Consensus and Guideline

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Expert consensus on the application of angiotensin-converting enzyme inhibitors in the prevention and treatment of cardiovascular diseases

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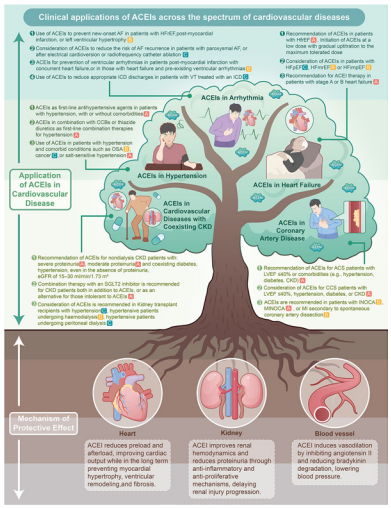
Graphical abstract



Abstract Angiotensin-converting enzyme inhibitors (ACEIs) have therapeutic value in various cardiovascular diseases and have protective effects on the heart, blood vessels, and kidneys; they are cornerstone drugs in the management of hypertension, heart failure, and chronic kidney disease. Despite the continual emergence of new drugs, ACEIs remain indispensable. The appropriate use of ACEIs helps reduce the risks of adverse cardiovascular events and mortality. In light of updates on the concept of interdisciplinary integration and the further accumulation of evidence from evidence-based medicine, the Chinese Society of Cardiology, the Editorial Board of the *Chinese Journal of Cardiology*, and the Hypertension Professional Committee of the Cross-Strait Medical and Health Exchange Association convened domestic experts in relevant fields to update the recommendations for applying ACEIs in cardiovascular diseases and to compile this consensus, with the aim of providing a reference for clinical physicians in China and improving the prevention and treatment of cardiovascular diseases.

Keywords: angiotensin-converting enzyme inhibitors, cardiovascular diseases, expert consensus, prevention and treatment

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Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
AF	atrial fibrillation
AMI	acute myocardial infarction
Ang II	angiotensin II
ARB	angiotensin II receptor blocker
ARNI	angiotensin receptor-neprilysin inhibitor
BP	blood pressure
CCB	calcium channel blocker
CCS	chronic coronary syndrome
CHD	coronary heart disease
CHF	chronic heart failure
CKD	chronic kidney disease
CMD	coronary microvascular dysfunction
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
GDMT	guideline-directed medical therapy
HFimpEF	heart failure with improved ejection fraction
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
ICD	implantable cardioverter-defibrillator
INOCA	ischaemia with nonobstructive coronary arteries
ISIS-4	Fourth International Study of Infarct Survival
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MACE	major adverse cardiovascular event
MI	myocardial infarction
MINOCA	myocardial infarction with nonobstructive coronary arteries
NYHA	New York Heart Association
OSA	obstructive sleep apnoea
RAAS	renin–angiotensin–aldosterone system
RAS	renin–angiotensin system
RASI	renin–angiotensin system inhibitor
RCT	randomized controlled trial
GLT2i	sodium–glucose cotransporter-2 inhibitor
SPS	sodium polystyrene sulfonate

1. Introduction

Despite continual advancements in cardiovascular disease treatment, the incidence and mortality rates of cardiovascular diseases in China continue to increase, making cardiovascular disease the leading cause of death among both urban and rural residents[1]. Approximately 330 million individuals are currently affected by cardiovascular diseases in China; this number includes 245 million people with hypertension, 11.39 million with coronary heart disease (CHD), 8.90 million with heart failure, and 4.87 million with atrial fibrillation (AF).[1] Recent studies suggest that the actual prevalence of these diseases may be even greater. For example, the prevalence of AF is now estimated to be 1.6%.[2] Given the high burden of cardiovascular diseases in China, we must focus on the prevention, control, and management of cardiovascular diseases throughout the process, with the goal of developing individualized and precise pharmacological treatments to reduce the risk of adverse cardiovascular events and mortality.[3]

The renin–angiotensin–aldosterone system (RAAS) plays a crucial role in cardiovascular diseases; notably, the excessive production of angiotensin II (Ang II) is a key factor mediating disease occurrence and progression. Angiotensin-converting enzyme inhibitors (ACEIs) inhibit the conversion of Ang I to Ang II, demonstrating therapeutic value in various cardiovascular diseases and exerting protective effects on the heart, blood vessels, and kidneys.

Since the introduction of ACEIs in 1981, evidence from clinical studies and real-world data has confirmed their cornerstone status in the treatment of hypertension, heart failure, and chronic kidney disease (CKD).[4] Given the accumulation of evidence from evidence-based medicine and the concept of interdisciplinary integration, the Chinese Society of Cardiology, the Editorial Board of the *Chinese Journal of Cardiology*, and the Hypertension Professional Committee of the Cross-Strait Medical and Health Exchange Association have convened relevant experts to draft this consensus as a reference for cardiovascular physicians.

This consensus provides updated recommendations for the use of ACEIs in cardiovascular diseases and is structured into four main sections: an overview of ACEIs, the use of ACEIs in cardiovascular diseases, the application of ACEIs in cardiovascular diseases combined with CKD, and common adverse reactions to ACEIs and management strategies. The consensus is problem-oriented, concise, and clinically instructive.

The consensus adopts an internationally recognized grading system to evaluate the evidence levels for the indications of ACEIs in various diseases (Table 1).

2. Overview of ACEIs

2.1. Clinical question 1: What is the mechanism of action of ACEIs?

The RAAS is among the most powerful cardiovascular regulatory systems and plays important roles in diseases such as hypertension and heart failure by regulating blood pressure (BP), fluid balance, and cardiac function.[5] Moreover, the RAAS is a key target for drugs such as ACEIs. ACEIs have been demonstrated to substantially reduce morbidity and mortality in patients with cardiovascular disease and have shown potential in the treatment of comorbidities such as diabetes and cancer.[6–9]

The classic pathway of the RAAS is the angiotensin-converting enzyme (ACE)–Ang II–Ang II type 1 receptor axis. Alternative pathways include the ACE2–Ang(1–7)–Mas axis and the ACE2–Ang(1–9)–Ang II type 2 receptor axis, both of which counteract the effects of the classic pathway and exert cardioprotective and renoprotective effects.[10,11] Ang II can also be converted into Ang III (Ang 2–8) by aminopeptidase A. Ang III acts on both Ang II type 1 and type 2 receptors, producing effects similar to those of Ang II.

ACEIs mainly inhibit ACE activity, preventing the conversion of Ang I to Ang II and thereby blocking the generation of Ang II. Circulating Ang II is the most active peptide in the RAAS and is involved in the pathophysiology of diseases such as hypertension, heart failure, myocardial infarction (MI), and diabetic nephropathy.[10,11] ACEIs have several beneficial effects, including increasing the vasodilation of arteries and veins, increasing sodium and water excretion, inhibiting excessive sympathetic activation, and alleviating oxidative stress. These effects not only lower BP but also participate in reversing myocardial and vascular remodelling while protecting the kidneys (Table 2).[5,12,13]

The secondary effect of ACEIs is that they modulate alternative pathways, which increases the levels of Ang(1–9) and Ang(1–7).[14] Ang(1–9) and Ang(1–7) exert vasodilatory, anti-inflammatory, antifibrotic, and anti-apoptotic effects by activating the Ang II type 2 receptor and Mas receptor, thus providing cardiovascular and renal protection.[13]

ACE also mediates the degradation of bradykinin, substance *P*, and other peptides.[12,15] Therefore, ACEIs can increase plasma bradykinin levels, contributing to vasodilation and the protection of endothelial function.[12,15] Bradykinin and substance *P* account for some of the adverse effects of ACEIs, such as dry cough and angioedema.[16]

2.2. Clinical question 2: Are all ACEI formulations equivalent?

The indications, adverse effects, and contraindications of various ACEI formulations are generally similar and exhibit a "class effect." However, differences in ACE binding affinity in tissues and pharmacokinetic properties lead to variations in tissue concentrations, which in turn cause different clinical effects. When an ACEI formulation is selected, the following four factors should be considered (Table 3).

2.2.1. Drug efficacy. Drug efficacy is one of the key considerations when selecting an ACEI agent.

2.2.2. Prodrug status. Lisinopril and captopril are the only two non-prodrug ACEIs used.[17] Prodrugs must be metabolized into their active form to exert their effects, and this process typically occurs in the liver. Therefore, non-prodrug drugs are preferred for patients with liver disease.[18]

2.2.3. Pharmacokinetics.

1. Absorption: There are significant differences in the absorption rates of various ACEIs (25%–75%). After oral administration, the time to reach the peak plasma concentration ranged from 1 h to 10 h. The impact of food on absorption should be considered during administration.
2. Excretion: Most ACEIs are eliminated primarily via the kidneys. In cases of renal dysfunction (creatinine clearance ≤ 30 mL/min), the drug dosage should be adjusted on the basis of the patient's clinical condition, and close monitoring is needed. Fosinopril is eliminated equally by the liver and kidneys.
3. Half-life: The effective half-life of ACEIs varies.[19]

2.2.4. Other factors. In theory, patients with higher plasma renin activity respond better to ACEIs.[20] Therefore, for patients with heart failure or salt depletion, a lower initial dose should be used. Patients undergoing dialysis with high-flow polyacrylonitrile membranes may develop allergic reactions to ACEIs, requiring discontinuation or switching to other dialysis membranes. When treating different cardiovascular diseases, the selection of the ACEI type and dosage should be based on evidence from clinical studies.

3. Application of ACEIs in cardiovascular diseases

3.1. The use of ACEIs in hypertension

3.1.1. Clinical question 1: What is the role of ACEIs in the management of hypertension, and for which specific patient populations are they recommended?

3.1.1.1. Consensus recommendation

1. ACEIs are recommended as first-line antihypertensive agents in the initial treatment of hypertension without other complications (grade A).
2. ACEIs are recommended as first-line antihypertensive agents in hypertensive patients with comorbidities such as left ventricular hypertrophy (LVH), proteinuria, heart failure, CHD, CKD, diabetes, and AF, and in those with high cardiovascular risk (grade A).

3.1.1.2. Recommendation explanation. ACEIs provide dual benefits through BP reduction and target organ protection, which are mediated by the modulation of bradykinin and angiotensin (1–7) metabolism. The efficacy of these drugs in reducing major adverse cardiovascular events (MACEs) is comparable to that of dihydropyridine calcium channel blockers (CCBs) and thiazide diuretics. Specific advantages in terms of comorbidities are detailed in the subsequent sections (ACEIs in HF, ACEIs in CHD, ACEIs in CKD, and ACEIs in AF).

LVH is a common form of subclinical hypertension-mediated organ damage. Echocardiographic studies have reported an LVH detection rate of 35.6% to 40.9%[21] in hypertensive patients, which correlates positively with the severity of hypertension. Several ACEIs, including enalapril, benazepril, lisinopril, and ramipril, have been shown to effectively reverse hypertension-induced LVH[22–25] with superior efficacy to that of CCBs, diuretics, and β-blockers.

Table 1

Explanation of evidence-level grading according to international standards.

Level of evidence	Definition
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized clinical trial or large nonrandomized studies
C	Consensus of opinion of experts and/or small studies, retrospective studies, and registries

ACEIs selectively affect glomerular arterioles, reducing renal hyperperfusion and decreasing urinary protein excretion. Meta-analyses have indicated that ACEI therapy leads to an average reduction of 0.46 g/day in urinary protein excretion[26] with greater benefits observed in patients with more severe proteinuria. Notably, a 29% decrease in proteinuria occurs independent of BP-lowering effects.[27]

Compared with angiotensin II receptor blockers (ARBs), β-blockers, CCBs, and diuretics, ACEIs demonstrate superior cardiovascular protective effects in patients with diabetes compared with nondiabetic patients.[28] A meta-analysis revealed that ACEIs reduce the risk of new-onset diabetes by 16%, whereas β-blockers and thiazide diuretics increase this risk by 48% and 20%, respectively.[29] In addition, ACEIs lower the risk of all-cause mortality by 13%, cardiovascular mortality by 17%, and major cardiovascular events by 14% in diabetic patients, with significantly greater therapeutic benefits than those provided by ARBs.[7]

3.1.2. Clinical question 2: What are the advantages of combining ACEIs with other medications in hypertensive patients?

3.1.2.1. Consensus recommendation

1. ACEIs and CCBs are recommended as first-line combination therapy for hypertension (grade A).
2. ACEIs and thiazide diuretics are recommended as first-line combination therapy for hypertension (grade A).

3.1.2.2. Recommendation explanation. Compared with high-dose monotherapy, appropriate combination therapy for hypertension can provide significantly greater cardiac protection.[30] Unless contraindicated, renin–angiotensin system inhibitors (RASIs), including ACEIs and ARBs, are typically key components of combination antihypertensive treatment strategies.

The combination of ACEIs and CCBs can mitigate both volume overload and pressure overload, significantly enhancing the antihypertensive effect and providing stronger protection for target organs. Research has shown that compared with high-dose monotherapy, ACEI and CCB combination therapy is more effective at improving arterial compliance and reducing the left ventricular mass index. In addition, ACEIs can ameliorate ankle oedema caused by CCBs, and the combination of these two drugs has no adverse effects on lipid or glucose metabolism.

The combination of ACEIs and thiazide diuretics offers dual blockade of the RAAS and volume-mediated mechanisms, significantly enhancing the antihypertensive effect. Moreover, ACEIs counteract thiazide-associated hypokalaemia, thereby improving long-term medication adherence.

For patients whose systolic BP is > 20 mmHg above the target (1 mmHg = 0.133 kPa) and/or whose diastolic BP is > 10 mmHg above the target, ACEIs combined with other antihypertensive drugs are recommended. When combination therapy is used, long-acting single-pill combinations should be prioritized.

3.1.3. Clinical question 3: What are the benefits of using ACEIs in hypertensive patients with obstructive sleep apnoea (OSA)?

3.1.3.1. Consensus recommendation. ACEIs are recommended for antihypertensive treatment in patients with hypertension and OSA (grade B).

3.1.3.2. Recommendation explanation. OSA is a common secondary factor contributing to hypertension[31] and is also an important risk factor for resistant hypertension. The activation of the RAAS and the sympathetic nervous system constitutes the primary pathophysiological mechanism underlying OSA-related elevations in BP, especially nocturnal hypertension. Mineralocorticoid receptor antagonists, RASIs, and thiazide diuretics can all be used for antihypertensive treatment in patients with hypertension and OSA.

A meta-analysis revealed that ACEIs effectively lower both office systolic and diastolic BP, as well as 24-h systolic BP, in hypertensive patients with OSA.[32] In addition, ACEIs can reduce sleep systolic BP, with a particularly noteworthy effect on controlling nocturnal BP.[33,34] A double-blind, crossover clinical study comparing equivalent doses of doxazosin and enalapril in male patients with OSA and hypertension revealed that ACEIs significantly reduced both the nocturnal heart rate and BP.[35]

3.1.4. Clinical question 4: What are the advantages of ACEIs in patients with salt-sensitive hypertension?

3.1.4.1. Consensus recommendation. ACEIs are recommended for use in salt-sensitive hypertensive patients (grade A).

3.1.4.2. Recommendation explanation. The prevalence of salt-sensitive hypertension is high, with detection rates ranging from 28% to 74% among individuals with hypertension.[36] High sodium intake can activate the RAAS, leading to elevated levels of Ang II, which exacerbates hypertension-mediated organ damage. Therefore, blocking RAAS activity in tissues plays a crucial role in both the treatment of salt-sensitive hypertension and the protection of target organs. A meta-analysis revealed that combining ACEIs with diuretics effectively reduces 24-h

Table 2

Cardiovascular and renal protective effects of ACEIs.

Site of action	Mechanism of protective effect of ACEIs
Heart and blood vessels	(1) Reduction of systemic arterial pressure (2) Lowering of pulmonary circulation pressure, including pulmonary arterial pressure and pulmonary capillary wedge pressure (3) Decrease in both volume load and pressure load on the heart, with a consequent increase the cardiac output and cardiac index. Through BP reduction, there is a reduction in left ventricular pressure load and systolic wall tension. Simultaneously, there is promotion of sodium and water excretion via renal effects, leading to a decrease in volume overload, which in turn causes a reduction in cardiac volume load and diastolic wall tension. There is also a decrease in venous return to the heart through venous dilation (4) Improvement in cardiac remodelling and inhibition of ventricular dilation through the inhibition of Ang II-induced myocardial cell proliferation, the inhibition of Ang II and aldosterone-induced cardiac hypertrophy, interstitial and perivascular fibrosis, and the reduction of myocardial apoptosis caused by excessive pressure overload via the alleviation of volume and pressure loads
Kidneys	(1) Lowering of BP and dilation of afferent arterioles, resulting in the reduction of glomerular capillary pressure (intraglomerular pressure) and alleviation of glomerular injury (2) Increase in glomerular filtration membrane selectivity and reduction in mesangial cell proliferation and matrix production, with exertion of anti-inflammatory effects and reduction in proteinuria (3) Improvement in renal haemodynamics and reduction in the renal effects of aldosterone and Ang II, leading to the promotion of sodium excretion and lowering of BP

ACEI = angiotensin-converting enzyme inhibitor, Ang II = angiotensin II, BP = blood pressure.

ambulatory BP variability in patients with salt-sensitive hypertension.[37]

3.1.5. Clinical question 5: Do ACEIs have an advantage in the treatment of hypertension in cancer patients?

3.1.5.1. Consensus recommendation.

1. ACEIs, ARBs, β-blockers, and CCBs are recommended as first-line antihypertensive agents in patients with cancer (grade C).
2. For oncology patients with a systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 100 mmHg, the combination of an ACEI or ARB with a dihydropyridine-type CCB is recommended (grade C).

3.1.5.2. Recommendation explanation. Vascular endothelial growth factor (VEGF) inhibitors can induce newly diagnosed hypertension or increase BP variability in hypertensive patients by 11% to 45%.[38] RASIs, including ACEIs and ARBs, not only lower BP but also prolong survival in patients with cancer and hypertension, reducing mortality risk by nearly 40%. The median overall survival time among RASI users was nearly twice as long as that of nonusers (26.8 vs. 15.2 months),[39] with even greater survival advantages observed in patients with gastrointestinal and genitourinary malignancies.[40] A retrospective analysis was performed to assess the impact of RASIs on patients with metastatic renal cell carcinoma receiving targeted therapy. The results indicated that compared with hypertensive patients who did not receive RASIs, hypertensive patients treated with RASIs had significantly improved survival outcomes, with a 26.3%

Table 3

Commonly used ACEIs.

Drug	Half-life (h)	Standard dose range (mg/day)	Dosing frequency	Impact of food on absorption	Prodrug
Sulfhydryl-containing					
Captopril	2	6.25–150.00	Bid or Tid	Food reduces absorption by 30% to 40%; take 1–2 h before meals	No
Carboxyl-containing					
Benazepril	11	2.50–40.00	Qd or Bid	Food has minimal impact on absorption	Yes
Enalapril	11	2.50–40.00	Qd or Bid	Food does not affect absorption	Yes
Perindopril	3–10	2.00–8.00	Qd	Food reduces bioavailability by 35%; take before meals	Yes
Ramipril	13–17	1.25–10.00	Qd or Bid	Food does not affect absorption	Yes
Lisinopril	12	2.50–40.00	Qd	Food does not affect absorption	No
Fosinopril	8	2.50–10.00	Qd	–	Yes
Cilazapril	10	0.50–5.00	Qd	Food does not affect absorption	Yes
Quinapril	2–4	2.50–40.00	Qd or Bid	Normal diet does not affect absorption; a high-fat diet reduces absorption by 30%	Yes
Trandolapril	16–24	1.00–4.00	Qd	Food does not affect absorption	Yes
Moexipril	2–12	3.75–30.00	Qd or Bid	Food significantly reduces bioavailability; take 1 h before meals	Yes
Phosphonate-containing					
Fosinopril	12	10.00–40.00	Qd	Food does not affect absorption	Yes

"–" Indicates no data available.

ACEIs = angiotensin-converting enzyme inhibitors, Bid = twice daily, Qd = once daily, Tid = 3 times daily.

reduction in mortality risk and a prolonged median overall survival (31.1 vs. 21.9 months).[41]

3.2. Use of ACEIs in heart failure

3.2.1. Clinical question 1: Should ACEIs be routinely used in patients with heart failure with reduced ejection fraction (HFrEF)?

3.2.1.1. Consensus recommendation.

1. For patients with symptomatic HFrEF corresponding to New York Heart Association (NYHA) functional classes II–IV, the use of ACEIs is recommended to reduce heart failure–related morbidity and mortality, unless contraindicated or not tolerated (grade A).
2. ACEIs should be initiated early, at a low starting dose, and titrated gradually on the basis of patient BP and other tolerance indicators until the maximum tolerated dose or guideline-recommended target dose is achieved (Table 4). The uptitration process and dose adjustment should be individualized. After initiation and dose adjustment, BP, serum potassium levels, and renal function should be monitored. Once the optimal maintenance dose is established, it should be continued long term, and abrupt discontinuation should be avoided.[42]

3.2.1.2. Recommendation explanation. Currently, for patients with HFrEF, the use of angiotensin receptor-neprilysin inhibitors (ARNIs) (grade A), ACEIs (grade A), or ARBs (grade A) is recommended, as all 3 drugs inhibit the renin–angiotensin system (RAS) and are associated with reductions in heart failure–related morbidity and mortality.[43] For patients with symptomatic (NYHA Class II–III) HFrEF despite the use of ACEIs or ARBs, the replacement of ACEIs or ARBs with ARNIs is recommended to further reduce heart failure morbidity and mortality (grade B). However, there is insufficient evidence for the use of ARNIs in patients with NYHA class IV disease. ACEIs, as classic RASIs, are strongly supported by evidence-based medicine for improving clinical symptoms and exercise capacity and for reducing the risk of hospitalization and mortality in HFrEF patients.

In the late 1970s, Turini et al.[44] first demonstrated that captopril could reduce the volume load and pressure load of heart failure patients in the short term, thereby improving cardiac function. The Acute Infarction Ramipril Efficacy (AIRE) trial revealed that ramipril significantly reduced the incidence of MACEs (including death, severe or refractory heart failure, MI, and stroke) and all-cause mortality in patients with acute myocardial infarction (AMI) complicated by heart failure.[45] The distal radial access versus transradial access in ST-elevation MI study indicated that in patients with large anterior MI and reduced left ventricular ejection fraction (LVEF), adding ACEIs to a regimen of isosorbide dinitrate not only reduced ventricular dilation but also improved LVEF recovery.[46] In asymptomatic patients with left ventricular systolic dysfunction, if the AMI and LVEF are ≤ 40% or if the LVEF is ≤ 35% for various reasons, ACEIs can delay or promote left ventricular remodelling; increase the LVEF; increase exercise tolerance; and reduce the risk of morbidity, mortality, and hospitalization for heart failure.[47]

ACEI therapy provides benefits for patients with HFrEF of any severity-mild, moderate, or severe-regardless of the presence of coronary artery disease[48]. The Studies Of Left Ventricular Dysfunction (SOLVD) demonstrated that patients with left ventricular systolic dysfunction treated with enalapril for 3–4 years had significantly increased survival and prolonged life expectancy.[49] Meta-analyses have shown that ACEIs significantly reduce all-cause mortality by 20% to 26% and the risk of mortality, heart failure hospitalization by 27% to 33%, and the effects were similar across different types of ACEIs ("class effect").[50,51] Another network meta-analysis revealed that ACEIs, whether administered as monotherapy or in combination with other guideline-directed medical therapy (GDMT), were associated with reductions in all-cause mortality, cardiovascular mortality, heart failure rehospitalization, and all-cause rehospitalization in patients with HFrEF.[52]

3.2.2. Clinical question 2: Should ACEIs be routinely used for patients with heart failure with mildly reduced ejection fraction (HFmrEF)?

3.2.2.1. Consensus recommendation. For patients with symptomatic HFmrEF, ACEI treatment should be considered to reduce the risk of hospitalization for heart failure and cardiovascular mortality (grade B).

3.2.2.2. Recommendation explanation. There is currently limited direct evidence on the use of ACEIs for treating HFmrEF. Most existing guidelines treat it as reasonable to apply the GDMT for HFrEF in the treatment of HFmrEF.[53,54]

A network meta-analysis revealed that ACEIs reduce the risk of heart failure hospitalization in HFmrEF patients by 28%, whereas sodium–glucose cotransporter two inhibitors (SGLT2is) reduce the risk by 26%. In contrast, β-blockers and aldosterone receptor antagonists did not significantly reduce risk.[55] In addition, the Kyoto Congestive Heart Failure registry study demonstrated that among HFmrEF patients, compared with the non-ACEI group, the ACEI treatment group exhibited a 39% reduction in the composite risk of all-cause mortality and heart failure hospitalization.[56]

3.2.3. Clinical question 3: What are the indications for the use of ACEIs in patients with heart failure with preserved ejection fraction (HFpEF)?

3.2.3.1. Consensus recommendation. In HFpEF patients with concomitant hypertension, ACEIs should be considered[57] (grade C).

3.2.3.2. Recommendation explanation. Although clinical studies concerning the benefit of ACEIs in patients with HFpEF are limited and the majority of clinical trials have had negative or inconclusive outcomes, ACEIs have established benefits in managing comorbid conditions commonly associated with HFpEF, such as hypertension and coronary artery disease.[58,59]

A multicentre cohort study revealed that treatment with ACEIs or ARBs, either as monotherapy or in combination with β-blockers, was associated with a reduction in all-cause mortality in patients with HFmrEF and HFpEF.[60] However, because this study did not distinguish between HFmrEF and HFpEF or analyse ACEIs and ARBs separately, it is not possible to draw a definitive conclusion

Table 4

Commonly used ACEIs and their dosages for the treatment of chronic HFrEF.

Drug	Starting dosage	Target dosage
Captopril	6.25 mg, Tid	50 mg, Tid
Enalapril	2.50 mg, Bid	10 mg, Bid
Fosinopril	5.00 mg, Qd	20–30 mg, Qd
Lisinopril	5.00 mg, Qd	20–35 mg, Qd
Perindopril	2.00 mg, Qd	4–8 mg, Qd
Ramipril	1.25 mg, Qd	5 mg, Bid
Benazepril	2.50 mg, Qd	10–20 mg, Qd

ACEIs = angiotensin-converting enzyme inhibitors, Bid = twice daily, HFrEF = heart failure with reduced ejection fraction, Qd = once daily, Tid = 3 times daily.

regarding the ability of ACEIs to improve outcomes in HFpEF patients. Post hoc analysis of the OPTIMIZE-HF study indicated that in patients with HFpEF, the 60- to 90-day hospital readmission rate was not significantly different between patients who used ACEIs and those who did not.[61] In addition, the perindopril in elderly people with chronic heart failure (CHF) study revealed that perindopril did not reduce the all-cause mortality risk or heart failure–related hospitalization rate in elderly HFpEF patients aged 70 years or older.[62] Furthermore, a meta-analysis revealed that ACEIs did not reduce cardiovascular mortality in patients with HFpEF; although there was a trend toward a reduction in heart failure–related hospitalizations, the difference was not statistically significant.[63]

3.2.4. Clinical question 4: Should ACEIs be continued in patients with heart failure with improved ejection fraction (HFimpEF)?

3.2.4.1. Consensus recommendation. For patients with HFrEF whose ejection fraction improves and meets the criteria for HFimpEF, continuing GDMT treatment for HFrEF, including ACEIs, is recommended to prevent the recurrence of heart failure and left ventricular systolic dysfunction, regardless of symptom status (grade B).

3.2.4.2. Recommendation explanation. Currently, no clinical studies have specifically investigated the effects of ACEIs on improving clinical outcomes in patients with HFimpEF. Most current guidelines recommend continuation of the treatment regimen for HFrEF in these patients.[64] The Therapy withdrawal in REcovered Dilated cardiomyopathy—Heart Failure study is the only small exploratory study to investigate treatment regimens for such patients, but in this study, medications were tapered sequentially, with ACEIs or ARBs being the last to be discontinued. Therefore, the independent effect of ACEIs on reducing adverse events in HFimpEF patients cannot be determined.[65]

3.2.5. Clinical question 5: What are the treatment recommendations for ACEIs in patients at risk for heart failure and patients with preheart failure?

3.2.5.1. Consensus recommendation.

1. For stage A heart failure patients (those at high risk for heart failure because of comorbid conditions such as hypertension and diabetes), ACEIs are recommended to prevent the onset and progression of heart failure (grade A).
2. For stage B heart failure patients (those with structural heart disease but without signs or symptoms of heart failure), ACEI therapy is recommended regardless of a history of AMI (grade A).

3.2.5.2. Recommendation explanation. Heart failure is a progressive disease, and its occurrence and development can be divided into 4 stages. Stage A refers to individuals at risk for heart failure, characterized by the presence of risk factors such as hypertension and diabetes but without symptoms and/or signs of heart failure, without structural or functional heart disease, or abnormal biomarkers indicative of myocardial stress or injury. Stage B refers to preheart failure, defined as the current or previous absence of symptoms and/or signs of heart failure but with at least 1 of the following abnormalities: structural and/or functional cardiac abnormalities; evidence of increased filling pressures; and the presence of risk factors, along with increased natriuretic peptide levels or persistently elevated myocardial troponins. ACEIs play a crucial role in preventing symptomatic heart failure in stage A and stage B heart failure patients.

A network meta-analysis revealed that ACEIs can reduce overall cardiovascular event risk by 25%, cardiovascular mortality risk by 20%, and all-cause mortality risk by 17% in hypertensive patients.[66,67] Among hypertensive patients with type 2 diabetes mellitus, therapy with RASIs (including ACEIs) reduced the incidence of major cardiovascular events (comprising both fatal and nonfatal MI, stroke, and congestive heart failure) by 22% and reduced heart failure risk by 28% compared with CCB therapy.[68] Compared with β-blockers, ACEI therapy reduces the risk of major cardiovascular events by 24%, heart failure risk by 40%, and all-cause mortality risk by 37%.[68]

In stage B heart failure patients, regardless of a history of AMI, ACEIs can reduce the incidence and mortality of symptomatic heart failure.[69] A double-blind, placebo-controlled trial revealed that captopril attenuated left ventricular remodelling after anterior wall MI, reduced filling pressure, and increased exercise capacity.[70] In asymptomatic patients with an LVEF ≤ 35%, preventive treatment with enalapril significantly reduces the incidence of MI, unstable angina, and heart failure–related mortality.[71]

3.3. The use of ACEIs in coronary artery disease

3.3.1. Clinical question 1: Should all patients with acute coronary syndrome (ACS) use ACEIs?

3.3.1.1. Consensus recommendation.

1. For ACS patients with an LVEF ≤ 40% or those with comorbidities such as hypertension, diabetes, or CKD, long-term administration of ACEIs is recommended in the absence of contraindications (grade A).
2. Unless contraindicated or not tolerated, ACEI therapy is recommended for all patients with ACS (grade A).
3. In patients with acute ST-elevation MI, ACEIs should be initiated within 24 h of symptom onset, as soon as possible, provided that there are no contraindications (such as hypotension) (grade A).

3.3.1.2. Recommendation explanation. The survival and ventricular enlargement study revealed that in patients with an LVEF ≤ 40% who were treated 3 days to 16 days after AMI, compared with a placebo, captopril reduced all-cause mortality by 19%, cardiovascular mortality by 21%, the risk of severe heart failure by 37%, the risk of hospitalization for congestive heart failure by 22%, and the risk of recurrent MI by 25%.[72]

The Fourth International Study of Infarct Survival (ISIS-4) study demonstrated that administering captopril within 24 h of AMI reduced all-cause mortality by 7% within 5 weeks, with the survival benefit continuing for up to 12 months.[73] The Survival of Myocardial Infarction Long-term Evaluation (SMILE) study indicated that compared with the administration of a placebo, the administration of zofenopril within 24 h of acute anterior wall MI reduced the combined risk of cardiac death and congestive heart failure by 28% at 6 weeks and decreased 1-year all-cause mortality by 29%.[74]

3.3.2. Clinical question 2: Which patients with chronic coronary syndrome (CCS) should be recommended ACEIs?

3.3.2.1. Consensus recommendation.

1. ACEIs are recommended for patients with CCS who have an LVEF ≤ 40% and who have hypertension, diabetes, or CKD (grade A).[51,72,75]
2. In patients with symptomatic heart failure after MI or asymptomatic left ventricular systolic dysfunction, long-term ACEI therapy is recommended to alleviate symptoms and reduce morbidity and mortality (grade A).[76,77]
3. For high-risk CCS patients, ACEIs are recommended to reduce the incidence of adverse cardiovascular outcomes (grade A).[78–82]
4. In CCS patients without hypertension, diabetes, or CKD and with an LVEF > 40% who are not at high cardiovascular risk, ACEIs may be considered to reduce cardiovascular event risk (grade B).[78,79,81,83]

3.3.2.2. Recommendation explanation. Patients with CCS and left ventricular systolic dysfunction and/or comorbidities such as hypertension, diabetes, or CKD are at significantly greater risk for developing symptomatic heart failure and experiencing recurrent cardiovascular events.[84] In the absence of contraindications, ACEIs are recommended for CCS patients with left ventricular systolic dysfunction (LVEF ≤ 40%), hypertension, diabetes, and/or CKD.

The HOPE trial enrolled 9,541 patients with coronary artery disease, stroke, peripheral vascular disease, diabetes mellitus, or at least one other cardiovascular risk factor. Compared with the placebo group, the ramipril group presented a 22% reduction in the composite endpoint of MI, stroke, and cardiovascular death; a 26% reduction in cardiovascular mortality; and a 20% reduction in the incidence of MI.[78] The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators trial involved 12,218 patients with a history of MI, angiographically confirmed coronary artery disease, or prior coronary artery revascularization or a positive stress test. Compared with the placebo, perindopril reduced the incidence of the primary composite endpoint (cardiovascular death, MI, and sudden cardiac arrest) by 20%.[79] A pooled analysis of the HOPE, EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators, and PEACE trials revealed that in 29,805 CCS patients, the ACEI group had a 12% reduction in all-cause mortality compared with the placebo group, along with significant reductions in cardiovascular mortality, nonfatal MI, and heart failure events.[77]

3.3.3. Clinical question 3: How should ACEIs be applied in patients with ischaemia with nonobstructive coronary arteries (INOCA) and MI with nonobstructive coronary arteries (MINOCA)?

3.3.3.1. Consensus recommendation.

1. ACEIs are recommended as first-line therapy for the management of hypertension in patients with coexisting coronary microvascular dysfunction (CMD) (grade A).
2. ACEIs should be considered as part of antianginal therapy in patients with CMD or CMD combined with coronary artery spasm (grade B).
3. In patients with INOCA and coexisting atherosclerosis, ACEIs should be considered for the secondary prevention of cardiovascular events (grade B).
4. ACEIs are recommended for patients with MINOCA caused by plaque rupture or erosion, especially those with left ventricular systolic dysfunction (LVEF ≤ 40%), hypertension, diabetes, or CKD (grade A).
5. ACEIs should be considered for secondary prevention in MINOCA patients whose underlying CMD is presumed aetiology (grade B).

3.3.3.2. Recommendation explanation. INOCA encompasses 2 main aetiologies: CMD and epicardial coronary artery spasm. The antianginal effects of ACEIs are applicable mainly to CMD-related INOCA. Risk factor modification and secondary prevention strategies apply broadly to INOCAs of various aetiologies. The therapeutic application of ACEIs in MINOCA is similar to the established indications for ACEI application in atherosclerotic MI.[85]

A meta-analysis revealed that ACEIs improve coronary flow reserve (CFR) in patients with hypertension and CMD.[86] A subgroup analysis of the Women's Ischemia Syndrome Evaluation (WISE) study revealed that, compared with placebo, quinapril improved coronary flow reserve and angina symptoms in CMD patients.[87] The EMMACE-2 registry study, which included 350 CMD patients with atherosclerosis, revealed that ACEI therapy was significantly associated with a lower 6-month mortality risk.[88] The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) cohort analysis revealed that ACEIs reduced the risk of MACEs (including all-cause mortality, hospitalization for AMI, ischaemic stroke, and heart failure) by 18% in MINOCA patients.[50] A meta-analysis of data from 5 observational studies involving 10,546 MINOCA patients revealed that ACEIs reduced the risk of MACEs by 35%.[89]

3.3.4. Clinical question 4: Can ACEIs be used for spontaneous coronary artery dissection and other coronary artery diseases?

3.3.4.1. Consensus recommendation. ACEIs are recommended for patients with MI secondary to spontaneous coronary artery

dissection who present with left ventricular systolic dysfunction or hypertension (grade C).

3.3.4.2. Recommendation explanation. Currently, there is a lack of evidence from randomized clinical trials regarding the efficacy of ACEIs in the treatment of spontaneous coronary artery dissection, coronary arteritis, myocardial bridging, coronary artery ectasia, or coronary artery aneurysm. However, for patients with coronary artery atherosclerosis or related risk factors (such as hypertension) and those with AMI caused by the aforementioned diseases, the use of ACEIs may be beneficial.

3.4. ACEIs in arrhythmia

3.4.1. Clinical question 1: Which patients can use ACEIs to prevent new-onset AF?

3.4.1.1. Consensus recommendation.

1. For patients with HFrEF, ACEIs should be considered to prevent new-onset AF[90] (grade B).
2. After MI, especially in patients with concomitant heart failure, ACEIs should be considered to reduce the risk of new-onset AF (grade B).
3. In hypertensive patients, particularly those with myocardial hypertrophy, ACEIs should be considered for the prevention of new-onset AF (grade B).

3.4.1.2. Recommendation explanation. Post hoc analysis of the SOLVD study results revealed that ACEIs can reduce the risk of new-onset AF in patients with heart failure and an LVEF ≤ 35%.[90] A 2–4-year follow-up study involving 1,577 patients with heart failure after MI revealed that the risk of AF was lower in the ACEI group than in the placebo group.[91]

Another study involving 10,926 hypertensive patients with a median follow-up of 4.5 years indicated that, compared with CCBs, ACEIs significantly reduced the risk of new-onset AF.[92] Similarly, a nested case-control study from Denmark, which included hypertensive patients enrolled from 1995 to 2010, demonstrated that compared with β-adrenergic receptor blockers and diuretics, ACEIs significantly reduced the risk of new-onset AF.[93] In patients with hypertrophic cardiomyopathy, compared with nonuse, the use of ACEIs or ARBs was associated with a lower risk of AF.[94]

3.4.2. Clinical question 2: Can ACEIs reduce AF recurrence risk?

3.4.2.1. Consensus recommendation.

1. In patients with AF who have undergone electrical cardioversion, ACEIs should be considered to reduce the risk of AF recurrence (grade C).
2. In patients with AF undergoing radiofrequency catheter ablation, ACEIs should be considered to reduce the risk of AF recurrence (grade C).
3. In patients with paroxysmal AF, ACEIs should be considered to reduce the risk of AF episodes (grade C).

3.4.2.2. Recommendation explanation. ACEIs not only reduce the risk of new-onset AF but also effectively decrease the risk of AF recurrence.[95–97] In patients with AF, ACEIs have been shown to increase the success rate of electrical cardioversion and reduce AF recurrence risk after conversion.[98–100] For patients with persistent AF undergoing electrical cardioversion, a nonrandomized controlled study demonstrated that ACEIs combined with amiodarone significantly reduced both short-term and long-term AF recurrence rates.[101]

A randomized controlled trial (RCT) conducted in China revealed that ACEIs reduce the recurrence rate of paroxysmal AF in patients who have undergone radiofrequency catheter ablation.[102] In patients with paroxysmal AF, ACEIs combined with amiodarone significantly decreased the number of AF episodes and reduced the degree of atrial remodelling.[103]

3.4.3. Clinical question 3: Can ACEIs reduce the risk of ventricular arrhythmias?

3.4.3.1. Consensus recommendation.

1. After MI, especially in patients with concurrent heart failure, ACEIs should be considered to prevent the occurrence of ventricular arrhythmias (grade B).
2. In patients with ventricular tachycardia treated with an implantable cardioverter-defibrillator (ICD), ACEIs should be considered to reduce the number of ICD shocks triggered (grade C).
3. In patients with heart failure and ventricular arrhythmias, ACEIs should be considered to suppress the occurrence of ventricular arrhythmic events (grade B).

3.4.3.2. Recommendation explanation. A meta-analysis revealed that the use of ACEIs in patients with MI is significantly associated with a reduced incidence of sudden cardiac death.[104] Post hoc analysis of the ISIS-4 study indicated that the administration of ACEIs after MI was associated with decreases in both the incidence and frequency of ventricular arrhythmias within the first 14 days postinfarction.[105] In patients who develop heart failure after MI, ACEI therapy is associated with fewer premature ventricular contractions and a lower risk of new-onset ventricular arrhythmias.[106]

In heart failure patients with a LVEF ≤ 30% who have an implanted ICD, ACEIs significantly reduce the incidence of appropriate ICD shock over a 5-year follow-up period.[107] A retrospective study revealed that although ACEIs did not reduce the incidence of rapid ventricular arrhythmias during a 5-year follow-up period, they significantly decreased the frequency of ICD discharges.[108]

An RCT demonstrated that in patients with chronic congestive heart failure, compared with nitrate therapy, ACEIs reduced the risk of ventricular tachycardia (VT).[109] Another small RCT revealed that ACEIs significantly reduced the incidence of ventricular arrhythmias in patients with congestive heart failure.[110] In patients with arrhythmogenic right ventricular cardiomyopathy, ACEI treatment was significantly associated with a lower incidence of malignant ventricular arrhythmias.[111]

3.5. Application of ACEIs in cardiovascular diseases with coexisting CKD

3.5.1. Clinical question 1: Is the use of ACEIs recommended in patients with CKD?

3.5.1.1. Consensus recommendation.

1. For nondialysis CKD patients with severe proteinuria (G1 [estimated glomerular filtration rate – (eGFR) ≥ 90 mL·min^{-1}·1.73/m^{-2}] to G4 [eGFR

15–29 mL·min^{-1}·1.73/m^{-2}] and A3 [urinary albumin ≥ 300 mg/g]), the use of ACEIs is recommended regardless of the presence of hypertension or diabetes (grade A).
2. For nondialysis CKD patients with moderate proteinuria (G1–G4 and A2 [urinary albumin concentration of 30–299 mg/g]) and coexisting diabetes, the use of ACEIs is recommended regardless of the presence of hypertension (grade A).
3. For CKD patients without proteinuria but with hypertension, the use of ACEIs is advised (grade A).
4. CKD patients with an eGFR of 15–30 mL·min^{-1}·1.73/m^{-2} can continue ACEI treatment (grade B).

3.5.1.2. Recommendation explanation. ACEIs serve as a fundamental treatment for CKD and should be recommended on the basis of the patient's renal function (including serum creatinine and urinary protein levels), as well as the presence of comorbid hypertension and diabetes.[112] In CKD patients without proteinuria but with hypertension, there is no clear evidence that ACEIs slow the progression of CKD. However, from the perspective of cardiovascular protection, ACEIs may provide clinical benefit in this patient population.[113]

A meta-analysis demonstrated that ACEIs significantly reduce the risk of end-stage renal disease (ESRD) as well as composite endpoints, including doubled serum creatinine levels or ESRD and the composite endpoint of ESRD or death.[26] Multiple RCTs have shown that in CKD patients with severe proteinuria, regardless of whether they also have hypertension or diabetes, ACEIs can reduce the risk of kidney failure and cardiovascular events.[114–116] An RCT involving 3394 CKD patients without proteinuria or with mildly increased albuminuria (approximately one-third of whom had diabetes) revealed that, compared with placebo, ACEIs reduced all-cause mortality by 20%, MI risk by 26%, and stroke risk by 31%.[117]

Even in patients with an eGFR < 30 mL·min^{-1}·1.73/m^{-2}, ACEIs may continue to provide renal protection and can be safely used with appropriate precautions.[118] However, high doses should be avoided, and regular monitoring of serum creatinine and potassium levels is essential.[119] The STOP-ACEIs study enrolled 411 CKD patients with eGFR < 30 mL·min^{-1}·1.73/m^{-2} and reported that the discontinuation of RASIs (including ACEIs and ARBs) did not confer renal or cardiovascular benefits compared with continued use over a 3-year follow-up period.[120] Similarly, data from the Swedish Renal Registry indicated that, compared with continued RASI treatment, the discontinuation of RASIs was associated with a greater absolute risk of 5-year mortality in patients with advanced CKD (eGFR < 30 mL·min^{-1}·1.73/m^{-2}).[121]

3.5.2. Clinical question 2: Can ACEIs and SGLT2is be used in combination for the treatment of CKD?

3.5.2.1. Consensus recommendation.

1. CKD patients are recommended to receive a combination of SGLT2i and ACEIs as part of their treatment regimen (grade A).
2. SGLT2i is recommended as an alternative treatment for CKD patients who are intolerant to ACEIs (grade A).

3.5.2.2. Recommendation explanation. Currently, both SGLT2i and ACEIs are considered foundational therapies for CKD. Compared with either ACEIs or SGLT2is alone, the combination of ACEIs and SGLT2is can further reduce the risk of renal function decline and delay progression to ESRD.[122,123]

A meta-analysis demonstrated that SGLT2i alone can reduce the risk of renal function decline by 29%, whereas SGLT2i combined with RAS inhibitors (including ACEIs) further reduces this risk by 42%.[124] Compared with ACEI monotherapy, the combination of ACEIs and SGLT2is led to greater reductions in systolic and diastolic BP, 24-h ambulatory BP, the urinary albumin-to-creatinine ratio, the eGFR, glycated haemoglobin, fasting blood glucose, and body weight.[125]

In CKD patients with type two diabetes, SGLT2i has been shown to reduce the risk of hyperkalaemia (serum potassium concentration > 6 mmol/L).[126] In addition, for CKD patients with proteinuria, SGLT2i decreased the relative risk of ACEI discontinuation owing to adverse effects by 15%, with even more pronounced benefits in patients with a urinary albumin-to-creatinine ratio ≥ 1,000 mg/g.[127]

3.5.3. Clinical question 3: Can ACEIs be used in dialysis and kidney transplant patients?

3.5.3.1. Consensus recommendation.

1. For haemodialysis patients with hypertension, common antihypertensive medications, including ACEIs, can be used (grade B).
2. The choice of ACEIs and the treatment plan should be based on the dialysis clearance characteristics and the individual circumstances of the patient (grade C).
3. For peritoneal dialysis patients, commonly used antihypertensive medications, including ACEIs, are also appropriate (grade C).
4. RASI and CCB are preferred for BP control in kidney transplant recipients with hypertension (grade C).

3.5.3.2. Recommendation explanation. Common first-line antihypertensive medications, such as ACEIs, ARBs, and CCBs, can all be used as first-line antihypertensive agents for dialysis patients. A meta-analysis revealed that ACEIs can delay renal function deterioration in dialysis patients.[128] Moreover, perindopril can reduce the left ventricular mass in haemodialysis patients and improve vascular function.[129]

There are significant differences in the pharmacokinetics of different ACEIs during haemodialysis. When selecting an ACEI, it is important to consider the clearance of the drug by dialysis and the patient's BP during dialysis (Table 5). If a patient frequently experiences hypotension during dialysis, ACEIs that are not cleared by dialysis should be avoided. On the other hand, for patients whose BP is relatively stable during dialysis, ACEIs with low dialysability are recommended.[130]

A meta-analysis indicated that ACEIs can delay the loss of residual kidney function in peritoneal dialysis patients and improve their prognosis.[131] ACEIs can reverse LVH in peritoneal dialysis patients and provide cardiovascular protection by ameliorating congestive heart failure, reducing sympathetic nervous activity, alleviating oxidative stress, and improving endothelial function.[132,133] In addition, ACEIs effectively reduce BP and proteinuria in kidney transplant patients and can also improve graft survival.[134]

4. Common adverse reactions to ACEIs and management recommendations

4.1. Clinical question 1: Should ACEIs be reduced in dose or discontinued if hyperkalaemia occurs during treatment?

4.1.1. Consensus recommendation.

1. Potassium levels should be checked before initiating ACEI therapy, and potassium levels should be monitored 2 weeks to 4 weeks after initiation or after any dose adjustment.
2. When hyperkalaemia related to ACEIs occurs, whether to reduce the dose or discontinue ACEIs depends on the potassium level and clinical situation:
   i. Potassium concentration of 5.1 mmol/L to 5.9 mmol/L: Adding potassium-lowering medications should be considered, and discontinuation of ACEIs should be avoided if possible.
   ii. Potassium concentration of 6.0 mmol/L to 6.4 mmol/L: Dose reduction or discontinuation of ACEIs should be considered, potassium-lowering therapy should be initiated immediately, and potassium levels should be rechecked within 24 h. Once the potassium concentration is ≤ 5.0 mmol/L, the ACEI dose should be gradually increased to the maximum tolerated level, as recommended by the guidelines. If potassium-lowering medications are ineffective, ACEIs may be discontinued.
   iii. Potassium concentration ≥ 6.5 mmol/L: ACEIs should be discontinued immediately, and patients should be assessed for any emergency conditions related to hyperkalaemia. If potassium-lowering medications are ineffective, haemodialysis should be initiated to remove potassium.

4.1.2. Recommendation explanation. Hyperkalaemia is among the main adverse effects of ACEIs, especially in patients with CKD, who should be vigilant for its occurrence. Reducing the dose or discontinuing ACEIs can correct hyperkalaemia, but this may increase the patient's long-term risk of death and cardiovascular diseases, thus severely affecting the patient's prognosis.[135,136]

The specific treatment methods for hyperkalaemia that occurs during ACEI use are shown in Table 6. With respect to the emergency treatment of hyperkalaemia, in addition to traditional potassium-lowering diuretics and the combined use of glucose and insulin, several new oral potassium-lowering agents, such as zirconium cyclosilicate, have recently gained clinical recognition. Some of these new agents can also be used as adjuncts to ACEIs for long-term treatment to maintain stable potassium levels, thus reducing the need to limit ACEI use owing to elevated potassium levels[137] (Table 7).

A 6-month observational study on CKD and/or heart failure patients with hyperkalaemia revealed that 69% to 79% of those treated with zirconium cyclosilicate were able to continue using RASIs (including ACEIs). In contrast, only 48% to 56% of patients who did not receive potassium-lowering treatment were able to continue RASI therapy. Zirconium cyclosilicate increased the RASI usage rate by 2.56-fold.[138]

According to the 2024 KDIGO guidelines for the evaluation and management of ACEI-related hyperkalaemia, potassium-lowering medications can be actively added without the need to reduce the ACEI dose or discontinue the drug.[139]

4.2. Clinical question 2: Should ACEIs be reduced or discontinued if the serum creatinine level increases after ACEI treatment?

4.2.1. Consensus recommendation.

1. Renal function should be monitored before starting ACEI treatment and again within 2 weeks to 4 weeks after initiating treatment or adjusting the dose.
2. If the serum creatinine level increases by less than 30% from baseline within 2 weeks to 4 weeks after initiating treatment or increasing the dose, no special intervention is needed. ACEI treatment should be continued, and monitoring should be increased.
3. If the serum creatinine level increases by 30% or more within 2 weeks to 4 weeks after initiating treatment or increasing the dose, potential causes of renal function decline (e.g., renal artery stenosis) should be investigated. Any volume depletion should be corrected, and other concomitant medications (e.g., diuretics and nonsteroidal anti-inflammatory drugs) should be assessed. If these measures do not explain the decline in renal function, the ACEI dose should be reduced.
4. For patients with an eGFR < 15 mL·min^{-1}·1.73/m^{-2} and significant uraemic symptoms, if dialysis is not available, ACEIs should be reduced or discontinued, and referrals to nephrologists should be made. Notably, most patients' serum creatinine levels stabilize or return to baseline after the discontinuation of ACEIs.

4.2.2. Recommendation explanation. A retrospective study analysing 12 RCTs revealed that patients with an acute increase in serum creatinine of approximately 30% after ACEI therapy were more likely to maintain long-term kidney function. This increase in creatinine is not considered an adverse effect of ACEIs.[140]

The 2024 KDIGO guidelines for the evaluation and management of CKD recommend that for CKD patients, if the serum creatinine level increases by no more than 30% within 4 weeks of starting RASI (including ACEI and ARB) treatment, RASIs can be continued. For patients with an eGFR < 15 mL·min^{-1}·1.73/m^{-2} and significant uraemic symptoms, dose reduction or discontinuation of ACEIs should be considered.[139]

4.3. Clinical question 3: Should ACEIs be reduced or discontinued if hypotension occurs after ACEI treatment?

4.3.1. Consensus recommendation.

1. In most patients who experience hypotension (systolic BP < 90 mmHg) during ACEI treatment, the ACEI dose should be reduced or ACEI treatment should be discontinued.
2. For patients with CHF or CKD, if hypotension occurs during ACEI treatment and if the patient is asymptomatic, ACEI treatment may be continued with caution. First, other concomitant antihypertensive medications (e.g., nitrates, CCBs, diuretics) should be reduced. If hypotension persists with a

Table 5

***In vivo* metabolic characteristics, dialysis clearance rates, and dose adjustment guidelines for common angiotensin-converting enzyme inhibitors.**

Drug	Primary metabolic organs	Dose adjustment in renal failure	Dose adjustment in liver failure	Haemodialysis clearance rate	Supplemental dose after each dialysis (mg)
Benazepril	Kidneys 88% to 89%, liver 11% to 12%	Reduce	No adjustment	Minimal	5.0–10.0
Captopril	Kidneys 95%	Reduce	No adjustment	50%	12.5–25.0
Enalapril	Kidneys 94%	Reduce	Reduce	50%	2.5–5.0
Fosinopril	Kidneys 50%, liver 50%	No adjustment	Reduce	None	None
Lisinopril	Kidneys 100%	No adjustment	No adjustment	50%	2.5–5.0
Perindopril	Kidneys 100%	Reduce	No adjustment	50%	2.0
Ramipril	Kidneys 60%, liver 40%	Reduce	No adjustment	20%	2.5

systolic BP < 90 mmHg despite these measures, ACEI dose reduction or discontinuation should be considered.

4.3.2. Recommendation explanation. Hypotension after ACEI use is common, especially with the initial dose or during dose escalation, and occurs more frequently in patients with CHF or those receiving high-dose diuretics; in most cases, the condition is asymptomatic. The 2024 KDIGO guidelines for CKD evaluation and treatment recommend considering ACEI dose reduction or discontinuation only if the patient develops symptomatic hypotension.[139]

4.4. Clinical question 4: Should ACEIs be discontinued if cough occurs after ACEI treatment?

4.4.1. Consensus recommendation.

1. It is important to determine whether a chronic cough is caused by ACEIs. If the cough is because of other causes, treatment should target the underlying condition, and ACEIs can be continued.
2. If the cough is suspected to be related to ACEIs but the patient can tolerate the symptoms, ACEIs may be continued with caution.
3. If the cough persists, ACEIs can be temporarily discontinued. Typically, cough symptoms subside within 1 to 4 weeks after discontinuation. If symptoms do not resolve, other causes should be investigated.
4. For patients who cannot tolerate ACEI-induced cough, switching to an ARB is recommended.

4.4.2. Recommendation explanation. Cough (usually dry cough) is a relatively common adverse effect of ACEIs, affecting 5% to 10% of patients, with a relatively high prevalence in female patients and Asian individuals.[141] These side effects vary among different types of ACEIs, and elevated bradykinin levels may be the mechanism underlying cough. Cough commonly occurs within the first few months of treatment, and if the cough resolves after discontinuation and reappears upon readministration, it strongly suggests that ACEIs are the cause of dry cough.

4.5. Clinical question 5: Should ACEIs be discontinued if angioedema occurs after ACEI treatment?

4.5.1. Consensus recommendation. If angioedema occurs, ACEIs should be immediately discontinued, and symptom treatments, such as antihistamines, should be administered. ACEIs should be permanently avoided in the future.

4.5.2. Recommendation explanation. Angioedema caused by ACEIs is relatively rare (occurring in 0.1%–0.7% of cases)[16] but it can be life-threatening. ACEI-induced angioedema most often occurs within the first 24 h after the initial dose or treatment. If symptoms such as laryngeal or throat swelling or difficulty breathing arise, immediate medical attention is needed, and treatment with epinephrine or dexamethasone should be initiated. For patients with severe respiratory distress and significantly reduced blood oxygen levels, intubation should be performed to relieve airway obstruction.

4.6. Clinical question 6: What are the contraindications for ACEI use?

4.6.1. Consensus recommendation.

1. Absolute contraindications Pregnancy and planned pregnancy: ACEIs are contraindicated during pregnancy, especially in the 2nd and 3rd trimesters, owing to known teratogenic risks; ACEI-induced angioedema; bilateral renal artery stenosis or the presence of a single kidney with severe renal artery stenosis; severe hyperkalaemia (serum potassium > 6.0 mmol/L); contraindicated concomitant use of ACEIs with ARBs or direct renin inhibitors; and the concomitant use of ACEIs with ARNIs. If ACEIs are switched from ACEIs to ARNIs, ACEIs should be discontinued for at least 36 h to prevent adverse reactions.
2. Conditional contraindications Lactation; eGFR < 15 $mL \cdot min^{-1} \cdot 1.73/m^{-2}$ without dialysis; mild hyperkalaemia (serum potassium > 5.5 and ≤ 6.0 mmol/L); hypotension (systolic BP < 90 mmHg): symptoms should be treated, and after haemodynamic stabilization, the benefits

Table 6

Management of different serum potassium levels during ACEI treatment.

Serum potassium level (mmol/L)	ACEI usage	Hypokalaemia treatment	Frequency of potassium recheck
≤ 5.0	Gradually increase ACEI dose to the maximum tolerated dose recommended by the guidelines	No hypokalaemia treatment required	Check potassium level every 1 weeks to 2 weeks during ACEI initiation and dose escalation. After reaching the maximum tolerated dose, check monthly. Once stable, check every 3 months to 6 months
5.1 to 5.9	Maintain the current dose, then gradually increase ACEI dose to the maximum tolerated dose recommended by the guidelines after potassium ≤ 5.0 mmol/L	Start potassium-lowering treatment immediately, and maintain as necessary to reduce potassium to ≤ 5.0 mmol/L	Recheck potassium within 3 days
≥ 6.0	Reduce or discontinue ACEIs as needed, and then gradually increase ACEI dose to the maximum-tolerated dose recommended by the guidelines after potassium is reduced to ≤ 5.0 mmol/L	Start potassium-lowering treatment immediately, and continue treatment after potassium is reduced to ≤ 5.0 mmol/L	Recheck potassium within 1 day. If potassium ≥ 6.5 mmol/L, immediate assessment and symptomatic treatment are needed

ACEI = angiotensin-converting enzyme inhibitor.

and risks should be weighed to determine whether ACEIs can be used; and haemodynamically significant aortic stenosis or hypertrophic obstructive cardiomyopathy. For these indications, the use of ACEIs should be carefully evaluated.

4.6.2.Recommendation explanation. ACEIs can affect foetal development; therefore, they are contraindicated during pregnancy and in women planning to become pregnant. Women of childbearing age who must use ACEIs should use effective contraception.

For most breastfeeding women, the use of ACEIs is not recommended. Captopril, enalapril, and benazepril are present at low concentrations in breast milk; therefore, ACEIs may be considered for a small number of breastfeeding women who urgently require ACEI therapy.[142,143] However, given the limited clinical evidence regarding ACEI use during lactation, this decision should be made cautiously under the guidance of a healthcare professional.

ACEIs exert a stronger dilating effect on the efferent arterioles than on the afferent arterioles; thus, in patients with bilateral renal artery stenosis, ACEIs may reduce glomerular perfusion pressure and cause acute kidney injury. ACEIs should be avoided in these patients.

Although combining ACEIs and ARBs can block the RAAS pathway at two time points and reduce proteinuria, the exact benefit for kidney function remains unclear. Furthermore, this combination increases the risk of hyperkalaemia, acute kidney injury, and a 40% deterioration in renal function, with a 44% increase in the risk of hyperkalaemia and a 42% increase in the risk of hypotension.[144]

ACEIs can dilate peripheral vessels, reducing the cardiac pressure load. Therefore, in patients with

Table 7

Common new oral potassium-lowering medications.

Type	Mechanism of action	Common dosage and method	Precautions
CPS and SPS	Cation exchange resins that bind potassium ions in the colon via calcium/sodium–potassium exchange, reducing systemic absorption and increasing faecal excretion	CPS: 15.0 g/day to 60.0 g/day, divided into 2 to 3 oral doses; SPS: 15.0–30.0 g/day, divided into 2 to 3 oral doses	Avoid concomitant oral medications for 3.0 h; CPS takes effect after 1 day, and normal potassium levels can be restored within 3 days
SZC	Selective potassium binder that selectively captures potassium ions throughout the gastrointestinal tract, reducing potassium absorption	Acute hyperkalaemia: 10.0 g/day in 3 divided doses (max: 48 h); chronic hyperkalaemia: start at 5.0 g/day, titrate based on potassium levels (range: 5.0 g every other day to 10.0 g/day)	SZC begins lowering potassium levels 1.0 h after 1st dose, median time to normal potassium is 2.2 h; few side effects, mainly diarrhoea
Patiromer	A new potassium-binding agent that selectively binds with potassium ions in the gastrointestinal tract, primarily increasing potassium excretion in the distal colon	Initial 8.4 g/day, increase by 8.4 g/day weekly (max: 25.2 g/day); maintenance 8.4–25.2 g/day	Takes effect 4.0–7.0 h after administration, potassium levels can be restored to normal within 1 week; no other medications should be taken within 3.0 h before or after administration

ACEI = angiotensin-converting enzyme inhibitor, CPS = calcium polystyrene sulfonate, SPS = sodium polystyrene sulfonate, SZC = sodium zirconium cyclosilicate.

haemodynamically significant aortic stenosis or hypertrophic obstructive cardiomyopathy, the use of ACEIs should be evaluated carefully, and the risks and benefits should be weighed.

In summary, despite the emergence of new drugs in recent years, ACEIs remain a cornerstone of 1st line treatment for cardiovascular diseases. They have demonstrated excellent efficacy in reducing the incidence of cardiovascular events and improving prognosis. In addition to their widespread use in cardiovascular diseases, ACEIs are also being increasingly recognized as useful treatments for complex conditions such as cardiovascular diseases combined with kidney disease, type two diabetes, and cancers. Emerging evidence supports the combination of ACEIs with newer drugs, such as SGLT2is. This consensus aims to provide cutting-edge and scientific guidance for clinical practice to further standardize and optimize the clinical use of ACEIs, improve treatment outcomes, reduce adverse reactions, and ultimately improve patient survival and quality of life.

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Ethical statement

This study did not involve human participants, animal subjects, or any primary data collection requiring ethical approval.

Conflict of interest

JC serves as the Editor-in-Chief of *Cardiac Research*. He was not involved in the editorial review or decision-making process for this manuscript. All editorial decisions were made independently by other members of the Editorial Board who have no conflicts of interest. The remaining authors have no conflicts of interest to disclose.

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AI statement

During the preparation of this work, the authors used ChatGPT (version GPT-4o) to assist in language polishing and improving the readability of the manuscript. Following the use of this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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