscoring ARBs as the therapeutic platform upon which newer agents exert additive benefits. Novel dual-pathway drugs such as sparsentan further illustrate the potential of augmenting ARB pharmacology to achieve superior antiproteinuric and antifibrotic effects.

These findings support a modern multidrug approach, where ARBs anchor a layered strategy of renoprotection.

Looking ahead, the role of ARBs is poised to expand through integration with precision medicine and novel drug design. Biomarker-guided therapy could identify patients most likely to respond to ARBs or require early escalation to dual or triple therapy. Advances in potassium binders may allow fuller optimization of ARB dosing without compromising safety. Meanwhile, long-term outcome trials of dual-acting and next-generation ARB derivatives will clarify their place in glomerular disease management. Collectively, these developments suggest that while ARBs represent an established therapy, they also remain a dynamic platform for innovation. The next decade is likely to see ARBs evolve from a monotherapy backbone to the centerpiece of personalized, multidrug strategies for kidney and cardiovascular protection in CKD.

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