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ACE INHIBITORS, ANGIOTENSIN RECEPTOR BLOCKERS, AND ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITORS IN CONTEMPORARY CARDIOVASCULAR AND RENAL CARE: A NARRATIVE REVIEW

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ABSTRACT

This narrative review critically compares angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and angiotensin receptor-neprilysin inhibitors (ARNIs) in contemporary cardiovascular and renal care, with particular emphasis on guideline-directed use, safety monitoring, adherence, and treatment implementation. A structured narrative search of PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library was completed on 28 June 2026. Randomized trials, systematic reviews, large observational studies, target-trial emulations, and international guideline documents were prioritized. ACEIs and ARBs provide broadly comparable blood pressure reduction and nephroprotection in many populations, whereas ARBs are usually better tolerated, mainly because cough and bradykinin-mediated angioedema are less frequent. ACEIs remain particularly well established after myocardial infarction. ARNIs have the most clearly confirmed advantage in eligible symptomatic patients with HFrEF, but their benefit should not be automatically extrapolated to uncomplicated hypertension, CKD without heart failure, or post-myocardial infarction patients without a heart failure phenotype. Optimal selection requires integration of evidence, laboratory monitoring, availability, costs, and patient preferences.

KEYWORDS

ACE Inhibitors, Angiotensin Receptor Blockers, Sacubitril/Valsartan, Heart Failure, Chronic Kidney Disease, Guideline-Directed Therapy

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1. Introduction

Cardiovascular diseases remain among the leading causes of death and disability, and their coexistence with chronic kidney disease (CKD), type 2 diabetes, and hypertension represents one of the major clinical challenges in contemporary medicine. The renin-angiotensin-aldosterone system (RAAS) is a shared pathophysiological pathway in these conditions. Persistent or maladaptive RAAS activation promotes vasoconstriction, sodium retention, endothelial dysfunction, oxidative stress, fibrosis, myocardial remodeling, albuminuria, and progressive kidney injury (Triebel & Castrop, 2024; Morat et al., 2025).

Pharmacological RAAS modulation is one of the best documented strategies for reducing cardiovascular and renal risk. ACEIs were the first widely used class of RAAS-inhibiting drugs and continue to have an important role in HFrEF, post-myocardial infarction care, hypertension, and CKD with albuminuria. ARBs were introduced to achieve similar blockade of the angiotensin axis with less interference with bradykinin metabolism. ARNIs, especially sacubitril/valsartan, combine AT1 receptor blockade with neprilysin inhibition, augmenting the natriuretic peptide system and improving prognosis in patients with HFrEF (McMurray et al., 2014; McDonagh et al., 2021; Heidenreich et al., 2022).

The practical clinical question is no longer which drug class is universally best, but which RAAS-modifying strategy is appropriate for a specific patient phenotype, taking into account blood pressure, estimated glomerular filtration rate (eGFR), serum potassium, previous adverse effects, treatment availability, costs, monitoring capacity, and the likelihood of long-term adherence.

The aim of this article is to critically compare ACEIs, ARBs, and ARNIs in the context of contemporary cardiovascular and nephrology guidelines and to present a practical decision framework that incorporates both clinical evidence and barriers to implementation.

2. Methods

This article was designed as a narrative review because the available evidence covers heterogeneous populations, different drug classes, variable end points, different follow-up periods, and varying degrees of relevance to clinical practice and guidelines.

The literature search was performed in PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library. The final verification search was completed on 28 June 2026. Search terms included, among others: ACE inhibitor, angiotensin-converting enzyme inhibitor, ARB, angiotensin receptor blocker, ARNI, sacubitril/valsartan, heart failure, HFrEF, HFmrEF, HFpEF, hypertension, chronic kidney disease, diabetic kidney disease, albuminuria, cardiovascular outcomes, renal outcomes, mortality, hospitalization, myocardial infarction, RAAS inhibition, and guideline.

Randomized clinical trials, systematic reviews, meta-analyses, large observational studies, and recommendations from international societies were prioritized. Publications addressing blood pressure control, cardiovascular mortality, heart failure hospitalization, albuminuria, CKD progression, adverse events, and treatment discontinuation were included.

Evidence from 2024-2026 was highlighted when available; however, older landmark trials such as PARADIGM-HF and PARAGON-HF were retained because they continue to determine current recommendations. Interpretation of the evidence followed an evidence hierarchy: guidelines, randomized trials, and high-quality systematic reviews were weighted more strongly than single observational studies.

3. What this review adds

This review aims to synthesize the place of ACEIs, ARBs, and ARNIs in contemporary treatment. Instead of presenting these drug classes as interchangeable, the article organizes their use according to the dominant clinical problem of the patient, including cardiovascular and renal phenotypes such as HFrEF, HFmrEF/HFpEF, CKD with albuminuria, type 2 diabetes, post-myocardial infarction status, advanced CKD, older age, and long-term care.

A second element of added value is the emphasis on implementation of recommendations. The article links mechanisms of action and clinical end points with practical issues such as creatinine and potassium monitoring, hypotension, treatment costs, and avoidance of unjustified discontinuation of RAAS therapy. This perspective is particularly important because treatment failure often results not from lack of pharmacological efficacy but from suboptimal implementation.

4. Pathophysiology of the renin-angiotensin-aldosterone system

The RAAS regulates arterial pressure, intravascular volume, sodium-potassium balance, vascular tone, glomerular hemodynamics, and tissue remodeling. Under physiological conditions, RAAS activation is an adaptive response to renal hypoperfusion, sodium depletion, or sympathetic stimulation. In chronic disease, however, the same axis becomes a mechanism sustaining hypertension, myocardial hypertrophy and fibrosis, vascular inflammation, albuminuria, and CKD progression.

The classical cascade begins with renin release from juxtaglomerular cells. Renin converts angiotensinogen into angiotensin I, which is subsequently converted to angiotensin II by angiotensin-converting enzyme. Through the AT1 receptor, angiotensin II promotes vasoconstriction, aldosterone secretion, sodium retention, sympathetic activation, oxidative stress, inflammation, hypertrophy, and fibrosis. These effects are relevant in HFrEF, hypertension, diabetic kidney disease, and proteinuric CKD.

Aldosterone increases sodium reabsorption and potassium excretion in the distal nephron. In the short term this is an adaptive response, whereas chronic aldosterone excess promotes myocardial fibrosis, arterial stiffness, endothelial dysfunction, albuminuria, and deterioration of kidney function. Counter-regulatory pathways include the AT2 receptor and the natriuretic peptide system, which support vasodilatation, natriuresis, diuresis, and antifibrotic signaling.

Neprilysin is a neutral endopeptidase that degrades natriuretic peptides and other vasoactive mediators. Neprilysin inhibition increases the availability of atrial and B-type natriuretic peptides, thereby enhancing diuresis, natriuresis, vasodilatation, and antihypertrophic signaling. Clinically effective neprilysin inhibition therefore requires simultaneous AT1 receptor blockade to avoid an unfavorable increase in angiotensin II signaling (McMurray et al., 2014; Solomon et al., 2019).

5. Comparative mechanisms of action of ACEIs, ARBs, and ARNIs

ACEIs reduce the conversion of angiotensin I to angiotensin II, thereby attenuating AT1 receptor stimulation, vasoconstriction, aldosterone secretion, sodium retention, and adverse remodeling. They also inhibit bradykinin degradation. Increased bradykinin may support nitric oxide and prostacyclin release, but it is also responsible for dry cough and contributes to some cases of angioedema (Li et al., 2014; Hu et al., 2023).

ARBs selectively block angiotensin II binding to the AT1 receptor. They do not meaningfully inhibit bradykinin degradation; therefore, cough and angioedema occur less often than during ACEI therapy. Circulating angiotensin II may increase, and part of the signal may be redirected through the AT2 receptor, although the clinical relevance of this phenomenon is complex and context-dependent (Chen et al., 2021).

ARNIs provide dual neurohormonal modulation. Sacubitril/valsartan combines valsartan, an ARB, with sacubitril, a prodrug of the active neprilysin inhibitor LBQ657. Valsartan blocks the AT1 receptor, whereas sacubitril increases natriuretic peptide availability. This combination simultaneously attenuates maladaptive RAAS signaling and enhances vasodilatory, natriuretic, diuretic, and antifibrotic mechanisms (McMurray et al., 2014; Park et al., 2022; Evbayekha et al., 2025).

Table 1. Comparative mechanisms of action of ACEIs, ARBs, and ARNIs.

Mechanistic feature	ACEIs	ARBs	ARNIs
Primary target	Angiotensin-converting enzyme	AT1 receptor	AT1 receptor and neprilysin
Angiotensin II generation	Reduced	Not reduced	Not reduced
AT1 receptor blockade	Indirect	Direct	Direct
Effect on bradykinin	Increased	Minimal	No ACE-dependent accumulation; angioedema risk is relevant with ACEI coadministration
Natriuretic peptides	No direct increase	No direct increase	Increased through neprilysin inhibition
Main tolerability issue	Cough and angioedema	Hyperkalemia	Symptomatic hypotension
Key clinical strength	Post-MI evidence and HFrEF therapy when ARNI is unavailable	Tolerability and adherence	Best outcomes in eligible patients with HFrEF

6. Angiotensin-converting enzyme inhibitors

ACEIs remain one of the best studied classes of cardiovascular drugs. Their efficacy has been documented in hypertension, HFrEF, asymptomatic left ventricular systolic dysfunction, CKD with albuminuria, diabetic kidney disease, and secondary prevention after myocardial infarction (Li et al., 2014; McDonagh et al., 2021; Kidney Disease: Improving Global Outcomes CKD Work Group, 2024).

The clinical mechanism of ACEIs combines reduced angiotensin II formation with greater bradykinin availability. The result is vasodilatation, afterload reduction, decreased aldosterone secretion, lower sodium retention, and attenuation of adverse cardiac and vascular remodeling. Conversely, bradykinin is responsible for cough and may participate in the pathogenesis of angioedema.

After myocardial infarction, ACEIs are particularly important in patients with left ventricular dysfunction, hypertension, diabetes, CKD, or symptoms of heart failure. In CKD, they reduce intraglomerular pressure and albuminuria, thereby slowing kidney disease progression. Serum creatinine and potassium should be monitored after treatment initiation, but a moderate early decline in eGFR often reflects a hemodynamic effect and should not automatically lead to permanent drug discontinuation (KDIGO CKD Work Group, 2024; Lee et al., 2023).

The main limitations of ACEIs include cough, angioedema, hyperkalemia, symptomatic hypotension, and deterioration of kidney function in susceptible patients. Contraindications include pregnancy, a history of ACEI-associated angioedema, and clinically significant bilateral renal artery stenosis.

Table 2. Mechanistic and clinical effects of ACE inhibition.

Mechanism	Principal effects and benefits	Clinical considerations
Reduced angiotensin II formation	Vasodilatation, lower blood pressure, lower intraglomerular pressure	Expected early eGFR decline may occur
Reduced aldosterone secretion	Less sodium and water retention; lower cardiac load	Risk of hyperkalemia, especially in CKD and with MRAs
Reduced endothelin and sympathetic activation	Improved endothelial function and vascular compliance	Component of cardiometabolic benefit
Increased renin release	Compensatory response after interruption of feedback signaling	Does not negate clinical benefit
Reduced bradykinin degradation	Potential endothelial effect through nitric oxide and prostacyclin	Dry cough and angioedema
Antiremodeling effects	Antifibrotic and antiproliferative effects	Important after MI and in HFrEF

Table 3. Selected adverse effects of ACEIs.

Adverse effect	Frequency or characterization	Mechanism or clinical note
Dry cough	Common; often estimated at 5-20% depending on population	Related to bradykinin and substance P; may lead to discontinuation
Angioedema	Rare but potentially life-threatening	Bradykinin-mediated; requires permanent ACEI discontinuation
Hyperkalemia	Requires monitoring	Reduced aldosterone secretion; higher risk in CKD, diabetes, and with MRAs
Hypotension	More frequent with hypovolemia or high initial doses	Assess hydration status and diuretic dosing
Worsening renal function	Context-dependent	Evaluate renal artery stenosis, dehydration, NSAID use, and excessive diuresis

7. Angiotensin receptor blockers

ARBs provide effective RAAS blockade without typical bradykinin-mediated adverse effects. These drugs block AT1 receptors, thereby reducing vasoconstriction, aldosterone release, sodium retention, sympathetic activation, oxidative stress, inflammation, and fibrosis. This explains their similar clinical efficacy to ACEIs in many indications and their more favorable tolerability profile (Chen et al., 2021; Li et al., 2014).

In hypertension, ACEIs and ARBs are equivalent first-line options among RAAS-modifying agents. The 2024 ESC guidelines identify ACEIs or ARBs, dihydropyridine calcium-channel blockers, and thiazide or thiazide-like diuretics as the principal first-line pharmacological classes. ARBs should therefore not be presented as universally preferred over ACEIs in every patient with target-organ damage; their main advantage is tolerability rather than general antihypertensive superiority (McEvoy et al., 2024).

ARBs are widely used in CKD with albuminuria, diabetic kidney disease, left ventricular hypertrophy, and ACEI intolerance. In HFrEF, they are used mainly when ACEIs or ARNIs are contraindicated or not tolerated. After myocardial infarction, ARBs are appropriate alternatives for patients who do not tolerate ACEIs, although in patients who tolerate ACEIs the historical evidence base after MI remains stronger for ACE inhibition (Lee et al., 2023).

The most important practical advantage of ARBs is less frequent discontinuation due to cough and angioedema. Studies suggest similar cardiovascular effectiveness of ACEIs and ARBs in many first-line settings, often with better tolerability for ARBs (Chen et al., 2021; Xie et al., 2025). ARBs still require monitoring for hyperkalemia, hypotension, and kidney function, particularly in advanced CKD, older adults, hypovolemia, and combination therapy with MRAs.

Newer data in type 2 diabetes indicate that ACEIs and ARBs provide broadly comparable cardiovascular and renal protection, although some analyses describe a possible small mortality signal favoring ACEIs. In practice, this supports individualized selection, especially when albuminuria, tolerability, and adherence are considered together (Alqurain et al., 2026; KDIGO Diabetes Work Group, 2022).

8. Angiotensin receptor-neprilysin inhibitors

ARNIs represent the most recent major advance among RAAS-related cardiovascular therapies. Sacubitril/valsartan combines valsartan-mediated AT1 receptor blockade with sacubitril-mediated neprilysin inhibition. Sacubitril is converted to the active neprilysin inhibitor LBQ657, which increases concentrations of natriuretic peptides and other vasoactive mediators (McMurray et al., 2014).

ARNI therapy is best established in HFrEF. In PARADIGM-HF, sacubitril/valsartan reduced the risk of the composite end point of cardiovascular death or heart failure hospitalization compared with enalapril. Subsequent systematic reviews and network meta-analyses support favorable positioning of sacubitril/valsartan in HFrEF, although the magnitude of benefit depends on the population, baseline therapy, and end point definitions (McMurray et al., 2014; Park et al., 2022; Evbayekha et al., 2025).

In HFmrEF and HFpEF, the role of ARNIs is more selective. PARAGON-HF did not show as unequivocal an effect as PARADIGM-HF, and potential benefit appears greater in patients with ejection fraction below the normal range or closer to the lower boundary. The 2023 ESC update places the strongest emphasis in HFmrEF/HFpEF on SGLT2 inhibitors, whereas ACEIs, ARBs, ARNIs, beta-blockers, and MRAs have weaker or more selective roles (Solomon et al., 2019; McDonagh et al., 2023).

ARNIs lower blood pressure, but they are not routine first-line therapy for uncomplicated hypertension in the absence of a heart failure indication. Similarly, in albuminuric CKD without heart failure, ACEIs or ARBs remain the standard nephroprotective therapy. After myocardial infarction without established HFrEF, ARNIs should not be treated as universal ACEI substitutes; in PARADISE-MI, sacubitril/valsartan did not significantly reduce the risk of cardiovascular death or incident heart failure compared with ramipril (Pfeffer et al., 2021).

The principal limitation of ARNIs is symptomatic hypotension. Hyperkalemia and changes in kidney function may occur, so renal parameters and electrolytes must be monitored. Sacubitril/valsartan must not be combined with an ACEI; when switching from an ACEI, a washout period of at least 36 hours is required because of the increased risk of angioedema (McDonagh et al., 2021; Heidenreich et al., 2022).

9. Comparative clinical efficacy

In uncomplicated hypertension, ACEIs and ARBs have broadly comparable antihypertensive efficacy. The choice depends on comorbidities, tolerability, patient preference, pregnancy potential, kidney function, serum potassium, and anticipated long-term continuation of therapy. ARBs are often selected after ACEI-induced cough or when adherence is a central goal. ARNIs can lower blood pressure, but they are not routine first-line therapy solely for uncomplicated hypertension (Li et al., 2014; Chen et al., 2021; McEvoy et al., 2024).

In HFrEF, differences between classes have the greatest clinical relevance. ACEIs reduce both morbidity and mortality and remain appropriate when ARNIs are unavailable, contraindicated, or not tolerated. ARBs are alternatives in ACEI intolerance. ARNIs are preferred in eligible symptomatic patients because sacubitril/valsartan reduces cardiovascular mortality and heart failure hospitalization compared with enalapril (McMurray et al., 2014; McDonagh et al., 2021; Heidenreich et al., 2022).

After myocardial infarction, ACEIs remain particularly well studied, especially in the presence of left ventricular dysfunction, concomitant hypertension, diabetes, CKD, or heart failure. ARBs are appropriate when ACEIs are not tolerated. ARNIs may be considered when a patient develops a qualifying heart failure phenotype, particularly HFrEF, but they are not automatic ACEI substitutes without such an indication (Lee et al., 2023; Pfeffer et al., 2021).

In CKD with albuminuria and diabetic kidney disease, ACEIs and ARBs remain the principal nephroprotective RAAS inhibitors. Both classes reduce intraglomerular pressure and albuminuria. ARBs are especially useful when ACEIs cause cough. Recent CKD reviews support the benefits of optimized RAAS blockade while emphasizing monitoring and an individualized pharmacotherapeutic plan that accounts for patient-specific risk management (Avula et al., 2025; KDIGO CKD Work Group, 2024).

Table 4. Comparative clinical efficacy of ACEIs, ARBs, and ARNIs.

Clinical domain	ACEIs	ARBs	ARNIs
Uncomplicated hypertension	First-line option; high efficacy	First-line option; high efficacy and better tolerability	Lower BP, but not routinely used as first-line therapy solely for hypertension
Mortality in HFrEF	Proven reduction when ARNIs are not used	Alternative when ACEIs/ARNIs are not tolerated	Preferred in eligible symptomatic patients
HF hospitalization	Reduced in HFrEF	Reduced in selected HFrEF populations	Strongest reduction in eligible patients with HFrEF
Post-myocardial infarction	Historically best established; preferred if tolerated	Alternative with ACEI intolerance	Consider mainly when HFrEF criteria are present
Albuminuric CKD	Strong nephroprotective evidence	Strong evidence and better tolerability	Possible renal benefit in HF; not first-line standard in CKD
Adherence	Limited by cough and angioedema	Usually best among conventional RAAS inhibitors	Good if blood pressure permits titration from starting to therapeutic dose

10. Cardiovascular and renal outcomes

ACEIs, ARBs, and ARNIs reduce cardiovascular risk through partly overlapping but distinct mechanisms. In broad hypertensive populations, ACEIs and ARBs provide generally comparable protection when blood pressure reduction and dosing are similar. ACEIs may retain an advantage in selected post-myocardial infarction populations or in patients with concomitant ischemic heart disease, whereas ARBs may achieve similar population-level effectiveness through better tolerability and persistence with treatment (Chen et al., 2021; Xie et al., 2025; Lee et al., 2023).

Reduction in cardiovascular mortality depends on disease etiology. ACEIs have a strong evidence base in HFrEF, after MI, and in prevention among high-risk patients. ARBs are indispensable alternatives in ACEI intolerance. ARNIs show the clearest advantage in HFrEF because they simultaneously modulate RAAS and augment protective natriuretic peptide pathways (McMurray et al., 2014; Park et al., 2022; Evbayekha et al., 2025).

Heart failure hospitalization is most strongly reduced by ARNIs in HFrEF. In HFmrEF and HFpEF, benefits are more heterogeneous and require individualization, whereas SGLT2 inhibitors currently have the strongest evidence-based position across a broad spectrum of ejection fraction according to the 2023 ESC update (McDonagh et al., 2023).

In CKD with albuminuria, ACEIs and ARBs are key therapies. Their benefit results from lowering intraglomerular pressure and reducing albuminuria. KDIGO 2024 recommends ACEI or ARB therapy in CKD with moderately or severely increased albuminuria, titration to the highest approved tolerated dose, and monitoring of blood pressure, creatinine, and potassium after initiation or dose escalation (KDIGO CKD Work Group, 2024).

In advanced CKD, automatic discontinuation of ACEIs or ARBs solely because of low eGFR is not justified. An individual participant data meta-analysis suggests that initiating ACEIs or ARBs in advanced CKD may reduce the risk of kidney failure without a clear adverse effect on mortality, supporting careful individualized use rather than reflexive avoidance (Ku et al., 2024).

11. Safety and tolerability

Safety and tolerability are crucial for most patients and often determine the long-term effectiveness of RAAS therapy. ACEIs are limited mainly by dry cough and bradykinin-mediated angioedema. Cough may impair quality of life and lead to treatment discontinuation. Angioedema is rare but potentially life-threatening and usually requires permanent discontinuation of the ACEI (Hu et al., 2023).

ARBs have the most favorable tolerability profile among conventional RAAS inhibitors. Cough is uncommon, and angioedema occurs substantially less often than with ACEIs. ARBs still share class-related

risks: hyperkalemia, hypotension, dizziness, and worsening kidney function. Risk increases in CKD, in older adults, with hypovolemia, and during treatment with MRAs, potassium supplements, trimethoprim, or non-steroidal anti-inflammatory drugs.

A less common safety signal is acute pancreatitis. A 2025 systematic review and meta-analysis of observational studies reported an association between ACEI use and increased risk of acute pancreatitis, whereas ARBs were not associated with increased risk and in pooled analyses may have had a protective effect. Because these are observational data, they should not independently guide routine class selection, but they may be relevant in unexplained pancreatitis in a patient exposed to RAAS-modifying drugs (Alves et al., 2025).

ARNIs are limited mainly by symptomatic hypotension resulting from AT1 blockade and natriuretic peptide-mediated vasodilatation. They may cause hyperkalemia and renal dysfunction. Cough occurs less often than with ACEIs. Angioedema is rare but clinically important; ARNIs must not be combined with ACEIs, and at least a 36-hour washout period is required after ACEI therapy (McMurray et al., 2014; McDonagh et al., 2021).

ACEIs, ARBs, and ARNIs are contraindicated in pregnancy because fetal RAAS inhibition may cause fetotoxicity, including renal injury, oligohydramnios, skull hypoplasia, pulmonary hypoplasia, and fetal death. Caution is also required in bilateral renal artery stenosis, uncontrolled hyperkalemia, unstable kidney function, and severe symptomatic hypotension.

Table 5. Comparative safety profile.

Safety parameter	ACEIs	ARBs	ARNIs
Dry cough	Common	Rare	Less common than with ACEIs
Angioedema	Higher risk; contraindicated after previous ACEI angioedema	Rare; use cautiously after ACEI angioedema	Rare; avoid with ACEIs and in related angioedema history
Hyperkalemia	Possible		
Renal function decline	Possible; monitor creatinine/eGFR		
Symptomatic hypotension	Possible	Possible	More frequent, especially during initiation and dose changes
Treatment discontinuation	More frequent due to cough/angioedema	Usually lowest among conventional RAAS inhibitors	Acceptable with careful initiation and dose modification, but limited by BP
Pregnancy	Contraindicated		

12. Current international recommendations

Guidelines support individualization of RAAS-modifying therapy according to disease phenotype. In hypertension, ESC 2024 positions ACEIs or ARBs, dihydropyridine calcium-channel blockers, and thiazide or thiazide-like diuretics as principal first-line options. Treatment intensity and blood pressure targets should be adjusted to tolerability, frailty, orthostatic symptoms, and interaction risk (McEvoy et al., 2024).

In HFrEF, RAAS modulation is one of the pillars of disease-modifying therapy. ESC 2021 and the 2023 update support ARNI use in eligible symptomatic patients, ACEI use when ARNIs are not feasible, and ARB use in ACEI intolerance. The contemporary HFrEF framework includes four pillars: ARNI or ACEI/ARB, an evidence-based beta-blocker, an MRA, and an SGLT2 inhibitor (McDonagh et al., 2021; McDonagh et al., 2023; Heidenreich et al., 2022).

In HFmrEF and HFpEF, ACEIs and ARBs are used mainly because of coexisting hypertension, CKD, diabetes, or ischemic heart disease. ARNIs may be considered in selected patients, particularly those with ejection fraction below the normal range and a phenotype closer to HFrEF. The strongest recommendation in HFmrEF/HFpEF concerns dapagliflozin or empagliflozin (McDonagh et al., 2023).

After myocardial infarction, ACEIs remain strongly established in patients with left ventricular dysfunction, diabetes, hypertension, CKD, anterior infarction, or heart failure. ARBs are alternatives when ACEIs are not tolerated. ARNIs should be considered mainly when the patient meets heart failure criteria,

because PARADISE-MI did not establish sacubitril/valsartan as a universal substitute for ramipril after acute myocardial infarction (Pfeffer et al., 2021).

In CKD with albuminuria, KDIGO 2024 recommends ACEI or ARB therapy at the highest approved tolerated dose, with monitoring of blood pressure, serum creatinine, and potassium after initiation and dose escalation. Hyperkalemia should usually be managed with potassium-lowering strategies before reducing or discontinuing RAAS inhibitors when the prognostic indication is strong. KDIGO also recommends avoiding the combination of ACEIs, ARBs, and direct renin inhibitors in CKD (KDIGO CKD Work Group, 2024).

In diabetes with CKD, KDIGO 2022 recommends RAAS inhibition in patients with diabetes, hypertension, and albuminuria, with gradual titration to the maximum tolerated approved therapeutic dose. This is part of multidrug therapy that also includes SGLT2 inhibitors, non-steroidal MRAs in selected patients, and GLP-1 receptor agonists when appropriate (KDIGO Diabetes Work Group, 2022).

Table 6. Guideline-concordant positioning of ACEIs, ARBs, and ARNIs.

Clinical indication	ACEIs	ARBs	ARNIs
Hypertension	First-line option	First-line option	Not routinely first-line therapy for isolated hypertension
CKD with albuminuria	Recommended	Recommended	Consider only when a HF indication exists
HFrEF	When ARNI is not feasible	When ACEIs/ARNIs are not tolerated	Preferred in eligible symptomatic patients
HFmrEF/HFpEF	Mainly for comorbidities	Mainly for comorbidities	Selected patients; weaker evidence than in HFrEF
Post-myocardial infarction	Strongly established	Alternative with ACEI intolerance	Mainly when HFrEF criteria are met
ACEI-induced cough	Discontinue or switch	Preferred substitute	Possible when indicated and no history of angioedema
ACEI-associated angioedema	Contraindicated	Use cautiously after risk assessment	Avoid in related angioedema history

13. Initiation, titration, and monitoring

The efficacy of ACEIs, ARBs, and ARNIs observed in clinical trials does not automatically translate into benefit in practice if treatment is not initiated correctly, therapeutic doses are not achieved, or therapy is not maintained long term. Strategy selection should account for the indication, baseline blood pressure, orthostatic symptoms, hydration status, renal parameters including eGFR and creatinine, serum potassium, comorbidities, drug interactions, and adverse-event risk.

The risk of adverse effects increases with advanced CKD, dehydration, chronic non-steroidal anti-inflammatory drug use, potassium supplementation, potassium-containing salt substitutes, and treatment with MRAs, finerenone, trimethoprim, or drugs that intensify diuresis. Risk assessment is particularly important in older patients and in those with diabetes, heart failure, multimorbidity, or frailty.

After initiating or increasing the dose of an ACEI or ARB, blood pressure, serum creatinine, and potassium should usually be checked within approximately 2-4 weeks. A moderate creatinine increase may be an expected hemodynamic effect. An increase exceeding approximately 30% within several weeks should prompt evaluation for dehydration, excessive diuresis, non-steroidal anti-inflammatory drug exposure, renal artery stenosis, or other reversible causes (KDIGO CKD Work Group, 2024).

Hyperkalemia is a common reason for underuse or discontinuation of RAAS inhibitors, but importantly it does not always require withdrawal. Potassium intake assessment, discontinuation of supplements, review of potassium-raising drugs, diuretic optimization, correction of metabolic acidosis, and potassium binders may be considered when available and clinically justified.

When switching from an ACEI to an ARNI, a washout period of at least 36 hours is required. When switching from an ARB, no formal washout is required, but the ARB should be discontinued because sacubitril/valsartan contains valsartan. Lower starting doses are reasonable in patients with low blood pressure, hypovolemia, intensive diuretic therapy, or advanced age.

14. Special clinical populations

14.1. Older adults

In older adults, the efficacy of RAAS-modifying drugs must be balanced against a higher risk of orthostatic hypotension, dehydration, electrolyte disturbances, drug-drug interactions, and falls. Chronological age alone should not be a reason to withhold treatment when a strong indication exists and prognostic benefit is plausible. Frailty, daily functioning, blood pressure tolerance, eGFR, comorbidities, and patient expectations are more important.

In patients with frailty, recurrent falls, symptomatic orthostatic hypotension, or limited life expectancy, lower starting doses, slower titration to therapeutic doses, and less aggressive blood pressure targets may be appropriate. ESC 2024 emphasizes treatment intensification in many patients, but also individualized care when intolerance or orthostatic symptoms are present (McEvoy et al., 2024).

14.2. Type 2 diabetes and diabetic kidney disease

In type 2 diabetes, ACEIs and ARBs are particularly important in diabetic kidney disease because they reduce intraglomerular pressure and albuminuria. Contemporary treatment of diabetic kidney disease requires a multidrug strategy: RAAS inhibitors are combined with SGLT2 inhibitors, non-steroidal MRAs, statins, glycemic control, and GLP-1 receptor agonists when indicated (KDIGO Diabetes Work Group, 2022).

Evidence comparing ACEIs and ARBs in type 2 diabetes suggests broadly similar renal and cardiovascular protection. Any small possible ACEI benefit in mortality should be interpreted in light of tolerability. In a patient with albuminuria and ACEI-induced cough, an ARB is usually preferable to no RAAS blockade (Alqurain et al., 2026).

14.3. Advanced chronic kidney disease

Advanced CKD often raises concerns among physicians and may lead to excessive caution in selecting RAAS inhibitors. Automatic discontinuation solely because of low eGFR is not justified in every patient. If the drug is tolerated, potassium can be controlled, and symptomatic hypotension is absent, continuation may be beneficial, especially in the presence of albuminuria or heart failure. KDIGO 2024 supports continuation of ACEIs or ARBs even when eGFR is below 30 mL/min/1.73 m2 if treatment remains tolerated.

Dual RAAS blockade should be avoided because combining an ACEI with an ARB or a direct renin inhibitor increases the risk of hyperkalemia, hypotension, and acute kidney injury without proportional benefit. Decisions on continuation, dose reduction, or temporary interruption should be based on the eGFR trajectory, serum potassium, blood pressure, hydration status, comorbid conditions, and especially cardiac indications (Ku et al., 2024; Avula et al., 2025).

14.4. Women of childbearing potential and pregnancy

ACEIs, ARBs, and ARNIs are contraindicated in pregnancy because of fetotoxicity resulting from RAAS inhibition. In women of childbearing potential, the possibility of pregnancy should be considered and contraception should be discussed before treatment initiation. If pregnancy is planned or diagnosed, RAAS-modifying therapy should be discontinued and replaced with agents considered safer in pregnancy.

14.5. Patients after myocardial infarction

After myocardial infarction, ACEIs are particularly well established in patients with left ventricular dysfunction, hypertension, diabetes, CKD, anterior infarction, or heart failure. ARBs are alternatives when ACEIs are not tolerated. ARNIs should not be treated as universal ACEI substitutes immediately after myocardial infarction in patients who do not meet HFrEF criteria. PARADISE-MI did not show a significant reduction in the primary end point for sacubitril/valsartan compared with ramipril (Pfeffer et al., 2021; Lee et al., 2023).

15. ACEIs, ARBs, and ARNIs in the era of multidrug therapy

Contemporary cardiovascular and renal care is increasingly rarely based on a single therapeutic pathway. ACEIs, ARBs, and ARNIs are components of broader strategies that reduce cardiovascular risk, protect the kidneys, control blood pressure, reduce symptom burden, and prevent hospitalizations.

In HFrEF, disease-modifying therapy includes an ARNI or ACEI/ARB, an evidence-based beta-blocker, an MRA, an SGLT2 inhibitor, and diuretics as needed for congestion. When pharmacotherapy is initiated, early introduction of all foundational drug classes at tolerated starting doses followed by careful optimization is generally preferable to focusing on achieving the maximum dose of a single drug first (McDonagh et al., 2021; McDonagh et al., 2023; Heidenreich et al., 2022).

In chronic kidney disease and type 2 diabetes, RAAS blockade remains the basis of albuminuria treatment, but it does not exhaust nephroprotection. SGLT2 inhibitors reduce CKD progression and cardiovascular event risk in many populations, including selected patients without diabetes. KDIGO positions RAAS inhibitors, SGLT2 inhibitors, non-steroidal MRAs, and GLP-1 receptor agonists as complementary therapies selected according to phenotype and risk.

Combination therapy requires safety discipline. ACEI plus ARB therapy, or a RAAS inhibitor combined with a direct renin inhibitor, should not be used routinely. Combining a single RAAS inhibitor with an MRA or finerenone may benefit selected patients, but potassium monitoring is required.

16. Implementation and health-system implications

The largest gap between evidence and practice often concerns not drug efficacy itself but implementation. A patient eligible for ARNI therapy may not receive it because of cost, reimbursement restrictions, low blood pressure, insufficient time for titration from starting to therapeutic doses, or lack of efficient monitoring. A patient with CKD may lose ACEI/ARB therapy after a transient creatinine increase or an episode of hyperkalemia, even though monitored continuation could be beneficial.

Health systems should support simple monitoring and reassessment pathways after initiation or dose escalation of RAAS inhibitors: scheduled blood pressure, creatinine, and potassium checks; rapid contact with the patient when results are abnormal; medication review for potassium-raising agents; and access to diuretics, dietary correction, and potassium binders when needed. Without these conditions, clinicians concerned about patient safety may more often choose conservative management and permanent discontinuation.

Access and costs have clinical importance. ACEIs and many ARBs are inexpensive and widely available; therefore, they remain important in resource-limited systems. ARNIs have an advantage in HFrEF, but costs and reimbursement criteria may restrict their use. From a public health perspective, optimization of inexpensive and tolerated RAAS inhibitors in CKD and hypertension may provide substantial population benefit even when the individual pharmacological advantage over an alternative is modest.

17. Common misinterpretations in practice

The first misinterpretation is treating ARNIs as drugs that replace ACEIs or ARBs across all RAAS-related indications. The strongest data support ARNIs in eligible symptomatic HFrEF. In uncomplicated hypertension, CKD without heart failure, and post-MI care without an HFrEF phenotype, ARNIs are not standard universal substitutes.

The second error is assuming that ARBs are always better than ACEIs. ARBs are usually better tolerated, but this does not mean general superiority for every end point. After myocardial infarction and in some high-risk populations, ACEIs have a particularly strong historical evidence base. Selection should depend on phenotype, tolerability, and risk.

The third error is automatic discontinuation of RAAS inhibitors after a moderate creatinine increase. An early fall in eGFR may be an expected hemodynamic effect. Creatinine increase should be interpreted in the context of hydration, concomitant medications, blood pressure changes, serum potassium, and eGFR trajectory. Permanent withdrawal is justified in severe or uncontrolled hyperkalemia, symptomatic hypotension, severe acute kidney injury, or an unfavorable risk-benefit balance.

The fourth error is delaying other HFrEF pillars until the maximum dose of one drug is achieved. Contemporary strategy favors early initiation of all key classes at tolerated starting doses, followed by gradual dose modification with enough interval to identify which drug or dose change is responsible for adverse effects.

18. Practical framework for choosing an ACEI, ARB, or ARNI

In clinical practice, selection can be simplified by identifying the dominant disease phenotype. In symptomatic HFrEF, the preferred RAAS-modifying drug is an ARNI if blood pressure, kidney function, potassium, absence of a relevant angioedema history, and access allow safe treatment. If an ARNI is not feasible, an ACEI is appropriate; in ACEI intolerance, an ARB should be used.

In CKD and diabetic kidney disease, the standard approach is an ACEI or ARB at the highest approved tolerated dose. In uncomplicated hypertension, ACEIs and ARBs are equivalent first-line options, whereas ARBs may have practical advantages in patients with cough, angioedema risk, or high risk of treatment discontinuation. After myocardial infarction, ACEIs remain particularly well established, ARBs are alternatives, and ARNIs are considered mainly when HF criteria, especially HFrEF, are met.

Table 7. Practical RAAS-modifying strategy according to clinical phenotype.

Clinical phenotype	Preferred strategy	Rationale
Symptomatic HFrEF	ARNI if tolerated	Greatest reduction in cardiovascular death and HF hospitalization
HFrEF when ARNI is not feasible	ACEI	Proven reduction in morbidity and mortality
HFrEF with ACEI intolerance	ARB	Alternative for cough or intolerance
CKD with albuminuria	ACEI or ARB	Reduction in albuminuria and intraglomerular pressure
Diabetic kidney disease	ACEI or ARB plus complementary therapy	Multidirectional reduction in renal and CV risk
Uncomplicated hypertension	ACEI or ARB	Similar antihypertensive efficacy; selection depends on tolerability
ACEI-induced cough	ARB	No clinically meaningful inhibition of bradykinin degradation
ACEI-associated angioedema	Avoid ACEI; cautious ARB use; avoid ARNI with related history	Risk of recurrent bradykinin-mediated angioedema
Post-MI with LV dysfunction	ACEI; ARB if intolerant	Best established evidence after MI
HFmrEF/HFpEF	Treat comorbidities and prioritize SGLT2i; ARNI for selected patients	ARNI evidence is weaker than in HFrEF

19. Costs, access, and adherence

The real-world effectiveness of RAAS inhibitors depends not only on pharmacological efficacy but also on availability, cost, dosing simplicity, and tolerability. ACEIs are usually inexpensive, widely available, and familiar to clinicians, which maintains their importance in many health care systems and resource-limited settings.

ARBs have similar availability and, in many indications, offer comparable efficacy with better tolerability. The lower frequency of cough and angioedema may improve long-term continuation, which is especially important in hypertension and CKD, where benefits depend on years of sustained therapy (Chen et al., 2021; Hu et al., 2023).

ARNIs are more advanced and clinically beneficial in HFrEF, but their use may be limited by cost, reimbursement restrictions, the need for monitoring, and symptomatic hypotension in some patients. The advantage of ARNIs in HFrEF should be interpreted together with patient preferences, access, and the feasibility of safely implementing other components of multidrug therapy.

20. Discussion

This review shows that the question of universal superiority of ACEIs or ARBs has no simple answer and that claiming one class is always more effective is an oversimplification. RAAS-modifying therapy should be selected according to patient phenotype, expected benefit, tolerability, risk, access, and guideline position. ACEIs, ARBs, and ARNIs are related but non-interchangeable therapeutic strategies.

ACEIs and ARBs are comparable in many populations for blood pressure control and nephroprotection. In uncomplicated hypertension, neither class has a consistent universal advantage when dose and blood pressure reduction are comparable. In CKD, both classes reduce albuminuria and intraglomerular pressure, and guidelines permit either an ACEI or an ARB at the highest tolerated approved dose.

Tolerability is the key practical difference between ACEIs and ARBs. ACEIs are a very well studied drug class with clearly documented benefits, but they may cause burdensome adverse effects, including cough and angioedema, which limit patient persistence with therapy. ARBs are often easier to maintain long term. In chronic prevention, this tolerability advantage may be as important as small differences in efficacy.

Clinical context substantially influences treatment choice. ACEIs remain well established after myocardial infarction and in classic high-risk populations. ARBs are appropriate when ACEIs are not tolerated. ARNIs are superior to ACEIs in eligible symptomatic HFrEF, but this advantage should not be automatically extended to uncomplicated hypertension, CKD without HF, or post-MI status without an HF phenotype (McMurray et al., 2014; Pfeffer et al., 2021).

Safe use requires early monitoring in particular. ACEIs also require patient education about adverse effects and vigilance for cough, angioedema, hyperkalemia, and decline in kidney function. ARBs require potassium and renal function monitoring despite better tolerability. ARNIs require assessment of blood pressure, kidney function, and potassium, avoidance of concomitant ACEI therapy, and adherence to the 36-hour washout period.

The most practical approach has three pillars: ACEIs as historically validated and effective therapies; ARBs as similarly effective and often better tolerated alternatives in many chronic indications; and ARNIs as dual-pathway drugs with the strongest evidence in HFrEF. In all settings, RAAS blockade should be integrated with SGLT2 inhibitors, MRAs, GLP-1 receptor agonists, statins, diuretics, and patient-specific lifestyle interventions.

21. Limitations

This review has several limitations. First, it is narrative rather than systematic. Consequently, it does not include formal grading of evidence certainty or quantitative pooling of results. Second, comparisons among ACEIs, ARBs, and ARNIs are complicated by differences in populations, indications, doses, follow-up duration, concomitant therapy, and end point definitions.

Third, randomized trials do not fully reflect real-world patients with frailty, multimorbidity, advanced CKD, low blood pressure, recurrent hyperkalemia, or polypharmacy. This is especially important for ARNIs, which may be more difficult to use in patients with low baseline blood pressure or limited access to monitoring.

Fourth, the positioning of ARNIs beyond HFrEF remains less certain. Data suggest potential benefit in selected HFmrEF/HFpEF subgroups, especially at lower ejection fractions, but the strength of evidence is lower than in HFrEF. Fifth, some of the most important evidence is older because landmark trials still form the basis of clinical practice.

Finally, some newer publications from 2025-2026, particularly systematic reviews, are useful for context but should not be weighted above large randomized trials and international guidelines. They were included only as supplementary evidence in selected sections of the article.

22. Future research directions

Future studies should further compare treatment strategies involving ACEIs, ARBs, and ARNIs, including principles of implementation, dose titration, and care pathways with special attention to the characteristics of the studied population. Treatment efficacy, drug tolerability, quality-of-life improvement, and cost-effectiveness should be evaluated. Relevant objective end points may include renal and cardiovascular parameters as well as long-term safety that is meaningful to patients.

Subgroup analyses are needed to identify patients who may derive greater benefit from ACEIs or ARBs, taking into account age, sex, ancestry, diabetes, CKD stage, albuminuria category, cardiovascular phenotype, and post-myocardial infarction status. The role of ARNIs beyond classic HFrEF requires more precise phenotyping in HFmrEF and HFpEF.

An important priority is evaluation of how RAAS inhibitors should be integrated with SGLT2 inhibitors, steroidal and non-steroidal MRAs, GLP-1 receptor agonists, potassium binders, digital monitoring, and multidisciplinary care pathways. A particularly practical question is how to maintain prognostically important RAAS blockade while safely managing hyperkalemia and changes in kidney function.

23. Conclusions

ACEIs, ARBs, and ARNIs represent three major strategies for modifying RAAS-related pathways. ACEIs remain among the most validated therapies in cardiovascular medicine, particularly after myocardial infarction, in classic high-risk populations, in HFrEF when ARNIs are not feasible, and in chronic kidney disease with albuminuria.

ARBs have been tested across many populations and provide comparable efficacy, especially when blood pressure reduction and nephroprotection are considered as key end points, while offering better tolerability. They are particularly useful in patients requiring long-term RAAS blockade who develop cough or intolerance to ACEIs.

ARNIs, especially sacubitril/valsartan, provide the greatest prognostic benefit in eligible symptomatic patients with HFrEF by reducing cardiovascular mortality and heart failure hospitalization compared with ACEIs. Their main limitation is symptomatic hypotension, and their use requires assessment of renal function and serum potassium. Particular caution is warranted in older adults because abrupt symptomatic hypotension may increase the risk of falls, which are especially hazardous in this age group.

When selecting an optimal treatment strategy, the decision should account for the individual features of the clinical case. The dominant disease, comorbidities, other patient symptoms, and patient needs must be considered. ACEIs remain foundational therapy, ARBs offer similar efficacy with better tolerability in many chronic situations, and ARNIs should be prioritized in eligible symptomatic patients with HFrEF. Contemporary care requires simultaneous integration of RAAS inhibitors with SGLT2 inhibitors, MRAs, GLP-1 receptor agonists, and other phenotype-based strategies.

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Abbreviations

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; AT1, angiotensin II type 1 receptor; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KDIGO, Kidney Disease: Improving Global Outcomes; LV, left ventricular; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT2, sodium-glucose cotransporter-2.

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